

Ribociclib EBC

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Table of contents

1 Patient disposition, demographic and disease characteristics, follow-up times and PRO return rates	10
Table 1-1 Patient disposition (Full Analysis Set)	10
Table 1-2 Patient demographics (Full Analysis Set)	12
Table 1-3 Patient baseline disease characteristics (Full Analysis Set)	14
Table 1-4 Drug exposure and follow-up times by endpoint and study treatment (Full Analysis Set)	19
Table 1-5 Drug exposure and follow-up times by endpoint and study treatment (Safety Set)	25
Table 1-6.1 Prior anti-cancer therapies (Full Analysis Set)	26
Table 1-6.2 Prior anti-neoplastic medications by ATC class and preferred name (Full Analysis Set)	27
Table 1-7 Post treatment anti-cancer therapies (Full Analysis Set)	30
Table 1-8 Subgroups (Full Analysis Set)	32
2 Efficacy	35
2-1 Overall survival	35
Table 2-1.1 Overall survival: time to event analysis (Full Analysis Set)	35
Figure 2-1.1 Overall survival: Kaplan-Meier plot (Full Analysis Set)	36
Table 2-1.2 Overall survival: binary analysis (Full Analysis Set)	37
2-2 Invasive disease-free survival	38
Table 2-2.1 Invasive disease-free survival: time to event analysis (Full Analysis Set)	38
Figure 2-2.1 Invasive disease-free survival: Kaplan-Meier plot (Full Analysis Set)	39
Table 2-2.2 Invasive disease-free survival: binary analysis (Full Analysis Set)	40
2-3 Distant disease-free survival	41
Table 2-3.1 Distant disease-free survival: time to event analysis (Full Analysis Set)	41
Figure 2-3.1 Distant disease-free survival: Kaplan-Meier plot (Full Analysis Set)	42
Table 2-3.2 Distant disease-free survival: binary analysis (Full Analysis Set)	43
3 PRO	44
3-0 Analysis PRO	44
3-1 EORTC QLQ-C30 Symptoms	44
Table 3-1.0 EORTC QLQ-C30 Symptoms: return rates (Full Analysis Set)	44
Table 3-1.1 EORTC QLQ-C30 Symptoms: change from baseline analysis (Full Analysis Set)	46
Figure 3-1.1 EORTC QLQ-C30 Symptoms: line chart of change from baseline (Full Analysis Set)	57
3-2 EORTC QLQ-C30 QoL	65
Table 3-2.0 EORTC QLQ-C30 QoL: return rates (Full Analysis Set)	65
Table 3-2.1 EORTC QLQ-C30 QoL: change from baseline analysis (Full Analysis Set)	66
Figure 3-2.1 EORTC QLQ-C30 QoL: line chart of change from baseline (Full Analysis Set)	74
3-3 EORTC QLQ-BR23 Symptoms	80
Table 3-3.0 EORTC QLQ-BR23 Symptoms: return rates (Full Analysis Set)	80
Table 3-3.1 EORTC QLQ-BR23 Symptoms: change from baseline analysis (Full Analysis Set)	81
Figure 3-3.1 EORTC QLQ-BR23 Symptoms: line chart of change from baseline (Full Analysis Set)	87
3-4 EORTC QLQ-BR23 QoL	91
Table 3-4.0 EORTC QLQ-BR23 QoL: return rates (Full Analysis Set)	91
Table 3-4.1 EORTC QLQ-BR23 QoL: change from baseline analysis (Full Analysis Set)	92
Figure 3-4.1 EORTC QLQ-BR23 QoL: line chart of change from baseline (Full Analysis Set)	97
3-5 EQ-5D VAS	101
Table 3-5.0 EQ-5D VAS: return rates (Full Analysis Set)	101
Table 3-5.1 EQ-5D VAS: change from baseline analysis (Full Analysis Set)	102
Figure 3-5.1 EQ-5D VAS: line chart of change from baseline (Full Analysis Set)	104
3-6 HADS	105
Table 3-6.0 HADS: return rates (Full Analysis Set)	105
Table 3-6.1 HADS: change from baseline analysis (Full Analysis Set)	106
Figure 3-6.1 HADS: line chart of change from baseline (Full Analysis Set)	109
4 Adverse events	111
Table 4-1 Adverse events: binary analysis (Safety Set)	111
Table 4-2 Adverse events by SOC and PT: binary analysis (Safety Set)	112
Table 4-3 Grade ≥ 3 adverse events by SOC and PT: binary analysis (Safety Set)	127
Table 4-4 Serious adverse events by SOC and PT: binary analysis (Safety Set)	130
Table 4-5 Adverse events leading to treatment discontinuation of ribociclib, by SOC and PT: frequency table (Safety Set)	131

Table 4-6 Adverse events leading to treatment discontinuation of NSAI, by SOC and PT: frequency table (Safety Set).....	135
Table 4-7 Adverse events leading to treatment discontinuation of any component, by SOC and PT: frequency table (Safety Set).....	138
Table 4-8 Adverse events of special interest: binary analysis (Safety Set).....	143
5 Subgroup analysis	146
5-1 Subgroup analysis for efficacy	146
5-1.1 Overall survival.....	146
5-1.2 Invasive disease-free survival.....	149
5-2 Subgroup analysis for PRO.....	154
5-2.1 EORTC QLQ-C30 Symptoms	154
5-2.2 EORTC QLQ-C30 QoL	211
5-2.3 EORTC QLQ-BR23 Symptoms.....	261
5-2.4 EORTC QLQ-BR23 QoL.....	291
5-2.5 EQ-5D VAS	319
5-2.6 HADS	326
5-3 Subgroup analysis for safety	345
5-3.1 Subgroup analysis for adverse events	345
5-3.2 Subgroup analysis for adverse events by SOC and PT.....	361
5-3.3 Subgroup analysis for grade ≥ 3 adverse events by SOC and PT	634
5-3.4 Subgroup analysis for serious adverse events by SOC and PT.....	673
5-3.5 Subgroup analysis for adverse events of special interest.....	685

List of tables and figures

1 Patient disposition, demographic and disease characteristics, follow-up times and PRO return rates	10
Table 1-1 Patient disposition (Full Analysis Set)	10
Table 1-2 Patient demographics (Full Analysis Set)	12
Table 1-3 Patient baseline disease characteristics (Full Analysis Set)	14
Table 1-4 Drug exposure and follow-up times by endpoint and study treatment (Full Analysis Set)	19
Table 1-5 Drug exposure and follow-up times by endpoint and study treatment (Safety Set)	25
Table 1-6.1 Prior anti-cancer therapies (Full Analysis Set)	26
Table 1-6.2 Prior anti-neoplastic medications by ATC class and preferred name (Full Analysis Set)	27
Table 1-7 Post treatment anti-cancer therapies (Full Analysis Set)	30
Table 1-8 Subgroups (Full Analysis Set)	32
2 Efficacy	35
2-1 Overall survival	35
Table 2-1.1 Overall survival: time to event analysis (Full Analysis Set)	35
Figure 2-1.1 Overall survival: Kaplan-Meier plot (Full Analysis Set)	36
Table 2-1.2 Overall survival: binary analysis (Full Analysis Set)	37
2-2 Invasive disease-free survival	38
Table 2-2.1 Invasive disease-free survival: time to event analysis (Full Analysis Set)	38
Figure 2-2.1 Invasive disease-free survival: Kaplan-Meier plot (Full Analysis Set)	39
Table 2-2.2 Invasive disease-free survival: binary analysis (Full Analysis Set)	40
2-3 Distant disease-free survival	41
Table 2-3.1 Distant disease-free survival: time to event analysis (Full Analysis Set)	41
Figure 2-3.1 Distant disease-free survival: Kaplan-Meier plot (Full Analysis Set)	42
Table 2-3.2 Distant disease-free survival: binary analysis (Full Analysis Set)	43
3 PRO	44
3-0 Analysis PRO	44
3-1 EORTC QLQ-C30 Symptoms	44
Table 3-1.0 EORTC QLQ-C30 Symptoms: return rates (Full Analysis Set)	44
Table 3-1.1 EORTC QLQ-C30 Symptoms: change from baseline analysis (Full Analysis Set)	46
Figure 3-1.1 EORTC QLQ-C30 Symptoms: line chart of change from baseline (Full Analysis Set)	57
3-2 EORTC QLQ-C30 QoL	65
Table 3-2.0 EORTC QLQ-C30 QoL: return rates (Full Analysis Set)	65
Table 3-2.1 EORTC QLQ-C30 QoL: change from baseline analysis (Full Analysis Set)	66
Figure 3-2.1 EORTC QLQ-C30 QoL: line chart of change from baseline (Full Analysis Set)	74
3-3 EORTC QLQ-BR23 Symptoms	80
Table 3-3.0 EORTC QLQ-BR23 Symptoms: return rates (Full Analysis Set)	80
Table 3-3.1 EORTC QLQ-BR23 Symptoms: change from baseline analysis (Full Analysis Set)	81
Figure 3-3.1 EORTC QLQ-BR23 Symptoms: line chart of change from baseline (Full Analysis Set)	87
3-4 EORTC QLQ-BR23 QoL	91
Table 3-4.0 EORTC QLQ-BR23 QoL: return rates (Full Analysis Set)	91
Table 3-4.1 EORTC QLQ-BR23 QoL: change from baseline analysis (Full Analysis Set)	92
Figure 3-4.1 EORTC QLQ-BR23 QoL: line chart of change from baseline (Full Analysis Set)	97
3-5 EQ-5D VAS	101
Table 3-5.0 EQ-5D VAS: return rates (Full Analysis Set)	101
Table 3-5.1 EQ-5D VAS: change from baseline analysis (Full Analysis Set)	102
Figure 3-5.1 EQ-5D VAS: line chart of change from baseline (Full Analysis Set)	104
3-6 HADS	105
Table 3-6.0 HADS: return rates (Full Analysis Set)	105
Table 3-6.1 HADS: change from baseline analysis (Full Analysis Set)	106
Figure 3-6.1 HADS: line chart of change from baseline (Full Analysis Set)	109
4 Adverse events	111
Table 4-1 Adverse events: binary analysis (Safety Set)	111
Table 4-2 Adverse events by SOC and PT: binary analysis (Safety Set)	112
Table 4-3 Grade ≥ 3 adverse events by SOC and PT: binary analysis (Safety Set)	127
Table 4-4 Serious adverse events by SOC and PT: binary analysis (Safety Set)	130
Table 4-5 Adverse events leading to treatment discontinuation of ribociclib, by SOC and PT: frequency table (Safety Set)	131
Table 4-6 Adverse events leading to treatment discontinuation of NSAID, by SOC and PT: frequency table (Safety Set)	135

Table 4-7 Adverse events leading to treatment discontinuation of any component, by SOC and PT: frequency table (Safety Set).....	138
Table 4-8 Adverse events of special interest: binary analysis (Safety Set).....	143
5 Subgroup analysis	146
5-1 Subgroup analysis for efficacy	146
5-1.1 Overall survival	146
Table 5-1.1.1 Overall survival: time to event analysis - subgroup analysis (Full Analysis Set)	146
5-1.2 Invasive disease-free survival	149
Table 5-1.2.1 Invasive disease-free survival: time to event analysis - subgroup analysis (Full Analysis Set)	149
Figure 5-1.2.1 Invasive disease-free survival: Kaplan-Meier plot - subgroup analysis (Full Analysis Set)	152
5-2 Subgroup analysis for PRO	154
5-2.1 EORTC QLQ-C30 Symptoms	154
Table 5-2.1.1.1 QLQ-C30 - Fatigue: change from baseline analysis - subgroup analysis (Full Analysis Set)	154
Figure 5-2.1.1.1 QLQ-C30 - Fatigue: line chart of change from baseline - subgroup analysis (Full Analysis Set)	159
Table 5-2.1.2.1 QLQ-C30 - Nausea and Vomiting: change from baseline analysis - subgroup analysis (Full Analysis Set).....	163
Table 5-2.1.3.1 QLQ-C30 - Pain: change from baseline analysis - subgroup analysis (Full Analysis Set).....	168
Figure 5-2.1.3.1 QLQ-C30 - Pain: line chart of change from baseline - subgroup analysis (Full Analysis Set)	173
Table 5-2.1.4.1 QLQ-C30 - Dyspnoea: change from baseline analysis - subgroup analysis (Full Analysis Set)	178
Figure 5-2.1.4.1 QLQ-C30 - Dyspnoea: line chart of change from baseline - subgroup analysis (Full Analysis Set)	183
Table 5-2.1.5.1 QLQ-C30 - Insomnia: change from baseline analysis - subgroup analysis (Full Analysis Set)	187
Table 5-2.1.6.1 QLQ-C30 - Appetite Loss: change from baseline analysis - subgroup analysis (Full Analysis Set)	192
Figure 5-2.1.6.1 QLQ-C30 - Appetite Loss: line chart of change from baseline - subgroup analysis (Full Analysis Set)	197
Table 5-2.1.7.1 QLQ-C30 - Constipation: change from baseline analysis - subgroup analysis (Full Analysis Set)	199
Figure 5-2.1.7.1 QLQ-C30 - Constipation: line chart of change from baseline - subgroup analysis (Full Analysis Set)	204
Table 5-2.1.8.1 QLQ-C30 - Diarrhoea: change from baseline analysis - subgroup analysis (Full Analysis Set)	206
5-2.2 EORTC QLQ-C30 QoL	211
Table 5-2.2.1.1 QLQ-C30 - Global Health/QoL: change from baseline analysis - subgroup analysis (Full Analysis Set)	211
Figure 5-2.2.1.1 QLQ-C30 - Global Health/QoL: line chart of change from baseline - subgroup analysis (Full Analysis Set).....	216
Table 5-2.2.2.1 QLQ-C30 - Physical Functioning: change from baseline analysis - subgroup analysis (Full Analysis Set).....	218
Figure 5-2.2.2.1 QLQ-C30 - Physical Functioning: line chart of change from baseline - subgroup analysis (Full Analysis Set).....	223
Table 5-2.2.3.1 QLQ-C30 - Role Functioning: change from baseline analysis - subgroup analysis (Full Analysis Set)	225
Table 5-2.2.4.1 QLQ-C30 - Emotional Functioning: change from baseline analysis - subgroup analysis (Full Analysis Set).....	230
Figure 5-2.2.4.1 QLQ-C30 - Emotional Functioning: line chart of change from baseline - subgroup analysis (Full Analysis Set).....	235
Table 5-2.2.5.1 QLQ-C30 - Cognitive Functioning: change from baseline analysis - subgroup analysis (Full Analysis Set).....	239
Figure 5-2.2.5.1 QLQ-C30 - Cognitive Functioning: line chart of change from baseline - subgroup analysis (Full Analysis Set).....	244
Table 5-2.2.6.1 QLQ-C30 - Social Functioning: change from baseline analysis - subgroup analysis (Full Analysis Set)	254

Figure 5-2.2.6.1 QLQ-C30 - Social Functioning: line chart of change from baseline - subgroup analysis (Full Analysis Set)	259
5-2.3 EORTC QLQ-BR23 Symptoms	261
Table 5-2.3.1.1 QLQ-BR23 - Side Effects Of Systemic Therapy: change from baseline analysis - subgroup analysis (Full Analysis Set)	261
Figure 5-2.3.1.1 QLQ-BR23 - Side Effects Of Systemic Therapy: line chart of change from baseline - subgroup analysis (Full Analysis Set)	266
Table 5-2.3.2.1 QLQ-BR23 - Breast Symptoms: change from baseline analysis - subgroup analysis (Full Analysis Set)	270
Figure 5-2.3.2.1 QLQ-BR23 - Breast Symptoms: line chart of change from baseline - subgroup analysis (Full Analysis Set)	275
Table 5-2.3.3.1 QLQ-BR23 - Arm Symptoms: change from baseline analysis - subgroup analysis (Full Analysis Set)	279
Figure 5-2.3.3.1 QLQ-BR23 - Arm Symptoms: line chart of change from baseline - subgroup analysis (Full Analysis Set)	284
Table 5-2.3.4.1 QLQ-BR23 - Being Upset With Hair Loss: change from baseline analysis - subgroup analysis (Full Analysis Set)	286
5-2.4 EORTC QLQ-BR23 QoL	291
Table 5-2.4.1.1 QLQ-BR23 - Body Image: change from baseline analysis - subgroup analysis (Full Analysis Set)	291
Table 5-2.4.2.1 QLQ-BR23 - Sexual Functioning: change from baseline analysis - subgroup analysis (Full Analysis Set)	296
Figure 5-2.4.2.1 QLQ-BR23 - Sexual Functioning: line chart of change from baseline - subgroup analysis (Full Analysis Set)	301
Table 5-2.4.3.1 QLQ-BR23 - Sexual Enjoyment: change from baseline analysis - subgroup analysis (Full Analysis Set)	307
Figure 5-2.4.3.1 QLQ-BR23 - Sexual Enjoyment: line chart of change from baseline - subgroup analysis (Full Analysis Set)	312
Table 5-2.4.4.1 QLQ-BR23 - Future Perspective: change from baseline analysis - subgroup analysis (Full Analysis Set)	314
5-2.5 EQ-5D VAS	319
Table 5-2.5.1.1 EQ5D01-Health Today: change from baseline analysis - subgroup analysis (Full Analysis Set)	319
Figure 5-2.5.1.1 EQ5D01-Health Today: line chart of change from baseline - subgroup analysis (Full Analysis Set)	324
5-2.6 HADS	326
Table 5-2.6.1.1 HADS - Anxiety: change from baseline analysis - subgroup analysis (Full Analysis Set)	326
Figure 5-2.6.1.1 HADS - Anxiety: line chart of change from baseline - subgroup analysis (Full Analysis Set)	331
Table 5-2.6.2.1 HADS - Depression: change from baseline analysis - subgroup analysis (Full Analysis Set)	333
Figure 5-2.6.2.1 HADS - Depression: line chart of change from baseline - subgroup analysis (Full Analysis Set)	338
5-3 Subgroup analysis for safety	345
5-3.1 Subgroup analysis for adverse events	345
Table 5-3.1.1 Any adverse event: binary analysis - subgroup analysis (Safety Set)	345
Table 5-3.1.2 Any grade ≥ 3 adverse event: binary analysis - subgroup analysis (Safety Set)	348
Table 5-3.1.3 Any serious adverse event: binary analysis - subgroup analysis (Safety Set)	351
Table 5-3.1.4 Any adverse event leading to treatment discontinuation of ribociclib: binary analysis - subgroup analysis (Safety Set)	354
Table 5-3.1.5 Any adverse event leading to treatment discontinuation of NSAID: binary analysis - subgroup analysis (Safety Set)	355
Table 5-3.1.6 Any adverse event leading to treatment discontinuation of any component: binary analysis - subgroup analysis (Safety Set)	358
5-3.2 Subgroup analysis for adverse events by SOC and PT	361
Table 5-3.2.1 SOC investigations: binary analysis - subgroup analysis (Safety Set)	361
Table 5-3.2.2 PT alanine aminotransferase increased: binary analysis - subgroup analysis (Safety Set)	364
Table 5-3.2.3 PT neutrophil count decreased: binary analysis - subgroup analysis (Safety Set)	367

Table 5-3.2.4 PT aspartate aminotransferase increased: binary analysis - subgroup analysis (Safety Set)	370
Table 5-3.2.5 PT sars-cov-2 test positive: binary analysis - subgroup analysis (Safety Set)	373
Table 5-3.2.6 PT white blood cell count decreased: binary analysis - subgroup analysis (Safety Set)	376
Table 5-3.2.7 PT sars-cov-2 test negative: binary analysis - subgroup analysis (Safety Set)	379
Table 5-3.2.8 PT gamma-glutamyltransferase increased: binary analysis - subgroup analysis (Safety Set)	382
Table 5-3.2.9 PT blood creatinine increased: binary analysis - subgroup analysis (Safety Set) ...	385
Table 5-3.2.10 PT electrocardiogram qt prolonged: binary analysis - subgroup analysis (Safety Set)	388
Table 5-3.2.11 PT blood magnesium decreased: binary analysis - subgroup analysis (Safety Set)	391
Table 5-3.2.12 PT blood bilirubin increased: binary analysis - subgroup analysis (Safety Set) ...	394
Table 5-3.2.13 PT glomerular filtration rate decreased: binary analysis - subgroup analysis (Safety Set)	397
Table 5-3.2.14 PT platelet count decreased: binary analysis - subgroup analysis (Safety Set)	400
Table 5-3.2.15 PT lymphocyte count decreased: binary analysis - subgroup analysis (Safety Set)	403
Table 5-3.2.16 PT adjusted calcium decreased: binary analysis - subgroup analysis (Safety Set)	406
Table 5-3.2.17 PT blood potassium increased: binary analysis - subgroup analysis (Safety Set)	409
Table 5-3.2.18 SOC musculoskeletal and connective tissue disorders: binary analysis - subgroup analysis (Safety Set)	412
Table 5-3.2.19 PT arthralgia: binary analysis - subgroup analysis (Safety Set)	415
Table 5-3.2.20 PT joint swelling: binary analysis - subgroup analysis (Safety Set)	418
Table 5-3.2.21 SOC general disorders and administration site conditions: binary analysis - subgroup analysis (Safety Set)	421
Table 5-3.2.22 PT fatigue: binary analysis - subgroup analysis (Safety Set)	424
Table 5-3.2.23 PT asthenia: binary analysis - subgroup analysis (Safety Set)	427
Table 5-3.2.24 PT pyrexia: binary analysis - subgroup analysis (Safety Set)	430
Table 5-3.2.25 PT oedema peripheral: binary analysis - subgroup analysis (Safety Set)	433
Table 5-3.2.26 PT influenza like illness: binary analysis - subgroup analysis (Safety Set)	436
Table 5-3.2.27 PT pain: binary analysis - subgroup analysis (Safety Set)	439
Table 5-3.2.28 PT mucosal inflammation: binary analysis - subgroup analysis (Safety Set)	442
Table 5-3.2.29 PT chills: binary analysis - subgroup analysis (Safety Set)	445
Table 5-3.2.30 SOC gastrointestinal disorders: binary analysis - subgroup analysis (Safety Set)	448
Table 5-3.2.31 PT nausea: binary analysis - subgroup analysis (Safety Set)	451
Table 5-3.2.32 PT diarrhoea: binary analysis - subgroup analysis (Safety Set)	454
Table 5-3.2.33 PT constipation: binary analysis - subgroup analysis (Safety Set)	457
Table 5-3.2.34 PT vomiting: binary analysis - subgroup analysis (Safety Set)	460
Table 5-3.2.35 PT abdominal pain: binary analysis - subgroup analysis (Safety Set)	463
Table 5-3.2.36 PT abdominal pain upper: binary analysis - subgroup analysis (Safety Set)	466
Table 5-3.2.37 PT dyspepsia: binary analysis - subgroup analysis (Safety Set)	469
Table 5-3.2.38 PT dry mouth: binary analysis - subgroup analysis (Safety Set)	472
Table 5-3.2.39 PT stomatitis: binary analysis - subgroup analysis (Safety Set)	475
Table 5-3.2.40 PT toothache: binary analysis - subgroup analysis (Safety Set)	478
Table 5-3.2.41 PT abdominal distension: binary analysis - subgroup analysis (Safety Set)	481
Table 5-3.2.42 PT haemorrhoids: binary analysis - subgroup analysis (Safety Set)	484
Table 5-3.2.43 PT mouth ulceration: binary analysis - subgroup analysis (Safety Set)	487
Table 5-3.2.44 SOC infections and infestations: binary analysis - subgroup analysis (Safety Set)	490
Table 5-3.2.45 PT covid-19: binary analysis - subgroup analysis (Safety Set)	493
Table 5-3.2.46 PT urinary tract infection: binary analysis - subgroup analysis (Safety Set)	496
Table 5-3.2.47 PT upper respiratory tract infection: binary analysis - subgroup analysis (Safety Set)	499
Table 5-3.2.48 PT suspected covid-19: binary analysis - subgroup analysis (Safety Set)	502
Table 5-3.2.49 SOC blood and lymphatic system disorders: binary analysis - subgroup analysis (Safety Set)	505
Table 5-3.2.50 PT neutropenia: binary analysis - subgroup analysis (Safety Set)	508
Table 5-3.2.51 PT leukopenia: binary analysis - subgroup analysis (Safety Set)	511
Table 5-3.2.52 PT anaemia: binary analysis - subgroup analysis (Safety Set)	514

Table 5-3.2.53 PT thrombocytopenia: binary analysis - subgroup analysis (Safety Set)	517
Table 5-3.2.54 PT lymphopenia: binary analysis - subgroup analysis (Safety Set)	520
Table 5-3.2.55 SOC nervous system disorders: binary analysis - subgroup analysis (Safety Set)	523
Table 5-3.2.56 PT headache: binary analysis - subgroup analysis (Safety Set)	526
Table 5-3.2.57 PT dizziness: binary analysis - subgroup analysis (Safety Set)	529
Table 5-3.2.58 PT dysgeusia: binary analysis - subgroup analysis (Safety Set)	532
Table 5-3.2.59 PT migraine: binary analysis - subgroup analysis (Safety Set)	535
Table 5-3.2.60 PT taste disorder: binary analysis - subgroup analysis (Safety Set)	538
Table 5-3.2.61 SOC skin and subcutaneous tissue disorders: binary analysis - subgroup analysis (Safety Set)	541
Table 5-3.2.62 PT alopecia: binary analysis - subgroup analysis (Safety Set)	544
Table 5-3.2.63 PT pruritus: binary analysis - subgroup analysis (Safety Set)	547
Table 5-3.2.64 PT rash: binary analysis - subgroup analysis (Safety Set)	550
Table 5-3.2.65 PT dry skin: binary analysis - subgroup analysis (Safety Set)	553
Table 5-3.2.66 SOC metabolism and nutrition disorders: binary analysis - subgroup analysis (Safety Set)	556
Table 5-3.2.67 PT hypomagnesaemia: binary analysis - subgroup analysis (Safety Set)	559
Table 5-3.2.68 PT hyperkalaemia: binary analysis - subgroup analysis (Safety Set)	562
Table 5-3.2.69 PT decreased appetite: binary analysis - subgroup analysis (Safety Set)	565
Table 5-3.2.70 PT hypocalcaemia: binary analysis - subgroup analysis (Safety Set)	568
Table 5-3.2.71 PT hypokalaemia: binary analysis - subgroup analysis (Safety Set)	571
Table 5-3.2.72 PT hypercalcaemia: binary analysis - subgroup analysis (Safety Set)	574
Table 5-3.2.73 PT hypermagnesaemia: binary analysis - subgroup analysis (Safety Set)	577
Table 5-3.2.74 SOC respiratory, thoracic and mediastinal disorders: binary analysis - subgroup analysis (Safety Set)	580
Table 5-3.2.75 PT cough: binary analysis - subgroup analysis (Safety Set)	583
Table 5-3.2.76 PT dyspnoea: binary analysis - subgroup analysis (Safety Set)	586
Table 5-3.2.77 PT oropharyngeal pain: binary analysis - subgroup analysis (Safety Set)	589
Table 5-3.2.78 PT rhinorrhoea: binary analysis - subgroup analysis (Safety Set)	592
Table 5-3.2.79 PT nasal congestion: binary analysis - subgroup analysis (Safety Set)	595
Table 5-3.2.80 PT epistaxis: binary analysis - subgroup analysis (Safety Set)	598
Table 5-3.2.81 SOC psychiatric disorders: binary analysis - subgroup analysis (Safety Set)	601
Table 5-3.2.82 PT depression: binary analysis - subgroup analysis (Safety Set)	604
Table 5-3.2.83 PT fall: binary analysis - subgroup analysis (Safety Set)	607
Table 5-3.2.84 SOC reproductive system and breast disorders: binary analysis - subgroup analysis (Safety Set)	610
Table 5-3.2.85 SOC eye disorders: binary analysis - subgroup analysis (Safety Set)	613
Table 5-3.2.86 PT dry eye: binary analysis - subgroup analysis (Safety Set)	616
Table 5-3.2.87 PT lacrimation increased: binary analysis - subgroup analysis (Safety Set)	619
Table 5-3.2.88 PT palpitations: binary analysis - subgroup analysis (Safety Set)	622
Table 5-3.2.89 SOC ear and labyrinth disorders: binary analysis - subgroup analysis (Safety Set)	625
Table 5-3.2.90 PT vertigo: binary analysis - subgroup analysis (Safety Set)	628
Table 5-3.2.91 SOC hepatobiliary disorders: binary analysis - subgroup analysis (Safety Set)	631
5-3.3 Subgroup analysis for grade ≥ 3 adverse events by SOC and PT	634
Table 5-3.3.1 SOC blood and lymphatic system disorders: binary analysis - subgroup analysis (Safety Set)	634
Table 5-3.3.2 PT neutropenia: binary analysis - subgroup analysis (Safety Set)	637
Table 5-3.3.3 PT leukopenia: binary analysis - subgroup analysis (Safety Set)	640
Table 5-3.3.4 SOC investigations: binary analysis - subgroup analysis (Safety Set)	643
Table 5-3.3.5 PT neutrophil count decreased: binary analysis - subgroup analysis (Safety Set)	646
Table 5-3.3.6 PT alanine aminotransferase increased: binary analysis - subgroup analysis (Safety Set)	649
Table 5-3.3.7 PT aspartate aminotransferase increased: binary analysis - subgroup analysis (Safety Set)	652
Table 5-3.3.8 PT white blood cell count decreased: binary analysis - subgroup analysis (Safety Set)	655
Table 5-3.3.9 SOC infections and infestations: binary analysis - subgroup analysis (Safety Set)	658
Table 5-3.3.10 SOC nervous system disorders: binary analysis - subgroup analysis (Safety Set)	661
Table 5-3.3.11 SOC general disorders and administration site conditions: binary analysis - subgroup analysis (Safety Set)	664

Table 5-3.3.12 PT fatigue: binary analysis - subgroup analysis (Safety Set).....	667
Table 5-3.3.13 SOC hepatobiliary disorders: binary analysis - subgroup analysis (Safety Set)...	670
5-3.4 Subgroup analysis for serious adverse events by SOC and PT.....	673
Table 5-3.4.1 SOC infections and infestations: binary analysis - subgroup analysis (Safety Set)	673
Table 5-3.4.2 SOC respiratory, thoracic and mediastinal disorders: binary analysis - subgroup analysis (Safety Set)	676
Table 5-3.4.3 SOC general disorders and administration site conditions: binary analysis - subgroup analysis (Safety Set)	679
Table 5-3.4.4 SOC hepatobiliary disorders: binary analysis - subgroup analysis (Safety Set)....	682
5-3.5 Subgroup analysis for adverse events of special interest	685
Table 5-3.5.1 Hepatobiliary toxicity: binary analysis - subgroup analysis (Safety Set)	685
Table 5-3.5.2 ILD Pneumonitis: binary analysis - subgroup analysis (Safety Set)	688
Table 5-3.5.3 Infections: binary analysis - subgroup analysis (Safety Set).....	691
Table 5-3.5.4 Myelosuppression - Anaemia: binary analysis - subgroup analysis (Safety Set)	694
Table 5-3.5.5 Myelosuppression - Leukopenia: binary analysis - subgroup analysis (Safety Set)	697
Table 5-3.5.6 Myelosuppression - Neutropenia: binary analysis - subgroup analysis (Safety Set)	700
Table 5-3.5.7 Myelosuppression - Other: binary analysis - subgroup analysis (Safety Set)	703
Table 5-3.5.8 Myelosuppression - Thrombocytopenia: binary analysis - subgroup analysis (Safety Set).....	706
Table 5-3.5.9 QT interval prolongation: binary analysis - subgroup analysis (Safety Set).....	709
Table 5-3.5.10 Renal toxicity: binary analysis - subgroup analysis (Safety Set).....	712
Table 5-3.5.11 Reproductive toxicity: binary analysis - subgroup analysis (Safety Set)	715
Table 5-3.5.12 Second Primary Malignancies: binary analysis - subgroup analysis (Safety Set)	718

1 Patient disposition, demographic and disease characteristics, follow-up times and PRO return rates

Table 1-1 Patient disposition (Full Analysis Set)

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
Randomized	1424	1420	2844
Randomized but not treated	13 (0.9)	60 (4.2)	73 (2.6)
Treated with any treatment	1411 (99.1)	1360 (95.8)	2771 (97.4)
Treated with Ribociclib	1409 (98.9)	0 (0.0)	1409 (49.5)
Treated with NSAI	1411 (99.1)	1360 (95.8)	2771 (97.4)
Treated with Goserelin	5 (0.4)	8 (0.6)	13 (0.5)
Still on treatment	970 (68.1)	892 (62.8)	1862 (65.5)
Discontinued from treatment for all the components of study treatment	372 (26.1)	461 (32.5)	833 (29.3)
Discontinued from Ribociclib	588 (41.3)	0 (0.0)	588 (20.7)
Discontinued from NSAI	434 (30.5)	461 (32.5)	895 (31.5)
Discontinued from Goserelin	3 (0.2)	4 (0.3)	7 (0.2)
<u>Primary reason for discontinuation of Ribociclib</u>			
Adverse event	326 (22.9)	0 (0.0)	326 (11.5)
Death	5 (0.4)	0 (0.0)	5 (0.2)
Disease relapse	78 (5.5)	0 (0.0)	78 (2.7)
Lost to follow-up	6 (0.4)	0 (0.0)	6 (0.2)
Endocrine therapy discontinuation	2 (0.1)	0 (0.0)	2 (0.1)
Patient decision to discontinue treatment	88 (6.2)	0 (0.0)	88 (3.1)
Physician decision	16 (1.1)	0 (0.0)	16 (0.6)
Protocol deviation	3 (0.2)	0 (0.0)	3 (0.1)
Withdrawal by subject	49 (3.4)	0 (0.0)	49 (1.7)
Other	15 (1.1)	0 (0.0)	15 (0.5)
<u>Primary reason for discontinuation of NSAI</u>			
Adverse event	91 (6.4)	68 (4.8)	159 (5.6)
Death	7 (0.5)	5 (0.4)	12 (0.4)
Disease relapse	121 (8.5)	157 (11.1)	278 (9.8)
Lost to follow-up	10 (0.7)	12 (0.8)	22 (0.8)
Patient decision to discontinue treatment	100 (7.0)	87 (6.1)	187 (6.6)
Physician decision	18 (1.3)	16 (1.1)	34 (1.2)
Protocol deviation	2 (0.1)	4 (0.3)	6 (0.2)
Withdrawal by subject	81 (5.7)	103 (7.3)	184 (6.5)
Other	4 (0.3)	9 (0.6)	13 (0.5)
<u>Primary reason for discontinuation of Goserelin</u>			
Physician decision	1 (0.1)	0 (0.0)	1 (0.0)
Other	2 (0.1)	4 (0.3)	6 (0.2)

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
Completed treatment with Ribociclib	821 (57.7)	0 (0.0)	821 (28.9)
Completed treatment with NSAI	7 (0.5)	7 (0.5)	14 (0.5)
Entered the follow-up phase	233 (16.4)	267 (18.8)	500 (17.6)
Discontinued from trial	279 (19.6)	323 (22.7)	602 (21.2)
<u>Primary reason for discontinuation of trial</u>			
Withdrawal by subject	167 (11.7)	217 (15.3)	384 (13.5)
Other	2 (0.1)	1 (0.1)	3 (0.1)
Death	74 (5.2)	75 (5.3)	149 (5.2)
Lost to follow-up	21 (1.5)	20 (1.4)	41 (1.4)
Physician decision	14 (1.0)	7 (0.5)	21 (0.7)
Protocol deviation	1 (0.1)	3 (0.2)	4 (0.1)
ET: Endocrine therapy (Anastrozole/Letrozole) NSAI: Non-steroidal aromatase inhibitor			

Table 1-2 Patient demographics (Full Analysis Set)

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
Age group 1 at randomization, n (%)			
<45	60 (4.2)	58 (4.1)	118 (4.1)
45 to 54	303 (21.3)	333 (23.5)	636 (22.4)
55 to 64	658 (46.2)	668 (47.0)	1326 (46.6)
≥65	403 (28.3)	361 (25.4)	764 (26.9)
Age group 2 at randomization (median for subpopulation post-menopausal female patients), n (%)			
<Median	639 (44.9)	653 (46.0)	1292 (45.4)
≥Median	785 (55.1)	767 (54.0)	1552 (54.6)
Age (years) at randomization			
n	1424	1420	2844
Mean ± SD	59.6 ± 8.46	59.4 ± 8.53	59.5 ± 8.49
Median	60.0	59.0	59.0
Range 1st to 3rd quartile	54.0 to 65.0	54.0 to 65.0	54.0 to 65.0
Range minimum to maximum	32.0 to 90.0	24.0 to 89.0	24.0 to 90.0
Gender, n (%)			
Female	1424 (100.0)	1420 (100.0)	2844 (100.0)
Race, n (%)			
American Indian or Alaska Native	1 (0.1)	1 (0.1)	2 (0.1)
Asian	129 (9.1)	134 (9.4)	263 (9.2)
Black or African American	25 (1.8)	25 (1.8)	50 (1.8)
Native Hawaiian or other Pacific Islander	2 (0.1)	0 (0.0)	2 (0.1)
White	1114 (78.2)	1103 (77.7)	2217 (78.0)
Other	73 (5.1)	89 (6.3)	162 (5.7)
Not reported	80 (5.6)	68 (4.8)	148 (5.2)
Ethnicity, n (%)			
Hispanic or Latino	109 (7.7)	117 (8.2)	226 (7.9)
Not Hispanic or Latino	1167 (82.0)	1159 (81.6)	2326 (81.8)
Unknown	97 (6.8)	101 (7.1)	198 (7.0)
Not reported	51 (3.6)	43 (3.0)	94 (3.3)
Geographic region, n (%)			
Europe	840 (59.0)	843 (59.4)	1683 (59.2)
North America/Australia	406 (28.5)	395 (27.8)	801 (28.2)
Asia	103 (7.2)	108 (7.6)	211 (7.4)
Latin America	75 (5.3)	74 (5.2)	149 (5.2)

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
Weight (kg) at baseline			
n	1418	1414	2832
Mean ± SD	74.2 ± 16.27	74.1 ± 15.66	74.2 ± 15.97
Median	71.9	72.9	72.0
Range 1st to 3rd quartile	63.0 to 83.0	63.0 to 83.0	63.0 to 83.0
Range minimum to maximum	40.0 to 166.0	41.8 to 168.9	40.0 to 168.9
Height (cm) at baseline			
n	1413	1401	2814
Mean ± SD	162.1 ± 6.76	161.8 ± 6.77	162.0 ± 6.77
Median	162.0	162.0	162.0
Range 1st to 3rd quartile	157.5 to 167.0	157.0 to 166.5	157.0 to 167.0
Range minimum to maximum	140.0 to 198.0	140.0 to 191.0	140.0 to 198.0
Body mass index (kg/m²) at baseline			
n	1410	1401	2811
Mean ± SD	28.2 ± 5.81	28.3 ± 5.77	28.3 ± 5.79
Median	27.3	27.6	27.4
Range 1st to 3rd quartile	24.0 to 31.5	24.2 to 31.7	24.0 to 31.6
Range minimum to maximum	15.6 to 55.5	15.2 to 59.1	15.2 to 59.1
ECOG performance status at baseline, n (%)			
0	1131 (79.4)	1148 (80.8)	2279 (80.1)
1	292 (20.5)	271 (19.1)	563 (19.8)
Not reported	1 (0.1)	1 (0.1)	2 (0.1)
ET: Endocrine therapy (Anastrozole/Letrozole) ECOG: Eastern Cooperative Oncology Group			

Table 1-3 Patient baseline disease characteristics (Full Analysis Set)

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
Histological grade			
<u>At diagnosis</u>			
G1	124 (8.7)	136 (9.6)	260 (9.1)
G2	817 (57.4)	795 (56.0)	1612 (56.7)
G3	304 (21.3)	325 (22.9)	629 (22.1)
Gx	21 (1.5)	17 (1.2)	38 (1.3)
Not done	144 (10.1)	135 (9.5)	279 (9.8)
Missing	14 (1.0)	12 (0.8)	26 (0.9)
<u>On surgical specimen</u>			
G1	102 (7.2)	110 (7.7)	212 (7.5)
G2	849 (59.6)	797 (56.1)	1646 (57.9)
G3	381 (26.8)	420 (29.6)	801 (28.2)
Gx	16 (1.1)	16 (1.1)	32 (1.1)
Not done	75 (5.3)	76 (5.4)	151 (5.3)
Missing	1 (0.1)	1 (0.1)	2 (0.1)
TNM-Status			
T-Status			
<u>At diagnosis</u>			
T0	2 (0.1)	6 (0.4)	8 (0.3)
T1a	45 (3.2)	34 (2.4)	79 (2.8)
T1b	39 (2.7)	31 (2.2)	70 (2.5)
T1c	207 (14.5)	195 (13.7)	402 (14.1)
T1mi	2 (0.1)	6 (0.4)	8 (0.3)
T2	639 (44.9)	688 (48.5)	1327 (46.7)
T3	233 (16.4)	241 (17.0)	474 (16.7)
T4a	38 (2.7)	27 (1.9)	65 (2.3)
T4b	55 (3.9)	45 (3.2)	100 (3.5)
T4c	4 (0.3)	2 (0.1)	6 (0.2)
T4d	20 (1.4)	17 (1.2)	37 (1.3)
Tis	1 (0.1)	0 (0.0)	1 (0.0)
Tx	114 (8.0)	106 (7.5)	220 (7.7)
Missing	25 (1.8)	22 (1.5)	47 (1.7)
<u>On surgical specimen</u>			
T0	28 (2.0)	30 (2.1)	58 (2.0)
T1a	60 (4.2)	49 (3.5)	109 (3.8)
T1b	59 (4.1)	60 (4.2)	119 (4.2)
T1c	284 (19.9)	305 (21.5)	589 (20.7)
T1mi	5 (0.4)	7 (0.5)	12 (0.4)
T2	677 (47.5)	667 (47.0)	1344 (47.3)

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
T3	223 (15.7)	236 (16.6)	459 (16.1)
T4a	24 (1.7)	22 (1.5)	46 (1.6)
T4b	35 (2.5)	30 (2.1)	65 (2.3)
T4c	1 (0.1)	0 (0.0)	1 (0.0)
T4d	5 (0.4)	5 (0.4)	10 (0.4)
Tis	9 (0.6)	4 (0.3)	13 (0.5)
Tx	13 (0.9)	5 (0.4)	18 (0.6)
Missing	1 (0.1)	0 (0.0)	1 (0.0)
N-Status			
<u>At diagnosis</u>			
N0	407 (28.6)	445 (31.3)	852 (30.0)
N1	544 (38.2)	549 (38.7)	1093 (38.4)
N2a	187 (13.1)	156 (11.0)	343 (12.1)
N2b	7 (0.5)	7 (0.5)	14 (0.5)
N3a	58 (4.1)	68 (4.8)	126 (4.4)
N3b	7 (0.5)	9 (0.6)	16 (0.6)
N3c	16 (1.1)	10 (0.7)	26 (0.9)
Nx	169 (11.9)	154 (10.8)	323 (11.4)
Missing	29 (2.0)	22 (1.5)	51 (1.8)
<u>On surgical specimen</u>			
N0	220 (15.4)	239 (16.8)	459 (16.1)
N0(i+)	14 (1.0)	9 (0.6)	23 (0.8)
N0(mol+)	0 (0.0)	3 (0.2)	3 (0.1)
N1a	484 (34.0)	458 (32.3)	942 (33.1)
N1b	12 (0.8)	7 (0.5)	19 (0.7)
N1c	12 (0.8)	25 (1.8)	37 (1.3)
N1mi	59 (4.1)	63 (4.4)	122 (4.3)
N2b	393 (27.6)	378 (26.6)	771 (27.1)
N2c	6 (0.4)	5 (0.4)	11 (0.4)
N3a	212 (14.9)	209 (14.7)	421 (14.8)
N3b	5 (0.4)	12 (0.8)	17 (0.6)
N3c	5 (0.4)	8 (0.6)	13 (0.5)
Nx	1 (0.1)	3 (0.2)	4 (0.1)
Missing	1 (0.1)	1 (0.1)	2 (0.1)
M-Status			
<u>At diagnosis</u>			
M0	1424 (100.0)	1420 (100.0)	2844 (100.0)
<u>On surgical specimen</u>			
Missing	1424 (100.0)	1420 (100.0)	2844 (100.0)
K67 Score			
<u>At diagnosis</u>			

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
n	1026	1025	2051
Mean ± SD	26.3 ± 19.56	26.4 ± 19.50	26.4 ± 19.53
Median	20.0	20.0	20.0
Range 1st to 3rd quartile	11.0 to 35.0	11.0 to 35.0	11.0 to 35.0
Range minimum to maximum	0.0 to 99.0	0.0 to 95.0	0.0 to 99.0
<u>On surgical specimen</u>			
n	689	708	1397
Mean ± SD	20.8 ± 17.38	22.2 ± 18.23	21.5 ± 17.82
Median	15.0	18.0	17.0
Range 1st to 3rd quartile	10.0 to 30.0	10.0 to 30.0	10.0 to 30.0
Range minimum to maximum	0.0 to 99.0	0.0 to 90.0	0.0 to 99.0
<u>At diagnosis</u>			
≤14%	293 (20.6)	285 (20.1)	578 (20.3)
>14%	733 (51.5)	740 (52.1)	1473 (51.8)
Missing	398 (27.9)	395 (27.8)	793 (27.9)
<u>On surgical specimen</u>			
≤14%	277 (19.5)	282 (19.9)	559 (19.7)
>14%	412 (28.9)	426 (30.0)	838 (29.5)
Missing	735 (51.6)	712 (50.1)	1447 (50.9)
<u>At diagnosis</u>			
≤20%	544 (38.2)	530 (37.3)	1074 (37.8)
>20%	482 (33.8)	495 (34.9)	977 (34.4)
Missing	398 (27.9)	395 (27.8)	793 (27.9)
<u>On surgical specimen</u>			
≤20%	447 (31.4)	436 (30.7)	883 (31.0)
>20%	242 (17.0)	272 (19.2)	514 (18.1)
Missing	735 (51.6)	712 (50.1)	1447 (50.9)
AJCC 8th edition anatomic stage			
IA	0 (0.0)	3 (0.2)	3 (0.1)
IB	6 (0.4)	2 (0.1)	8 (0.3)
IIA	306 (21.5)	315 (22.2)	621 (21.8)
IIB	281 (19.7)	283 (19.9)	564 (19.8)
IIIA	487 (34.2)	476 (33.5)	963 (33.9)
IIIB	100 (7.0)	86 (6.1)	186 (6.5)
IIIC	243 (17.1)	254 (17.9)	497 (17.5)
Missing	1 (0.1)	1 (0.1)	2 (0.1)
Prior neo-/adjuvant chemotherapy			
No	215 (15.1)	221 (15.6)	436 (15.3)
Yes	1209 (84.9)	1199 (84.4)	2408 (84.7)
Time since diagnosis			

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
n	1407	1411	2818
Mean ± SD	11.7 ± 3.73	11.7 ± 3.80	11.7 ± 3.76
Median	11.7	11.6	11.7
Range 1st to 3rd quartile	9.5 to 14.3	9.5 to 14.2	9.5 to 14.3
Range minimum to maximum	1.1 to 22.8	0.8 to 26.8	0.8 to 26.8
Predominant histology			
Invasive ductal carcinoma nos	1038 (72.9)	1059 (74.6)	2097 (73.7)
Invasive lobular	293 (20.6)	285 (20.1)	578 (20.3)
Mucinous	9 (0.6)	3 (0.2)	12 (0.4)
Papillary	9 (0.6)	8 (0.6)	17 (0.6)
Tubular	5 (0.4)	3 (0.2)	8 (0.3)
Other	69 (4.8)	62 (4.4)	131 (4.6)
Missing	1 (0.1)	0 (0.0)	1 (0.0)
Prior surgery			
Axillary lymph node dissection	1187 (83.4)	1178 (83.0)	2365 (83.2)
Breast conserving surgery	614 (43.1)	585 (41.2)	1199 (42.2)
Mastectomy	865 (60.7)	884 (62.3)	1749 (61.5)
Sentinel lymph node biopsy	524 (36.8)	516 (36.3)	1040 (36.6)
Other	77 (5.4)	90 (6.3)	167 (5.9)
Estrogen receptor (ER) status			
<u>Prior to surgery</u>			
Negative	4 (0.3)	8 (0.6)	12 (0.4)
Positive	1311 (92.1)	1293 (91.1)	2604 (91.6)
Missing	6 (0.4)	3 (0.2)	9 (0.3)
<u>On surgical specimen</u>			
Negative	1 (0.1)	3 (0.2)	4 (0.1)
Positive	756 (53.1)	740 (52.1)	1496 (52.6)
Unknown	2 (0.1)	2 (0.1)	4 (0.1)
Missing	56 (3.9)	56 (3.9)	112 (3.9)
Progesterone receptor (PR) status			
<u>Prior to surgery</u>			
Negative	204 (14.3)	207 (14.6)	411 (14.5)
Positive	1101 (77.3)	1086 (76.5)	2187 (76.9)
Unknown	10 (0.7)	8 (0.6)	18 (0.6)
Missing	6 (0.4)	3 (0.2)	9 (0.3)
<u>On surgical specimen</u>			
Negative	132 (9.3)	141 (9.9)	273 (9.6)
Positive	623 (43.8)	604 (42.5)	1227 (43.1)
Unknown	5 (0.4)	1 (0.1)	6 (0.2)
Missing	55 (3.9)	55 (3.9)	110 (3.9)
Combinations ER+PR+ vs. ER+PR- vs. ER-PR+			
ER+/PR+	1191 (83.6)	1166 (82.1)	2357 (82.9)

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
ER+/PR-	221 (15.5)	241 (17.0)	462 (16.2)
ER-/PR+	1 (0.1)	6 (0.4)	7 (0.2)
Missing	11 (0.8)	7 (0.5)	18 (0.6)
ET: Endocrine therapy (Anastrozole/Letrozole) AJJC: American Joint Commission on Cancer			

Table 1-4 Drug exposure and follow-up times by endpoint and study treatment (Full Analysis Set)

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
Duration of exposure (months)			
Ribociclib			
n	1409	0	1409
Mean ± SD	25.2 ± 14.09	n.a.	25.2 ± 14.09
Median	35.7	n.a.	35.7
Range 1st to 3rd quartile	8.7 to 35.7	n.a.	8.7 to 35.7
Range minimum to maximum	0.0 to 37.0	n.a.	0.0 to 37.0
NSAI			
n	1411	1360	2771
Mean ± SD	38.8 ± 16.91	38.4 ± 17.51	38.6 ± 17.20
Median	45.0	45.0	45.0
Range 1st to 3rd quartile	34.5 to 51.3	30.5 to 51.5	32.8 to 51.3
Range minimum to maximum	0.0 to 60.8	0.0 to 60.1	0.0 to 60.8
Goserelin			
n	5	8	13
Mean ± SD	14.5 ± 15.27	17.7 ± 14.71	16.5 ± 14.37
Median	5.5	16.1	13.8
Range 1st to 3rd quartile	4.6 to 23.8	4.3 to 28.9	4.6 to 27.9
Range minimum to maximum	1.8 to 37.0	0.9 to 42.2	0.9 to 42.2
Follow-up time (months) - Efficacy			
Overall Survival Event			
n	1424	1420	2844
Mean ± SD	40.9 ± 13.94	39.3 ± 15.93	40.1 ± 14.99
Median	44.3	44.2	44.3
Range 1st to 3rd quartile	38.6 to 49.7	35.9 to 49.7	37.1 to 49.7
Range minimum to maximum	0.1 to 62.7	0.0 to 62.9	0.0 to 62.9
First iDFS Event			
n	1424	1420	2844
Mean ± SD	38.5 ± 15.60	36.3 ± 17.35	37.4 ± 16.53
Median	44.2	44.2	44.2
Range 1st to 3rd quartile	33.4 to 49.7	29.9 to 49.7	33.1 to 49.7
Range minimum to maximum	0.0 to 60.9	0.0 to 62.9	0.0 to 62.9
Recurrence Free Survival Event			
n	1424	1420	2844
Mean ± SD	38.8 ± 15.38	36.7 ± 17.17	37.7 ± 16.33
Median	44.2	44.2	44.2
Range 1st to 3rd quartile	33.9 to 49.7	31.8 to 49.7	33.2 to 49.7
Range minimum to maximum	0.0 to 60.9	0.0 to 62.9	0.0 to 62.9

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
Distant Disease Free Survival Event			
n	1424	1420	2844
Mean ± SD	38.6 ± 15.51	36.6 ± 17.25	37.6 ± 16.43
Median	44.2	44.2	44.2
Range 1st to 3rd quartile	33.6 to 49.7	30.8 to 49.7	33.1 to 49.7
Range minimum to maximum	0.0 to 60.9	0.0 to 62.9	0.0 to 62.9
Loco Regional Recurrence Free Survival Event			
n	1424	1420	2844
Mean ± SD	39.2 ± 14.99	37.2 ± 16.79	38.2 ± 15.94
Median	44.2	44.2	44.2
Range 1st to 3rd quartile	35.5 to 49.7	33.1 to 49.7	33.3 to 49.7
Range minimum to maximum	0.0 to 60.9	0.0 to 62.9	0.0 to 62.9
Follow-up time (months) - EORTC-QLQ-C30 Symptoms			
Fatigue			
n	1325	1263	2588
Mean ± SD	39.7 ± 13.70	40.1 ± 13.54	39.9 ± 13.62
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.9	33.6 to 49.9	33.7 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8
Nausea and Vomiting			
n	1325	1263	2588
Mean ± SD	39.7 ± 13.70	40.1 ± 13.55	39.9 ± 13.62
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.9	33.6 to 49.9	33.7 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8
Pain			
n	1328	1263	2591
Mean ± SD	39.7 ± 13.69	40.1 ± 13.55	39.9 ± 13.62
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.9	33.6 to 49.9	33.7 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8
Dyspnoea			
n	1322	1260	2582
Mean ± SD	39.8 ± 13.68	40.1 ± 13.55	39.9 ± 13.62
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.9	33.6 to 49.9	33.7 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
Insomnia			
n	1322	1261	2583
Mean ± SD	39.7 ± 13.71	40.2 ± 13.51	39.9 ± 13.61
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.9	33.6 to 49.9	33.7 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8
Appetite Loss			
n	1325	1261	2586
Mean ± SD	39.7 ± 13.70	40.1 ± 13.55	39.9 ± 13.63
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.9	33.6 to 49.9	33.7 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8
Constipation			
n	1323	1263	2586
Mean ± SD	39.8 ± 13.68	40.1 ± 13.55	39.9 ± 13.61
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.9	33.6 to 49.9	33.7 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8
Diarrhoea			
n	1322	1259	2581
Mean ± SD	39.7 ± 13.68	40.1 ± 13.56	39.9 ± 13.62
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.9	33.6 to 49.9	33.7 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8
Follow-up time (months) - EORTC-QLQ-C30 QoL			
Global Health/QoL			
n	1322	1258	2580
Mean ± SD	39.7 ± 13.68	40.1 ± 13.56	39.9 ± 13.62
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.9	33.6 to 49.9	33.7 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8
Physical Functioning			
n	1326	1264	2590
Mean ± SD	39.7 ± 13.73	40.1 ± 13.54	39.9 ± 13.64
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.9	33.6 to 49.9	33.7 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
Role Functioning			
n	1325	1264	2589
Mean ± SD	39.7 ± 13.74	40.1 ± 13.54	39.9 ± 13.64
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.9	33.6 to 49.9	33.7 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8
Emotional Functioning			
n	1323	1259	2582
Mean ± SD	39.7 ± 13.67	40.1 ± 13.57	39.9 ± 13.62
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.9	33.6 to 49.9	33.7 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8
Cognitive Functioning			
n	1322	1260	2582
Mean ± SD	39.7 ± 13.68	40.1 ± 13.56	39.9 ± 13.62
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.9	33.6 to 49.9	33.7 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8
Social Functioning			
n	1323	1259	2582
Mean ± SD	39.7 ± 13.67	40.1 ± 13.57	39.9 ± 13.62
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.9	33.6 to 49.9	33.7 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8
Follow-up time (months) - EORTC-QLQ-BR23 Symptoms			
Side Effects Of Systemic Therapy			
n	1329	1257	2586
Mean ± SD	39.7 ± 13.74	40.1 ± 13.47	39.9 ± 13.61
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.9	33.6 to 49.9	33.7 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8
Breast Symptoms			
n	1322	1259	2581
Mean ± SD	39.7 ± 13.72	40.1 ± 13.51	39.9 ± 13.62
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.9	33.6 to 49.9	33.6 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
Arm Symptoms			
n	1323	1261	2584
Mean ± SD	39.7 ± 13.72	40.1 ± 13.51	39.9 ± 13.61
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.9	33.6 to 49.9	33.6 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8
Being Upset With Hair Loss			
n	356	351	707
Mean ± SD	36.2 ± 13.83	34.0 ± 14.98	35.1 ± 14.44
Median	39.0	38.8	38.9
Range 1st to 3rd quartile	28.1 to 45.0	22.5 to 44.8	25.3 to 44.9
Range minimum to maximum	1.2 to 56.2	1.3 to 56.6	1.2 to 56.6
Follow-up time (months) - EORTC-QLQ-BR23 QoL			
Body Image			
n	1327	1254	2581
Mean ± SD	39.7 ± 13.73	40.1 ± 13.48	39.9 ± 13.61
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.9	33.6 to 49.9	33.7 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8
Sexual Functioning			
n	1297	1221	2518
Mean ± SD	39.0 ± 14.12	39.9 ± 13.49	39.4 ± 13.82
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.5 to 49.9	33.6 to 49.9	33.5 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8
Sexual Enjoyment			
n	584	513	1097
Mean ± SD	35.1 ± 14.92	34.5 ± 15.26	34.8 ± 15.08
Median	38.9	38.9	38.9
Range 1st to 3rd quartile	27.4 to 44.9	22.4 to 47.4	22.8 to 45.1
Range minimum to maximum	1.2 to 62.8	0.5 to 61.4	0.5 to 62.8
Future Perspective			
n	1327	1252	2579
Mean ± SD	39.7 ± 13.74	40.1 ± 13.47	39.9 ± 13.61
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.9	33.6 to 49.9	33.7 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
Follow-up time (months) - EQ-5D VAS			
EQ-5D VAS			
n	1323	1259	2582
Mean ± SD	39.7 ± 13.69	40.1 ± 13.56	39.9 ± 13.63
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.9	33.6 to 49.9	33.6 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8
Follow-up time (months) - HADS (QoL)			
Anxiety			
n	1315	1257	2572
Mean ± SD	39.7 ± 13.75	40.1 ± 13.59	39.9 ± 13.67
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.9	33.6 to 49.9	33.6 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8
Depression			
n	1313	1257	2570
Mean ± SD	39.7 ± 13.73	40.0 ± 13.59	39.9 ± 13.66
Median	44.4	44.4	44.4
Range 1st to 3rd quartile	33.7 to 49.9	33.6 to 49.9	33.6 to 49.9
Range minimum to maximum	1.2 to 62.8	0.2 to 61.4	0.2 to 62.8
ET: Endocrine therapy (Anastrozole/Letrozole) OS: Overall survival iDFS: Invasive disease-free survival RFS: Recurrence-free survival DDFS: Distant disease-free survival LRRFS: Loco-regional recurrence-free survival LRRFS: Loco-regional recurrence-free survival EORTC-QLQ: European Organization for Research and Treatment of Cancers Core Quality of Life Questionnaire HADS: Hospital Anxiety and Depression Scale VAS: Visual Analogue Scale			

Table 1-5 Drug exposure and follow-up times by endpoint and study treatment (Safety Set)

	Treatment Groups		
	Ribociclib + ET (N=1409)	ET (N=1362)	Total (N=2771)
Duration of exposure (months)			
Ribociclib			
n	1409	0	1409
Mean ± SD	25.2 ± 14.09	n.a.	25.2 ± 14.09
Median	35.7	n.a.	35.7
Range 1st to 3rd quartile	8.7 to 35.7	n.a.	8.7 to 35.7
Range minimum to maximum	0.0 to 37.0	n.a.	0.0 to 37.0
NSAI			
n	1409	1362	2771
Mean ± SD	38.9 ± 16.86	38.3 ± 17.55	38.6 ± 17.20
Median	45.0	45.0	45.0
Range 1st to 3rd quartile	35.2 to 51.3	30.4 to 51.5	32.8 to 51.3
Range minimum to maximum	0.0 to 60.8	0.0 to 60.1	0.0 to 60.8
Goserelin			
n	5	8	13
Mean ± SD	14.5 ± 15.27	17.7 ± 14.71	16.5 ± 14.37
Median	5.5	16.1	13.8
Range 1st to 3rd quartile	4.6 to 23.8	4.3 to 28.9	4.6 to 27.9
Range minimum to maximum	1.8 to 37.0	0.9 to 42.2	0.9 to 42.2
Follow-up time (months)			
Adverse Events			
n	1409	1362	2771
Mean ± SD	39.1 ± 16.61	38.5 ± 17.33	38.8 ± 16.96
Median	45.1	45.1	45.1
Range 1st to 3rd quartile	36.0 to 51.3	31.3 to 51.4	33.3 to 51.3
Range minimum to maximum	0.2 to 61.7	0.0 to 61.0	0.0 to 61.7
ET: Endocrine therapy (Anastrozole/Letrozole)			

Table 1-6.1 Prior anti-cancer therapies (Full Analysis Set)

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
Patients who received any prior anti-cancer therapy	1424 (100.0)	1420 (100.0)	2844 (100.0)
Therapy type, n (%)			
Setting, n (%)			
Biologic/targeted therapy	1 (0.1)	5 (0.4)	6 (0.2)
Adjuvant	0 (0.0)	2 (0.1)	2 (0.1)
Neoadjuvant	1 (0.1)	4 (0.3)	5 (0.2)
Chemotherapy	1209 (84.9)	1199 (84.4)	2408 (84.7)
Adjuvant	702 (49.3)	705 (49.6)	1407 (49.5)
Neoadjuvant	535 (37.6)	524 (36.9)	1059 (37.2)
Endocrine therapy	967 (67.9)	979 (68.9)	1946 (68.4)
Adjuvant	959 (67.3)	969 (68.2)	1928 (67.8)
Neoadjuvant	60 (4.2)	75 (5.3)	135 (4.7)
Other	2 (0.1)	2 (0.1)	4 (0.1)
Adjuvant	1 (0.1)	1 (0.1)	2 (0.1)
Neoadjuvant	1 (0.1)	1 (0.1)	2 (0.1)
Prior radiotherapy	1267 (89.0)	1259 (88.7)	2526 (88.8)
Prior surgery for breast cancer	1424 (100.0)	1420 (100.0)	2844 (100.0)
ET: Endocrine therapy (Anastrozole/Letrozole)			
.....			

Table 1-6.2 Prior anti-neoplastic medications by ATC class and preferred name (Full Analysis Set)

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
Patients who received any prior anti-neoplastic medication	1329 (93.3)	1342 (94.5)	2671 (93.9)
ATC class, n (%)			
Preferred name, n (%)			
Actinomycines	1 (0.1)	0 (0.0)	1 (0.0)
Actinomycines	1 (0.1)	0 (0.0)	1 (0.0)
Anthracyclines and related substances	1056 (74.2)	1063 (74.9)	2119 (74.5)
Anthracyclines and related substances	2 (0.1)	0 (0.0)	2 (0.1)
Daunorubicin	0 (0.0)	1 (0.1)	1 (0.0)
Doxorubicin	693 (48.7)	692 (48.7)	1385 (48.7)
Doxorubicin hydrochloride	18 (1.3)	12 (0.8)	30 (1.1)
Epirubicin	313 (22.0)	329 (23.2)	642 (22.6)
Epirubicin hydrochloride	22 (1.5)	15 (1.1)	37 (1.3)
Liposomal doxorubicin	1 (0.1)	1 (0.1)	2 (0.1)
Liposomal doxorubicin hydrochloride	10 (0.7)	10 (0.7)	20 (0.7)
Pegylated liposomal doxorubicin hydrochloride	0 (0.0)	1 (0.1)	1 (0.0)
Pirarubicin	0 (0.0)	3 (0.2)	3 (0.1)
Pirarubicin hydrochloride	2 (0.1)	1 (0.1)	3 (0.1)
Anti-estrogens	81 (5.7)	95 (6.7)	176 (6.2)
Fulvestrant	0 (0.0)	1 (0.1)	1 (0.0)
Tamoxifen	81 (5.7)	92 (6.5)	173 (6.1)
Tamoxifen citrate	0 (0.0)	2 (0.1)	2 (0.1)
Antineoplastic cell and gene therapy	0 (0.0)	1 (0.1)	1 (0.0)
Talimogene laherparepvec	0 (0.0)	1 (0.1)	1 (0.0)
Aromatase inhibitors	930 (65.3)	940 (66.2)	1870 (65.8)
Anastrozole	326 (22.9)	320 (22.5)	646 (22.7)
Exemestane	21 (1.5)	20 (1.4)	41 (1.4)
Letrozole	618 (43.4)	627 (44.2)	1245 (43.8)
Bisphosphonates	1 (0.1)	0 (0.0)	1 (0.0)
Ibandronic acid	1 (0.1)	0 (0.0)	1 (0.0)
Zoledronic acid	1 (0.1)	0 (0.0)	1 (0.0)
Colony stimulating factors	0 (0.0)	1 (0.1)	1 (0.0)
Filgrastim	0 (0.0)	1 (0.1)	1 (0.0)
Cyclin-dependent kinase (cdk) inhibitors	0 (0.0)	1 (0.1)	1 (0.0)
Palbociclib	0 (0.0)	1 (0.1)	1 (0.0)
Folic acid analogues	2 (0.1)	4 (0.3)	6 (0.2)
Methotrexate	2 (0.1)	3 (0.2)	5 (0.2)
Methotrexate sodium	0 (0.0)	1 (0.1)	1 (0.0)

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
Glucocorticoids	1 (0.1)	1 (0.1)	2 (0.1)
Dexamethasone	1 (0.1)	1 (0.1)	2 (0.1)
Gonadotropin releasing hormone analogues	24 (1.7)	22 (1.5)	46 (1.6)
Goserelin	13 (0.9)	11 (0.8)	24 (0.8)
Goserelin acetate	6 (0.4)	5 (0.4)	11 (0.4)
Leuprorelin	0 (0.0)	2 (0.1)	2 (0.1)
Leuprorelin acetate	2 (0.1)	4 (0.3)	6 (0.2)
Triptorelin	2 (0.1)	0 (0.0)	2 (0.1)
Triptorelin acetate	1 (0.1)	0 (0.0)	1 (0.0)
Her2 (human epidermal growth factor receptor 2) inhibitors	0 (0.0)	2 (0.1)	2 (0.1)
Pertuzumab	0 (0.0)	1 (0.1)	1 (0.0)
Trastuzumab	0 (0.0)	2 (0.1)	2 (0.1)
Investigational drug	1 (0.1)	1 (0.1)	2 (0.1)
Investigational drug	1 (0.1)	0 (0.0)	1 (0.0)
Sd 101	0 (0.0)	1 (0.1)	1 (0.0)
Nitrogen mustard analogues	1164 (81.7)	1157 (81.5)	2321 (81.6)
Cyclophosphamide	1164 (81.7)	1156 (81.4)	2320 (81.6)
Ifosfamide	0 (0.0)	1 (0.1)	1 (0.0)
Other antineoplastic agents	1 (0.1)	0 (0.0)	1 (0.0)
Eribulin	1 (0.1)	0 (0.0)	1 (0.0)
Other immunostimulants	0 (0.0)	1 (0.1)	1 (0.0)
Ubenimex	0 (0.0)	1 (0.1)	1 (0.0)
Other immunosuppressants	0 (0.0)	1 (0.1)	1 (0.0)
Methotrexate	0 (0.0)	1 (0.1)	1 (0.0)
Other monoclonal antibodies and antibody drug conjugates	0 (0.0)	2 (0.1)	2 (0.1)
Tremelimumab	0 (0.0)	2 (0.1)	2 (0.1)
Pd-1/pdl-1 (programmed cell death protein 1/death ligand 1) inhibitors	1 (0.1)	4 (0.3)	5 (0.2)
Atezolizumab	0 (0.0)	1 (0.1)	1 (0.0)
Durvalumab	0 (0.0)	2 (0.1)	2 (0.1)
Pembrolizumab	1 (0.1)	1 (0.1)	2 (0.1)
Platinum compounds	21 (1.5)	18 (1.3)	39 (1.4)
Carboplatin	18 (1.3)	13 (0.9)	31 (1.1)
Cisplatin	3 (0.2)	5 (0.4)	8 (0.3)
Poly (adp-ribose) polymerase (parp) inhibitors	0 (0.0)	1 (0.1)	1 (0.0)
Olaparib	0 (0.0)	1 (0.1)	1 (0.0)
Pyrimidine analogues	49 (3.4)	63 (4.4)	112 (3.9)
Capecitabine	10 (0.7)	16 (1.1)	26 (0.9)
Fluorouracil	39 (2.7)	47 (3.3)	86 (3.0)
Gemcitabine	1 (0.1)	2 (0.1)	3 (0.1)
Quaternary ammonium compounds	0 (0.0)	1 (0.1)	1 (0.0)

Treatment Groups			
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
Didecyldimethylammonium chlorid	0 (0.0)	1 (0.1)	1 (0.0)
Taxanes	1136 (79.8)	1124 (79.2)	2260 (79.5)
Docetaxel	368 (25.8)	362 (25.5)	730 (25.7)
Paclitaxel	773 (54.3)	770 (54.2)	1543 (54.3)
Paclitaxel liposome	2 (0.1)	1 (0.1)	3 (0.1)
Paclitaxel nanoparticle albumin-bound	23 (1.6)	13 (0.9)	36 (1.3)
Vinca alkaloids and analogues	2 (0.1)	0 (0.0)	2 (0.1)
Vinorelbine	1 (0.1)	0 (0.0)	1 (0.0)
Vinorelbine tartrate	1 (0.1)	0 (0.0)	1 (0.0)
ET: Endocrine therapy (Anastrozole/Letrozole) ATC: Anatomical Therapeutic Chemical			

Table 1-7 Post treatment anti-cancer therapies (Full Analysis Set)

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
Patients who received any post treatment anti-cancer therapy	255 (17.9)	283 (19.9)	538 (18.9)
Post treatment anti-neoplastic medications: ATC class, n (%)			
Anthracyclines and related substances	10 (0.7)	10 (0.7)	20 (0.7)
Anti-estrogens	83 (5.8)	135 (9.5)	218 (7.7)
Aromatase inhibitors	143 (10.0)	133 (9.4)	276 (9.7)
Bisphosphonates	8 (0.6)	6 (0.4)	14 (0.5)
Cd20 (clusters of differentiation 20) inhibitors	0 (0.0)	1 (0.1)	1 (0.0)
Combinations of antineoplastic agents	1 (0.1)	1 (0.1)	2 (0.1)
Cyclin-dependent kinase (cdk) inhibitors	32 (2.2)	115 (8.1)	147 (5.2)
Detoxifying agents for antineoplastic treatment	4 (0.3)	1 (0.1)	5 (0.2)
Egfr (epidermal growth factor receptor) inhibitors	1 (0.1)	1 (0.1)	2 (0.1)
Endocrine therapy	1 (0.1)	0 (0.0)	1 (0.0)
Folic acid analogues	1 (0.1)	2 (0.1)	3 (0.1)
Folic acid and derivatives	0 (0.0)	2 (0.1)	2 (0.1)
Glucocorticoids	0 (0.0)	1 (0.1)	1 (0.0)
Gonadotropin releasing hormone analogues	1 (0.1)	2 (0.1)	3 (0.1)
Her2 (human epidermal growth factor receptor 2) inhibitors	11 (0.8)	14 (1.0)	25 (0.9)
Human epidermal growth factor receptor 2 (her2) tyrosine kinase inhibitors	1 (0.1)	1 (0.1)	2 (0.1)
Investigational drug	0 (0.0)	1 (0.1)	1 (0.0)
Mammalian target of rapamycin (mTOR) kinase inhibitors	5 (0.4)	3 (0.2)	8 (0.3)
Nitrogen mustard analogues	9 (0.6)	12 (0.8)	21 (0.7)
Other alkylating agents	1 (0.1)	0 (0.0)	1 (0.0)
Other antineoplastic agents	14 (1.0)	17 (1.2)	31 (1.1)
Other cytotoxic antibiotics	1 (0.1)	0 (0.0)	1 (0.0)
Other drugs affecting bone structure and mineralization	12 (0.8)	7 (0.5)	19 (0.7)
Other immunosuppressants	2 (0.1)	2 (0.1)	4 (0.1)
Other monoclonal antibodies and antibody drug conjugates	5 (0.4)	5 (0.4)	10 (0.4)
Other protein kinase inhibitors	3 (0.2)	0 (0.0)	3 (0.1)
Pd-1/pdl-1 (programmed cell death protein 1/death ligand 1) inhibitors	4 (0.3)	2 (0.1)	6 (0.2)
Phosphatidylinositol-3-kinase (pi3k) inhibitors	6 (0.4)	3 (0.2)	9 (0.3)
Platinum compounds	16 (1.1)	18 (1.3)	34 (1.2)
Podophyllotoxin derivatives	1 (0.1)	0 (0.0)	1 (0.0)

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
Poly (adp-ribose) polymerase (parp) inhibitors	3 (0.2)	3 (0.2)	6 (0.2)
Purine analogues	1 (0.1)	1 (0.1)	2 (0.1)
Pyrimidine analogues	46 (3.2)	46 (3.2)	92 (3.2)
Retinoids for cancer treatment	0 (0.0)	1 (0.1)	1 (0.0)
Taxanes	33 (2.3)	37 (2.6)	70 (2.5)
Topoisomerase 1 (top1) inhibitors	3 (0.2)	1 (0.1)	4 (0.1)
Various	1 (0.1)	0 (0.0)	1 (0.0)
Vegf/vegfr (vascular endothelial growth factor) inhibitors	5 (0.4)	5 (0.4)	10 (0.4)
Vinca alkaloids and analogues	6 (0.4)	4 (0.3)	10 (0.4)
Post treatment anti-neoplastic radiotherapy/surgery, n (%)			
Radiotherapy	28 (2.0)	17 (1.2)	45 (1.6)
Surgery	26 (1.8)	17 (1.2)	43 (1.5)
ET: Endocrine therapy (Anastrozole/Letrozole) ATC: Anatomical Therapeutic Chemical			

Table 1-8 Subgroups (Full Analysis Set)

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
Region, n (%)			
NA/WE/O	913 (64.1)	902 (63.5)	1815 (63.8)
ROW	511 (35.9)	518 (36.5)	1029 (36.2)
Geographical region, n (%)			
Europe	840 (59.0)	843 (59.4)	1683 (59.2)
North America/Australia	406 (28.5)	395 (27.8)	801 (28.2)
Asia	103 (7.2)	108 (7.6)	211 (7.4)
Latin America	75 (5.3)	74 (5.2)	149 (5.2)
Age group 1 at randomization, n (%)			
<45	60 (4.2)	58 (4.1)	118 (4.1)
45 to 54	303 (21.3)	333 (23.5)	636 (22.4)
55 to 64	658 (46.2)	668 (47.0)	1326 (46.6)
≥65	403 (28.3)	361 (25.4)	764 (26.9)
Age group 2 at randomization (median for subpopulation post-menopausal female patients), n (%)			
<Median	639 (44.9)	653 (46.0)	1292 (45.4)
≥Median	785 (55.1)	767 (54.0)	1552 (54.6)
Race, n (%)			
Asian	129 (9.1)	134 (9.4)	263 (9.2)
Non-Asian	1215 (85.3)	1218 (85.8)	2433 (85.5)
Missing values	80 (5.6)	68 (4.8)	148 (5.2)
BMI at screening, n (%)			
≥25	945 (66.4)	969 (68.2)	1914 (67.3)
<25	465 (32.7)	432 (30.4)	897 (31.5)
Missing values	14 (1.0)	19 (1.3)	33 (1.2)
AJCC Anatomic Stage Group, n (%)			
Group I	6 (0.4)	5 (0.4)	11 (0.4)
Group II	587 (41.2)	598 (42.1)	1185 (41.7)
Group III	830 (58.3)	816 (57.5)	1646 (57.9)
Missing values	1 (0.1)	1 (0.1)	2 (0.1)
Anatomic stages, n (%)			
IA	0 (0.0)	3 (0.2)	3 (0.1)
IB	6 (0.4)	2 (0.1)	8 (0.3)
IIA	306 (21.5)	315 (22.2)	621 (21.8)
IIB	281 (19.7)	283 (19.9)	564 (19.8)
IIIA	487 (34.2)	476 (33.5)	963 (33.9)
IIIB	100 (7.0)	86 (6.1)	186 (6.5)
IIIC	243 (17.1)	254 (17.9)	497 (17.5)
Missing values	1 (0.1)	1 (0.1)	2 (0.1)

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
Tumor category, n (%)			
T0	5 (0.4)	5 (0.4)	10 (0.4)
T1-T3	1302 (91.4)	1312 (92.4)	2614 (91.9)
>T3	113 (7.9)	101 (7.1)	214 (7.5)
Missing values	4 (0.3)	2 (0.1)	6 (0.2)
Nodal status, n (%)			
N0	191 (13.4)	208 (14.6)	399 (14.0)
N1-N3	1230 (86.4)	1210 (85.2)	2440 (85.8)
Missing values	3 (0.2)	2 (0.1)	5 (0.2)
Histological grade at time of surgery, n (%)			
Grade 1	102 (7.2)	110 (7.7)	212 (7.5)
Grade 2	849 (59.6)	797 (56.1)	1646 (57.9)
Grade 3	381 (26.8)	420 (29.6)	801 (28.2)
Missing values	92 (6.5)	93 (6.5)	185 (6.5)
Histological subtype, n (%)			
Ductal	1038 (72.9)	1059 (74.6)	2097 (73.7)
Lobular	293 (20.6)	285 (20.1)	578 (20.3)
Other	92 (6.5)	76 (5.4)	168 (5.9)
Missing values	1 (0.1)	0 (0.0)	1 (0.0)
Ki67 status from surgical specimen, n (%)			
Ki67≤20	667 (46.8)	656 (46.2)	1323 (46.5)
Ki67>20	493 (34.6)	536 (37.7)	1029 (36.2)
Missing values	264 (18.5)	228 (16.1)	492 (17.3)
ER+PR+ vs ER-PR+ vs ER+RP, n (%)			
ER+/PR+	1191 (83.6)	1166 (82.1)	2357 (82.9)
ER-/PR+	1 (0.1)	6 (0.4)	7 (0.2)
ER+/PR-	221 (15.5)	241 (17.0)	462 (16.2)
Missing values	11 (0.8)	7 (0.5)	18 (0.6)
Type of NSAI, n (%)			
Letrozole	908 (63.8)	894 (63.0)	1802 (63.4)
Anastrozole	503 (35.3)	466 (32.8)	969 (34.1)
Missing values	13 (0.9)	60 (4.2)	73 (2.6)
Prior neo/adjuvant chemotherapy, n (%)			
Yes	1209 (84.9)	1199 (84.4)	2408 (84.7)
No	215 (15.1)	221 (15.6)	436 (15.3)
Prior adjuvant chemotherapy, n (%)			
Yes	702 (49.3)	705 (49.6)	1407 (49.5)
No	722 (50.7)	715 (50.4)	1437 (50.5)
Prior neoadjuvant chemotherapy, n (%)			
Yes	535 (37.6)	524 (36.9)	1059 (37.2)
No	889 (62.4)	896 (63.1)	1785 (62.8)

	Treatment Groups		
	Ribociclib + ET (N=1424)	ET (N=1420)	Total (N=2844)
Prior endocrine therapy, n (%)			
Yes	967 (67.9)	979 (68.9)	1946 (68.4)
No	457 (32.1)	441 (31.1)	898 (31.6)
Prior mastectomy, n (%)			
Yes	865 (60.7)	884 (62.3)	1749 (61.5)
No	559 (39.3)	536 (37.7)	1095 (38.5)
Prior radiotherapy, n (%)			
Yes	1267 (89.0)	1259 (88.7)	2526 (88.8)
No	157 (11.0)	161 (11.3)	318 (11.2)
ET: Endocrine therapy (Anastrozole/Letrozole) BMI: Body mass index AJCC: American Joint Commission on Cancer NSAI: Non-steroidal aromatase inhibitor			

2 Efficacy

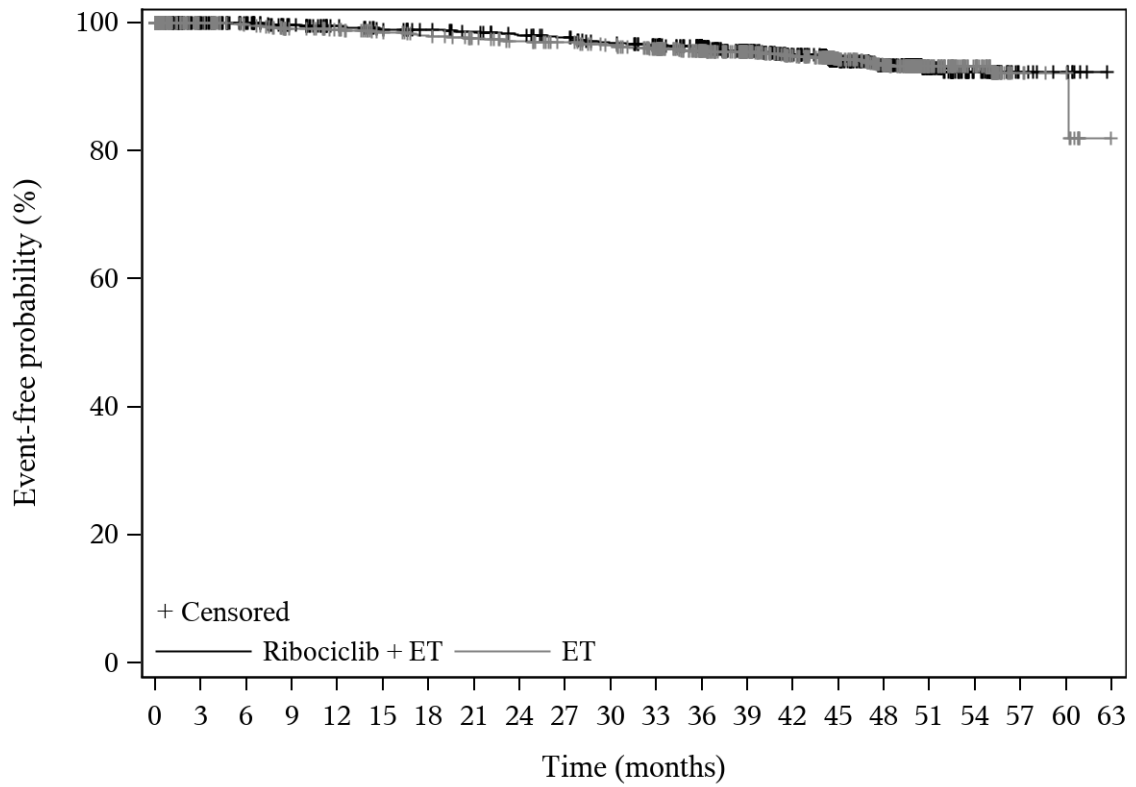
2-1 Overall survival

Table 2-1.1 Overall survival: time to event analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)	HR	[95% CI]	p-value
Time to Overall Survival Event					
N'	1424	1420			
Patients with event, n (%)					
Death (any cause)	74 (5.2)	75 (5.3)			
Patients censored, n (%)					
Any	1350 (94.8)	1345 (94.7)			
Alive	1137 (79.8)	1084 (76.3)			
Lost to follow-up	213 (15.0)	261 (18.4)			
Percentiles (months) [95% CI]					
25 th	N.E. [N.E.]	N.E. [N.E.]			
Median	N.E. [N.E.]	N.E. [N.E.]	0.94	[0.68; 1.30]	0.724
N: Number of patients N': Number of patients included in the analysis n: Number and percentage of patients with event/censored CI: Confidence interval HR: Hazard ratio KM: Kaplan-Meier N.E.: Not estimable ET: Endocrine therapy (Anastrozole/Letrozole) Analysis methods: Median time to event and other quartiles by KM estimation, 95% CIs using the method of Brookmeyer and Crowley with linear transformation. HR with 95% CI from stratified Cox proportional hazards model: $\log(\text{hazard ratio}) = \text{treatment}$ The model was stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region. ET was the reference group for treatment group comparison. Two-sided p-value from Log-rank test, stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region.					

Figure 2-1.1 Overall survival: Kaplan-Meier plot (Full Analysis Set)

Time to Overall Survival Event



Ribociclib + ET	1424	1341	1294	1270	1248	1220	1134	904	580	109	8
ET	1420	1281	1247	1218	1193	1168	1063	878	573	117	10

Table 2-1.2 Overall survival: binary analysis (Full Analysis Set)

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Overall Survival Event						
Event, n / N' (%)	74 / 1424 (5.2)	75 / 1420 (5.3)	OR	0.99	[0.71; 1.38]	0.938
			RR	0.99	[0.72; 1.35]	
			RD	-0.00	[-0.02; 0.02]	
N: Number of patients N': Number of patients in the analysis n: Number of patients with event CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference CMH: Cochran-Mantel-Haenszel ET: Endocrine therapy (Anastrozole/Letrozole) Analysis methods: OR, RR, RD with 95% CIs estimated by CMH method, stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region. ET was the reference group for treatment group comparison. Two-sided p-value from CMH Chi-square test, stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region.						

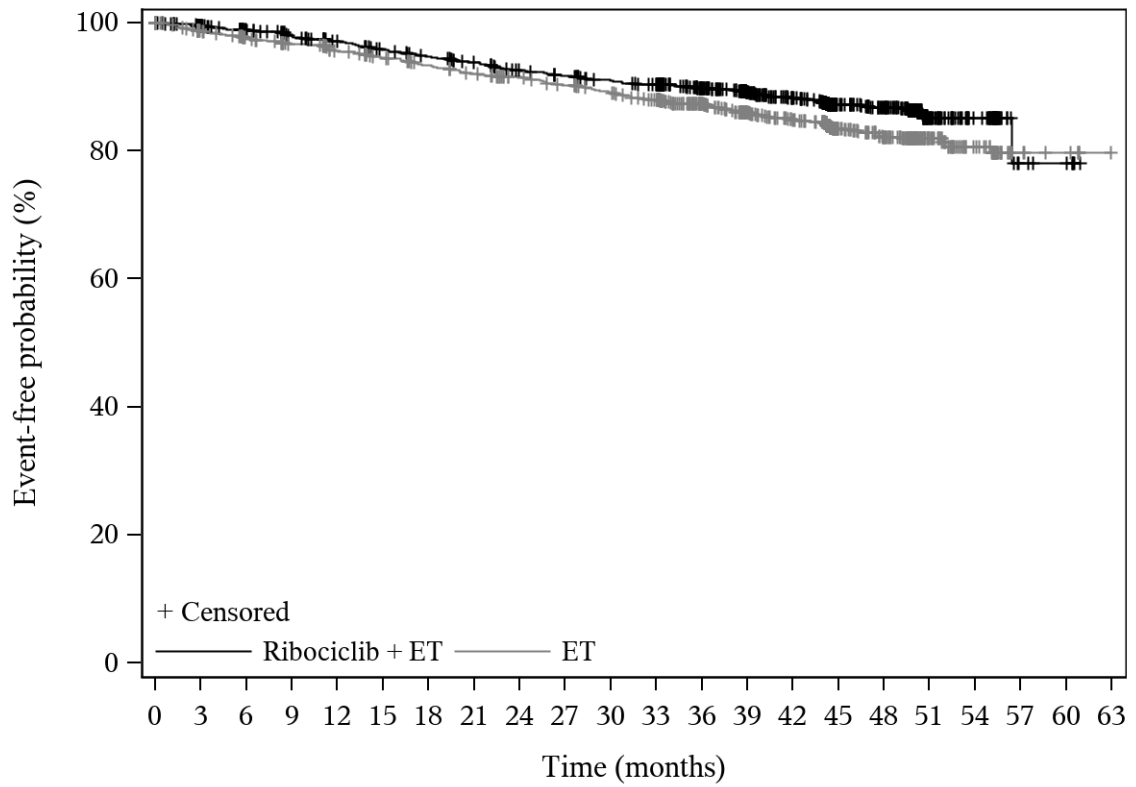
2-2 Invasive disease-free survival

Table 2-2.1 Invasive disease-free survival: time to event analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)	HR	[95% CI]	p-value
Time to First iDFS Event					
N'	1424	1420			
Patients with event, n (%)					
Any	164 (11.5)	203 (14.3)			
Death (any cause)	13 (0.9)	8 (0.6)			
Invasive breast recurrence event	4 (0.3)	6 (0.4)			
Regional invasive recurrence event	13 (0.9)	31 (2.2)			
Contralateral invasive recurrence event	8 (0.6)	4 (0.3)			
Distant recurrence event	110 (7.7)	142 (10.0)			
New primary malignancy event	24 (1.7)	27 (1.9)			
Patients censored, n (%)					
Any	1260 (88.5)	1217 (85.7)			
Lost to follow-up	16 (1.1)	19 (1.3)			
Ongoing without event	1089 (76.5)	994 (70.0)			
Withdrew consent	155 (10.9)	204 (14.4)			
Percentiles (months) [95% CI]					
25 th	N.E. [N.E.]	N.E. [N.E.]			
Median	N.E. [N.E.]	N.E. [N.E.]	0.75	[0.61; 0.92]	0.005
<p>N: Number of patients N': Number of patients included in the analysis n: Number and percentage of patients with event/censored CI: Confidence interval HR: Hazard ratio KM: Kaplan-Meier N.E.: Not estimable ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis methods: Median time to event and other quartiles by KM estimation, 95% CIs using the method of Brookmeyer and Crowley with linear transformation. HR with 95% CI from stratified Cox proportional hazards model: $\log(\text{hazard ratio}) = \text{treatment}$ The model was stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region. ET was the reference group for treatment group comparison. Two-sided p-value from Log-rank test, stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region.</p> <p>Multiple events may have occurred on the same day. Therefore the sum of all event types may exceed the number of events.</p>					

Figure 2-2.1 Invasive disease-free survival: Kaplan-Meier plot (Full Analysis Set)

Time to First iDFS Event



Ribociclib + ET	1424	1305	1254	1212	1167	1133	1027	830	535	96	6
ET	1420	1237	1187	1143	1105	1064	944	768	495	96	6

Table 2-2.2 Invasive disease-free survival: binary analysis (Full Analysis Set)

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
First iDFS Event						
Event, n / N' (%)	164 / 1424 (11.5)	203 / 1420 (14.3)	OR	0.78	[0.62; 0.97]	0.027
			RR	0.81	[0.67; 0.98]	
			RD	-0.03	[-0.05; -0.00]	
N: Number of patients N': Number of patients in the analysis n: Number of patients with event CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference CMH: Cochran-Mantel-Haenszel ET: Endocrine therapy (Anastrozole/Letrozole) Analysis methods: OR, RR, RD with 95% CIs estimated by CMH method, stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region. ET was the reference group for treatment group comparison. Two-sided p-value from CMH Chi-square test, stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region.						

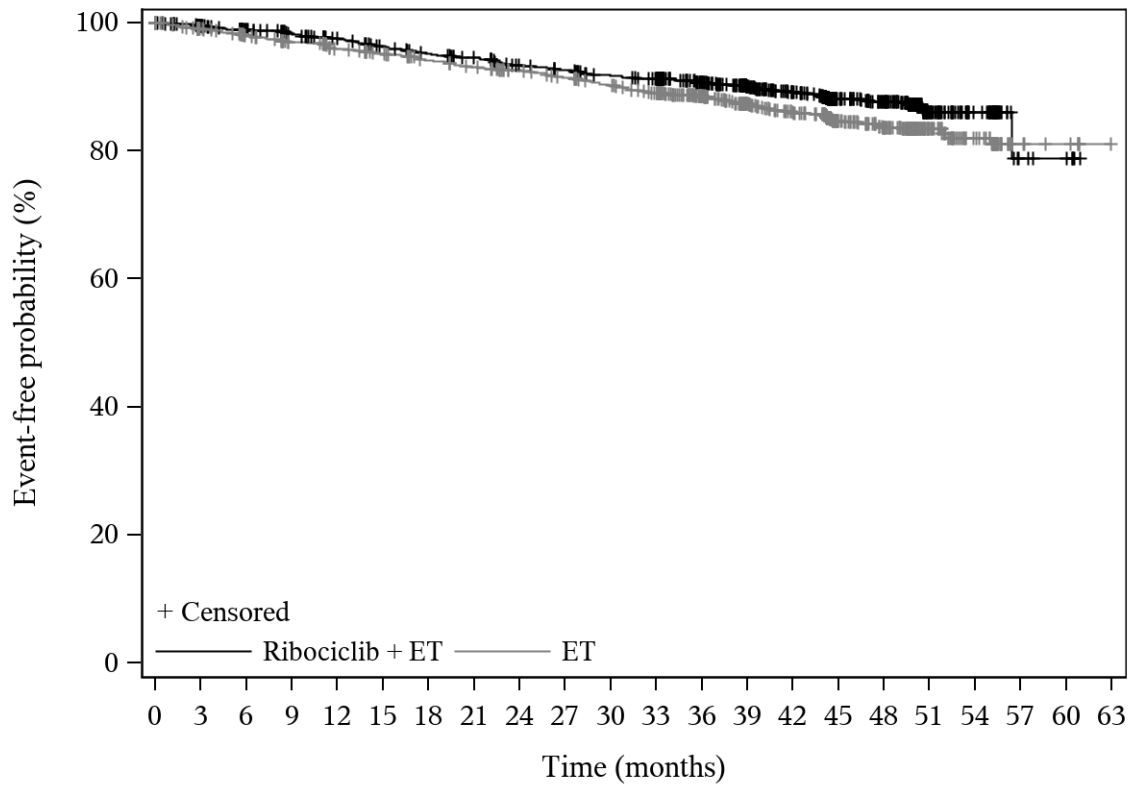
2-3 Distant disease-free survival

Table 2-3.1 Distant disease-free survival: time to event analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)	HR	[95% CI]	p-value
Time to Distant Disease-Free Survival Event					
N'	1424	1420			
Patients with event, n (%)					
Any	152 (10.7)	186 (13.1)			
Death (any cause)	15 (1.1)	11 (0.8)			
Distant recurrence event	113 (7.9)	148 (10.4)			
New primary malignancy event	24 (1.7)	27 (1.9)			
Patients censored, n (%)					
Any	1272 (89.3)	1234 (86.9)			
Lost to follow-up	18 (1.3)	20 (1.4)			
Ongoing without event	1098 (77.1)	1007 (70.9)			
Withdrew consent	156 (11.0)	207 (14.6)			
Percentiles (months) [95% CI]					
25 th	N.E. [N.E.]	N.E. [N.E.]			
Median	N.E. [N.E.]	N.E. [N.E.]	0.76	[0.61; 0.94]	0.012
<p>N: Number of patients N': Number of patients included in the analysis n: Number and percentage of patients with event/censored CI: Confidence interval HR: Hazard ratio KM: Kaplan-Meier N.E.: Not estimable ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis methods: Median time to event and other quartiles by KM estimation, 95% CIs using the method of Brookmeyer and Crowley with linear transformation. HR with 95% CI from stratified Cox proportional hazards model: $\log(\text{hazard ratio}) = \text{treatment}$ The model was stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region. ET was the reference group for treatment group comparison. Two-sided p-value from Log-rank test, stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region.</p> <p>Multiple events may have occurred on the same day. Therefore the sum of all event types may exceed the number of events.</p>					

Figure 2-3.1 Distant disease-free survival: Kaplan-Meier plot (Full Analysis Set)

Time to Distant Disease-Free Survival Event



Ribociclib + ET	1424	1306	1257	1215	1174	1139	1033	833	536	96	6
ET	1420	1241	1189	1150	1115	1073	955	776	502	97	6

Table 2-3.2 Distant disease-free survival: binary analysis (Full Analysis Set)

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Distant Disease-Free Survival Event						
Event, n / N' (%)	152 / 1424 (10.7)	186 / 1420 (13.1)	OR	0.79	[0.63; 1.00]	0.046
			RR	0.82	[0.67; 1.00]	
			RD	-0.02	[-0.05; -0.00]	
N: Number of patients N': Number of patients in the analysis n: Number of patients with event CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference CMH: Cochran-Mantel-Haenszel ET: Endocrine therapy (Anastrozole/Letrozole) Analysis methods: OR, RR, RD with 95% CIs estimated by CMH method, stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region. ET was the reference group for treatment group comparison. Two-sided p-value from CMH Chi-square test, stratified by AJCC Anatomic Stage Group, prior neo-/adjuvant chemotherapy and region.						

3 PRO

3-0 Analysis PRO

Change from baseline is analyzed based on a mixed model for repeated measures (MMRM) and includes both on- and off-treatment data in accordance with the ITT principle, whereby the values collected after an iDFS event are assigned to regular visits. All data collected will be included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there are at least 50 patients in each arm. Missing values are not imputed.

The adjusted mean differences between the treatment groups over the entire period including the 95% confidence interval as well as the standardized mean difference (Hedges' g) with the associated confidence interval are reported. A line plot of adjusted mean change within treatment arms along with confidence limits is also produced.

3-1 EORTC QLQ-C30 Symptoms

Table 3-1.0 EORTC QLQ-C30 Symptoms: return rates (Full Analysis Set)

	Treatment groups			
	Ribociclib + ET (N = 1424)		ET (N = 1420)	
	N' (%)	Returns n (%)	N' (%)	Returns n (%)
Baseline	1424 (100.0)	1386 (97.3)	1420 (100.0)	1376 (96.9)
Week 13	1424 (100.0)	1306 (91.7)	1420 (100.0)	1235 (87.0)
Week 25	1423 (99.9)	1248 (87.7)	1418 (99.9)	1179 (83.1)
Week 37	1420 (99.7)	1251 (88.1)	1410 (99.3)	1172 (83.1)
Week 49	1418 (99.6)	1224 (86.3)	1408 (99.2)	1169 (83.0)
Week 61	1414 (99.3)	1211 (85.6)	1404 (98.9)	1144 (81.5)
Week 73	1411 (99.1)	1202 (85.2)	1399 (98.5)	1130 (80.8)
Week 85	1409 (98.9)	1168 (82.9)	1392 (98.0)	1114 (80.0)
Week 97	1406 (98.7)	1165 (82.9)	1387 (97.7)	1096 (79.0)
Week 121	1393 (97.8)	1116 (80.1)	1382 (97.3)	1074 (77.7)
Week 145	1379 (96.8)	1100 (79.8)	1369 (96.4)	1039 (75.9)
Week 169	1370 (96.2)	939 (68.5)	1364 (96.1)	893 (65.5)
Week 193	1362 (95.6)	792 (58.1)	1357 (95.6)	750 (55.3)
Week 217	1352 (94.9)	497 (36.8)	1347 (94.9)	494 (36.7)

	Treatment groups			
	Ribociclib + ET (N = 1424)		ET (N = 1420)	
	N' (%)	Returns n (%)	N' (%)	Returns n (%)
Week 241	1350 (94.8)	93 (6.9)	1346 (94.8)	96 (7.1)
Week 265	1350 (94.8)	6 (0.4)	1345 (94.7)	4 (0.3)

N': Number of patients who have not died until the respective visit
 ET: Endocrine therapy (Anastrozole/Letrozole)

The number of returns is the number of patients with non-missing data (i.e. at least one [sub-]score present) at the respective visit.

A patients is considered to have not died until the visit if no death was documented during the study, if returns for this PRO are present at the visit or, if no returns are present for this PRO and the patient died, if the death date is after the scheduled visit date.

Percentages of returns refer to N' per group. For N' percentages refer to N per group.

Table 3-1.1 EORTC QLQ-C30 Symptoms: change from baseline analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-C30 - Fatigue						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1325	1263				
Baseline	1325 26.56 (20.29)	1263 27.39 (20.86)				
Week 13	1270 28.68 (20.80)	1199 28.96 (21.17)				
Week 25	1219 28.00 (20.10)	1154 27.86 (21.15)				
Week 37	1215 29.09 (21.54)	1145 28.38 (21.93)				
Week 49	1188 29.00 (21.18)	1143 29.11 (22.34)				
Week 61	1176 28.99 (21.12)	1116 29.57 (22.51)				
Week 73	1168 29.78 (21.81)	1105 28.99 (22.17)				
Week 85	1131 29.27 (21.78)	1088 30.02 (22.32)				
Week 97	1129 29.61 (21.92)	1068 30.52 (23.38)				
Week 121	1081 29.12 (21.01)	1048 29.85 (22.60)				
Week 145	1068 29.09 (21.99)	1012 29.96 (22.37)				
Week 169	908 28.43 (21.24)	873 29.43 (22.57)				
Week 193	767 28.93 (22.14)	735 30.73 (24.07)				
Week 217	478 27.62 (20.60)	483 29.66 (23.07)				
Week 241	91 26.37 (20.13)	95 30.12 (21.89)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	2.17 (0.48)	1.64 (0.49)	Difference	0.53	[-0.82; 1.88]	0.440
			Hedges G	0.03	[-0.05; 0.11]	
Week 25	1.53 (0.48)	0.69 (0.50)	Difference	0.84	[-0.51; 2.20]	0.223
			Hedges G	0.05	[-0.03; 0.13]	
Week 37	2.73 (0.52)	1.23 (0.53)	Difference	1.49	[0.04; 2.95]	0.044
			Hedges G	0.08	[0.00; 0.16]	
Week 49	2.48 (0.53)	2.03 (0.54)	Difference	0.45	[-1.03; 1.92]	0.550
			Hedges G	0.02	[-0.06; 0.11]	
Week 61	2.84 (0.53)	2.55 (0.55)	Difference	0.29	[-1.20; 1.79]	0.701
			Hedges G	0.02	[-0.07; 0.10]	
Week 73	3.63 (0.56)	2.23 (0.57)	Difference	1.40	[-0.16; 2.96]	0.079
			Hedges G	0.07	[-0.01; 0.16]	
Week 85	3.19 (0.55)	3.26 (0.57)	Difference	-0.07	[-1.63; 1.48]	0.927
			Hedges G	-0.00	[-0.09; 0.08]	
Week 97	3.49 (0.58)	3.72 (0.59)	Difference	-0.23	[-1.86; 1.39]	0.778
			Hedges G	-0.01	[-0.10; 0.07]	
Week 121	3.17 (0.56)	2.99 (0.57)	Difference	0.18	[-1.39; 1.76]	0.819
			Hedges G	0.01	[-0.08; 0.09]	
Week 145	3.35 (0.58)	3.16 (0.60)	Difference	0.19	[-1.44; 1.83]	0.819

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Esti- mate	[95% CI]	p-value
Week 169	2.75 (0.60)	2.63 (0.62)	Hedges G	0.01	[-0.08; 0.10]	
			Difference	0.12	[-1.57; 1.82]	0.889
Week 193	2.99 (0.66)	3.99 (0.68)	Hedges G	0.01	[-0.09; 0.10]	
			Difference	-1.00	[-2.86; 0.87]	0.294
Week 217	2.55 (0.76)	3.56 (0.76)	Hedges G	-0.05	[-0.16; 0.05]	
			Difference	-1.01	[-3.12; 1.11]	0.351
Week 241	1.93 (1.25)	4.48 (1.24)	Hedges G	-0.06	[-0.19; 0.07]	
			Difference	-2.55	[-6.00; 0.90]	0.148
Overall effect	2.77 (0.42)	2.73 (0.43)	Difference	0.05	[-1.13; 1.22]	0.939
			Hedges G	0.00	[-0.07; 0.08]	
QLQ-C30 - Nausea and Vomiting						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1325	1263				
Baseline	1325 3.12 (9.16)	1263 3.18 (9.04)				
Week 13	1269 4.94 (11.51)	1200 3.12 (8.81)				
Week 25	1219 4.92 (11.03)	1153 3.53 (10.16)				
Week 37	1214 5.27 (11.96)	1145 3.73 (9.86)				
Week 49	1187 5.03 (11.12)	1142 3.91 (10.75)				
Week 61	1176 5.23 (11.23)	1116 3.69 (9.84)				
Week 73	1168 5.22 (12.00)	1106 3.96 (10.87)				
Week 85	1130 4.93 (11.35)	1089 3.58 (10.52)				
Week 97	1130 5.32 (11.80)	1067 4.33 (12.43)				
Week 121	1081 5.27 (11.91)	1048 3.96 (11.02)				
Week 145	1068 5.04 (11.15)	1012 3.82 (10.15)				
Week 169	909 3.85 (9.64)	873 3.99 (10.81)				
Week 193	767 4.04 (10.20)	735 3.47 (9.07)				
Week 217	478 3.94 (10.07)	483 4.42 (12.05)				
Week 241	91 3.66 (10.48)	96 3.82 (10.40)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	1.94 (0.27)	-0.01 (0.28)	Difference	1.95	[1.19; 2.72]	<.001
			Hedges G	0.20	[0.12; 0.28]	
Week 25	1.98 (0.29)	0.46 (0.30)	Difference	1.52	[0.70; 2.35]	<.001
			Hedges G	0.15	[0.07; 0.23]	
Week 37	2.36 (0.30)	0.67 (0.31)	Difference	1.69	[0.84; 2.55]	<.001
			Hedges G	0.16	[0.08; 0.24]	
Week 49	2.05 (0.30)	0.95 (0.31)	Difference	1.10	[0.25; 1.95]	0.011
			Hedges G	0.11	[0.02; 0.19]	
Week 61	2.28 (0.30)	0.85 (0.31)	Difference	1.43	[0.59; 2.27]	<.001
			Hedges G	0.14	[0.06; 0.22]	
Week 73	2.27 (0.33)	1.05 (0.34)	Difference	1.22	[0.30; 2.13]	0.010
			Hedges G	0.11	[0.03; 0.19]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Week 85	2.07 (0.32)	0.81 (0.33)	Difference	1.26	[0.35; 2.16]	0.006
			Hedges G	0.12	[0.03; 0.20]	
Week 97	2.41 (0.35)	1.59 (0.36)	Difference	0.82	[-0.17; 1.81]	0.106
			Hedges G	0.07	[-0.01; 0.15]	
Week 121	2.48 (0.34)	1.23 (0.35)	Difference	1.25	[0.29; 2.20]	0.011
			Hedges G	0.11	[0.03; 0.20]	
Week 145	2.24 (0.32)	1.20 (0.33)	Difference	1.05	[0.15; 1.94]	0.022
			Hedges G	0.10	[0.01; 0.19]	
Week 169	1.11 (0.33)	1.40 (0.34)	Difference	-0.29	[-1.22; 0.63]	0.537
			Hedges G	-0.03	[-0.12; 0.06]	
Week 193	1.21 (0.33)	0.87 (0.34)	Difference	0.34	[-0.59; 1.28]	0.470
			Hedges G	0.04	[-0.06; 0.14]	
Week 217	1.42 (0.48)	2.10 (0.48)	Difference	-0.68	[-2.01; 0.65]	0.316
			Hedges G	-0.06	[-0.19; 0.06]	
Week 241	1.81 (0.84)	2.13 (0.82)	Difference	-0.32	[-2.61; 1.98]	0.786
			Hedges G	-0.04	[-0.33; 0.25]	
Overall effect	1.97 (0.20)	1.09 (0.20)	Difference	0.88	[0.33; 1.44]	0.002
			Hedges G	0.12	[0.05; 0.20]	
QLQ-C30 - Pain						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1328	1263				
Baseline	1328 21.30 (21.78)	1263 21.26 (22.16)				
Week 13	1273 22.14 (23.24)	1202 25.17 (24.11)				
Week 25	1223 22.64 (22.72)	1154 24.87 (24.13)				
Week 37	1219 23.75 (23.49)	1146 25.73 (23.84)				
Week 49	1192 23.55 (24.23)	1144 26.01 (24.45)				
Week 61	1179 24.17 (24.38)	1117 25.95 (24.76)				
Week 73	1171 23.93 (24.15)	1107 25.55 (24.80)				
Week 85	1135 23.60 (24.30)	1088 26.55 (24.99)				
Week 97	1133 23.68 (24.08)	1071 24.93 (24.72)				
Week 121	1087 23.89 (24.21)	1047 24.90 (24.00)				
Week 145	1071 23.50 (24.15)	1016 23.95 (23.79)				
Week 169	912 25.04 (25.21)	872 24.52 (25.14)				
Week 193	769 24.23 (24.65)	736 24.03 (24.88)				
Week 217	480 21.94 (25.64)	484 23.04 (23.79)				
Week 241	91 21.43 (23.48)	96 24.83 (25.82)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	1.25 (0.55)	3.91 (0.57)	Difference	-2.66	[-4.22; -1.11]	<.001
			Hedges G	-0.14	[-0.21; -0.06]	
Week 25	1.94 (0.57)	3.96 (0.58)	Difference	-2.03	[-3.62; -0.43]	0.013
			Hedges G	-0.10	[-0.18; -0.02]	
Week 37	2.86 (0.59)	4.87 (0.60)	Difference	-2.01	[-3.66; -0.36]	0.017

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Week 49	2.70 (0.61)	5.04 (0.62)	Hedges G	-0.10	[-0.18; -0.02]	
			Difference	-2.35	[-4.05; -0.65]	0.007
Week 61	3.54 (0.62)	5.37 (0.64)	Hedges G	-0.11	[-0.19; -0.03]	
			Difference	-1.83	[-3.59; -0.08]	0.041
Week 73	3.10 (0.62)	4.94 (0.64)	Hedges G	-0.09	[-0.17; -0.00]	
			Difference	-1.84	[-3.58; -0.09]	0.040
Week 85	2.83 (0.65)	6.10 (0.66)	Hedges G	-0.09	[-0.17; -0.00]	
			Difference	-3.27	[-5.09; -1.45]	<.001
Week 97	2.97 (0.64)	4.44 (0.66)	Hedges G	-0.15	[-0.23; -0.07]	
			Difference	-1.47	[-3.28; 0.34]	0.112
Week 121	3.36 (0.65)	4.48 (0.66)	Hedges G	-0.07	[-0.15; 0.02]	
			Difference	-1.13	[-2.94; 0.68]	0.223
Week 145	3.09 (0.64)	3.50 (0.66)	Hedges G	-0.05	[-0.14; 0.03]	
			Difference	-0.41	[-2.22; 1.39]	0.655
Week 169	4.71 (0.71)	3.98 (0.73)	Hedges G	-0.02	[-0.11; 0.07]	
			Difference	0.73	[-1.27; 2.72]	0.476
Week 193	3.56 (0.75)	4.00 (0.77)	Hedges G	0.03	[-0.06; 0.13]	
			Difference	-0.45	[-2.56; 1.66]	0.679
Week 217	2.69 (0.88)	3.49 (0.89)	Hedges G	-0.02	[-0.12; 0.08]	
			Difference	-0.80	[-3.26; 1.66]	0.523
Week 241	3.46 (1.72)	5.18 (1.68)	Hedges G	-0.04	[-0.17; 0.09]	
			Difference	-1.72	[-6.44; 3.00]	0.475
Overall effect	3.00 (0.46)	4.52 (0.47)	Difference	-1.52	[-2.82; -0.21]	0.022
			Hedges G	-0.09	[-0.17; -0.01]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Esti- mate	[95% CI]	p-value
QLQ-C30 - Dyspnoea						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1322	1260				
Baseline	1322 11.12 (19.02)	1260 12.46 (20.94)				
Week 13	1267 12.37 (19.95)	1196 13.43 (21.47)				
Week 25	1216 13.68 (20.91)	1148 13.70 (22.18)				
Week 37	1210 13.91 (21.36)	1141 14.05 (21.68)				
Week 49	1181 14.59 (21.23)	1140 15.18 (22.97)				
Week 61	1172 14.96 (21.25)	1106 15.46 (23.41)				
Week 73	1164 14.60 (20.88)	1101 15.50 (22.69)				
Week 85	1128 15.19 (22.72)	1082 16.02 (23.08)				
Week 97	1126 15.69 (22.80)	1064 15.13 (22.81)				
Week 121	1077 16.09 (23.06)	1042 15.87 (23.05)				
Week 145	1062 16.57 (22.69)	1007 16.75 (23.77)				
Week 169	908 15.35 (22.56)	869 15.84 (23.10)				
Week 193	764 14.75 (21.87)	732 16.03 (24.68)				
Week 217	477 13.35 (20.41)	480 15.97 (22.48)				
Week 241	91 13.55 (21.65)	96 17.36 (26.92)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	1.11 (0.50)	1.10 (0.52)	Difference	0.01	[-1.40; 1.42]	0.986
			Hedges G	0.00	[-0.08; 0.08]	
Week 25	2.24 (0.54)	1.36 (0.55)	Difference	0.88	[-0.63; 2.40]	0.254
			Hedges G	0.05	[-0.03; 0.13]	
Week 37	2.52 (0.55)	1.75 (0.56)	Difference	0.77	[-0.77; 2.31]	0.326
			Hedges G	0.04	[-0.04; 0.12]	
Week 49	3.11 (0.56)	3.00 (0.57)	Difference	0.11	[-1.46; 1.68]	0.892
			Hedges G	0.01	[-0.08; 0.09]	
Week 61	3.55 (0.57)	3.47 (0.59)	Difference	0.08	[-1.53; 1.69]	0.924
			Hedges G	0.00	[-0.08; 0.09]	
Week 73	3.33 (0.57)	3.51 (0.58)	Difference	-0.18	[-1.78; 1.42]	0.828
			Hedges G	-0.01	[-0.09; 0.07]	
Week 85	3.89 (0.60)	4.14 (0.62)	Difference	-0.25	[-1.94; 1.44]	0.775
			Hedges G	-0.01	[-0.10; 0.07]	
Week 97	4.38 (0.61)	3.15 (0.63)	Difference	1.23	[-0.49; 2.95]	0.160
			Hedges G	0.06	[-0.02; 0.14]	
Week 121	4.88 (0.63)	3.98 (0.64)	Difference	0.90	[-0.86; 2.65]	0.317
			Hedges G	0.04	[-0.04; 0.13]	
Week 145	5.37 (0.64)	4.82 (0.66)	Difference	0.55	[-1.25; 2.34]	0.549
			Hedges G	0.03	[-0.06; 0.11]	
Week 169	4.15 (0.67)	4.27 (0.68)	Difference	-0.12	[-1.99; 1.75]	0.901
			Hedges G	-0.01	[-0.10; 0.09]	
Week 193	3.50 (0.71)	4.05 (0.72)	Difference	-0.56	[-2.54; 1.43]	0.583

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Week 217	2.56 (0.81)	3.96 (0.81)	Hedges G	-0.03	[-0.13; 0.07]	
			Difference	-1.40	[-3.64; 0.84]	0.220
Week 241	4.83 (1.63)	5.30 (1.60)	Hedges G	-0.08	[-0.21; 0.05]	
			Difference	-0.46	[-4.94; 4.01]	0.840
Overall effect	3.53 (0.42)	3.42 (0.43)	Difference	0.11	[-1.08; 1.30]	0.853
			Hedges G	0.01	[-0.07; 0.08]	
QLQ-C30 - Insomnia						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1322	1261				
Baseline	1322 30.21 (29.61)	1261 29.26 (28.50)				
Week 13	1264 31.28 (29.35)	1197 31.89 (29.33)				
Week 25	1210 30.36 (28.89)	1151 31.91 (29.14)				
Week 37	1210 31.29 (29.69)	1141 32.02 (29.60)				
Week 49	1181 31.08 (29.67)	1141 32.84 (30.02)				
Week 61	1173 31.32 (29.29)	1114 32.26 (29.96)				
Week 73	1164 32.13 (30.23)	1103 31.58 (28.88)				
Week 85	1125 31.29 (29.51)	1086 31.34 (28.68)				
Week 97	1126 32.12 (30.36)	1067 32.68 (29.81)				
Week 121	1078 30.95 (29.46)	1047 31.96 (29.68)				
Week 145	1063 31.33 (29.44)	1009 33.27 (30.36)				
Week 169	907 31.35 (29.27)	871 32.41 (29.84)				
Week 193	763 32.85 (30.85)	735 33.42 (30.88)				
Week 217	475 31.51 (29.23)	483 34.23 (31.51)				
Week 241	91 28.94 (26.86)	95 30.53 (31.00)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	1.61 (0.70)	2.58 (0.71)	Difference	-0.96	[-2.92; 0.99]	0.335
			Hedges G	-0.04	[-0.12; 0.04]	
Week 25	0.96 (0.70)	2.77 (0.72)	Difference	-1.81	[-3.78; 0.16]	0.072
			Hedges G	-0.07	[-0.15; 0.01]	
Week 37	1.97 (0.73)	2.62 (0.75)	Difference	-0.65	[-2.72; 1.41]	0.536
			Hedges G	-0.03	[-0.11; 0.06]	
Week 49	1.44 (0.74)	3.69 (0.75)	Difference	-2.24	[-4.31; -0.18]	0.033
			Hedges G	-0.09	[-0.17; -0.01]	
Week 61	2.01 (0.75)	3.11 (0.77)	Difference	-1.09	[-3.19; 1.01]	0.307
			Hedges G	-0.04	[-0.12; 0.04]	
Week 73	2.68 (0.75)	2.49 (0.77)	Difference	0.19	[-1.91; 2.29]	0.862
			Hedges G	0.01	[-0.08; 0.09]	
Week 85	1.83 (0.75)	2.33 (0.76)	Difference	-0.50	[-2.59; 1.59]	0.638
			Hedges G	-0.02	[-0.10; 0.06]	
Week 97	2.42 (0.77)	3.70 (0.79)	Difference	-1.27	[-3.45; 0.90]	0.250
			Hedges G	-0.05	[-0.13; 0.03]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Week 121	1.52 (0.77)	3.01 (0.78)	Difference	-1.48	[-3.64; 0.67]	0.178
			Hedges G	-0.06	[-0.14; 0.03]	
Week 145	1.78 (0.79)	4.04 (0.81)	Difference	-2.27	[-4.48; -0.05]	0.045
			Hedges G	-0.09	[-0.17; -0.00]	
Week 169	1.92 (0.82)	3.67 (0.84)	Difference	-1.75	[-4.05; 0.56]	0.137
			Hedges G	-0.07	[-0.16; 0.02]	
Week 193	3.46 (0.92)	4.38 (0.93)	Difference	-0.92	[-3.49; 1.64]	0.482
			Hedges G	-0.04	[-0.14; 0.06]	
Week 217	4.51 (1.09)	5.07 (1.09)	Difference	-0.56	[-3.59; 2.46]	0.716
			Hedges G	-0.02	[-0.15; 0.10]	
Week 241	2.85 (2.05)	4.64 (2.02)	Difference	-1.79	[-7.43; 3.86]	0.535
			Hedges G	-0.09	[-0.38; 0.20]	
Overall effect	2.21 (0.54)	3.43 (0.56)	Difference	-1.22	[-2.75; 0.30]	0.116
			Hedges G	-0.06	[-0.14; 0.02]	
QLQ-C30 - Appetite Loss						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1325	1261				
Baseline	1325 8.10 (18.45)	1261 8.86 (19.15)				
Week 13	1266 8.79 (19.02)	1199 7.78 (17.62)				
Week 25	1215 8.09 (17.78)	1152 8.13 (18.02)				
Week 37	1213 8.08 (18.24)	1143 7.84 (17.19)				
Week 49	1184 8.90 (19.18)	1143 8.25 (17.50)				
Week 61	1172 8.22 (18.22)	1112 8.45 (18.18)				
Week 73	1167 9.48 (19.99)	1101 8.42 (17.86)				
Week 85	1129 8.41 (18.00)	1089 7.96 (17.62)				
Week 97	1129 9.60 (19.79)	1067 9.06 (19.19)				
Week 121	1080 9.29 (19.28)	1043 8.50 (18.36)				
Week 145	1065 9.64 (19.84)	1007 9.47 (19.63)				
Week 169	909 8.32 (17.78)	871 9.34 (18.76)				
Week 193	764 9.08 (18.67)	734 9.22 (19.81)				
Week 217	477 8.74 (18.60)	482 9.47 (19.59)				
Week 241	91 9.52 (20.05)	96 8.33 (16.75)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	0.62 (0.46)	-0.80 (0.47)	Difference	1.42	[0.12; 2.72]	0.032
			Hedges G	0.09	[0.01; 0.17]	
Week 25	0.06 (0.47)	-0.45 (0.48)	Difference	0.51	[-0.81; 1.83]	0.450
			Hedges G	0.03	[-0.05; 0.11]	
Week 37	0.00 (0.47)	-0.75 (0.48)	Difference	0.75	[-0.57; 2.07]	0.265
			Hedges G	0.05	[-0.03; 0.13]	
Week 49	0.83 (0.50)	-0.06 (0.51)	Difference	0.89	[-0.51; 2.29]	0.212
			Hedges G	0.05	[-0.03; 0.13]	
Week 61	0.28 (0.49)	0.21 (0.51)	Difference	0.07	[-1.31; 1.46]	0.917

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Week 73	1.48 (0.52)	0.34 (0.54)	Hedges G	0.00	[-0.08; 0.09]	
			Difference	1.14	[-0.33; 2.60]	0.129
Week 85	0.55 (0.50)	-0.19 (0.51)	Hedges G	0.06	[-0.02; 0.15]	
			Difference	0.74	[-0.65; 2.12]	0.299
Week 97	1.69 (0.54)	0.87 (0.55)	Hedges G	0.04	[-0.04; 0.13]	
			Difference	0.82	[-0.70; 2.34]	0.292
Week 121	1.54 (0.53)	0.63 (0.55)	Hedges G	0.05	[-0.04; 0.13]	
			Difference	0.91	[-0.59; 2.40]	0.236
Week 145	1.93 (0.56)	1.60 (0.58)	Hedges G	0.05	[-0.03; 0.14]	
			Difference	0.34	[-1.24; 1.92]	0.675
Week 169	0.77 (0.56)	1.69 (0.57)	Hedges G	0.02	[-0.07; 0.10]	
			Difference	-0.93	[-2.50; 0.64]	0.248
Week 193	1.26 (0.63)	1.63 (0.65)	Hedges G	-0.05	[-0.15; 0.04]	
			Difference	-0.37	[-2.15; 1.40]	0.679
Week 217	1.55 (0.73)	1.83 (0.73)	Hedges G	-0.02	[-0.12; 0.08]	
			Difference	-0.28	[-2.31; 1.74]	0.786
Week 241	2.15 (1.25)	1.61 (1.23)	Hedges G	-0.02	[-0.14; 0.11]	
			Difference	0.54	[-2.90; 3.98]	0.759
Overall effect	1.05 (0.35)	0.58 (0.36)	Difference	0.47	[-0.51; 1.44]	0.349
			Hedges G	0.04	[-0.04; 0.11]	
QLQ-C30 - Constipation						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1323	1263				
Baseline	1323 10.86 (20.76)	1263 11.30 (21.50)				
Week 13	1267 16.05 (25.66)	1198 11.77 (21.66)				
Week 25	1213 14.67 (24.47)	1151 11.35 (20.86)				
Week 37	1211 16.18 (25.58)	1144 11.92 (21.62)				
Week 49	1183 16.54 (26.19)	1140 12.66 (22.45)				
Week 61	1171 15.88 (25.90)	1114 12.48 (22.45)				
Week 73	1165 16.19 (25.68)	1103 12.90 (22.98)				
Week 85	1127 15.20 (24.32)	1085 11.77 (21.61)				
Week 97	1128 16.43 (25.55)	1065 13.36 (23.79)				
Week 121	1078 15.43 (25.25)	1049 12.49 (22.46)				
Week 145	1066 15.95 (24.60)	1009 13.18 (23.08)				
Week 169	904 12.79 (23.26)	872 12.77 (23.15)				
Week 193	764 14.40 (23.81)	734 12.85 (22.90)				
Week 217	478 12.06 (21.71)	482 12.24 (22.03)				
Week 241	91 12.45 (19.02)	96 11.11 (20.33)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	5.19 (0.58)	0.29 (0.60)	Difference	4.89	[3.25; 6.54]	<.001
			Hedges G	0.24	[0.16; 0.31]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Week 25	3.82 (0.59)	0.34 (0.61)	Difference	3.48	[1.82; 5.15]	<.001
			Hedges G	0.17	[0.09; 0.25]	
Week 37	5.41 (0.59)	0.54 (0.61)	Difference	4.86	[3.19; 6.53]	<.001
			Hedges G	0.24	[0.15; 0.32]	
Week 49	5.65 (0.60)	1.54 (0.61)	Difference	4.11	[2.43; 5.79]	<.001
			Hedges G	0.20	[0.12; 0.28]	
Week 61	5.09 (0.60)	1.42 (0.62)	Difference	3.67	[1.98; 5.35]	<.001
			Hedges G	0.18	[0.10; 0.26]	
Week 73	5.26 (0.60)	1.84 (0.62)	Difference	3.42	[1.72; 5.11]	<.001
			Hedges G	0.17	[0.08; 0.25]	
Week 85	4.34 (0.61)	0.52 (0.62)	Difference	3.82	[2.11; 5.53]	<.001
			Hedges G	0.19	[0.10; 0.27]	
Week 97	5.42 (0.61)	2.13 (0.63)	Difference	3.29	[1.58; 5.01]	<.001
			Hedges G	0.16	[0.08; 0.24]	
Week 121	4.37 (0.62)	1.34 (0.63)	Difference	3.03	[1.29; 4.77]	<.001
			Hedges G	0.15	[0.06; 0.23]	
Week 145	4.81 (0.63)	2.07 (0.64)	Difference	2.74	[0.99; 4.50]	0.002
			Hedges G	0.13	[0.05; 0.22]	
Week 169	1.44 (0.66)	1.93 (0.67)	Difference	-0.49	[-2.34; 1.36]	0.605
			Hedges G	-0.02	[-0.12; 0.07]	
Week 193	3.18 (0.70)	2.39 (0.72)	Difference	0.79	[-1.18; 2.76]	0.431
			Hedges G	0.04	[-0.06; 0.14]	
Week 217	1.77 (0.84)	2.40 (0.84)	Difference	-0.63	[-2.96; 1.71]	0.600
			Hedges G	-0.03	[-0.16; 0.09]	
Week 241	1.74 (1.76)	-0.14 (1.72)	Difference	1.87	[-2.95; 6.70]	0.447
			Hedges G	0.11	[-0.18; 0.40]	
Overall effect	4.11 (0.43)	1.33 (0.44)	Difference	2.78	[1.57; 3.98]	<.001
			Hedges G	0.18	[0.10; 0.26]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Esti- mate	[95% CI]	p-value
QLQ-C30 - Diarrhoea						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1322	1259				
Baseline	1322 5.77 (14.36)	1259 5.40 (14.22)				
Week 13	1260 5.66 (15.08)	1194 6.03 (15.10)				
Week 25	1214 5.66 (14.36)	1145 6.06 (15.40)				
Week 37	1206 6.30 (15.27)	1136 5.87 (14.90)				
Week 49	1181 6.44 (15.94)	1137 6.48 (15.83)				
Week 61	1165 6.18 (15.93)	1110 7.00 (16.51)				
Week 73	1163 7.31 (17.52)	1102 7.05 (16.50)				
Week 85	1125 6.55 (16.02)	1081 7.09 (16.82)				
Week 97	1122 6.51 (15.81)	1061 6.85 (16.42)				
Week 121	1077 6.44 (15.13)	1038 7.71 (17.09)				
Week 145	1060 6.29 (15.74)	1008 7.64 (17.77)				
Week 169	906 6.70 (15.96)	867 7.73 (17.42)				
Week 193	763 6.68 (16.66)	730 7.90 (17.11)				
Week 217	477 7.55 (16.98)	480 7.36 (16.86)				
Week 241	91 6.23 (17.15)	94 5.32 (13.21)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	0.18 (0.40)	0.62 (0.41)	Difference	-0.44	[-1.56; 0.68]	0.444
			Hedges G	-0.03	[-0.11; 0.05]	
Week 25	0.33 (0.40)	0.60 (0.41)	Difference	-0.27	[-1.40; 0.86]	0.641
			Hedges G	-0.02	[-0.10; 0.06]	
Week 37	0.89 (0.40)	0.44 (0.42)	Difference	0.45	[-0.69; 1.59]	0.439
			Hedges G	0.03	[-0.05; 0.11]	
Week 49	0.87 (0.43)	1.18 (0.44)	Difference	-0.31	[-1.51; 0.89]	0.614
			Hedges G	-0.02	[-0.10; 0.06]	
Week 61	0.77 (0.45)	1.63 (0.46)	Difference	-0.86	[-2.12; 0.40]	0.181
			Hedges G	-0.06	[-0.14; 0.03]	
Week 73	1.84 (0.47)	1.76 (0.49)	Difference	0.08	[-1.25; 1.41]	0.907
			Hedges G	0.00	[-0.08; 0.09]	
Week 85	1.32 (0.47)	1.89 (0.47)	Difference	-0.57	[-1.87; 0.73]	0.392
			Hedges G	-0.04	[-0.12; 0.05]	
Week 97	1.21 (0.45)	1.65 (0.46)	Difference	-0.43	[-1.69; 0.82]	0.498
			Hedges G	-0.03	[-0.11; 0.05]	
Week 121	1.24 (0.47)	2.48 (0.48)	Difference	-1.24	[-2.55; 0.07]	0.064
			Hedges G	-0.08	[-0.17; 0.00]	
Week 145	0.99 (0.49)	2.68 (0.50)	Difference	-1.69	[-3.07; -0.31]	0.016
			Hedges G	-0.11	[-0.19; -0.02]	
Week 169	1.55 (0.52)	2.83 (0.53)	Difference	-1.28	[-2.73; 0.16]	0.082
			Hedges G	-0.08	[-0.18; 0.01]	
Week 193	1.46 (0.55)	2.79 (0.57)	Difference	-1.33	[-2.89; 0.22]	0.092

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Week 217	2.58 (0.69)	2.11 (0.69)	Hedges G	-0.09	[-0.19; 0.01]	
			Difference	0.47	[-1.44; 2.39]	0.627
Week 241	1.06 (1.24)	1.79 (1.22)	Hedges G	0.03	[-0.10; 0.16]	
			Difference	-0.72	[-4.14; 2.70]	0.678
Overall effect	1.16 (0.28)	1.75 (0.28)	Difference	-0.58	[-1.36; 0.20]	0.144
			Hedges G	-0.06	[-0.13; 0.02]	

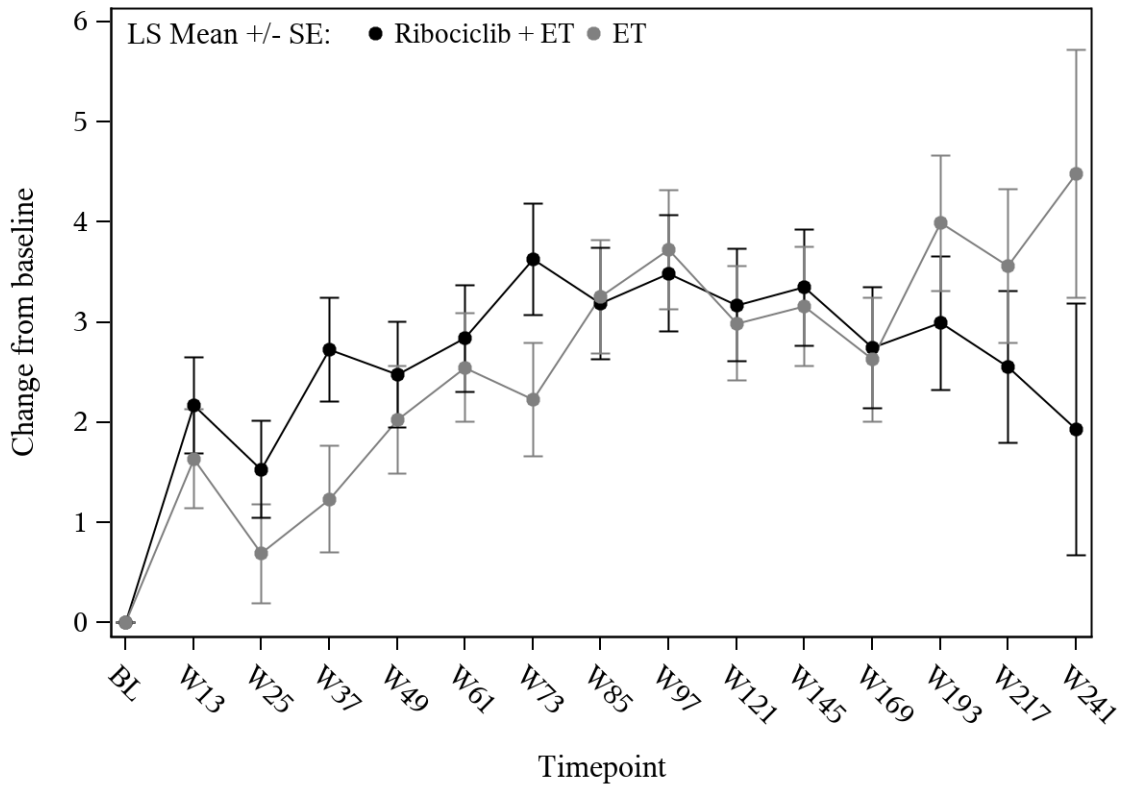
N: Number of patients
 N': Number of patients in the analysis
 CI: Confidence interval
 SD: Standard deviation
 LS Mean: Least square mean
 SE: Standard error
 MMRM: Mixed model for repeated measures
 ET: Endocrine therapy (Anastrozole/Letrozole)

Analysis methods:
 Adjusted mean (LS Mean) change from baseline and difference obtained from MMRM with unstructured covariance matrix:
 change from baseline = treatment + visit + treatment * visit + baseline value + AJCC Anatomic Stage + prior neo/adjuvant chemotherapy + region
 ET was the reference group for treatment group comparison.
 If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
 All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit.

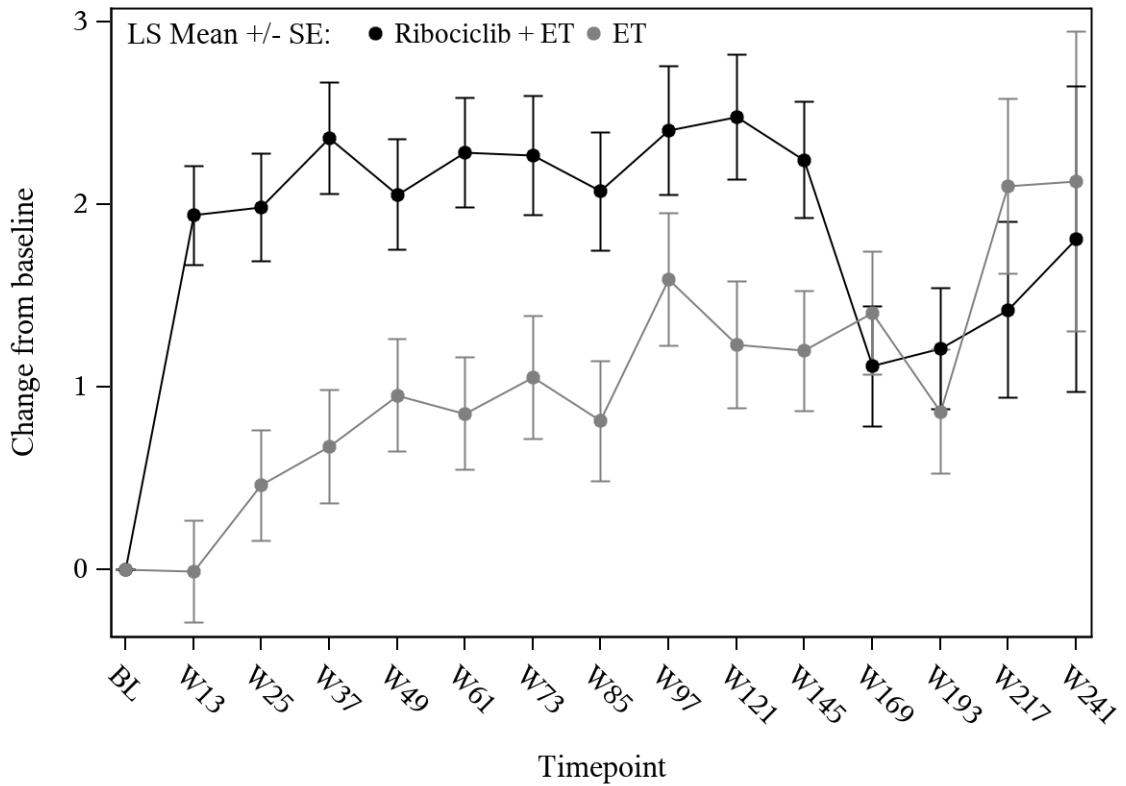
Figure 3-1.1 EORTC QLQ-C30 Symptoms: line chart of change from baseline (Full Analysis Set)

QLQ-C30 - Fatigue



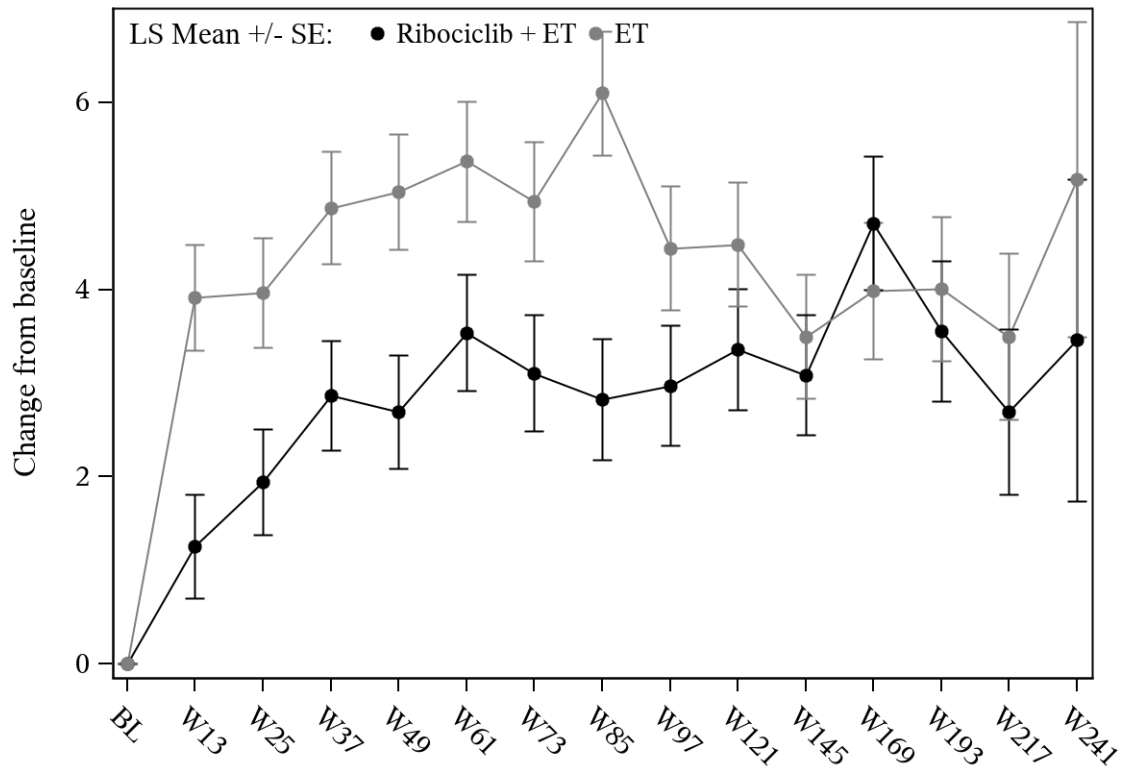
Ribociclib + ET	1325	1270	1219	1215	1188	1176	1168	1131	1129	1081	1068	908	767	478	91
ET	1263	1199	1154	1145	1143	1116	1105	1088	1068	1048	1012	873	735	483	95

QLQ-C30 - Nausea and Vomiting



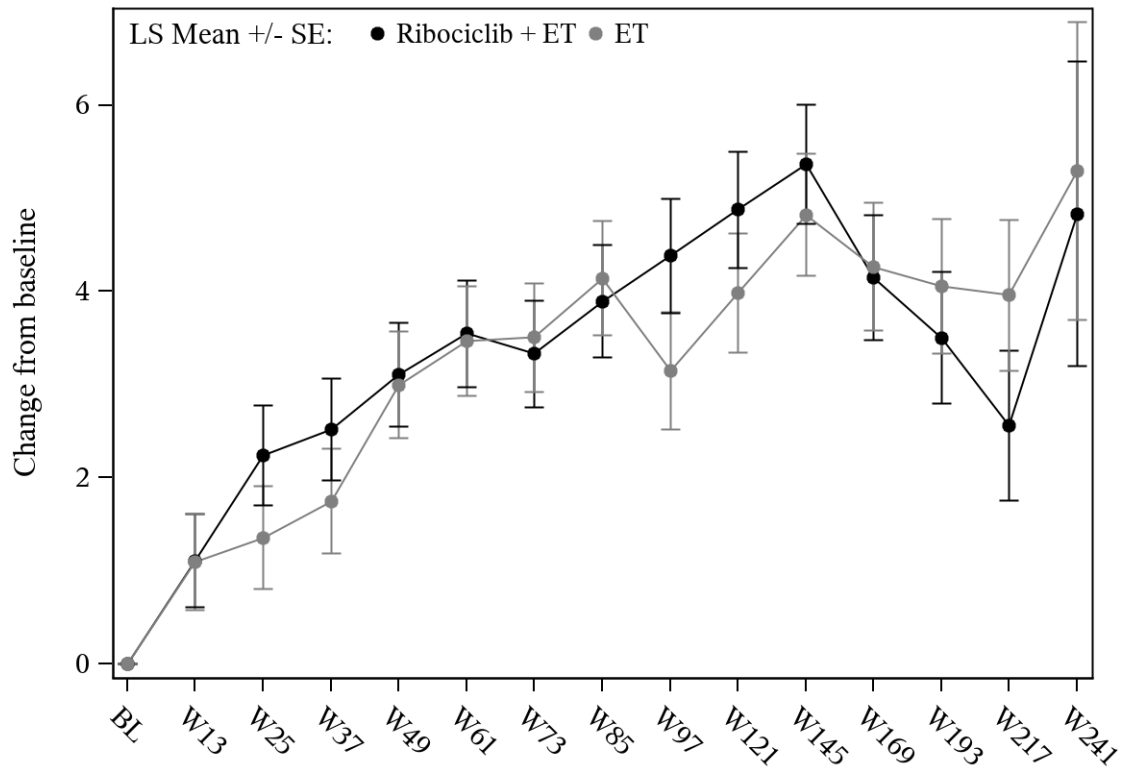
Ribociclib + ET	1325	1269	1219	1214	1187	1176	1168	1130	1130	1081	1068	909	767	478	91
ET	1263	1200	1153	1145	1142	1116	1106	1089	1067	1048	1012	873	735	483	96

QLQ-C30 - Pain



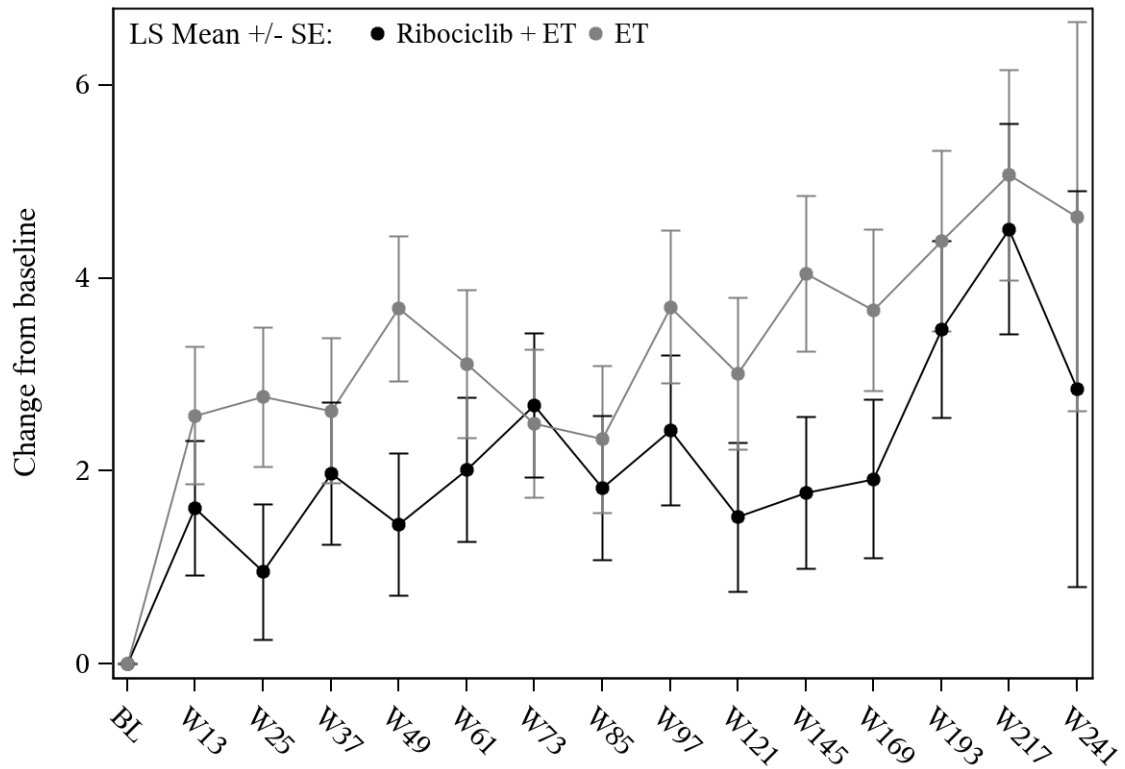
Ribociclib + ET	1328	1273	1223	1219	1192	1179	1171	1135	1133	1087	1071	912	769	480	91
ET	1263	1202	1154	1146	1144	1117	1107	1088	1071	1047	1016	872	736	484	96

QLQ-C30 - Dyspnoea



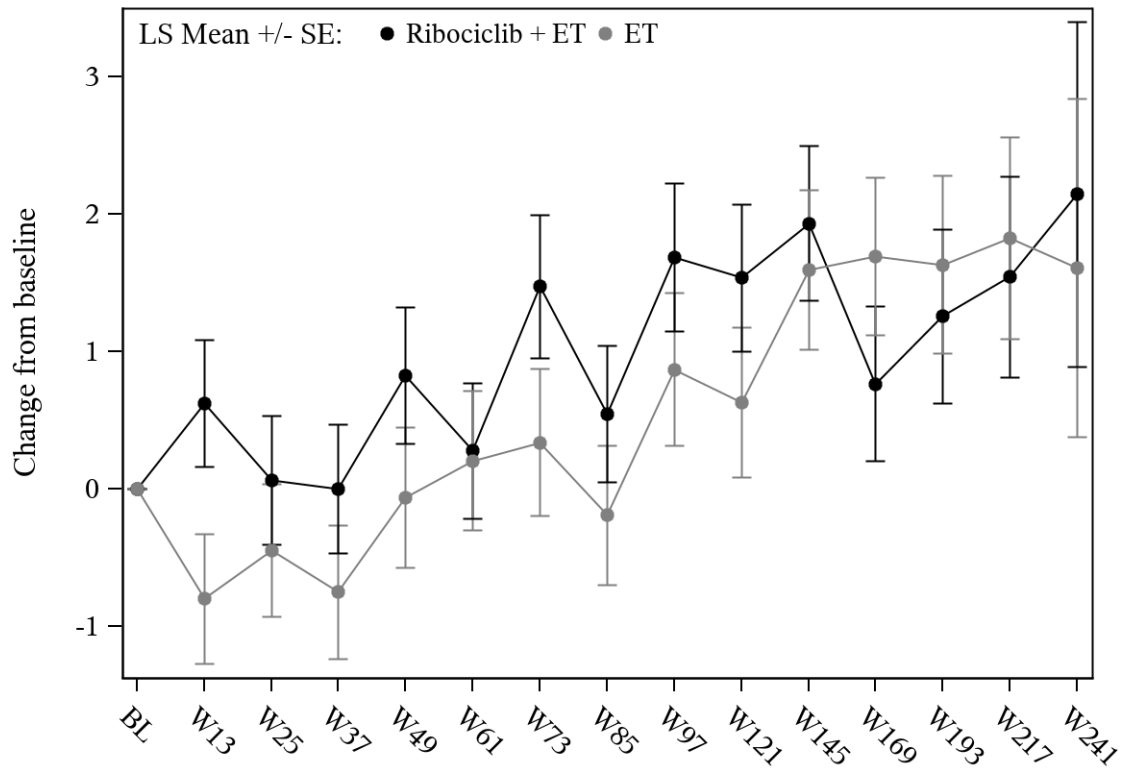
Ribociclib + ET	1322	1267	1216	1210	1181	1172	1164	1128	1126	1077	1062	908	764	477	91
ET	1260	1196	1148	1141	1140	1106	1101	1082	1064	1042	1007	869	732	480	96

QLQ-C30 - Insomnia



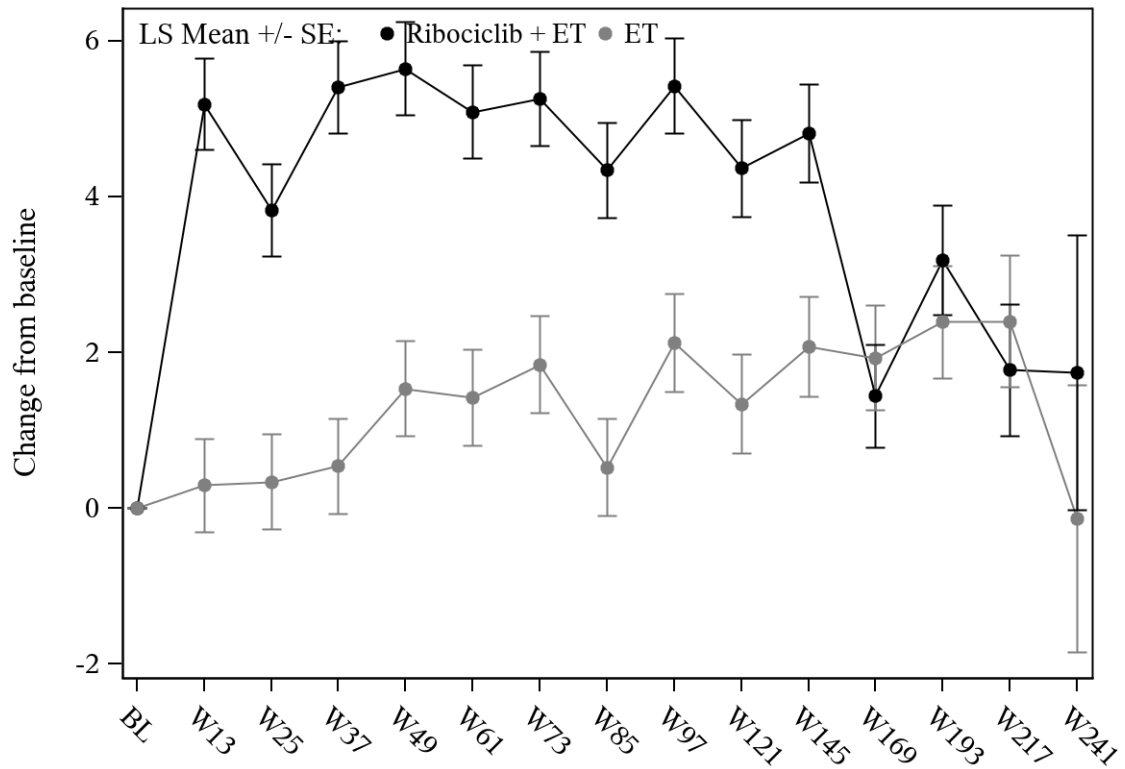
Ribociclib + ET	1322	1264	1210	1210	1181	1173	1164	1125	1126	1078	1063	907	763	475	91
ET	1261	1197	1151	1141	1141	1114	1103	1086	1067	1047	1009	871	735	483	95

QLQ-C30 - Appetite Loss



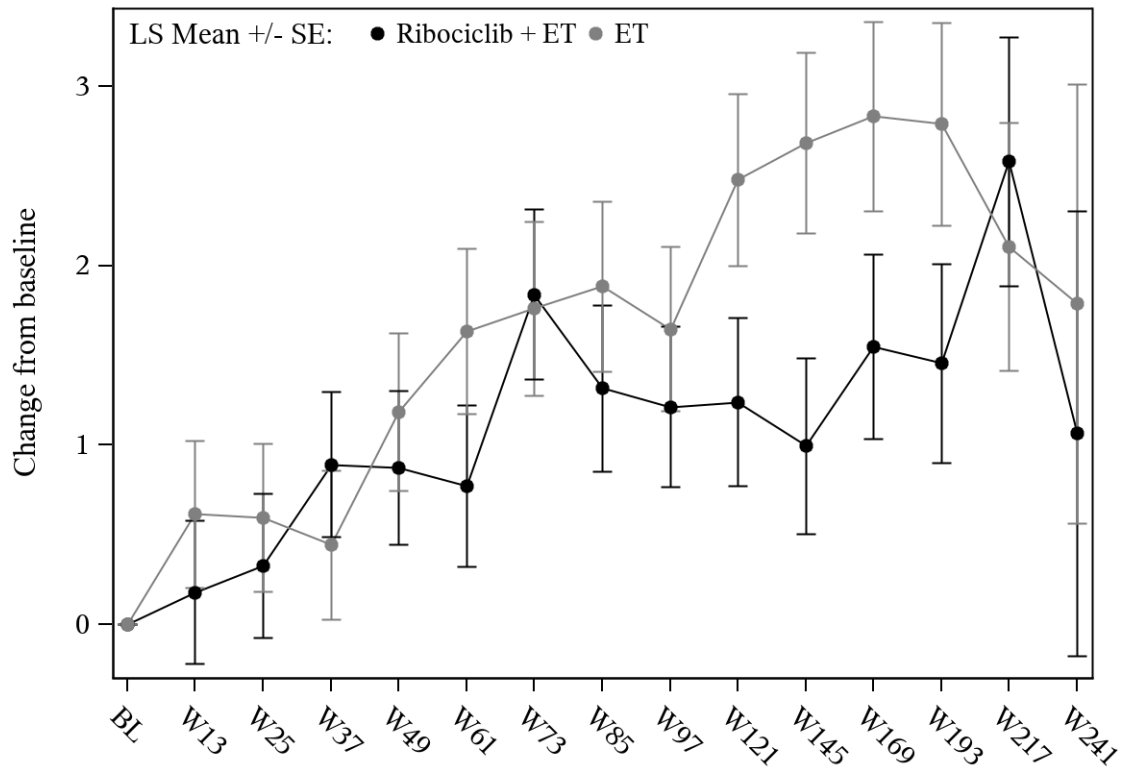
Ribociclib + ET	1325	1266	1215	1213	1184	1172	1167	1129	1129	1080	1065	909	764	477	91
ET	1261	1199	1152	1143	1143	1112	1101	1089	1067	1043	1007	871	734	482	96

QLQ-C30 - Constipation



Ribociclib + ET	1323	1267	1213	1211	1183	1171	1165	1127	1128	1078	1066	904	764	478	91
ET	1263	1198	1151	1144	1140	1114	1103	1085	1065	1049	1009	872	734	482	96

QLQ-C30 - Diarrhoea



Ribociclib + ET	1322	1260	1214	1206	1181	1165	1163	1125	1122	1077	1060	906	763	477	91
ET	1259	1194	1145	1136	1137	1110	1102	1081	1061	1038	1008	867	730	480	94

3-2 EORTC QLQ-C30 QoL

Table 3-2.0 EORTC QLQ-C30 QoL: return rates (Full Analysis Set)

	Treatment groups			
	Ribociclib + ET (N = 1424)		ET (N = 1420)	
	N' (%)	Returns n (%)	N' (%)	Returns n (%)
Baseline	1424 (100.0)	1387 (97.4)	1420 (100.0)	1377 (97.0)
Week 13	1424 (100.0)	1306 (91.7)	1420 (100.0)	1235 (87.0)
Week 25	1423 (99.9)	1248 (87.7)	1419 (99.9)	1180 (83.2)
Week 37	1420 (99.7)	1251 (88.1)	1410 (99.3)	1172 (83.1)
Week 49	1418 (99.6)	1224 (86.3)	1408 (99.2)	1169 (83.0)
Week 61	1414 (99.3)	1211 (85.6)	1404 (98.9)	1144 (81.5)
Week 73	1411 (99.1)	1202 (85.2)	1399 (98.5)	1130 (80.8)
Week 85	1409 (98.9)	1168 (82.9)	1392 (98.0)	1114 (80.0)
Week 97	1406 (98.7)	1165 (82.9)	1387 (97.7)	1096 (79.0)
Week 121	1393 (97.8)	1116 (80.1)	1382 (97.3)	1074 (77.7)
Week 145	1379 (96.8)	1100 (79.8)	1369 (96.4)	1039 (75.9)
Week 169	1370 (96.2)	939 (68.5)	1364 (96.1)	893 (65.5)
Week 193	1362 (95.6)	791 (58.1)	1357 (95.6)	750 (55.3)
Week 217	1352 (94.9)	497 (36.8)	1347 (94.9)	494 (36.7)
Week 241	1350 (94.8)	93 (6.9)	1346 (94.8)	96 (7.1)
Week 265	1350 (94.8)	6 (0.4)	1345 (94.7)	4 (0.3)

N': Number of patients who have not died until the respective visit
 ET: Endocrine therapy (Anastrozole/Letrozole)

The number of returns is the number of patients with non-missing data (i.e. at least one [sub-]score present) at the respective visit.

A patients is considered to have not died until the visit if no death was documented during the study, if returns for this PRO are present at the visit or, if no returns are present for this PRO and the patient died, if the death date is after the scheduled visit date.

Percentages of returns refer to N' per group. For N' percentages refer to N per group.

Table 3-2.1 EORTC QLQ-C30 QoL: change from baseline analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Esti- mate	[95% CI]	p-value
QLQ-C30 - Global Health/QoL						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1322	1258				
Baseline	1322 73.95 (17.71)	1258 73.19 (18.37)				
Week 13	1262 72.64 (17.88)	1195 72.22 (18.56)				
Week 25	1215 72.24 (17.88)	1145 72.50 (18.94)				
Week 37	1212 71.56 (18.13)	1135 71.93 (19.44)				
Week 49	1183 71.14 (18.28)	1134 71.18 (19.14)				
Week 61	1166 71.13 (18.29)	1107 70.99 (19.72)				
Week 73	1163 71.33 (18.41)	1103 71.54 (18.43)				
Week 85	1128 71.63 (18.13)	1080 70.98 (18.95)				
Week 97	1124 70.69 (18.42)	1062 70.57 (19.29)				
Week 121	1078 71.37 (18.65)	1040 70.59 (18.49)				
Week 145	1060 71.16 (18.38)	1006 71.38 (18.16)				
Week 169	906 71.52 (18.71)	865 71.79 (18.99)				
Week 193	763 72.48 (18.21)	729 70.95 (19.01)				
Week 217	478 70.94 (18.74)	479 71.19 (19.64)				
Week 241	91 72.71 (15.77)	93 71.42 (18.85)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	-1.19 (0.46)	-1.08 (0.47)	Difference	-0.11	[-1.40; 1.17]	0.861
			Hedges G	-0.01	[-0.09; 0.07]	
Week 25	-1.73 (0.46)	-0.95 (0.48)	Difference	-0.79	[-2.09; 0.52]	0.238
			Hedges G	-0.05	[-0.13; 0.03]	
Week 37	-2.55 (0.46)	-1.52 (0.48)	Difference	-1.04	[-2.34; 0.27]	0.120
			Hedges G	-0.06	[-0.15; 0.02]	
Week 49	-2.89 (0.47)	-2.41 (0.48)	Difference	-0.48	[-1.80; 0.83]	0.471
			Hedges G	-0.03	[-0.11; 0.05]	
Week 61	-3.16 (0.47)	-2.62 (0.48)	Difference	-0.54	[-1.86; 0.79]	0.427
			Hedges G	-0.03	[-0.12; 0.05]	
Week 73	-2.99 (0.47)	-2.21 (0.48)	Difference	-0.78	[-2.10; 0.55]	0.250
			Hedges G	-0.05	[-0.13; 0.03]	
Week 85	-2.61 (0.48)	-2.68 (0.49)	Difference	0.07	[-1.26; 1.41]	0.916
			Hedges G	0.00	[-0.08; 0.09]	
Week 97	-3.53 (0.48)	-3.12 (0.49)	Difference	-0.41	[-1.75; 0.93]	0.549
			Hedges G	-0.03	[-0.11; 0.06]	
Week 121	-3.07 (0.48)	-3.14 (0.49)	Difference	0.07	[-1.28; 1.42]	0.921
			Hedges G	0.00	[-0.08; 0.09]	
Week 145	-3.35 (0.48)	-2.23 (0.50)	Difference	-1.12	[-2.48; 0.24]	0.106
			Hedges G	-0.07	[-0.16; 0.02]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Week 169	-3.15 (0.51)	-1.96 (0.52)	Difference	-1.19	[-2.62; 0.24]	0.103
			Hedges G	-0.08	[-0.17; 0.02]	
Week 193	-2.01 (0.54)	-2.65 (0.55)	Difference	0.64	[-0.87; 2.15]	0.406
			Hedges G	0.04	[-0.06; 0.14]	
Week 217	-4.06 (0.64)	-2.98 (0.64)	Difference	-1.09	[-2.86; 0.68]	0.229
			Hedges G	-0.08	[-0.20; 0.05]	
Week 241	-2.85 (1.31)	-3.61 (1.30)	Difference	0.76	[-2.86; 4.39]	0.680
			Hedges G	0.06	[-0.23; 0.35]	
Overall effect	-2.80 (0.35)	-2.37 (0.35)	Difference	-0.43	[-1.40; 0.54]	0.388
			Hedges G	-0.03	[-0.11; 0.04]	
QLQ-C30 - Physical Functioning						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1326	1264				
Baseline	1326 84.54 (15.15)	1264 83.48 (15.51)				
Week 13	1270 83.56 (15.79)	1201 81.99 (16.54)				
Week 25	1217 83.69 (15.11)	1155 82.02 (17.06)				
Week 37	1213 83.39 (16.10)	1144 81.95 (17.02)				
Week 49	1187 83.58 (15.88)	1145 81.51 (18.08)				
Week 61	1174 83.26 (15.85)	1114 81.34 (17.88)				
Week 73	1167 82.40 (16.94)	1105 81.96 (17.21)				
Week 85	1128 82.84 (16.75)	1088 81.61 (17.52)				
Week 97	1127 82.19 (17.83)	1069 80.89 (18.51)				
Week 121	1080 82.61 (16.91)	1045 81.35 (17.43)				
Week 145	1067 82.77 (17.52)	1013 81.34 (18.20)				
Week 169	908 82.73 (17.33)	872 81.12 (18.27)				
Week 193	766 82.73 (17.45)	736 80.83 (18.24)				
Week 217	478 83.69 (16.62)	480 80.72 (18.56)				
Week 241	91 80.27 (17.43)	96 79.17 (21.33)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	-0.97 (0.34)	-1.53 (0.35)	Difference	0.56	[-0.40; 1.51]	0.254
			Hedges G	0.05	[-0.03; 0.12]	
Week 25	-0.77 (0.35)	-1.63 (0.36)	Difference	0.86	[-0.12; 1.85]	0.086
			Hedges G	0.07	[-0.01; 0.15]	
Week 37	-1.20 (0.36)	-1.79 (0.37)	Difference	0.59	[-0.43; 1.61]	0.257
			Hedges G	0.05	[-0.03; 0.13]	
Week 49	-1.01 (0.38)	-2.26 (0.39)	Difference	1.25	[0.19; 2.32]	0.021
			Hedges G	0.10	[0.01; 0.18]	
Week 61	-1.51 (0.39)	-2.70 (0.40)	Difference	1.18	[0.10; 2.27]	0.033
			Hedges G	0.09	[0.01; 0.17]	
Week 73	-2.31 (0.40)	-2.19 (0.41)	Difference	-0.12	[-1.25; 1.01]	0.835
			Hedges G	-0.01	[-0.09; 0.07]	
Week 85	-1.97 (0.41)	-2.66 (0.42)	Difference	0.69	[-0.46; 1.83]	0.242

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Week 97	-2.76 (0.44)	-3.33 (0.45)	Hedges G	0.05	[-0.03; 0.13]	
			Difference	0.57	[-0.68; 1.81]	0.372
Week 121	-2.43 (0.41)	-2.90 (0.42)	Hedges G	0.04	[-0.05; 0.12]	
			Difference	0.47	[-0.69; 1.63]	0.427
Week 145	-2.48 (0.45)	-2.93 (0.46)	Hedges G	0.03	[-0.05; 0.12]	
			Difference	0.45	[-0.80; 1.71]	0.480
Week 169	-2.84 (0.47)	-3.24 (0.48)	Hedges G	0.03	[-0.06; 0.12]	
			Difference	0.40	[-0.91; 1.71]	0.550
Week 193	-2.59 (0.50)	-3.46 (0.51)	Hedges G	0.03	[-0.06; 0.12]	
			Difference	0.87	[-0.52; 2.26]	0.219
Week 217	-2.53 (0.55)	-4.34 (0.56)	Hedges G	0.06	[-0.04; 0.16]	
			Difference	1.81	[0.26; 3.35]	0.022
Week 241	-4.77 (1.00)	-4.21 (0.99)	Hedges G	0.15	[0.02; 0.28]	
			Difference	-0.56	[-3.32; 2.20]	0.691
Overall effect	-2.15 (0.33)	-2.80 (0.33)	Difference	0.64	[-0.27; 1.56]	0.168
			Hedges G	0.05	[-0.02; 0.13]	
QLQ-C30 - Role Functioning						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1325	1264				
Baseline	1325 84.82 (20.96)	1264 84.26 (21.47)				
Week 13	1269 83.82 (21.70)	1200 82.56 (22.52)				
Week 25	1218 83.35 (21.72)	1154 82.05 (22.65)				
Week 37	1214 83.07 (21.79)	1145 82.17 (22.43)				
Week 49	1186 82.69 (21.69)	1145 82.18 (22.91)				
Week 61	1175 82.77 (21.56)	1116 81.15 (23.37)				
Week 73	1166 82.10 (22.68)	1107 81.20 (23.13)				
Week 85	1131 82.48 (21.78)	1089 81.62 (22.52)				
Week 97	1128 81.04 (23.34)	1067 80.85 (23.79)				
Week 121	1081 81.85 (22.40)	1049 81.47 (22.07)				
Week 145	1065 82.02 (22.43)	1014 81.08 (22.79)				
Week 169	908 81.53 (22.49)	874 81.46 (22.75)				
Week 193	765 81.81 (22.09)	737 80.46 (22.88)				
Week 217	479 83.26 (22.30)	483 81.78 (21.75)				
Week 241	91 83.88 (19.79)	95 79.82 (24.78)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	-1.16 (0.53)	-1.81 (0.55)	Difference	0.65	[-0.86; 2.15]	0.399
			Hedges G	0.03	[-0.04; 0.11]	
Week 25	-1.67 (0.56)	-2.36 (0.57)	Difference	0.69	[-0.88; 2.26]	0.388
			Hedges G	0.04	[-0.05; 0.12]	
Week 37	-1.93 (0.55)	-2.43 (0.57)	Difference	0.51	[-1.05; 2.06]	0.523
			Hedges G	0.03	[-0.05; 0.11]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Week 49	-2.31 (0.57)	-2.46 (0.58)	Difference	0.15	[-1.44; 1.73]	0.856
			Hedges G	0.01	[-0.07; 0.09]	
Week 61	-2.34 (0.58)	-3.64 (0.59)	Difference	1.29	[-0.33; 2.91]	0.118
			Hedges G	0.07	[-0.02; 0.15]	
Week 73	-2.98 (0.60)	-3.70 (0.61)	Difference	0.72	[-0.96; 2.41]	0.400
			Hedges G	0.04	[-0.05; 0.12]	
Week 85	-2.69 (0.59)	-3.43 (0.60)	Difference	0.74	[-0.92; 2.40]	0.384
			Hedges G	0.04	[-0.05; 0.12]	
Week 97	-4.18 (0.63)	-4.27 (0.64)	Difference	0.09	[-1.67; 1.86]	0.918
			Hedges G	0.00	[-0.08; 0.09]	
Week 121	-3.44 (0.60)	-3.60 (0.61)	Difference	0.16	[-1.53; 1.85]	0.854
			Hedges G	0.01	[-0.08; 0.09]	
Week 145	-3.54 (0.63)	-3.97 (0.64)	Difference	0.42	[-1.33; 2.18]	0.638
			Hedges G	0.02	[-0.07; 0.11]	
Week 169	-4.17 (0.65)	-3.62 (0.67)	Difference	-0.55	[-2.38; 1.29]	0.560
			Hedges G	-0.03	[-0.12; 0.07]	
Week 193	-3.72 (0.69)	-4.67 (0.70)	Difference	0.95	[-0.97; 2.87]	0.333
			Hedges G	0.05	[-0.05; 0.15]	
Week 217	-3.40 (0.78)	-3.88 (0.79)	Difference	0.48	[-1.70; 2.65]	0.666
			Hedges G	0.03	[-0.10; 0.15]	
Week 241	-3.97 (1.49)	-5.67 (1.47)	Difference	1.70	[-2.40; 5.80]	0.416
			Hedges G	0.12	[-0.17; 0.41]	
Overall effect	-2.96 (0.43)	-3.54 (0.44)	Difference	0.57	[-0.63; 1.78]	0.353
			Hedges G	0.04	[-0.04; 0.11]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-C30 - Emotional Functioning						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1323	1259				
Baseline	1323 80.35 (19.56)	1259 80.56 (19.54)				
Week 13	1264 79.36 (19.74)	1195 78.81 (20.75)				
Week 25	1217 78.91 (20.54)	1147 79.31 (20.91)				
Week 37	1214 79.08 (20.35)	1138 78.28 (20.96)				
Week 49	1184 78.20 (20.68)	1136 77.00 (21.72)				
Week 61	1169 78.21 (21.18)	1110 76.85 (21.63)				
Week 73	1166 77.13 (21.08)	1104 78.03 (21.61)				
Week 85	1130 77.49 (21.65)	1081 76.68 (22.38)				
Week 97	1126 77.32 (21.69)	1062 76.45 (22.67)				
Week 121	1081 77.75 (20.91)	1040 76.78 (22.05)				
Week 145	1063 77.94 (21.07)	1009 76.37 (22.80)				
Week 169	907 77.97 (21.02)	867 77.10 (22.07)				
Week 193	764 78.48 (21.25)	730 76.31 (22.56)				
Week 217	478 79.70 (20.46)	480 77.34 (22.17)				
Week 241	91 81.41 (17.35)	94 78.19 (22.14)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	-1.10 (0.45)	-1.68 (0.46)	Difference	0.58	[-0.69; 1.84]	0.369
			Hedges G	0.04	[-0.04; 0.12]	
Week 25	-1.83 (0.48)	-1.38 (0.50)	Difference	-0.45	[-1.80; 0.91]	0.518
			Hedges G	-0.03	[-0.11; 0.05]	
Week 37	-1.70 (0.48)	-2.49 (0.49)	Difference	0.79	[-0.55; 2.13]	0.249
			Hedges G	0.05	[-0.03; 0.13]	
Week 49	-2.49 (0.50)	-3.86 (0.51)	Difference	1.37	[-0.03; 2.78]	0.056
			Hedges G	0.08	[-0.00; 0.16]	
Week 61	-2.64 (0.51)	-3.94 (0.52)	Difference	1.30	[-0.13; 2.73]	0.074
			Hedges G	0.07	[-0.01; 0.16]	
Week 73	-3.67 (0.51)	-2.97 (0.53)	Difference	-0.70	[-2.15; 0.75]	0.342
			Hedges G	-0.04	[-0.12; 0.04]	
Week 85	-3.37 (0.54)	-4.20 (0.55)	Difference	0.82	[-0.70; 2.35]	0.287
			Hedges G	0.05	[-0.04; 0.13]	
Week 97	-3.36 (0.55)	-4.64 (0.57)	Difference	1.28	[-0.27; 2.84]	0.106
			Hedges G	0.07	[-0.01; 0.15]	
Week 121	-3.11 (0.54)	-4.04 (0.56)	Difference	0.92	[-0.61; 2.45]	0.237
			Hedges G	0.05	[-0.03; 0.14]	
Week 145	-3.07 (0.56)	-4.57 (0.58)	Difference	1.50	[-0.09; 3.08]	0.064
			Hedges G	0.08	[-0.00; 0.17]	
Week 169	-2.98 (0.59)	-4.14 (0.61)	Difference	1.16	[-0.51; 2.82]	0.173
			Hedges G	0.06	[-0.03; 0.16]	
Week 193	-2.52 (0.62)	-5.07 (0.64)	Difference	2.55	[0.80; 4.30]	0.004

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Esti- mate	[95% CI]	p-value
Week 217	-2.95 (0.72)	-4.71 (0.72)	Hedges G	0.15	[0.05; 0.25]	
			Difference	1.76	[-0.24; 3.76]	0.085
Week 241	-4.65 (1.09)	-5.46 (1.08)	Hedges G	0.11	[-0.02; 0.24]	
			Difference	0.81	[-2.20; 3.81]	0.599
Overall effect	-2.82 (0.40)	-3.80 (0.41)	Difference	0.98	[-0.14; 2.10]	0.088
			Hedges G	0.07	[-0.01; 0.14]	
QLQ-C30 - Cognitive Functioning						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1322	1260				
Baseline	1322 85.20 (18.71)	1260 83.96 (19.44)				
Week 13	1263 83.04 (19.79)	1196 81.40 (20.25)				
Week 25	1216 82.85 (20.16)	1148 81.55 (20.89)				
Week 37	1213 81.77 (20.00)	1139 81.08 (20.64)				
Week 49	1183 81.59 (20.40)	1137 79.64 (21.77)				
Week 61	1168 81.45 (20.74)	1111 79.54 (21.63)				
Week 73	1165 80.86 (20.58)	1105 80.47 (20.99)				
Week 85	1129 80.38 (21.43)	1081 79.09 (21.74)				
Week 97	1125 79.93 (21.47)	1064 78.90 (22.03)				
Week 121	1080 80.00 (20.63)	1042 79.01 (22.29)				
Week 145	1062 80.46 (21.08)	1010 78.35 (22.22)				
Week 169	906 80.04 (21.05)	869 79.23 (21.06)				
Week 193	764 80.10 (21.28)	731 79.23 (21.33)				
Week 217	478 81.66 (19.17)	481 78.83 (22.27)				
Week 241	91 84.62 (16.15)	94 79.08 (20.15)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	-2.05 (0.44)	-2.80 (0.45)	Difference	0.75	[-0.49; 1.99]	0.237
			Hedges G	0.05	[-0.03; 0.13]	
Week 25	-2.54 (0.48)	-2.85 (0.49)	Difference	0.31	[-1.04; 1.66]	0.657
			Hedges G	0.02	[-0.06; 0.10]	
Week 37	-3.61 (0.48)	-3.44 (0.49)	Difference	-0.17	[-1.52; 1.18]	0.808
			Hedges G	-0.01	[-0.09; 0.07]	
Week 49	-3.70 (0.51)	-4.85 (0.52)	Difference	1.14	[-0.28; 2.57]	0.116
			Hedges G	0.07	[-0.02; 0.15]	
Week 61	-4.01 (0.51)	-4.93 (0.52)	Difference	0.92	[-0.51; 2.34]	0.207
			Hedges G	0.05	[-0.03; 0.14]	
Week 73	-4.52 (0.51)	-4.17 (0.52)	Difference	-0.34	[-1.78; 1.09]	0.639
			Hedges G	-0.02	[-0.10; 0.06]	
Week 85	-5.06 (0.55)	-5.44 (0.56)	Difference	0.38	[-1.15; 1.91]	0.624
			Hedges G	0.02	[-0.06; 0.10]	
Week 97	-5.51 (0.55)	-5.89 (0.56)	Difference	0.38	[-1.15; 1.91]	0.627
			Hedges G	0.02	[-0.06; 0.10]	

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Week 121	-5.55 (0.54)	-5.54 (0.55)	Difference	-0.01	[-1.53; 1.51]	0.989
			Hedges G	-0.00	[-0.09; 0.08]	
Week 145	-5.12 (0.56)	-6.33 (0.57)	Difference	1.21	[-0.35; 2.78]	0.129
			Hedges G	0.07	[-0.02; 0.15]	
Week 169	-5.84 (0.59)	-5.78 (0.60)	Difference	-0.06	[-1.70; 1.59]	0.946
			Hedges G	-0.00	[-0.10; 0.09]	
Week 193	-5.71 (0.60)	-5.97 (0.62)	Difference	0.27	[-1.43; 1.96]	0.759
			Hedges G	0.02	[-0.09; 0.12]	
Week 217	-5.25 (0.71)	-6.82 (0.72)	Difference	1.57	[-0.41; 3.55]	0.120
			Hedges G	0.10	[-0.03; 0.23]	
Week 241	-4.69 (1.13)	-7.07 (1.12)	Difference	2.39	[-0.73; 5.50]	0.133
			Hedges G	0.22	[-0.07; 0.51]	
Overall effect	-4.51 (0.40)	-5.14 (0.41)	Difference	0.62	[-0.50; 1.75]	0.278
			Hedges G	0.04	[-0.03; 0.12]	
QLQ-C30 - Social Functioning						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1323	1259				
Baseline	1323 85.90 (20.41)	1259 84.56 (22.23)				
Week 13	1264 86.89 (20.41)	1194 87.09 (20.22)				
Week 25	1217 86.76 (20.36)	1147 86.34 (21.27)				
Week 37	1213 87.15 (20.10)	1137 87.06 (20.36)				
Week 49	1181 86.57 (20.51)	1135 86.34 (21.36)				
Week 61	1169 86.67 (20.60)	1110 86.01 (21.04)				
Week 73	1166 86.94 (20.20)	1104 86.65 (20.81)				
Week 85	1130 86.28 (20.42)	1081 85.46 (21.91)				
Week 97	1126 86.00 (21.11)	1060 85.93 (22.04)				
Week 121	1081 85.88 (21.07)	1038 86.05 (20.94)				
Week 145	1062 86.72 (20.31)	1009 85.89 (21.78)				
Week 169	907 86.66 (20.26)	867 86.14 (21.67)				
Week 193	764 87.09 (20.35)	730 85.71 (21.39)				
Week 217	478 88.01 (18.42)	480 86.74 (20.72)				
Week 241	91 87.91 (18.77)	94 84.93 (22.41)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	1.09 (0.53)	1.86 (0.55)	Difference	-0.76	[-2.26; 0.74]	0.319
			Hedges G	-0.04	[-0.12; 0.04]	
Week 25	0.73 (0.54)	1.07 (0.55)	Difference	-0.34	[-1.85; 1.17]	0.660
			Hedges G	-0.02	[-0.10; 0.06]	
Week 37	0.99 (0.54)	1.54 (0.56)	Difference	-0.55	[-2.07; 0.97]	0.479
			Hedges G	-0.03	[-0.11; 0.05]	
Week 49	0.37 (0.55)	0.73 (0.56)	Difference	-0.36	[-1.90; 1.18]	0.645
			Hedges G	-0.02	[-0.10; 0.06]	
Week 61	0.51 (0.55)	0.48 (0.57)	Difference	0.03	[-1.52; 1.58]	0.973

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Week 73	0.89 (0.55)	1.05 (0.57)	Hedges G	0.00	[-0.08; 0.08]	
			Difference	-0.15	[-1.71; 1.40]	0.847
Week 85	0.19 (0.56)	-0.07 (0.57)	Hedges G	-0.01	[-0.09; 0.07]	
			Difference	0.27	[-1.30; 1.84]	0.737
Week 97	-0.11 (0.56)	0.25 (0.58)	Hedges G	0.01	[-0.07; 0.10]	
			Difference	-0.36	[-1.94; 1.22]	0.656
Week 121	-0.44 (0.57)	0.42 (0.58)	Hedges G	-0.02	[-0.10; 0.06]	
			Difference	-0.85	[-2.46; 0.75]	0.296
Week 145	0.36 (0.58)	0.27 (0.59)	Hedges G	-0.05	[-0.13; 0.04]	
			Difference	0.09	[-1.53; 1.71]	0.914
Week 169	0.27 (0.61)	0.33 (0.63)	Hedges G	0.00	[-0.08; 0.09]	
			Difference	-0.06	[-1.77; 1.66]	0.947
Week 193	0.48 (0.66)	-0.11 (0.68)	Hedges G	-0.00	[-0.10; 0.09]	
			Difference	0.59	[-1.26; 2.44]	0.532
Week 217	0.88 (0.81)	0.44 (0.81)	Hedges G	0.03	[-0.07; 0.13]	
			Difference	0.44	[-1.79; 2.67]	0.699
Week 241	-0.48 (1.69)	-1.83 (1.67)	Hedges G	0.02	[-0.10; 0.15]	
			Difference	1.34	[-3.32; 6.00]	0.572
Overall effect	0.41 (0.30)	0.46 (0.31)	Difference	-0.05	[-0.90; 0.80]	0.911
			Hedges G	-0.00	[-0.08; 0.07]	

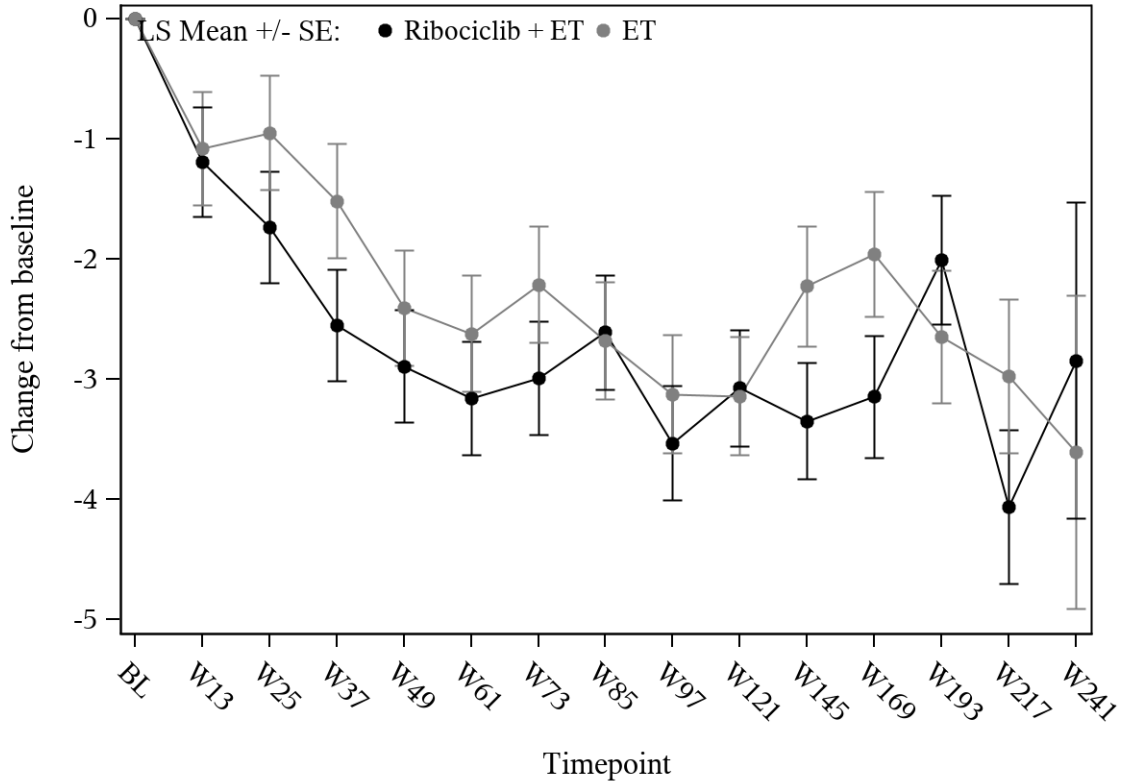
N: Number of patients
 N': Number of patients in the analysis
 CI: Confidence interval
 SD: Standard deviation
 LS Mean: Least square mean
 SE: Standard error
 MMRM: Mixed model for repeated measures
 ET: Endocrine therapy (Anastrozole/Letrozole)

Analysis methods:
 Adjusted mean (LS Mean) change from baseline and difference obtained from MMRM with unstructured covariance matrix:
 change from baseline = treatment + visit + treatment * visit + baseline value + AJCC Anatomic Stage + prior neo/adjuvant chemotherapy + region
 ET was the reference group for treatment group comparison.
 If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
 All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit.

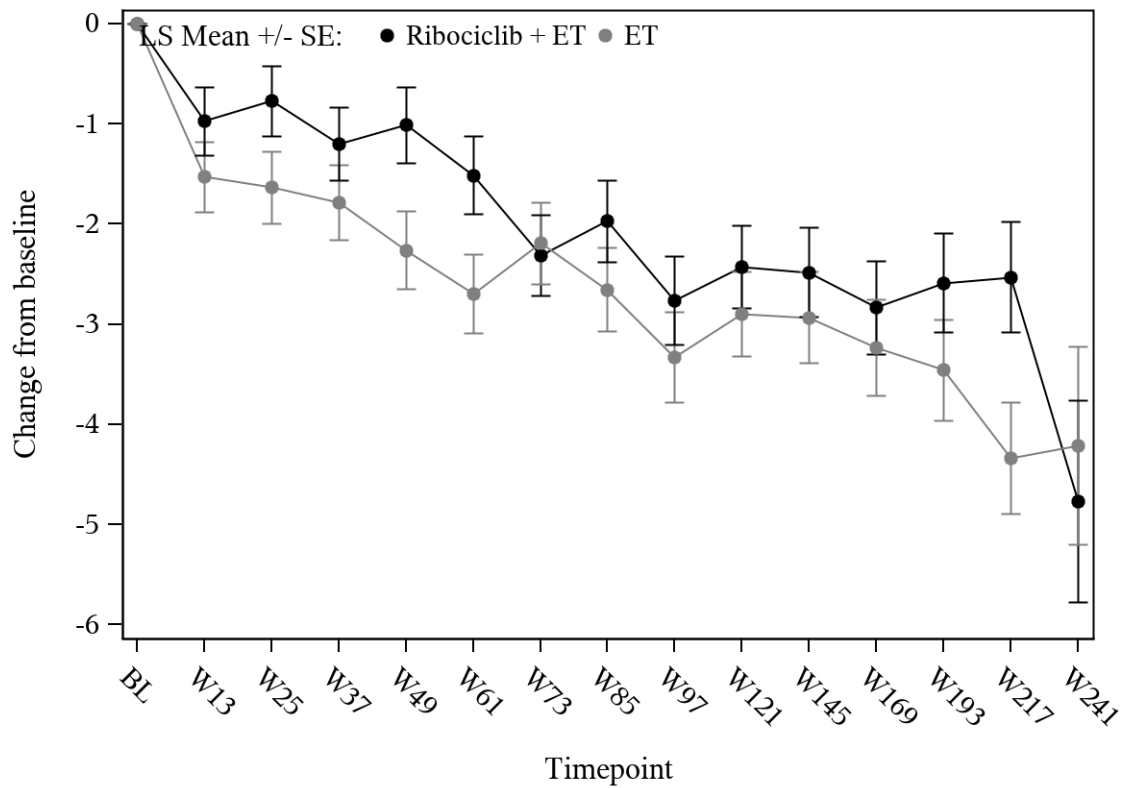
Figure 3-2.1 EORTC QLQ-C30 QoL: line chart of change from baseline (Full Analysis Set)

QLQ-C30 - Global Health/QoL



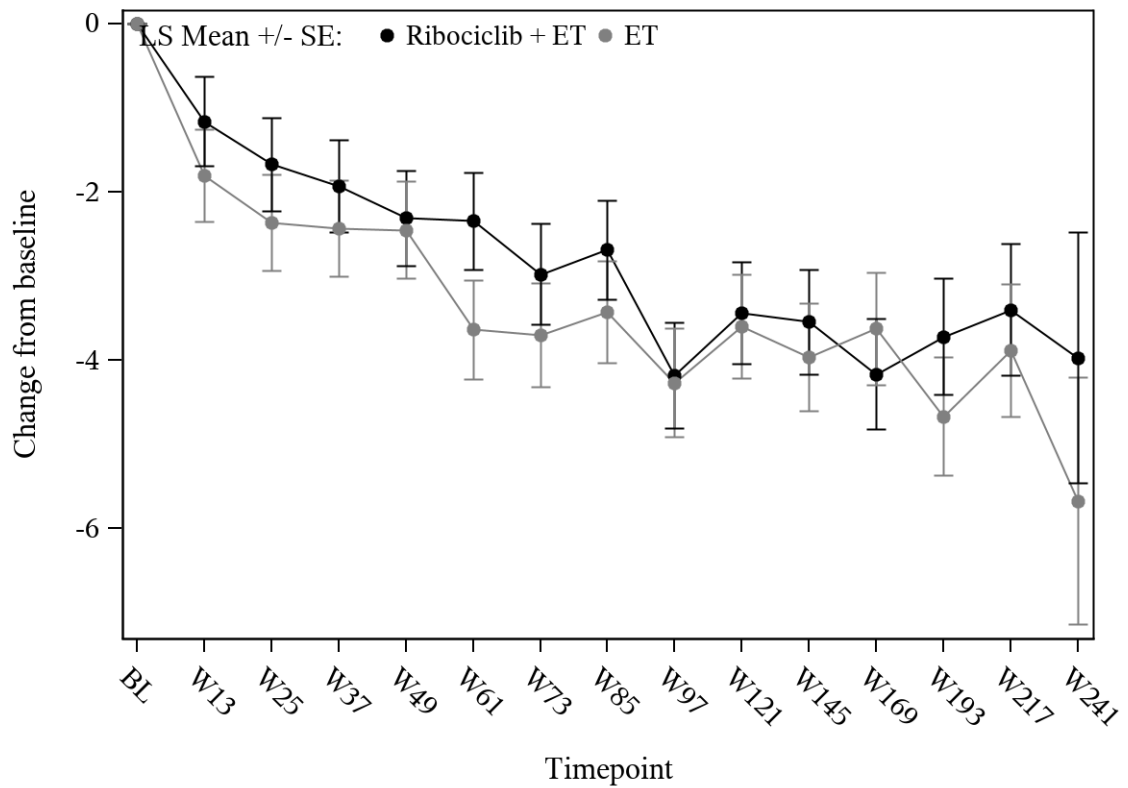
Ribociclib + ET	1322	1262	1215	1212	1183	1166	1163	1128	1124	1078	1060	906	763	478	91
ET	1258	1195	1145	1135	1134	1107	1103	1080	1062	1040	1006	865	729	479	93

QLQ-C30 - Physical Functioning



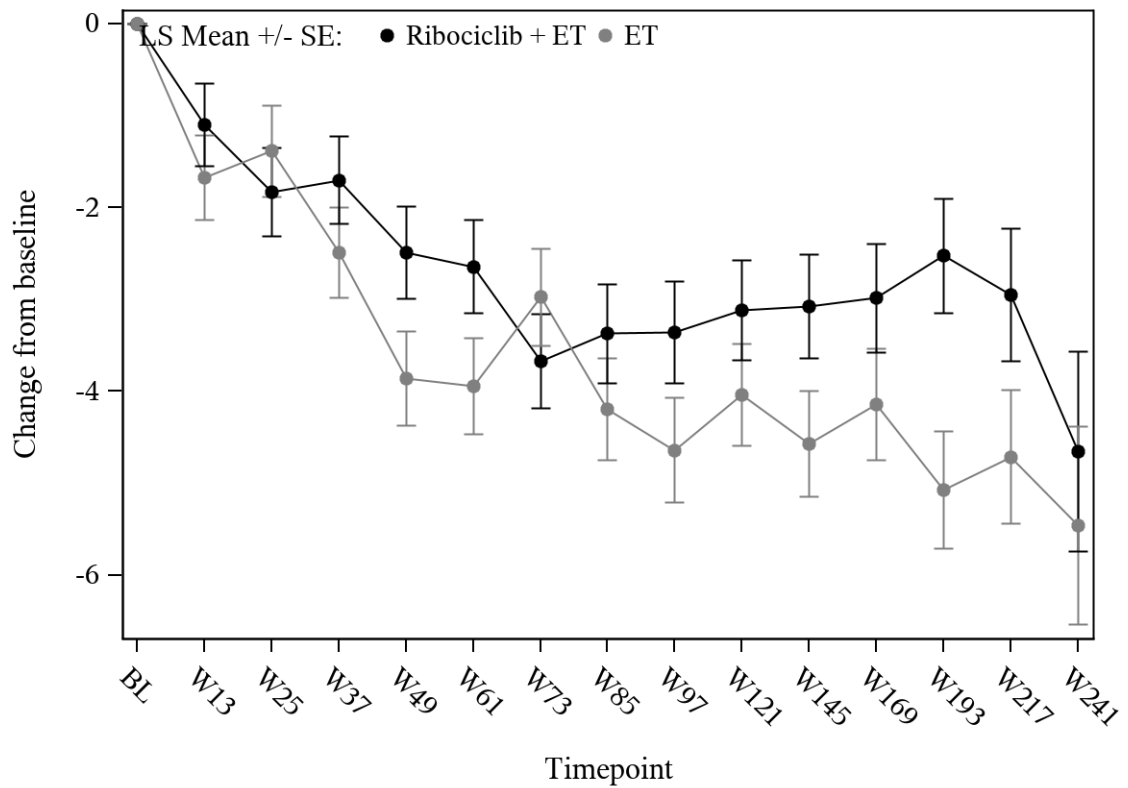
Ribociclib + ET	1326	1270	1217	1213	1187	1174	1167	1128	1127	1080	1067	908	766	478	91
ET	1264	1201	1155	1144	1145	1114	1105	1088	1069	1045	1013	872	736	480	96

QLQ-C30 - Role Functioning



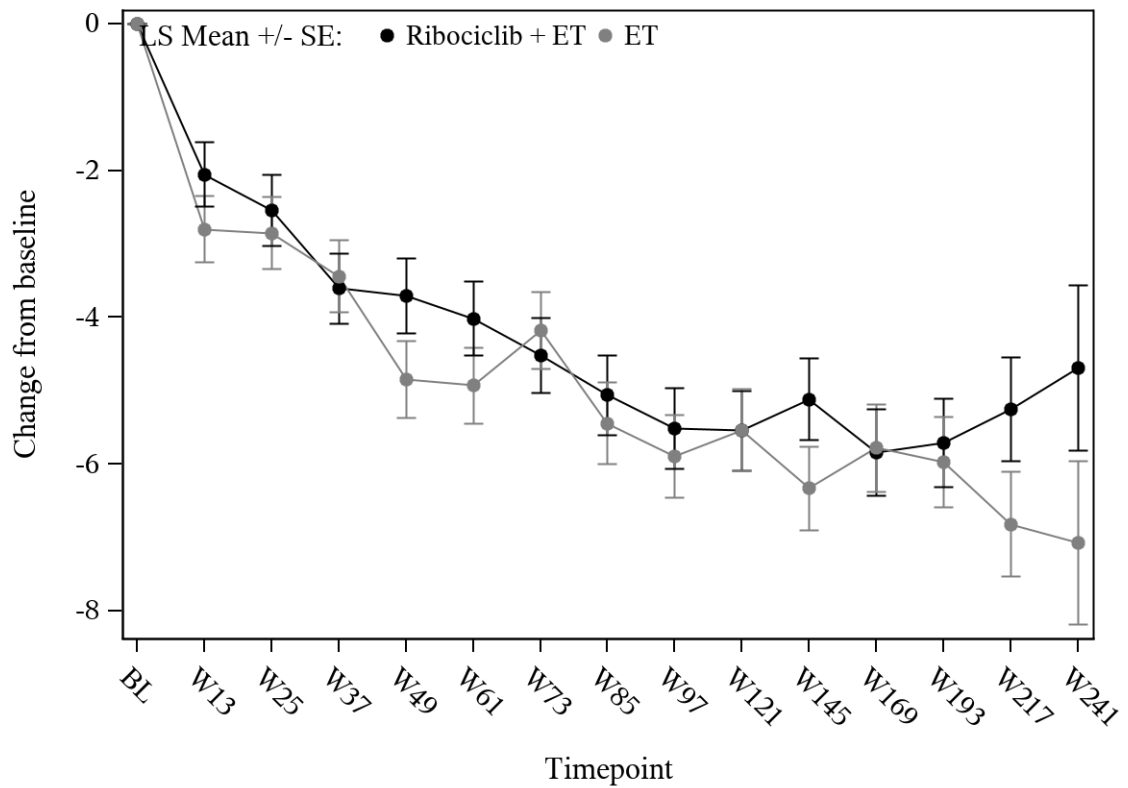
Ribociclib + ET	1325	1269	1218	1214	1186	1175	1166	1131	1128	1081	1065	908	765	479	91
ET	1264	1200	1154	1145	1145	1116	1107	1089	1067	1049	1014	874	737	483	95

QLQ-C30 - Emotional Functioning



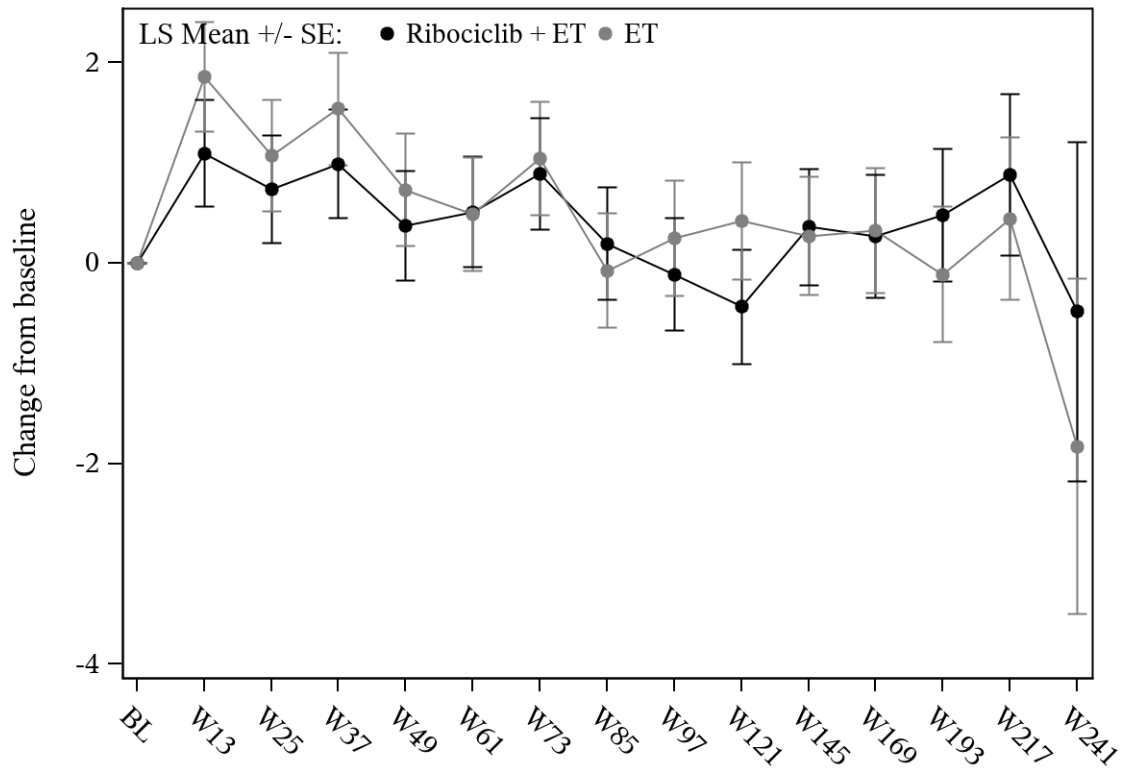
Ribociclib + ET	1323	1264	1217	1214	1184	1169	1166	1130	1126	1081	1063	907	764	478	91
ET	1259	1195	1147	1138	1136	1110	1104	1081	1062	1040	1009	867	730	480	94

QLQ-C30 - Cognitive Functioning



Ribociclib + ET	1322	1263	1216	1213	1183	1168	1165	1129	1125	1080	1062	906	764	478	91
ET	1260	1196	1148	1139	1137	1111	1105	1081	1064	1042	1010	869	731	481	94

QLQ-C30 - Social Functioning



Ribociclib + ET	1323	1264	1217	1213	1181	1169	1166	1130	1126	1081	1062	907	764	478	91
ET	1259	1194	1147	1137	1135	1110	1104	1081	1060	1038	1009	867	730	480	94

3-3 EORTC QLQ-BR23 Symptoms

Table 3-3.0 EORTC QLQ-BR23 Symptoms: return rates (Full Analysis Set)

	Treatment groups			
	Ribociclib + ET (N = 1424)		ET (N = 1420)	
	N' (%)	Returns n (%)	N' (%)	Returns n (%)
Baseline	1424 (100.0)	1388 (97.5)	1420 (100.0)	1375 (96.8)
Week 13	1424 (100.0)	1304 (91.6)	1420 (100.0)	1233 (86.8)
Week 25	1423 (99.9)	1247 (87.6)	1419 (99.9)	1177 (82.9)
Week 37	1420 (99.7)	1249 (88.0)	1410 (99.3)	1167 (82.8)
Week 49	1418 (99.6)	1225 (86.4)	1408 (99.2)	1168 (83.0)
Week 61	1414 (99.3)	1213 (85.8)	1404 (98.9)	1143 (81.4)
Week 73	1411 (99.1)	1198 (84.9)	1399 (98.5)	1131 (80.8)
Week 85	1409 (98.9)	1164 (82.6)	1392 (98.0)	1115 (80.1)
Week 97	1406 (98.7)	1164 (82.8)	1387 (97.7)	1099 (79.2)
Week 121	1393 (97.8)	1114 (80.0)	1382 (97.3)	1071 (77.5)
Week 145	1379 (96.8)	1101 (79.8)	1369 (96.4)	1038 (75.8)
Week 169	1370 (96.2)	936 (68.3)	1364 (96.1)	892 (65.4)
Week 193	1362 (95.6)	790 (58.0)	1357 (95.6)	749 (55.2)
Week 217	1352 (94.9)	494 (36.5)	1347 (94.9)	492 (36.5)
Week 241	1350 (94.8)	93 (6.9)	1346 (94.8)	96 (7.1)
Week 265	1350 (94.8)	6 (0.4)	1345 (94.7)	4 (0.3)

N': Number of patients who have not died until the respective visit
 ET: Endocrine therapy (Anastrozole/Letrozole)

The number of returns is the number of patients with non-missing data (i.e. at least one [sub-]score present) at the respective visit.

A patients is considered to have not died until the visit if no death was documented during the study, if returns for this PRO are present at the visit or, if no returns are present for this PRO and the patient died, if the death date is after the scheduled visit date.

Percentages of returns refer to N' per group. For N' percentages refer to N per group.

Table 3-3.1 EORTC QLQ-BR23 Symptoms: change from baseline analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-BR23 - Side Effects Of Systemic Therapy						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1329	1257				
Baseline	1329 16.02 (13.52)	1257 16.21 (13.70)				
Week 13	1272 18.62 (13.64)	1191 17.26 (13.50)				
Week 25	1221 18.73 (13.85)	1148 17.15 (13.47)				
Week 37	1217 19.94 (14.43)	1138 17.30 (14.05)				
Week 49	1191 20.68 (15.14)	1140 17.99 (13.86)				
Week 61	1180 20.70 (15.54)	1112 18.33 (14.39)				
Week 73	1166 21.03 (15.94)	1105 18.54 (14.90)				
Week 85	1131 20.75 (15.65)	1086 19.09 (14.82)				
Week 97	1130 21.12 (15.82)	1072 19.12 (14.95)				
Week 121	1083 20.96 (15.70)	1041 19.33 (15.44)				
Week 145	1071 21.16 (16.28)	1011 19.78 (15.49)				
Week 169	909 19.58 (15.13)	869 19.89 (15.37)				
Week 193	768 19.25 (15.65)	730 20.06 (15.38)				
Week 217	479 17.28 (13.60)	478 19.93 (15.11)				
Week 241	93 17.27 (13.33)	96 21.59 (16.84)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	2.67 (0.31)	0.91 (0.32)	Difference	1.76	[0.87; 2.64]	<.001
			Hedges G	0.16	[0.08; 0.24]	
Week 25	2.95 (0.33)	1.00 (0.34)	Difference	1.95	[1.02; 2.87]	<.001
			Hedges G	0.17	[0.09; 0.25]	
Week 37	4.17 (0.35)	1.26 (0.36)	Difference	2.91	[1.93; 3.88]	<.001
			Hedges G	0.24	[0.16; 0.32]	
Week 49	4.88 (0.35)	1.96 (0.36)	Difference	2.92	[1.92; 3.91]	<.001
			Hedges G	0.24	[0.16; 0.32]	
Week 61	4.87 (0.37)	2.37 (0.38)	Difference	2.50	[1.47; 3.54]	<.001
			Hedges G	0.20	[0.12; 0.28]	
Week 73	5.24 (0.39)	2.58 (0.40)	Difference	2.67	[1.58; 3.75]	<.001
			Hedges G	0.20	[0.12; 0.28]	
Week 85	4.96 (0.39)	3.15 (0.40)	Difference	1.81	[0.73; 2.90]	0.001
			Hedges G	0.14	[0.06; 0.22]	
Week 97	5.16 (0.39)	3.21 (0.40)	Difference	1.95	[0.85; 3.05]	<.001
			Hedges G	0.15	[0.06; 0.23]	
Week 121	5.07 (0.40)	3.38 (0.41)	Difference	1.70	[0.57; 2.82]	0.003
			Hedges G	0.13	[0.04; 0.21]	
Week 145	5.44 (0.41)	3.81 (0.42)	Difference	1.62	[0.48; 2.77]	0.006

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Week 169	3.72 (0.42)	3.98 (0.43)	Hedges G	0.12	[0.04; 0.21]	
			Difference	-0.26	[-1.43; 0.91]	0.665
Week 193	3.31 (0.45)	4.25 (0.46)	Hedges G	-0.02	[-0.11; 0.07]	
			Difference	-0.94	[-2.19; 0.32]	0.143
Week 217	2.35 (0.49)	4.60 (0.50)	Hedges G	-0.08	[-0.18; 0.03]	
			Difference	-2.26	[-3.63; -0.88]	0.001
Week 241	4.03 (0.80)	5.25 (0.80)	Hedges G	-0.21	[-0.34; -0.08]	
			Difference	-1.22	[-3.44; 0.99]	0.279
Overall effect	4.20 (0.30)	2.98 (0.31)	Difference	1.22	[0.37; 2.07]	0.005
			Hedges G	0.11	[0.03; 0.19]	
QLQ-BR23 - Breast Symptoms						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1322	1259				
Baseline	1322 18.92 (17.78)	1259 19.83 (18.73)				
Week 13	1259 16.19 (17.28)	1186 17.86 (17.93)				
Week 25	1212 14.23 (15.54)	1145 15.77 (16.94)				
Week 37	1199 14.72 (16.45)	1132 15.25 (16.73)				
Week 49	1175 14.05 (16.23)	1131 14.97 (16.75)				
Week 61	1169 13.81 (16.21)	1112 13.98 (16.00)				
Week 73	1155 13.48 (16.14)	1101 13.64 (15.90)				
Week 85	1118 13.14 (16.46)	1082 13.50 (15.68)				
Week 97	1118 12.70 (16.34)	1068 13.30 (15.89)				
Week 121	1074 12.15 (14.74)	1040 12.54 (14.77)				
Week 145	1059 12.49 (15.58)	1007 12.63 (15.18)				
Week 169	899 12.81 (16.32)	864 11.84 (14.89)				
Week 193	759 11.96 (16.36)	724 12.00 (15.02)				
Week 217	475 10.19 (14.16)	479 11.24 (15.14)				
Week 241	92 8.70 (12.29)	96 11.37 (16.50)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	-2.68 (0.41)	-1.55 (0.42)	Difference	-1.13	[-2.29; 0.03]	0.055
			Hedges G	-0.08	[-0.16; 0.00]	
Week 25	-4.33 (0.40)	-3.66 (0.41)	Difference	-0.67	[-1.79; 0.44]	0.236
			Hedges G	-0.05	[-0.13; 0.03]	
Week 37	-4.01 (0.41)	-3.89 (0.42)	Difference	-0.12	[-1.26; 1.02]	0.841
			Hedges G	-0.01	[-0.09; 0.07]	
Week 49	-4.74 (0.41)	-4.33 (0.42)	Difference	-0.41	[-1.55; 0.73]	0.478
			Hedges G	-0.03	[-0.11; 0.05]	
Week 61	-4.85 (0.41)	-5.18 (0.42)	Difference	0.33	[-0.82; 1.47]	0.575
			Hedges G	0.02	[-0.06; 0.11]	
Week 73	-5.29 (0.41)	-5.60 (0.42)	Difference	0.31	[-0.83; 1.46]	0.593
			Hedges G	0.02	[-0.06; 0.11]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Week 85	-5.57 (0.42)	-5.65 (0.42)	Difference	0.08	[-1.09; 1.25]	0.892
			Hedges G	0.01	[-0.08; 0.09]	
Week 97	-5.97 (0.42)	-5.88 (0.43)	Difference	-0.09	[-1.28; 1.10]	0.882
			Hedges G	-0.01	[-0.09; 0.08]	
Week 121	-6.65 (0.39)	-6.59 (0.40)	Difference	-0.06	[-1.17; 1.04]	0.910
			Hedges G	-0.00	[-0.09; 0.08]	
Week 145	-6.15 (0.42)	-6.59 (0.43)	Difference	0.45	[-0.73; 1.63]	0.459
			Hedges G	0.03	[-0.05; 0.12]	
Week 169	-6.14 (0.46)	-7.01 (0.47)	Difference	0.87	[-0.41; 2.15]	0.181
			Hedges G	0.06	[-0.03; 0.16]	
Week 193	-6.97 (0.46)	-6.91 (0.47)	Difference	-0.07	[-1.36; 1.23]	0.919
			Hedges G	-0.01	[-0.11; 0.10]	
Week 217	-7.35 (0.52)	-7.22 (0.52)	Difference	-0.13	[-1.57; 1.31]	0.861
			Hedges G	-0.01	[-0.14; 0.12]	
Week 241	-6.14 (0.98)	-6.94 (0.97)	Difference	0.80	[-1.91; 3.50]	0.564
			Hedges G	0.08	[-0.20; 0.37]	
Overall effect	-5.49 (0.31)	-5.50 (0.32)	Difference	0.01	[-0.87; 0.89]	0.981
			Hedges G	0.00	[-0.08; 0.08]	
QLQ-BR23 - Arm Symptoms						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1323	1261				
Baseline	1323 22.19 (20.61)	1261 23.99 (21.68)				
Week 13	1259 23.53 (21.76)	1189 27.38 (22.51)				
Week 25	1213 23.55 (20.84)	1147 26.78 (22.55)				
Week 37	1201 24.83 (21.76)	1133 25.90 (22.83)				
Week 49	1178 24.72 (22.09)	1133 25.35 (22.08)				
Week 61	1170 24.48 (22.15)	1113 23.97 (21.62)				
Week 73	1157 23.60 (21.89)	1102 22.85 (21.38)				
Week 85	1120 22.27 (21.13)	1085 22.66 (20.99)				
Week 97	1118 21.61 (20.59)	1070 21.60 (21.50)				
Week 121	1077 21.40 (20.53)	1041 20.77 (19.95)				
Week 145	1062 21.43 (21.42)	1008 20.93 (21.02)				
Week 169	899 22.28 (21.79)	865 20.39 (21.09)				
Week 193	762 21.11 (21.66)	727 20.20 (20.50)				
Week 217	475 17.81 (20.72)	480 19.28 (21.10)				
Week 241	92 17.75 (19.56)	96 17.88 (22.36)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	1.10 (0.51)	3.79 (0.52)	Difference	-2.69	[-4.12; -1.26]	<.001
			Hedges G	-0.15	[-0.23; -0.07]	
Week 25	1.27 (0.52)	3.29 (0.54)	Difference	-2.02	[-3.49; -0.55]	0.007
			Hedges G	-0.11	[-0.19; -0.03]	
Week 37	2.51 (0.55)	2.66 (0.57)	Difference	-0.15	[-1.70; 1.41]	0.854

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Week 49	2.32 (0.54)	1.95 (0.56)	Hedges G	-0.01	[-0.09; 0.07]	
			Difference	0.36	[-1.16; 1.89]	0.640
Week 61	2.13 (0.55)	0.87 (0.56)	Hedges G	0.02	[-0.06; 0.10]	
			Difference	1.26	[-0.28; 2.81]	0.108
Week 73	1.38 (0.55)	-0.18 (0.56)	Hedges G	0.07	[-0.01; 0.15]	
			Difference	1.56	[0.02; 3.10]	0.048
Week 85	-0.05 (0.55)	-0.30 (0.56)	Hedges G	0.08	[0.00; 0.17]	
			Difference	0.25	[-1.28; 1.79]	0.746
Week 97	-0.76 (0.55)	-1.27 (0.56)	Hedges G	0.01	[-0.07; 0.10]	
			Difference	0.51	[-1.03; 2.06]	0.515
Week 121	-0.86 (0.54)	-2.05 (0.55)	Hedges G	0.03	[-0.06; 0.11]	
			Difference	1.19	[-0.33; 2.70]	0.125
Week 145	-0.63 (0.57)	-2.11 (0.58)	Hedges G	0.07	[-0.02; 0.15]	
			Difference	1.48	[-0.12; 3.08]	0.070
Week 169	-0.10 (0.60)	-2.47 (0.62)	Hedges G	0.08	[-0.01; 0.17]	
			Difference	2.38	[0.68; 4.07]	0.006
Week 193	-1.21 (0.62)	-2.43 (0.64)	Hedges G	0.13	[0.04; 0.22]	
			Difference	1.22	[-0.53; 2.97]	0.172
Week 217	-2.29 (0.75)	-2.22 (0.75)	Hedges G	0.07	[-0.03; 0.17]	
			Difference	-0.07	[-2.15; 2.02]	0.950
Week 241	-1.35 (1.31)	-4.16 (1.29)	Hedges G	-0.00	[-0.13; 0.12]	
			Difference	2.81	[-0.79; 6.41]	0.126
Overall effect	0.25 (0.41)	-0.33 (0.42)	Difference	0.58	[-0.58; 1.74]	0.329
			Hedges G	0.04	[-0.04; 0.12]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-BR23 - Being Upset With Hair Loss						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	356	351				
Baseline	356 26.31 (34.45)	351 26.88 (35.13)				
Week 13	190 27.37 (33.76)	180 20.74 (28.87)				
Week 25	203 29.72 (34.12)	177 25.99 (32.22)				
Week 37	237 31.79 (34.34)	156 27.78 (33.40)				
Week 49	233 36.34 (34.54)	176 27.08 (31.35)				
Week 61	233 35.91 (33.66)	177 27.87 (30.59)				
Week 73	207 37.20 (35.31)	178 25.66 (31.45)				
Week 85	214 34.27 (33.40)	169 28.60 (30.49)				
Week 97	221 34.99 (34.41)	184 29.89 (31.27)				
Week 121	218 31.50 (31.79)	180 27.96 (32.13)				
Week 145	222 31.98 (32.08)	168 33.13 (34.51)				
Week 169	159 32.29 (31.69)	148 30.63 (33.56)				
Week 193	129 29.72 (31.52)	116 33.91 (34.33)				
Week 217	76 27.19 (32.07)	74 32.43 (32.16)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	-0.09 (1.95)	-7.06 (2.01)	Difference	6.97	[1.48; 12.46]	0.013
			Hedges G	0.26	[0.05; 0.46]	
Week 25	1.62 (1.96)	-3.72 (2.08)	Difference	5.34	[-0.26; 10.94]	0.062
			Hedges G	0.19	[-0.01; 0.39]	
Week 37	2.58 (1.90)	-2.79 (2.19)	Difference	5.37	[-0.32; 11.07]	0.064
			Hedges G	0.19	[-0.01; 0.39]	
Week 49	8.10 (1.87)	-1.64 (2.06)	Difference	9.74	[4.27; 15.21]	<.001
			Hedges G	0.35	[0.15; 0.55]	
Week 61	5.47 (1.83)	-3.16 (2.01)	Difference	8.63	[3.28; 13.97]	0.002
			Hedges G	0.32	[0.12; 0.51]	
Week 73	5.98 (1.94)	-4.33 (2.06)	Difference	10.31	[4.74; 15.87]	<.001
			Hedges G	0.37	[0.17; 0.57]	
Week 85	4.75 (1.79)	-2.78 (1.93)	Difference	7.53	[2.35; 12.71]	0.004
			Hedges G	0.29	[0.09; 0.50]	
Week 97	6.01 (1.89)	-1.05 (2.02)	Difference	7.05	[1.62; 12.49]	0.011
			Hedges G	0.25	[0.06; 0.45]	
Week 121	2.94 (1.85)	-1.83 (1.97)	Difference	4.77	[-0.53; 10.07]	0.077
			Hedges G	0.18	[-0.02; 0.38]	
Week 145	2.62 (1.94)	1.79 (2.14)	Difference	0.83	[-4.84; 6.50]	0.774
			Hedges G	0.03	[-0.17; 0.23]	
Week 169	2.38 (2.09)	2.20 (2.18)	Difference	0.18	[-5.75; 6.10]	0.954
			Hedges G	0.01	[-0.22; 0.23]	
Week 193	1.43 (2.39)	4.15 (2.52)	Difference	-2.72	[-9.53; 4.09]	0.433
			Hedges G	-0.10	[-0.35; 0.15]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Week 217	-0.75 (2.71)	1.54 (2.78)	Difference	-2.29	[-9.91; 5.33]	0.556
			Hedges G	-0.10	[-0.42; 0.22]	
Overall effect	3.31 (1.29)	-1.44 (1.33)	Difference	4.75	[1.11; 8.38]	0.011
			Hedges G	0.19	[0.05; 0.34]	

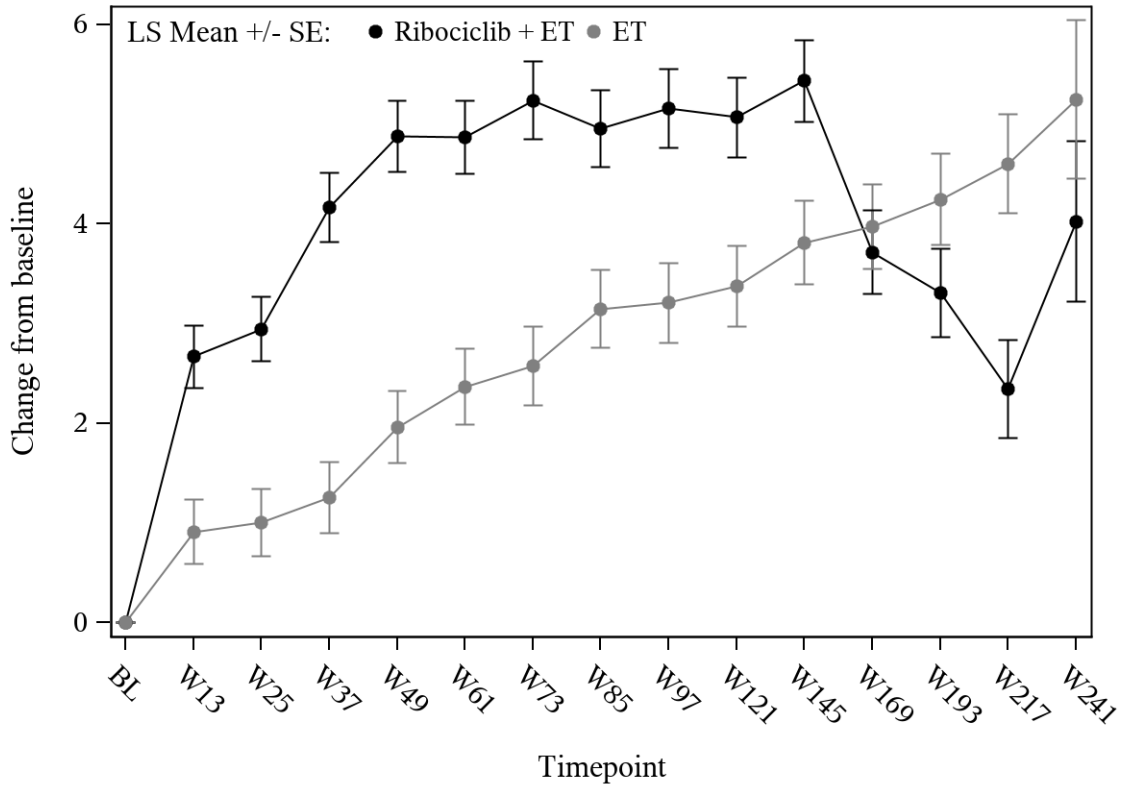
N: Number of patients
 N': Number of patients in the analysis
 CI: Confidence interval
 SD: Standard deviation
 LS Mean: Least square mean
 SE: Standard error
 MMRM: Mixed model for repeated measures
 ET: Endocrine therapy (Anastrozole/Letrozole)

Analysis methods:
 Adjusted mean (LS Mean) change from baseline and difference obtained from MMRM with unstructured covariance matrix:
 change from baseline = treatment + visit + treatment * visit + baseline value + AJCC Anatomic Stage + prior neo/adjuvant chemotherapy + region
 ET was the reference group for treatment group comparison.
 If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
 All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit.

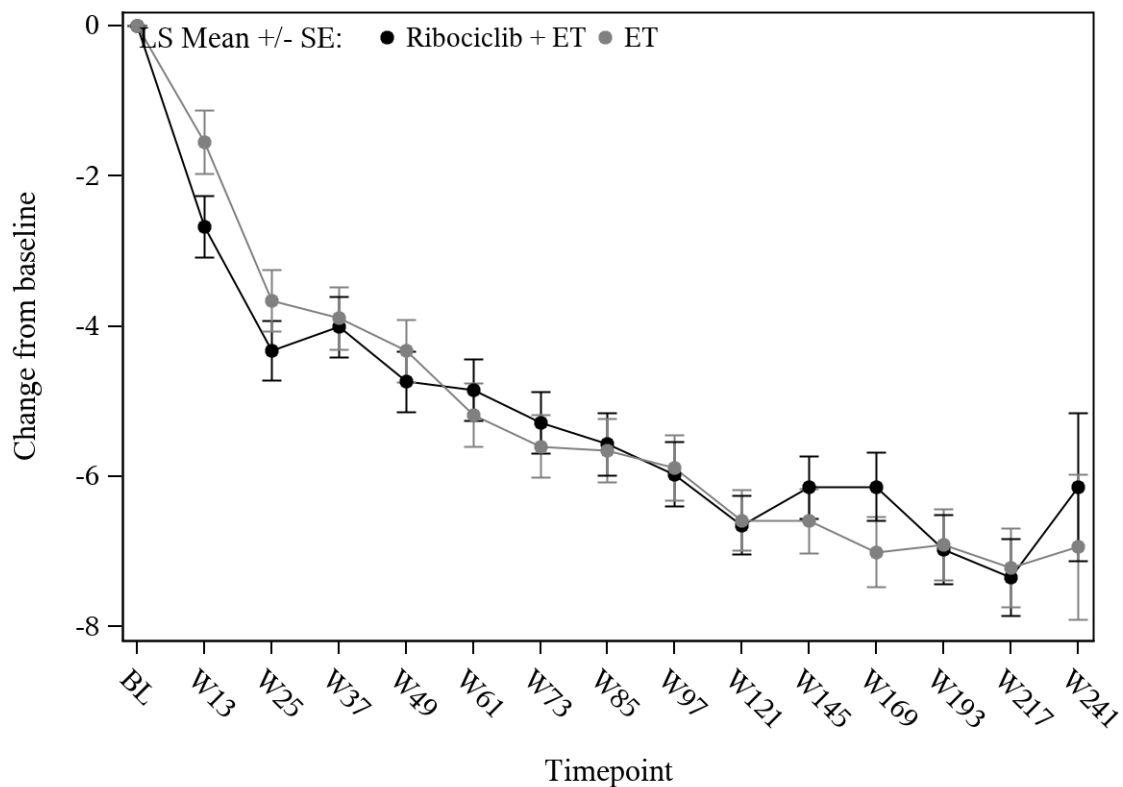
Figure 3-3.1 EORTC QLQ-BR23 Symptoms: line chart of change from baseline (Full Analysis Set)

QLQ-BR23 - Side Effects Of Systemic Therapy



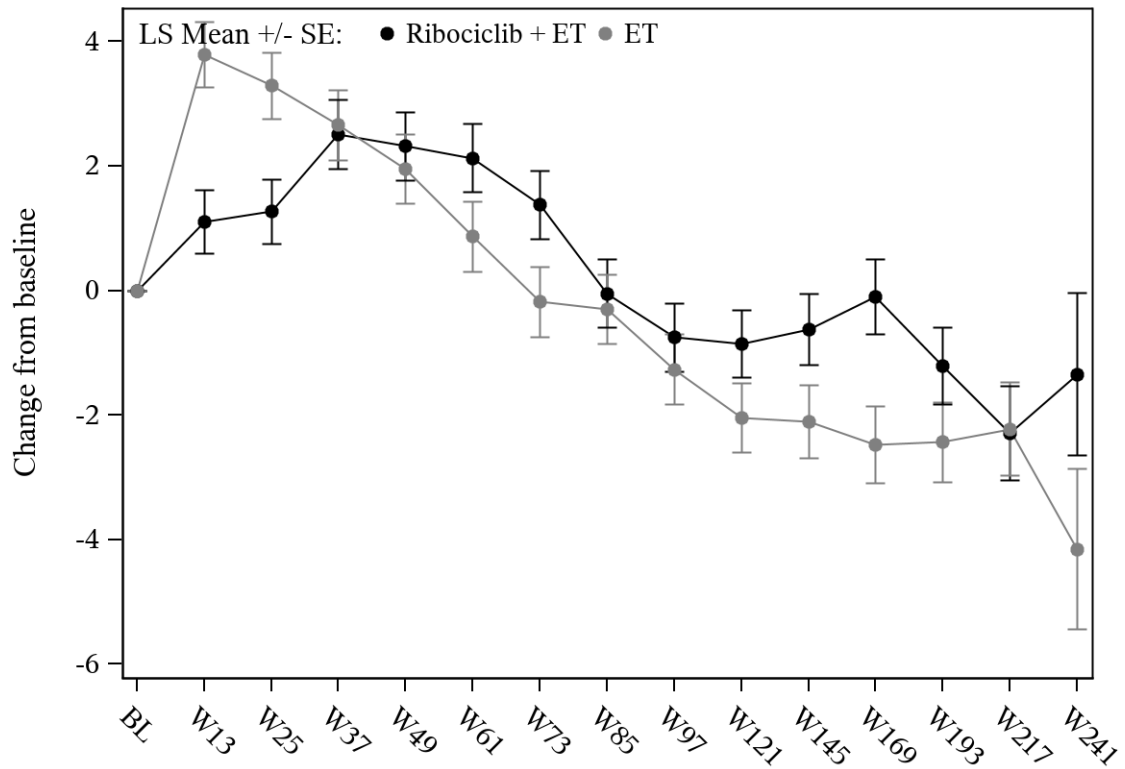
Ribociclib + ET	1329	1272	1221	1217	1191	1180	1166	1131	1130	1083	1071	909	768	479	93
ET	1257	1191	1148	1138	1140	1112	1105	1086	1072	1041	1011	869	730	478	96

QLQ-BR23 - Breast Symptoms



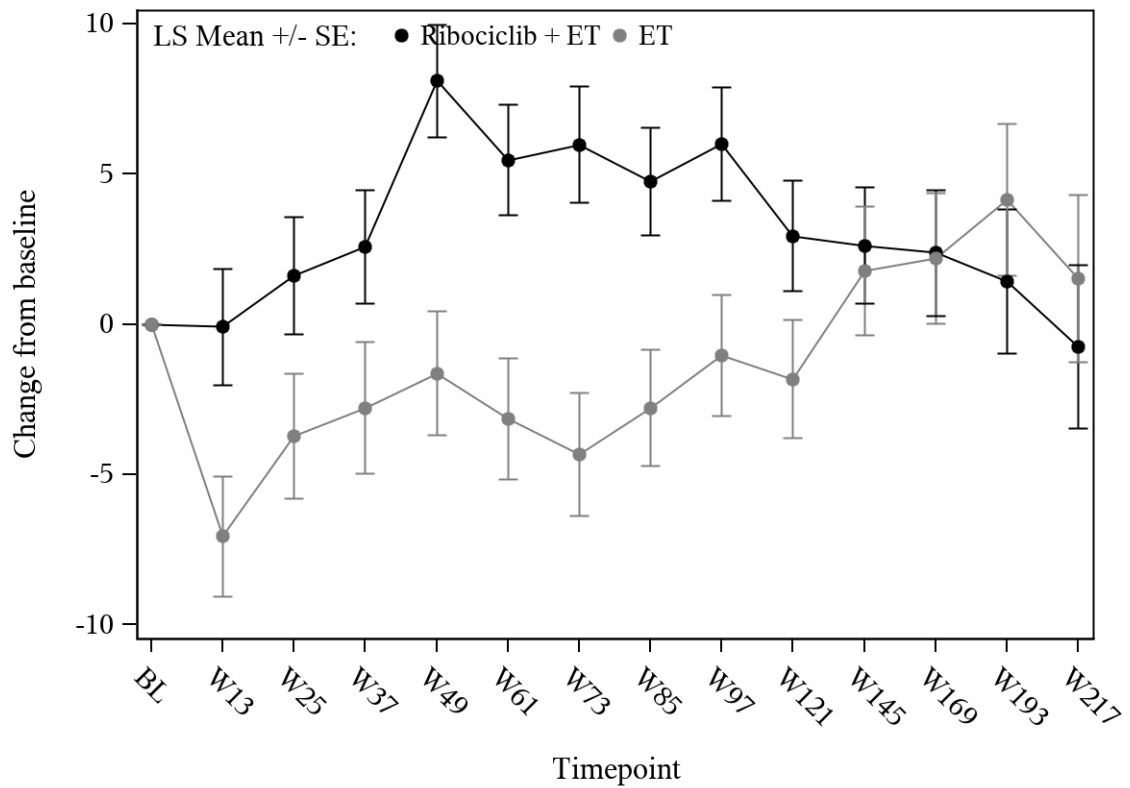
Ribociclib + ET	1322	1259	1212	1199	1175	1169	1155	1118	1118	1074	1059	899	759	475	92
ET	1259	1186	1145	1132	1131	1112	1101	1082	1068	1040	1007	864	724	479	96

QLQ-BR23 - Arm Symptoms



Ribociclib + ET	1323	1259	1213	1201	1178	1170	1157	1120	1118	1077	1062	899	762	475	92
ET	1261	1189	1147	1133	1133	1113	1102	1085	1070	1041	1008	865	727	480	96

QLQ-BR23 - Being Upset With Hair Loss



Ribociclib + ET	356	190	203	237	233	233	207	214	221	218	222	159	129	76
ET	351	180	177	156	176	177	178	169	184	180	168	148	116	74

3-4 EORTC QLQ-BR23 QoL

Table 3-4.0 EORTC QLQ-BR23 QoL: return rates (Full Analysis Set)

	Treatment groups			
	Ribociclib + ET (N = 1424)		ET (N = 1420)	
	N' (%)	Returns n (%)	N' (%)	Returns n (%)
Baseline	1424 (100.0)	1386 (97.3)	1420 (100.0)	1370 (96.5)
Week 13	1424 (100.0)	1302 (91.4)	1420 (100.0)	1228 (86.5)
Week 25	1423 (99.9)	1246 (87.6)	1419 (99.9)	1177 (82.9)
Week 37	1420 (99.7)	1249 (88.0)	1410 (99.3)	1166 (82.7)
Week 49	1418 (99.6)	1223 (86.2)	1408 (99.2)	1166 (82.8)
Week 61	1414 (99.3)	1212 (85.7)	1404 (98.9)	1142 (81.3)
Week 73	1411 (99.1)	1197 (84.8)	1399 (98.5)	1131 (80.8)
Week 85	1409 (98.9)	1164 (82.6)	1392 (98.0)	1114 (80.0)
Week 97	1406 (98.7)	1161 (82.6)	1387 (97.7)	1099 (79.2)
Week 121	1393 (97.8)	1111 (79.8)	1382 (97.3)	1068 (77.3)
Week 145	1379 (96.8)	1101 (79.8)	1369 (96.4)	1037 (75.7)
Week 169	1370 (96.2)	935 (68.2)	1364 (96.1)	891 (65.3)
Week 193	1362 (95.6)	788 (57.9)	1357 (95.6)	749 (55.2)
Week 217	1352 (94.9)	493 (36.5)	1347 (94.9)	489 (36.3)
Week 241	1350 (94.8)	93 (6.9)	1346 (94.8)	96 (7.1)
Week 265	1350 (94.8)	6 (0.4)	1345 (94.7)	4 (0.3)

N': Number of patients who have not died until the respective visit
 ET: Endocrine therapy (Anastrozole/Letrozole)

The number of returns is the number of patients with non-missing data (i.e. at least one [sub-]score present) at the respective visit.

A patients is considered to have not died until the visit if no death was documented during the study, if returns for this PRO are present at the visit or, if no returns are present for this PRO and the patient died, if the death date is after the scheduled visit date.

Percentages of returns refer to N' per group. For N' percentages refer to N per group.

Table 3-4.1 EORTC QLQ-BR23 QoL: change from baseline analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-BR23 - Body Image						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1327	1254				
Baseline	1327 74.27 (25.89)	1254 74.26 (26.40)				
Week 13	1265 77.19 (25.01)	1184 75.74 (25.15)				
Week 25	1218 77.70 (24.28)	1145 75.95 (25.95)				
Week 37	1212 77.13 (24.39)	1133 77.36 (25.50)				
Week 49	1190 77.18 (24.73)	1136 76.24 (26.07)				
Week 61	1177 76.90 (25.15)	1106 76.46 (25.86)				
Week 73	1164 76.98 (24.78)	1101 76.96 (25.52)				
Week 85	1128 77.57 (25.38)	1083 76.56 (25.85)				
Week 97	1127 77.23 (25.60)	1070 75.99 (26.79)				
Week 121	1080 77.63 (25.44)	1037 76.88 (26.23)				
Week 145	1070 77.84 (25.17)	1009 76.92 (26.15)				
Week 169	905 78.66 (24.14)	866 77.43 (25.38)				
Week 193	766 79.43 (24.22)	728 76.97 (25.98)				
Week 217	479 81.24 (22.88)	475 78.52 (25.48)				
Week 241	92 78.89 (21.20)	96 74.31 (27.83)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	2.57 (0.51)	1.58 (0.53)	Difference	0.99	[-0.45; 2.42]	0.176
			Hedges G	0.05	[-0.02; 0.13]	
Week 25	2.88 (0.53)	1.66 (0.55)	Difference	1.21	[-0.29; 2.72]	0.113
			Hedges G	0.07	[-0.02; 0.15]	
Week 37	2.48 (0.55)	2.67 (0.57)	Difference	-0.18	[-1.74; 1.37]	0.818
			Hedges G	-0.01	[-0.09; 0.07]	
Week 49	2.38 (0.57)	1.49 (0.58)	Difference	0.90	[-0.69; 2.48]	0.270
			Hedges G	0.05	[-0.04; 0.13]	
Week 61	2.01 (0.58)	1.88 (0.60)	Difference	0.14	[-1.49; 1.76]	0.870
			Hedges G	0.01	[-0.08; 0.09]	
Week 73	2.13 (0.58)	2.02 (0.59)	Difference	0.10	[-1.52; 1.72]	0.901
			Hedges G	0.01	[-0.08; 0.09]	
Week 85	2.65 (0.59)	1.93 (0.61)	Difference	0.72	[-0.94; 2.38]	0.397
			Hedges G	0.04	[-0.05; 0.12]	
Week 97	2.39 (0.62)	1.32 (0.63)	Difference	1.07	[-0.67; 2.80]	0.229
			Hedges G	0.05	[-0.03; 0.14]	
Week 121	2.70 (0.63)	2.17 (0.64)	Difference	0.53	[-1.23; 2.29]	0.557
			Hedges G	0.03	[-0.06; 0.11]	
Week 145	2.80 (0.63)	2.37 (0.64)	Difference	0.43	[-1.34; 2.19]	0.634
			Hedges G	0.02	[-0.07; 0.11]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Week 169	3.62 (0.64)	2.67 (0.66)	Difference	0.95	[-0.86; 2.76]	0.303
			Hedges G	0.05	[-0.04; 0.14]	
Week 193	3.54 (0.67)	1.99 (0.69)	Difference	1.56	[-0.34; 3.45]	0.107
			Hedges G	0.08	[-0.02; 0.18]	
Week 217	4.00 (0.78)	3.58 (0.80)	Difference	0.42	[-1.77; 2.61]	0.706
			Hedges G	0.02	[-0.10; 0.15]	
Week 241	1.54 (1.25)	2.37 (1.24)	Difference	-0.83	[-4.28; 2.61]	0.635
			Hedges G	-0.07	[-0.36; 0.22]	
Overall effect	2.69 (0.47)	2.12 (0.49)	Difference	0.57	[-0.76; 1.90]	0.401
			Hedges G	0.03	[-0.04; 0.11]	
QLQ-BR23 - Sexual Functioning						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1297	1221				
Baseline	1297 18.34 (21.68)	1221 16.80 (21.17)				
Week 13	1225 18.39 (21.58)	1142 17.48 (20.88)				
Week 25	1177 18.32 (21.60)	1099 16.95 (21.00)				
Week 37	1165 18.60 (21.23)	1091 16.54 (21.31)				
Week 49	1136 17.72 (21.19)	1097 16.12 (20.82)				
Week 61	1115 17.44 (21.32)	1071 15.87 (20.83)				
Week 73	1103 17.30 (21.21)	1054 15.67 (21.20)				
Week 85	1067 16.84 (21.29)	1035 15.10 (20.37)				
Week 97	1067 16.98 (21.29)	1021 14.94 (20.49)				
Week 121	1017 16.27 (20.71)	989 14.09 (20.74)				
Week 145	1003 16.48 (21.52)	959 14.44 (20.54)				
Week 169	852 16.14 (21.39)	817 14.44 (20.81)				
Week 193	710 15.80 (20.60)	686 13.00 (19.44)				
Week 217	444 14.08 (19.47)	450 12.93 (20.00)				
Week 241	89 10.11 (18.05)	90 13.33 (19.55)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	0.27 (0.44)	0.26 (0.46)	Difference	0.01	[-1.25; 1.26]	0.993
			Hedges G	0.00	[-0.08; 0.08]	
Week 25	0.40 (0.45)	0.05 (0.47)	Difference	0.35	[-0.92; 1.63]	0.587
			Hedges G	0.02	[-0.06; 0.10]	
Week 37	0.34 (0.46)	-0.48 (0.48)	Difference	0.82	[-0.49; 2.13]	0.218
			Hedges G	0.05	[-0.03; 0.13]	
Week 49	-0.46 (0.47)	-0.99 (0.48)	Difference	0.53	[-0.79; 1.85]	0.434
			Hedges G	0.03	[-0.05; 0.12]	
Week 61	-1.02 (0.48)	-1.18 (0.49)	Difference	0.16	[-1.18; 1.50]	0.815
			Hedges G	0.01	[-0.07; 0.09]	
Week 73	-1.35 (0.49)	-1.58 (0.50)	Difference	0.23	[-1.13; 1.59]	0.741
			Hedges G	0.01	[-0.07; 0.10]	
Week 85	-1.82 (0.48)	-2.02 (0.49)	Difference	0.20	[-1.15; 1.54]	0.775

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Week 97	-1.66 (0.48)	-2.21 (0.49)	Hedges G	0.01	[-0.07; 0.10]	
			Difference	0.55	[-0.80; 1.90]	0.423
Week 121	-2.21 (0.49)	-2.99 (0.50)	Hedges G	0.04	[-0.05; 0.12]	
			Difference	0.78	[-0.59; 2.15]	0.266
Week 145	-2.25 (0.51)	-2.68 (0.52)	Hedges G	0.05	[-0.04; 0.14]	
			Difference	0.43	[-1.00; 1.86]	0.555
Week 169	-3.07 (0.54)	-2.81 (0.55)	Hedges G	0.03	[-0.06; 0.12]	
			Difference	-0.27	[-1.77; 1.24]	0.727
Week 193	-3.52 (0.54)	-3.68 (0.55)	Hedges G	-0.02	[-0.11; 0.08]	
			Difference	0.16	[-1.34; 1.67]	0.833
Week 217	-4.82 (0.63)	-4.25 (0.63)	Hedges G	0.01	[-0.09; 0.12]	
			Difference	-0.56	[-2.30; 1.17]	0.524
Week 241	-5.93 (1.04)	-4.29 (1.04)	Hedges G	-0.04	[-0.17; 0.09]	
			Difference	-1.64	[-4.53; 1.25]	0.267
Overall effect	-1.94 (0.36)	-2.06 (0.37)	Hedges G	-0.17	[-0.46; 0.13]	
			Difference	0.12	[-0.88; 1.13]	0.808
			Hedges G	0.01	[-0.07; 0.09]	
QLQ-BR23 - Sexual Enjoyment						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	583	513				
Baseline	583 44.65 (31.10)	513 41.85 (32.33)				
Week 13	439 44.87 (30.61)	388 42.53 (30.19)				
Week 25	415 46.27 (29.96)	361 44.97 (31.13)				
Week 37	414 45.97 (28.95)	334 45.11 (30.36)				
Week 49	418 44.18 (28.82)	337 42.24 (30.21)				
Week 61	399 43.44 (29.24)	335 41.69 (28.78)				
Week 73	389 43.27 (29.86)	326 42.84 (30.41)				
Week 85	368 44.02 (29.74)	321 41.12 (29.43)				
Week 97	372 44.89 (30.19)	307 41.69 (30.35)				
Week 121	351 43.11 (29.75)	288 43.06 (31.08)				
Week 145	333 41.54 (31.14)	281 42.23 (29.21)				
Week 169	283 44.29 (31.03)	220 42.73 (29.76)				
Week 193	231 45.31 (29.91)	180 41.30 (29.77)				
Week 217	130 48.21 (29.37)	125 40.53 (32.68)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	-3.13 (1.00)	-3.73 (1.07)	Difference	0.60	[-2.28; 3.48]	0.683
			Hedges G	0.03	[-0.11; 0.17]	
Week 25	-2.88 (1.05)	-1.99 (1.13)	Difference	-0.89	[-3.92; 2.14]	0.564
			Hedges G	-0.04	[-0.18; 0.10]	
Week 37	-3.89 (1.06)	-2.79 (1.17)	Difference	-1.10	[-4.20; 1.99]	0.484
			Hedges G	-0.05	[-0.20; 0.09]	
Week 49	-4.98 (1.02)	-4.47 (1.13)	Difference	-0.51	[-3.49; 2.48]	0.740

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Week 61	-6.82 (1.07)	-5.37 (1.16)	Hedges G	-0.02	[-0.17; 0.12]	
			Difference	-1.46	[-4.56; 1.65]	0.358
Week 73	-6.38 (1.10)	-4.70 (1.19)	Hedges G	-0.07	[-0.21; 0.08]	
			Difference	-1.68	[-4.86; 1.50]	0.300
Week 85	-6.15 (1.11)	-6.00 (1.19)	Hedges G	-0.08	[-0.23; 0.07]	
			Difference	-0.15	[-3.35; 3.05]	0.928
Week 97	-5.82 (1.06)	-6.21 (1.16)	Hedges G	-0.01	[-0.16; 0.14]	
			Difference	0.39	[-2.69; 3.47]	0.804
Week 121	-7.21 (1.12)	-6.22 (1.22)	Hedges G	0.02	[-0.13; 0.17]	
			Difference	-0.99	[-4.24; 2.25]	0.548
Week 145	-9.12 (1.20)	-6.78 (1.30)	Hedges G	-0.05	[-0.20; 0.11]	
			Difference	-2.34	[-5.82; 1.13]	0.186
Week 169	-7.67 (1.28)	-7.90 (1.42)	Hedges G	-0.11	[-0.27; 0.05]	
			Difference	0.23	[-3.51; 3.97]	0.904
Week 193	-9.33 (1.40)	-9.49 (1.56)	Hedges G	0.01	[-0.17; 0.19]	
			Difference	0.16	[-3.95; 4.27]	0.939
Week 217	-8.12 (1.68)	-7.90 (1.74)	Hedges G	0.01	[-0.19; 0.20]	
			Difference	-0.22	[-4.96; 4.52]	0.928
Overall effect	-6.27 (0.77)	-5.66 (0.82)	Difference	-0.61	[-2.82; 1.60]	0.586
			Hedges G	-0.03	[-0.15; 0.09]	
QLQ-BR23 - Future Perspective						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1327	1252				
Baseline	1327 52.15 (31.21)	1252 51.28 (31.70)				
Week 13	1260 56.75 (30.29)	1178 56.40 (30.68)				
Week 25	1214 58.59 (29.42)	1137 58.14 (30.59)				
Week 37	1209 59.17 (29.35)	1130 59.71 (29.77)				
Week 49	1184 60.50 (29.40)	1130 59.03 (29.29)				
Week 61	1173 60.50 (29.45)	1096 59.37 (29.29)				
Week 73	1156 60.41 (29.66)	1097 60.29 (28.55)				
Week 85	1125 60.92 (29.67)	1077 60.14 (28.77)				
Week 97	1123 61.65 (29.34)	1064 59.99 (29.50)				
Week 121	1074 60.74 (29.79)	1032 60.82 (29.82)				
Week 145	1066 62.57 (29.37)	1002 60.68 (29.27)				
Week 169	904 63.02 (28.24)	864 62.15 (29.87)				
Week 193	765 63.88 (28.45)	726 61.48 (30.46)				
Week 217	478 65.90 (28.75)	472 62.43 (29.80)				
Week 241	93 68.10 (24.53)	95 63.51 (28.38)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	4.89 (0.71)	5.18 (0.73)	Difference	-0.28	[-2.29; 1.72]	0.781
			Hedges G	-0.01	[-0.09; 0.07]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Week 25	6.65 (0.72)	6.66 (0.74)	Difference	-0.01	[-2.04; 2.01]	0.991
			Hedges G	-0.00	[-0.08; 0.08]	
Week 37	7.18 (0.72)	7.97 (0.74)	Difference	-0.79	[-2.82; 1.24]	0.446
			Hedges G	-0.03	[-0.11; 0.05]	
Week 49	8.63 (0.73)	7.21 (0.75)	Difference	1.42	[-0.62; 3.46]	0.172
			Hedges G	0.06	[-0.02; 0.14]	
Week 61	8.57 (0.73)	7.61 (0.75)	Difference	0.96	[-1.10; 3.01]	0.360
			Hedges G	0.04	[-0.04; 0.12]	
Week 73	8.50 (0.73)	8.13 (0.75)	Difference	0.37	[-1.69; 2.43]	0.724
			Hedges G	0.01	[-0.07; 0.10]	
Week 85	9.05 (0.74)	8.49 (0.76)	Difference	0.56	[-1.52; 2.64]	0.599
			Hedges G	0.02	[-0.06; 0.11]	
Week 97	9.90 (0.74)	8.11 (0.76)	Difference	1.80	[-0.29; 3.88]	0.091
			Hedges G	0.07	[-0.01; 0.16]	
Week 121	9.02 (0.75)	9.22 (0.77)	Difference	-0.20	[-2.31; 1.91]	0.852
			Hedges G	-0.01	[-0.09; 0.08]	
Week 145	10.45 (0.76)	8.91 (0.78)	Difference	1.55	[-0.58; 3.68]	0.155
			Hedges G	0.06	[-0.02; 0.15]	
Week 169	11.04 (0.80)	9.78 (0.82)	Difference	1.26	[-0.99; 3.50]	0.272
			Hedges G	0.05	[-0.04; 0.15]	
Week 193	11.45 (0.85)	9.13 (0.87)	Difference	2.32	[-0.07; 4.71]	0.057
			Hedges G	0.10	[-0.00; 0.20]	
Week 217	11.37 (1.02)	8.99 (1.03)	Difference	2.38	[-0.46; 5.21]	0.100
			Hedges G	0.11	[-0.02; 0.23]	
Week 241	10.39 (2.09)	8.52 (2.07)	Difference	1.87	[-3.90; 7.64]	0.526
			Hedges G	0.09	[-0.19; 0.38]	
Overall effect	9.08 (0.53)	8.14 (0.54)	Difference	0.94	[-0.55; 2.43]	0.215
			Hedges G	0.05	[-0.03; 0.13]	

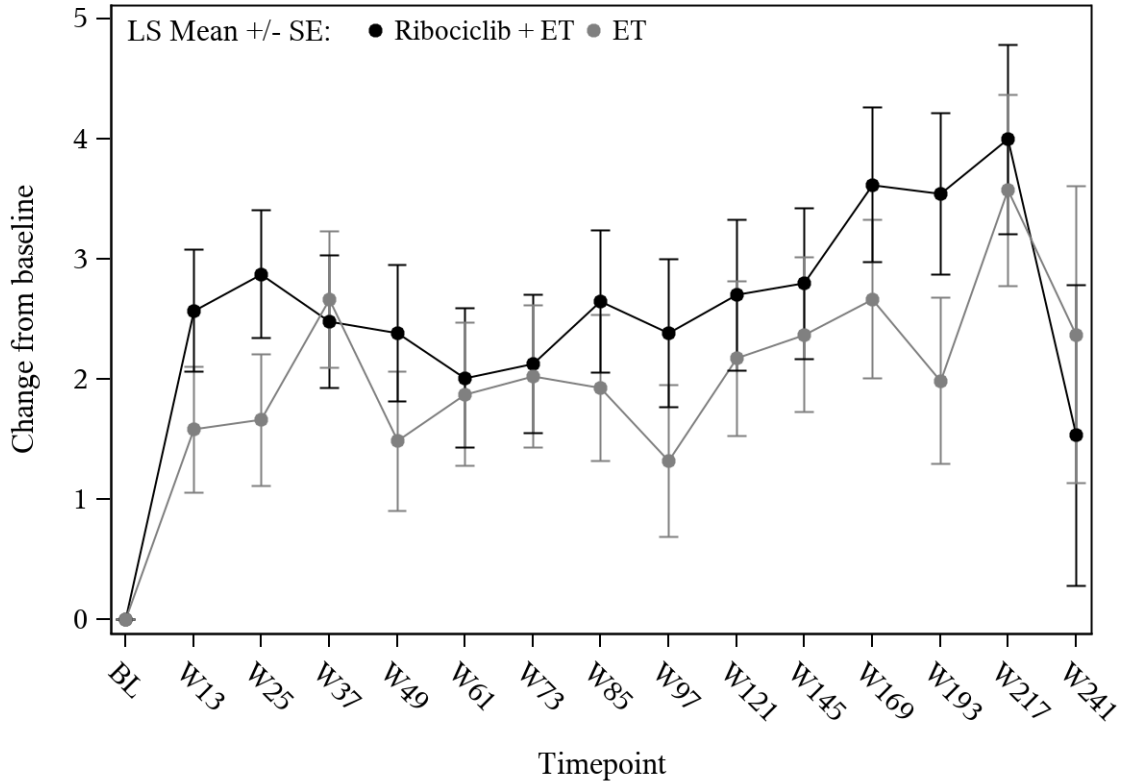
N: Number of patients
 N': Number of patients in the analysis
 CI: Confidence interval
 SD: Standard deviation
 LS Mean: Least square mean
 SE: Standard error
 MMRM: Mixed model for repeated measures
 ET: Endocrine therapy (Anastrozole/Letrozole)

Analysis methods:
 Adjusted mean (LS Mean) change from baseline and difference obtained from MMRM with unstructured covariance matrix:
 change from baseline = treatment + visit + treatment * visit + baseline value + AJCC Anatomic Stage + prior neo/adjvant chemotherapy + region
 ET was the reference group for treatment group comparison.
 If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
 All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit.

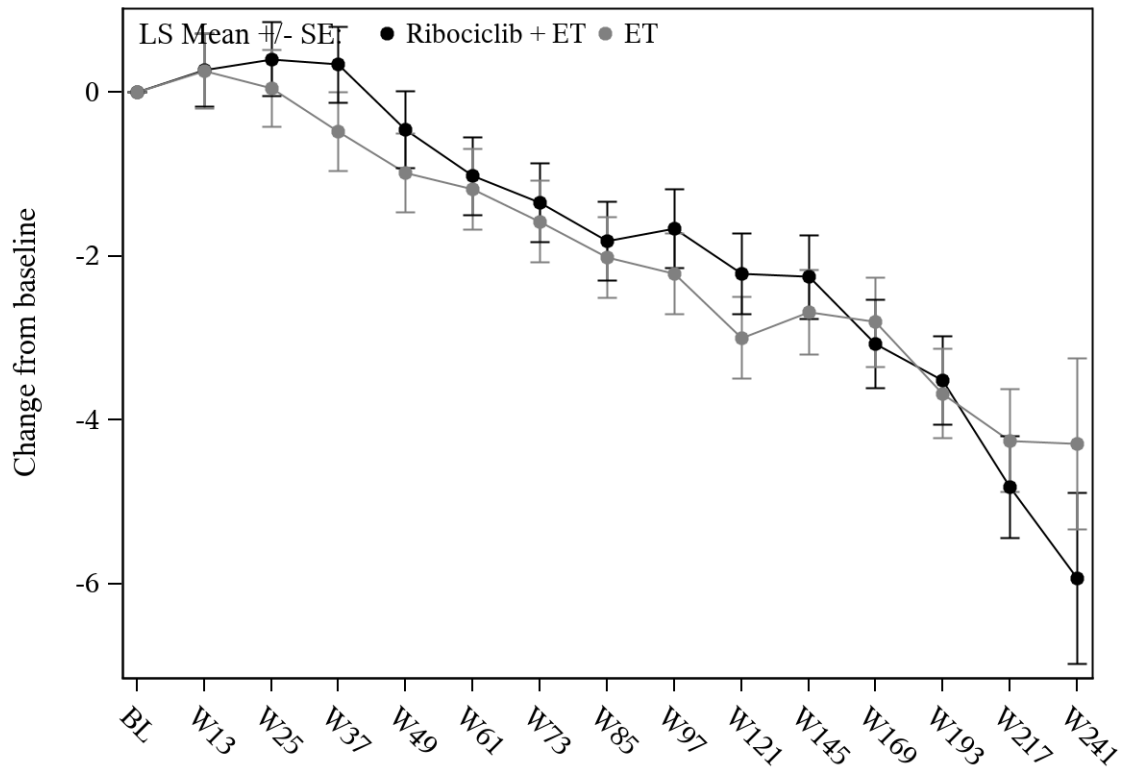
Figure 3-4.1 EORTC QLQ-BR23 QoL: line chart of change from baseline (Full Analysis Set)

QLQ-BR23 - Body Image



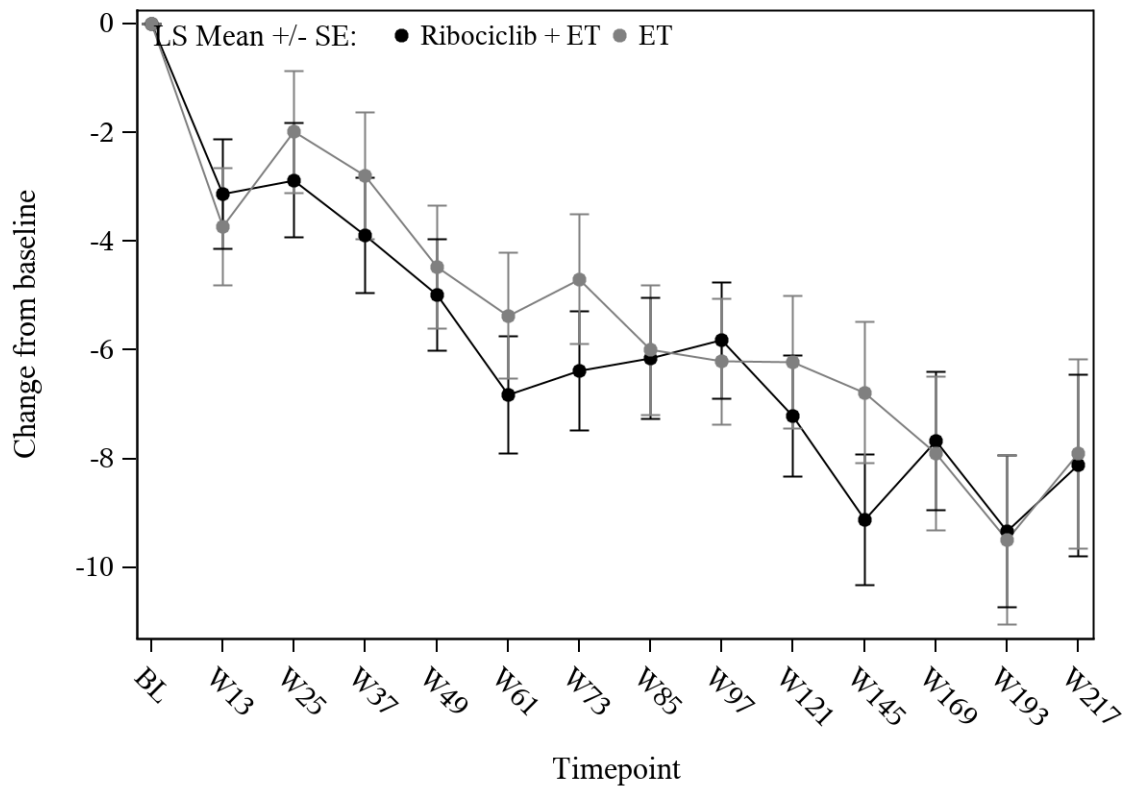
Ribociclib + ET	1327	1265	1218	1212	1190	1177	1164	1128	1127	1080	1070	905	766	479	92
ET	1254	1184	1145	1133	1136	1106	1101	1083	1070	1037	1009	866	728	475	96

QLQ-BR23 - Sexual Functioning



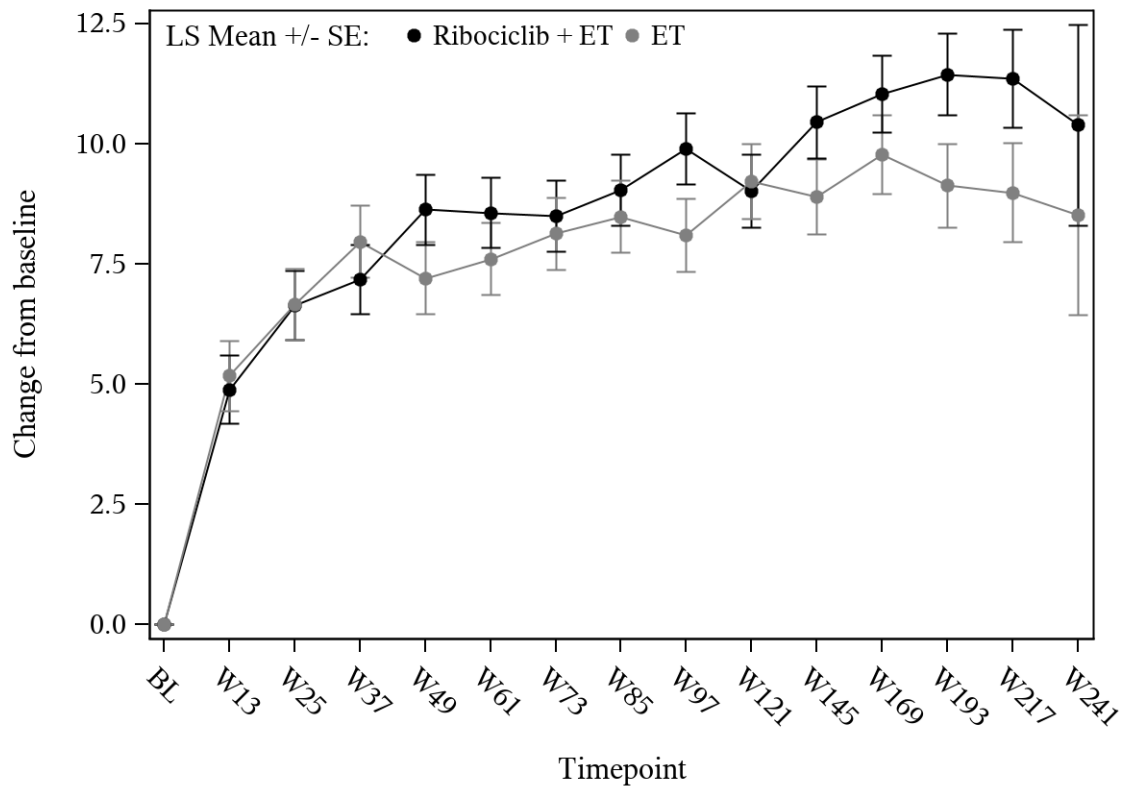
Ribociclib + ET	1297	1225	1177	1165	1136	1115	1103	1067	1067	1017	1003	852	710	444	89
ET	1221	1142	1099	1091	1097	1071	1054	1035	1021	989	959	817	686	450	90

QLQ-BR23 - Sexual Enjoyment



Ribociclib + ET	583	439	415	414	418	399	389	368	372	351	333	283	231	130
ET	513	388	361	334	337	335	326	321	307	288	281	220	180	125

QLQ-BR23 - Future Perspective



Ribociclib + ET	1327	1260	1214	1209	1184	1173	1156	1125	1123	1074	1066	904	765	478	93
ET	1252	1178	1137	1130	1130	1096	1097	1077	1064	1032	1002	864	726	472	95

3-5 EQ-5D VAS

Table 3-5.0 EQ-5D VAS: return rates (Full Analysis Set)

	Treatment groups			
	Ribociclib + ET (N = 1424)		ET (N = 1420)	
	N' (%)	Returns n (%)	N' (%)	Returns n (%)
Baseline	1424 (100.0)	1380 (96.9)	1420 (100.0)	1371 (96.5)
Week 13	1424 (100.0)	1289 (90.5)	1420 (100.0)	1220 (85.9)
Week 25	1423 (99.9)	1238 (87.0)	1418 (99.9)	1172 (82.7)
Week 37	1420 (99.7)	1236 (87.0)	1410 (99.3)	1153 (81.8)
Week 49	1418 (99.6)	1218 (85.9)	1408 (99.2)	1156 (82.1)
Week 61	1414 (99.3)	1203 (85.1)	1404 (98.9)	1133 (80.7)
Week 73	1411 (99.1)	1189 (84.3)	1399 (98.5)	1129 (80.7)
Week 85	1409 (98.9)	1161 (82.4)	1392 (98.0)	1110 (79.7)
Week 97	1406 (98.7)	1157 (82.3)	1387 (97.7)	1092 (78.7)
Week 121	1393 (97.8)	1110 (79.7)	1382 (97.3)	1068 (77.3)
Week 145	1379 (96.8)	1092 (79.2)	1369 (96.4)	1032 (75.4)
Week 169	1370 (96.2)	936 (68.3)	1364 (96.1)	894 (65.5)
Week 193	1362 (95.6)	787 (57.8)	1357 (95.6)	746 (55.0)
Week 217	1352 (94.9)	493 (36.5)	1347 (94.9)	491 (36.5)
Week 241	1350 (94.8)	90 (6.7)	1346 (94.8)	95 (7.1)
Week 265	1350 (94.8)	6 (0.4)	1345 (94.7)	3 (0.2)

N': Number of patients who have not died until the respective visit
 ET: Endocrine therapy (Anastrozole/Letrozole)

The number of returns is the number of patients with non-missing data (i.e. at least one [sub-]score present) at the respective visit.

A patients is considered to have not died until the visit if no death was documented during the study, if returns for this PRO are present at the visit or, if no returns are present for this PRO and the patient died, if the death date is after the scheduled visit date.

Percentages of returns refer to N' per group. For N' percentages refer to N per group.

Table 3-5.1 EQ-5D VAS: change from baseline analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
EQ5D01-Health Today						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1323	1259				
Baseline	1323 78.56 (14.91)	1259 78.23 (14.79)				
Week 13	1254 77.40 (15.38)	1184 77.60 (15.48)				
Week 25	1208 77.98 (15.33)	1143 78.02 (15.69)				
Week 37	1200 77.53 (15.93)	1125 77.85 (16.39)				
Week 49	1184 77.42 (16.09)	1129 77.50 (16.55)				
Week 61	1168 77.64 (15.83)	1103 76.99 (16.63)				
Week 73	1154 77.45 (16.29)	1102 77.94 (16.00)				
Week 85	1124 77.53 (16.12)	1082 77.30 (16.66)				
Week 97	1121 77.06 (16.13)	1064 76.89 (16.90)				
Week 121	1078 77.22 (16.75)	1040 76.94 (16.82)				
Week 145	1060 77.17 (16.67)	1007 77.41 (16.38)				
Week 169	908 77.63 (16.37)	870 76.84 (17.14)				
Week 193	764 77.37 (16.76)	728 76.73 (17.05)				
Week 217	477 77.72 (16.36)	480 77.10 (17.24)				
Week 241	90 78.74 (16.64)	95 78.63 (15.77)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	-1.21 (0.39)	-0.76 (0.40)	Difference	-0.46	[-1.54; 0.63]	0.408
			Hedges G	-0.03	[-0.11; 0.05]	
Week 25	-0.76 (0.39)	-0.41 (0.40)	Difference	-0.35	[-1.45; 0.74]	0.530
			Hedges G	-0.03	[-0.11; 0.05]	
Week 37	-1.31 (0.39)	-0.69 (0.40)	Difference	-0.62	[-1.72; 0.48]	0.267
			Hedges G	-0.05	[-0.13; 0.04]	
Week 49	-1.44 (0.39)	-1.12 (0.40)	Difference	-0.33	[-1.43; 0.77]	0.559
			Hedges G	-0.02	[-0.11; 0.06]	
Week 61	-1.43 (0.39)	-1.66 (0.41)	Difference	0.24	[-0.87; 1.35]	0.675
			Hedges G	0.02	[-0.06; 0.10]	
Week 73	-1.45 (0.40)	-0.78 (0.41)	Difference	-0.67	[-1.79; 0.44]	0.235
			Hedges G	-0.05	[-0.13; 0.03]	
Week 85	-1.41 (0.40)	-1.34 (0.41)	Difference	-0.07	[-1.19; 1.05]	0.901
			Hedges G	-0.01	[-0.09; 0.08]	
Week 97	-1.93 (0.40)	-1.73 (0.41)	Difference	-0.20	[-1.32; 0.93]	0.731
			Hedges G	-0.01	[-0.10; 0.07]	
Week 121	-1.83 (0.41)	-1.77 (0.41)	Difference	-0.06	[-1.20; 1.07]	0.913
			Hedges G	-0.00	[-0.09; 0.08]	
Week 145	-2.04 (0.41)	-1.29 (0.42)	Difference	-0.76	[-1.90; 0.39]	0.196
			Hedges G	-0.06	[-0.14; 0.03]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Week 169	-1.59 (0.43)	-1.83 (0.44)	Difference	0.24	[-0.96; 1.43]	0.700
			Hedges G	0.02	[-0.07; 0.11]	
Week 193	-1.73 (0.45)	-1.91 (0.46)	Difference	0.18	[-1.08; 1.45]	0.778
			Hedges G	0.01	[-0.09; 0.12]	
Week 217	-2.00 (0.53)	-2.03 (0.53)	Difference	0.03	[-1.44; 1.50]	0.970
			Hedges G	0.00	[-0.12; 0.13]	
Week 241	-1.66 (1.03)	-0.75 (1.01)	Difference	-0.92	[-3.76; 1.92]	0.525
			Hedges G	-0.09	[-0.38; 0.20]	
Overall effect	-1.56 (0.31)	-1.29 (0.31)	Difference	-0.27	[-1.13; 0.59]	0.540
			Hedges G	-0.02	[-0.10; 0.05]	

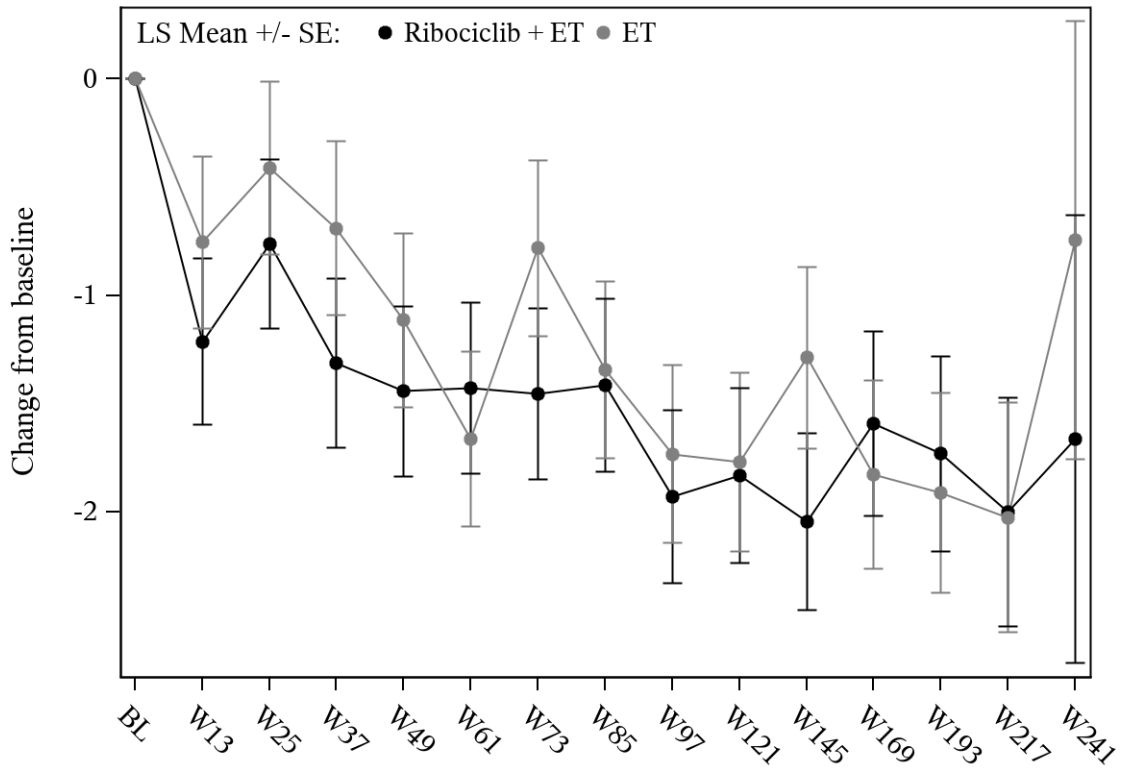
N: Number of patients
 N': Number of patients in the analysis
 CI: Confidence interval
 SD: Standard deviation
 LS Mean: Least square mean
 SE: Standard error
 MMRM: Mixed model for repeated measures
 ET: Endocrine therapy (Anastrozole/Letrozole)

Analysis methods:
 Adjusted mean (LS Mean) change from baseline and difference obtained from MMRM with unstructured covariance matrix:
 change from baseline = treatment + visit + treatment * visit + baseline value + AJCC Anatomic Stage + prior neo/adjuvant chemotherapy + region
 ET was the reference group for treatment group comparison.
 If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
 All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit.

Figure 3-5.1 EQ-5D VAS: line chart of change from baseline (Full Analysis Set)

EQ5D01-Health Today



Ribociclib + ET	1323	1254	1208	1200	1184	1168	1154	1124	1121	1078	1060	908	764	477	90
ET	1259	1184	1143	1125	1129	1103	1102	1082	1064	1040	1007	870	728	480	95

3-6 HADS

Table 3-6.0 HADS: return rates (Full Analysis Set)

	Treatment groups			
	Ribociclib + ET (N = 1424)		ET (N = 1420)	
	N' (%)	Returns n (%)	N' (%)	Returns n (%)
Baseline	1424 (100.0)	1371 (96.3)	1420 (100.0)	1368 (96.3)
Week 13	1424 (100.0)	1274 (89.5)	1420 (100.0)	1206 (84.9)
Week 25	1423 (99.9)	1226 (86.2)	1418 (99.9)	1153 (81.3)
Week 37	1420 (99.7)	1232 (86.8)	1410 (99.3)	1154 (81.8)
Week 49	1418 (99.6)	1209 (85.3)	1408 (99.2)	1152 (81.8)
Week 61	1414 (99.3)	1194 (84.4)	1404 (98.9)	1128 (80.3)
Week 73	1411 (99.1)	1186 (84.1)	1399 (98.5)	1121 (80.1)
Week 85	1409 (98.9)	1158 (82.2)	1392 (98.0)	1105 (79.4)
Week 97	1406 (98.7)	1149 (81.7)	1387 (97.7)	1087 (78.4)
Week 121	1393 (97.8)	1098 (78.8)	1382 (97.3)	1062 (76.8)
Week 145	1379 (96.8)	1083 (78.5)	1369 (96.4)	1035 (75.6)
Week 169	1370 (96.2)	925 (67.5)	1364 (96.1)	887 (65.0)
Week 193	1362 (95.6)	784 (57.6)	1357 (95.6)	744 (54.8)
Week 217	1352 (94.9)	495 (36.6)	1347 (94.9)	489 (36.3)
Week 241	1350 (94.8)	92 (6.8)	1346 (94.8)	96 (7.1)
Week 265	1350 (94.8)	6 (0.4)	1345 (94.7)	4 (0.3)

N': Number of patients who have not died until the respective visit
 ET: Endocrine therapy (Anastrozole/Letrozole)

The number of returns is the number of patients with non-missing data (i.e. at least one [sub-]score present) at the respective visit.

A patients is considered to have not died until the visit if no death was documented during the study, if returns for this PRO are present at the visit or, if no returns are present for this PRO and the patient died, if the death date is after the scheduled visit date.

Percentages of returns refer to N' per group. For N' percentages refer to N per group.

Table 3-6.1 HADS: change from baseline analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Esti- mate	[95% CI]	p-value
HADS - Anxiety						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1315	1257				
Baseline	1315 5.62 (3.59)	1257 5.76 (3.75)				
Week 13	1232 5.75 (3.77)	1169 5.84 (3.86)				
Week 25	1189 5.76 (3.88)	1124 5.75 (3.96)				
Week 37	1190 5.81 (3.88)	1121 5.75 (3.96)				
Week 49	1167 5.80 (4.02)	1121 5.90 (4.05)				
Week 61	1153 5.78 (4.00)	1095 5.95 (4.15)				
Week 73	1144 5.95 (4.23)	1091 5.83 (4.09)				
Week 85	1118 5.85 (4.19)	1078 5.97 (4.21)				
Week 97	1106 5.85 (4.14)	1058 5.99 (4.27)				
Week 121	1059 5.92 (4.19)	1030 6.04 (4.22)				
Week 145	1044 5.84 (4.23)	1006 5.97 (4.25)				
Week 169	890 5.77 (4.09)	861 5.99 (4.24)				
Week 193	754 5.66 (4.19)	724 6.10 (4.38)				
Week 217	475 5.48 (4.11)	477 5.93 (4.30)				
Week 241	92 5.16 (3.62)	96 5.56 (4.07)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	0.11 (0.08)	0.12 (0.08)	Difference	-0.01	[-0.23; 0.21]	0.928
			Hedges G	-0.00	[-0.08; 0.08]	
Week 25	0.15 (0.08)	0.09 (0.08)	Difference	0.06	[-0.17; 0.29]	0.589
			Hedges G	0.02	[-0.06; 0.10]	
Week 37	0.25 (0.09)	0.11 (0.09)	Difference	0.14	[-0.10; 0.38]	0.253
			Hedges G	0.05	[-0.03; 0.13]	
Week 49	0.24 (0.09)	0.22 (0.09)	Difference	0.02	[-0.24; 0.27]	0.901
			Hedges G	0.01	[-0.08; 0.09]	
Week 61	0.22 (0.09)	0.26 (0.09)	Difference	-0.05	[-0.30; 0.21]	0.719
			Hedges G	-0.02	[-0.10; 0.07]	
Week 73	0.36 (0.09)	0.16 (0.10)	Difference	0.20	[-0.07; 0.46]	0.148
			Hedges G	0.06	[-0.02; 0.14]	
Week 85	0.30 (0.10)	0.25 (0.10)	Difference	0.05	[-0.22; 0.32]	0.721
			Hedges G	0.02	[-0.07; 0.10]	
Week 97	0.26 (0.10)	0.33 (0.10)	Difference	-0.07	[-0.34; 0.21]	0.639
			Hedges G	-0.02	[-0.10; 0.06]	
Week 121	0.33 (0.10)	0.33 (0.10)	Difference	0.00	[-0.28; 0.28]	0.994
			Hedges G	0.00	[-0.09; 0.09]	
Week 145	0.32 (0.10)	0.30 (0.10)	Difference	0.02	[-0.26; 0.30]	0.877
			Hedges G	0.01	[-0.08; 0.09]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Week 169	0.27 (0.10)	0.35 (0.11)	Difference	-0.08	[-0.37; 0.21]	0.582
			Hedges G	-0.03	[-0.12; 0.07]	
Week 193	0.15 (0.11)	0.48 (0.12)	Difference	-0.33	[-0.65; -0.01]	0.041
			Hedges G	-0.11	[-0.21; -0.00]	
Week 217	0.29 (0.13)	0.36 (0.13)	Difference	-0.08	[-0.44; 0.28]	0.675
			Hedges G	-0.03	[-0.15; 0.10]	
Week 241	0.21 (0.21)	0.29 (0.21)	Difference	-0.08	[-0.66; 0.50]	0.782
			Hedges G	-0.04	[-0.33; 0.25]	
Overall effect	0.25 (0.08)	0.26 (0.08)	Difference	-0.01	[-0.23; 0.20]	0.892
			Hedges G	-0.01	[-0.08; 0.07]	
HADS - Depression						
	N' Mean (SD)	N' Mean (SD)				
Overall N'	1313	1257				
Baseline	1313 3.52 (3.12)	1257 3.68 (3.17)				
Week 13	1229 3.97 (3.43)	1168 4.00 (3.49)				
Week 25	1188 3.94 (3.46)	1120 3.92 (3.40)				
Week 37	1186 4.10 (3.60)	1118 4.13 (3.58)				
Week 49	1164 4.11 (3.56)	1119 4.22 (3.60)				
Week 61	1151 4.16 (3.70)	1092 4.23 (3.66)				
Week 73	1144 4.27 (3.83)	1093 4.23 (3.67)				
Week 85	1114 4.19 (3.89)	1076 4.32 (3.73)				
Week 97	1105 4.30 (3.82)	1057 4.46 (3.93)				
Week 121	1058 4.41 (3.80)	1030 4.42 (3.92)				
Week 145	1040 4.30 (3.85)	1003 4.45 (3.94)				
Week 169	889 4.25 (3.83)	863 4.40 (3.86)				
Week 193	752 4.24 (3.83)	724 4.39 (4.00)				
Week 217	474 3.96 (3.68)	477 4.41 (3.85)				
Week 241	92 3.93 (3.42)	96 4.30 (4.07)				
Adjusted change	Mean (SE)	Mean (SE)				
Week 13	0.43 (0.07)	0.35 (0.08)	Difference	0.08	[-0.13; 0.28]	0.455
			Hedges G	0.03	[-0.05; 0.11]	
Week 25	0.47 (0.08)	0.33 (0.08)	Difference	0.14	[-0.08; 0.36]	0.216
			Hedges G	0.05	[-0.03; 0.13]	
Week 37	0.65 (0.08)	0.57 (0.09)	Difference	0.09	[-0.15; 0.32]	0.474
			Hedges G	0.03	[-0.05; 0.11]	
Week 49	0.65 (0.08)	0.62 (0.08)	Difference	0.03	[-0.20; 0.26]	0.787
			Hedges G	0.01	[-0.07; 0.09]	
Week 61	0.74 (0.08)	0.62 (0.09)	Difference	0.12	[-0.12; 0.36]	0.327
			Hedges G	0.04	[-0.04; 0.12]	
Week 73	0.84 (0.09)	0.66 (0.09)	Difference	0.19	[-0.06; 0.43]	0.133
			Hedges G	0.06	[-0.02; 0.15]	
Week 85	0.77 (0.09)	0.72 (0.09)	Difference	0.06	[-0.20; 0.31]	0.663

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Week 97	0.89 (0.09)	0.87 (0.09)	Hedges G	0.02	[-0.07; 0.10]	
			Difference	0.02	[-0.24; 0.28]	0.879
Week 121	0.99 (0.09)	0.82 (0.10)	Hedges G	0.01	[-0.08; 0.09]	
			Difference	0.17	[-0.09; 0.43]	0.199
Week 145	0.93 (0.10)	0.86 (0.10)	Hedges G	0.06	[-0.03; 0.14]	
			Difference	0.07	[-0.20; 0.34]	0.591
Week 169	0.92 (0.10)	0.86 (0.10)	Hedges G	0.02	[-0.06; 0.11]	
			Difference	0.05	[-0.23; 0.33]	0.712
Week 193	0.92 (0.11)	0.88 (0.11)	Hedges G	0.02	[-0.08; 0.11]	
			Difference	0.04	[-0.25; 0.34]	0.777
Week 217	0.84 (0.12)	1.00 (0.12)	Hedges G	0.01	[-0.09; 0.12]	
			Difference	-0.16	[-0.48; 0.17]	0.347
Week 241	0.75 (0.18)	1.06 (0.18)	Hedges G	-0.06	[-0.19; 0.07]	
			Difference	-0.31	[-0.82; 0.20]	0.228
Overall effect	0.77 (0.07)	0.73 (0.07)	Difference	0.04	[-0.16; 0.24]	0.677
			Hedges G	0.02	[-0.06; 0.09]	

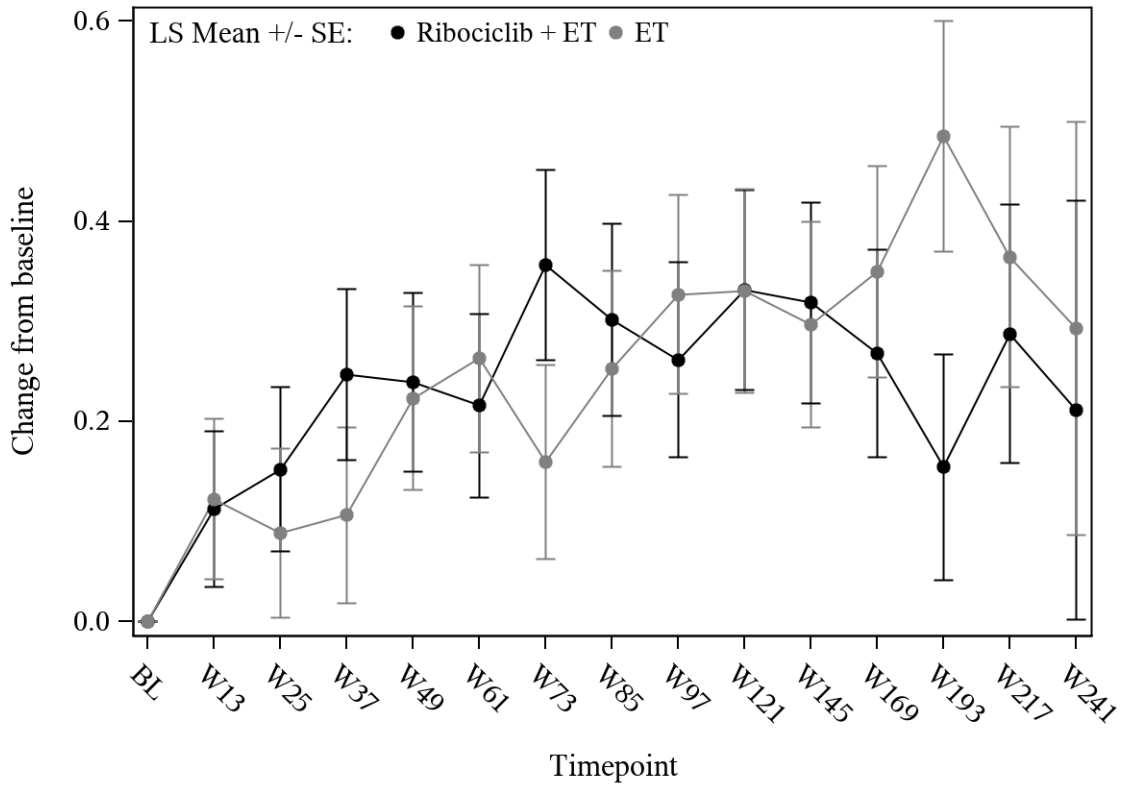
N: Number of patients
 N': Number of patients in the analysis
 CI: Confidence interval
 SD: Standard deviation
 LS Mean: Least square mean
 SE: Standard error
 MMRM: Mixed model for repeated measures
 ET: Endocrine therapy (Anastrozole/Letrozole)

Analysis methods:
 Adjusted mean (LS Mean) change from baseline and difference obtained from MMRM with unstructured covariance matrix:
 change from baseline = treatment + visit + treatment * visit + baseline value + AJCC Anatomic Stage + prior neo/adjuvant chemotherapy + region
 ET was the reference group for treatment group comparison.
 If the model did not converge for a parameter, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.

Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis.
 All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit.

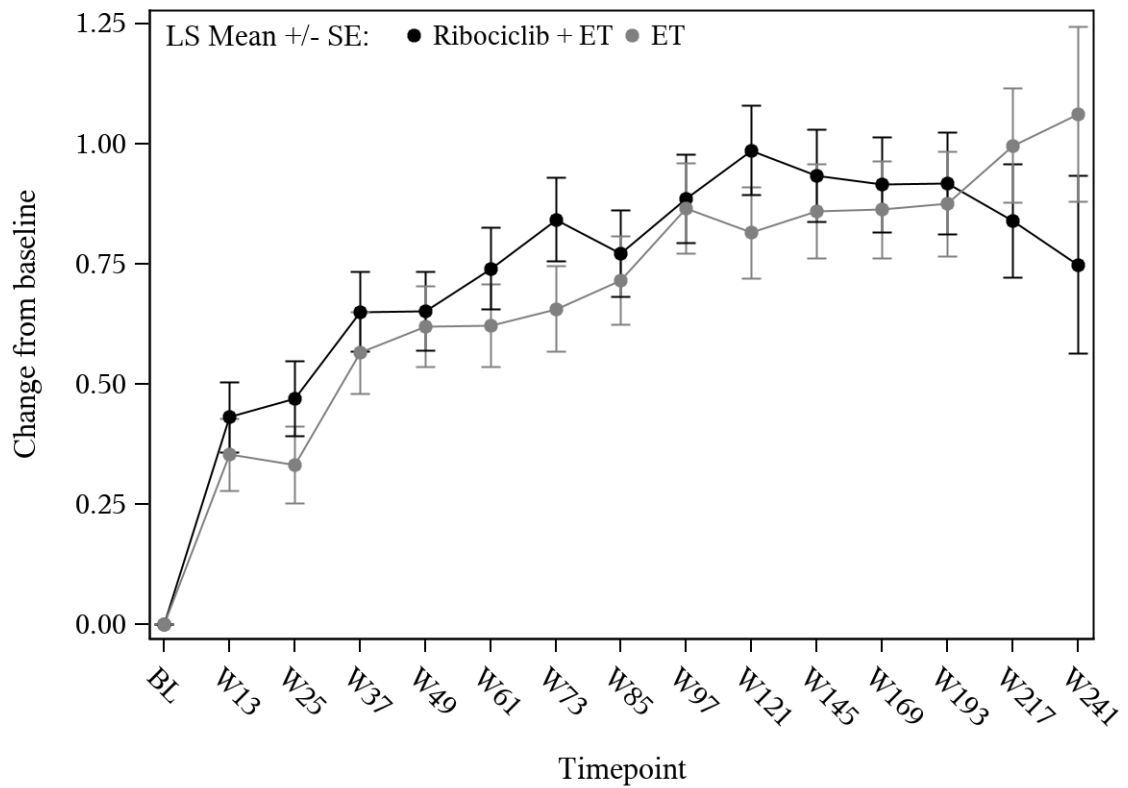
Figure 3-6.1 HADS: line chart of change from baseline (Full Analysis Set)

HADS - Anxiety



Ribociclib + ET	1315	1232	1189	1190	1167	1153	1144	1118	1106	1059	1044	890	754	475	92
ET	1257	1169	1124	1121	1121	1095	1091	1078	1058	1030	1006	861	724	477	96

HADS - Depression



Ribociclib + ET	1313	1229	1188	1186	1164	1151	1144	1114	1105	1058	1040	889	752	474	92
ET	1257	1168	1120	1118	1119	1092	1093	1076	1057	1030	1003	863	724	477	96

4 Adverse events

Table 4-1 Adverse events: binary analysis (Safety Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1409)	ET (N = 1362)	Para- meter	Esti- mate	[95% CI]	p-value
Any adverse event, n (%)	1376 (97.7)	1183 (86.9)	OR	6.31	[4.32; 9.22]	<.001
			RR	1.12	[1.10; 1.15]	<.001
			RD	0.11	[0.09; 0.13]	<.001
Any grade ≥ 3 adverse event, n (%)	883 (62.7)	280 (20.6)	OR	6.49	[5.47; 7.69]	<.001
			RR	3.05	[2.73; 3.41]	<.001
			RD	0.42	[0.39; 0.45]	<.001
Any serious adverse event, n (%)	229 (16.3)	162 (11.9)	OR	1.44	[1.16; 1.79]	0.001
			RR	1.37	[1.13; 1.65]	0.001
			RD	0.04	[0.02; 0.07]	<.001
Any adverse event leading to treatment discontinuation of ribociclib, n (%)	330 (23.4)	N.A.	OR	N.A.		
			RR	N.A.		
			RD	N.A.		
Any adverse event leading to treatment discontinuation of NSAI, n (%)	94 (6.7)	68 (5.0)	OR	1.36	[0.99; 1.88]	0.061
			RR	1.34	[0.99; 1.81]	0.061
			RD	0.02	[-0.00; 0.03]	0.059
Any adverse event leading to treatment discontinuation of any component, n (%)	340 (24.1)	68 (5.0)	OR	6.05	[4.61; 7.95]	<.001
			RR	4.83	[3.77; 6.20]	<.001
			RD	0.19	[0.17; 0.22]	<.001
N: Number of patients n: Number of patients with event CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference N.A.: Not applicable ET: Endocrine therapy (Anastrozole/Letrozole) Analysis methods: OR with Wald 95% CI and p-value obtained from logistic regression model: $\text{logit}(\text{proportion}) = \text{treatment}$ RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.						

Table 4-2 Adverse events by SOC and PT: binary analysis (Safety Set)

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)		Estimate	[95% CI]	p-value
Investigations, n (%)	902 (64.0)	417 (30.6)	OR	4.03	[3.44; 4.72]	<.001
			RR	2.09	[1.91; 2.29]	<.001
			RD	0.33	[0.30; 0.37]	<.001
Alanine aminotransferase increased, n (%)	302 (21.4)	71 (5.2)	OR	4.96	[3.78; 6.50]	<.001
			RR	4.11	[3.21; 5.27]	<.001
			RD	0.16	[0.14; 0.19]	<.001
Neutrophil count decreased, n (%)	302 (21.4)	13 (1.0)	OR	28.30	[16.15; 49.59]	<.001
			RR	22.46	[12.95; 38.93]	<.001
			RD	0.20	[0.18; 0.23]	<.001
Aspartate aminotransferase increased, n (%)	261 (18.5)	78 (5.7)	OR	3.74	[2.87; 4.88]	<.001
			RR	3.23	[2.54; 4.12]	<.001
			RD	0.13	[0.10; 0.15]	<.001
SARS-CoV-2 test positive, n (%)	256 (18.2)	159 (11.7)	OR	1.68	[1.36; 2.08]	<.001
			RR	1.56	[1.30; 1.87]	<.001
			RD	0.06	[0.04; 0.09]	<.001
White blood cell count decreased, n (%)	116 (8.2)	14 (1.0)	OR	8.64	[4.93; 15.12]	<.001
			RR	8.01	[4.62; 13.88]	<.001
			RD	0.07	[0.06; 0.09]	<.001
SARS-CoV-2 test negative, n (%)	84 (6.0)	42 (3.1)	OR	1.99	[1.37; 2.91]	<.001
			RR	1.93	[1.34; 2.78]	<.001
			RD	0.03	[0.01; 0.04]	<.001
Gamma-glutamyltransferase increased, n (%)	77 (5.5)	44 (3.2)	OR	1.73	[1.19; 2.53]	0.004
			RR	1.69	[1.18; 2.43]	0.005
			RD	0.02	[0.01; 0.04]	0.004
Blood creatinine increased, n (%)	75 (5.3)	19 (1.4)	OR	3.97	[2.39; 6.61]	<.001
			RR	3.82	[2.32; 6.28]	<.001
			RD	0.04	[0.03; 0.05]	<.001
Electrocardiogram QT prolonged, n (%)	55 (3.9)	10 (0.7)	OR	5.49	[2.79; 10.82]	<.001
			RR	5.32	[2.72; 10.39]	<.001
			RD	0.03	[0.02; 0.04]	<.001
Blood magnesium decreased, n (%)	53 (3.8)	18 (1.3)	OR	2.92	[1.70; 5.01]	<.001
			RR	2.85	[1.68; 4.83]	<.001
			RD	0.02	[0.01; 0.04]	<.001
Weight increased, n (%)	43 (3.1)	32 (2.3)	OR	1.31	[0.82; 2.08]	0.256
			RR	1.30	[0.83; 2.04]	0.256
			RD	0.01	[-0.01; 0.02]	0.254
Blood bilirubin increased, n (%)	38 (2.7)	16 (1.2)	OR	2.33	[1.29; 4.20]	0.005
			RR	2.30	[1.29; 4.10]	0.005

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1409)	ET (N = 1362)	Para- meter	Esti- mate	[95% CI]	p-value
			RD	0.02	[0.01; 0.03]	0.003
Blood lactate dehydrogenase increased, n (%)	38 (2.7)	24 (1.8)	OR	1.55	[0.92; 2.59]	0.099
			RR	1.53	[0.92; 2.54]	0.099
			RD	0.01	[-0.00; 0.02]	0.095
Blood alkaline phosphatase increased, n (%)	36 (2.6)	37 (2.7)	OR	0.94	[0.59; 1.49]	0.791
			RR	0.94	[0.60; 1.48]	0.791
			RD	-0.00	[-0.01; 0.01]	0.791
Lipase increased, n (%)	36 (2.6)	25 (1.8)	OR	1.40	[0.84; 2.35]	0.199
			RR	1.39	[0.84; 2.31]	0.199
			RD	0.01	[-0.00; 0.02]	0.196
Weight decreased, n (%)	35 (2.5)	21 (1.5)	OR	1.63	[0.94; 2.81]	0.081
			RR	1.61	[0.94; 2.75]	0.081
			RD	0.01	[-0.00; 0.02]	0.077
Glomerular filtration rate decreased, n (%)	32 (2.3)	11 (0.8)	OR	2.85	[1.43; 5.68]	0.003
			RR	2.81	[1.42; 5.56]	0.003
			RD	0.01	[0.01; 0.02]	0.002
Platelet count decreased, n (%)	32 (2.3)	6 (0.4)	OR	5.25	[2.19; 12.60]	<.001
			RR	5.16	[2.16; 12.29]	<.001
			RD	0.02	[0.01; 0.03]	<.001
Lymphocyte count decreased, n (%)	30 (2.1)	11 (0.8)	OR	2.67	[1.33; 5.35]	0.006
			RR	2.64	[1.33; 5.24]	0.006
			RD	0.01	[0.00; 0.02]	0.004
Blood uric acid increased, n (%)	25 (1.8)	23 (1.7)	OR	1.05	[0.59; 1.86]	0.863
			RR	1.05	[0.60; 1.84]	0.863
			RD	0.00	[-0.01; 0.01]	0.863
Blood cholesterol increased, n (%)	15 (1.1)	24 (1.8)	OR	0.60	[0.31; 1.15]	0.123
			RR	0.60	[0.32; 1.15]	0.123
			RD	-0.01	[-0.02; 0.00]	0.121
Blood urea increased, n (%)	23 (1.6)	24 (1.8)	OR	0.93	[0.52; 1.65]	0.791
			RR	0.93	[0.53; 1.63]	0.791
			RD	-0.00	[-0.01; 0.01]	0.792
Blood sodium decreased, n (%)	23 (1.6)	15 (1.1)	OR	1.49	[0.77; 2.87]	0.233
			RR	1.48	[0.78; 2.83]	0.233
			RD	0.01	[-0.00; 0.01]	0.228
Amylase increased, n (%)	22 (1.6)	19 (1.4)	OR	1.12	[0.60; 2.08]	0.717
			RR	1.12	[0.61; 2.06]	0.717
			RD	0.00	[-0.01; 0.01]	0.717
Adjusted calcium decreased, n (%)	20 (1.4)	6 (0.4)	OR	3.25	[1.30; 8.13]	0.012
			RR	3.22	[1.30; 8.00]	0.012
			RD	0.01	[0.00; 0.02]	0.007

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1409)	ET (N = 1362)	Para- meter	Esti- mate	[95% CI]	p-value
Blood calcium decreased, n (%)	17 (1.2)	8 (0.6)	OR	2.07	[0.89; 4.81]	0.092
			RR	2.05	[0.89; 4.74]	0.092
			RD	0.01	[-0.00; 0.01]	0.083
Blood glucose increased, n (%)	12 (0.9)	17 (1.2)	OR	0.68	[0.32; 1.43]	0.308
			RR	0.68	[0.33; 1.42]	0.308
			RD	-0.00	[-0.01; 0.00]	0.307
Blood phosphorus increased, n (%)	16 (1.1)	16 (1.2)	OR	0.97	[0.48; 1.94]	0.923
			RR	0.97	[0.49; 1.93]	0.923
			RD	-0.00	[-0.01; 0.01]	0.923
Blood potassium increased, n (%)	15 (1.1)	2 (0.1)	OR	7.32	[1.67; 32.05]	0.008
			RR	7.25	[1.66; 31.64]	0.008
			RD	0.01	[0.00; 0.01]	0.002
Musculoskeletal and connective tissue disorders, n (%)	832 (59.0)	861 (63.2)	OR	0.84	[0.72; 0.98]	0.025
			RR	0.93	[0.88; 0.99]	0.025
			RD	-0.04	[-0.08; -0.01]	0.024
Arthralgia, n (%)	504 (35.8)	575 (42.2)	OR	0.76	[0.65; 0.89]	<.001
			RR	0.85	[0.77; 0.93]	<.001
			RD	-0.06	[-0.10; -0.03]	<.001
Back pain, n (%)	146 (10.4)	129 (9.5)	OR	1.10	[0.86; 1.42]	0.433
			RR	1.09	[0.87; 1.37]	0.433
			RD	0.01	[-0.01; 0.03]	0.433
Pain in extremity, n (%)	140 (9.9)	132 (9.7)	OR	1.03	[0.80; 1.32]	0.829
			RR	1.03	[0.82; 1.28]	0.829
			RD	0.00	[-0.02; 0.02]	0.829
Myalgia, n (%)	99 (7.0)	81 (5.9)	OR	1.20	[0.88; 1.62]	0.250
			RR	1.18	[0.89; 1.57]	0.250
			RD	0.01	[-0.01; 0.03]	0.248
Bone pain, n (%)	54 (3.8)	63 (4.6)	OR	0.82	[0.57; 1.19]	0.300
			RR	0.83	[0.58; 1.18]	0.300
			RD	-0.01	[-0.02; 0.01]	0.300
Muscle spasms, n (%)	60 (4.3)	45 (3.3)	OR	1.30	[0.88; 1.93]	0.190
			RR	1.29	[0.88; 1.88]	0.190
			RD	0.01	[-0.00; 0.02]	0.187
Osteoporosis, n (%)	41 (2.9)	50 (3.7)	OR	0.79	[0.52; 1.20]	0.262
			RR	0.79	[0.53; 1.19]	0.262
			RD	-0.01	[-0.02; 0.01]	0.262
Musculoskeletal chest pain, n (%)	44 (3.1)	44 (3.2)	OR	0.97	[0.63; 1.48]	0.871
			RR	0.97	[0.64; 1.46]	0.872
			RD	-0.00	[-0.01; 0.01]	0.872
Osteopenia, n (%)	43 (3.1)	26 (1.9)	OR	1.62	[0.99; 2.65]	0.056
			RR	1.60	[0.99; 2.59]	0.056

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1409)	ET (N = 1362)	Para- meter	Esti- mate	[95% CI]	p-value
			RD	0.01	[-0.00; 0.02]	0.053
Osteoarthritis, n (%)	41 (2.9)	39 (2.9)	OR	1.02	[0.65; 1.59]	0.942
			RR	1.02	[0.66; 1.57]	0.942
			RD	0.00	[-0.01; 0.01]	0.942
Joint stiffness, n (%)	32 (2.3)	35 (2.6)	OR	0.88	[0.54; 1.43]	0.609
			RR	0.88	[0.55; 1.42]	0.609
			RD	-0.00	[-0.01; 0.01]	0.609
Musculoskeletal pain, n (%)	23 (1.6)	33 (2.4)	OR	0.67	[0.39; 1.14]	0.142
			RR	0.67	[0.40; 1.14]	0.142
			RD	-0.01	[-0.02; 0.00]	0.140
Neck pain, n (%)	31 (2.2)	23 (1.7)	OR	1.31	[0.76; 2.26]	0.332
			RR	1.30	[0.76; 2.22]	0.332
			RD	0.01	[-0.01; 0.02]	0.329
Spinal pain, n (%)	30 (2.1)	22 (1.6)	OR	1.33	[0.76; 2.31]	0.320
			RR	1.32	[0.76; 2.27]	0.321
			RD	0.01	[-0.00; 0.02]	0.318
Musculoskeletal stiffness, n (%)	22 (1.6)	27 (2.0)	OR	0.78	[0.44; 1.38]	0.402
			RR	0.79	[0.45; 1.38]	0.402
			RD	-0.00	[-0.01; 0.01]	0.401
Arthritis, n (%)	18 (1.3)	21 (1.5)	OR	0.83	[0.44; 1.56]	0.555
			RR	0.83	[0.44; 1.55]	0.555
			RD	-0.00	[-0.01; 0.01]	0.555
Tendonitis, n (%)	11 (0.8)	19 (1.4)	OR	0.56	[0.26; 1.17]	0.123
			RR	0.56	[0.27; 1.17]	0.124
			RD	-0.01	[-0.01; 0.00]	0.120
Joint swelling, n (%)	18 (1.3)	7 (0.5)	OR	2.50	[1.04; 6.02]	0.040
			RR	2.49	[1.04; 5.93]	0.040
			RD	0.01	[0.00; 0.01]	0.032
Flank pain, n (%)	15 (1.1)	7 (0.5)	OR	2.08	[0.85; 5.12]	0.110
			RR	2.07	[0.85; 5.06]	0.110
			RD	0.01	[-0.00; 0.01]	0.100
Trigger finger, n (%)	13 (0.9)	14 (1.0)	OR	0.90	[0.42; 1.91]	0.778
			RR	0.90	[0.42; 1.90]	0.778
			RD	-0.00	[-0.01; 0.01]	0.778
General disorders and administration site conditions, n (%)	774 (54.9)	496 (36.4)	OR	2.13	[1.83; 2.48]	<.001
			RR	1.51	[1.39; 1.64]	<.001
			RD	0.19	[0.15; 0.22]	<.001
Fatigue, n (%)	335 (23.8)	182 (13.4)	OR	2.02	[1.66; 2.47]	<.001
			RR	1.78	[1.51; 2.10]	<.001
			RD	0.10	[0.08; 0.13]	<.001

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1409)	ET (N = 1362)	Para- meter	Esti- mate	[95% CI]	p-value
Asthenia, n (%)	241 (17.1)	159 (11.7)	OR	1.56	[1.26; 1.94]	<.001
			RR	1.47	[1.22; 1.76]	<.001
			RD	0.05	[0.03; 0.08]	<.001
Pyrexia, n (%)	133 (9.4)	70 (5.1)	OR	1.92	[1.43; 2.60]	<.001
			RR	1.84	[1.39; 2.43]	<.001
			RD	0.04	[0.02; 0.06]	<.001
Oedema peripheral, n (%)	89 (6.3)	50 (3.7)	OR	1.77	[1.24; 2.52]	0.002
			RR	1.72	[1.23; 2.41]	0.002
			RD	0.03	[0.01; 0.04]	0.001
Influenza like illness, n (%)	43 (3.1)	25 (1.8)	OR	1.68	[1.02; 2.77]	0.041
			RR	1.66	[1.02; 2.71]	0.041
			RD	0.01	[0.00; 0.02]	0.038
Pain, n (%)	43 (3.1)	19 (1.4)	OR	2.23	[1.29; 3.84]	0.004
			RR	2.19	[1.28; 3.73]	0.004
			RD	0.02	[0.01; 0.03]	0.003
Mucosal inflammation, n (%)	35 (2.5)	5 (0.4)	OR	6.91	[2.70; 17.70]	<.001
			RR	6.77	[2.66; 17.22]	<.001
			RD	0.02	[0.01; 0.03]	<.001
Chest pain, n (%)	33 (2.3)	34 (2.5)	OR	0.94	[0.58; 1.52]	0.792
			RR	0.94	[0.58; 1.51]	0.792
			RD	-0.00	[-0.01; 0.01]	0.792
Non-cardiac chest pain, n (%)	32 (2.3)	18 (1.3)	OR	1.74	[0.97; 3.11]	0.064
			RR	1.72	[0.97; 3.05]	0.064
			RD	0.01	[-0.00; 0.02]	0.059
Peripheral swelling, n (%)	30 (2.1)	24 (1.8)	OR	1.21	[0.71; 2.09]	0.485
			RR	1.21	[0.71; 2.06]	0.485
			RD	0.00	[-0.01; 0.01]	0.484
Axillary pain, n (%)	28 (2.0)	21 (1.5)	OR	1.29	[0.73; 2.29]	0.375
			RR	1.29	[0.74; 2.26]	0.375
			RD	0.00	[-0.01; 0.01]	0.373
Chills, n (%)	25 (1.8)	10 (0.7)	OR	2.44	[1.17; 5.10]	0.018
			RR	2.42	[1.17; 5.01]	0.018
			RD	0.01	[0.00; 0.02]	0.013
Chest discomfort, n (%)	19 (1.3)	11 (0.8)	OR	1.68	[0.80; 3.54]	0.174
			RR	1.67	[0.80; 3.50]	0.174
			RD	0.01	[-0.00; 0.01]	0.167
Malaise, n (%)	17 (1.2)	7 (0.5)	OR	2.36	[0.98; 5.72]	0.056
			RR	2.35	[0.98; 5.64]	0.057
			RD	0.01	[0.00; 0.01]	0.048
Gastrointestinal disorders, n (%)	760 (53.9)	384 (28.2)	OR	2.98	[2.55; 3.49]	<.001
			RR	1.91	[1.74; 2.11]	<.001

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1409)	ET (N = 1362)	Para- meter	Esti- mate	[95% CI]	p-value
			RD	0.26	[0.22; 0.29]	<.001
Nausea, n (%)	346 (24.6)	99 (7.3)	OR	4.15	[3.27; 5.27]	<.001
			RR	3.38	[2.74; 4.17]	<.001
			RD	0.17	[0.15; 0.20]	<.001
Diarrhoea, n (%)	241 (17.1)	86 (6.3)	OR	3.06	[2.36; 3.96]	<.001
			RR	2.71	[2.14; 3.43]	<.001
			RD	0.11	[0.08; 0.13]	<.001
Constipation, n (%)	187 (13.3)	70 (5.1)	OR	2.82	[2.12; 3.76]	<.001
			RR	2.58	[1.98; 3.36]	<.001
			RD	0.08	[0.06; 0.10]	<.001
Vomiting, n (%)	119 (8.4)	51 (3.7)	OR	2.37	[1.69; 3.32]	<.001
			RR	2.26	[1.64; 3.10]	<.001
			RD	0.05	[0.03; 0.06]	<.001
Abdominal pain, n (%)	89 (6.3)	42 (3.1)	OR	2.12	[1.46; 3.08]	<.001
			RR	2.05	[1.43; 2.93]	<.001
			RD	0.03	[0.02; 0.05]	<.001
Abdominal pain upper, n (%)	67 (4.8)	43 (3.2)	OR	1.53	[1.04; 2.26]	0.032
			RR	1.51	[1.03; 2.19]	0.033
			RD	0.02	[0.00; 0.03]	0.031
Dyspepsia, n (%)	66 (4.7)	32 (2.3)	OR	2.04	[1.33; 3.14]	0.001
			RR	1.99	[1.32; 3.02]	0.001
			RD	0.02	[0.01; 0.04]	<.001
Dry mouth, n (%)	58 (4.1)	30 (2.2)	OR	1.91	[1.22; 2.98]	0.005
			RR	1.87	[1.21; 2.89]	0.005
			RD	0.02	[0.01; 0.03]	0.004
Stomatitis, n (%)	49 (3.5)	6 (0.4)	OR	8.14	[3.48; 19.07]	<.001
			RR	7.89	[3.39; 18.37]	<.001
			RD	0.03	[0.02; 0.04]	<.001
Gastroesophageal reflux disease, n (%)	41 (2.9)	30 (2.2)	OR	1.33	[0.83; 2.14]	0.240
			RR	1.32	[0.83; 2.10]	0.241
			RD	0.01	[-0.00; 0.02]	0.238
Toothache, n (%)	26 (1.8)	8 (0.6)	OR	3.18	[1.44; 7.05]	0.004
			RR	3.14	[1.43; 6.91]	0.004
			RD	0.01	[0.00; 0.02]	0.002
Abdominal distension, n (%)	25 (1.8)	6 (0.4)	OR	4.08	[1.67; 9.98]	0.002
			RR	4.03	[1.66; 9.79]	0.002
			RD	0.01	[0.01; 0.02]	<.001
Haemorrhoids, n (%)	23 (1.6)	6 (0.4)	OR	3.75	[1.52; 9.24]	0.004
			RR	3.71	[1.51; 9.07]	0.004
			RD	0.01	[0.00; 0.02]	0.002

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1409)	ET (N = 1362)	Para- meter	Esti- mate	[95% CI]	p-value
Mouth ulceration, n (%)	18 (1.3)	2 (0.1)	OR	8.80	[2.04; 37.97]	0.004
			RR	8.70	[2.02; 37.42]	0.004
			RD	0.01	[0.01; 0.02]	<.001
Abdominal discomfort, n (%)	15 (1.1)	12 (0.9)	OR	1.21	[0.56; 2.60]	0.623
			RR	1.21	[0.57; 2.57]	0.623
			RD	0.00	[-0.01; 0.01]	0.622
Infections and infestations, n (%)	694 (49.3)	477 (35.0)	OR	1.80	[1.55; 2.10]	<.001
			RR	1.41	[1.29; 1.54]	<.001
			RD	0.14	[0.11; 0.18]	<.001
COVID-19, n (%)	263 (18.7)	168 (12.3)	OR	1.63	[1.32; 2.01]	<.001
			RR	1.51	[1.27; 1.81]	<.001
			RD	0.06	[0.04; 0.09]	<.001
Urinary tract infection, n (%)	109 (7.7)	75 (5.5)	OR	1.44	[1.06; 1.95]	0.019
			RR	1.40	[1.06; 1.87]	0.019
			RD	0.02	[0.00; 0.04]	0.018
Nasopharyngitis, n (%)	81 (5.7)	57 (4.2)	OR	1.40	[0.99; 1.98]	0.060
			RR	1.37	[0.99; 1.91]	0.060
			RD	0.02	[-0.00; 0.03]	0.058
Upper respiratory tract infection, n (%)	61 (4.3)	39 (2.9)	OR	1.53	[1.02; 2.31]	0.040
			RR	1.51	[1.02; 2.24]	0.040
			RD	0.01	[0.00; 0.03]	0.038
Herpes zoster, n (%)	36 (2.6)	29 (2.1)	OR	1.21	[0.73; 1.98]	0.460
			RR	1.20	[0.74; 1.95]	0.460
			RD	0.00	[-0.01; 0.02]	0.458
Sinusitis, n (%)	33 (2.3)	27 (2.0)	OR	1.19	[0.71; 1.98]	0.516
			RR	1.18	[0.71; 1.95]	0.516
			RD	0.00	[-0.01; 0.01]	0.515
Suspected COVID-19, n (%)	29 (2.1)	11 (0.8)	OR	2.58	[1.28; 5.19]	0.008
			RR	2.55	[1.28; 5.08]	0.008
			RD	0.01	[0.00; 0.02]	0.005
Pneumonia, n (%)	24 (1.7)	16 (1.2)	OR	1.46	[0.77; 2.76]	0.246
			RR	1.45	[0.77; 2.72]	0.246
			RD	0.01	[-0.00; 0.01]	0.242
Respiratory tract infection viral, n (%)	23 (1.6)	14 (1.0)	OR	1.60	[0.82; 3.12]	0.170
			RR	1.59	[0.82; 3.07]	0.170
			RD	0.01	[-0.00; 0.01]	0.164
Bronchitis, n (%)	22 (1.6)	18 (1.3)	OR	1.18	[0.63; 2.22]	0.597
			RR	1.18	[0.64; 2.19]	0.597
			RD	0.00	[-0.01; 0.01]	0.596
Cellulitis, n (%)	22 (1.6)	15 (1.1)	OR	1.42	[0.74; 2.76]	0.294
			RR	1.42	[0.74; 2.72]	0.294

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1409)	ET (N = 1362)	Para- meter	Esti- mate	[95% CI]	p-value
			RD	0.00	[-0.00; 0.01]	0.290
Tooth infection, n (%)	20 (1.4)	12 (0.9)	OR	1.62	[0.79; 3.33]	0.189
			RR	1.61	[0.79; 3.28]	0.189
			RD	0.01	[-0.00; 0.01]	0.183
Gastroenteritis, n (%)	19 (1.3)	10 (0.7)	OR	1.85	[0.86; 3.99]	0.118
			RR	1.84	[0.86; 3.94]	0.118
			RD	0.01	[-0.00; 0.01]	0.110
Conjunctivitis, n (%)	17 (1.2)	10 (0.7)	OR	1.65	[0.75; 3.62]	0.210
			RR	1.64	[0.76; 3.58]	0.211
			RD	0.00	[-0.00; 0.01]	0.204
Cystitis, n (%)	17 (1.2)	11 (0.8)	OR	1.50	[0.70; 3.21]	0.297
			RR	1.49	[0.70; 3.18]	0.297
			RD	0.00	[-0.00; 0.01]	0.292
Influenza, n (%)	16 (1.1)	13 (1.0)	OR	1.19	[0.57; 2.49]	0.640
			RR	1.19	[0.57; 2.46]	0.640
			RD	0.00	[-0.01; 0.01]	0.639
Oral herpes, n (%)	15 (1.1)	11 (0.8)	OR	1.32	[0.60; 2.89]	0.484
			RR	1.32	[0.61; 2.86]	0.485
			RD	0.00	[-0.00; 0.01]	0.482
Blood and lymphatic system disorders, n (%)	686 (48.7)	114 (8.4)	OR	10.39	[8.35; 12.92]	<.001
			RR	5.82	[4.84; 6.99]	<.001
			RD	0.40	[0.37; 0.43]	<.001
Neutropenia, n (%)	581 (41.2)	31 (2.3)	OR	30.13	[20.78; 43.68]	<.001
			RR	18.12	[12.72; 25.80]	<.001
			RD	0.39	[0.36; 0.42]	<.001
Leukopenia, n (%)	215 (15.3)	21 (1.5)	OR	11.50	[7.30; 18.12]	<.001
			RR	9.90	[6.36; 15.40]	<.001
			RD	0.14	[0.12; 0.16]	<.001
Anaemia, n (%)	136 (9.7)	42 (3.1)	OR	3.36	[2.36; 4.79]	<.001
			RR	3.13	[2.23; 4.39]	<.001
			RD	0.07	[0.05; 0.08]	<.001
Thrombocytopenia, n (%)	75 (5.3)	23 (1.7)	OR	3.27	[2.04; 5.25]	<.001
			RR	3.15	[1.99; 5.00]	<.001
			RD	0.04	[0.02; 0.05]	<.001
Lymphopenia, n (%)	52 (3.7)	6 (0.4)	OR	8.66	[3.71; 20.22]	<.001
			RR	8.38	[3.61; 19.44]	<.001
			RD	0.03	[0.02; 0.04]	<.001
Nervous system disorders, n (%)	548 (38.9)	411 (30.2)	OR	1.47	[1.26; 1.72]	<.001
			RR	1.29	[1.16; 1.43]	<.001
			RD	0.09	[0.05; 0.12]	<.001

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1409)	ET (N = 1362)	Para- meter	Esti- mate	[95% CI]	p-value
Headache, n (%)	265 (18.8)	189 (13.9)	OR	1.44	[1.17; 1.76]	<.001
			RR	1.36	[1.14; 1.61]	<.001
			RD	0.05	[0.02; 0.08]	<.001
Dizziness, n (%)	129 (9.2)	63 (4.6)	OR	2.08	[1.52; 2.84]	<.001
			RR	1.98	[1.48; 2.65]	<.001
			RD	0.05	[0.03; 0.06]	<.001
Neuropathy peripheral, n (%)	33 (2.3)	34 (2.5)	OR	0.94	[0.58; 1.52]	0.792
			RR	0.94	[0.58; 1.51]	0.792
			RD	-0.00	[-0.01; 0.01]	0.792
Dysgeusia, n (%)	30 (2.1)	7 (0.5)	OR	4.21	[1.84; 9.62]	<.001
			RR	4.14	[1.83; 9.40]	<.001
			RD	0.02	[0.01; 0.02]	<.001
Paraesthesia, n (%)	25 (1.8)	30 (2.2)	OR	0.80	[0.47; 1.37]	0.420
			RR	0.81	[0.48; 1.36]	0.420
			RD	-0.00	[-0.01; 0.01]	0.420
Amnesia, n (%)	24 (1.7)	16 (1.2)	OR	1.46	[0.77; 2.76]	0.246
			RR	1.45	[0.77; 2.72]	0.246
			RD	0.01	[-0.00; 0.01]	0.242
Migraine, n (%)	21 (1.5)	7 (0.5)	OR	2.93	[1.24; 6.91]	0.014
			RR	2.90	[1.24; 6.80]	0.014
			RD	0.01	[0.00; 0.02]	0.009
Peripheral sensory neuropathy, n (%)	20 (1.4)	17 (1.2)	OR	1.14	[0.59; 2.18]	0.695
			RR	1.14	[0.60; 2.16]	0.695
			RD	0.00	[-0.01; 0.01]	0.694
Sciatica, n (%)	20 (1.4)	17 (1.2)	OR	1.14	[0.59; 2.18]	0.695
			RR	1.14	[0.60; 2.16]	0.695
			RD	0.00	[-0.01; 0.01]	0.694
Taste disorder, n (%)	18 (1.3)	6 (0.4)	OR	2.92	[1.16; 7.39]	0.023
			RR	2.90	[1.15; 7.28]	0.023
			RD	0.01	[0.00; 0.02]	0.016
Memory impairment, n (%)	17 (1.2)	14 (1.0)	OR	1.18	[0.58; 2.39]	0.655
			RR	1.17	[0.58; 2.37]	0.655
			RD	0.00	[-0.01; 0.01]	0.654
Cerebrovascular disorder, n (%)	16 (1.1)	13 (1.0)	OR	1.19	[0.57; 2.49]	0.640
			RR	1.19	[0.57; 2.46]	0.640
			RD	0.00	[-0.01; 0.01]	0.639
Disturbance in attention, n (%)	16 (1.1)	10 (0.7)	OR	1.55	[0.70; 3.43]	0.277
			RR	1.55	[0.70; 3.40]	0.277
			RD	0.00	[-0.00; 0.01]	0.271
Anosmia, n (%)	15 (1.1)	6 (0.4)	OR	2.43	[0.94; 6.29]	0.067
			RR	2.42	[0.94; 6.21]	0.067

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1409)	ET (N = 1362)	Parameter	Estimate	[95% CI]	p-value
			RD	0.01	[-0.00; 0.01]	0.056
Carpal tunnel syndrome, n (%)	10 (0.7)	15 (1.1)	OR	0.64	[0.29; 1.43]	0.280
			RR	0.64	[0.29; 1.43]	0.280
			RD	-0.00	[-0.01; 0.00]	0.277
Hypoaesthesia, n (%)	15 (1.1)	9 (0.7)	OR	1.62	[0.71; 3.71]	0.256
			RR	1.61	[0.71; 3.67]	0.256
			RD	0.00	[-0.00; 0.01]	0.249
Skin and subcutaneous tissue disorders, n (%)	536 (38.0)	274 (20.1)	OR	2.44	[2.06; 2.89]	<.001
			RR	1.89	[1.67; 2.14]	<.001
			RD	0.18	[0.15; 0.21]	<.001
Alopecia, n (%)	231 (16.4)	66 (4.8)	OR	3.85	[2.90; 5.12]	<.001
			RR	3.38	[2.60; 4.40]	<.001
			RD	0.12	[0.09; 0.14]	<.001
Pruritus, n (%)	108 (7.7)	43 (3.2)	OR	2.55	[1.77; 3.66]	<.001
			RR	2.43	[1.72; 3.43]	<.001
			RD	0.05	[0.03; 0.06]	<.001
Rash, n (%)	102 (7.2)	38 (2.8)	OR	2.72	[1.86; 3.98]	<.001
			RR	2.59	[1.80; 3.74]	<.001
			RD	0.04	[0.03; 0.06]	<.001
Dry skin, n (%)	46 (3.3)	18 (1.3)	OR	2.52	[1.45; 4.37]	<.001
			RR	2.47	[1.44; 4.24]	0.001
			RD	0.02	[0.01; 0.03]	<.001
Erythema, n (%)	29 (2.1)	19 (1.4)	OR	1.49	[0.83; 2.66]	0.184
			RR	1.48	[0.83; 2.62]	0.184
			RD	0.01	[-0.00; 0.02]	0.179
Scar pain, n (%)	18 (1.3)	23 (1.7)	OR	0.75	[0.40; 1.40]	0.372
			RR	0.76	[0.41; 1.40]	0.372
			RD	-0.00	[-0.01; 0.00]	0.371
Rash maculo-papular, n (%)	16 (1.1)	7 (0.5)	OR	2.22	[0.91; 5.42]	0.079
			RR	2.21	[0.91; 5.35]	0.079
			RD	0.01	[-0.00; 0.01]	0.069
Metabolism and nutrition disorders, n (%)	460 (32.6)	233 (17.1)	OR	2.35	[1.96; 2.81]	<.001
			RR	1.91	[1.66; 2.19]	<.001
			RD	0.16	[0.12; 0.19]	<.001
Hypomagnesaemia, n (%)	108 (7.7)	30 (2.2)	OR	3.68	[2.44; 5.56]	<.001
			RR	3.48	[2.34; 5.18]	<.001
			RD	0.05	[0.04; 0.07]	<.001
Hyperkalaemia, n (%)	82 (5.8)	18 (1.3)	OR	4.61	[2.75; 7.73]	<.001
			RR	4.40	[2.66; 7.29]	<.001
			RD	0.04	[0.03; 0.06]	<.001

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1409)	ET (N = 1362)	Para- meter	Esti- mate	[95% CI]	p-value
Decreased appetite, n (%)	71 (5.0)	34 (2.5)	OR	2.07	[1.37; 3.14]	<.001
			RR	2.02	[1.35; 3.02]	<.001
			RD	0.03	[0.01; 0.04]	<.001
Hypocalcaemia, n (%)	62 (4.4)	8 (0.6)	OR	7.79	[3.72; 16.33]	<.001
			RR	7.49	[3.60; 15.58]	<.001
			RD	0.04	[0.03; 0.05]	<.001
Hyperglycaemia, n (%)	61 (4.3)	58 (4.3)	OR	1.02	[0.70; 1.47]	0.927
			RR	1.02	[0.72; 1.45]	0.927
			RD	0.00	[-0.01; 0.02]	0.927
Hypokalaemia, n (%)	49 (3.5)	22 (1.6)	OR	2.19	[1.32; 3.65]	0.002
			RR	2.15	[1.31; 3.54]	0.003
			RD	0.02	[0.01; 0.03]	0.002
Hypercalcaemia, n (%)	31 (2.2)	16 (1.2)	OR	1.89	[1.03; 3.48]	0.040
			RR	1.87	[1.03; 3.41]	0.040
			RD	0.01	[0.00; 0.02]	0.036
Hyperuricaemia, n (%)	25 (1.8)	17 (1.2)	OR	1.43	[0.77; 2.66]	0.260
			RR	1.42	[0.77; 2.62]	0.260
			RD	0.01	[-0.00; 0.01]	0.256
Hypercholesterolaemia, n (%)	21 (1.5)	22 (1.6)	OR	0.92	[0.50; 1.68]	0.790
			RR	0.92	[0.51; 1.67]	0.790
			RD	-0.00	[-0.01; 0.01]	0.791
Hypermagnesaemia, n (%)	18 (1.3)	2 (0.1)	OR	8.80	[2.04; 37.97]	0.004
			RR	8.70	[2.02; 37.42]	0.004
			RD	0.01	[0.01; 0.02]	<.001
Type 2 diabetes mellitus, n (%)	14 (1.0)	14 (1.0)	OR	0.97	[0.46; 2.03]	0.928
			RR	0.97	[0.46; 2.02]	0.928
			RD	-0.00	[-0.01; 0.01]	0.928
Vascular disorders, n (%)	433 (30.7)	419 (30.8)	OR	1.00	[0.85; 1.17]	0.985
			RR	1.00	[0.89; 1.12]	0.985
			RD	-0.00	[-0.03; 0.03]	0.985
Hot flush, n (%)	227 (16.1)	221 (16.2)	OR	0.99	[0.81; 1.21]	0.934
			RR	0.99	[0.84; 1.18]	0.934
			RD	-0.00	[-0.03; 0.03]	0.934
Hypertension, n (%)	124 (8.8)	105 (7.7)	OR	1.16	[0.88; 1.52]	0.297
			RR	1.14	[0.89; 1.46]	0.297
			RD	0.01	[-0.01; 0.03]	0.296
Lymphoedema, n (%)	92 (6.5)	102 (7.5)	OR	0.86	[0.64; 1.16]	0.323
			RR	0.87	[0.66; 1.14]	0.323
			RD	-0.01	[-0.03; 0.01]	0.323
	416 (29.5)	257 (18.9)	OR	1.80	[1.51; 2.15]	<.001
			RR	1.56	[1.37; 1.79]	<.001

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)		Estimate	[95% CI]	p-value
Respiratory, thoracic and mediastinal disorders, n (%)			RD	0.11	[0.07; 0.14]	<.001
Cough, n (%)	172 (12.2)	114 (8.4)	OR	1.52	[1.19; 1.95]	<.001
			RR	1.46	[1.16; 1.83]	<.001
			RD	0.04	[0.02; 0.06]	<.001
Dyspnoea, n (%)	115 (8.2)	66 (4.8)	OR	1.75	[1.28; 2.38]	<.001
			RR	1.68	[1.26; 2.26]	<.001
			RD	0.03	[0.01; 0.05]	<.001
Oropharyngeal pain, n (%)	72 (5.1)	34 (2.5)	OR	2.10	[1.39; 3.18]	<.001
			RR	2.05	[1.37; 3.06]	<.001
			RD	0.03	[0.01; 0.04]	<.001
Rhinorrhoea, n (%)	37 (2.6)	16 (1.2)	OR	2.27	[1.26; 4.10]	0.007
			RR	2.24	[1.25; 4.00]	0.007
			RD	0.01	[0.00; 0.02]	0.005
Nasal congestion, n (%)	29 (2.1)	14 (1.0)	OR	2.02	[1.06; 3.85]	0.031
			RR	2.00	[1.06; 3.77]	0.032
			RD	0.01	[0.00; 0.02]	0.027
Epistaxis, n (%)	23 (1.6)	7 (0.5)	OR	3.21	[1.37; 7.51]	0.007
			RR	3.18	[1.37; 7.38]	0.007
			RD	0.01	[0.00; 0.02]	0.004
Rhinitis allergic, n (%)	21 (1.5)	14 (1.0)	OR	1.46	[0.74; 2.88]	0.279
			RR	1.45	[0.74; 2.84]	0.279
			RD	0.00	[-0.00; 0.01]	0.274
Productive cough, n (%)	16 (1.1)	7 (0.5)	OR	2.22	[0.91; 5.42]	0.079
			RR	2.21	[0.91; 5.35]	0.079
			RD	0.01	[-0.00; 0.01]	0.069
Psychiatric disorders, n (%)	316 (22.4)	255 (18.7)	OR	1.26	[1.04; 1.51]	0.016
			RR	1.20	[1.03; 1.39]	0.016
			RD	0.04	[0.01; 0.07]	0.016
Insomnia, n (%)	154 (10.9)	125 (9.2)	OR	1.21	[0.95; 1.56]	0.126
			RR	1.19	[0.95; 1.49]	0.126
			RD	0.02	[-0.00; 0.04]	0.125
Anxiety, n (%)	72 (5.1)	51 (3.7)	OR	1.38	[0.96; 2.00]	0.082
			RR	1.36	[0.96; 1.94]	0.082
			RD	0.01	[-0.00; 0.03]	0.080
Depression, n (%)	68 (4.8)	40 (2.9)	OR	1.68	[1.13; 2.49]	0.011
			RR	1.64	[1.12; 2.41]	0.011
			RD	0.02	[0.00; 0.03]	0.010
Depressed mood, n (%)	22 (1.6)	16 (1.2)	OR	1.33	[0.70; 2.55]	0.383
			RR	1.33	[0.70; 2.52]	0.383

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1409)	ET (N = 1362)	Para- meter	Esti- mate	[95% CI]	p-value
			RD	0.00	[-0.00; 0.01]	0.380
Sleep disorder, n (%)	22 (1.6)	22 (1.6)	OR	0.97	[0.53; 1.75]	0.910
			RR	0.97	[0.54; 1.74]	0.910
			RD	-0.00	[-0.01; 0.01]	0.910
Injury, poisoning and procedural complications, n (%)	198 (14.1)	192 (14.1)	OR	1.00	[0.80; 1.23]	0.973
			RR	1.00	[0.83; 1.20]	0.973
			RD	-0.00	[-0.03; 0.03]	0.973
Procedural pain, n (%)	28 (2.0)	40 (2.9)	OR	0.67	[0.41; 1.09]	0.108
			RR	0.68	[0.42; 1.09]	0.109
			RD	-0.01	[-0.02; 0.00]	0.107
Fall, n (%)	18 (1.3)	34 (2.5)	OR	0.51	[0.28; 0.90]	0.020
			RR	0.51	[0.29; 0.90]	0.020
			RD	-0.01	[-0.02; -0.00]	0.019
Contusion, n (%)	21 (1.5)	16 (1.2)	OR	1.27	[0.66; 2.45]	0.470
			RR	1.27	[0.66; 2.42]	0.470
			RD	0.00	[-0.01; 0.01]	0.468
Humerus fracture, n (%)	15 (1.1)	6 (0.4)	OR	2.43	[0.94; 6.29]	0.067
			RR	2.42	[0.94; 6.21]	0.067
			RD	0.01	[-0.00; 0.01]	0.056
Reproductive system and breast disorders, n (%)	165 (11.7)	195 (14.3)	OR	0.79	[0.64; 0.99]	0.042
			RR	0.82	[0.67; 0.99]	0.042
			RD	-0.03	[-0.05; -0.00]	0.041
Breast pain, n (%)	49 (3.5)	66 (4.8)	OR	0.71	[0.49; 1.03]	0.072
			RR	0.72	[0.50; 1.03]	0.072
			RD	-0.01	[-0.03; 0.00]	0.072
Vulvovaginal dryness, n (%)	43 (3.1)	47 (3.5)	OR	0.88	[0.58; 1.34]	0.554
			RR	0.88	[0.59; 1.33]	0.554
			RD	-0.00	[-0.02; 0.01]	0.554
Eye disorders, n (%)	182 (12.9)	105 (7.7)	OR	1.78	[1.38; 2.29]	<.001
			RR	1.68	[1.33; 2.11]	<.001
			RD	0.05	[0.03; 0.07]	<.001
Dry eye, n (%)	49 (3.5)	21 (1.5)	OR	2.30	[1.37; 3.86]	0.002
			RR	2.26	[1.36; 3.74]	0.002
			RD	0.02	[0.01; 0.03]	0.001
Lacrimation increased, n (%)	48 (3.4)	12 (0.9)	OR	3.97	[2.10; 7.50]	<.001
			RR	3.87	[2.06; 7.25]	<.001
			RD	0.03	[0.01; 0.04]	<.001
Cataract, n (%)	15 (1.1)	26 (1.9)	OR	0.55	[0.29; 1.05]	0.070
			RR	0.56	[0.30; 1.05]	0.070
			RD	-0.01	[-0.02; 0.00]	0.067

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1409)	ET (N = 1362)	Para- meter	Esti- mate	[95% CI]	p-value
Vision blurred, n (%)	17 (1.2)	8 (0.6)	OR	2.07	[0.89; 4.81]	0.092
			RR	2.05	[0.89; 4.74]	0.092
			RD	0.01	[-0.00; 0.01]	0.083
Cardiac disorders, n (%)	123 (8.7)	103 (7.6)	OR	1.17	[0.89; 1.54]	0.262
			RR	1.15	[0.90; 1.48]	0.262
			RD	0.01	[-0.01; 0.03]	0.261
Palpitations, n (%)	47 (3.3)	20 (1.5)	OR	2.32	[1.36; 3.93]	0.002
			RR	2.27	[1.35; 3.81]	0.002
			RD	0.02	[0.01; 0.03]	0.001
Tachycardia, n (%)	18 (1.3)	15 (1.1)	OR	1.16	[0.58; 2.32]	0.669
			RR	1.16	[0.59; 2.29]	0.669
			RD	0.00	[-0.01; 0.01]	0.669
Atrial fibrillation, n (%)	13 (0.9)	16 (1.2)	OR	0.78	[0.38; 1.63]	0.515
			RR	0.79	[0.38; 1.63]	0.515
			RD	-0.00	[-0.01; 0.01]	0.515
Renal and urinary disorders, n (%)	101 (7.2)	83 (6.1)	OR	1.19	[0.88; 1.61]	0.257
			RR	1.18	[0.89; 1.56]	0.257
			RD	0.01	[-0.01; 0.03]	0.255
Pollakiuria, n (%)	17 (1.2)	10 (0.7)	OR	1.65	[0.75; 3.62]	0.210
			RR	1.64	[0.76; 3.58]	0.211
			RD	0.00	[-0.00; 0.01]	0.204
Dysuria, n (%)	15 (1.1)	15 (1.1)	OR	0.97	[0.47; 1.98]	0.926
			RR	0.97	[0.47; 1.97]	0.926
			RD	-0.00	[-0.01; 0.01]	0.926
Ear and labyrinth disorders, n (%)	97 (6.9)	53 (3.9)	OR	1.83	[1.30; 2.57]	<.001
			RR	1.77	[1.28; 2.45]	<.001
			RD	0.03	[0.01; 0.05]	<.001
Vertigo, n (%)	50 (3.5)	25 (1.8)	OR	1.97	[1.21; 3.20]	0.006
			RR	1.93	[1.20; 3.11]	0.006
			RD	0.02	[0.01; 0.03]	0.005
Hepatobiliary disorders, n (%)	76 (5.4)	44 (3.2)	OR	1.71	[1.17; 2.49]	0.006
			RR	1.67	[1.16; 2.40]	0.006
			RD	0.02	[0.01; 0.04]	0.005
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n (%)	63 (4.5)	76 (5.6)	OR	0.79	[0.56; 1.12]	0.182
			RR	0.80	[0.58; 1.11]	0.182
			RD	-0.01	[-0.03; 0.01]	0.182
Endocrine disorders, n (%)	30 (2.1)	42 (3.1)	OR	0.68	[0.43; 1.10]	0.116
			RR	0.69	[0.43; 1.10]	0.117
			RD	-0.01	[-0.02; 0.00]	0.115
Hypothyroidism, n (%)	15 (1.1)	22 (1.6)	OR	0.66	[0.34; 1.27]	0.210
			RR	0.66	[0.34; 1.27]	0.210

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1409)	ET (N = 1362)	Para- meter	Esti- mate	[95% CI]	p-value
			RD	-0.01	[-0.01; 0.00]	0.208
Immune system disorders, n (%)	25 (1.8)	18 (1.3)	OR	1.35	[0.73; 2.48]	0.337
			RR	1.34	[0.74; 2.45]	0.337
			RD	0.00	[-0.00; 0.01]	0.334
<p>N: Number of patients n: Number of patients with event CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis methods: OR with Wald 95% CI and p-value obtained from logistic regression model: $\text{logit}(\text{proportion}) = \text{treatment}$ RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p> <p>MedDRA Version: 21.1</p>						

Table 4-3 Grade ≥ 3 adverse events by SOC and PT: binary analysis (Safety Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1409)	ET (N = 1362)	Para- meter	Esti- mate	[95% CI]	p-value
Blood and lymphatic system disorders, n (%)	396 (28.1)	13 (1.0)	OR	40.57	[23.21; 70.90]	<.001
			RR	29.45	[17.03; 50.90]	<.001
			RD	0.27	[0.25; 0.30]	<.001
Neutropenia, n (%)	374 (26.5)	4 (0.3)	OR	>99.99	[45.65; >99.99]	<.001
			RR	90.38	[33.84; 241.39]	<.001
			RD	0.26	[0.24; 0.29]	<.001
Leukopenia, n (%)	56 (4.0)	1 (0.1)	OR	56.32	[7.79; >99.99]	<.001
			RR	54.13	[7.50; 390.49]	<.001
			RD	0.04	[0.03; 0.05]	<.001
Investigations, n (%)	371 (26.3)	47 (3.5)	OR	10.00	[7.30; 13.69]	<.001
			RR	7.63	[5.69; 10.24]	<.001
			RD	0.23	[0.20; 0.25]	<.001
Neutrophil count decreased, n (%)	202 (14.3)	3 (0.2)	OR	75.79	[24.18; >99.99]	<.001
			RR	65.09	[20.87; 203.01]	<.001
			RD	0.14	[0.12; 0.16]	<.001
Alanine aminotransferase increased, n (%)	122 (8.7)	5 (0.4)	OR	25.72	[10.48; 63.09]	<.001
			RR	23.59	[9.67; 57.50]	<.001
			RD	0.08	[0.07; 0.10]	<.001
Aspartate aminotransferase increased, n (%)	74 (5.3)	6 (0.4)	OR	12.53	[5.43; 28.88]	<.001
			RR	11.92	[5.21; 27.30]	<.001
			RD	0.05	[0.04; 0.06]	<.001
White blood cell count decreased, n (%)	39 (2.8)	3 (0.2)	OR	12.90	[3.98; 41.83]	<.001
			RR	12.57	[3.89; 40.57]	<.001
			RD	0.03	[0.02; 0.03]	<.001
Gamma-glutamyltransferase increased, n (%)	19 (1.3)	13 (1.0)	OR	1.42	[0.70; 2.88]	0.334
			RR	1.41	[0.70; 2.85]	0.334
			RD	0.00	[-0.00; 0.01]	0.330
Infections and infestations, n (%)	89 (6.3)	51 (3.7)	OR	1.73	[1.22; 2.47]	0.002
			RR	1.69	[1.21; 2.36]	0.002
			RD	0.03	[0.01; 0.04]	0.002
Vascular disorders, n (%)	49 (3.5)	49 (3.6)	OR	0.97	[0.65; 1.44]	0.864
			RR	0.97	[0.66; 1.43]	0.864
			RD	-0.00	[-0.01; 0.01]	0.864
Hypertension, n (%)	37 (2.6)	44 (3.2)	OR	0.81	[0.52; 1.26]	0.346
			RR	0.81	[0.53; 1.25]	0.346
			RD	-0.01	[-0.02; 0.01]	0.346
	42 (3.0)	34 (2.5)	OR	1.20	[0.76; 1.90]	0.436
			RR	1.19	[0.76; 1.87]	0.436

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1409)	ET (N = 1362)	Parameter	Estimate	[95% CI]	p-value
Musculoskeletal and connective tissue disorders, n (%)			RD	0.00	[-0.01; 0.02]	0.434
Arthralgia, n (%)	15 (1.1)	17 (1.2)	OR	0.85	[0.42; 1.71]	0.651
			RR	0.85	[0.43; 1.70]	0.651
			RD	-0.00	[-0.01; 0.01]	0.652
Nervous system disorders, n (%)	40 (2.8)	16 (1.2)	OR	2.46	[1.37; 4.41]	0.003
			RR	2.42	[1.36; 4.29]	0.003
			RD	0.02	[0.01; 0.03]	0.002
Respiratory, thoracic and mediastinal disorders, n (%)	38 (2.7)	23 (1.7)	OR	1.61	[0.96; 2.72]	0.073
			RR	1.60	[0.96; 2.67]	0.073
			RD	0.01	[-0.00; 0.02]	0.069
Gastrointestinal disorders, n (%)	36 (2.6)	24 (1.8)	OR	1.46	[0.87; 2.46]	0.154
			RR	1.45	[0.87; 2.42]	0.154
			RD	0.01	[-0.00; 0.02]	0.150
General disorders and administration site conditions, n (%)	34 (2.4)	13 (1.0)	OR	2.57	[1.35; 4.88]	0.004
			RR	2.53	[1.34; 4.77]	0.004
			RD	0.01	[0.01; 0.02]	0.003
Fatigue, n (%)	15 (1.1)	3 (0.2)	OR	4.87	[1.41; 16.88]	0.012
			RR	4.83	[1.40; 16.66]	0.013
			RD	0.01	[0.00; 0.01]	0.005
Metabolism and nutrition disorders, n (%)	28 (2.0)	20 (1.5)	OR	1.36	[0.76; 2.43]	0.297
			RR	1.35	[0.77; 2.39]	0.297
			RD	0.01	[-0.00; 0.01]	0.294
Injury, poisoning and procedural complications, n (%)	25 (1.8)	24 (1.8)	OR	1.01	[0.57; 1.77]	0.981
			RR	1.01	[0.58; 1.75]	0.981
			RD	0.00	[-0.01; 0.01]	0.981
Hepatobiliary disorders, n (%)	23 (1.6)	2 (0.1)	OR	11.28	[2.66; 47.95]	0.001
			RR	11.12	[2.63; 47.06]	0.001
			RD	0.01	[0.01; 0.02]	<.001
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n (%)	21 (1.5)	22 (1.6)	OR	0.92	[0.50; 1.68]	0.790
			RR	0.92	[0.51; 1.67]	0.790
			RD	-0.00	[-0.01; 0.01]	0.791
Cardiac disorders, n (%)	20 (1.4)	16 (1.2)	OR	1.21	[0.63; 2.35]	0.570
			RR	1.21	[0.63; 2.32]	0.570
			RD	0.00	[-0.01; 0.01]	0.569

Treatment Groups			Comparison			
Ribociclib + ET (N = 1409)	ET (N = 1362)	Parameter	Estimate	[95% CI]	p-value	
<p>N: Number of patients n: Number of patients with event CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis methods: OR with Wald 95% CI and p-value obtained from logistic regression model: $\text{logit}(\text{proportion}) = \text{treatment}$ RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p> <p>MedDRA Version: 21.1</p>						

Table 4-4 Serious adverse events by SOC and PT: binary analysis (Safety Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1409)	ET (N = 1362)	Parameter	Estimate	[95% CI]	p-value
Infections and infestations, n (%)	82 (5.8)	46 (3.4)	OR	1.77	[1.22; 2.56]	0.002
			RR	1.72	[1.21; 2.45]	0.003
			RD	0.02	[0.01; 0.04]	0.002
Respiratory, thoracic and mediastinal disorders, n (%)	34 (2.4)	16 (1.2)	OR	2.08	[1.14; 3.79]	0.017
			RR	2.05	[1.14; 3.70]	0.017
			RD	0.01	[0.00; 0.02]	0.014
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n (%)	23 (1.6)	27 (2.0)	OR	0.82	[0.47; 1.44]	0.490
			RR	0.82	[0.47; 1.43]	0.490
			RD	-0.00	[-0.01; 0.01]	0.490
Injury, poisoning and procedural complications, n (%)	24 (1.7)	22 (1.6)	OR	1.06	[0.59; 1.89]	0.856
			RR	1.05	[0.59; 1.87]	0.856
			RD	0.00	[-0.01; 0.01]	0.856
Cardiac disorders, n (%)	20 (1.4)	16 (1.2)	OR	1.21	[0.63; 2.35]	0.570
			RR	1.21	[0.63; 2.32]	0.570
			RD	0.00	[-0.01; 0.01]	0.569
Nervous system disorders, n (%)	19 (1.3)	12 (0.9)	OR	1.54	[0.74; 3.18]	0.246
			RR	1.53	[0.75; 3.14]	0.246
			RD	0.00	[-0.00; 0.01]	0.240
Gastrointestinal disorders, n (%)	13 (0.9)	17 (1.2)	OR	0.74	[0.36; 1.52]	0.410
			RR	0.74	[0.36; 1.52]	0.410
			RD	-0.00	[-0.01; 0.00]	0.409
General disorders and administration site conditions, n (%)	15 (1.1)	5 (0.4)	OR	2.92	[1.06; 8.06]	0.038
			RR	2.90	[1.06; 7.96]	0.039
			RD	0.01	[0.00; 0.01]	0.029
Hepatobiliary disorders, n (%)	15 (1.1)	1 (0.1)	OR	14.64	[1.93; >99.99]	0.009
			RR	14.50	[1.92; 109.62]	0.010
			RD	0.01	[0.00; 0.02]	<.001
<p>N: Number of patients n: Number of patients with event CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis methods: OR with Wald 95% CI and p-value obtained from logistic regression model: $\text{logit}(\text{proportion}) = \text{treatment}$ RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p> <p>MedDRA Version: 21.1</p>						

Table 4-5 Adverse events leading to treatment discontinuation of ribociclib, by SOC and PT: frequency table (Safety Set)

	Treatment Groups	
	Ribociclib + ET (N = 1409)	ET (N = 1362)
Investigations, n (%)	164 (11.6)	0 (0.0)
Alanine aminotransferase increased, n (%)	112 (7.9)	0 (0.0)
Aspartate aminotransferase increased, n (%)	43 (3.1)	0 (0.0)
Blood creatinine increased, n (%)	7 (0.5)	0 (0.0)
Blood magnesium decreased, n (%)	6 (0.4)	0 (0.0)
Electrocardiogram QT prolonged, n (%)	5 (0.4)	0 (0.0)
Gamma-glutamyltransferase increased, n (%)	3 (0.2)	0 (0.0)
Neutrophil count decreased, n (%)	3 (0.2)	0 (0.0)
Amylase increased, n (%)	2 (0.1)	0 (0.0)
Lipase increased, n (%)	2 (0.1)	0 (0.0)
Blood bilirubin increased, n (%)	1 (0.1)	0 (0.0)
Blood calcium decreased, n (%)	1 (0.1)	0 (0.0)
Blood potassium decreased, n (%)	1 (0.1)	0 (0.0)
Glomerular filtration rate decreased, n (%)	1 (0.1)	0 (0.0)
Lymphocyte count decreased, n (%)	1 (0.1)	0 (0.0)
Blood phosphorus increased, n (%)	1 (0.1)	0 (0.0)
Transaminases increased, n (%)	1 (0.1)	0 (0.0)
SARS-CoV-2 test positive, n (%)	1 (0.1)	0 (0.0)
General disorders and administration site conditions, n (%)	23 (1.6)	0 (0.0)
Fatigue, n (%)	11 (0.8)	0 (0.0)
Asthenia, n (%)	8 (0.6)	0 (0.0)
Malaise, n (%)	1 (0.1)	0 (0.0)
Mucosal inflammation, n (%)	1 (0.1)	0 (0.0)
Pyrexia, n (%)	1 (0.1)	0 (0.0)
Peripheral swelling, n (%)	1 (0.1)	0 (0.0)
Gastrointestinal disorders, n (%)	17 (1.2)	0 (0.0)
Nausea, n (%)	8 (0.6)	0 (0.0)
Diarrhoea, n (%)	5 (0.4)	0 (0.0)
Dyspepsia, n (%)	3 (0.2)	0 (0.0)
Abdominal pain, n (%)	2 (0.1)	0 (0.0)
Haemorrhoids, n (%)	1 (0.1)	0 (0.0)
Vomiting, n (%)	1 (0.1)	0 (0.0)
Gastrointestinal toxicity, n (%)	1 (0.1)	0 (0.0)
Skin and subcutaneous tissue disorders, n (%)	16 (1.1)	0 (0.0)
Rash, n (%)	5 (0.4)	0 (0.0)
Alopecia, n (%)	3 (0.2)	0 (0.0)
Rash maculo-papular, n (%)	2 (0.1)	0 (0.0)
Dermatitis, n (%)	1 (0.1)	0 (0.0)

	Treatment Groups	
	Ribociclib + ET (N = 1409)	ET (N = 1362)
Dermatitis allergic, n (%)	1 (0.1)	0 (0.0)
Eczema, n (%)	1 (0.1)	0 (0.0)
Rash pruritic, n (%)	1 (0.1)	0 (0.0)
Skin disorder, n (%)	1 (0.1)	0 (0.0)
Skin toxicity, n (%)	1 (0.1)	0 (0.0)
Blood and lymphatic system disorders, n (%)	15 (1.1)	0 (0.0)
Neutropenia, n (%)	9 (0.6)	0 (0.0)
Anaemia, n (%)	2 (0.1)	0 (0.0)
Leukopenia, n (%)	2 (0.1)	0 (0.0)
Lymphopenia, n (%)	1 (0.1)	0 (0.0)
Thrombocytopenia, n (%)	1 (0.1)	0 (0.0)
Hepatobiliary disorders, n (%)	15 (1.1)	0 (0.0)
Hepatotoxicity, n (%)	4 (0.3)	0 (0.0)
Hypertransaminaemia, n (%)	4 (0.3)	0 (0.0)
Hepatic cytolysis, n (%)	2 (0.1)	0 (0.0)
Cholecystitis chronic, n (%)	1 (0.1)	0 (0.0)
Hepatic function abnormal, n (%)	1 (0.1)	0 (0.0)
Hepatitis toxic, n (%)	1 (0.1)	0 (0.0)
Non-alcoholic steatohepatitis, n (%)	1 (0.1)	0 (0.0)
Hepatobiliary disease, n (%)	1 (0.1)	0 (0.0)
Infections and infestations, n (%)	15 (1.1)	0 (0.0)
COVID-19, n (%)	5 (0.4)	0 (0.0)
COVID-19 pneumonia, n (%)	3 (0.2)	0 (0.0)
Breast cellulitis, n (%)	1 (0.1)	0 (0.0)
Bronchitis, n (%)	1 (0.1)	0 (0.0)
Herpes zoster, n (%)	1 (0.1)	0 (0.0)
Mastitis, n (%)	1 (0.1)	0 (0.0)
Pneumonia, n (%)	1 (0.1)	0 (0.0)
Pneumonia viral, n (%)	1 (0.1)	0 (0.0)
Post procedural infection, n (%)	1 (0.1)	0 (0.0)
Nervous system disorders, n (%)	15 (1.1)	0 (0.0)
Headache, n (%)	4 (0.3)	0 (0.0)
Cerebrovascular accident, n (%)	3 (0.2)	0 (0.0)
Migraine, n (%)	2 (0.1)	0 (0.0)
Subarachnoid haemorrhage, n (%)	2 (0.1)	0 (0.0)
Amnesia, n (%)	1 (0.1)	0 (0.0)
Carpal tunnel syndrome, n (%)	1 (0.1)	0 (0.0)
Syncope, n (%)	1 (0.1)	0 (0.0)
Balance disorder, n (%)	1 (0.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders, n (%)	14 (1.0)	0 (0.0)
Pulmonary embolism, n (%)	5 (0.4)	0 (0.0)
Pneumonitis, n (%)	4 (0.3)	0 (0.0)

	Treatment Groups	
	Ribociclib + ET (N = 1409)	ET (N = 1362)
Dyspnoea, n (%)	2 (0.1)	0 (0.0)
Cough, n (%)	1 (0.1)	0 (0.0)
Epistaxis, n (%)	1 (0.1)	0 (0.0)
Pharyngeal inflammation, n (%)	1 (0.1)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n (%)	13 (0.9)	0 (0.0)
Papillary thyroid cancer, n (%)	2 (0.1)	0 (0.0)
Acute myeloid leukaemia, n (%)	1 (0.1)	0 (0.0)
Bladder transitional cell carcinoma, n (%)	1 (0.1)	0 (0.0)
Colon cancer stage I, n (%)	1 (0.1)	0 (0.0)
Glioma, n (%)	1 (0.1)	0 (0.0)
Lip and/or oral cavity cancer recurrent, n (%)	1 (0.1)	0 (0.0)
Malignant melanoma, n (%)	1 (0.1)	0 (0.0)
Rectal adenocarcinoma, n (%)	1 (0.1)	0 (0.0)
Rectosigmoid cancer, n (%)	1 (0.1)	0 (0.0)
Renal cell carcinoma, n (%)	1 (0.1)	0 (0.0)
Clear cell renal cell carcinoma, n (%)	1 (0.1)	0 (0.0)
Ductal adenocarcinoma of pancreas, n (%)	1 (0.1)	0 (0.0)
Musculoskeletal and connective tissue disorders, n (%)	12 (0.9)	0 (0.0)
Arthralgia, n (%)	8 (0.6)	0 (0.0)
Muscle spasms, n (%)	1 (0.1)	0 (0.0)
Muscular weakness, n (%)	1 (0.1)	0 (0.0)
Myalgia, n (%)	1 (0.1)	0 (0.0)
Rheumatoid arthritis, n (%)	1 (0.1)	0 (0.0)
Cardiac disorders, n (%)	9 (0.6)	0 (0.0)
Acute myocardial infarction, n (%)	2 (0.1)	0 (0.0)
Atrial fibrillation, n (%)	1 (0.1)	0 (0.0)
Bradycardia, n (%)	1 (0.1)	0 (0.0)
Cardiac failure, n (%)	1 (0.1)	0 (0.0)
Cardiogenic shock, n (%)	1 (0.1)	0 (0.0)
Myocardial infarction, n (%)	1 (0.1)	0 (0.0)
Myocarditis, n (%)	1 (0.1)	0 (0.0)
Palpitations, n (%)	1 (0.1)	0 (0.0)
Ventricular tachycardia, n (%)	1 (0.1)	0 (0.0)
Cardiopulmonary failure, n (%)	1 (0.1)	0 (0.0)
Stress cardiomyopathy, n (%)	1 (0.1)	0 (0.0)
Metabolism and nutrition disorders, n (%)	9 (0.6)	0 (0.0)
Hypomagnesaemia, n (%)	4 (0.3)	0 (0.0)
Hyperkalaemia, n (%)	3 (0.2)	0 (0.0)
Hypercalcaemia, n (%)	1 (0.1)	0 (0.0)
Hypocalcaemia, n (%)	1 (0.1)	0 (0.0)
Psychiatric disorders, n (%)	4 (0.3)	0 (0.0)

	Treatment Groups	
	Ribociclib + ET (N = 1409)	ET (N = 1362)
Anxiety, n (%)	3 (0.2)	0 (0.0)
Depression, n (%)	1 (0.1)	0 (0.0)
Eye disorders, n (%)	3 (0.2)	0 (0.0)
Papilloedema, n (%)	1 (0.1)	0 (0.0)
Vitreous haemorrhage, n (%)	1 (0.1)	0 (0.0)
Ulcerative keratitis, n (%)	1 (0.1)	0 (0.0)
Injury, poisoning and procedural complications, n (%)	3 (0.2)	0 (0.0)
Radiation pneumonitis, n (%)	1 (0.1)	0 (0.0)
Road traffic accident, n (%)	1 (0.1)	0 (0.0)
Post procedural hypothyroidism, n (%)	1 (0.1)	0 (0.0)
Vascular disorders, n (%)	3 (0.2)	0 (0.0)
Hypotension, n (%)	2 (0.1)	0 (0.0)
Hypertension, n (%)	1 (0.1)	0 (0.0)
Embolism, n (%)	1 (0.1)	0 (0.0)
Renal and urinary disorders, n (%)	2 (0.1)	0 (0.0)
Chronic kidney disease, n (%)	2 (0.1)	0 (0.0)
Ear and labyrinth disorders, n (%)	1 (0.1)	0 (0.0)
Ear discomfort, n (%)	1 (0.1)	0 (0.0)
N: Number of patients n: Number of patients with event ET: Endocrine therapy (Anastrozole/Letrozole) MedDRA Version: 21.1		

Table 4-6 Adverse events leading to treatment discontinuation of NSAI, by SOC and PT: frequency table (Safety Set)

	Treatment Groups	
	Ribociclib + ET (N = 1409)	ET (N = 1362)
Musculoskeletal and connective tissue disorders, n (%)	27 (1.9)	35 (2.6)
Arthralgia, n (%)	20 (1.4)	25 (1.8)
Arthritis, n (%)	0 (0.0)	2 (0.1)
Back pain, n (%)	1 (0.1)	2 (0.1)
Osteoporosis, n (%)	0 (0.0)	2 (0.1)
Joint stiffness, n (%)	1 (0.1)	0 (0.0)
Muscular weakness, n (%)	1 (0.1)	0 (0.0)
Musculoskeletal pain, n (%)	0 (0.0)	1 (0.1)
Myalgia, n (%)	1 (0.1)	1 (0.1)
Neck pain, n (%)	1 (0.1)	0 (0.0)
Pain in extremity, n (%)	0 (0.0)	1 (0.1)
Rheumatoid arthritis, n (%)	1 (0.1)	1 (0.1)
Trigger finger, n (%)	1 (0.1)	0 (0.0)
Investigations, n (%)	19 (1.3)	2 (0.1)
Alanine aminotransferase increased, n (%)	14 (1.0)	1 (0.1)
Aspartate aminotransferase increased, n (%)	5 (0.4)	0 (0.0)
Neutrophil count decreased, n (%)	2 (0.1)	0 (0.0)
Glomerular filtration rate decreased, n (%)	1 (0.1)	0 (0.0)
SARS-CoV-2 test positive, n (%)	0 (0.0)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n (%)	8 (0.6)	11 (0.8)
Colon cancer, n (%)	0 (0.0)	2 (0.1)
Acute myeloid leukaemia, n (%)	1 (0.1)	1 (0.1)
Colon cancer stage I, n (%)	1 (0.1)	0 (0.0)
Endometrial cancer, n (%)	0 (0.0)	1 (0.1)
Fallopian tube cancer, n (%)	1 (0.1)	0 (0.0)
Gastric cancer, n (%)	0 (0.0)	1 (0.1)
Lip and/or oral cavity cancer recurrent, n (%)	1 (0.1)	0 (0.0)
Lung adenocarcinoma, n (%)	0 (0.0)	1 (0.1)
Myelodysplastic syndrome, n (%)	0 (0.0)	1 (0.1)
Ovarian cancer, n (%)	0 (0.0)	1 (0.1)
Rectal adenocarcinoma, n (%)	1 (0.1)	1 (0.1)
Rectosigmoid cancer, n (%)	1 (0.1)	0 (0.0)
Squamous cell carcinoma of lung, n (%)	0 (0.0)	1 (0.1)
Neuroendocrine tumour, n (%)	1 (0.1)	0 (0.0)
Ovarian clear cell carcinoma, n (%)	0 (0.0)	1 (0.1)
Ductal adenocarcinoma of pancreas, n (%)	1 (0.1)	0 (0.0)
General disorders and administration site conditions, n (%)	9 (0.6)	2 (0.1)
Asthenia, n (%)	4 (0.3)	0 (0.0)

	Treatment Groups	
	Ribociclib + ET (N = 1409)	ET (N = 1362)
Fatigue, n (%)	4 (0.3)	0 (0.0)
Oedema peripheral, n (%)	0 (0.0)	1 (0.1)
Peripheral swelling, n (%)	1 (0.1)	0 (0.0)
Non-cardiac chest pain, n (%)	0 (0.0)	1 (0.1)
Infections and infestations, n (%)	7 (0.5)	3 (0.2)
COVID-19, n (%)	3 (0.2)	1 (0.1)
COVID-19 pneumonia, n (%)	2 (0.1)	0 (0.0)
Breast cellulitis, n (%)	1 (0.1)	0 (0.0)
Sepsis, n (%)	0 (0.0)	1 (0.1)
Staphylococcal infection, n (%)	0 (0.0)	1 (0.1)
Post procedural infection, n (%)	1 (0.1)	0 (0.0)
Hepatobiliary disorders, n (%)	5 (0.4)	0 (0.0)
Hepatotoxicity, n (%)	2 (0.1)	0 (0.0)
Hepatic cytolysis, n (%)	1 (0.1)	0 (0.0)
Hypertransaminasaemia, n (%)	1 (0.1)	0 (0.0)
Drug-induced liver injury, n (%)	1 (0.1)	0 (0.0)
Nervous system disorders, n (%)	4 (0.3)	4 (0.3)
Carpal tunnel syndrome, n (%)	2 (0.1)	0 (0.0)
Migraine, n (%)	1 (0.1)	0 (0.0)
Neuropathy peripheral, n (%)	0 (0.0)	1 (0.1)
Paraparesis, n (%)	0 (0.0)	1 (0.1)
Sciatica, n (%)	0 (0.0)	1 (0.1)
Subarachnoid haemorrhage, n (%)	1 (0.1)	0 (0.0)
Neuromyelitis optica spectrum disorder, n (%)	0 (0.0)	1 (0.1)
Respiratory, thoracic and mediastinal disorders, n (%)	4 (0.3)	4 (0.3)
Pulmonary embolism, n (%)	4 (0.3)	1 (0.1)
Dyspnoea, n (%)	0 (0.0)	2 (0.1)
Pleurisy, n (%)	0 (0.0)	1 (0.1)
Respiratory failure, n (%)	0 (0.0)	1 (0.1)
Skin and subcutaneous tissue disorders, n (%)	4 (0.3)	1 (0.1)
Alopecia, n (%)	1 (0.1)	0 (0.0)
Erythema, n (%)	1 (0.1)	0 (0.0)
Rash, n (%)	0 (0.0)	1 (0.1)
Rash maculo-papular, n (%)	1 (0.1)	0 (0.0)
Skin toxicity, n (%)	1 (0.1)	0 (0.0)
Cardiac disorders, n (%)	2 (0.1)	3 (0.2)
Acute myocardial infarction, n (%)	1 (0.1)	0 (0.0)
Cardiac failure congestive, n (%)	0 (0.0)	1 (0.1)
Myocardial infarction, n (%)	0 (0.0)	1 (0.1)
Cardiopulmonary failure, n (%)	1 (0.1)	0 (0.0)
Acute coronary syndrome, n (%)	0 (0.0)	1 (0.1)
Gastrointestinal disorders, n (%)	1 (0.1)	3 (0.2)

	Treatment Groups	
	Ribociclib + ET (N = 1409)	ET (N = 1362)
Abdominal pain upper, n (%)	0 (0.0)	1 (0.1)
Diarrhoea, n (%)	1 (0.1)	1 (0.1)
Nausea, n (%)	1 (0.1)	1 (0.1)
Vomiting, n (%)	1 (0.1)	0 (0.0)
Injury, poisoning and procedural complications, n (%)	2 (0.1)	1 (0.1)
Femur fracture, n (%)	0 (0.0)	1 (0.1)
Road traffic accident, n (%)	1 (0.1)	0 (0.0)
Spinal fracture, n (%)	1 (0.1)	0 (0.0)
Psychiatric disorders, n (%)	2 (0.1)	2 (0.1)
Anxiety, n (%)	1 (0.1)	0 (0.0)
Depression, n (%)	1 (0.1)	0 (0.0)
Insomnia, n (%)	0 (0.0)	1 (0.1)
Sleep disorder, n (%)	0 (0.0)	1 (0.1)
Blood and lymphatic system disorders, n (%)	1 (0.1)	0 (0.0)
Neutropenia, n (%)	1 (0.1)	0 (0.0)
Ear and labyrinth disorders, n (%)	1 (0.1)	0 (0.0)
Ear discomfort, n (%)	1 (0.1)	0 (0.0)
Eye disorders, n (%)	0 (0.0)	1 (0.1)
Epiretinal membrane, n (%)	0 (0.0)	1 (0.1)
Metabolism and nutrition disorders, n (%)	1 (0.1)	0 (0.0)
Hyperkalaemia, n (%)	1 (0.1)	0 (0.0)
Reproductive system and breast disorders, n (%)	1 (0.1)	0 (0.0)
Vulvovaginal dryness, n (%)	1 (0.1)	0 (0.0)
Vascular disorders, n (%)	0 (0.0)	1 (0.1)
Hot flush, n (%)	0 (0.0)	1 (0.1)
N: Number of patients n: Number of patients with event ET: Endocrine therapy (Anastrozole/Letrozole) MedDRA Version: 21.1		

Table 4-7 Adverse events leading to treatment discontinuation of any component, by SOC and PT: frequency table (Safety Set)

	Treatment Groups	
	Ribociclib + ET (N = 1409)	ET (N = 1362)
Investigations, n (%)	165 (11.7)	2 (0.1)
Alanine aminotransferase increased, n (%)	113 (8.0)	1 (0.1)
Aspartate aminotransferase increased, n (%)	47 (3.3)	0 (0.0)
Blood creatinine increased, n (%)	7 (0.5)	0 (0.0)
Blood magnesium decreased, n (%)	6 (0.4)	0 (0.0)
Electrocardiogram QT prolonged, n (%)	5 (0.4)	0 (0.0)
Gamma-glutamyltransferase increased, n (%)	3 (0.2)	0 (0.0)
Neutrophil count decreased, n (%)	3 (0.2)	0 (0.0)
Amylase increased, n (%)	2 (0.1)	0 (0.0)
Lipase increased, n (%)	2 (0.1)	0 (0.0)
Blood bilirubin increased, n (%)	1 (0.1)	0 (0.0)
Blood calcium decreased, n (%)	1 (0.1)	0 (0.0)
Blood potassium decreased, n (%)	1 (0.1)	0 (0.0)
Glomerular filtration rate decreased, n (%)	1 (0.1)	0 (0.0)
Lymphocyte count decreased, n (%)	1 (0.1)	0 (0.0)
Blood phosphorus increased, n (%)	1 (0.1)	0 (0.0)
Transaminases increased, n (%)	1 (0.1)	0 (0.0)
SARS-CoV-2 test positive, n (%)	1 (0.1)	1 (0.1)
Musculoskeletal and connective tissue disorders, n (%)	31 (2.2)	35 (2.6)
Arthralgia, n (%)	22 (1.6)	25 (1.8)
Arthritis, n (%)	0 (0.0)	2 (0.1)
Back pain, n (%)	1 (0.1)	2 (0.1)
Myalgia, n (%)	2 (0.1)	1 (0.1)
Osteoporosis, n (%)	0 (0.0)	2 (0.1)
Joint stiffness, n (%)	1 (0.1)	0 (0.0)
Muscle spasms, n (%)	1 (0.1)	0 (0.0)
Muscular weakness, n (%)	1 (0.1)	0 (0.0)
Musculoskeletal pain, n (%)	0 (0.0)	1 (0.1)
Neck pain, n (%)	1 (0.1)	0 (0.0)
Pain in extremity, n (%)	0 (0.0)	1 (0.1)
Rheumatoid arthritis, n (%)	1 (0.1)	1 (0.1)
Trigger finger, n (%)	1 (0.1)	0 (0.0)
General disorders and administration site conditions, n (%)	25 (1.8)	2 (0.1)
Fatigue, n (%)	12 (0.9)	0 (0.0)
Asthenia, n (%)	9 (0.6)	0 (0.0)
Malaise, n (%)	1 (0.1)	0 (0.0)
Mucosal inflammation, n (%)	1 (0.1)	0 (0.0)
Oedema peripheral, n (%)	0 (0.0)	1 (0.1)

	Treatment Groups	
	Ribociclib + ET (N = 1409)	ET (N = 1362)
Pyrexia, n (%)	1 (0.1)	0 (0.0)
Peripheral swelling, n (%)	1 (0.1)	0 (0.0)
Non-cardiac chest pain, n (%)	0 (0.0)	1 (0.1)
Gastrointestinal disorders, n (%)	18 (1.3)	3 (0.2)
Nausea, n (%)	9 (0.6)	1 (0.1)
Diarrhoea, n (%)	6 (0.4)	1 (0.1)
Dyspepsia, n (%)	3 (0.2)	0 (0.0)
Abdominal pain, n (%)	2 (0.1)	0 (0.0)
Vomiting, n (%)	2 (0.1)	0 (0.0)
Abdominal pain upper, n (%)	0 (0.0)	1 (0.1)
Haemorrhoids, n (%)	1 (0.1)	0 (0.0)
Gastrointestinal toxicity, n (%)	1 (0.1)	0 (0.0)
Skin and subcutaneous tissue disorders, n (%)	17 (1.2)	1 (0.1)
Rash, n (%)	5 (0.4)	1 (0.1)
Alopecia, n (%)	3 (0.2)	0 (0.0)
Rash maculo-papular, n (%)	2 (0.1)	0 (0.0)
Dermatitis, n (%)	1 (0.1)	0 (0.0)
Dermatitis allergic, n (%)	1 (0.1)	0 (0.0)
Eczema, n (%)	1 (0.1)	0 (0.0)
Erythema, n (%)	1 (0.1)	0 (0.0)
Rash pruritic, n (%)	1 (0.1)	0 (0.0)
Skin disorder, n (%)	1 (0.1)	0 (0.0)
Skin toxicity, n (%)	1 (0.1)	0 (0.0)
Hepatobiliary disorders, n (%)	16 (1.1)	0 (0.0)
Hepatotoxicity, n (%)	4 (0.3)	0 (0.0)
Hypertransaminasaemia, n (%)	4 (0.3)	0 (0.0)
Hepatic cytolysis, n (%)	2 (0.1)	0 (0.0)
Cholecystitis chronic, n (%)	1 (0.1)	0 (0.0)
Hepatic function abnormal, n (%)	1 (0.1)	0 (0.0)
Hepatitis toxic, n (%)	1 (0.1)	0 (0.0)
Non-alcoholic steatohepatitis, n (%)	1 (0.1)	0 (0.0)
Hepatobiliary disease, n (%)	1 (0.1)	0 (0.0)
Drug-induced liver injury, n (%)	1 (0.1)	0 (0.0)
Nervous system disorders, n (%)	16 (1.1)	4 (0.3)
Headache, n (%)	4 (0.3)	0 (0.0)
Cerebrovascular accident, n (%)	3 (0.2)	0 (0.0)
Carpal tunnel syndrome, n (%)	2 (0.1)	0 (0.0)
Migraine, n (%)	2 (0.1)	0 (0.0)
Subarachnoid haemorrhage, n (%)	2 (0.1)	0 (0.0)
Amnesia, n (%)	1 (0.1)	0 (0.0)
Neuropathy peripheral, n (%)	0 (0.0)	1 (0.1)
Paraparesis, n (%)	0 (0.0)	1 (0.1)

	Treatment Groups	
	Ribociclib + ET (N = 1409)	ET (N = 1362)
Sciatica, n (%)	0 (0.0)	1 (0.1)
Syncope, n (%)	1 (0.1)	0 (0.0)
Balance disorder, n (%)	1 (0.1)	0 (0.0)
Neuromyelitis optica spectrum disorder, n (%)	0 (0.0)	1 (0.1)
Blood and lymphatic system disorders, n (%)	15 (1.1)	0 (0.0)
Neutropenia, n (%)	9 (0.6)	0 (0.0)
Anaemia, n (%)	2 (0.1)	0 (0.0)
Leukopenia, n (%)	2 (0.1)	0 (0.0)
Lymphopenia, n (%)	1 (0.1)	0 (0.0)
Thrombocytopenia, n (%)	1 (0.1)	0 (0.0)
Infections and infestations, n (%)	15 (1.1)	3 (0.2)
COVID-19, n (%)	5 (0.4)	1 (0.1)
COVID-19 pneumonia, n (%)	3 (0.2)	0 (0.0)
Breast cellulitis, n (%)	1 (0.1)	0 (0.0)
Bronchitis, n (%)	1 (0.1)	0 (0.0)
Herpes zoster, n (%)	1 (0.1)	0 (0.0)
Mastitis, n (%)	1 (0.1)	0 (0.0)
Pneumonia, n (%)	1 (0.1)	0 (0.0)
Pneumonia viral, n (%)	1 (0.1)	0 (0.0)
Sepsis, n (%)	0 (0.0)	1 (0.1)
Staphylococcal infection, n (%)	0 (0.0)	1 (0.1)
Post procedural infection, n (%)	1 (0.1)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n (%)	15 (1.1)	11 (0.8)
Colon cancer, n (%)	0 (0.0)	2 (0.1)
Papillary thyroid cancer, n (%)	2 (0.1)	0 (0.0)
Acute myeloid leukaemia, n (%)	1 (0.1)	1 (0.1)
Bladder transitional cell carcinoma, n (%)	1 (0.1)	0 (0.0)
Colon cancer stage I, n (%)	1 (0.1)	0 (0.0)
Endometrial cancer, n (%)	0 (0.0)	1 (0.1)
Fallopian tube cancer, n (%)	1 (0.1)	0 (0.0)
Gastric cancer, n (%)	0 (0.0)	1 (0.1)
Glioma, n (%)	1 (0.1)	0 (0.0)
Lip and/or oral cavity cancer recurrent, n (%)	1 (0.1)	0 (0.0)
Lung adenocarcinoma, n (%)	0 (0.0)	1 (0.1)
Malignant melanoma, n (%)	1 (0.1)	0 (0.0)
Myelodysplastic syndrome, n (%)	0 (0.0)	1 (0.1)
Ovarian cancer, n (%)	0 (0.0)	1 (0.1)
Rectal adenocarcinoma, n (%)	1 (0.1)	1 (0.1)
Rectosigmoid cancer, n (%)	1 (0.1)	0 (0.0)
Squamous cell carcinoma of lung, n (%)	0 (0.0)	1 (0.1)
Neuroendocrine tumour, n (%)	1 (0.1)	0 (0.0)

	Treatment Groups	
	Ribociclib + ET (N = 1409)	ET (N = 1362)
Renal cell carcinoma, n (%)	1 (0.1)	0 (0.0)
Clear cell renal cell carcinoma, n (%)	1 (0.1)	0 (0.0)
Ovarian clear cell carcinoma, n (%)	0 (0.0)	1 (0.1)
Ductal adenocarcinoma of pancreas, n (%)	1 (0.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders, n (%)	14 (1.0)	4 (0.3)
Pulmonary embolism, n (%)	5 (0.4)	1 (0.1)
Pneumonitis, n (%)	4 (0.3)	0 (0.0)
Dyspnoea, n (%)	2 (0.1)	2 (0.1)
Cough, n (%)	1 (0.1)	0 (0.0)
Epistaxis, n (%)	1 (0.1)	0 (0.0)
Pleurisy, n (%)	0 (0.0)	1 (0.1)
Respiratory failure, n (%)	0 (0.0)	1 (0.1)
Pharyngeal inflammation, n (%)	1 (0.1)	0 (0.0)
Metabolism and nutrition disorders, n (%)	10 (0.7)	0 (0.0)
Hyperkalaemia, n (%)	4 (0.3)	0 (0.0)
Hypomagnesaemia, n (%)	4 (0.3)	0 (0.0)
Hypercalcaemia, n (%)	1 (0.1)	0 (0.0)
Hypocalcaemia, n (%)	1 (0.1)	0 (0.0)
Cardiac disorders, n (%)	9 (0.6)	3 (0.2)
Acute myocardial infarction, n (%)	2 (0.1)	0 (0.0)
Atrial fibrillation, n (%)	1 (0.1)	0 (0.0)
Bradycardia, n (%)	1 (0.1)	0 (0.0)
Cardiac failure, n (%)	1 (0.1)	0 (0.0)
Cardiac failure congestive, n (%)	0 (0.0)	1 (0.1)
Cardiogenic shock, n (%)	1 (0.1)	0 (0.0)
Myocardial infarction, n (%)	1 (0.1)	1 (0.1)
Myocarditis, n (%)	1 (0.1)	0 (0.0)
Palpitations, n (%)	1 (0.1)	0 (0.0)
Ventricular tachycardia, n (%)	1 (0.1)	0 (0.0)
Cardiopulmonary failure, n (%)	1 (0.1)	0 (0.0)
Acute coronary syndrome, n (%)	0 (0.0)	1 (0.1)
Stress cardiomyopathy, n (%)	1 (0.1)	0 (0.0)
Injury, poisoning and procedural complications, n (%)	4 (0.3)	1 (0.1)
Femur fracture, n (%)	0 (0.0)	1 (0.1)
Radiation pneumonitis, n (%)	1 (0.1)	0 (0.0)
Road traffic accident, n (%)	1 (0.1)	0 (0.0)
Spinal fracture, n (%)	1 (0.1)	0 (0.0)
Post procedural hypothyroidism, n (%)	1 (0.1)	0 (0.0)
Psychiatric disorders, n (%)	4 (0.3)	2 (0.1)
Anxiety, n (%)	3 (0.2)	0 (0.0)
Depression, n (%)	1 (0.1)	0 (0.0)
Insomnia, n (%)	0 (0.0)	1 (0.1)

	Treatment Groups	
	Ribociclib + ET (N = 1409)	ET (N = 1362)
Sleep disorder, n (%)	0 (0.0)	1 (0.1)
Eye disorders, n (%)	3 (0.2)	1 (0.1)
Papilloedema, n (%)	1 (0.1)	0 (0.0)
Vitreous haemorrhage, n (%)	1 (0.1)	0 (0.0)
Epiretinal membrane, n (%)	0 (0.0)	1 (0.1)
Ulcerative keratitis, n (%)	1 (0.1)	0 (0.0)
Vascular disorders, n (%)	3 (0.2)	1 (0.1)
Hypotension, n (%)	2 (0.1)	0 (0.0)
Hypertension, n (%)	1 (0.1)	0 (0.0)
Hot flush, n (%)	0 (0.0)	1 (0.1)
Embolism, n (%)	1 (0.1)	0 (0.0)
Renal and urinary disorders, n (%)	2 (0.1)	0 (0.0)
Chronic kidney disease, n (%)	2 (0.1)	0 (0.0)
Ear and labyrinth disorders, n (%)	1 (0.1)	0 (0.0)
Ear discomfort, n (%)	1 (0.1)	0 (0.0)
Reproductive system and breast disorders, n (%)	1 (0.1)	0 (0.0)
Vulvovaginal dryness, n (%)	1 (0.1)	0 (0.0)
N: Number of patients n: Number of patients with event ET: Endocrine therapy (Anastrozole/Letrozole) MedDRA Version: 21.1		

Table 4-8 Adverse events of special interest: binary analysis (Safety Set)

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)		Estimate	[95% CI]	p-value
Hepatobiliary toxicity, n (%)	403 (28.6)	152 (11.2)	OR	3.19	[2.60; 3.91]	<.001
			RR	2.56	[2.16; 3.04]	<.001
			RD	0.17	[0.15; 0.20]	<.001
Serious hepatobiliary toxicity, n (%)	16 (1.1)	2 (0.1)	OR	7.81	[1.79; 34.02]	0.006
			RR	7.73	[1.78; 33.57]	0.006
			RD	0.01	[0.00; 0.02]	0.001
Grade ≥3: hepatobiliary toxicity, n (%)	142 (10.1)	21 (1.5)	OR	7.16	[4.50; 11.39]	<.001
			RR	6.54	[4.16; 10.27]	<.001
			RD	0.09	[0.07; 0.10]	<.001
ILD Pneumonitis, n (%)	25 (1.8)	16 (1.2)	OR	1.52	[0.81; 2.86]	0.194
			RR	1.51	[0.81; 2.82]	0.195
			RD	0.01	[-0.00; 0.01]	0.190
Infections, n (%)	698 (49.5)	481 (35.3)	OR	1.80	[1.54; 2.09]	<.001
			RR	1.40	[1.28; 1.53]	<.001
			RD	0.14	[0.11; 0.18]	<.001
Serious infections, n (%)	82 (5.8)	46 (3.4)	OR	1.77	[1.22; 2.56]	0.002
			RR	1.72	[1.21; 2.45]	0.003
			RD	0.02	[0.01; 0.04]	0.002
Grade ≥3: infections, n (%)	90 (6.4)	51 (3.7)	OR	1.75	[1.23; 2.49]	0.002
			RR	1.71	[1.22; 2.39]	0.002
			RD	0.03	[0.01; 0.04]	0.001
Myelosuppression - Anaemia, n (%)	137 (9.7)	45 (3.3)	OR	3.15	[2.23; 4.45]	<.001
			RR	2.94	[2.12; 4.09]	<.001
			RD	0.06	[0.05; 0.08]	<.001
Serious myelosuppression - Anaemia, n (%)	3 (0.2)	3 (0.2)	OR	0.97	[0.19; 4.80]	0.967
			RR	0.97	[0.20; 4.78]	0.967
			RD	-0.00	[-0.00; 0.00]	0.967
Grade ≥3: myelosuppression - Anaemia, n (%)	6 (0.4)	7 (0.5)	OR	0.83	[0.28; 2.47]	0.735
			RR	0.83	[0.28; 2.46]	0.735
			RD	-0.00	[-0.01; 0.00]	0.735
Myelosuppression - Leukopenia, n (%)	342 (24.3)	45 (3.3)	OR	9.38	[6.80; 12.93]	<.001
			RR	7.35	[5.43; 9.93]	<.001
			RD	0.21	[0.19; 0.23]	<.001
Grade ≥3: myelosuppression - Leukopenia, n (%)	104 (7.4)	6 (0.4)	OR	18.01	[7.88; 41.15]	<.001
			RR	16.76	[7.38; 38.02]	<.001
			RD	0.07	[0.06; 0.08]	<.001
	845 (60.0)	44 (3.2)	OR	44.88	[32.63; 61.72]	<.001
			RR	18.56	[13.84; 24.90]	<.001

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1409)	ET (N = 1362)	Para- meter	Esti- mate	[95% CI]	p-value
Myelosuppression - Neutropenia, n (%)			RD	0.57	[0.54; 0.59]	<.001
Serious myelosuppression - Neutropenia, n (%)	2 (0.1)	0 (0.0)	OR	N.E.	N.E.	N.E.
			RR	4.83	[0.23; 100.58]	0.309
			RD	0.00	[-0.00; 0.00]	0.157
Grade ≥3: myelosuppression - Neutropenia, n (%)	558 (39.6)	7 (0.5)	OR	>99.99	[59.91; >99.99]	<.001
			RR	77.06	[36.70; 161.78]	<.001
			RD	0.39	[0.37; 0.42]	<.001
Myelosuppression - Other, n (%)	1 (0.1)	1 (0.1)	OR	0.97	[0.06; 15.47]	0.981
			RR	0.97	[0.06; 15.44]	0.981
			RD	-0.00	[-0.00; 0.00]	0.981
Serious myelosuppression - Other, n (%)	1 (0.1)	0 (0.0)	OR	N.E.	N.E.	N.E.
			RR	2.90	[0.12; 71.13]	0.514
			RD	0.00	[-0.00; 0.00]	0.317
Grade ≥3: myelosuppression - Other, n (%)	1 (0.1)	1 (0.1)	OR	0.97	[0.06; 15.47]	0.981
			RR	0.97	[0.06; 15.44]	0.981
			RD	-0.00	[-0.00; 0.00]	0.981
Myelosuppression - Thrombocytopenia, n (%)	106 (7.5)	29 (2.1)	OR	3.74	[2.46; 5.68]	<.001
			RR	3.53	[2.36; 5.29]	<.001
			RD	0.05	[0.04; 0.07]	<.001
Grade ≥3: myelosuppression - Thrombocytopenia, n (%)	3 (0.2)	1 (0.1)	OR	2.90	[0.30; 27.95]	0.356
			RR	2.90	[0.30; 27.84]	0.356
			RD	0.00	[-0.00; 0.00]	0.330
QT interval prolongation, n (%)	68 (4.8)	17 (1.2)	OR	4.01	[2.35; 6.86]	<.001
			RR	3.87	[2.28; 6.54]	<.001
			RD	0.04	[0.02; 0.05]	<.001
Serious qT interval prolongation, n (%)	3 (0.2)	1 (0.1)	OR	2.90	[0.30; 27.95]	0.356
			RR	2.90	[0.30; 27.84]	0.356
			RD	0.00	[-0.00; 0.00]	0.330
Grade ≥3: qT interval prolongation, n (%)	12 (0.9)	8 (0.6)	OR	1.45	[0.59; 3.57]	0.414
			RR	1.45	[0.59; 3.54]	0.414
			RD	0.00	[-0.00; 0.01]	0.410
Renal toxicity, n (%)	119 (8.4)	52 (3.8)	OR	2.32	[1.66; 3.25]	<.001
			RR	2.21	[1.61; 3.04]	<.001
			RD	0.05	[0.03; 0.06]	<.001
Serious renal toxicity, n (%)	2 (0.1)	1 (0.1)	OR	1.93	[0.18; 21.36]	0.590
			RR	1.93	[0.18; 21.30]	0.590
			RD	0.00	[-0.00; 0.00]	0.581
Grade ≥3: renal toxicity, n (%)	7 (0.5)	0 (0.0)	OR	N.E.	N.E.	N.E.
			RR	14.50	[0.83; 253.63]	0.067

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1409)	ET (N = 1362)	Para- meter	Esti- mate	[95% CI]	p-value
			RD	0.00	[0.00; 0.01]	0.008
Reproductive toxicity, n (%)	3 (0.2)	4 (0.3)	OR	0.72	[0.16; 3.24]	0.673
			RR	0.72	[0.16; 3.23]	0.673
			RD	-0.00	[-0.00; 0.00]	0.673
Serious reproductive toxicity, n (%)	1 (0.1)	2 (0.1)	OR	0.48	[0.04; 5.33]	0.553
			RR	0.48	[0.04; 5.32]	0.553
			RD	-0.00	[-0.00; 0.00]	0.546
Grade \geq 3: reproductive toxicity, n (%)	1 (0.1)	2 (0.1)	OR	0.48	[0.04; 5.33]	0.553
			RR	0.48	[0.04; 5.32]	0.553
			RD	-0.00	[-0.00; 0.00]	0.546
Second Primary Malignancies, n (%)	32 (2.3)	36 (2.6)	OR	0.86	[0.53; 1.39]	0.527
			RR	0.86	[0.54; 1.38]	0.527
			RD	-0.00	[-0.02; 0.01]	0.527
Serious second Primary Malignancies, n (%)	23 (1.6)	25 (1.8)	OR	0.89	[0.50; 1.57]	0.682
			RR	0.89	[0.51; 1.56]	0.682
			RD	-0.00	[-0.01; 0.01]	0.682
Grade \geq 3: second Primary Malignancies, n (%)	20 (1.4)	22 (1.6)	OR	0.88	[0.48; 1.61]	0.673
			RR	0.88	[0.48; 1.60]	0.673
			RD	-0.00	[-0.01; 0.01]	0.673
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval OR: Odds ratio RR: Relative risk RD: Risk difference ET: Endocrine therapy (Anastrozole/Letrozole) Analysis methods: OR with Wald 95% CI and p-value obtained from logistic regression model: $\text{logit}(\text{proportion}) = \text{treatment}$ RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.						

5 Subgroup analysis

5-1 Subgroup analysis for efficacy

5-1.1 Overall survival

Table 5-1.1.1 Overall survival: time to event analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)	HR	[95% CI]	p-value
Time to Overall Survival Event					
	n / N' (%)	n / N' (%)			
Region					
Interaction test	p = 0.545				
NA/WE/O	41 / 913 (4.5)	37 / 902 (4.1)	1.05	[0.68; 1.64]	0.818
ROW	33 / 511 (6.5)	38 / 518 (7.3)	0.86	[0.54; 1.38]	0.533
Geographical region					
Interaction test	p = 0.328				
Europe	52 / 840 (6.2)	47 / 843 (5.6)	1.11	[0.75; 1.65]	0.602
North America/Australia	17 / 406 (4.2)	16 / 395 (4.1)	0.97	[0.49; 1.91]	0.919
Asia	2 / 103 (1.9)	5 / 108 (4.6)	0.35	[0.07; 1.82]	0.194
Latin America	3 / 75 (4.0)	7 / 74 (9.5)	0.42	[0.11; 1.62]	0.193
Age group 1 at randomization					
Interaction test	p = 0.520				
<45	0 / 60 (0.0)	2 / 58 (3.4)	N.E.	N.E.	0.111
45 to 54	13 / 303 (4.3)	15 / 333 (4.5)	0.88	[0.42; 1.84]	0.729
55 to 64	39 / 658 (5.9)	31 / 668 (4.6)	1.26	[0.79; 2.02]	0.332
≥65	22 / 403 (5.5)	27 / 361 (7.5)	0.72	[0.41; 1.27]	0.259
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.632				
<Median	32 / 639 (5.0)	30 / 653 (4.6)	1.05	[0.64; 1.73]	0.841
≥Median	42 / 785 (5.4)	45 / 767 (5.9)	0.89	[0.59; 1.36]	0.600
Race					
Interaction test	p = 0.239				
Asian	2 / 129 (1.6)	5 / 134 (3.7)	0.35	[0.07; 1.81]	0.192
Non-Asian	66 / 1215 (5.4)	67 / 1218 (5.5)	0.96	[0.68; 1.35]	0.818
BMI at screening					
Interaction test	p = 0.055				
≥25	54 / 945 (5.7)	45 / 969 (4.6)	1.20	[0.81; 1.78]	0.363
<25	20 / 465 (4.3)	29 / 432 (6.7)	0.61	[0.35; 1.08]	0.089

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)	HR	[95% CI]	p-value
AJCC Anatomic Stage Group					
Interaction test	p = 0.477				
Group I/II	16 / 593 (2.7)	14 / 603 (2.3)	1.18	[0.57; 2.41]	0.657
Group III	58 / 830 (7.0)	61 / 816 (7.5)	0.87	[0.61; 1.25]	0.456
Anatomic stages					
Interaction test	p = 0.183				
IA/IB/IIA	2 / 312 (0.6)	6 / 320 (1.9)	0.33	[0.07; 1.64]	0.155
IIB	14 / 281 (5.0)	8 / 283 (2.8)	1.90	[0.80; 4.55]	0.140
IIIA	24 / 487 (4.9)	31 / 476 (6.5)	0.72	[0.43; 1.23]	0.233
IIIB	9 / 100 (9.0)	11 / 86 (12.8)	0.66	[0.27; 1.58]	0.344
IIIC	25 / 243 (10.3)	19 / 254 (7.5)	1.21	[0.67; 2.20]	0.532
Tumor category					
Interaction test	p = 0.938				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	63 / 1302 (4.8)	63 / 1312 (4.8)	0.98	[0.69; 1.39]	0.910
>T3	11 / 113 (9.7)	11 / 101 (10.9)	0.83	[0.36; 1.92]	0.663
Nodal status					
Interaction test	p = 0.942				
N0	7 / 191 (3.7)	8 / 208 (3.8)	0.92	[0.33; 2.53]	0.865
N1-N3	67 / 1230 (5.4)	67 / 1210 (5.5)	0.95	[0.68; 1.34]	0.787
Histological grade at time of surgery					
Interaction test	p = 0.266				
Grade 1	3 / 102 (2.9)	1 / 110 (0.9)	3.77	[0.39; 36.29]	0.217
Grade 2	40 / 849 (4.7)	43 / 797 (5.4)	0.83	[0.54; 1.28]	0.398
Grade 3	26 / 381 (6.8)	22 / 420 (5.2)	1.29	[0.73; 2.28]	0.378
Histological subtype					
Interaction test	p = 0.547				
Ductal	48 / 1038 (4.6)	56 / 1059 (5.3)	0.85	[0.58; 1.25]	0.408
Lobular	20 / 293 (6.8)	16 / 285 (5.6)	1.18	[0.61; 2.28]	0.617
Other	6 / 92 (6.5)	3 / 76 (3.9)	1.56	[0.39; 6.23]	0.528
Ki67 status from surgical specimen					
Interaction test	p = 0.608				
Ki67≤20	27 / 667 (4.0)	24 / 656 (3.7)	1.11	[0.64; 1.93]	0.706
Ki67>20	35 / 493 (7.1)	39 / 536 (7.3)	0.92	[0.58; 1.45]	0.713
Type of NSAI					
Interaction test	p = 0.713				
Letrozole	46 / 908 (5.1)	50 / 894 (5.6)	0.91	[0.61; 1.35]	0.630
Anastrozole	28 / 503 (5.6)	25 / 466 (5.4)	1.03	[0.60; 1.76]	0.920
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.620				
Yes	70 / 1209 (5.8)	69 / 1199 (5.8)	0.97	[0.69; 1.35]	0.835
No	4 / 215 (1.9)	6 / 221 (2.7)	0.69	[0.19; 2.45]	0.564

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)	HR	[95% CI]	p-value
Prior adjuvant chemotherapy					
Interaction test	p = 0.653				
Yes	32 / 702 (4.6)	30 / 705 (4.3)	1.04	[0.63; 1.71]	0.874
No	42 / 722 (5.8)	45 / 715 (6.3)	0.89	[0.58; 1.36]	0.588
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.970				
Yes	42 / 535 (7.9)	41 / 524 (7.8)	0.94	[0.61; 1.45]	0.781
No	32 / 889 (3.6)	34 / 896 (3.8)	0.93	[0.58; 1.51]	0.781
Prior endocrine therapy					
Interaction test	p = 0.171				
Yes	49 / 967 (5.1)	42 / 979 (4.3)	1.13	[0.75; 1.71]	0.555
No	25 / 457 (5.5)	33 / 441 (7.5)	0.72	[0.43; 1.21]	0.210
Prior mastectomy					
Interaction test	p = 0.173				
Yes	58 / 865 (6.7)	52 / 884 (5.9)	1.10	[0.76; 1.60]	0.624
No	16 / 559 (2.9)	23 / 536 (4.3)	0.67	[0.35; 1.27]	0.220
Prior radiotherapy					
Interaction test	p = 0.866				
Yes	68 / 1267 (5.4)	68 / 1259 (5.4)	0.96	[0.69; 1.34]	0.808
No	6 / 157 (3.8)	7 / 161 (4.3)	0.86	[0.29; 2.57]	0.792
N: Number of patients N': Number of patients included in the analysis n: Number and percentage of patients with event CI: Confidence interval HR: Hazard ratio KM: Kaplan-Meier N.E.: Not estimable ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from Cox proportional hazards model: $\log(\text{hazard ratio}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis methods for within-subgroup analysis: HR with 95% CI from Cox proportional hazards model: $\log(\text{hazard ratio}) = \text{treatment}$ ET was the reference group for treatment group comparison. Two-sided p-value from Log-rank test.					

5-1.2 Invasive disease-free survival

Table 5-1.2.1 Invasive disease-free survival: time to event analysis - subgroup analysis (Full Analysis Set)

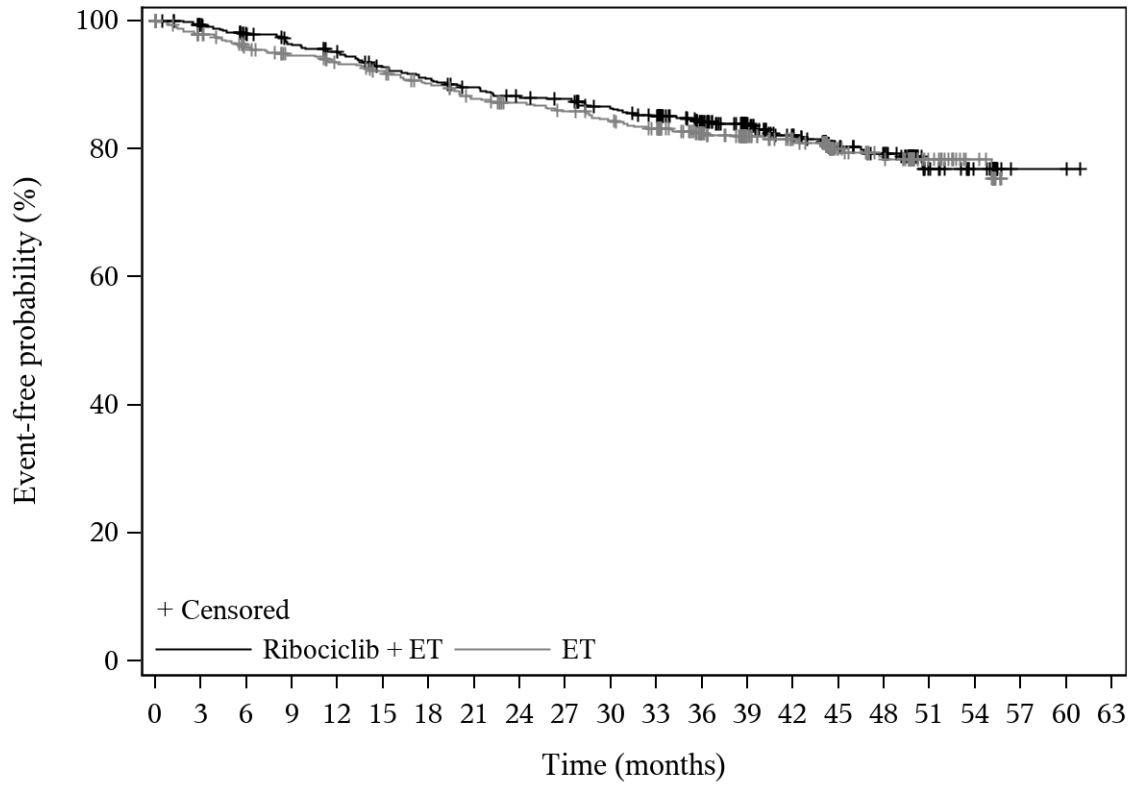
	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)	HR	[95% CI]	p-value
Time to First iDFS Event					
	n / N' (%)	n / N' (%)			
Region					
Interaction test	p = 0.298				
NA/WE/O	93 / 913 (10.2)	124 / 902 (13.7)	0.70	[0.53; 0.91]	0.008
ROW	71 / 511 (13.9)	79 / 518 (15.3)	0.86	[0.62; 1.18]	0.348
Geographical region					
Interaction test	p = 0.102				
Europe	109 / 840 (13.0)	119 / 843 (14.1)	0.91	[0.70; 1.18]	0.468
North America/Australia	39 / 406 (9.6)	52 / 395 (13.2)	0.65	[0.43; 0.99]	0.043
Asia	7 / 103 (6.8)	17 / 108 (15.7)	0.35	[0.14; 0.84]	0.014
Latin America	9 / 75 (12.0)	15 / 74 (20.3)	0.54	[0.24; 1.24]	0.140
Age group 1 at randomization					
Interaction test	p = 0.414				
<45	5 / 60 (8.3)	6 / 58 (10.3)	0.67	[0.20; 2.20]	0.507
45 to 54	27 / 303 (8.9)	36 / 333 (10.8)	0.75	[0.46; 1.24]	0.258
55 to 64	86 / 658 (13.1)	94 / 668 (14.1)	0.89	[0.67; 1.19]	0.439
≥65	46 / 403 (11.4)	67 / 361 (18.6)	0.59	[0.41; 0.86]	0.006
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.437				
<Median	71 / 639 (11.1)	81 / 653 (12.4)	0.84	[0.61; 1.15]	0.268
≥Median	93 / 785 (11.8)	122 / 767 (15.9)	0.71	[0.54; 0.93]	0.012
Race					
Interaction test	p = 0.090				
Asian	10 / 129 (7.8)	20 / 134 (14.9)	0.42	[0.20; 0.91]	0.022
Non-Asian	145 / 1215 (11.9)	169 / 1218 (13.9)	0.82	[0.66; 1.02]	0.080
BMI at screening					
Interaction test	p = 0.142				
≥25	119 / 945 (12.6)	136 / 969 (14.0)	0.85	[0.66; 1.08]	0.189
<25	45 / 465 (9.7)	65 / 432 (15.0)	0.61	[0.41; 0.89]	0.009
AJCC Anatomic Stage Group					
Interaction test	p = 0.830				
Group I/II	39 / 593 (6.6)	55 / 603 (9.1)	0.71	[0.47; 1.07]	0.102
Group III	125 / 830 (15.1)	148 / 816 (18.1)	0.75	[0.59; 0.95]	0.018

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)	HR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.353				
IA/IB/IIA	15 / 312 (4.8)	26 / 320 (8.1)	0.56	[0.30; 1.05]	0.069
IIB	24 / 281 (8.5)	29 / 283 (10.2)	0.85	[0.49; 1.46]	0.551
IIIA	53 / 487 (10.9)	78 / 476 (16.4)	0.61	[0.43; 0.87]	0.006
IIIB	17 / 100 (17.0)	20 / 86 (23.3)	0.68	[0.36; 1.30]	0.245
IIIC	55 / 243 (22.6)	50 / 254 (19.7)	1.00	[0.68; 1.46]	0.985
Tumor category					
Interaction test	p = 0.983				
T0	1 / 5 (20.0)	0 / 5 (0.0)	1.00	[1.00; 1.00]	N.E.
T1-T3	141 / 1302 (10.8)	179 / 1312 (13.6)	0.75	[0.60; 0.94]	0.011
>T3	20 / 113 (17.7)	23 / 101 (22.8)	0.72	[0.39; 1.31]	0.277
Nodal status					
Interaction test	p = 0.499				
N0	20 / 191 (10.5)	23 / 208 (11.1)	0.91	[0.50; 1.66]	0.759
N1-N3	144 / 1230 (11.7)	180 / 1210 (14.9)	0.74	[0.59; 0.92]	0.006
Histological grade at time of surgery					
Interaction test	p = 0.529				
Grade 1	5 / 102 (4.9)	9 / 110 (8.2)	0.64	[0.22; 1.92]	0.423
Grade 2	90 / 849 (10.6)	114 / 797 (14.3)	0.68	[0.52; 0.90]	0.007
Grade 3	53 / 381 (13.9)	63 / 420 (15.0)	0.89	[0.62; 1.28]	0.517
Histological subtype					
Interaction test	p = 0.929				
Ductal	115 / 1038 (11.1)	148 / 1059 (14.0)	0.74	[0.58; 0.95]	0.017
Lobular	40 / 293 (13.7)	47 / 285 (16.5)	0.80	[0.52; 1.21]	0.289
Other	9 / 92 (9.8)	8 / 76 (10.5)	0.85	[0.33; 2.21]	0.744
Ki67 status from surgical specimen					
Interaction test	p = 0.701				
Ki67≤20	69 / 667 (10.3)	85 / 656 (13.0)	0.78	[0.57; 1.07]	0.117
Ki67>20	72 / 493 (14.6)	85 / 536 (15.9)	0.85	[0.62; 1.16]	0.304
Type of NSAI					
Interaction test	p = 0.583				
Letrozole	108 / 908 (11.9)	132 / 894 (14.8)	0.79	[0.61; 1.02]	0.069
Anastrozole	56 / 503 (11.1)	71 / 466 (15.2)	0.70	[0.49; 0.99]	0.045
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.653				
Yes	148 / 1209 (12.2)	178 / 1199 (14.8)	0.77	[0.62; 0.96]	0.017
No	16 / 215 (7.4)	25 / 221 (11.3)	0.66	[0.35; 1.24]	0.196
Prior adjuvant chemotherapy					
Interaction test	p = 0.069				
Yes	60 / 702 (8.5)	94 / 705 (13.3)	0.60	[0.44; 0.83]	0.002
No	104 / 722 (14.4)	109 / 715 (15.2)	0.89	[0.68; 1.17]	0.412

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)	HR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.037				
Yes	93 / 535 (17.4)	89 / 524 (17.0)	0.94	[0.70; 1.25]	0.666
No	71 / 889 (8.0)	114 / 896 (12.7)	0.60	[0.45; 0.81]	<.001
Prior endocrine therapy					
Interaction test	p = 0.692				
Yes	106 / 967 (11.0)	129 / 979 (13.2)	0.78	[0.61; 1.01]	0.061
No	58 / 457 (12.7)	74 / 441 (16.8)	0.72	[0.51; 1.01]	0.058
Prior mastectomy					
Interaction test	p = 0.069				
Yes	122 / 865 (14.1)	136 / 884 (15.4)	0.87	[0.68; 1.11]	0.248
No	42 / 559 (7.5)	67 / 536 (12.5)	0.57	[0.39; 0.83]	0.003
Prior radiotherapy					
Interaction test	p = 0.577				
Yes	150 / 1267 (11.8)	181 / 1259 (14.4)	0.77	[0.62; 0.96]	0.020
No	14 / 157 (8.9)	22 / 161 (13.7)	0.63	[0.32; 1.23]	0.174
<p>N: Number of patients N': Number of patients included in the analysis n: Number and percentage of patients with event CI: Confidence interval HR: Hazard ratio KM: Kaplan-Meier N.E.: Not estimable ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from Cox proportional hazards model: $\log(\text{hazard ratio}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis methods for within-subgroup analysis: HR with 95% CI from Cox proportional hazards model: $\log(\text{hazard ratio}) = \text{treatment}$ ET was the reference group for treatment group comparison. Two-sided p-value from Log-rank test.</p>					

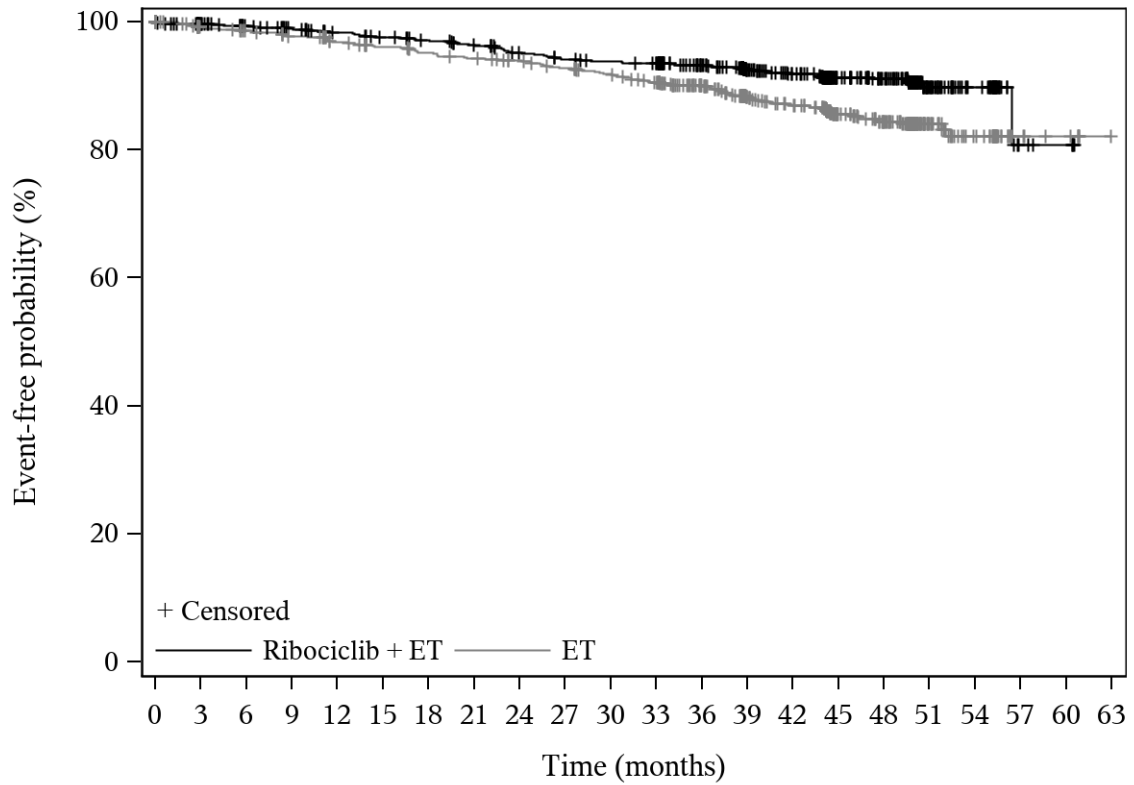
Figure 5-1.2.1 Invasive disease-free survival: Kaplan-Meier plot - subgroup analysis (Full Analysis Set)

Time to First iDFS Event
Prior neoadjuvant chemotherapy: Yes



Ribociclib + ET	535	491	468	445	427	409	357	257	154	26	2
ET	524	441	420	398	376	361	306	232	139	29	

Time to First iDFS Event
Prior neoadjuvant chemotherapy: No



Ribociclib + ET	889	814	786	767	740	724	670	573	381	70	4
ET	896	796	767	745	729	703	638	536	356	67	6

5-2 Subgroup analysis for PRO

5-2.1 EORTC QLQ-C30 Symptoms

Table 5-2.1.1.1 QLQ-C30 - Fatigue: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
QLQ-C30 - Fatigue						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.117					
NA/WE/O	826 2.86 (0.55)	774 2.04 (0.56)	Difference	0.82	[-0.72; 2.36]	0.296
			Hedges G	0.05	[-0.05; 0.15]	
ROW	499 2.84 (0.65)	489 3.84 (0.65)	Difference	-1.00	[-2.80; 0.81]	0.280
			Hedges G	-0.07	[-0.19; 0.06]	
Geographical region						
Interaction test	N.E.					
Europe	784 2.94 (0.56)	775 3.25 (0.56)	Difference	-0.31	[-1.85; 1.23]	0.696
			Hedges G	-0.02	[-0.12; 0.08]	
North America/Australia	368 2.24 (0.75)	324 0.66 (0.80)	Difference	1.58	[-0.57; 3.74]	0.150
			Hedges G	0.11	[-0.04; 0.26]	
Asia	101 N.E.	93 N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Latin America	72 3.92 (1.83)	71 4.28 (1.84)	Difference	-0.35	[-5.48; 4.78]	0.893
			Hedges G	-0.02	[-0.35; 0.31]	
Age group 1 at randomization						
Interaction test	p = 0.886					
<45	56 3.86 (2.33)	48 3.76 (2.56)	Difference	0.10	[-6.77; 6.96]	0.977
			Hedges G	0.01	[-0.38; 0.39]	
45 to 54	284 1.85 (0.94)	291 2.15 (0.93)	Difference	-0.31	[-2.91; 2.30]	0.818
			Hedges G	-0.02	[-0.18; 0.14]	
55 to 64	613 1.77 (0.57)	602 2.05 (0.57)	Difference	-0.28	[-1.87; 1.30]	0.725
			Hedges G	-0.02	[-0.13; 0.09]	
≥65	372 4.73 (0.74)	322 4.06 (0.79)	Difference	0.67	[-1.46; 2.80]	0.536
			Hedges G	0.05	[-0.10; 0.20]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.337					
<Median	598 1.89 (0.66)	580 2.49 (0.67)	Difference	-0.59	[-2.44; 1.25]	0.527
			Hedges G	-0.04	[-0.15; 0.08]	
≥Median	727 3.48 (0.54)	683 2.89 (0.55)	Difference	0.59	[-0.92; 2.10]	0.445
			Hedges G	0.04	[-0.06; 0.15]	
Race						
Interaction test	p = 0.965					
Asian	125 3.56 (1.11)	116 3.31 (1.24)	Difference	0.25	[-3.04; 3.54]	0.882
			Hedges G	0.02	[-0.23; 0.27]	
Non-Asian	1123 2.61 (0.45)	1083 2.48 (0.45)	Difference	0.13	[-1.12; 1.37]	0.842
			Hedges G	0.01	[-0.07; 0.09]	
BMI at screening						
Interaction test	p = 0.939					
≥25	875 2.76 (0.51)	862 2.70 (0.51)	Difference	0.06	[-1.35; 1.47]	0.933
			Hedges G	0.00	[-0.09; 0.10]	
<25	439 3.13 (0.74)	389 2.91 (0.78)	Difference	0.22	[-1.89; 2.33]	0.840
			Hedges G	0.01	[-0.12; 0.15]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.008					
Group I/II	544 3.25 (0.65)	554 1.65 (0.64)	Difference	1.60	[-0.19; 3.40]	0.080
			Hedges G	0.11	[-0.01; 0.22]	
Group III	780 2.20 (0.55)	709 3.59 (0.57)	Difference	-1.40	[-2.95; 0.16]	0.078
			Hedges G	-0.09	[-0.19; 0.01]	
Anatomic stages						
Interaction test	p = 0.188					
IA/IB/IIA	286 2.90 (0.88)	292 1.68 (0.87)	Difference	1.22	[-1.21; 3.65]	0.325
			Hedges G	0.08	[-0.08; 0.25]	
IIB	258 3.58 (0.92)	262 1.45 (0.91)	Difference	2.13	[-0.40; 4.66]	0.099
			Hedges G	0.14	[-0.03; 0.32]	
IIIA	461 2.86 (0.71)	414 4.37 (0.72)	Difference	-1.50	[-3.49; 0.48]	0.138
			Hedges G	-0.10	[-0.23; 0.03]	
IIIB	92 -0.93 (1.51)	78 -0.23 (1.65)	Difference	-0.70	[-5.12; 3.72]	0.755
			Hedges G	-0.05	[-0.35; 0.25]	
IIIC	227 2.63 (0.96)	217 3.65 (0.99)	Difference	-1.03	[-3.73; 1.68]	0.456
			Hedges G	-0.07	[-0.26; 0.12]	
Tumor category						
N.A. ⁺						

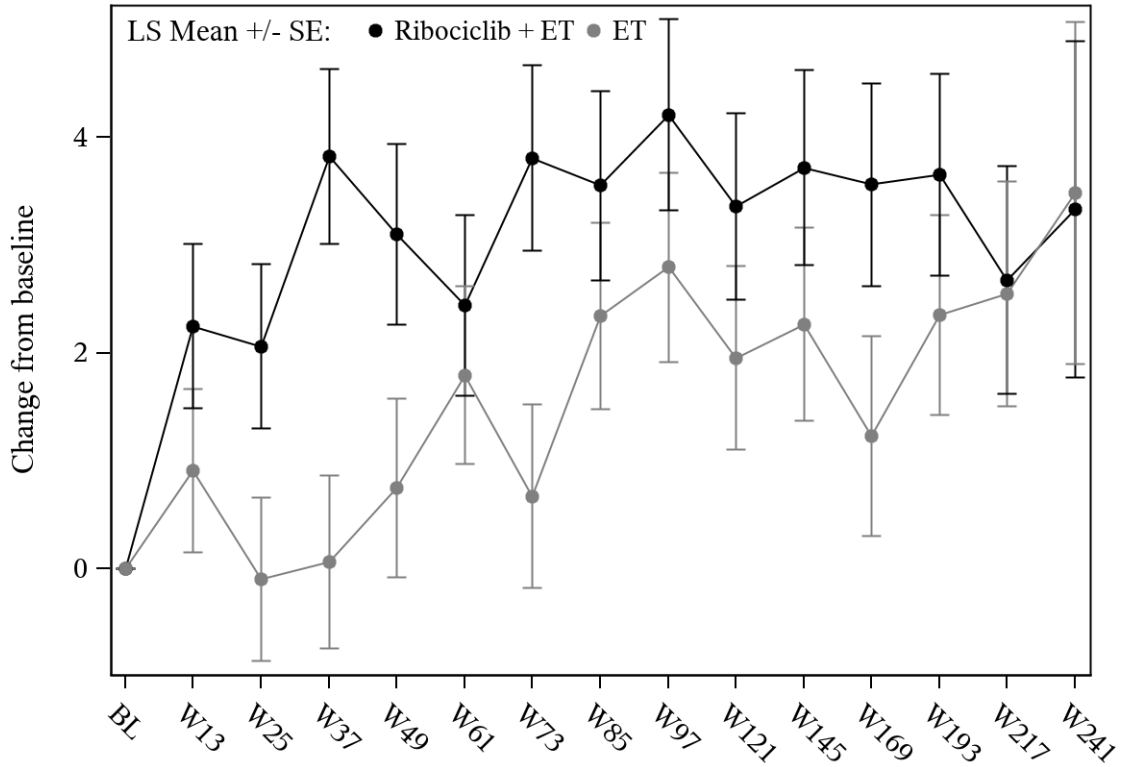
Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Nodal status						
Interaction test	p = 0.436					
N0	176 3.59 (1.13)	189 2.33 (1.10)	Difference	1.26	[-1.84; 4.37]	0.425
			Hedges G	0.08	[-0.12; 0.29]	
N1-N3	1146 2.62 (0.45)	1074 2.74 (0.46)	Difference	-0.13	[-1.40; 1.14]	0.844
			Hedges G	-0.01	[-0.09; 0.07]	
Histological grade at time of surgery						
Interaction test	p = 0.393					
Grade 1	94 4.06 (1.53)	102 4.59 (1.41)	Difference	-0.53	[-4.66; 3.60]	0.800
			Hedges G	-0.04	[-0.32; 0.24]	
Grade 2	788 2.33 (0.50)	704 1.59 (0.53)	Difference	0.73	[-0.70; 2.16]	0.315
			Hedges G	0.05	[-0.05; 0.15]	
Grade 3	357 2.69 (0.83)	372 3.60 (0.81)	Difference	-0.91	[-3.19; 1.36]	0.431
			Hedges G	-0.06	[-0.20; 0.09]	
Histological subtype						
Interaction test	p = 0.657					
Ductal	959 2.62 (0.36)	930 2.41 (0.37)	Difference	0.21	[-0.80; 1.22]	0.690
			Hedges G	0.02	[-0.07; 0.11]	
Lobular	277 1.88 (0.65)	263 2.30 (0.65)	Difference	-0.41	[-2.22; 1.39]	0.652
			Hedges G	-0.04	[-0.21; 0.13]	
Other	88 1.69 (1.24)	70 4.85 (1.45)	Difference	-3.17	[-6.94; 0.61]	0.100
			Hedges G	-0.27	[-0.58; 0.05]	
Ki67 status from surgical specimen						
Interaction test	p = 0.362					
Ki67≤20	619 2.96 (0.60)	592 2.82 (0.62)	Difference	0.14	[-1.55; 1.83]	0.871
			Hedges G	0.01	[-0.10; 0.12]	
Ki67>20	467 2.80 (0.73)	476 3.95 (0.72)	Difference	-1.15	[-3.17; 0.87]	0.264
			Hedges G	-0.07	[-0.20; 0.05]	
Type of NSAI						
Interaction test	p = 0.133					
Letrozole	848 3.51 (0.53)	825 2.75 (0.54)	Difference	0.76	[-0.72; 2.25]	0.315
			Hedges G	0.05	[-0.05; 0.15]	
Anastrozole	477 1.58 (0.67)	435 2.68 (0.70)	Difference	-1.10	[-3.01; 0.81]	0.259
			Hedges G	-0.07	[-0.20; 0.06]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.775					
Yes	1131 2.44 (0.45)	1055 2.28 (0.47)	Difference	0.17	[-1.12; 1.45]	0.800
			Hedges G	0.01	[-0.07; 0.09]	
No	194 4.46 (1.06)	208 4.81 (1.03)	Difference	-0.35	[-3.26; 2.56]	0.812
			Hedges G	-0.02	[-0.22; 0.17]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior adjuvant chemotherapy						
Interaction test	p = 0.479					
Yes	658 2.31 (0.58)	634 1.89 (0.58)	Difference	0.42	[-1.19; 2.03]	0.611
			Hedges G	0.03	[-0.08; 0.14]	
No	667 3.16 (0.60)	629 3.62 (0.62)	Difference	-0.46	[-2.16; 1.24]	0.593
			Hedges G	-0.03	[-0.14; 0.08]	
Prior neoadjuvant chemotherapy						
Interaction test	p = 0.687					
Yes	500 2.40 (0.67)	451 2.75 (0.71)	Difference	-0.34	[-2.26; 1.57]	0.725
			Hedges G	-0.02	[-0.15; 0.10]	
No	825 2.80 (0.51)	812 2.65 (0.51)	Difference	0.15	[-1.26; 1.56]	0.832
			Hedges G	0.01	[-0.09; 0.11]	
Prior endocrine therapy						
Interaction test	p = 0.775					
Yes	892 3.61 (0.50)	866 3.42 (0.50)	Difference	0.19	[-1.20; 1.58]	0.789
			Hedges G	0.01	[-0.08; 0.11]	
No	433 1.14 (0.77)	397 1.39 (0.80)	Difference	-0.25	[-2.42; 1.92]	0.822
			Hedges G	-0.02	[-0.15; 0.12]	
Prior mastectomy						
Interaction test	p = 0.019					
Yes	809 2.59 (0.55)	780 3.57 (0.56)	Difference	-0.98	[-2.52; 0.57]	0.215
			Hedges G	-0.06	[-0.16; 0.04]	
No	516 3.03 (0.63)	483 1.32 (0.65)	Difference	1.71	[-0.07; 3.49]	0.060
			Hedges G	0.12	[-0.01; 0.24]	
Prior radiotherapy						
Interaction test	p = 0.883					
Yes	1178 2.35 (0.44)	1115 2.33 (0.45)	Difference	0.02	[-1.22; 1.26]	0.973
			Hedges G	0.00	[-0.08; 0.08]	
No	147 5.60 (1.31)	148 5.41 (1.30)	Difference	0.20	[-3.43; 3.83]	0.915
			Hedges G	0.01	[-0.22; 0.24]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed N.E.: Not estimable ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + baseline value ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>* The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

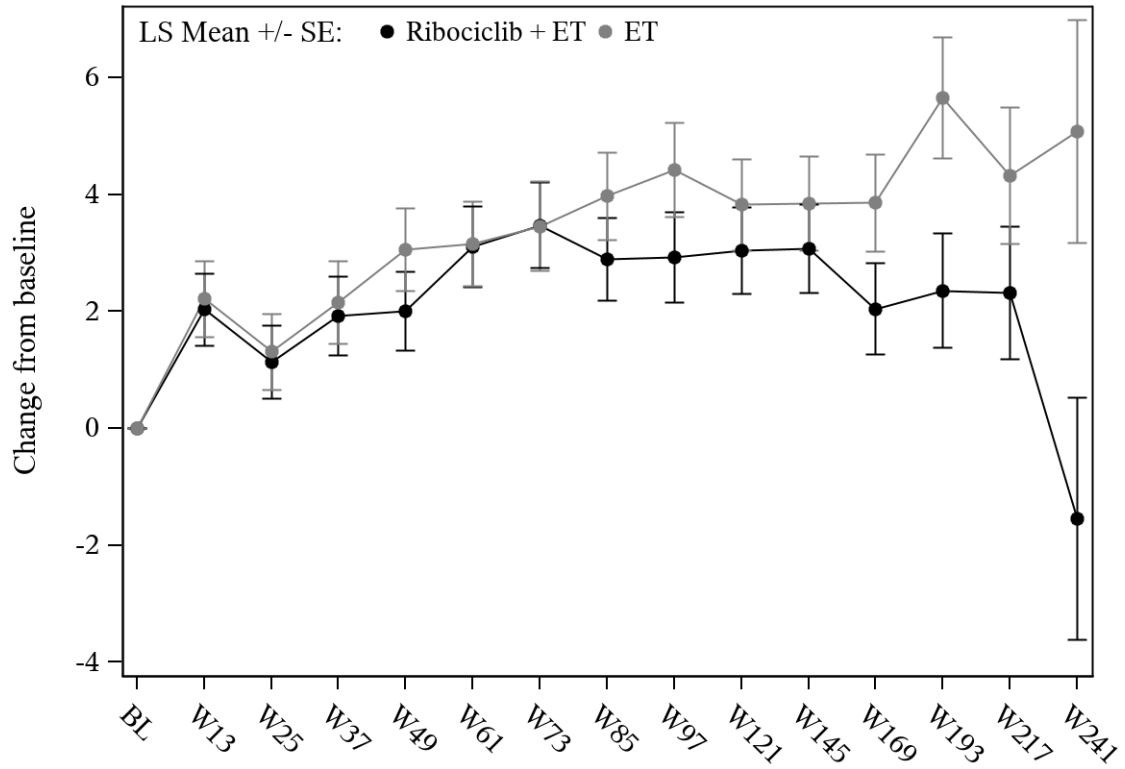
Figure 5-2.1.1.1 QLQ-C30 - Fatigue: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Fatigue
AJCC Anatomic Stage Group: Group I/II



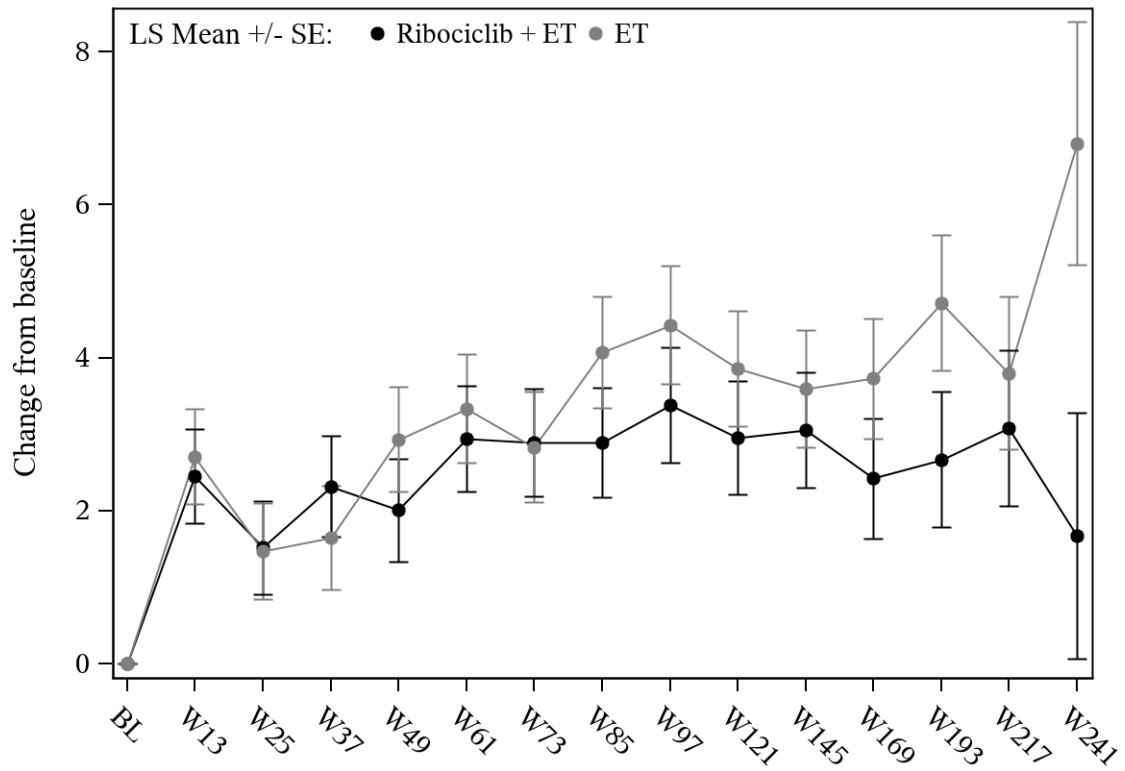
Ribociclib + ET	544	522	511	503	498	483	486	475	476	463	460	426	436	284	61
ET	554	522	508	509	515	500	493	496	485	480	466	447	437	295	58

QLQ-C30 - Fatigue
AJCC Anatomic Stage Group: Group III



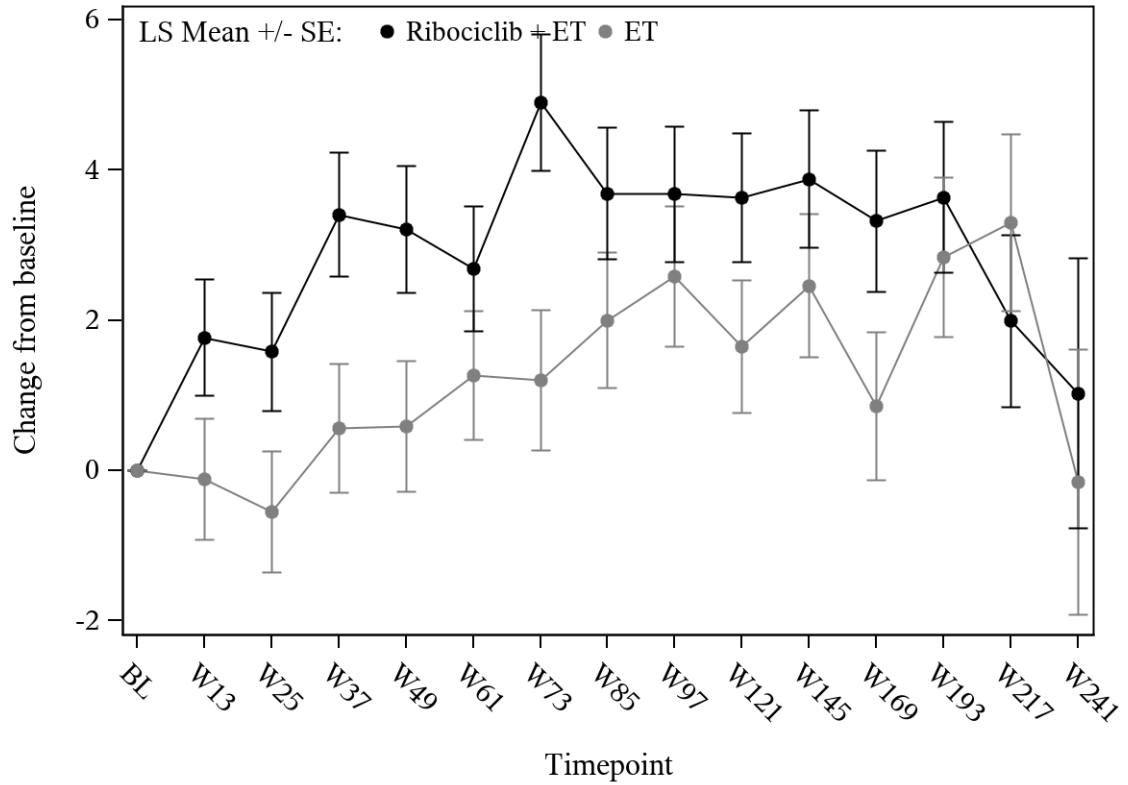
Ribociclib + ET	780	747	707	712	690	693	682	656	653	618	608	482	331	194	30
ET	709	677	646	636	628	616	612	592	583	568	546	426	298	188	37

QLQ-C30 - Fatigue
Prior mastectomy: Yes



Ribociclib + ET	809	773	761	740	728	726	716	684	683	647	636	519	413	271	57
ET	780	743	709	710	703	690	680	673	658	643	623	523	425	287	59

QLQ-C30 - Fatigue
Prior mastectomy: No



Ribociclib + ET	516	497	458	475	460	450	452	447	446	434	432	389	354	207	34
ET	483	456	445	435	440	426	425	415	410	405	389	350	310	196	36

Table 5-2.1.2.1 QLQ-C30 - Nausea and Vomiting: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-C30 - Nausea and Vomiting						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.918					
NA/WE/O	826 2.31 (0.26)	774 1.40 (0.27)	Difference	0.91	[0.18; 1.64]	0.015
			Hedges G	0.12	[0.02; 0.22]	
ROW	499 1.41 (0.30)	489 0.49 (0.30)	Difference	0.92	[0.09; 1.75]	0.030
			Hedges G	0.14	[0.01; 0.26]	
Geographical region						
Interaction test	p = 0.472					
Europe	784 1.79 (0.25)	775 0.80 (0.25)	Difference	0.99	[0.30; 1.68]	0.005
			Hedges G	0.14	[0.04; 0.24]	
North America/Australia	368 2.02 (0.40)	324 1.54 (0.42)	Difference	0.48	[-0.66; 1.61]	0.408
			Hedges G	0.06	[-0.09; 0.21]	
Asia	101 1.17 (0.53)	93 0.52 (0.62)	Difference	0.66	[-0.94; 2.26]	0.419
			Hedges G	0.12	[-0.17; 0.40]	
Latin America	72 3.97 (0.93)	71 1.42 (0.94)	Difference	2.55	[-0.07; 5.16]	0.056
			Hedges G	0.32	[-0.01; 0.65]	
Age group 1 at randomization						
Interaction test	p = 0.473					
<45	56 2.90 (1.11)	48 3.06 (1.19)	Difference	-0.16	[-3.38; 3.06]	0.921
			Hedges G	-0.02	[-0.41; 0.37]	
45 to 54	284 N.E.	291 N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
55 to 64	613 1.34 (0.31)	602 0.75 (0.30)	Difference	0.60	[-0.25; 1.44]	0.167
			Hedges G	0.08	[-0.03; 0.19]	
≥65	372 2.35 (0.34)	322 1.18 (0.36)	Difference	1.17	[0.19; 2.14]	0.019
			Hedges G	0.18	[0.03; 0.33]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.417					
<Median	598 1.91 (0.30)	580 1.28 (0.31)	Difference	0.62	[-0.22; 1.47]	0.148
			Hedges G	0.08	[-0.03; 0.20]	
≥Median	727 2.04 (0.26)	683 0.91 (0.27)	Difference	1.13	[0.39; 1.87]	0.003
			Hedges G	0.16	[0.05; 0.26]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Race						
Interaction test	N.E.					
Asian	125 1.21 (0.51)	116 -0.00 (0.60)	Difference	1.22	[-0.34; 2.77]	0.125
			Hedges G	0.20	[-0.05; 0.45]	
Non-Asian	1123 2.04 (0.22)	1083 1.15 (0.22)	Difference	0.89	[0.27; 1.51]	0.005
			Hedges G	0.12	[0.04; 0.20]	
BMI at screening						
Interaction test	p = 0.580					
≥25	875 2.25 (0.26)	862 1.26 (0.26)	Difference	0.99	[0.28; 1.70]	0.006
			Hedges G	0.13	[0.04; 0.23]	
<25	439 1.43 (0.30)	389 0.70 (0.31)	Difference	0.73	[-0.12; 1.58]	0.091
			Hedges G	0.12	[-0.02; 0.25]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.657					
Group I/II	544 1.67 (0.29)	554 0.70 (0.29)	Difference	0.97	[0.18; 1.77]	0.017
			Hedges G	0.14	[0.03; 0.26]	
Group III	780 2.18 (0.28)	709 1.45 (0.29)	Difference	0.73	[-0.06; 1.53]	0.070
			Hedges G	0.09	[-0.01; 0.20]	
Anatomic stages						
Interaction test	p = 0.488					
IA/IB/IIA	286 1.80 (0.40)	292 0.87 (0.40)	Difference	0.93	[-0.18; 2.04]	0.100
			Hedges G	0.14	[-0.03; 0.30]	
IIB	258 1.50 (0.41)	262 0.26 (0.41)	Difference	1.24	[0.10; 2.38]	0.033
			Hedges G	0.19	[0.02; 0.36]	
IIIA	461 1.93 (0.37)	414 1.61 (0.37)	Difference	0.32	[-0.71; 1.36]	0.540
			Hedges G	0.04	[-0.09; 0.17]	
IIIB	92 3.27 (0.70)	78 0.37 (0.77)	Difference	2.91	[0.86; 4.96]	0.006
			Hedges G	0.43	[0.13; 0.74]	
IIIC	227 2.48 (0.50)	217 1.42 (0.51)	Difference	1.06	[-0.35; 2.47]	0.141
			Hedges G	0.14	[-0.05; 0.33]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.180					
N0	176 2.80 (0.47)	189 0.81 (0.45)	Difference	1.99	[0.71; 3.27]	0.002
			Hedges G	0.32	[0.11; 0.53]	
N1-N3	1146 1.86 (0.22)	1074 1.13 (0.23)	Difference	0.73	[0.11; 1.35]	0.022
			Hedges G	0.10	[0.01; 0.18]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.543					
Grade 1	94 2.58 (0.80)	102 2.17 (0.73)	Difference	0.41	[-1.72; 2.55]	0.704
			Hedges G	0.05	[-0.23; 0.33]	
Grade 2	788 1.92 (0.25)	704 0.69 (0.26)	Difference	1.23	[0.52; 1.94]	<.001
			Hedges G	0.18	[0.08; 0.28]	
Grade 3	357 1.68 (0.38)	372 0.76 (0.37)	Difference	0.92	[-0.12; 1.97]	0.084
			Hedges G	0.13	[-0.02; 0.27]	
Histological subtype						
Interaction test	p = 0.057					
Ductal	959 1.86 (0.23)	930 1.30 (0.23)	Difference	0.56	[-0.09; 1.21]	0.090
			Hedges G	0.08	[-0.01; 0.17]	
Lobular	277 2.35 (0.42)	263 0.23 (0.43)	Difference	2.12	[0.95; 3.29]	<.001
			Hedges G	0.31	[0.14; 0.48]	
Other	88 1.53 (0.63)	70 0.03 (0.74)	Difference	1.49	[-0.44; 3.43]	0.129
			Hedges G	0.24	[-0.07; 0.56]	
Ki67 status from surgical specimen						
Interaction test	p = 0.109					
Ki67≤20	619 2.29 (0.28)	592 1.04 (0.29)	Difference	1.25	[0.46; 2.04]	0.002
			Hedges G	0.18	[0.07; 0.29]	
Ki67>20	467 1.76 (0.35)	476 1.46 (0.35)	Difference	0.30	[-0.67; 1.27]	0.542
			Hedges G	0.04	[-0.09; 0.17]	
Type of NSAI						
Interaction test	p = 0.814					
Letrozole	848 1.97 (0.26)	825 1.08 (0.26)	Difference	0.89	[0.17; 1.60]	0.015
			Hedges G	0.12	[0.02; 0.22]	
Anastrozole	477 1.99 (0.31)	435 1.06 (0.32)	Difference	0.93	[0.06; 1.80]	0.035
			Hedges G	0.14	[0.01; 0.27]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.571					
Yes	1131 2.08 (0.21)	1055 1.07 (0.22)	Difference	1.01	[0.41; 1.61]	<.001
			Hedges G	0.14	[0.06; 0.23]	
No	194 1.38 (0.51)	208 0.71 (0.50)	Difference	0.68	[-0.73; 2.08]	0.343
			Hedges G	0.09	[-0.10; 0.29]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.348					
Yes	658 2.08 (0.27)	634 0.89 (0.27)	Difference	1.19	[0.43; 1.95]	0.002
			Hedges G	0.17	[0.06; 0.28]	
No	667 1.82 (0.28)	629 1.29 (0.29)	Difference	0.53	[-0.26; 1.32]	0.189
			Hedges G	0.07	[-0.04; 0.18]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	p = 0.355					
Yes	500 2.03 (0.32)	451 1.46 (0.34)	Difference	0.57	[-0.35; 1.48]	0.224
			Hedges G	0.08	[-0.05; 0.21]	
No	825 1.91 (0.25)	812 0.85 (0.25)	Difference	1.05	[0.37; 1.74]	0.003
			Hedges G	0.15	[0.05; 0.25]	
Prior endocrine therapy						
Interaction test	p = 0.185					
Yes	892 2.14 (0.24)	866 1.50 (0.25)	Difference	0.64	[-0.04; 1.32]	0.066
			Hedges G	0.09	[-0.01; 0.18]	
No	433 1.81 (0.35)	397 0.29 (0.36)	Difference	1.52	[0.53; 2.51]	0.003
			Hedges G	0.21	[0.07; 0.35]	
Prior mastectomy						
Interaction test	p = 0.395					
Yes	809 1.91 (0.25)	780 0.75 (0.25)	Difference	1.15	[0.46; 1.85]	0.001
			Hedges G	0.16	[0.07; 0.26]	
No	516 2.17 (0.32)	483 1.49 (0.33)	Difference	0.68	[-0.23; 1.58]	0.144
			Hedges G	0.09	[-0.03; 0.22]	
Prior radiotherapy						
Interaction test	p = 0.167					
Yes	1178 1.95 (0.22)	1115 1.24 (0.22)	Difference	0.72	[0.12; 1.32]	0.020
			Hedges G	0.10	[0.02; 0.18]	
No	147 2.20 (0.57)	148 0.28 (0.57)	Difference	1.92	[0.34; 3.50]	0.018
			Hedges G	0.28	[0.05; 0.51]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed N.E.: Not estimable ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + baseline value ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>* The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

Table 5-2.1.3.1 QLQ-C30 - Pain: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-C30 - Pain						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.929					
NA/WE/O	829 3.40 (0.61)	774 4.97 (0.62)	Difference	-1.57	[-3.27; 0.13]	0.071
			Hedges G	-0.09	[-0.19; 0.01]	
ROW	499 2.27 (0.72)	489 3.78 (0.72)	Difference	-1.51	[-3.50; 0.49]	0.139
			Hedges G	-0.09	[-0.22; 0.03]	
Geographical region						
Interaction test	p = 0.217					
Europe	786 3.46 (0.60)	775 4.08 (0.60)	Difference	-0.62	[-2.29; 1.04]	0.464
			Hedges G	-0.04	[-0.14; 0.06]	
North America/ Australia	369 2.98 (0.77)	324 4.75 (0.82)	Difference	-1.77	[-3.97; 0.44]	0.117
			Hedges G	-0.12	[-0.27; 0.03]	
Asia	101 0.65 (1.25)	93 4.38 (1.43)	Difference	-3.73	[-7.47; 0.01]	0.051
			Hedges G	-0.28	[-0.57; 0.00]	
Latin America	72 1.84 (2.18)	71 5.10 (2.20)	Difference	-3.26	[-9.38; 2.87]	0.295
			Hedges G	-0.18	[-0.50; 0.15]	
Age group 1 at randomization						
Interaction test	p = 0.533					
<45	56 1.15 (2.22)	48 3.26 (2.43)	Difference	-2.10	[-8.64; 4.43]	0.525
			Hedges G	-0.13	[-0.51; 0.26]	
45 to 54	285 2.99 (1.03)	291 4.15 (1.02)	Difference	-1.17	[-4.02; 1.68]	0.422
			Hedges G	-0.07	[-0.23; 0.10]	
55 to 64	615 1.42 (0.64)	602 3.81 (0.64)	Difference	-2.39	[-4.16; -0.62]	0.008
			Hedges G	-0.15	[-0.26; -0.04]	
≥65	372 5.94 (0.83)	322 5.97 (0.89)	Difference	-0.04	[-2.42; 2.35]	0.976
			Hedges G	-0.00	[-0.15; 0.15]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.319					
<Median	600 1.79 (0.72)	580 4.08 (0.73)	Difference	-2.29	[-4.31; -0.28]	0.026
			Hedges G	-0.13	[-0.24; -0.02]	
≥Median	728 3.94 (0.60)	683 4.84 (0.62)	Difference	-0.90	[-2.59; 0.79]	0.296
			Hedges G	-0.06	[-0.16; 0.05]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.521					
Asian	125 0.70 (0.83)	116 4.00 (1.03)	Difference	-3.29	[-5.89; -0.69]	0.013
			Hedges G	-0.32	[-0.58; -0.07]	
Non-Asian	1126 2.96 (0.37)	1083 4.00 (0.37)	Difference	-1.04	[-2.07; -0.01]	0.047
			Hedges G	-0.08	[-0.17; -0.00]	
BMI at screening						
Interaction test	p = 0.856					
≥25	877 3.57 (0.57)	862 4.90 (0.57)	Difference	-1.33	[-2.91; 0.26]	0.101
			Hedges G	-0.08	[-0.17; 0.02]	
<25	440 1.91 (0.80)	389 3.75 (0.85)	Difference	-1.84	[-4.12; 0.45]	0.115
			Hedges G	-0.11	[-0.25; 0.03]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.051					
Group I/II	545 3.67 (0.71)	554 3.82 (0.70)	Difference	-0.15	[-2.10; 1.81]	0.884
			Hedges G	-0.01	[-0.13; 0.11]	
Group III	782 2.33 (0.64)	709 5.10 (0.66)	Difference	-2.77	[-4.57; -0.96]	0.003
			Hedges G	-0.16	[-0.26; -0.05]	
Anatomic stages						
Interaction test	N.E.					
IA/IB/IIA	287 3.54 (0.93)	292 3.34 (0.93)	Difference	0.20	[-2.39; 2.79]	0.877
			Hedges G	0.01	[-0.15; 0.18]	
IIB	258 3.86 (1.03)	262 4.19 (1.02)	Difference	-0.33	[-3.19; 2.52]	0.819
			Hedges G	-0.02	[-0.19; 0.15]	
IIIA	462 2.76 (0.81)	414 6.19 (0.83)	Difference	-3.43	[-5.71; -1.16]	0.003
			Hedges G	-0.20	[-0.33; -0.07]	
IIIB	92 -3.54 (1.55)	78 -0.14 (1.69)	Difference	-3.40	[-7.93; 1.13]	0.141
			Hedges G	-0.23	[-0.53; 0.07]	
IIIC	228 3.52 (1.02)	217 4.33 (1.05)	Difference	-0.81	[-3.68; 2.06]	0.580
			Hedges G	-0.05	[-0.24; 0.13]	
Tumor category						
N.A.+						
Nodal status						
Interaction test	p = 0.770					
N0	176 2.91 (1.20)	189 3.78 (1.17)	Difference	-0.87	[-4.17; 2.42]	0.603
			Hedges G	-0.05	[-0.26; 0.15]	
N1-N3	1149 3.02 (0.51)	1074 4.56 (0.52)	Difference	-1.54	[-2.96; -0.11]	0.035
			Hedges G	-0.09	[-0.17; -0.01]	

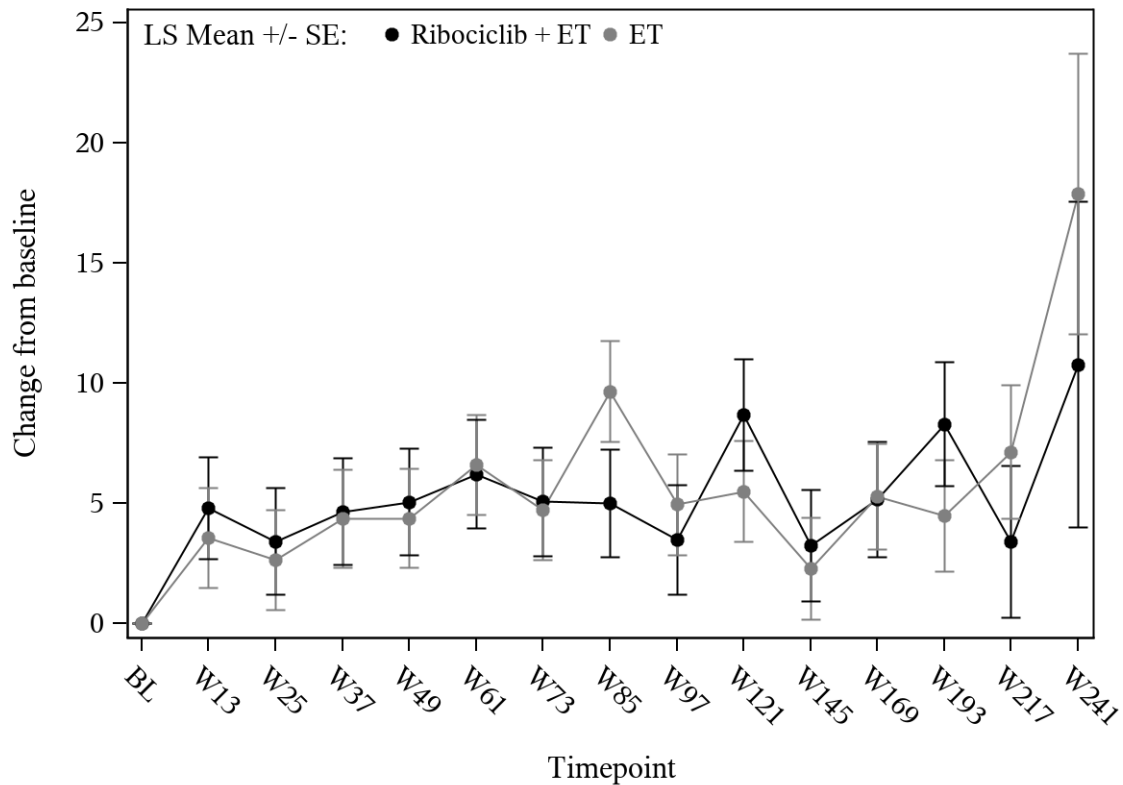
Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Esti- mate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.006					
Grade 1	94 5.52 (1.63)	102 5.96 (1.51)	Difference	-0.44	[-4.84; 3.96]	0.844
			Hedges G	-0.03	[-0.31; 0.25]	
Grade 2	791 2.74 (0.56)	704 3.09 (0.59)	Difference	-0.35	[-1.94; 1.25]	0.669
			Hedges G	-0.02	[-0.12; 0.08]	
Grade 3	357 2.56 (0.91)	372 6.07 (0.90)	Difference	-3.51	[-6.03; -1.00]	0.006
			Hedges G	-0.20	[-0.35; -0.06]	
Histological subtype						
Interaction test	p = 0.887					
Ductal	961 3.08 (0.53)	930 4.42 (0.54)	Difference	-1.34	[-2.84; 0.15]	0.077
			Hedges G	-0.08	[-0.17; 0.01]	
Lobular	278 2.17 (0.95)	263 3.65 (0.96)	Difference	-1.48	[-4.13; 1.16]	0.271
			Hedges G	-0.09	[-0.26; 0.07]	
Other	88 4.61 (1.53)	70 7.18 (1.77)	Difference	-2.57	[-7.19; 2.05]	0.273
			Hedges G	-0.18	[-0.49; 0.14]	
Ki67 status from surgical specimen						
Interaction test	p = 0.644					
Ki67≤20	621 2.43 (0.67)	592 3.65 (0.68)	Difference	-1.22	[-3.10; 0.65]	0.200
			Hedges G	-0.07	[-0.19; 0.04]	
Ki67>20	467 3.65 (0.80)	476 5.46 (0.80)	Difference	-1.81	[-4.02; 0.41]	0.110
			Hedges G	-0.10	[-0.23; 0.02]	
Type of NSAI						
Interaction test	p = 0.991					
Letrozole	851 2.93 (0.57)	825 4.50 (0.58)	Difference	-1.57	[-3.17; 0.03]	0.054
			Hedges G	-0.09	[-0.19; 0.00]	
Anastrozole	477 3.03 (0.79)	435 4.55 (0.83)	Difference	-1.53	[-3.77; 0.72]	0.182
			Hedges G	-0.09	[-0.22; 0.04]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.311					
Yes	1134 3.01 (0.51)	1055 4.75 (0.52)	Difference	-1.74	[-3.17; -0.32]	0.017
			Hedges G	-0.10	[-0.19; -0.02]	
No	194 2.57 (1.19)	208 2.38 (1.16)	Difference	0.20	[-3.07; 3.46]	0.906
			Hedges G	0.01	[-0.18; 0.21]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.835					
Yes	660 3.63 (0.66)	634 4.96 (0.66)	Difference	-1.32	[-3.15; 0.50]	0.156
			Hedges G	-0.08	[-0.19; 0.03]	
No	668 2.29 (0.66)	629 3.98 (0.68)	Difference	-1.69	[-3.55; 0.16]	0.073
			Hedges G	-0.10	[-0.21; 0.01]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	p = 0.368					
Yes	501 2.13 (0.76)	451 4.62 (0.81)	Difference	-2.49	[-4.67; -0.31]	0.025
			Hedges G	-0.15	[-0.27; -0.02]	
No	827 3.40 (0.58)	812 4.51 (0.58)	Difference	-1.11	[-2.73; 0.51]	0.178
			Hedges G	-0.07	[-0.16; 0.03]	
Prior endocrine therapy						
Interaction test	p = 0.492					
Yes	895 3.56 (0.56)	866 4.77 (0.56)	Difference	-1.20	[-2.76; 0.35]	0.130
			Hedges G	-0.07	[-0.17; 0.02]	
No	433 1.91 (0.82)	397 3.99 (0.85)	Difference	-2.08	[-4.40; 0.24]	0.078
			Hedges G	-0.12	[-0.26; 0.01]	
Prior mastectomy						
Interaction test	p = 0.495					
Yes	811 2.61 (0.60)	780 4.55 (0.61)	Difference	-1.94	[-3.62; -0.27]	0.023
			Hedges G	-0.11	[-0.21; -0.02]	
No	517 3.68 (0.72)	483 4.36 (0.74)	Difference	-0.68	[-2.72; 1.36]	0.513
			Hedges G	-0.04	[-0.17; 0.08]	
Prior radiotherapy						
Interaction test	p = 0.026					
Yes	1181 2.66 (0.50)	1115 4.64 (0.51)	Difference	-1.97	[-3.36; -0.58]	0.006
			Hedges G	-0.12	[-0.20; -0.03]	
No	147 5.50 (1.41)	148 3.09 (1.40)	Difference	2.41	[-1.50; 6.32]	0.226
			Hedges G	0.14	[-0.09; 0.37]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed N.E.: Not estimable ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + baseline value ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>* The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

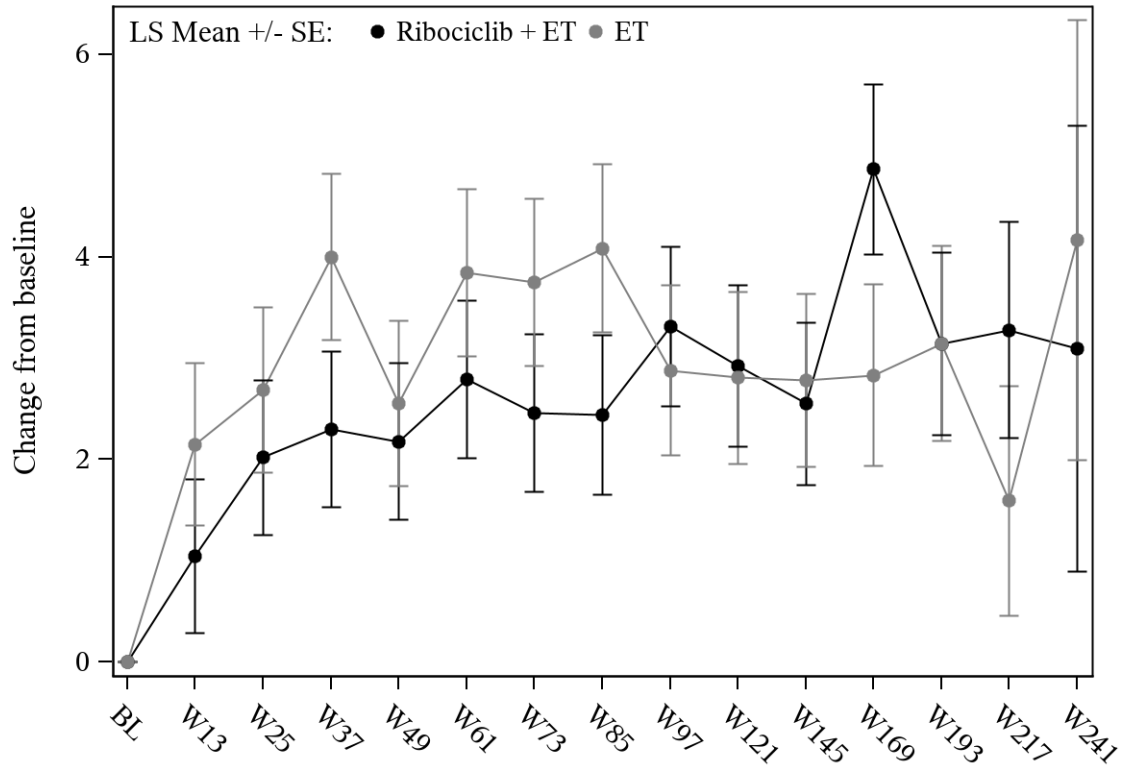
Figure 5-2.1.3.1 QLQ-C30 - Pain: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Pain
Histological grade at time of surgery: Grade 1



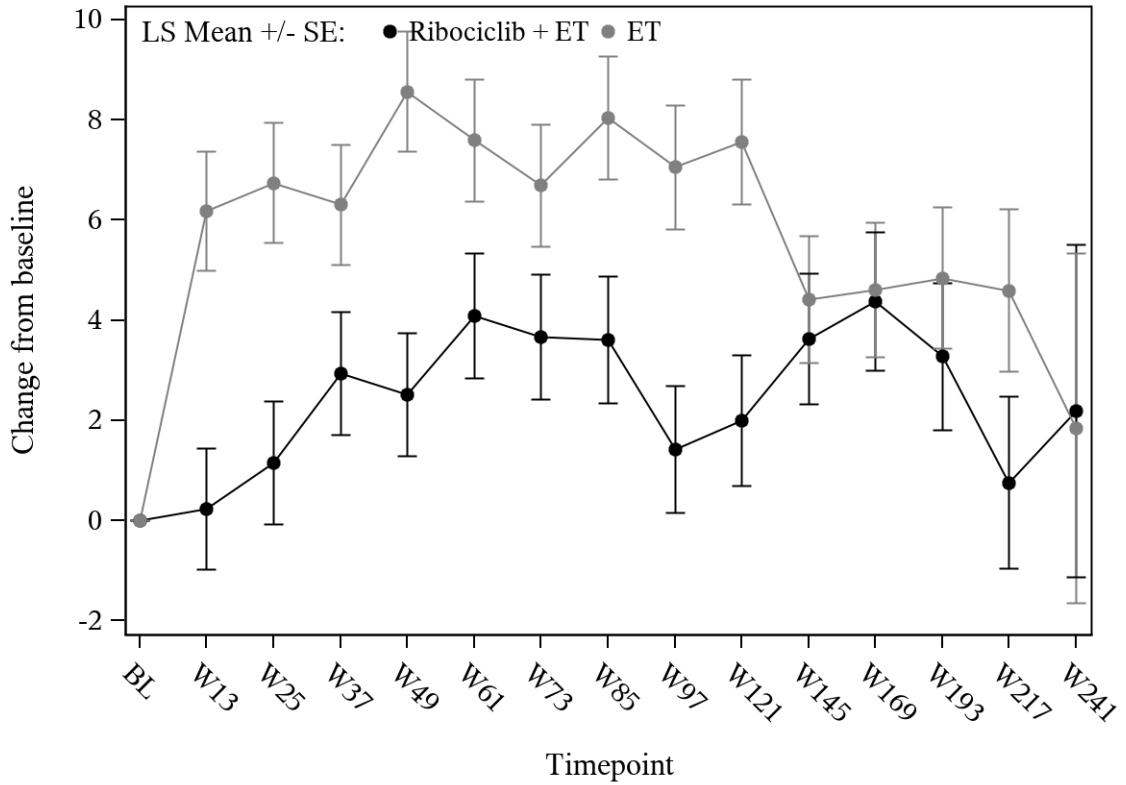
Ribociclib + ET	94	92	80	81	81	75	77	79	75	72	73	64	53	29	5
ET	102	94	93	98	95	94	94	89	93	90	87	79	68	39	7

QLQ-C30 - Pain
Histological grade at time of surgery: Grade 2



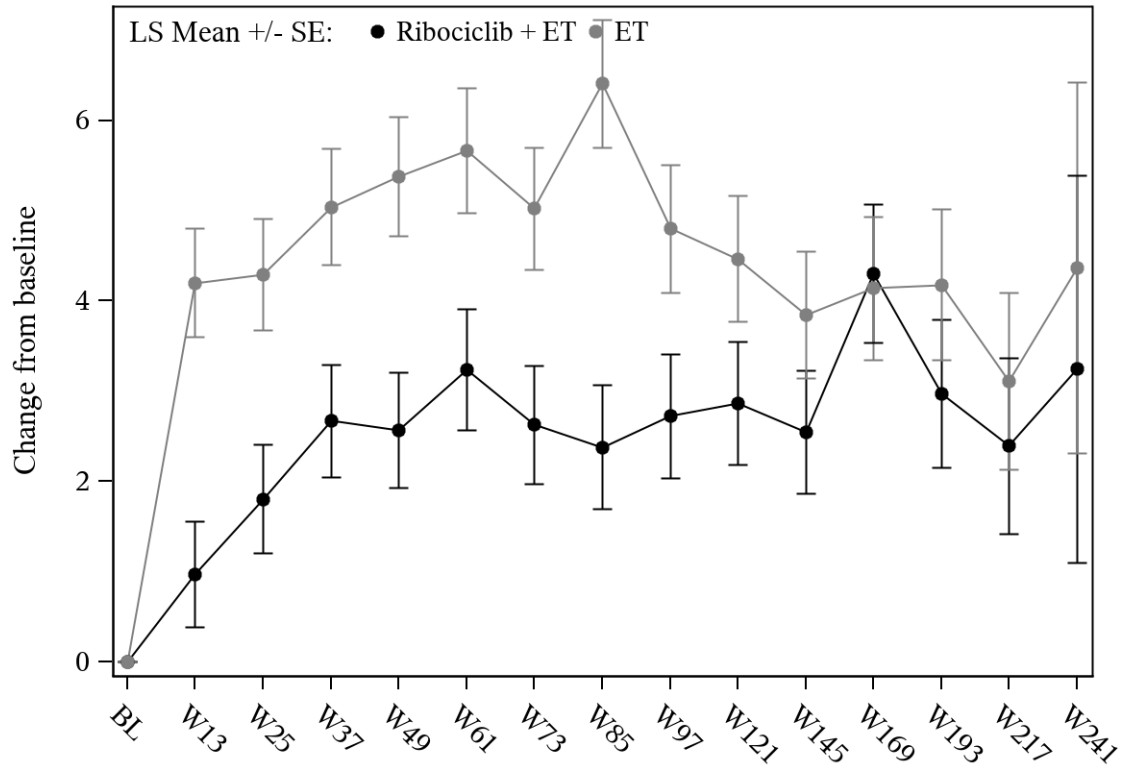
Ribociclib + ET	791	759	738	733	714	716	708	686	684	664	656	561	472	297	58
ET	704	673	640	639	640	625	621	612	603	587	571	496	410	267	60

QLQ-C30 - Pain
Histological grade at time of surgery: Grade 3



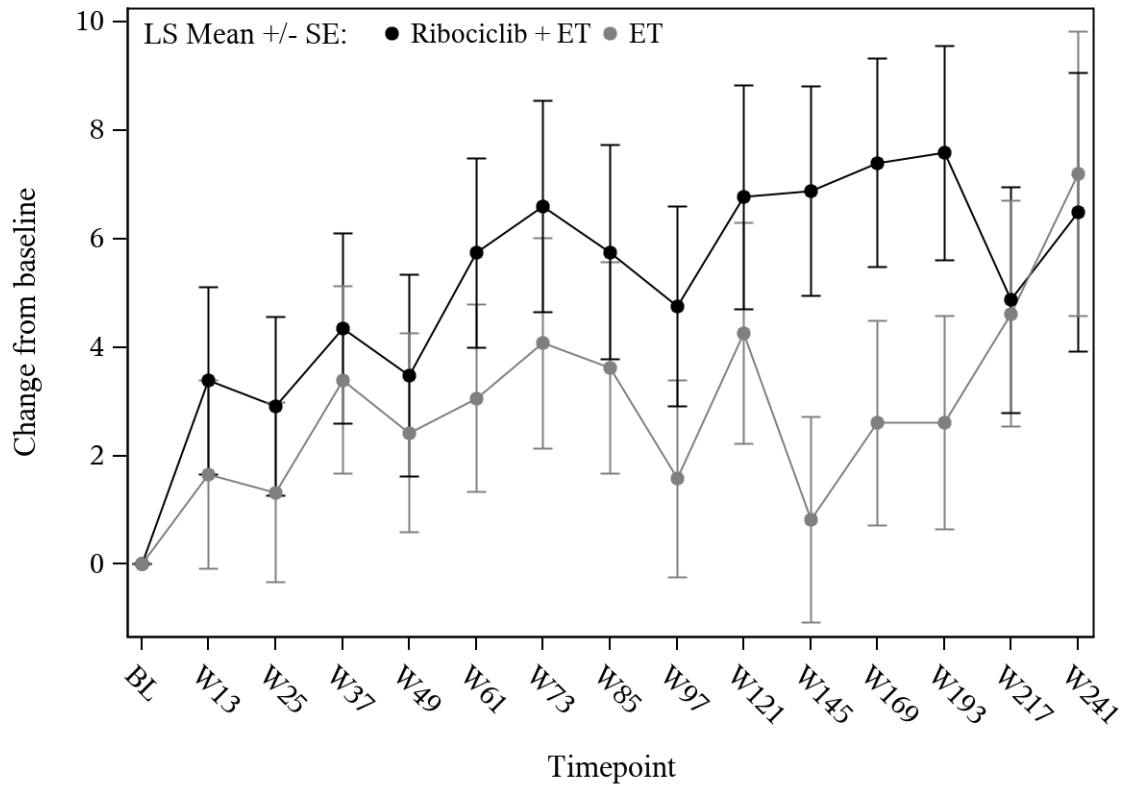
Ribociclib + ET	357	339	320	324	318	310	308	293	297	276	270	227	194	128	27
ET	372	351	340	336	335	324	320	318	307	301	291	245	212	145	24

QLQ-C30 - Pain
Prior radiotherapy: Yes



Ribociclib + ET	1181	1130	1081	1081	1057	1040	1032	1004	1002	959	945	797	656	401	68
ET	1115	1061	1015	1002	1003	975	972	949	934	913	884	750	625	407	75

QLQ-C30 - Pain
Prior radiotherapy: No



Ribociclib + ET	147	143	142	138	135	139	139	131	131	128	126	115	113	79	23
ET	148	141	139	144	141	142	135	139	137	134	132	122	111	77	21

Table 5-2.1.4.1 QLQ-C30 - Dyspnoea: change from baseline analysis - subgroup analysis (Full Analysis Set)

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-C30 - Dyspnoea						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.139					
NA/WE/O	823 4.60 (0.52)	773 3.84 (0.54)	Difference	0.76	[-0.71; 2.23]	0.309
			Hedges G	0.05	[-0.05; 0.15]	
ROW	499 1.72 (0.65)	487 2.66 (0.66)	Difference	-0.94	[-2.76; 0.89]	0.313
			Hedges G	-0.06	[-0.19; 0.06]	
Geographical region						
Interaction test	p = 0.948					
Europe	784 4.07 (0.57)	772 4.15 (0.56)	Difference	-0.08	[-1.65; 1.49]	0.920
			Hedges G	-0.01	[-0.10; 0.09]	
North America/Australia	365 3.15 (0.67)	324 2.63 (0.71)	Difference	0.52	[-1.40; 2.44]	0.594
			Hedges G	0.04	[-0.11; 0.19]	
Asia	101 1.71 (1.25)	93 2.25 (1.44)	Difference	-0.54	[-4.31; 3.23]	0.779
			Hedges G	-0.04	[-0.32; 0.24]	
Latin America	72 1.38 (1.38)	71 0.53 (1.40)	Difference	0.85	[-3.03; 4.73]	0.666
			Hedges G	0.07	[-0.26; 0.40]	
Age group 1 at randomization						
Interaction test	p = 0.683					
<45	55 3.64 (1.96)	48 6.92 (2.09)	Difference	-3.27	[-8.98; 2.43]	0.258
			Hedges G	-0.22	[-0.61; 0.16]	
45 to 54	284 3.24 (0.83)	291 2.82 (0.82)	Difference	0.42	[-1.89; 2.73]	0.720
			Hedges G	0.03	[-0.13; 0.19]	
55 to 64	611 3.05 (0.61)	601 3.29 (0.61)	Difference	-0.23	[-1.94; 1.47]	0.788
			Hedges G	-0.02	[-0.13; 0.10]	
≥65	372 4.23 (0.81)	320 3.77 (0.87)	Difference	0.46	[-1.88; 2.80]	0.700
			Hedges G	0.03	[-0.12; 0.18]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.120					
<Median	595 3.03 (0.61)	579 3.85 (0.62)	Difference	-0.82	[-2.53; 0.89]	0.345
			Hedges G	-0.06	[-0.17; 0.06]	
≥Median	727 4.09 (0.59)	681 3.13 (0.61)	Difference	0.96	[-0.70; 2.62]	0.258
			Hedges G	0.06	[-0.04; 0.16]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.761					
Asian	125 2.42 (1.09)	116 2.16 (1.24)	Difference	0.25	[-3.01; 3.52]	0.878
			Hedges G	0.02	[-0.23; 0.27]	
Non-Asian	1120 3.46 (0.45)	1080 3.45 (0.46)	Difference	0.01	[-1.25; 1.27]	0.987
			Hedges G	0.00	[-0.08; 0.08]	
BMI at screening						
Interaction test	p = 0.410					
≥25	872 3.06 (0.54)	861 3.31 (0.54)	Difference	-0.25	[-1.74; 1.24]	0.743
			Hedges G	-0.02	[-0.11; 0.08]	
<25	439 4.24 (0.68)	387 3.54 (0.72)	Difference	0.71	[-1.24; 2.66]	0.476
			Hedges G	0.05	[-0.09; 0.19]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.155					
Group I/II	543 3.66 (0.64)	553 2.53 (0.63)	Difference	1.13	[-0.63; 2.89]	0.208
			Hedges G	0.08	[-0.04; 0.19]	
Group III	778 3.41 (0.58)	707 4.07 (0.60)	Difference	-0.66	[-2.31; 0.98]	0.430
			Hedges G	-0.04	[-0.14; 0.06]	
Anatomic stages						
Interaction test	p = 0.108					
IA/IB/IIA	285 3.30 (0.85)	291 2.82 (0.84)	Difference	0.48	[-1.87; 2.83]	0.688
			Hedges G	0.03	[-0.13; 0.20]	
IIB	258 3.86 (0.90)	262 2.06 (0.89)	Difference	1.80	[-0.69; 4.30]	0.156
			Hedges G	0.12	[-0.05; 0.30]	
IIIA	461 2.00 (0.73)	414 4.15 (0.75)	Difference	-2.15	[-4.20; -0.09]	0.041
			Hedges G	-0.14	[-0.27; -0.01]	
IIIB	91 4.18 (1.63)	78 5.36 (1.77)	Difference	-1.17	[-5.92; 3.58]	0.627
			Hedges G	-0.08	[-0.38; 0.23]	
IIIC	226 5.89 (1.01)	215 3.59 (1.04)	Difference	2.30	[-0.55; 5.16]	0.114
			Hedges G	0.15	[-0.04; 0.34]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.531					
N0	175 3.68 (1.11)	189 2.69 (1.07)	Difference	0.99	[-2.04; 4.02]	0.521
			Hedges G	0.07	[-0.14; 0.27]	
N1-N3	1144 3.45 (0.46)	1071 3.51 (0.47)	Difference	-0.06	[-1.36; 1.24]	0.925
			Hedges G	-0.00	[-0.09; 0.08]	

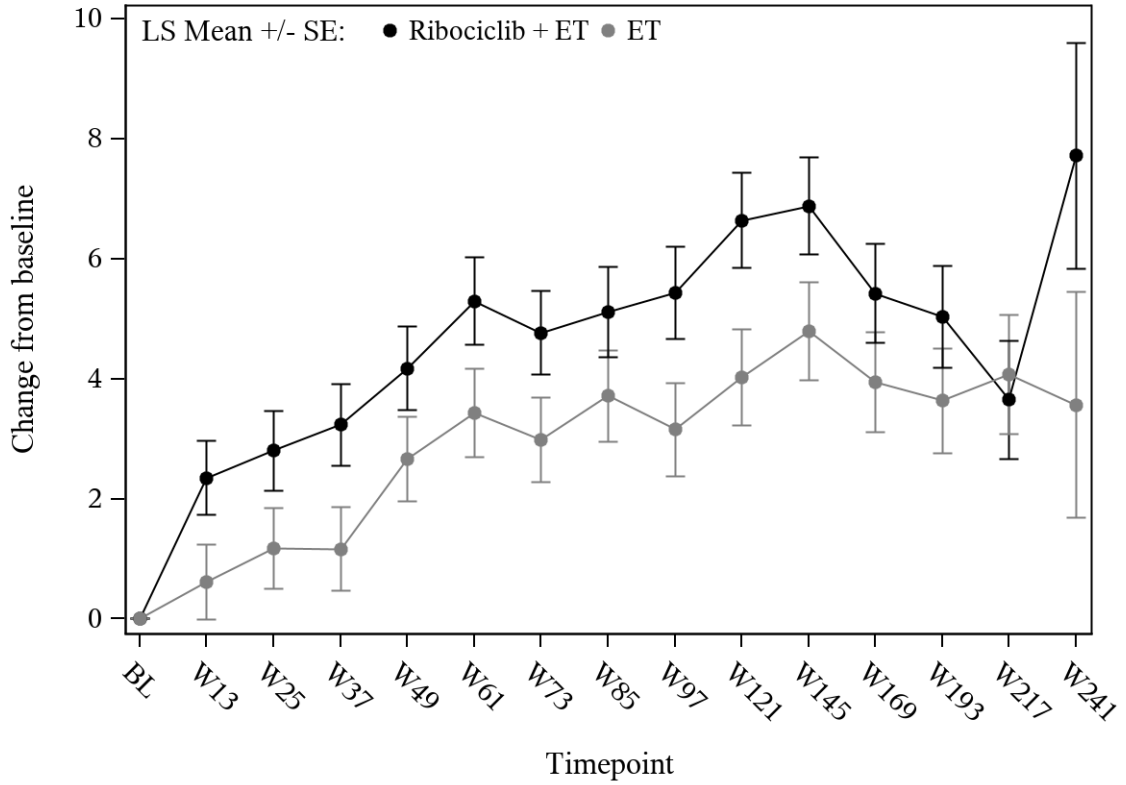
Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.312					
Grade 1	94 1.97 (1.55)	102 4.28 (1.43)	Difference	-2.30	[-6.48; 1.87]	0.278
			Hedges G	-0.16	[-0.44; 0.13]	
Grade 2	787 3.00 (0.53)	702 2.98 (0.56)	Difference	0.01	[-1.50; 1.52]	0.986
			Hedges G	0.00	[-0.10; 0.10]	
Grade 3	355 4.31 (0.78)	372 3.49 (0.76)	Difference	0.81	[-1.33; 2.95]	0.455
			Hedges G	0.06	[-0.09; 0.20]	
Histological subtype						
Interaction test	p = 0.940					
Ductal	958 3.65 (0.48)	927 3.65 (0.49)	Difference	0.01	[-1.34; 1.35]	0.994
			Hedges G	0.00	[-0.09; 0.09]	
Lobular	276 2.34 (0.87)	263 2.41 (0.88)	Difference	-0.07	[-2.50; 2.36]	0.956
			Hedges G	-0.00	[-0.17; 0.16]	
Other	87 4.69 (1.66)	70 3.07 (1.91)	Difference	1.62	[-3.38; 6.61]	0.523
			Hedges G	0.10	[-0.21; 0.42]	
Ki67 status from surgical specimen						
Interaction test	p = 0.664					
Ki67≤20	618 2.91 (0.62)	590 2.96 (0.63)	Difference	-0.05	[-1.79; 1.69]	0.956
			Hedges G	-0.00	[-0.12; 0.11]	
Ki67>20	467 3.63 (0.70)	475 4.21 (0.70)	Difference	-0.58	[-2.53; 1.36]	0.555
			Hedges G	-0.04	[-0.17; 0.09]	
Type of NSAI						
Interaction test	p = <.001					
Letrozole	846 4.90 (0.53)	824 3.07 (0.54)	Difference	1.82	[0.34; 3.31]	0.016
			Hedges G	0.12	[0.02; 0.21]	
Anastrozole	476 1.20 (0.69)	433 3.88 (0.72)	Difference	-2.68	[-4.65; -0.72]	0.007
			Hedges G	-0.18	[-0.31; -0.05]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.623					
Yes	1128 3.19 (0.46)	1052 3.19 (0.47)	Difference	0.01	[-1.29; 1.30]	0.992
			Hedges G	0.00	[-0.08; 0.08]	
No	194 5.60 (1.08)	208 4.42 (1.05)	Difference	1.18	[-1.78; 4.13]	0.433
			Hedges G	0.08	[-0.12; 0.27]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.564					
Yes	655 2.98 (0.60)	633 2.67 (0.61)	Difference	0.31	[-1.37; 1.99]	0.716
			Hedges G	0.02	[-0.09; 0.13]	
No	667 3.94 (0.58)	627 4.07 (0.60)	Difference	-0.13	[-1.77; 1.50]	0.872
			Hedges G	-0.01	[-0.12; 0.10]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	p = 0.253					
Yes	500 3.65 (0.67)	449 4.04 (0.71)	Difference	-0.39	[-2.32; 1.53]	0.689
			Hedges G	-0.03	[-0.15; 0.10]	
No	822 3.59 (0.54)	811 2.92 (0.54)	Difference	0.67	[-0.84; 2.17]	0.385
			Hedges G	0.04	[-0.05; 0.14]	
Prior endocrine therapy						
Interaction test	p = 0.264					
Yes	889 4.50 (0.51)	863 3.89 (0.52)	Difference	0.61	[-0.82; 2.04]	0.402
			Hedges G	0.04	[-0.05; 0.13]	
No	433 1.64 (0.75)	397 2.42 (0.78)	Difference	-0.79	[-2.90; 1.33]	0.466
			Hedges G	-0.05	[-0.19; 0.09]	
Prior mastectomy						
Interaction test	p = 0.016					
Yes	807 2.89 (0.55)	779 3.82 (0.55)	Difference	-0.94	[-2.46; 0.59]	0.230
			Hedges G	-0.06	[-0.16; 0.04]	
No	515 4.53 (0.66)	481 2.70 (0.68)	Difference	1.84	[-0.02; 3.70]	0.053
			Hedges G	0.12	[-0.00; 0.25]	
Prior radiotherapy						
Interaction test	p = 0.513					
Yes	1176 3.45 (0.45)	1112 3.19 (0.46)	Difference	0.26	[-0.99; 1.52]	0.681
			Hedges G	0.02	[-0.06; 0.10]	
No	146 3.69 (1.31)	148 4.53 (1.29)	Difference	-0.84	[-4.46; 2.78]	0.649
			Hedges G	-0.05	[-0.28; 0.18]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: $\text{change from baseline} = \text{treatment} + \text{visit} + \text{treatment} * \text{visit} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor} + \text{subgroup factor} * \text{visit} + \text{treatment} * \text{subgroup factor} * \text{visit} + \text{baseline value}$ If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: $\text{change from baseline} = \text{treatment} + \text{visit} + \text{treatment} * \text{visit} + \text{baseline value}$ ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>[†] The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

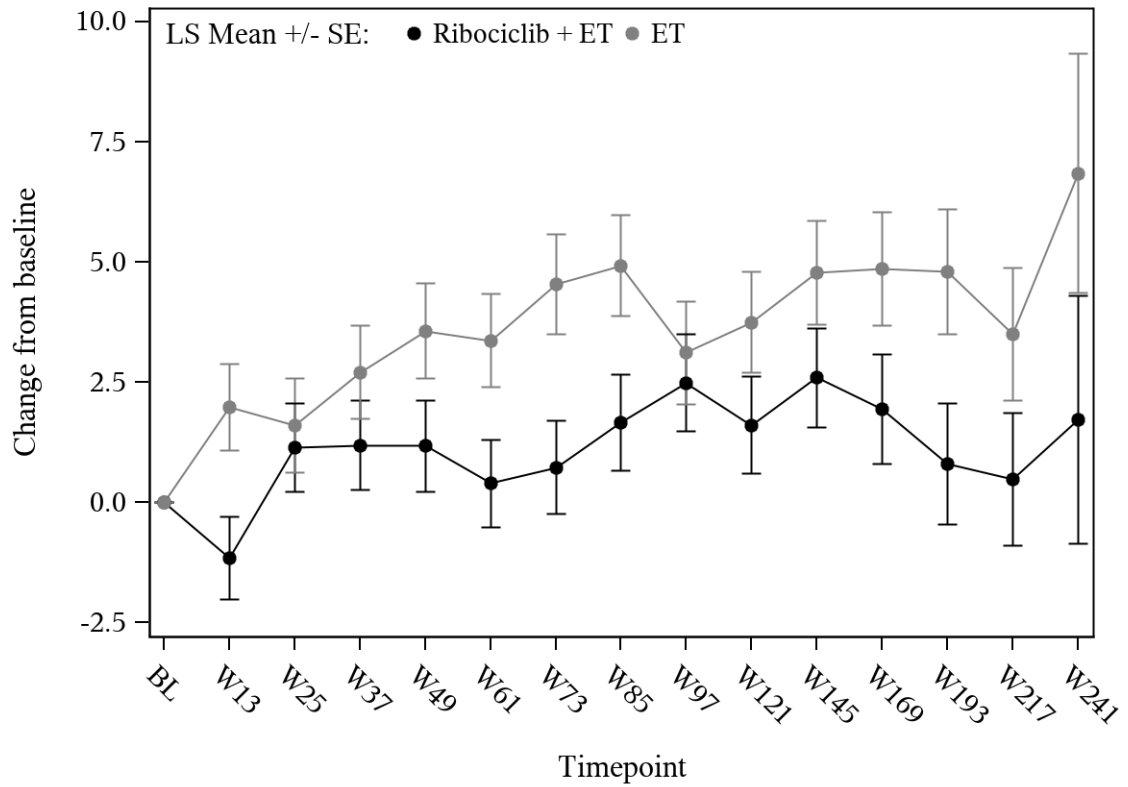
Figure 5-2.1.4.1 QLQ-C30 - Dyspnoea: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Dyspnoea
Type of NSAI: Letrozole



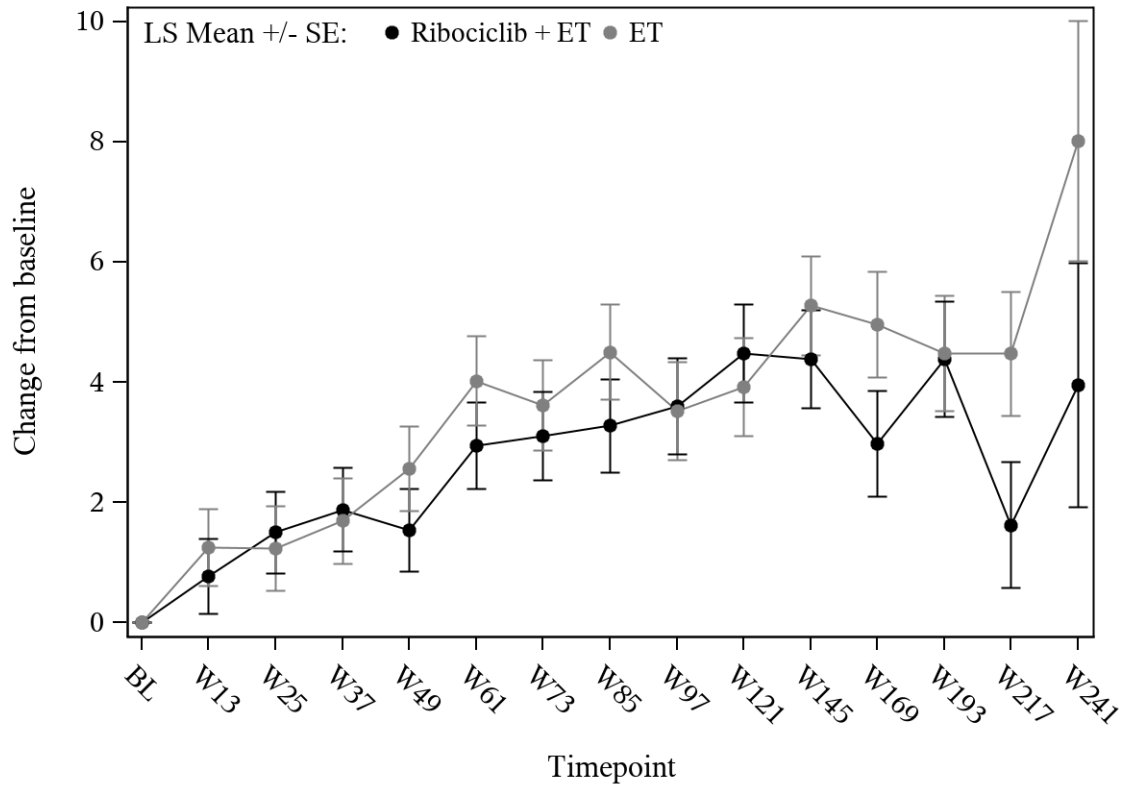
Ribociclib + ET	846	806	771	774	755	750	745	724	724	704	691	606	508	313	51
ET	824	787	759	741	754	739	740	722	718	703	681	583	488	311	52

QLQ-C30 - Dyspnoea
Type of NSAI: Anastrozole



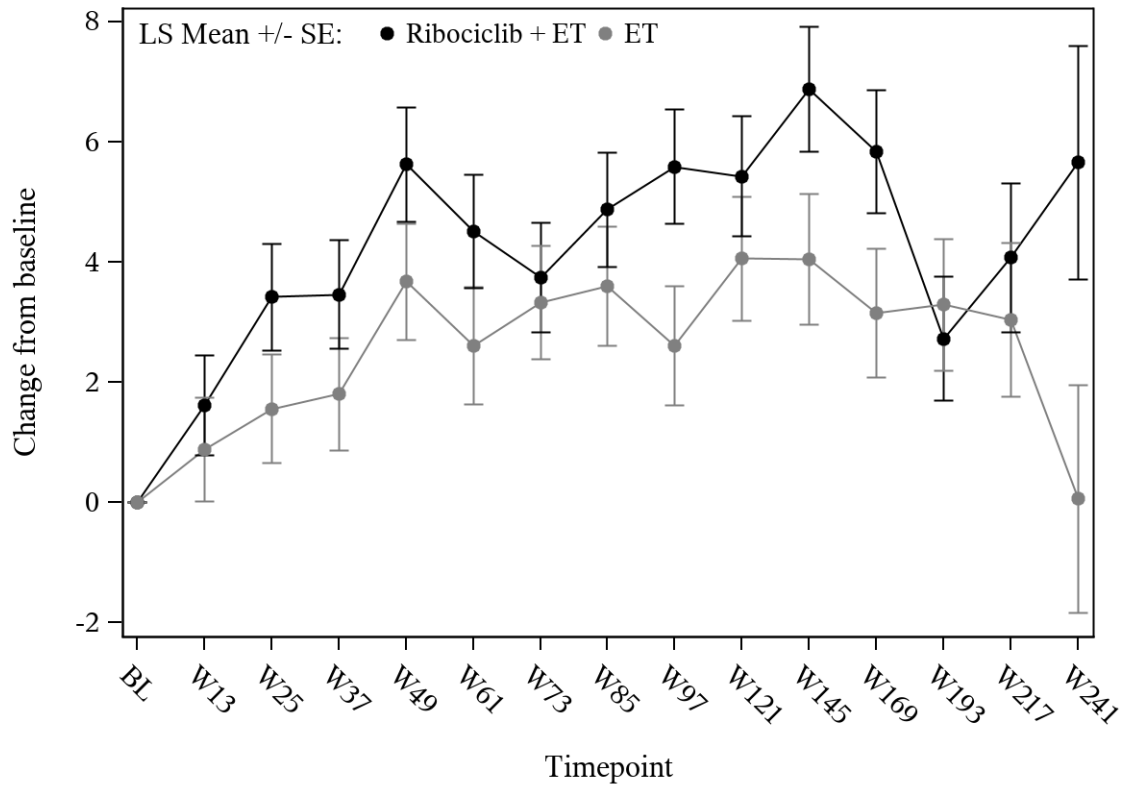
Ribociclib + ET	476	461	445	436	426	422	419	404	402	373	371	302	256	164	40
ET	433	407	388	399	386	365	361	360	345	339	325	286	244	169	44

QLQ-C30 - Dyspnoea
Prior mastectomy: Yes



Ribociclib + ET	807	771	759	736	724	724	713	681	680	644	631	519	412	270	57
ET	779	742	707	708	702	689	679	671	657	640	621	521	424	284	59

QLQ-C30 - Dyspnoea
Prior mastectomy: No



Ribociclib + ET	515	496	457	474	457	448	451	447	446	433	431	389	352	207	34
ET	481	454	441	433	438	417	422	411	407	402	386	348	308	196	37

Table 5-2.1.5.1 QLQ-C30 - Insomnia: change from baseline analysis - subgroup analysis (Full Analysis Set)

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-C30 - Insomnia						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.227					
NA/WE/O	824 1.28 (0.71)	772 1.86 (0.72)	Difference	-0.57	[-2.56; 1.41]	0.570
			Hedges G	-0.03	[-0.13; 0.07]	
ROW	498 3.58 (0.84)	489 5.54 (0.85)	Difference	-1.96	[-4.31; 0.39]	0.101
			Hedges G	-0.10	[-0.23; 0.02]	
Geographical region						
Interaction test	p = 0.654					
Europe	783 2.25 (0.70)	775 3.32 (0.70)	Difference	-1.07	[-3.01; 0.87]	0.281
			Hedges G	-0.05	[-0.15; 0.04]	
North America/Australia	366 1.37 (0.99)	322 1.84 (1.05)	Difference	-0.47	[-3.31; 2.37]	0.745
			Hedges G	-0.02	[-0.17; 0.12]	
Asia	101 4.47 (1.55)	93 5.79 (1.81)	Difference	-1.33	[-6.02; 3.37]	0.579
			Hedges G	-0.08	[-0.36; 0.20]	
Latin America	72 2.44 (2.49)	71 6.31 (2.50)	Difference	-3.87	[-10.89; 3.14]	0.277
			Hedges G	-0.18	[-0.51; 0.15]	
Age group 1 at randomization						
Interaction test	p = 0.699					
<45	55 2.36 (2.56)	48 2.62 (2.79)	Difference	-0.26	[-7.82; 7.30]	0.946
			Hedges G	-0.01	[-0.40; 0.37]	
45 to 54	284 1.03 (1.19)	290 2.23 (1.18)	Difference	-1.20	[-4.48; 2.08]	0.473
			Hedges G	-0.06	[-0.22; 0.10]	
55 to 64	612 1.30 (0.77)	602 3.39 (0.77)	Difference	-2.10	[-4.23; 0.04]	0.054
			Hedges G	-0.11	[-0.22; 0.00]	
≥65	371 4.16 (1.00)	321 4.30 (1.07)	Difference	-0.14	[-3.01; 2.74]	0.924
			Hedges G	-0.01	[-0.16; 0.14]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.220					
<Median	597 0.48 (0.82)	579 2.67 (0.83)	Difference	-2.19	[-4.47; 0.09]	0.060
			Hedges G	-0.11	[-0.22; 0.00]	
≥Median	725 3.54 (0.73)	682 3.93 (0.75)	Difference	-0.39	[-2.44; 1.66]	0.710
			Hedges G	-0.02	[-0.12; 0.08]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.952					
Asian	125 3.79 (1.39)	116 5.16 (1.59)	Difference	-1.37	[-5.54; 2.81]	0.519
			Hedges G	-0.08	[-0.34; 0.17]	
Non-Asian	1120 2.09 (0.59)	1081 3.50 (0.59)	Difference	-1.41	[-3.04; 0.23]	0.091
			Hedges G	-0.07	[-0.16; 0.01]	
BMI at screening						
Interaction test	p = 0.819					
≥25	874 2.41 (0.67)	860 3.73 (0.67)	Difference	-1.32	[-3.18; 0.54]	0.164
			Hedges G	-0.07	[-0.16; 0.03]	
<25	438 1.85 (0.93)	389 2.86 (0.99)	Difference	-1.01	[-3.68; 1.65]	0.456
			Hedges G	-0.05	[-0.19; 0.08]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.218					
Group I/II	543 2.95 (0.84)	554 3.14 (0.83)	Difference	-0.18	[-2.51; 2.15]	0.879
			Hedges G	-0.01	[-0.13; 0.11]	
Group III	778 1.64 (0.71)	707 3.69 (0.74)	Difference	-2.05	[-4.06; -0.04]	0.045
			Hedges G	-0.10	[-0.21; -0.00]	
Anatomic stages						
Interaction test	p = 0.168					
IA/IB/IIA	285 1.78 (1.13)	292 2.98 (1.12)	Difference	-1.20	[-4.33; 1.93]	0.451
			Hedges G	-0.06	[-0.23; 0.10]	
IIB	258 4.23 (1.22)	262 3.05 (1.20)	Difference	1.18	[-2.19; 4.54]	0.492
			Hedges G	0.06	[-0.11; 0.23]	
IIIA	459 1.85 (0.95)	414 4.53 (0.97)	Difference	-2.68	[-5.34; -0.02]	0.049
			Hedges G	-0.13	[-0.27; -0.00]	
IIIB	92 2.88 (1.88)	77 -0.81 (2.07)	Difference	3.69	[-1.83; 9.21]	0.189
			Hedges G	0.20	[-0.10; 0.51]	
IIIC	227 -0.18 (1.27)	216 2.74 (1.31)	Difference	-2.92	[-6.50; 0.67]	0.110
			Hedges G	-0.15	[-0.34; 0.03]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.709					
N0	175 1.55 (1.47)	189 3.04 (1.42)	Difference	-1.50	[-5.52; 2.52]	0.465
			Hedges G	-0.08	[-0.28; 0.13]	
N1-N3	1144 2.10 (0.57)	1072 3.30 (0.59)	Difference	-1.20	[-2.81; 0.42]	0.146
			Hedges G	-0.06	[-0.15; 0.02]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.423					
Grade 1	94 0.51 (1.94)	102 3.31 (1.78)	Difference	-2.80	[-7.99; 2.39]	0.288
			Hedges G	-0.15	[-0.43; 0.13]	
Grade 2	786 2.36 (0.68)	703 2.73 (0.72)	Difference	-0.37	[-2.31; 1.58]	0.711
			Hedges G	-0.02	[-0.12; 0.08]	
Grade 3	356 1.42 (1.04)	371 4.27 (1.02)	Difference	-2.85	[-5.71; 0.01]	0.051
			Hedges G	-0.15	[-0.29; 0.00]	
Histological subtype						
Interaction test	p = 0.247					
Ductal	957 2.42 (0.62)	928 3.17 (0.63)	Difference	-0.75	[-2.49; 0.99]	0.400
			Hedges G	-0.04	[-0.13; 0.05]	
Lobular	276 0.15 (1.17)	263 3.22 (1.19)	Difference	-3.07	[-6.35; 0.22]	0.067
			Hedges G	-0.16	[-0.33; 0.01]	
Other	88 5.50 (2.00)	70 6.10 (2.31)	Difference	-0.60	[-6.65; 5.46]	0.845
			Hedges G	-0.03	[-0.35; 0.28]	
Ki67 status from surgical specimen						
Interaction test	p = 0.336					
Ki67≤20	618 2.99 (0.79)	592 3.62 (0.80)	Difference	-0.63	[-2.83; 1.58]	0.577
			Hedges G	-0.03	[-0.14; 0.08]	
Ki67>20	466 1.39 (0.89)	476 3.58 (0.88)	Difference	-2.19	[-4.65; 0.27]	0.081
			Hedges G	-0.11	[-0.24; 0.01]	
Type of NSAI						
Interaction test	p = 0.268					
Letrozole	847 2.57 (0.68)	823 3.07 (0.68)	Difference	-0.51	[-2.39; 1.38]	0.598
			Hedges G	-0.03	[-0.12; 0.07]	
Anastrozole	475 1.67 (0.92)	435 4.09 (0.96)	Difference	-2.42	[-5.02; 0.19]	0.069
			Hedges G	-0.12	[-0.25; 0.01]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.404					
Yes	1128 1.79 (0.59)	1053 3.22 (0.60)	Difference	-1.43	[-3.08; 0.22]	0.090
			Hedges G	-0.07	[-0.16; 0.01]	
No	194 4.10 (1.43)	208 3.61 (1.39)	Difference	0.49	[-3.43; 4.40]	0.806
			Hedges G	0.02	[-0.17; 0.22]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.931					
Yes	655 1.25 (0.77)	633 2.41 (0.78)	Difference	-1.16	[-3.31; 0.99]	0.289
			Hedges G	-0.06	[-0.17; 0.05]	
No	667 3.02 (0.76)	628 4.57 (0.78)	Difference	-1.56	[-3.70; 0.58]	0.154
			Hedges G	-0.08	[-0.19; 0.03]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	p = 0.684					
Yes	500 2.59 (0.86)	450 4.15 (0.91)	Difference	-1.56	[-4.01; 0.89]	0.213
			Hedges G	-0.08	[-0.21; 0.05]	
No	822 1.92 (0.70)	811 2.91 (0.70)	Difference	-0.99	[-2.92; 0.95]	0.318
			Hedges G	-0.05	[-0.15; 0.05]	
Prior endocrine therapy						
Interaction test	p = 0.669					
Yes	890 2.44 (0.65)	865 3.82 (0.66)	Difference	-1.38	[-3.20; 0.44]	0.137
			Hedges G	-0.07	[-0.16; 0.02]	
No	432 1.73 (0.98)	396 2.33 (1.02)	Difference	-0.60	[-3.37; 2.17]	0.672
			Hedges G	-0.03	[-0.17; 0.11]	
Prior mastectomy						
Interaction test	p = 0.725					
Yes	807 2.17 (0.70)	778 3.61 (0.71)	Difference	-1.44	[-3.39; 0.52]	0.150
			Hedges G	-0.07	[-0.17; 0.03]	
No	515 2.35 (0.86)	483 3.06 (0.88)	Difference	-0.71	[-3.12; 1.71]	0.566
			Hedges G	-0.04	[-0.16; 0.09]	
Prior radiotherapy						
Interaction test	p = 0.535					
Yes	1176 1.67 (0.58)	1113 3.06 (0.59)	Difference	-1.39	[-3.00; 0.22]	0.090
			Hedges G	-0.07	[-0.15; 0.01]	
No	146 5.70 (1.74)	148 5.41 (1.72)	Difference	0.29	[-4.52; 5.10]	0.905
			Hedges G	0.01	[-0.21; 0.24]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: $\text{change from baseline} = \text{treatment} + \text{visit} + \text{treatment} * \text{visit} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor} + \text{subgroup factor} * \text{visit} + \text{treatment} * \text{subgroup factor} * \text{visit} + \text{baseline value}$ If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: $\text{change from baseline} = \text{treatment} + \text{visit} + \text{treatment} * \text{visit} + \text{baseline value}$ ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>† The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

Table 5-2.1.6.1 QLQ-C30 - Appetite Loss: change from baseline analysis - subgroup analysis (Full Analysis Set)

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-C30 - Appetite Loss						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.652					
NA/WE/O	826 0.96 (0.43)	772 0.67 (0.45)	Difference	0.29	[-0.93; 1.51]	0.641
			Hedges G	0.02	[-0.07; 0.12]	
ROW	499 1.08 (0.57)	489 0.34 (0.58)	Difference	0.74	[-0.85; 2.34]	0.362
			Hedges G	0.06	[-0.07; 0.18]	
Geographical region						
Interaction test	N.E.					
Europe	784 1.19 (0.46)	773 0.62 (0.46)	Difference	0.57	[-0.71; 1.85]	0.381
			Hedges G	0.04	[-0.05; 0.14]	
North America/Australia	368 0.08 (0.58)	324 0.04 (0.61)	Difference	0.04	[-1.61; 1.68]	0.965
			Hedges G	0.00	[-0.15; 0.15]	
Asia	101 -0.40 (1.25)	93 -0.95 (1.45)	Difference	0.55	[-3.22; 4.33]	0.772
			Hedges G	0.04	[-0.24; 0.32]	
Latin America	72 5.55 (1.35)	71 2.53 (1.36)	Difference	3.02	[-0.77; 6.81]	0.118
			Hedges G	0.26	[-0.07; 0.59]	
Age group 1 at randomization						
Interaction test	N.E.					
<45	56 1.37 (1.79)	48 2.73 (1.93)	Difference	-1.37	[-6.59; 3.86]	0.605
			Hedges G	-0.10	[-0.49; 0.28]	
45 to 54	284 0.69 (0.74)	290 1.18 (0.73)	Difference	-0.48	[-2.52; 1.56]	0.641
			Hedges G	-0.04	[-0.20; 0.12]	
55 to 64	613 0.37 (0.49)	602 -0.57 (0.49)	Difference	0.93	[-0.43; 2.30]	0.179
			Hedges G	0.08	[-0.04; 0.19]	
≥65	372 2.07 (0.68)	321 1.87 (0.73)	Difference	0.20	[-1.75; 2.16]	0.840
			Hedges G	0.02	[-0.13; 0.16]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.213					
<Median	598 0.87 (0.52)	579 1.13 (0.52)	Difference	-0.26	[-1.71; 1.19]	0.725
			Hedges G	-0.02	[-0.13; 0.09]	
≥Median	727 1.24 (0.47)	682 0.17 (0.48)	Difference	1.07	[-0.25; 2.39]	0.113
			Hedges G	0.08	[-0.02; 0.19]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.566					
Asian	125 N.E.	116 N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Non-Asian	1123 1.29 (0.38)	1081 0.65 (0.38)	Difference	0.64	[-0.42; 1.69]	0.238
			Hedges G	0.05	[-0.03; 0.13]	
BMI at screening						
Interaction test	p = 0.747					
≥25	875 0.98 (0.42)	861 0.49 (0.42)	Difference	0.49	[-0.67; 1.64]	0.410
			Hedges G	0.04	[-0.05; 0.13]	
<25	439 1.22 (0.63)	388 1.16 (0.67)	Difference	0.06	[-1.75; 1.87]	0.947
			Hedges G	0.00	[-0.13; 0.14]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.461					
Group I/II	544 0.58 (0.49)	554 -0.28 (0.49)	Difference	0.86	[-0.49; 2.22]	0.212
			Hedges G	0.08	[-0.04; 0.19]	
Group III	780 1.44 (0.48)	707 1.29 (0.50)	Difference	0.15	[-1.21; 1.51]	0.829
			Hedges G	0.01	[-0.09; 0.11]	
Anatomic stages						
Interaction test	p = 0.112					
IA/IB/IIA	286 0.68 (0.67)	292 -0.11 (0.66)	Difference	0.79	[-1.06; 2.63]	0.402
			Hedges G	0.07	[-0.09; 0.23]	
IIB	258 0.37 (0.72)	262 -0.52 (0.71)	Difference	0.89	[-1.11; 2.88]	0.382
			Hedges G	0.08	[-0.10; 0.25]	
IIIA	461 1.95 (0.63)	412 1.88 (0.64)	Difference	0.07	[-1.70; 1.84]	0.939
			Hedges G	0.01	[-0.13; 0.14]	
IIIB	92 1.66 (1.42)	78 -2.61 (1.55)	Difference	4.27	[0.13; 8.42]	0.043
			Hedges G	0.31	[0.01; 0.62]	
IIIC	227 0.13 (0.83)	217 1.46 (0.86)	Difference	-1.33	[-3.68; 1.02]	0.267
			Hedges G	-0.11	[-0.29; 0.08]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.698					
N0	176 2.33 (0.93)	189 1.06 (0.90)	Difference	1.27	[-1.27; 3.81]	0.327
			Hedges G	0.10	[-0.10; 0.31]	
N1-N3	1146 0.94 (0.38)	1072 0.53 (0.39)	Difference	0.41	[-0.66; 1.48]	0.451
			Hedges G	0.03	[-0.05; 0.12]	

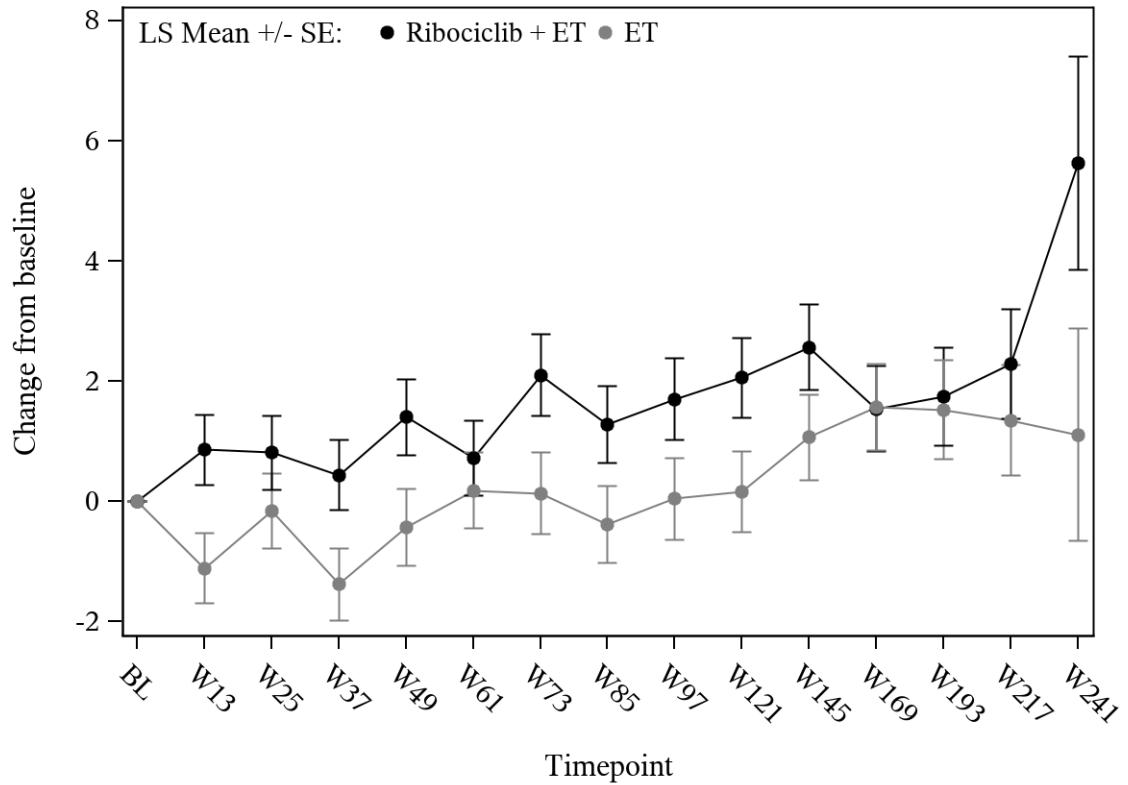
Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.934					
Grade 1	94 0.58 (1.41)	101 0.71 (1.30)	Difference	-0.13	[-3.91; 3.65]	0.946
			Hedges G	-0.01	[-0.29; 0.27]	
Grade 2	788 0.85 (0.44)	703 0.31 (0.47)	Difference	0.53	[-0.73; 1.80]	0.407
			Hedges G	0.04	[-0.06; 0.14]	
Grade 3	357 0.66 (0.66)	372 0.21 (0.64)	Difference	0.45	[-1.36; 2.26]	0.627
			Hedges G	0.04	[-0.11; 0.18]	
Histological subtype						
Interaction test	N.E.					
Ductal	959 1.27 (0.41)	928 0.32 (0.42)	Difference	0.96	[-0.19; 2.10]	0.103
			Hedges G	0.08	[-0.02; 0.17]	
Lobular	277 0.57 (0.73)	263 0.96 (0.75)	Difference	-0.39	[-2.43; 1.66]	0.709
			Hedges G	-0.03	[-0.20; 0.14]	
Other	88 1.29 (1.53)	70 1.98 (1.75)	Difference	-0.69	[-5.28; 3.90]	0.768
			Hedges G	-0.05	[-0.36; 0.27]	
Ki67 status from surgical specimen						
Interaction test	p = 0.409					
Ki67≤20	619 1.71 (0.52)	591 0.48 (0.53)	Difference	1.23	[-0.23; 2.69]	0.099
			Hedges G	0.09	[-0.02; 0.21]	
Ki67>20	467 1.09 (0.57)	475 0.69 (0.57)	Difference	0.40	[-1.18; 1.98]	0.618
			Hedges G	0.03	[-0.10; 0.16]	
Type of NSAI						
Interaction test	p = 0.014					
Letrozole	848 1.80 (0.45)	823 0.26 (0.46)	Difference	1.53	[0.27; 2.79]	0.017
			Hedges G	0.12	[0.02; 0.21]	
Anastrozole	477 -0.03 (0.54)	435 1.03 (0.57)	Difference	-1.06	[-2.60; 0.48]	0.179
			Hedges G	-0.09	[-0.22; 0.04]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.194					
Yes	1131 0.97 (0.38)	1053 0.73 (0.39)	Difference	0.23	[-0.83; 1.30]	0.665
			Hedges G	0.02	[-0.07; 0.10]	
No	194 1.84 (0.91)	208 -0.31 (0.89)	Difference	2.15	[-0.35; 4.65]	0.092
			Hedges G	0.17	[-0.03; 0.36]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.730					
Yes	658 0.40 (0.48)	634 0.06 (0.48)	Difference	0.33	[-1.01; 1.68]	0.626
			Hedges G	0.03	[-0.08; 0.14]	
No	667 1.54 (0.48)	627 1.05 (0.50)	Difference	0.48	[-0.88; 1.85]	0.485
			Hedges G	0.04	[-0.07; 0.15]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test p = 0.324						
Yes	500 1.54 (0.59)	449 1.61 (0.62)	Difference	-0.07	[-1.75; 1.61]	0.933
			Hedges G	-0.01	[-0.13; 0.12]	
No	825 0.76 (0.43)	812 -0.02 (0.43)	Difference	0.78	[-0.42; 1.98]	0.203
			Hedges G	0.06	[-0.03; 0.16]	
Prior endocrine therapy						
Interaction test p = 0.337						
Yes	892 1.77 (0.43)	864 1.62 (0.44)	Difference	0.14	[-1.06; 1.34]	0.818
			Hedges G	0.01	[-0.08; 0.10]	
No	433 -0.40 (0.59)	397 -1.58 (0.61)	Difference	1.18	[-0.50; 2.85]	0.168
			Hedges G	0.10	[-0.04; 0.23]	
Prior mastectomy						
Interaction test p = 0.073						
Yes	809 0.69 (0.46)	779 0.92 (0.47)	Difference	-0.22	[-1.51; 1.07]	0.735
			Hedges G	-0.02	[-0.12; 0.08]	
No	516 1.75 (0.53)	482 0.05 (0.55)	Difference	1.70	[0.20; 3.20]	0.026
			Hedges G	0.14	[0.02; 0.27]	
Prior radiotherapy						
Interaction test p = 0.519						
Yes	1178 1.09 (0.37)	1113 0.69 (0.37)	Difference	0.40	[-0.63; 1.42]	0.451
			Hedges G	0.03	[-0.05; 0.11]	
No	147 1.35 (1.15)	148 -0.58 (1.14)	Difference	1.93	[-1.25; 5.11]	0.234
			Hedges G	0.14	[-0.09; 0.37]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed N.E.: Not estimable ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + baseline value ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>+ The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

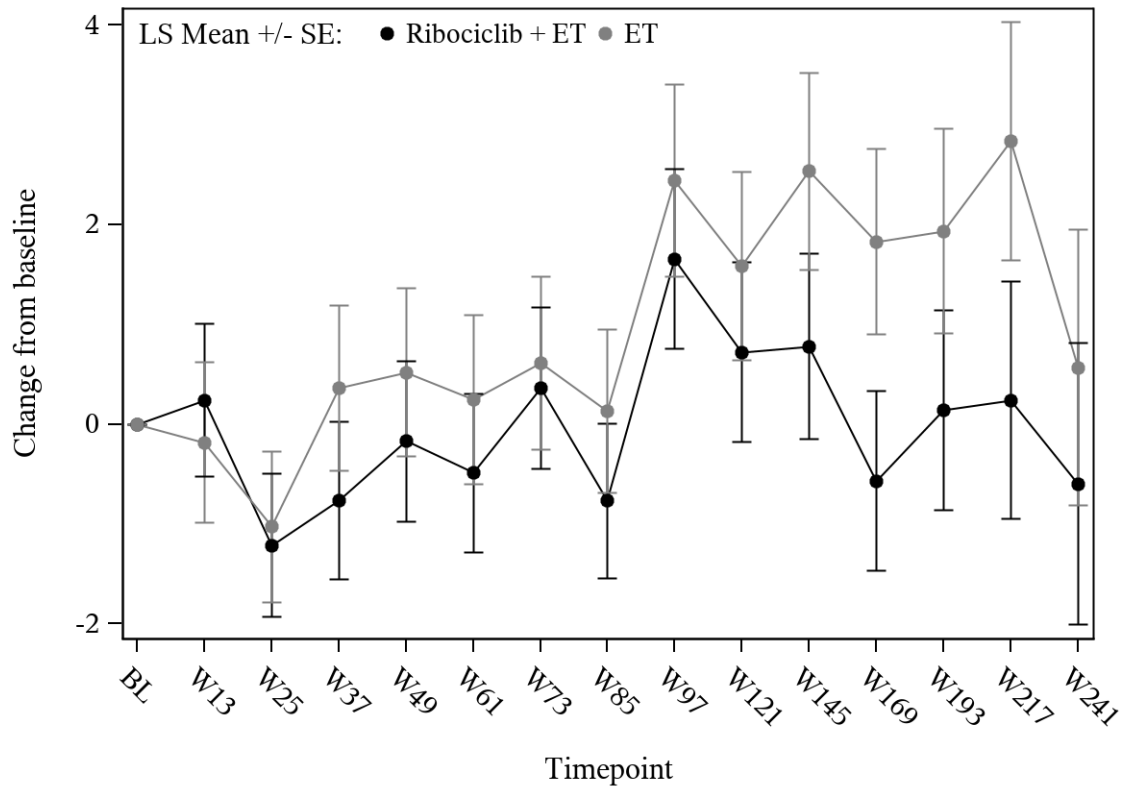
Figure 5-2.1.6.1 QLQ-C30 - Appetite Loss: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Appetite Loss
Type of NSAI: Letrozole



Ribociclib + ET	848	806	770	776	759	750	746	725	725	708	693	607	510	313	51
ET	823	787	760	741	754	742	739	726	719	703	679	583	488	313	52

QLQ-C30 - Appetite Loss
Type of NSAI: Anastrozole



Ribociclib + ET	477	460	445	437	425	422	421	404	404	372	372	302	254	164	40
ET	435	410	391	401	389	368	362	363	347	340	327	288	246	169	44

Table 5-2.1.7.1 QLQ-C30 - Constipation: change from baseline analysis - subgroup analysis (Full Analysis Set)

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-C30 - Constipation						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.552					
NA/WE/O	825 4.21 (0.54)	774 1.21 (0.55)	Difference	3.00	[1.50; 4.51]	<.001
			Hedges G	0.20	[0.10; 0.29]	
ROW	498 3.97 (0.71)	489 1.60 (0.71)	Difference	2.37	[0.40; 4.34]	0.018
			Hedges G	0.15	[0.03; 0.28]	
Geographical region						
Interaction test	p = 0.181					
Europe	783 4.07 (0.57)	775 0.39 (0.57)	Difference	3.68	[2.11; 5.25]	<.001
			Hedges G	0.23	[0.13; 0.33]	
North America/Australia	367 3.18 (0.74)	324 2.47 (0.78)	Difference	0.71	[-1.40; 2.81]	0.510
			Hedges G	0.05	[-0.10; 0.20]	
Asia	101 6.84 (1.45)	93 3.39 (1.65)	Difference	3.46	[-0.87; 7.78]	0.117
			Hedges G	0.23	[-0.06; 0.51]	
Latin America	72 5.14 (2.16)	71 3.26 (2.18)	Difference	1.88	[-4.20; 7.95]	0.542
			Hedges G	0.10	[-0.23; 0.43]	
Age group 1 at randomization						
Interaction test	p = 0.973					
<45	56 4.16 (2.47)	48 1.80 (2.70)	Difference	2.36	[-4.91; 9.62]	0.522
			Hedges G	0.13	[-0.26; 0.51]	
45 to 54	284 5.35 (0.91)	291 1.98 (0.89)	Difference	3.37	[0.87; 5.87]	0.008
			Hedges G	0.22	[0.06; 0.39]	
55 to 64	611 3.53 (0.63)	602 0.86 (0.62)	Difference	2.67	[0.94; 4.40]	0.003
			Hedges G	0.17	[0.06; 0.29]	
≥65	372 4.31 (0.81)	322 1.57 (0.87)	Difference	2.74	[0.41; 5.08]	0.022
			Hedges G	0.18	[0.03; 0.32]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	N.E.					
<Median	598 3.72 (0.64)	580 1.46 (0.65)	Difference	2.26	[0.47; 4.05]	0.013
			Hedges G	0.14	[0.03; 0.26]	
≥Median	725 4.37 (0.57)	683 1.13 (0.59)	Difference	3.24	[1.64; 4.85]	<.001
			Hedges G	0.21	[0.11; 0.32]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.900					
Asian	125 5.91 (1.26)	116 3.00 (1.43)	Difference	2.91	[-0.85; 6.68]	0.128
			Hedges G	0.20	[-0.06; 0.45]	
Non-Asian	1121 3.82 (0.47)	1083 1.32 (0.47)	Difference	2.50	[1.20; 3.81]	<.001
			Hedges G	0.16	[0.08; 0.24]	
BMI at screening						
Interaction test	p = 0.959					
≥25	874 4.34 (0.53)	862 1.55 (0.53)	Difference	2.79	[1.33; 4.26]	<.001
			Hedges G	0.18	[0.09; 0.27]	
<25	438 3.64 (0.75)	389 1.04 (0.79)	Difference	2.61	[0.47; 4.74]	0.017
			Hedges G	0.17	[0.03; 0.30]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.665					
Group I/II	543 4.09 (0.64)	554 1.03 (0.64)	Difference	3.06	[1.28; 4.83]	<.001
			Hedges G	0.20	[0.09; 0.32]	
Group III	779 3.95 (0.58)	709 1.48 (0.60)	Difference	2.47	[0.83; 4.10]	0.003
			Hedges G	0.15	[0.05; 0.26]	
Anatomic stages						
Interaction test	p = 0.965					
IA/IB/IIA	286 3.14 (0.87)	292 -0.05 (0.86)	Difference	3.19	[0.77; 5.60]	0.010
			Hedges G	0.22	[0.05; 0.38]	
IIB	257 5.31 (0.95)	262 2.08 (0.93)	Difference	3.23	[0.62; 5.84]	0.015
			Hedges G	0.21	[0.04; 0.39]	
IIIA	461 4.50 (0.83)	414 2.15 (0.85)	Difference	2.35	[0.02; 4.68]	0.048
			Hedges G	0.13	[0.00; 0.27]	
IIIB	92 5.02 (1.47)	78 1.46 (1.60)	Difference	3.56	[-0.73; 7.85]	0.103
			Hedges G	0.25	[-0.05; 0.56]	
IIIC	226 3.09 (0.97)	217 -0.23 (1.00)	Difference	3.32	[0.57; 6.06]	0.018
			Hedges G	0.23	[0.04; 0.41]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.627					
N0	176 4.57 (1.01)	189 0.69 (0.98)	Difference	3.88	[1.10; 6.65]	0.006
			Hedges G	0.29	[0.08; 0.49]	
N1-N3	1144 3.99 (0.47)	1074 1.26 (0.48)	Difference	2.72	[1.41; 4.04]	<.001
			Hedges G	0.17	[0.09; 0.26]	

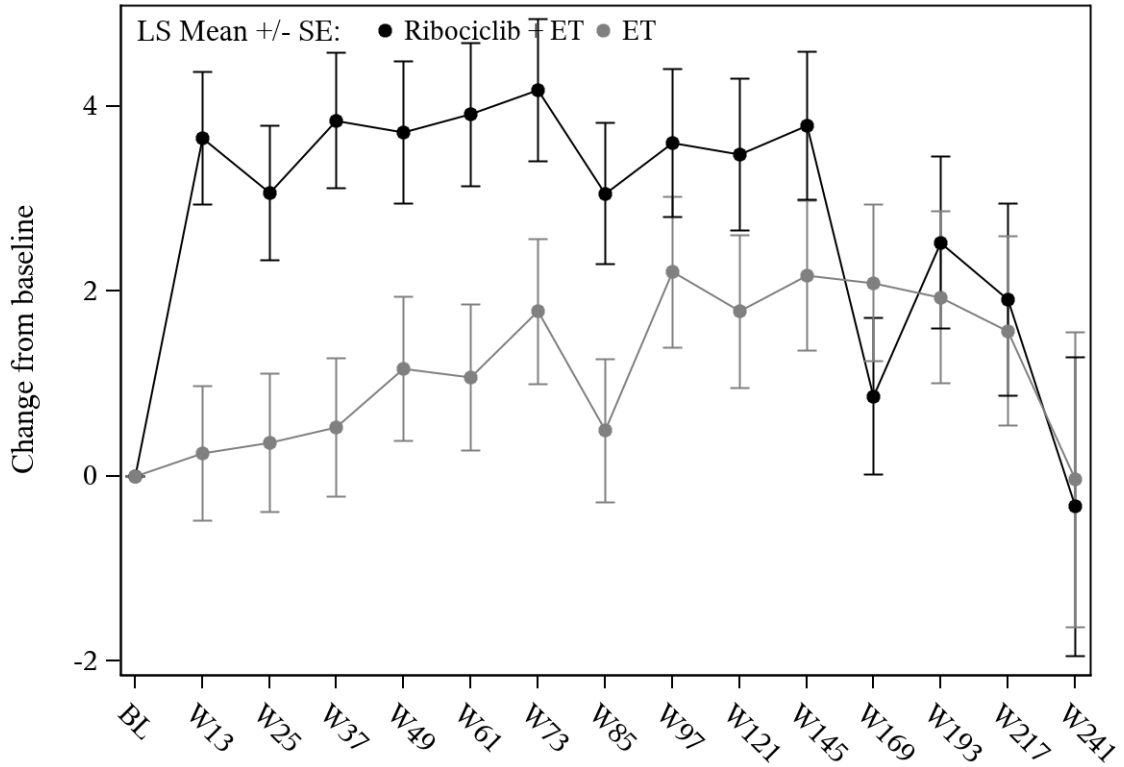
Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.394					
Grade 1	94 3.86 (1.62)	102 2.03 (1.49)	Difference	1.84	[-2.51; 6.19]	0.406
			Hedges G	0.12	[-0.16; 0.40]	
Grade 2	787 4.04 (0.57)	704 1.65 (0.60)	Difference	2.39	[0.77; 4.00]	0.004
			Hedges G	0.15	[0.05; 0.25]	
Grade 3	357 4.32 (0.80)	372 0.08 (0.79)	Difference	4.24	[2.04; 6.45]	<.001
			Hedges G	0.28	[0.13; 0.43]	
Histological subtype						
Interaction test	p = 0.684					
Ductal	957 4.24 (0.51)	930 1.23 (0.52)	Difference	3.02	[1.59; 4.44]	<.001
			Hedges G	0.19	[0.10; 0.28]	
Lobular	277 4.09 (0.93)	263 2.26 (0.95)	Difference	1.84	[-0.78; 4.45]	0.169
			Hedges G	0.12	[-0.05; 0.29]	
Other	88 1.74 (1.41)	70 -1.47 (1.64)	Difference	3.21	[-1.07; 7.49]	0.140
			Hedges G	0.24	[-0.08; 0.55]	
Ki67 status from surgical specimen						
Interaction test	p = 0.642					
Ki67≤20	618 4.00 (0.62)	592 1.38 (0.63)	Difference	2.62	[0.87; 4.36]	0.003
			Hedges G	0.17	[0.06; 0.28]	
Ki67>20	466 4.76 (0.72)	476 1.35 (0.72)	Difference	3.41	[1.42; 5.40]	<.001
			Hedges G	0.22	[0.09; 0.35]	
Type of NSAI						
Interaction test	p = 0.832					
Letrozole	847 4.14 (0.53)	825 1.56 (0.54)	Difference	2.57	[1.09; 4.06]	<.001
			Hedges G	0.17	[0.07; 0.26]	
Anastrozole	476 3.90 (0.72)	435 0.89 (0.75)	Difference	3.00	[0.95; 5.05]	0.004
			Hedges G	0.19	[0.06; 0.32]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.513					
Yes	1129 4.02 (0.47)	1055 1.20 (0.48)	Difference	2.81	[1.50; 4.13]	<.001
			Hedges G	0.18	[0.10; 0.26]	
No	194 4.90 (1.08)	208 1.46 (1.05)	Difference	3.44	[0.47; 6.41]	0.023
			Hedges G	0.23	[0.03; 0.42]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.572					
Yes	658 3.76 (0.62)	634 0.68 (0.62)	Difference	3.09	[1.38; 4.80]	<.001
			Hedges G	0.20	[0.09; 0.31]	
No	665 4.37 (0.60)	629 1.97 (0.62)	Difference	2.40	[0.71; 4.08]	0.005
			Hedges G	0.15	[0.05; 0.26]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	p = 0.518					
Yes	498 4.09 (0.68)	451 1.91 (0.72)	Difference	2.18	[0.24; 4.12]	0.027
			Hedges G	0.14	[0.02; 0.27]	
No	825 4.15 (0.55)	812 1.08 (0.55)	Difference	3.07	[1.54; 4.59]	<.001
			Hedges G	0.20	[0.10; 0.29]	
Prior endocrine therapy						
Interaction test	p = 0.925					
Yes	890 4.24 (0.52)	866 1.51 (0.53)	Difference	2.74	[1.28; 4.19]	<.001
			Hedges G	0.18	[0.08; 0.27]	
No	433 3.56 (0.73)	397 0.77 (0.76)	Difference	2.79	[0.71; 4.86]	0.008
			Hedges G	0.18	[0.05; 0.32]	
Prior mastectomy						
Interaction test	p = 0.029					
Yes	807 2.95 (0.54)	780 1.24 (0.55)	Difference	1.71	[0.19; 3.23]	0.028
			Hedges G	0.11	[0.01; 0.21]	
No	516 5.94 (0.70)	483 1.47 (0.72)	Difference	4.47	[2.51; 6.43]	<.001
			Hedges G	0.28	[0.16; 0.41]	
Prior radiotherapy						
Interaction test	p = 0.453					
Yes	1176 4.27 (0.46)	1115 1.60 (0.47)	Difference	2.67	[1.39; 3.96]	<.001
			Hedges G	0.17	[0.09; 0.25]	
No	147 3.32 (1.24)	148 -1.03 (1.23)	Difference	4.36	[0.92; 7.79]	0.013
			Hedges G	0.29	[0.06; 0.52]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed N.E.: Not estimable ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + baseline value ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>+ The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

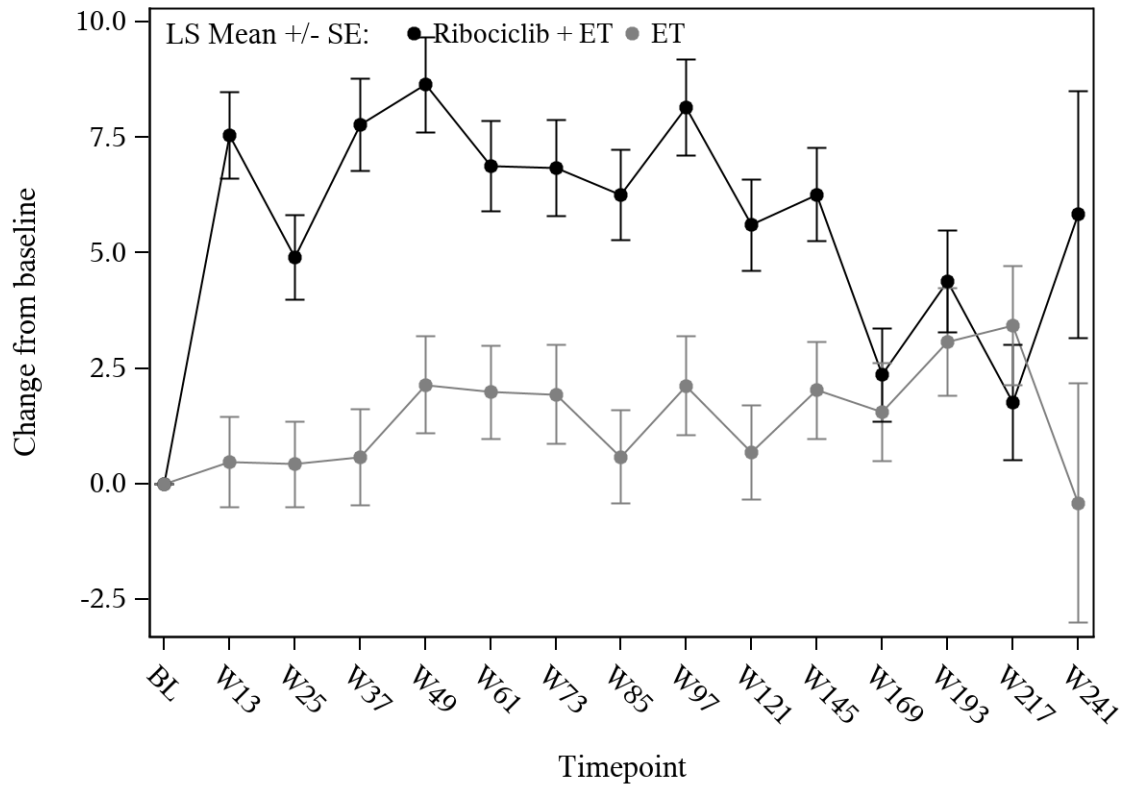
Figure 5-2.1.7.1 QLQ-C30 - Constipation: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Constipation
Prior mastectomy: Yes



Ribociclib + ET	807	770	758	737	724	722	715	680	682	645	634	516	413	271	57
ET	780	743	706	709	704	688	680	670	655	644	622	523	424	286	59

QLQ-C30 - Constipation
Prior mastectomy: No



Ribociclib + ET	516	497	455	474	459	449	450	447	446	433	432	388	351	207	34
ET	483	455	445	435	436	426	423	415	410	405	387	349	310	196	37

Table 5-2.1.8.1 QLQ-C30 - Diarrhoea: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-C30 - Diarrhoea						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.509					
NA/WE/O	824 1.21 (0.37)	770 2.01 (0.38)	Difference	-0.80	[-1.84; 0.25]	0.134
			Hedges G	-0.08	[-0.17; 0.02]	
ROW	498 1.15 (0.42)	489 1.46 (0.43)	Difference	-0.31	[-1.49; 0.86]	0.601
			Hedges G	-0.03	[-0.16; 0.09]	
Geographical region						
Interaction test	p = 0.468					
Europe	782 1.23 (0.37)	771 2.13 (0.36)	Difference	-0.90	[-1.91; 0.12]	0.083
			Hedges G	-0.09	[-0.19; 0.01]	
North America/Australia	367 1.19 (0.52)	324 1.39 (0.55)	Difference	-0.20	[-1.69; 1.29]	0.791
			Hedges G	-0.02	[-0.17; 0.13]	
Asia	101 1.35 (0.89)	93 0.27 (1.08)	Difference	1.08	[-1.68; 3.84]	0.440
			Hedges G	0.11	[-0.17; 0.39]	
Latin America	72 0.02 (1.03)	71 0.32 (1.03)	Difference	-0.31	[-3.19; 2.57]	0.834
			Hedges G	-0.04	[-0.36; 0.29]	
Age group 1 at randomization						
Interaction test	N.E.					
<45	56 0.61 (1.48)	47 4.80 (1.60)	Difference	-4.19	[-8.52; 0.14]	0.058
			Hedges G	-0.38	[-0.77; 0.01]	
45 to 54	284 1.36 (0.62)	290 1.10 (0.61)	Difference	0.25	[-1.46; 1.97]	0.771
			Hedges G	0.02	[-0.14; 0.19]	
55 to 64	612 1.47 (0.43)	601 1.90 (0.43)	Difference	-0.44	[-1.62; 0.75]	0.473
			Hedges G	-0.04	[-0.15; 0.07]	
≥65	370 0.85 (0.47)	321 1.61 (0.51)	Difference	-0.76	[-2.12; 0.60]	0.274
			Hedges G	-0.08	[-0.23; 0.07]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.646					
<Median	597 1.06 (0.43)	578 2.16 (0.44)	Difference	-1.10	[-2.30; 0.10]	0.073
			Hedges G	-0.10	[-0.22; 0.01]	
≥Median	725 1.26 (0.36)	681 1.59 (0.37)	Difference	-0.33	[-1.35; 0.69]	0.528
			Hedges G	-0.03	[-0.14; 0.07]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.238					
Asian	125 1.91 (0.78)	116 0.60 (0.93)	Difference	1.32	[-1.08; 3.71]	0.280
			Hedges G	0.14	[-0.11; 0.39]	
Non-Asian	1121 1.07 (0.30)	1082 2.01 (0.30)	Difference	-0.94	[-1.78; -0.10]	0.029
			Hedges G	-0.09	[-0.18; -0.01]	
BMI at screening						
Interaction test	p = 0.081					
≥25	872 1.23 (0.35)	860 2.32 (0.35)	Difference	-1.08	[-2.04; -0.12]	0.027
			Hedges G	-0.11	[-0.20; -0.01]	
<25	439 1.07 (0.49)	387 0.56 (0.51)	Difference	0.51	[-0.88; 1.89]	0.474
			Hedges G	0.05	[-0.09; 0.19]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.351					
Group I/II	541 1.07 (0.41)	551 1.31 (0.41)	Difference	-0.24	[-1.39; 0.90]	0.676
			Hedges G	-0.03	[-0.14; 0.09]	
Group III	780 1.23 (0.39)	708 2.23 (0.40)	Difference	-1.00	[-2.10; 0.10]	0.076
			Hedges G	-0.09	[-0.19; 0.01]	
Anatomic stages						
Interaction test	p = 0.367					
IA/IB/IIA	284 0.63 (0.56)	290 0.76 (0.56)	Difference	-0.13	[-1.70; 1.43]	0.870
			Hedges G	-0.01	[-0.18; 0.15]	
IIB	257 1.33 (0.60)	261 1.92 (0.59)	Difference	-0.59	[-2.25; 1.08]	0.489
			Hedges G	-0.06	[-0.23; 0.11]	
IIIA	460 1.22 (0.52)	413 2.96 (0.52)	Difference	-1.74	[-3.19; -0.30]	0.018
			Hedges G	-0.16	[-0.29; -0.03]	
IIIB	92 1.16 (0.90)	78 1.16 (0.98)	Difference	0.00	[-2.63; 2.63]	0.999
			Hedges G	0.00	[-0.30; 0.30]	
IIIC	228 1.51 (0.70)	217 1.32 (0.72)	Difference	0.19	[-1.78; 2.16]	0.848
			Hedges G	0.02	[-0.17; 0.20]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.534					
N0	174 1.78 (0.65)	188 1.85 (0.63)	Difference	-0.07	[-1.84; 1.70]	0.935
			Hedges G	-0.01	[-0.21; 0.20]	
N1-N3	1145 1.07 (0.31)	1071 1.77 (0.32)	Difference	-0.70	[-1.59; 0.18]	0.119
			Hedges G	-0.07	[-0.15; 0.02]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.323					
Grade 1	94 1.25 (0.93)	102 1.58 (0.85)	Difference	-0.33	[-2.82; 2.16]	0.793
			Hedges G	-0.04	[-0.32; 0.24]	
Grade 2	785 0.85 (0.37)	702 2.01 (0.39)	Difference	-1.16	[-2.20; -0.11]	0.030
			Hedges G	-0.11	[-0.21; -0.01]	
Grade 3	357 1.62 (0.53)	370 1.22 (0.52)	Difference	0.40	[-1.05; 1.86]	0.588
			Hedges G	0.04	[-0.11; 0.19]	
Histological subtype						
Interaction test	p = 0.535					
Ductal	956 1.21 (0.33)	927 1.79 (0.34)	Difference	-0.58	[-1.51; 0.35]	0.219
			Hedges G	-0.06	[-0.15; 0.03]	
Lobular	278 1.45 (0.62)	262 1.37 (0.63)	Difference	0.08	[-1.66; 1.82]	0.929
			Hedges G	0.01	[-0.16; 0.18]	
Other	87 0.45 (0.91)	70 2.39 (1.06)	Difference	-1.94	[-4.70; 0.83]	0.168
			Hedges G	-0.22	[-0.54; 0.09]	
Ki67 status from surgical specimen						
Interaction test	p = 0.276					
Ki67≤20	618 0.73 (0.38)	591 1.18 (0.39)	Difference	-0.46	[-1.53; 0.62]	0.404
			Hedges G	-0.05	[-0.16; 0.06]	
Ki67>20	466 1.57 (0.49)	473 2.78 (0.49)	Difference	-1.21	[-2.57; 0.15]	0.081
			Hedges G	-0.11	[-0.24; 0.01]	
Type of NSAI						
Interaction test	p = 0.401					
Letrozole	847 1.26 (0.36)	822 2.17 (0.36)	Difference	-0.91	[-1.91; 0.09]	0.074
			Hedges G	-0.09	[-0.18; 0.01]	
Anastrozole	475 1.08 (0.44)	434 1.06 (0.46)	Difference	0.03	[-1.23; 1.28]	0.964
			Hedges G	0.00	[-0.13; 0.13]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.794					
Yes	1129 1.20 (0.31)	1052 1.84 (0.32)	Difference	-0.64	[-1.51; 0.24]	0.154
			Hedges G	-0.06	[-0.15; 0.02]	
No	193 0.86 (0.64)	207 1.34 (0.63)	Difference	-0.48	[-2.24; 1.29]	0.596
			Hedges G	-0.05	[-0.25; 0.14]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.750					
Yes	656 1.17 (0.40)	631 1.83 (0.40)	Difference	-0.66	[-1.77; 0.46]	0.248
			Hedges G	-0.06	[-0.17; 0.04]	
No	666 1.19 (0.38)	628 1.64 (0.40)	Difference	-0.45	[-1.53; 0.64]	0.417
			Hedges G	-0.05	[-0.15; 0.06]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	N.E.					
Yes	500 1.59 (0.46)	451 2.01 (0.48)	Difference	-0.41	[-1.73; 0.90]	0.538
			Hedges G	-0.04	[-0.17; 0.09]	
No	822 1.00 (0.35)	808 1.61 (0.35)	Difference	-0.62	[-1.58; 0.35]	0.213
			Hedges G	-0.06	[-0.16; 0.04]	
Prior endocrine therapy						
Interaction test	p = 0.296					
Yes	894 1.20 (0.34)	865 2.02 (0.34)	Difference	-0.82	[-1.77; 0.13]	0.091
			Hedges G	-0.08	[-0.17; 0.01]	
No	428 1.07 (0.49)	394 1.18 (0.51)	Difference	-0.11	[-1.49; 1.27]	0.877
			Hedges G	-0.01	[-0.15; 0.13]	
Prior mastectomy						
Interaction test	p = 0.590					
Yes	808 1.33 (0.34)	777 1.69 (0.35)	Difference	-0.36	[-1.31; 0.59]	0.459
			Hedges G	-0.04	[-0.14; 0.06]	
No	514 0.89 (0.47)	482 1.80 (0.48)	Difference	-0.91	[-2.22; 0.40]	0.174
			Hedges G	-0.09	[-0.21; 0.04]	
Prior radiotherapy						
Interaction test	N.E.					
Yes	1176 0.92 (0.30)	1112 1.73 (0.31)	Difference	-0.81	[-1.65; 0.03]	0.059
			Hedges G	-0.08	[-0.16; 0.00]	
No	146 3.29 (0.82)	147 1.80 (0.81)	Difference	1.50	[-0.77; 3.76]	0.194
			Hedges G	0.15	[-0.08; 0.38]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed N.E.: Not estimable ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + baseline value ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>+ The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

5-2.2 EORTC QLQ-C30 QoL

Table 5-2.2.1.1 QLQ-C30 - Global Health/QoL: change from baseline analysis - subgroup analysis (Full Analysis Set)

Treatment Groups		Comparison				
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-C30 - Global Health/QoL						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.803					
NA/WE/O	824 -3.28 (0.44)	769 -2.80 (0.46)	Difference	-0.48	[-1.73; 0.77]	0.450
			Hedges G	-0.04	[-0.14; 0.06]	
ROW	498 -2.12 (0.57)	489 -1.84 (0.58)	Difference	-0.28	[-1.88; 1.32]	0.729
			Hedges G	-0.02	[-0.15; 0.10]	
Geographical region						
Interaction test	p = 0.696					
Europe	782 -2.71 (0.46)	770 -1.81 (0.46)	Difference	-0.90	[-2.18; 0.39]	0.171
			Hedges G	-0.07	[-0.17; 0.03]	
North America/Australia	367 -3.32 (0.59)	324 -3.18 (0.62)	Difference	-0.14	[-1.83; 1.55]	0.869
			Hedges G	-0.01	[-0.16; 0.14]	
Asia	101 -4.09 (1.14)	93 -3.04 (1.24)	Difference	-1.05	[-4.37; 2.27]	0.532
			Hedges G	-0.09	[-0.37; 0.19]	
Latin America	72 -1.35 (1.32)	71 -2.15 (1.33)	Difference	0.80	[-2.91; 4.51]	0.671
			Hedges G	0.07	[-0.26; 0.40]	
Age group 1 at randomization						
Interaction test	p = 0.164					
<45	56 -4.08 (1.53)	48 -4.93 (1.68)	Difference	0.85	[-3.65; 5.35]	0.710
			Hedges G	0.07	[-0.31; 0.46]	
45 to 54	284 -2.06 (0.74)	289 -2.89 (0.73)	Difference	0.83	[-1.21; 2.87]	0.423
			Hedges G	0.07	[-0.10; 0.23]	
55 to 64	613 -1.83 (0.52)	602 -1.66 (0.52)	Difference	-0.17	[-1.61; 1.26]	0.814
			Hedges G	-0.01	[-0.13; 0.10]	
≥65	369 -4.93 (0.63)	319 -2.76 (0.68)	Difference	-2.17	[-3.99; -0.35]	0.019
			Hedges G	-0.18	[-0.33; -0.03]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.027					
<Median	598 -2.18 (0.53)	578 -2.95 (0.54)	Difference	0.77	[-0.70; 2.25]	0.305
			Hedges G	0.06	[-0.05; 0.17]	
≥Median	724 -3.43 (0.47)	680 -2.01 (0.49)	Difference	-1.42	[-2.75; -0.09]	0.036
			Hedges G	-0.11	[-0.22; -0.01]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.775					
Asian	125 -3.25 (1.04)	116 -2.57 (1.14)	Difference	-0.68	[-3.71; 2.35]	0.657
			Hedges G	-0.06	[-0.31; 0.20]	
Non-Asian	1121 -2.75 (0.38)	1082 -2.16 (0.38)	Difference	-0.59	[-1.64; 0.47]	0.275
			Hedges G	-0.05	[-0.13; 0.04]	
BMI at screening						
Interaction test	p = 0.457					
≥25	872 -2.87 (0.43)	858 -2.69 (0.43)	Difference	-0.18	[-1.38; 1.02]	0.770
			Hedges G	-0.01	[-0.11; 0.08]	
<25	439 -2.97 (0.61)	388 -1.97 (0.65)	Difference	-1.00	[-2.76; 0.75]	0.263
			Hedges G	-0.08	[-0.21; 0.06]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.352					
Group I/II	541 -2.81 (0.54)	552 -1.84 (0.54)	Difference	-0.98	[-2.47; 0.52]	0.201
			Hedges G	-0.08	[-0.20; 0.04]	
Group III	780 -2.89 (0.47)	706 -3.05 (0.49)	Difference	0.16	[-1.18; 1.49]	0.818
			Hedges G	0.01	[-0.09; 0.11]	
Anatomic stages						
Interaction test	p = 0.539					
IA/IB/IIA	284 -2.82 (0.73)	290 -1.76 (0.72)	Difference	-1.06	[-3.07; 0.96]	0.304
			Hedges G	-0.09	[-0.25; 0.08]	
IIB	257 -2.78 (0.79)	262 -1.68 (0.78)	Difference	-1.11	[-3.28; 1.07]	0.319
			Hedges G	-0.09	[-0.26; 0.08]	
IIIA	460 -2.87 (0.60)	413 -3.58 (0.61)	Difference	0.71	[-0.98; 2.40]	0.408
			Hedges G	0.06	[-0.08; 0.19]	
IIIB	92 -0.54 (1.38)	78 -0.29 (1.51)	Difference	-0.25	[-4.29; 3.78]	0.902
			Hedges G	-0.02	[-0.32; 0.28]	
IIIC	228 -3.53 (0.84)	215 -2.23 (0.88)	Difference	-1.30	[-3.68; 1.09]	0.287
			Hedges G	-0.10	[-0.29; 0.09]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.666					
N0	175 -2.40 (0.94)	188 -2.46 (0.91)	Difference	0.06	[-2.50; 2.63]	0.961
			Hedges G	0.01	[-0.20; 0.21]	
N1-N3	1144 -2.88 (0.38)	1070 -2.41 (0.40)	Difference	-0.48	[-1.56; 0.61]	0.389
			Hedges G	-0.04	[-0.12; 0.05]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.726					
Grade 1	94 -1.81 (1.28)	102 -2.97 (1.19)	Difference	1.17	[-2.30; 4.64]	0.508
			Hedges G	0.09	[-0.19; 0.38]	
Grade 2	785 -2.30 (0.44)	701 -1.57 (0.46)	Difference	-0.73	[-1.98; 0.52]	0.252
			Hedges G	-0.06	[-0.16; 0.04]	
Grade 3	357 -3.81 (0.69)	370 -3.36 (0.68)	Difference	-0.45	[-2.35; 1.45]	0.642
			Hedges G	-0.03	[-0.18; 0.11]	
Histological subtype						
Interaction test	p = 0.181					
Ductal	955 N.E.	927 N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Lobular	278 N.E.	261 N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Other	88 0.19 (1.35)	70 -3.70 (1.55)	Difference	3.89	[-0.17; 7.95]	0.060
			Hedges G	0.30	[-0.01; 0.62]	
Ki67 status from surgical specimen						
Interaction test	p = 0.901					
Ki67≤20	619 -2.78 (0.51)	589 -2.31 (0.52)	Difference	-0.48	[-1.92; 0.96]	0.516
			Hedges G	-0.04	[-0.15; 0.08]	
Ki67>20	465 -3.50 (0.61)	474 -3.02 (0.61)	Difference	-0.47	[-2.17; 1.23]	0.587
			Hedges G	-0.04	[-0.16; 0.09]	
Type of NSAI						
Interaction test	p = 0.134					
Letrozole	847 -3.11 (0.44)	820 -2.21 (0.45)	Difference	-0.90	[-2.13; 0.33]	0.150
			Hedges G	-0.07	[-0.17; 0.03]	
Anastrozole	475 -2.46 (0.59)	435 -3.06 (0.62)	Difference	0.61	[-1.07; 2.28]	0.477
			Hedges G	0.05	[-0.08; 0.18]	
Prior neo/adjuvant chemotherapy						
Interaction test	N.E.					
Yes	1128 -2.83 (0.38)	1050 -2.33 (0.40)	Difference	-0.50	[-1.59; 0.58]	0.362
			Hedges G	-0.04	[-0.12; 0.04]	
No	194 -2.70 (0.88)	208 -2.83 (0.86)	Difference	0.13	[-2.30; 2.56]	0.917
			Hedges G	0.01	[-0.19; 0.21]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.166					
Yes	655 -3.23 (0.49)	630 -2.09 (0.49)	Difference	-1.14	[-2.50; 0.22]	0.101
			Hedges G	-0.09	[-0.20; 0.02]	
No	667 -2.42 (0.50)	628 -2.74 (0.52)	Difference	0.32	[-1.11; 1.74]	0.660
			Hedges G	0.02	[-0.08; 0.13]	

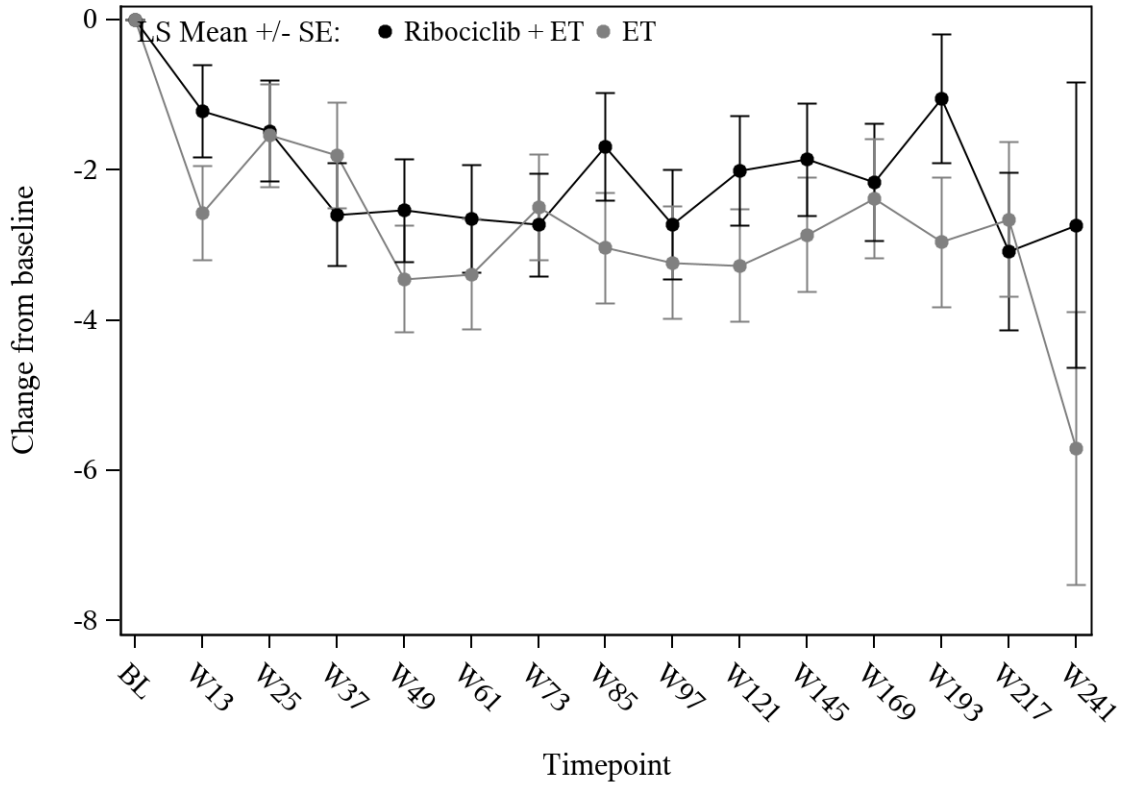
Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	p = 0.380					
Yes	500 -2.43 (0.59)	450 -2.77 (0.62)	Difference	0.34	[-1.34; 2.03]	0.691
			Hedges G	0.03	[-0.10; 0.15]	
No	822 -3.06 (0.44)	808 -2.38 (0.44)	Difference	-0.68	[-1.90; 0.54]	0.273
			Hedges G	-0.05	[-0.15; 0.04]	
Prior endocrine therapy						
Interaction test	p = 0.399					
Yes	894 -3.82 (0.42)	865 -3.02 (0.43)	Difference	-0.81	[-1.99; 0.37]	0.180
			Hedges G	-0.06	[-0.16; 0.03]	
No	428 -0.93 (0.63)	393 -1.13 (0.65)	Difference	0.19	[-1.58; 1.97]	0.831
			Hedges G	0.01	[-0.12; 0.15]	
Prior mastectomy						
Interaction test	p = 0.773					
Yes	808 -2.75 (0.46)	776 -2.50 (0.46)	Difference	-0.25	[-1.52; 1.03]	0.704
			Hedges G	-0.02	[-0.12; 0.08]	
No	514 -3.11 (0.56)	482 -2.35 (0.57)	Difference	-0.77	[-2.34; 0.80]	0.338
			Hedges G	-0.06	[-0.19; 0.06]	
Prior radiotherapy						
Interaction test	p = 0.693					
Yes	1176 -2.77 (0.37)	1110 -2.45 (0.38)	Difference	-0.32	[-1.37; 0.73]	0.548
			Hedges G	-0.03	[-0.11; 0.06]	
No	146 -3.34 (1.10)	148 -2.25 (1.09)	Difference	-1.08	[-4.12; 1.95]	0.483
			Hedges G	-0.08	[-0.31; 0.15]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed N.E.: Not estimable ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + baseline value ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>+ The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

Figure 5-2.2.1.1 QLQ-C30 - Global Health/QoL: line chart of change from baseline - subgroup analysis (Full Analysis Set)

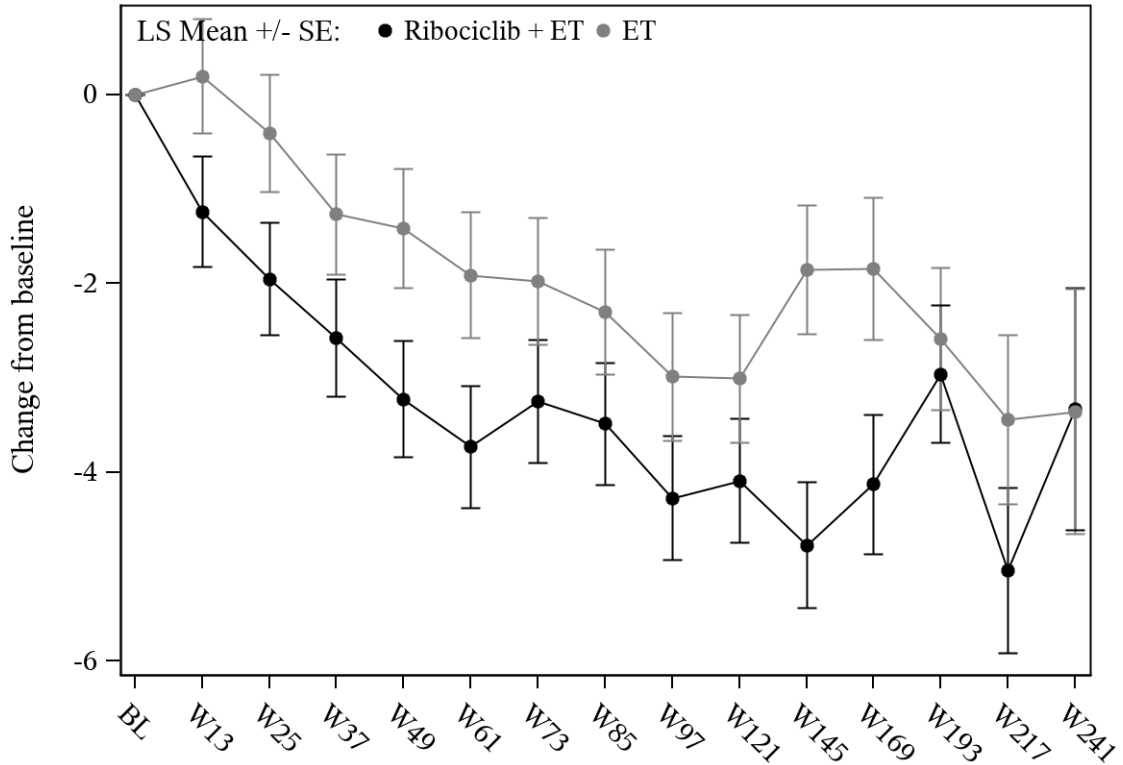
QLQ-C30 - Global Health/QoL

Age group 2 at randomization (median for subpopulation post-menopausal female patients): <Median



Ribociclib + ET	598	570	540	549	537	528	528	515	510	489	474	400	322	197	33
ET	578	549	523	512	508	503	497	487	477	471	462	383	321	214	37

QLQ-C30 - Global Health/QoL
Age group 2 at randomization (median for subpopulation post-menopausal female patients): \geq Median



Ribociclib + ET	724	692	675	663	646	638	635	613	614	589	586	506	441	281	58
ET	680	646	622	623	626	604	606	593	585	569	544	482	408	265	56

Table 5-2.2.2.1 QLQ-C30 - Physical Functioning: change from baseline analysis - subgroup analysis (Full Analysis Set)

Treatment Groups		Comparison				
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-C30 - Physical Functioning						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.960					
NA/WE/O	827 -2.06 (0.42)	775 -2.70 (0.43)	Difference	0.64	[-0.53; 1.81]	0.284
			Hedges G	0.05	[-0.04; 0.15]	
ROW	499 N.E.	489 N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Geographical region						
Interaction test	p = 0.718					
Europe	785 -2.30 (0.41)	776 -3.17 (0.41)	Difference	0.87	[-0.28; 2.02]	0.136
			Hedges G	0.08	[-0.02; 0.17]	
North America/Australia	368 -2.25 (0.55)	324 -2.14 (0.58)	Difference	-0.11	[-1.68; 1.47]	0.895
			Hedges G	-0.01	[-0.16; 0.14]	
Asia	101 -0.37 (0.90)	93 -0.45 (1.01)	Difference	0.08	[-2.59; 2.75]	0.955
			Hedges G	0.01	[-0.27; 0.29]	
Latin America	72 -2.55 (1.26)	71 -2.80 (1.28)	Difference	0.25	[-3.30; 3.81]	0.888
			Hedges G	0.02	[-0.30; 0.35]	
Age group 1 at randomization						
Interaction test	p = 0.402					
<45	56 -1.02 (1.61)	48 -4.09 (1.77)	Difference	3.07	[-1.67; 7.82]	0.202
			Hedges G	0.25	[-0.13; 0.64]	
45 to 54	285 -1.43 (0.68)	291 -2.74 (0.68)	Difference	1.32	[-0.57; 3.21]	0.171
			Hedges G	0.11	[-0.05; 0.28]	
55 to 64	613 -1.21 (0.43)	603 -1.99 (0.42)	Difference	0.77	[-0.41; 1.95]	0.198
			Hedges G	0.07	[-0.04; 0.19]	
≥65	372 -4.16 (0.61)	322 -3.89 (0.65)	Difference	-0.27	[-2.02; 1.48]	0.763
			Hedges G	-0.02	[-0.17; 0.13]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.224					
<Median	599 -1.04 (0.48)	580 -2.34 (0.48)	Difference	1.31	[-0.02; 2.64]	0.054
			Hedges G	0.11	[-0.00; 0.23]	
≥Median	727 -3.00 (0.45)	684 -3.17 (0.46)	Difference	0.17	[-1.08; 1.43]	0.789
			Hedges G	0.01	[-0.09; 0.12]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.618					
Asian	125 -0.79 (0.77)	116 -0.75 (0.86)	Difference	-0.04	[-2.31; 2.23]	0.971
			Hedges G	-0.00	[-0.26; 0.25]	
Non-Asian	1124 -2.27 (0.34)	1084 -2.92 (0.35)	Difference	0.66	[-0.30; 1.61]	0.178
			Hedges G	0.06	[-0.03; 0.14]	
BMI at screening						
Interaction test	p = 0.642					
≥25	875 -2.38 (0.41)	862 -3.08 (0.41)	Difference	0.69	[-0.45; 1.84]	0.235
			Hedges G	0.06	[-0.04; 0.15]	
<25	440 -1.91 (0.53)	390 -2.13 (0.56)	Difference	0.22	[-1.31; 1.75]	0.778
			Hedges G	0.02	[-0.12; 0.16]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.319					
Group I/II	545 -2.15 (0.48)	555 -2.28 (0.48)	Difference	0.13	[-1.21; 1.47]	0.849
			Hedges G	0.01	[-0.11; 0.13]	
Group III	780 -2.27 (0.45)	709 -3.19 (0.47)	Difference	0.92	[-0.35; 2.20]	0.155
			Hedges G	0.07	[-0.03; 0.18]	
Anatomic stages						
Interaction test	p = 0.432					
IA/IB/IIA	287 -1.47 (0.62)	292 -2.10 (0.62)	Difference	0.63	[-1.09; 2.35]	0.473
			Hedges G	0.06	[-0.10; 0.22]	
IIB	258 -3.04 (0.70)	263 -2.23 (0.68)	Difference	-0.81	[-2.73; 1.10]	0.405
			Hedges G	-0.07	[-0.24; 0.10]	
IIIA	461 -2.16 (0.55)	414 -3.93 (0.56)	Difference	1.77	[0.23; 3.31]	0.024
			Hedges G	0.15	[0.02; 0.29]	
IIIB	92 -0.38 (1.20)	78 -1.08 (1.31)	Difference	0.70	[-2.81; 4.21]	0.694
			Hedges G	0.06	[-0.24; 0.36]	
IIIC	227 -2.18 (0.76)	217 -2.54 (0.78)	Difference	0.36	[-1.79; 2.51]	0.743
			Hedges G	0.03	[-0.15; 0.22]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.840					
N0	176 -2.31 (0.88)	189 -2.74 (0.85)	Difference	0.43	[-1.98; 2.83]	0.726
			Hedges G	0.04	[-0.17; 0.24]	
N1-N3	1147 -2.11 (0.36)	1075 -2.74 (0.36)	Difference	0.63	[-0.37; 1.63]	0.216
			Hedges G	0.05	[-0.03; 0.14]	

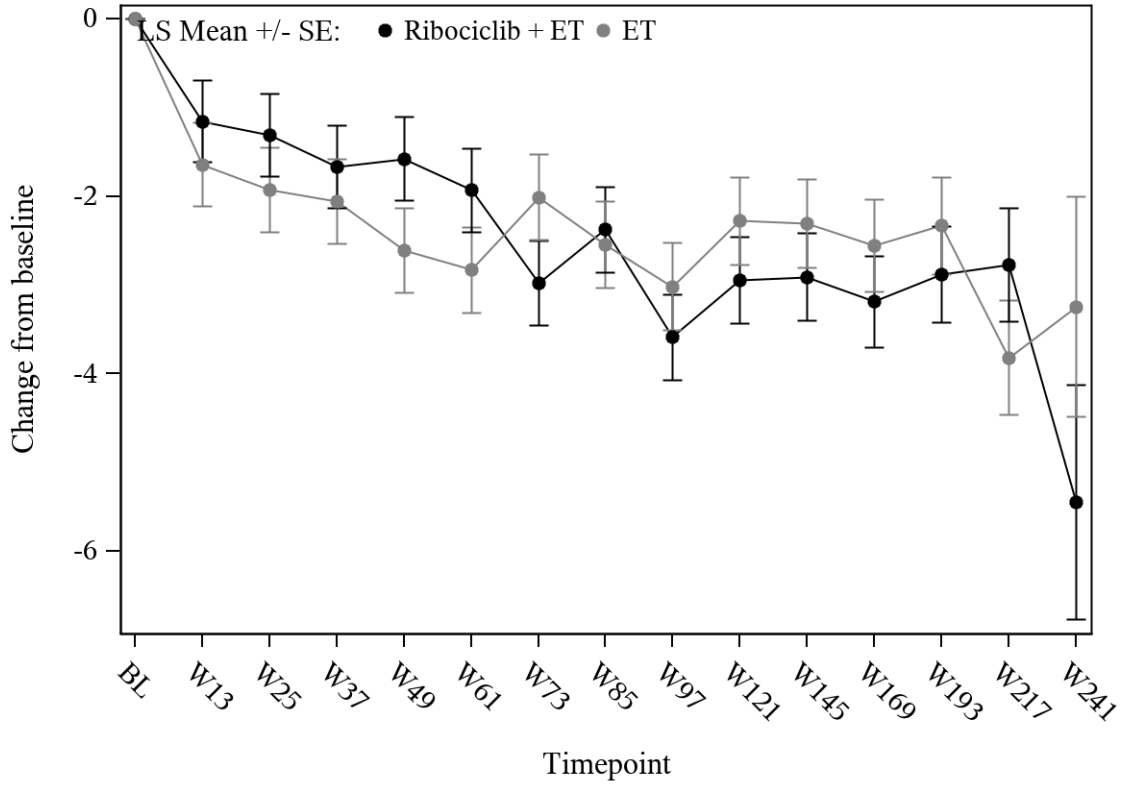
	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.107					
Grade 1	94 -2.93 (1.10)	102 -2.90 (1.02)	Difference	-0.03	[-3.03; 2.96]	0.982
			Hedges G	-0.00	[-0.28; 0.28]	
Grade 2	789 -2.03 (0.39)	705 -1.88 (0.42)	Difference	-0.15	[-1.28; 0.97]	0.792
			Hedges G	-0.01	[-0.12; 0.09]	
Grade 3	357 -1.74 (0.61)	372 -3.97 (0.60)	Difference	2.23	[0.55; 3.90]	0.009
			Hedges G	0.19	[0.05; 0.34]	
Histological subtype						
Interaction test	p = 0.320					
Ductal	960 -2.03 (0.36)	931 -2.81 (0.37)	Difference	0.78	[-0.24; 1.80]	0.134
			Hedges G	0.07	[-0.02; 0.16]	
Lobular	277 -2.51 (0.67)	263 -1.86 (0.68)	Difference	-0.65	[-2.52; 1.22]	0.496
			Hedges G	-0.06	[-0.23; 0.11]	
Other	88 -1.54 (1.10)	70 -5.07 (1.27)	Difference	3.53	[0.21; 6.84]	0.037
			Hedges G	0.34	[0.02; 0.65]	
Ki67 status from surgical specimen						
Interaction test	p = 0.854					
Ki67≤20	620 -1.58 (0.45)	593 -2.54 (0.46)	Difference	0.96	[-0.29; 2.21]	0.134
			Hedges G	0.09	[-0.03; 0.20]	
Ki67>20	467 -2.13 (0.54)	476 -3.52 (0.53)	Difference	1.39	[-0.10; 2.87]	0.067
			Hedges G	0.12	[-0.01; 0.25]	
Type of NSAI						
Interaction test	p = 0.427					
Letrozole	848 -2.41 (0.42)	826 -2.78 (0.42)	Difference	0.37	[-0.79; 1.53]	0.531
			Hedges G	0.03	[-0.07; 0.13]	
Anastrozole	478 -1.85 (0.53)	435 -2.87 (0.56)	Difference	1.02	[-0.50; 2.54]	0.187
			Hedges G	0.09	[-0.04; 0.22]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.959					
Yes	1132 -1.90 (0.35)	1055 -2.47 (0.36)	Difference	0.58	[-0.42; 1.57]	0.256
			Hedges G	0.05	[-0.04; 0.13]	
No	194 -3.57 (0.83)	209 -4.09 (0.80)	Difference	0.52	[-1.75; 2.78]	0.652
			Hedges G	0.04	[-0.15; 0.24]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.578					
Yes	659 -1.24 (0.45)	634 -2.13 (0.45)	Difference	0.89	[-0.36; 2.14]	0.164
			Hedges G	0.08	[-0.03; 0.19]	
No	667 -3.01 (0.47)	630 -3.39 (0.49)	Difference	0.38	[-0.95; 1.71]	0.574
			Hedges G	0.03	[-0.08; 0.14]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	p = 0.336					
Yes	500 -2.67 (0.54)	451 -2.76 (0.57)	Difference	0.09	[-1.46; 1.64]	0.911
			Hedges G	0.01	[-0.12; 0.13]	
No	826 -1.77 (0.41)	813 -2.78 (0.41)	Difference	1.01	[-0.13; 2.14]	0.081
			Hedges G	0.09	[-0.01; 0.18]	
Prior endocrine therapy						
Interaction test	p = 0.024					
Yes	893 -2.62 (0.37)	867 -2.51 (0.37)	Difference	-0.11	[-1.14; 0.92]	0.833
			Hedges G	-0.01	[-0.10; 0.08]	
No	433 -1.00 (0.55)	397 -3.17 (0.58)	Difference	2.16	[0.60; 3.73]	0.007
			Hedges G	0.19	[0.05; 0.32]	
Prior mastectomy						
Interaction test	p = 0.821					
Yes	809 -2.44 (0.44)	781 -3.09 (0.44)	Difference	0.65	[-0.57; 1.87]	0.295
			Hedges G	0.05	[-0.05; 0.15]	
No	517 -1.72 (0.49)	483 -2.42 (0.50)	Difference	0.70	[-0.68; 2.08]	0.318
			Hedges G	0.06	[-0.06; 0.19]	
Prior radiotherapy						
Interaction test	p = 0.401					
Yes	1179 -1.99 (0.35)	1115 -2.76 (0.36)	Difference	0.77	[-0.20; 1.75]	0.119
			Hedges G	0.07	[-0.02; 0.15]	
No	147 -3.40 (1.01)	149 -3.03 (1.00)	Difference	-0.37	[-3.18; 2.43]	0.794
			Hedges G	-0.03	[-0.26; 0.20]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed N.E.: Not estimable ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + baseline value ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>+ The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

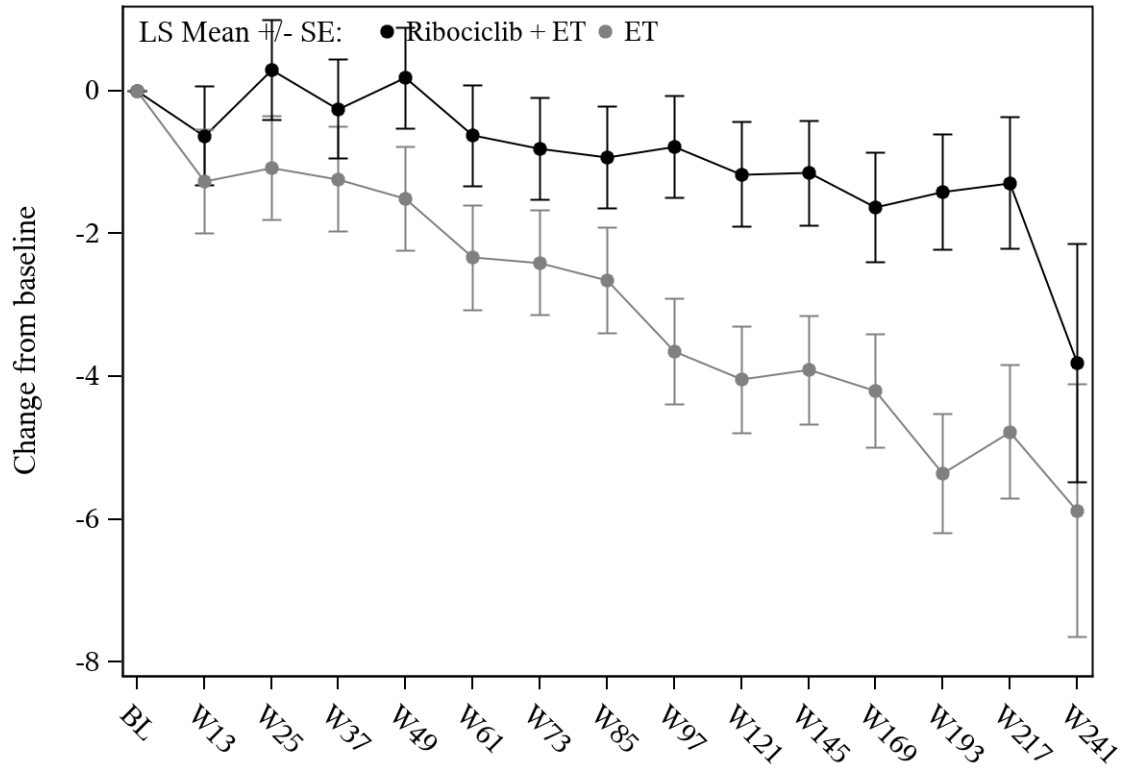
Figure 5-2.2.2.1 QLQ-C30 - Physical Functioning: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Physical Functioning
Prior endocrine therapy: Yes



Ribociclib + ET	893	856	819	816	806	794	791	763	757	735	723	621	516	311	55
ET	867	824	790	788	778	759	748	741	724	714	696	596	506	314	64

QLQ-C30 - Physical Functioning
Prior endocrine therapy: No



Ribociclib + ET	433	414	398	397	381	380	376	365	370	345	344	287	250	167	36
ET	397	377	365	356	367	355	357	347	345	331	317	276	230	166	32

Table 5-2.2.3.1 QLQ-C30 - Role Functioning: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-C30 - Role Functioning						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.889					
NA/WE/O	826 -2.80 (0.57)	775 -3.51 (0.58)	Difference	0.70	[-0.89; 2.30]	0.388
			Hedges G	0.04	[-0.05; 0.14]	
ROW	499 -3.16 (0.66)	489 -3.44 (0.66)	Difference	0.28	[-1.55; 2.11]	0.763
			Hedges G	0.02	[-0.11; 0.14]	
Geographical region						
Interaction test	p = 0.523					
Europe	784 -3.07 (0.56)	776 -3.76 (0.56)	Difference	0.69	[-0.88; 2.25]	0.388
			Hedges G	0.04	[-0.06; 0.14]	
North America/Australia	368 -3.17 (0.74)	324 -2.57 (0.78)	Difference	-0.60	[-2.72; 1.52]	0.582
			Hedges G	-0.04	[-0.19; 0.11]	
Asia	101 -3.39 (1.15)	93 -2.67 (1.33)	Difference	-0.72	[-4.19; 2.76]	0.685
			Hedges G	-0.06	[-0.34; 0.22]	
Latin America	72 0.02 (1.76)	71 -2.99 (1.78)	Difference	3.01	[-1.94; 7.96]	0.231
			Hedges G	0.20	[-0.13; 0.53]	
Age group 1 at randomization						
Interaction test	p = 0.581					
<45	56 -3.19 (2.40)	48 -1.09 (2.61)	Difference	-2.09	[-9.13; 4.95]	0.557
			Hedges G	-0.12	[-0.50; 0.27]	
45 to 54	285 -2.24 (0.97)	291 -2.75 (0.96)	Difference	0.50	[-2.18; 3.18]	0.714
			Hedges G	0.03	[-0.13; 0.19]	
55 to 64	612 -1.30 (0.59)	603 -2.61 (0.59)	Difference	1.31	[-0.32; 2.95]	0.116
			Hedges G	0.09	[-0.02; 0.20]	
≥65	372 -6.24 (0.77)	322 -5.89 (0.83)	Difference	-0.34	[-2.56; 1.88]	0.762
			Hedges G	-0.02	[-0.17; 0.13]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.217					
<Median	599 -0.95 (0.66)	580 -2.39 (0.67)	Difference	1.43	[-0.41; 3.28]	0.128
			Hedges G	0.09	[-0.03; 0.20]	
≥Median	726 -4.46 (0.56)	684 -4.28 (0.57)	Difference	-0.18	[-1.75; 1.39]	0.819
			Hedges G	-0.01	[-0.12; 0.09]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.577					
Asian	125 -2.50 (1.02)	116 -1.87 (1.17)	Difference	-0.62	[-3.68; 2.43]	0.689
			Hedges G	-0.05	[-0.30; 0.20]	
Non-Asian	1123 -2.91 (0.47)	1084 -3.45 (0.47)	Difference	0.54	[-0.75; 1.84]	0.411
			Hedges G	0.03	[-0.05; 0.12]	
BMI at screening						
Interaction test	p = 0.945					
≥25	875 -3.20 (0.53)	862 -3.67 (0.53)	Difference	0.47	[-1.00; 1.95]	0.530
			Hedges G	0.03	[-0.06; 0.12]	
<25	439 -2.95 (0.75)	390 -3.30 (0.79)	Difference	0.35	[-1.78; 2.49]	0.746
			Hedges G	0.02	[-0.11; 0.16]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.152					
Group I/II	544 -2.65 (0.65)	555 -2.35 (0.64)	Difference	-0.30	[-2.09; 1.49]	0.744
			Hedges G	-0.02	[-0.14; 0.10]	
Group III	780 -3.09 (0.58)	709 -4.66 (0.60)	Difference	1.57	[-0.08; 3.21]	0.062
			Hedges G	0.10	[-0.00; 0.20]	
Anatomic stages						
Interaction test	N.E.					
IA/IB/IIA	286 -1.97 (0.87)	292 -2.29 (0.87)	Difference	0.33	[-2.09; 2.75]	0.791
			Hedges G	0.02	[-0.14; 0.19]	
IIB	258 -3.38 (0.94)	263 -2.25 (0.92)	Difference	-1.13	[-3.71; 1.45]	0.391
			Hedges G	-0.08	[-0.25; 0.10]	
IIIA	461 -3.39 (0.73)	414 -6.00 (0.74)	Difference	2.60	[0.56; 4.65]	0.013
			Hedges G	0.17	[0.04; 0.30]	
IIIB	92 -1.58 (1.57)	78 -0.89 (1.72)	Difference	-0.68	[-5.28; 3.91]	0.770
			Hedges G	-0.05	[-0.35; 0.26]	
IIIC	227 -3.52 (1.08)	217 -3.07 (1.12)	Difference	-0.45	[-3.51; 2.61]	0.773
			Hedges G	-0.03	[-0.21; 0.16]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.890					
N0	176 -2.92 (1.12)	189 -3.20 (1.08)	Difference	0.28	[-2.78; 3.34]	0.858
			Hedges G	0.02	[-0.19; 0.22]	
N1-N3	1146 -3.06 (0.47)	1075 -3.59 (0.48)	Difference	0.53	[-0.79; 1.85]	0.434
			Hedges G	0.03	[-0.05; 0.12]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.160					
Grade 1	94 -2.89 (1.59)	102 -5.57 (1.47)	Difference	2.69	[-1.58; 6.95]	0.216
			Hedges G	0.18	[-0.10; 0.46]	
Grade 2	788 -2.51 (0.52)	705 -2.04 (0.55)	Difference	-0.47	[-1.96; 1.02]	0.537
			Hedges G	-0.03	[-0.13; 0.07]	
Grade 3	357 -3.26 (0.85)	372 -4.91 (0.83)	Difference	1.65	[-0.67; 3.97]	0.164
			Hedges G	0.10	[-0.04; 0.25]	
Histological subtype						
Interaction test	p = 0.767					
Ductal	959 -3.23 (0.50)	931 -3.35 (0.50)	Difference	0.12	[-1.27; 1.51]	0.865
			Hedges G	0.01	[-0.08; 0.10]	
Lobular	277 -2.15 (0.88)	263 -3.25 (0.90)	Difference	1.10	[-1.37; 3.57]	0.382
			Hedges G	0.08	[-0.09; 0.24]	
Other	88 -1.12 (1.54)	70 -5.95 (1.78)	Difference	4.83	[0.18; 9.49]	0.042
			Hedges G	0.33	[0.01; 0.64]	
Ki67 status from surgical specimen						
Interaction test	p = 0.873					
Ki67≤20	619 -2.63 (0.62)	593 -3.56 (0.63)	Difference	0.94	[-0.79; 2.66]	0.289
			Hedges G	0.06	[-0.05; 0.17]	
Ki67>20	467 -2.73 (0.75)	476 -3.56 (0.75)	Difference	0.83	[-1.27; 2.92]	0.439
			Hedges G	0.05	[-0.08; 0.18]	
Type of NSAI						
Interaction test	p = 0.672					
Letrozole	847 -3.53 (0.55)	826 -3.87 (0.55)	Difference	0.34	[-1.17; 1.86]	0.656
			Hedges G	0.02	[-0.07; 0.12]	
Anastrozole	478 -2.11 (0.72)	435 -2.93 (0.76)	Difference	0.82	[-1.23; 2.87]	0.435
			Hedges G	0.05	[-0.08; 0.18]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.604					
Yes	1132 -2.67 (0.47)	1055 -3.33 (0.48)	Difference	0.65	[-0.67; 1.98]	0.334
			Hedges G	0.04	[-0.04; 0.13]	
No	193 -4.63 (1.03)	209 -4.20 (1.00)	Difference	-0.42	[-3.26; 2.41]	0.769
			Hedges G	-0.03	[-0.23; 0.17]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.988					
Yes	659 -2.70 (0.61)	634 -3.20 (0.61)	Difference	0.50	[-1.19; 2.19]	0.562
			Hedges G	0.03	[-0.08; 0.14]	
No	666 -3.25 (0.61)	630 -3.83 (0.63)	Difference	0.58	[-1.13; 2.30]	0.505
			Hedges G	0.04	[-0.07; 0.15]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test p = 0.897						
Yes	500 -3.03 (0.71)	451 -3.52 (0.75)	Difference	0.49	[-1.54; 2.51]	0.637
			Hedges G	0.03	[-0.10; 0.16]	
No	825 -2.95 (0.54)	813 -3.51 (0.54)	Difference	0.57	[-0.93; 2.06]	0.459
			Hedges G	0.04	[-0.06; 0.13]	
Prior endocrine therapy						
Interaction test p = 0.061						
Yes	893 -3.96 (0.52)	867 -3.66 (0.53)	Difference	-0.30	[-1.75; 1.15]	0.684
			Hedges G	-0.02	[-0.11; 0.07]	
No	432 -0.86 (0.74)	397 -3.05 (0.77)	Difference	2.19	[0.09; 4.29]	0.041
			Hedges G	0.14	[0.01; 0.28]	
Prior mastectomy						
Interaction test p = 0.400						
Yes	809 -2.77 (0.56)	781 -3.68 (0.57)	Difference	0.91	[-0.66; 2.48]	0.257
			Hedges G	0.06	[-0.04; 0.16]	
No	516 -3.26 (0.67)	483 -3.11 (0.69)	Difference	-0.15	[-2.03; 1.72]	0.872
			Hedges G	-0.01	[-0.13; 0.11]	
Prior radiotherapy						
Interaction test p = 0.383						
Yes	1178 -2.94 (0.46)	1115 -3.74 (0.47)	Difference	0.80	[-0.50; 2.10]	0.230
			Hedges G	0.05	[-0.03; 0.13]	
No	147 -3.24 (1.20)	149 -2.33 (1.18)	Difference	-0.90	[-4.22; 2.42]	0.592
			Hedges G	-0.06	[-0.29; 0.17]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed N.E.: Not estimable ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + baseline value ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>+ The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

Table 5-2.2.4.1 QLQ-C30 - Emotional Functioning: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-C30 - Emotional Functioning						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.758					
NA/WE/O	824 -2.62 (0.52)	770 -3.69 (0.54)	Difference	1.07	[-0.40; 2.54]	0.155
			Hedges G	0.07	[-0.03; 0.17]	
ROW	499 -3.10 (0.61)	489 -3.89 (0.62)	Difference	0.79	[-0.91; 2.49]	0.361
			Hedges G	0.06	[-0.07; 0.18]	
Geographical region						
Interaction test	p = 0.312					
Europe	783 -2.83 (0.52)	771 -3.79 (0.52)	Difference	0.96	[-0.49; 2.41]	0.193
			Hedges G	0.07	[-0.03; 0.17]	
North America/Australia	367 -2.23 (0.66)	324 -3.36 (0.70)	Difference	1.13	[-0.76; 3.02]	0.241
			Hedges G	0.09	[-0.06; 0.24]	
Asia	101 -4.17 (1.11)	93 -7.34 (1.25)	Difference	3.17	[-0.12; 6.46]	0.059
			Hedges G	0.27	[-0.01; 0.56]	
Latin America	72 -3.00 (1.81)	71 -0.61 (1.83)	Difference	-2.39	[-7.50; 2.71]	0.355
			Hedges G	-0.16	[-0.48; 0.17]	
Age group 1 at randomization						
Interaction test	p = 0.524					
<45	56 -4.82 (1.91)	47 -7.78 (2.13)	Difference	2.96	[-2.73; 8.66]	0.305
			Hedges G	0.20	[-0.18; 0.59]	
45 to 54	284 -2.54 (0.91)	290 -4.86 (0.90)	Difference	2.32	[-0.19; 4.83]	0.070
			Hedges G	0.15	[-0.01; 0.32]	
55 to 64	613 -2.30 (0.56)	601 -2.95 (0.56)	Difference	0.65	[-0.91; 2.21]	0.415
			Hedges G	0.05	[-0.07; 0.16]	
≥65	370 -3.28 (0.67)	321 -3.60 (0.72)	Difference	0.31	[-1.62; 2.25]	0.752
			Hedges G	0.02	[-0.13; 0.17]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.020					
<Median	598 -2.48 (0.61)	578 -4.83 (0.62)	Difference	2.35	[0.64; 4.06]	0.007
			Hedges G	0.16	[0.04; 0.27]	
≥Median	725 -3.11 (0.52)	681 -2.84 (0.54)	Difference	-0.27	[-1.74; 1.20]	0.719
			Hedges G	-0.02	[-0.12; 0.09]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.406					
Asian	125 -3.71 (0.96)	116 -6.44 (1.08)	Difference	2.73	[-0.11; 5.57]	0.060
			Hedges G	0.24	[-0.01; 0.50]	
Non-Asian	1122 -2.56 (0.43)	1082 -3.50 (0.43)	Difference	0.94	[-0.25; 2.13]	0.121
			Hedges G	0.07	[-0.02; 0.15]	
BMI at screening						
Interaction test	N.E.					
≥25	873 -2.91 (0.50)	860 -3.63 (0.50)	Difference	0.73	[-0.66; 2.11]	0.304
			Hedges G	0.05	[-0.04; 0.14]	
<25	439 -2.51 (0.68)	387 -4.18 (0.72)	Difference	1.68	[-0.28; 3.63]	0.092
			Hedges G	0.12	[-0.02; 0.25]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.035					
Group I/II	542 -3.14 (0.60)	551 -2.75 (0.59)	Difference	-0.39	[-2.05; 1.27]	0.644
			Hedges G	-0.03	[-0.15; 0.09]	
Group III	780 -2.46 (0.53)	708 -4.56 (0.56)	Difference	2.09	[0.58; 3.61]	0.007
			Hedges G	0.14	[0.04; 0.24]	
Anatomic stages						
Interaction test	p = 0.185					
IA/IB/IIA	285 -2.56 (0.81)	290 -2.01 (0.80)	Difference	-0.56	[-2.80; 1.68]	0.625
			Hedges G	-0.04	[-0.20; 0.12]	
IIB	257 -3.64 (0.84)	261 -3.50 (0.83)	Difference	-0.14	[-2.46; 2.17]	0.904
			Hedges G	-0.01	[-0.18; 0.16]	
IIIA	460 -3.51 (0.70)	413 -4.77 (0.72)	Difference	1.27	[-0.70; 3.23]	0.206
			Hedges G	0.09	[-0.05; 0.22]	
IIIB	92 -0.20 (1.55)	78 -2.56 (1.69)	Difference	2.36	[-2.16; 6.89]	0.304
			Hedges G	0.16	[-0.14; 0.46]	
IIIC	228 -1.67 (0.89)	217 -4.56 (0.92)	Difference	2.89	[0.36; 5.41]	0.025
			Hedges G	0.21	[0.03; 0.40]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.696					
N0	175 -2.04 (1.04)	188 -2.60 (1.01)	Difference	0.55	[-2.30; 3.41]	0.703
			Hedges G	0.04	[-0.17; 0.25]	
N1-N3	1145 -2.95 (0.43)	1071 -3.97 (0.45)	Difference	1.02	[-0.20; 2.24]	0.101
			Hedges G	0.07	[-0.01; 0.15]	

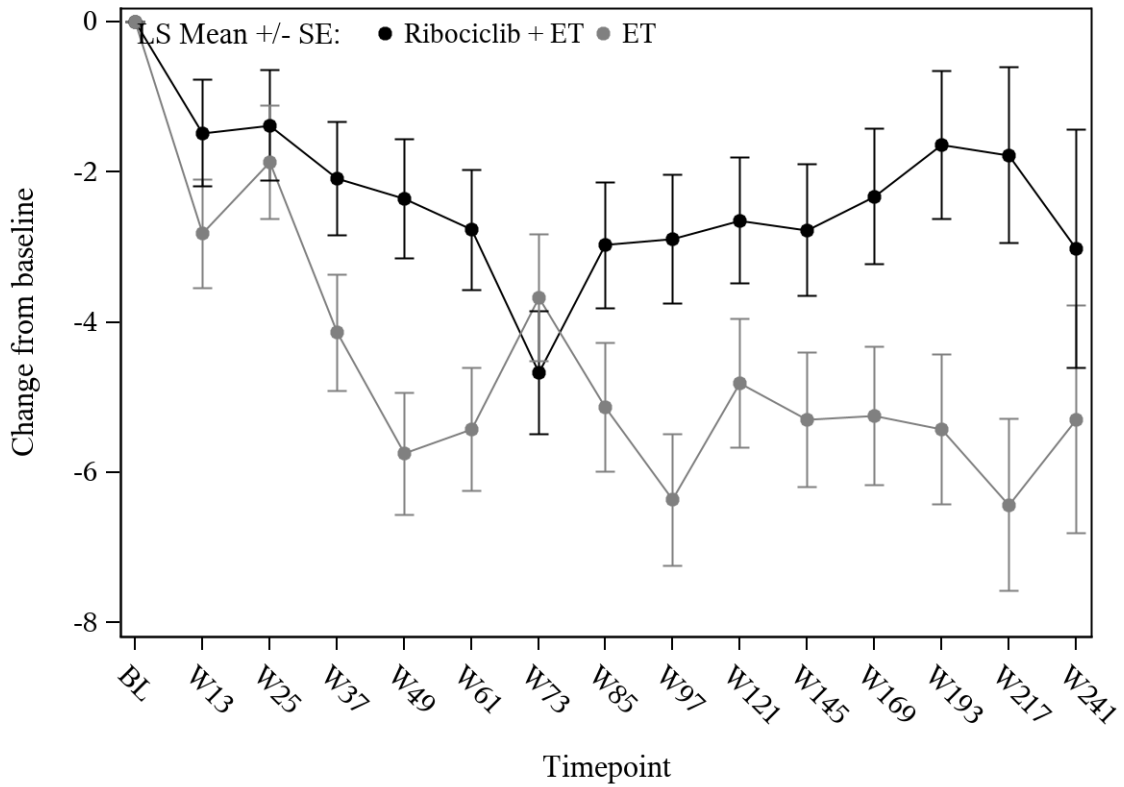
Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.563					
Grade 1	94 -2.52 (1.28)	102 -5.14 (1.17)	Difference	2.62	[-0.82; 6.06]	0.135
			Hedges G	0.21	[-0.07; 0.50]	
Grade 2	786 -2.47 (0.49)	702 -3.30 (0.52)	Difference	0.83	[-0.57; 2.23]	0.247
			Hedges G	0.06	[-0.04; 0.16]	
Grade 3	357 -3.50 (0.76)	370 -4.24 (0.75)	Difference	0.73	[-1.36; 2.83]	0.492
			Hedges G	0.05	[-0.09; 0.20]	
Histological subtype						
Interaction test	p = 0.144					
Ductal	956 -3.14 (0.45)	927 -3.63 (0.46)	Difference	0.49	[-0.77; 1.75]	0.447
			Hedges G	0.04	[-0.06; 0.13]	
Lobular	278 -2.25 (0.85)	262 -3.81 (0.87)	Difference	1.56	[-0.83; 3.95]	0.201
			Hedges G	0.11	[-0.06; 0.28]	
Other	88 0.67 (1.45)	70 -4.02 (1.67)	Difference	4.69	[0.31; 9.07]	0.036
			Hedges G	0.34	[0.02; 0.65]	
Ki67 status from surgical specimen						
Interaction test	p = 0.629					
Ki67≤20	619 -2.80 (0.58)	591 -3.44 (0.59)	Difference	0.64	[-0.98; 2.26]	0.439
			Hedges G	0.04	[-0.07; 0.16]	
Ki67>20	466 -3.06 (0.69)	473 -4.34 (0.68)	Difference	1.28	[-0.62; 3.18]	0.188
			Hedges G	0.09	[-0.04; 0.21]	
Type of NSAI						
Interaction test	p = 0.610					
Letrozole	848 -3.02 (0.50)	822 -3.61 (0.51)	Difference	0.59	[-0.82; 1.99]	0.412
			Hedges G	0.04	[-0.06; 0.14]	
Anastrozole	475 -2.60 (0.65)	434 -3.90 (0.68)	Difference	1.30	[-0.54; 3.15]	0.167
			Hedges G	0.09	[-0.04; 0.22]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.726					
Yes	1129 -3.06 (0.44)	1052 -4.13 (0.46)	Difference	1.07	[-0.18; 2.32]	0.094
			Hedges G	0.07	[-0.01; 0.16]	
No	194 -1.40 (0.90)	207 -1.99 (0.88)	Difference	0.60	[-1.89; 3.08]	0.636
			Hedges G	0.05	[-0.15; 0.24]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.190					
Yes	656 -3.30 (0.56)	631 -3.47 (0.56)	Difference	0.17	[-1.38; 1.72]	0.830
			Hedges G	0.01	[-0.10; 0.12]	
No	667 -2.39 (0.58)	628 -4.20 (0.60)	Difference	1.81	[0.18; 3.44]	0.029
			Hedges G	0.12	[0.01; 0.23]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	p = 0.071					
Yes	500 -2.76 (0.69)	451 -5.15 (0.73)	Difference	2.39	[0.43; 4.35]	0.017
			Hedges G	0.16	[0.03; 0.28]	
No	823 -2.78 (0.49)	808 -2.99 (0.49)	Difference	0.21	[-1.13; 1.56]	0.755
			Hedges G	0.02	[-0.08; 0.11]	
Prior endocrine therapy						
Interaction test	p = 0.824					
Yes	894 -3.49 (0.49)	865 -4.35 (0.50)	Difference	0.86	[-0.51; 2.22]	0.219
			Hedges G	0.06	[-0.03; 0.15]	
No	429 -1.52 (0.67)	394 -2.60 (0.69)	Difference	1.08	[-0.81; 2.97]	0.262
			Hedges G	0.08	[-0.06; 0.22]	
Prior mastectomy						
Interaction test	p = 0.071					
Yes	808 -2.42 (0.52)	777 -4.18 (0.52)	Difference	1.77	[0.32; 3.21]	0.016
			Hedges G	0.12	[0.02; 0.22]	
No	515 -3.55 (0.63)	482 -3.09 (0.65)	Difference	-0.46	[-2.24; 1.32]	0.613
			Hedges G	-0.03	[-0.16; 0.09]	
Prior radiotherapy						
Interaction test	p = 0.587					
Yes	1177 -2.79 (0.43)	1112 -3.80 (0.44)	Difference	1.01	[-0.19; 2.21]	0.099
			Hedges G	0.07	[-0.01; 0.15]	
No	146 -3.26 (1.15)	147 -3.56 (1.14)	Difference	0.29	[-2.90; 3.49]	0.857
			Hedges G	0.02	[-0.21; 0.25]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed N.E.: Not estimable ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + baseline value ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>* The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

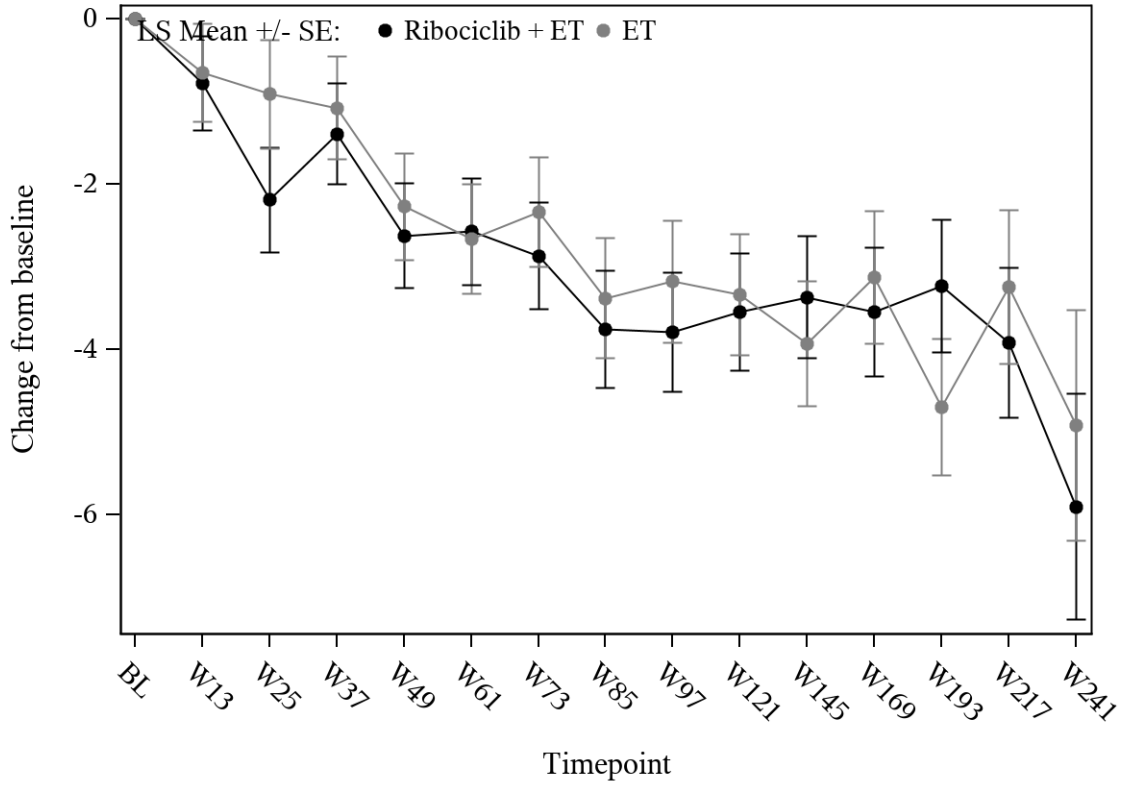
Figure 5-2.2.4.1 QLQ-C30 - Emotional Functioning: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Emotional Functioning
Age group 2 at randomization (median for subpopulation post-menopausal female patients): <Median



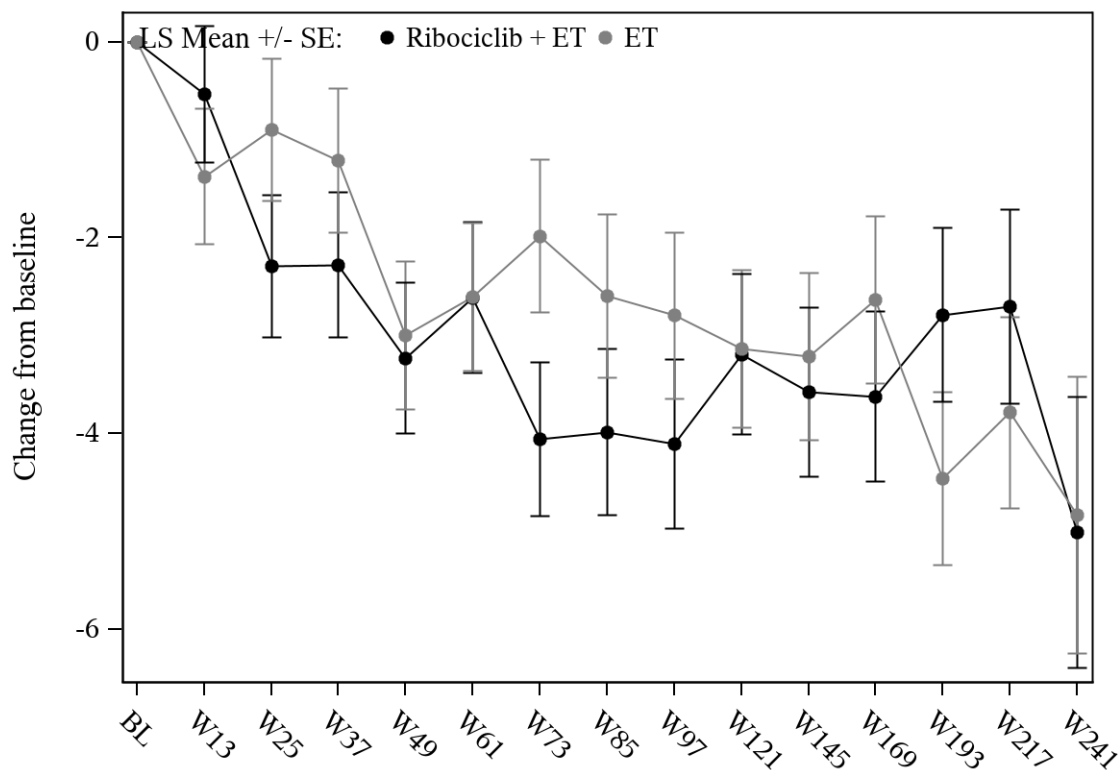
Ribociclib + ET	598	570	540	549	537	529	529	515	510	489	475	400	322	196	33
ET	578	548	524	512	508	503	497	487	477	471	462	384	321	214	38

QLQ-C30 - Emotional Functioning
Age group 2 at randomization (median for subpopulation post-menopausal female patients): \geq Median



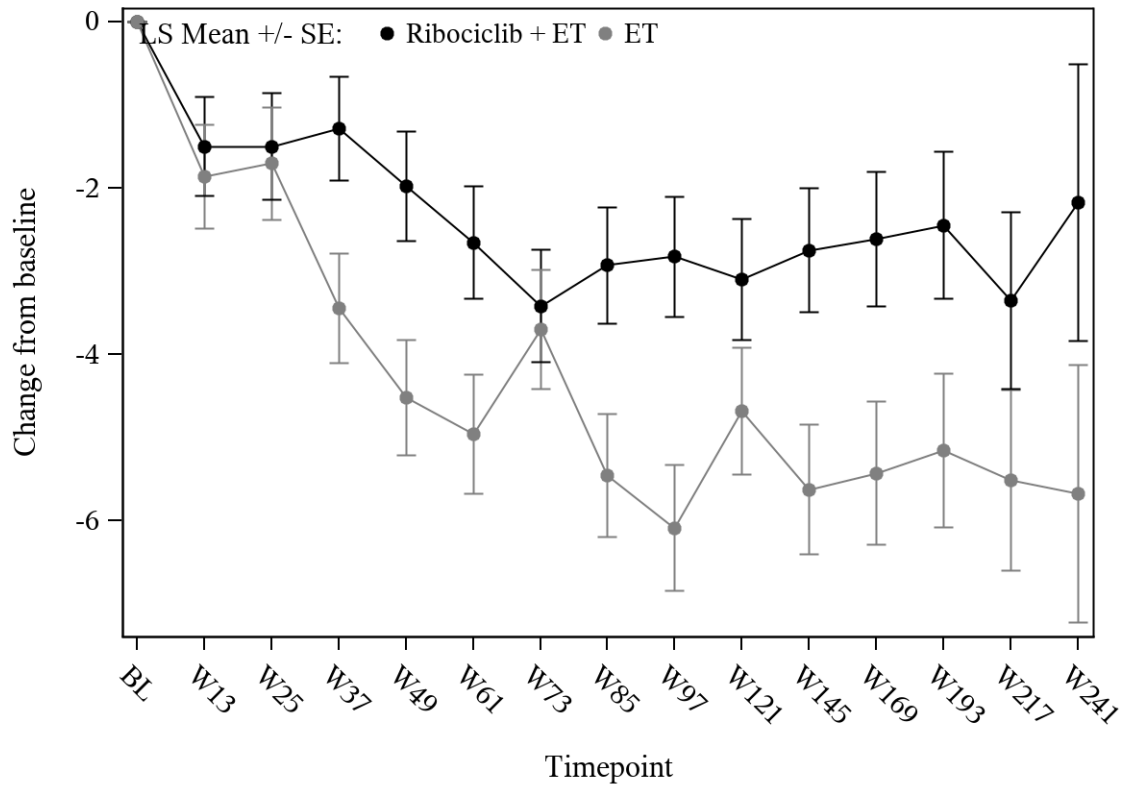
Ribociclib + ET	725	694	677	665	647	640	637	615	616	592	588	507	442	282	58
ET	681	647	623	626	628	607	607	594	585	569	547	483	409	266	56

QLQ-C30 - Emotional Functioning
AJCC Anatomic Stage Group: Group I/II



Ribociclib + ET	542	520	508	500	495	477	484	473	474	461	456	425	433	284	61
ET	551	522	505	504	511	496	492	490	484	476	463	445	432	293	57

QLQ-C30 - Emotional Functioning
AJCC Anatomic Stage Group: Group III



Ribociclib + ET	780	743	708	714	689	692	682	657	652	620	607	482	331	194	30
ET	708	673	642	634	625	614	612	591	578	564	546	422	298	187	37

Table 5-2.2.5.1 QLQ-C30 - Cognitive Functioning: change from baseline analysis - subgroup analysis (Full Analysis Set)

Treatment Groups		Comparison				
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-C30 - Cognitive Functioning						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.765					
NA/WE/O	823 -3.89 (0.53)	771 -4.66 (0.54)	Difference	0.76	[-0.72; 2.24]	0.314
			Hedges G	0.05	[-0.05; 0.15]	
ROW	499 -5.43 (0.62)	489 -5.88 (0.63)	Difference	0.45	[-1.27; 2.18]	0.605
			Hedges G	0.03	[-0.09; 0.16]	
Geographical region						
Interaction test	p = 0.366					
Europe	782 -5.20 (0.52)	772 -6.19 (0.52)	Difference	1.00	[-0.45; 2.44]	0.176
			Hedges G	0.07	[-0.03; 0.17]	
North America/Australia	367 -2.29 (0.67)	324 -2.05 (0.71)	Difference	-0.24	[-2.16; 1.68]	0.805
			Hedges G	-0.02	[-0.17; 0.13]	
Asia	101 -3.63 (1.07)	93 -4.94 (1.21)	Difference	1.31	[-1.90; 4.52]	0.421
			Hedges G	0.12	[-0.17; 0.40]	
Latin America	72 -6.81 (1.85)	71 -5.27 (1.86)	Difference	-1.54	[-6.73; 3.64]	0.558
			Hedges G	-0.10	[-0.43; 0.23]	
Age group 1 at randomization						
Interaction test	p = 0.851					
<45	56 -7.62 (2.35)	48 -6.55 (2.57)	Difference	-1.07	[-7.99; 5.86]	0.760
			Hedges G	-0.06	[-0.45; 0.33]	
45 to 54	284 -4.67 (0.93)	290 -6.36 (0.92)	Difference	1.69	[-0.88; 4.26]	0.197
			Hedges G	0.11	[-0.06; 0.27]	
55 to 64	613 -4.29 (0.56)	601 -4.38 (0.56)	Difference	0.09	[-1.46; 1.63]	0.911
			Hedges G	0.01	[-0.11; 0.12]	
≥65	369 -4.29 (0.64)	321 -5.05 (0.68)	Difference	0.76	[-1.07; 2.60]	0.415
			Hedges G	0.06	[-0.09; 0.21]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.020					
<Median	598 -4.17 (0.66)	579 -6.17 (0.67)	Difference	2.01	[0.17; 3.84]	0.032
			Hedges G	0.12	[0.01; 0.24]	
≥Median	724 -4.78 (0.49)	681 -4.13 (0.50)	Difference	-0.66	[-2.03; 0.72]	0.349
			Hedges G	-0.05	[-0.15; 0.05]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.550					
Asian	125 -2.57 (0.94)	116 -4.27 (1.05)	Difference	1.70	[-1.09; 4.48]	0.231
			Hedges G	0.15	[-0.10; 0.41]	
Non-Asian	1122 -4.76 (0.43)	1083 -5.20 (0.44)	Difference	0.44	[-0.77; 1.64]	0.478
			Hedges G	0.03	[-0.05; 0.11]	
BMI at screening						
Interaction test	p = 0.987					
≥25	873 -4.64 (0.50)	860 -5.30 (0.50)	Difference	0.66	[-0.72; 2.04]	0.350
			Hedges G	0.04	[-0.05; 0.14]	
<25	438 -4.36 (0.69)	388 -4.78 (0.73)	Difference	0.41	[-1.56; 2.39]	0.681
			Hedges G	0.03	[-0.11; 0.17]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.039					
Group I/II	542 -4.66 (0.62)	552 -3.98 (0.61)	Difference	-0.68	[-2.39; 1.04]	0.439
			Hedges G	-0.05	[-0.17; 0.07]	
Group III	779 -4.33 (0.53)	708 -6.06 (0.55)	Difference	1.73	[0.22; 3.23]	0.024
			Hedges G	0.12	[0.02; 0.22]	
Anatomic stages						
Interaction test	p = 0.276					
IA/IB/IIA	285 -4.55 (0.82)	291 -3.46 (0.82)	Difference	-1.09	[-3.37; 1.20]	0.351
			Hedges G	-0.08	[-0.24; 0.09]	
IIB	257 -4.71 (0.91)	261 -4.53 (0.90)	Difference	-0.18	[-2.69; 2.33]	0.888
			Hedges G	-0.01	[-0.18; 0.16]	
IIIA	460 -5.43 (0.69)	413 -6.92 (0.71)	Difference	1.49	[-0.46; 3.44]	0.134
			Hedges G	0.10	[-0.03; 0.23]	
IIIB	92 -4.70 (1.57)	78 -5.13 (1.71)	Difference	0.42	[-4.16; 5.01]	0.855
			Hedges G	0.03	[-0.27; 0.33]	
IIIC	227 -2.13 (0.91)	217 -4.62 (0.93)	Difference	2.49	[-0.07; 5.06]	0.057
			Hedges G	0.18	[-0.01; 0.37]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.503					
N0	175 -4.36 (1.03)	188 -4.06 (1.00)	Difference	-0.30	[-3.12; 2.53]	0.836
			Hedges G	-0.02	[-0.23; 0.18]	
N1-N3	1144 -4.54 (0.44)	1072 -5.30 (0.45)	Difference	0.76	[-0.47; 2.00]	0.224
			Hedges G	0.05	[-0.03; 0.14]	

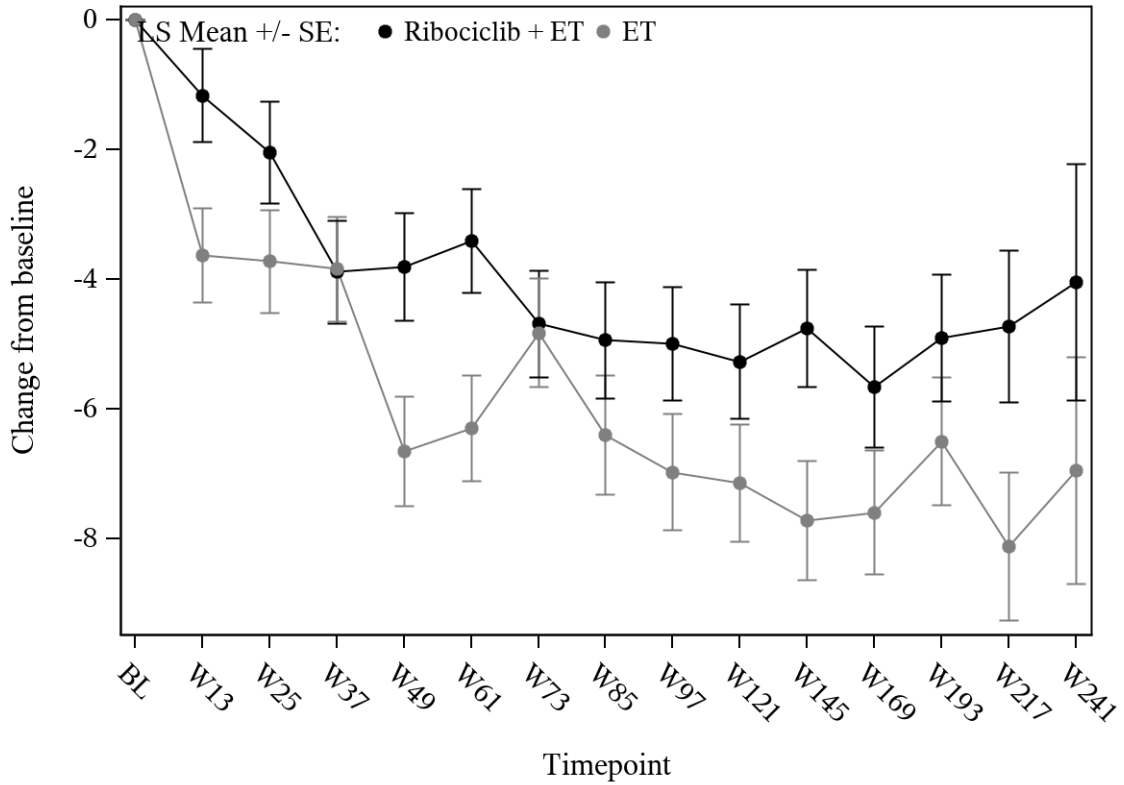
Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.240					
Grade 1	94 -5.61 (1.36)	102 -5.91 (1.25)	Difference	0.30	[-3.35; 3.95]	0.871
			Hedges G	0.02	[-0.26; 0.30]	
Grade 2	785 -4.52 (0.48)	703 -4.21 (0.50)	Difference	-0.30	[-1.67; 1.06]	0.662
			Hedges G	-0.02	[-0.12; 0.08]	
Grade 3	357 -4.18 (0.80)	370 -5.93 (0.79)	Difference	1.76	[-0.45; 3.96]	0.119
			Hedges G	0.12	[-0.03; 0.26]	
Histological subtype						
Interaction test	p = 0.275					
Ductal	956 -4.56 (0.46)	928 -4.89 (0.46)	Difference	0.33	[-0.94; 1.60]	0.611
			Hedges G	0.02	[-0.07; 0.11]	
Lobular	278 -3.97 (0.82)	262 -5.07 (0.84)	Difference	1.10	[-1.19; 3.40]	0.345
			Hedges G	0.08	[-0.09; 0.25]	
Other	87 -3.51 (1.54)	70 -7.70 (1.75)	Difference	4.19	[-0.43; 8.81]	0.075
			Hedges G	0.29	[-0.03; 0.60]	
Ki67 status from surgical specimen						
Interaction test	p = 0.261					
Ki67≤20	618 -5.21 (0.57)	591 -5.42 (0.58)	Difference	0.21	[-1.39; 1.80]	0.800
			Hedges G	0.01	[-0.10; 0.13]	
Ki67>20	466 -4.28 (0.70)	474 -6.01 (0.70)	Difference	1.73	[-0.21; 3.68]	0.081
			Hedges G	0.11	[-0.01; 0.24]	
Type of NSAI						
Interaction test	p = 0.043					
Letrozole	847 -5.03 (0.51)	822 -4.71 (0.51)	Difference	-0.32	[-1.73; 1.10]	0.658
			Hedges G	-0.02	[-0.12; 0.07]	
Anastrozole	475 -3.63 (0.66)	435 -5.73 (0.70)	Difference	2.09	[0.20; 3.98]	0.030
			Hedges G	0.14	[0.01; 0.27]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.075					
Yes	1128 -3.94 (0.44)	1053 -4.99 (0.46)	Difference	1.05	[-0.21; 2.30]	0.102
			Hedges G	0.07	[-0.01; 0.15]	
No	194 -7.36 (0.94)	207 -5.70 (0.92)	Difference	-1.66	[-4.25; 0.93]	0.209
			Hedges G	-0.13	[-0.32; 0.07]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.805					
Yes	656 -4.36 (0.57)	632 -4.70 (0.57)	Difference	0.34	[-1.23; 1.92]	0.670
			Hedges G	0.02	[-0.09; 0.13]	
No	666 -4.74 (0.57)	628 -5.51 (0.59)	Difference	0.77	[-0.84; 2.38]	0.349
			Hedges G	0.05	[-0.06; 0.16]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	p = 0.049					
Yes	499 -3.53 (0.68)	451 -5.69 (0.71)	Difference	2.17	[0.24; 4.10]	0.028
			Hedges G	0.14	[0.02; 0.27]	
No	823 -5.10 (0.49)	809 -4.89 (0.50)	Difference	-0.21	[-1.58; 1.16]	0.766
			Hedges G	-0.01	[-0.11; 0.08]	
Prior endocrine therapy						
Interaction test	p = 0.395					
Yes	894 -4.28 (0.47)	866 -5.35 (0.47)	Difference	1.08	[-0.23; 2.38]	0.107
			Hedges G	0.08	[-0.02; 0.17]	
No	428 -4.76 (0.68)	394 -4.59 (0.71)	Difference	-0.17	[-2.11; 1.76]	0.862
			Hedges G	-0.01	[-0.15; 0.12]	
Prior mastectomy						
Interaction test	p = 0.043					
Yes	808 -4.34 (0.54)	777 -5.83 (0.55)	Difference	1.49	[-0.02; 3.01]	0.054
			Hedges G	0.10	[-0.00; 0.20]	
No	514 -4.88 (0.59)	483 -3.93 (0.60)	Difference	-0.95	[-2.60; 0.70]	0.260
			Hedges G	-0.07	[-0.20; 0.05]	
Prior radiotherapy						
Interaction test	p = 0.912					
Yes	1176 -4.26 (0.43)	1113 -4.92 (0.44)	Difference	0.66	[-0.54; 1.86]	0.284
			Hedges G	0.04	[-0.04; 0.13]	
No	146 -6.17 (1.19)	147 -6.58 (1.18)	Difference	0.40	[-2.89; 3.69]	0.809
			Hedges G	0.03	[-0.20; 0.26]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: $\text{change from baseline} = \text{treatment} + \text{visit} + \text{treatment} * \text{visit} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor} + \text{subgroup factor} * \text{visit} + \text{treatment} * \text{subgroup factor} * \text{visit} + \text{baseline value}$ If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: $\text{change from baseline} = \text{treatment} + \text{visit} + \text{treatment} * \text{visit} + \text{baseline value}$ ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>† The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

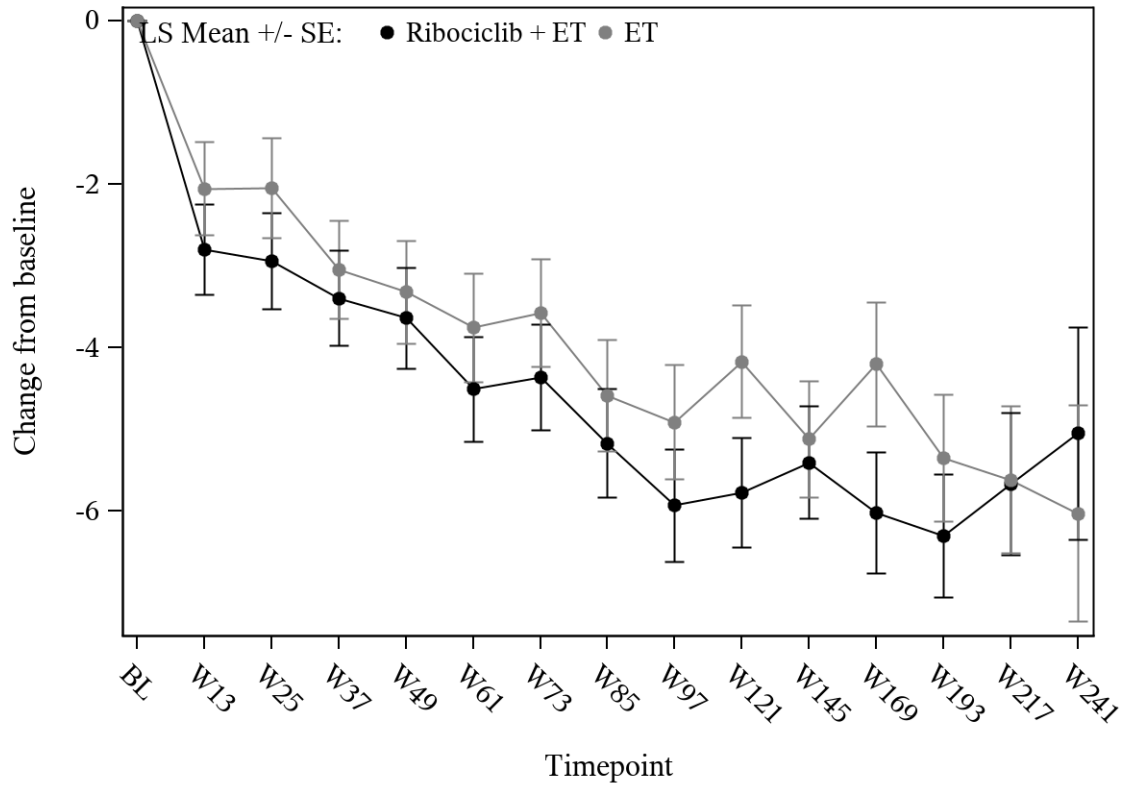
Figure 5-2.2.5.1 QLQ-C30 - Cognitive Functioning: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Cognitive Functioning
Age group 2 at randomization (median for subpopulation post-menopausal female patients): <Median



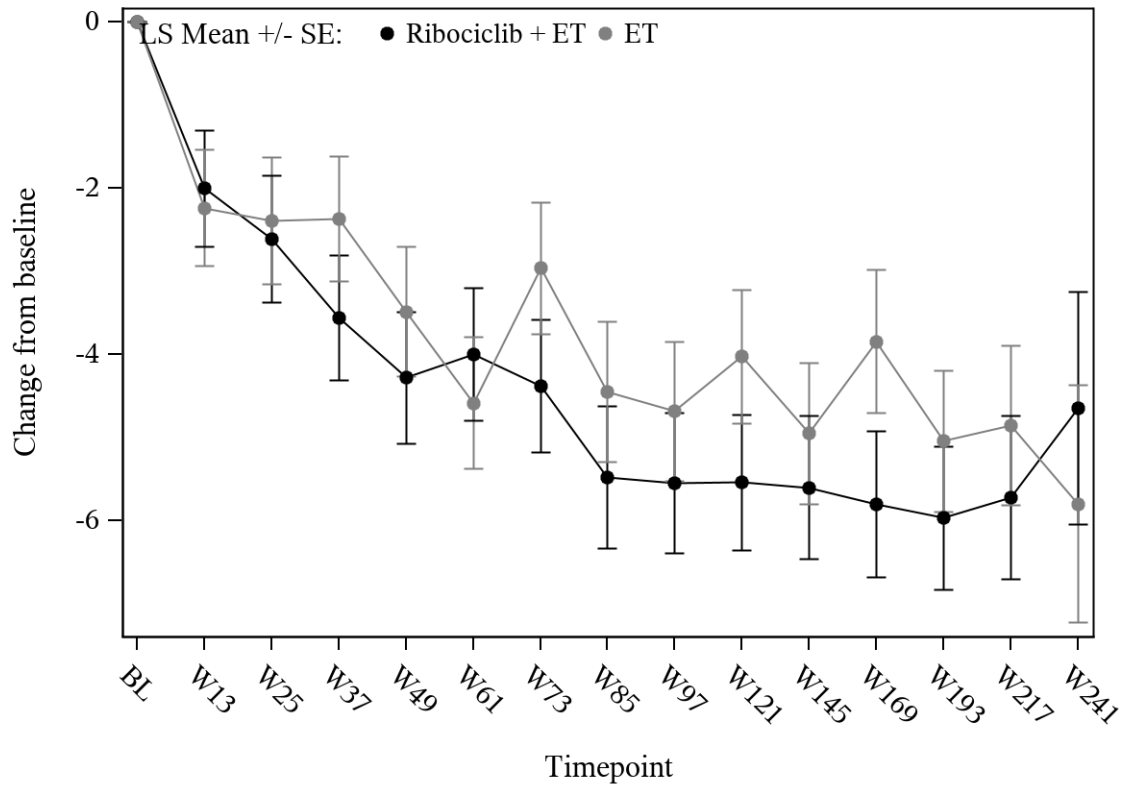
Ribociclib + ET	598	570	540	549	537	529	529	515	510	489	475	400	322	196	33
ET	579	549	525	513	509	504	498	488	478	472	463	385	322	215	38

QLQ-C30 - Cognitive Functioning
Age group 2 at randomization (median for subpopulation post-menopausal female patients): \geq Median



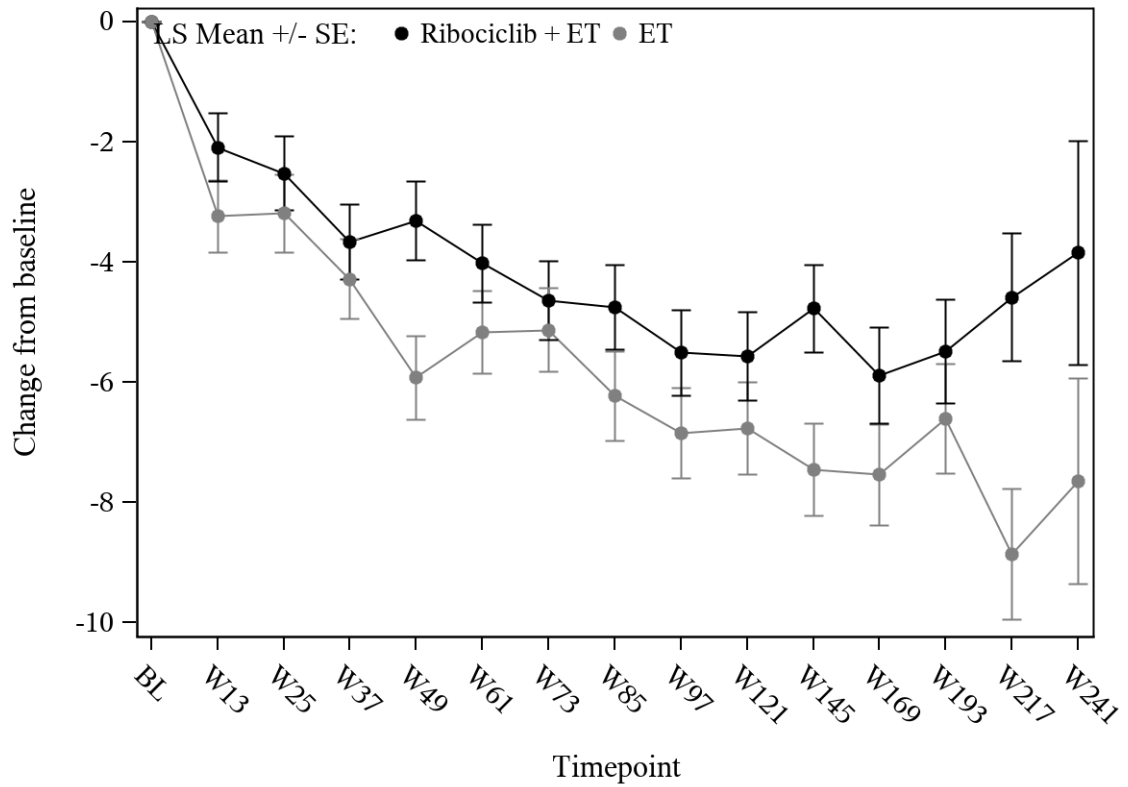
Ribociclib + ET	724	693	676	664	646	639	636	614	615	591	587	506	442	282	58
ET	681	647	623	626	628	607	607	593	586	570	547	484	409	266	56

QLQ-C30 - Cognitive Functioning
AJCC Anatomic Stage Group: Group I/II



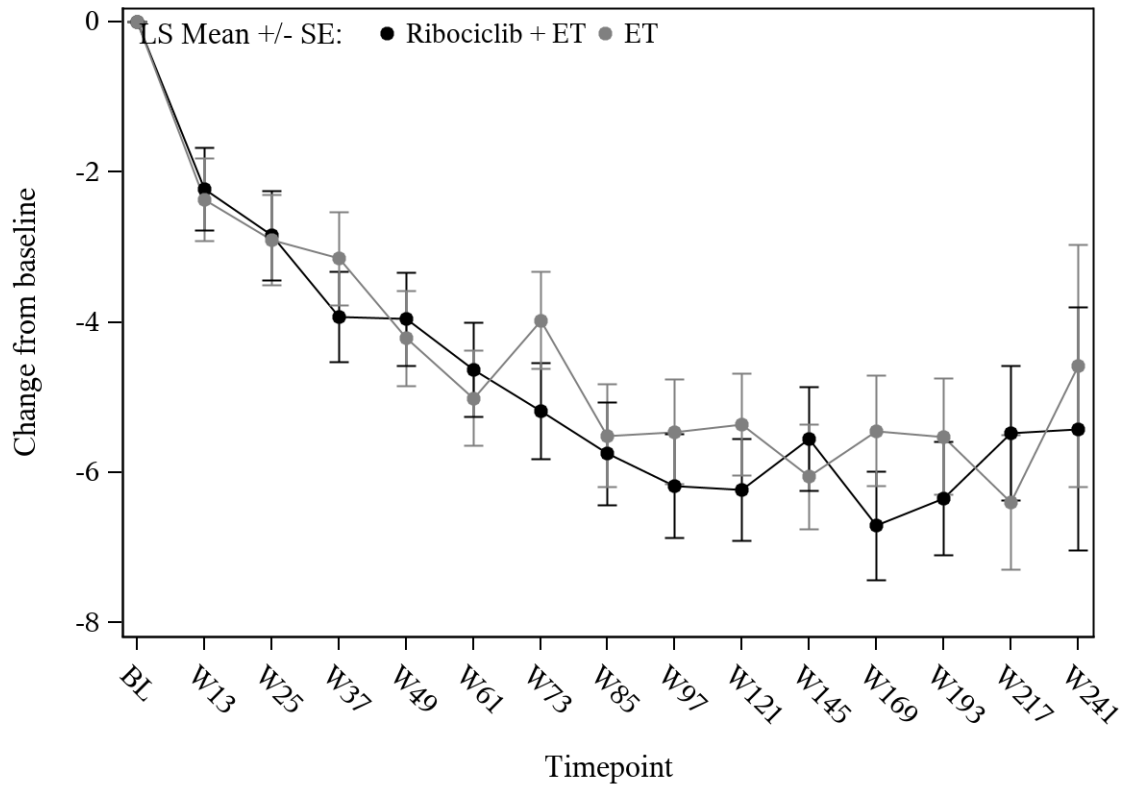
Ribociclib + ET	542	520	508	500	495	477	484	473	474	461	456	425	433	284	61
ET	552	523	506	505	512	497	493	491	485	477	464	446	433	294	57

QLQ-C30 - Cognitive Functioning
AJCC Anatomic Stage Group: Group III



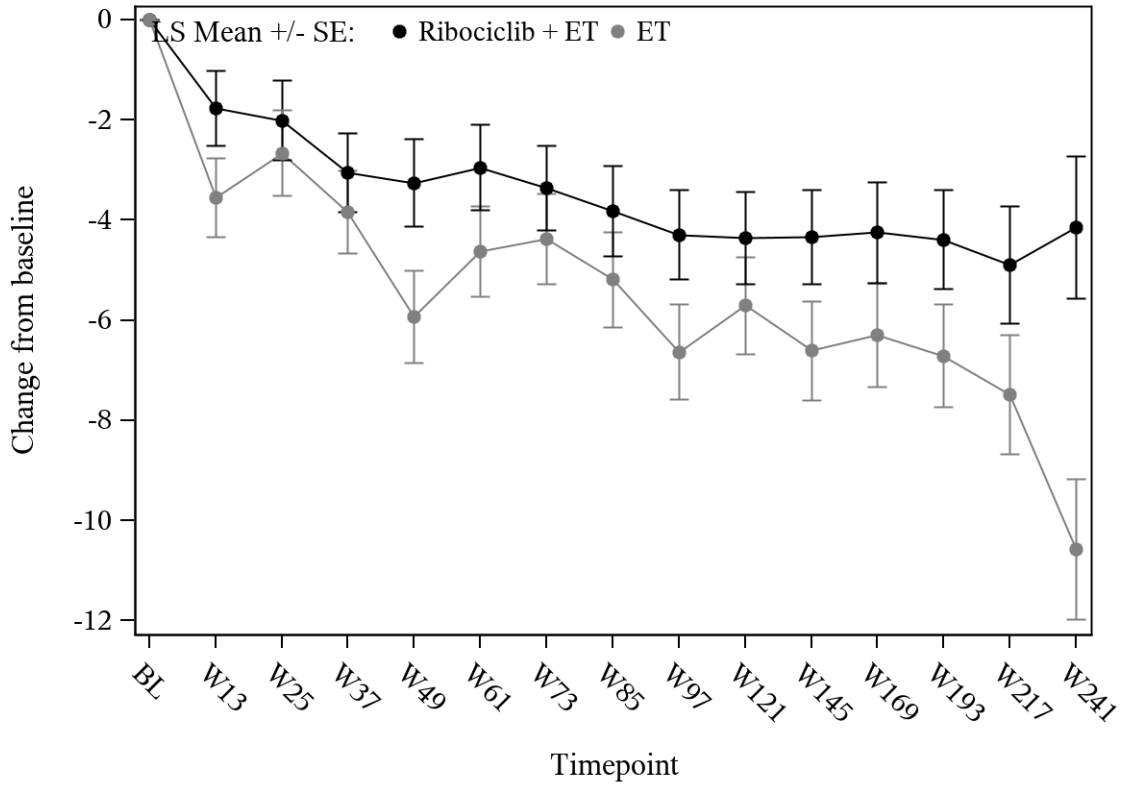
Ribociclib + ET	779	742	707	713	688	691	681	656	651	619	606	481	331	194	30
ET	708	673	642	634	625	614	612	590	579	565	546	423	298	187	37

QLQ-C30 - Cognitive Functioning
Type of NSAI: Letrozole



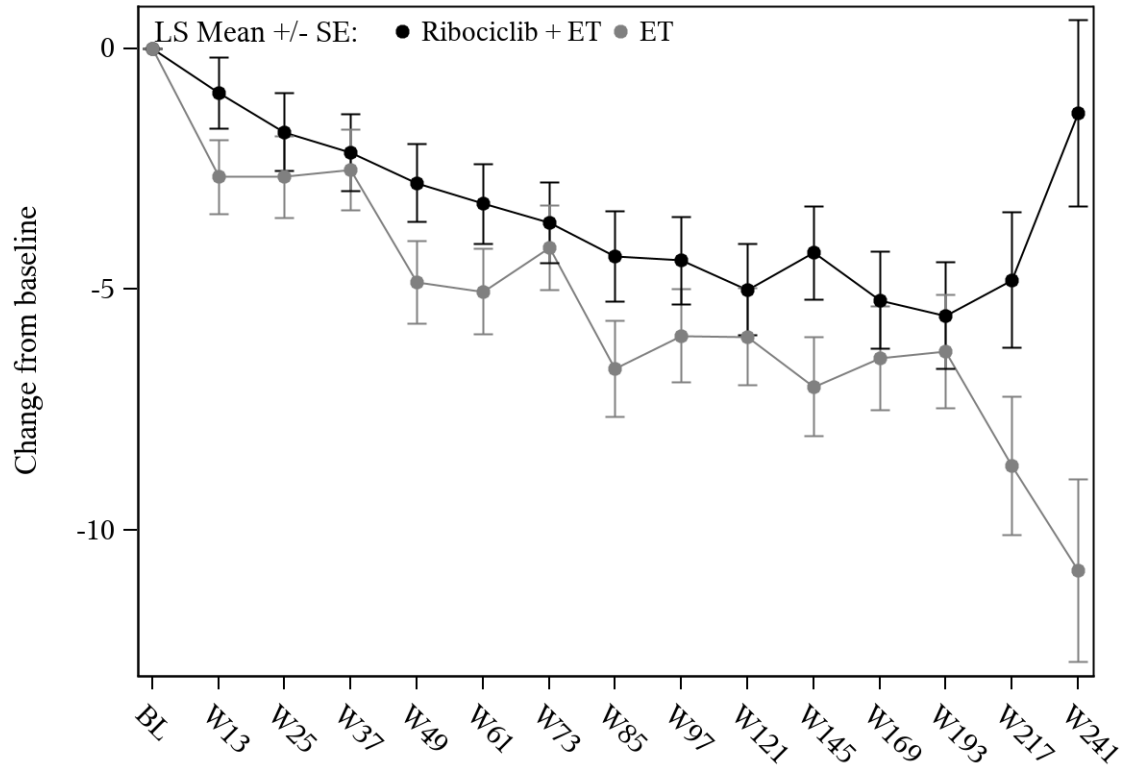
Ribociclib + ET	847	804	772	778	756	751	746	726	723	709	694	607	509	313	51
ET	822	784	759	737	749	739	741	720	717	703	679	581	486	311	52

QLQ-C30 - Cognitive Functioning
Type of NSAI: Anastrozole



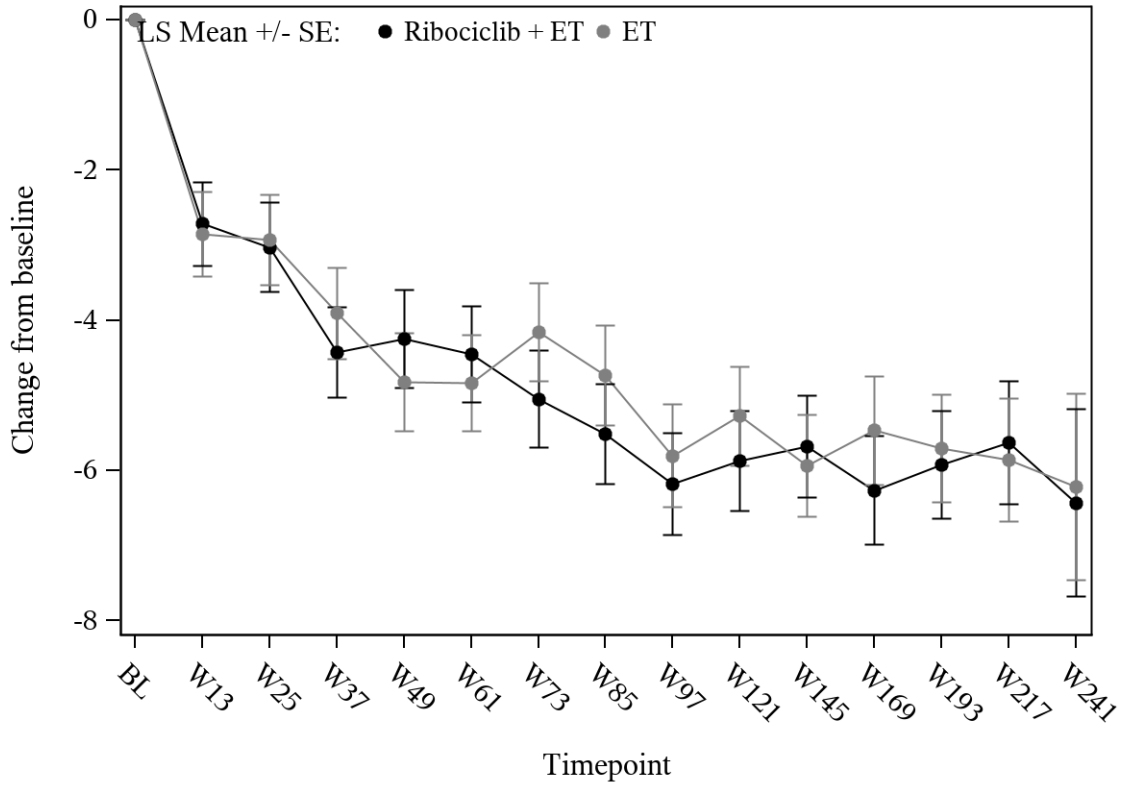
Ribociclib + ET	475	459	444	435	427	417	419	403	402	371	368	299	255	165	40
ET	435	411	388	401	388	370	364	361	346	339	330	288	245	170	42

QLQ-C30 - Cognitive Functioning
Prior neoadjuvant chemotherapy: Yes



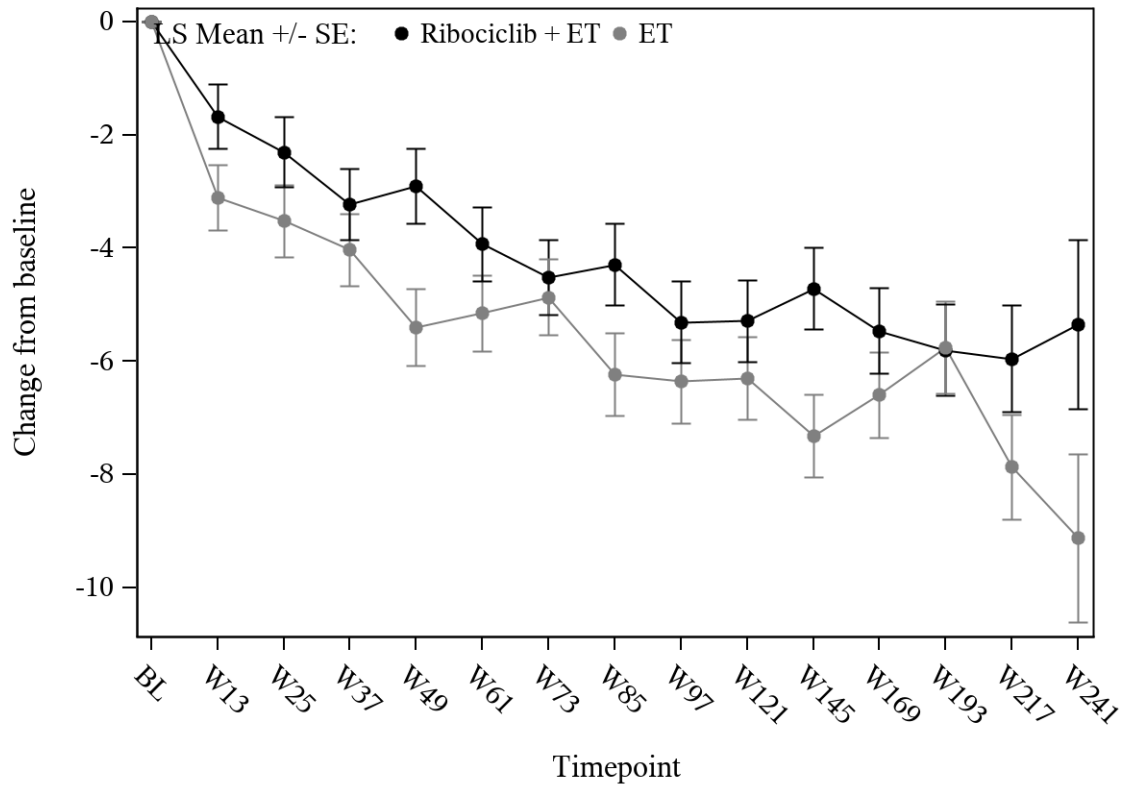
Ribociclib + ET	499	475	463	450	448	440	436	425	420	400	391	311	240	139	24
ET	451	432	411	396	394	387	385	373	362	352	345	272	215	138	25

QLQ-C30 - Cognitive Functioning
Prior neoadjuvant chemotherapy: No



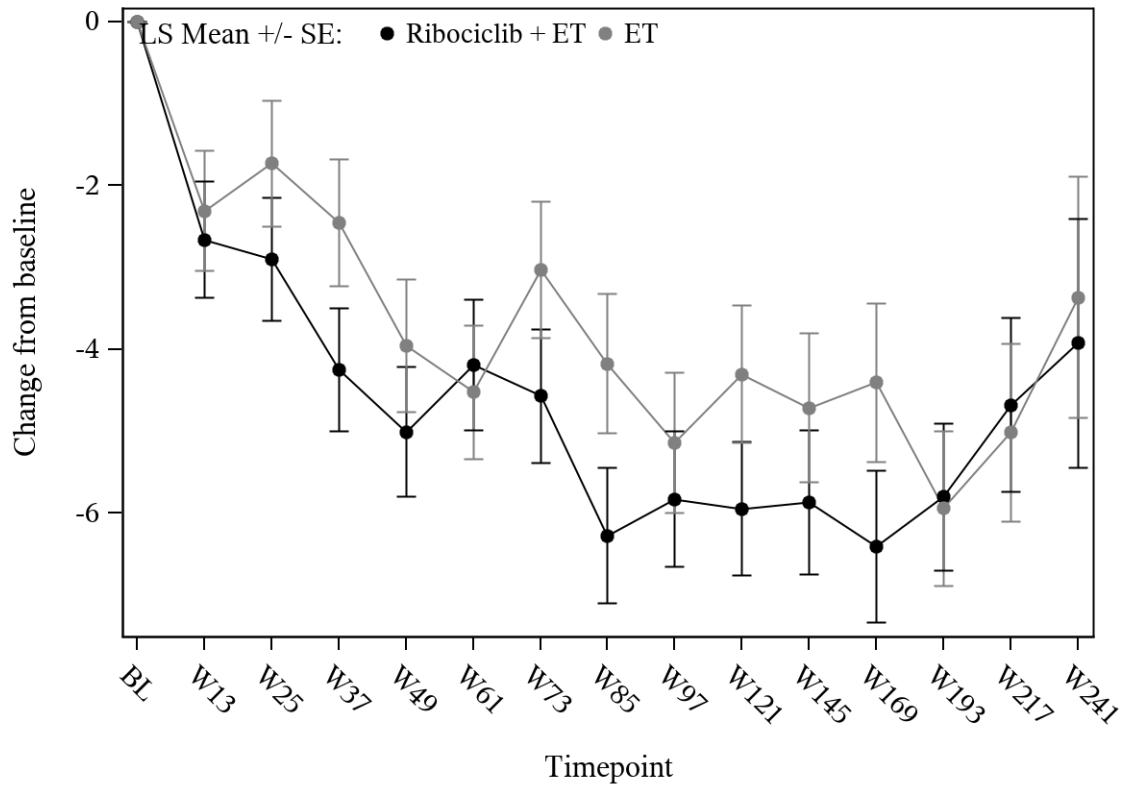
Ribociclib + ET	823	788	753	763	735	728	729	704	705	680	671	595	524	339	67
ET	809	764	737	743	743	724	720	708	702	690	665	597	516	343	69

QLQ-C30 - Cognitive Functioning
Prior mastectomy: Yes



Ribociclib + ET	808	769	761	742	728	725	716	683	681	648	633	519	413	271	57
ET	777	742	704	704	700	686	680	667	655	639	622	519	421	285	57

QLQ-C30 - Cognitive Functioning
Prior mastectomy: No



Ribociclib + ET	514	494	455	471	455	443	449	446	444	432	429	387	351	207	34
ET	483	454	444	435	437	425	425	414	409	403	388	350	310	196	37

Table 5-2.2.6.1 QLQ-C30 - Social Functioning: change from baseline analysis - subgroup analysis (Full Analysis Set)

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-C30 - Social Functioning						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.534					
NA/WE/O	824 0.01 (0.53)	770 0.19 (0.55)	Difference	-0.18	[-1.68; 1.31]	0.811
			Hedges G	-0.01	[-0.11; 0.09]	
ROW	499 -0.04 (0.67)	489 0.46 (0.68)	Difference	-0.50	[-2.37; 1.38]	0.604
			Hedges G	-0.03	[-0.16; 0.09]	
Geographical region						
Interaction test	p = 0.802					
Europe	783 0.03 (0.54)	771 0.42 (0.54)	Difference	-0.40	[-1.90; 1.10]	0.601
			Hedges G	-0.03	[-0.13; 0.07]	
North America/Australia	367 0.10 (0.68)	324 0.43 (0.72)	Difference	-0.33	[-2.28; 1.62]	0.741
			Hedges G	-0.03	[-0.17; 0.12]	
Asia	101 -0.31 (1.42)	93 -1.03 (1.59)	Difference	0.72	[-3.49; 4.93]	0.736
			Hedges G	0.05	[-0.23; 0.33]	
Latin America	72 -0.07 (1.77)	71 0.33 (1.79)	Difference	-0.40	[-5.39; 4.59]	0.873
			Hedges G	-0.03	[-0.35; 0.30]	
Age group 1 at randomization						
Interaction test	p = 0.522					
<45	56 -2.51 (2.27)	48 -1.98 (2.48)	Difference	-0.53	[-7.21; 6.15]	0.876
			Hedges G	-0.03	[-0.42; 0.35]	
45 to 54	284 0.42 (0.96)	290 -0.06 (0.95)	Difference	0.48	[-2.18; 3.13]	0.725
			Hedges G	0.03	[-0.13; 0.19]	
55 to 64	613 1.26 (0.57)	601 1.02 (0.57)	Difference	0.23	[-1.36; 1.83]	0.776
			Hedges G	0.02	[-0.10; 0.13]	
≥65	370 -1.69 (0.69)	320 -0.18 (0.74)	Difference	-1.51	[-3.51; 0.49]	0.138
			Hedges G	-0.11	[-0.26; 0.04]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.065					
<Median	598 0.61 (0.67)	579 -0.09 (0.68)	Difference	0.71	[-1.16; 2.57]	0.457
			Hedges G	0.04	[-0.07; 0.16]	
≥Median	725 -0.41 (0.52)	680 0.80 (0.53)	Difference	-1.21	[-2.67; 0.25]	0.104
			Hedges G	-0.09	[-0.19; 0.02]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.951					
Asian	125 0.46 (1.20)	116 0.48 (1.33)	Difference	-0.02	[-3.55; 3.51]	0.991
			Hedges G	-0.00	[-0.25; 0.25]	
Non-Asian	1122 0.14 (0.45)	1082 0.47 (0.45)	Difference	-0.32	[-1.57; 0.92]	0.609
			Hedges G	-0.02	[-0.11; 0.06]	
BMI at screening						
Interaction test	p = 0.880					
≥25	873 -0.10 (0.52)	859 0.13 (0.53)	Difference	-0.22	[-1.68; 1.24]	0.764
			Hedges G	-0.01	[-0.11; 0.08]	
<25	439 -0.18 (0.71)	388 0.36 (0.75)	Difference	-0.53	[-2.56; 1.49]	0.604
			Hedges G	-0.04	[-0.17; 0.10]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.197					
Group I/II	542 0.42 (0.63)	552 1.38 (0.62)	Difference	-0.95	[-2.70; 0.79]	0.283
			Hedges G	-0.06	[-0.18; 0.05]	
Group III	780 -0.21 (0.57)	707 -0.70 (0.59)	Difference	0.49	[-1.12; 2.10]	0.554
			Hedges G	0.03	[-0.07; 0.13]	
Anatomic stages						
Interaction test	p = 0.736					
IA/IB/IIA	285 0.79 (0.77)	291 1.49 (0.76)	Difference	-0.70	[-2.82; 1.43]	0.520
			Hedges G	-0.05	[-0.22; 0.11]	
IIB	257 0.09 (0.95)	261 1.58 (0.94)	Difference	-1.49	[-4.12; 1.13]	0.265
			Hedges G	-0.10	[-0.27; 0.07]	
IIIA	460 -0.80 (0.73)	413 -1.41 (0.74)	Difference	0.61	[-1.43; 2.65]	0.560
			Hedges G	0.04	[-0.09; 0.17]	
IIIB	92 0.91 (1.58)	78 1.68 (1.73)	Difference	-0.77	[-5.40; 3.86]	0.742
			Hedges G	-0.05	[-0.35; 0.25]	
IIIC	228 0.57 (0.99)	216 -0.32 (1.02)	Difference	0.88	[-1.91; 3.67]	0.534
			Hedges G	0.06	[-0.13; 0.25]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.731					
N0	175 0.38 (1.06)	188 0.10 (1.03)	Difference	0.28	[-2.63; 3.18]	0.852
			Hedges G	0.02	[-0.19; 0.23]	
N1-N3	1145 -0.05 (0.46)	1071 0.33 (0.47)	Difference	-0.38	[-1.67; 0.92]	0.569
			Hedges G	-0.02	[-0.11; 0.06]	

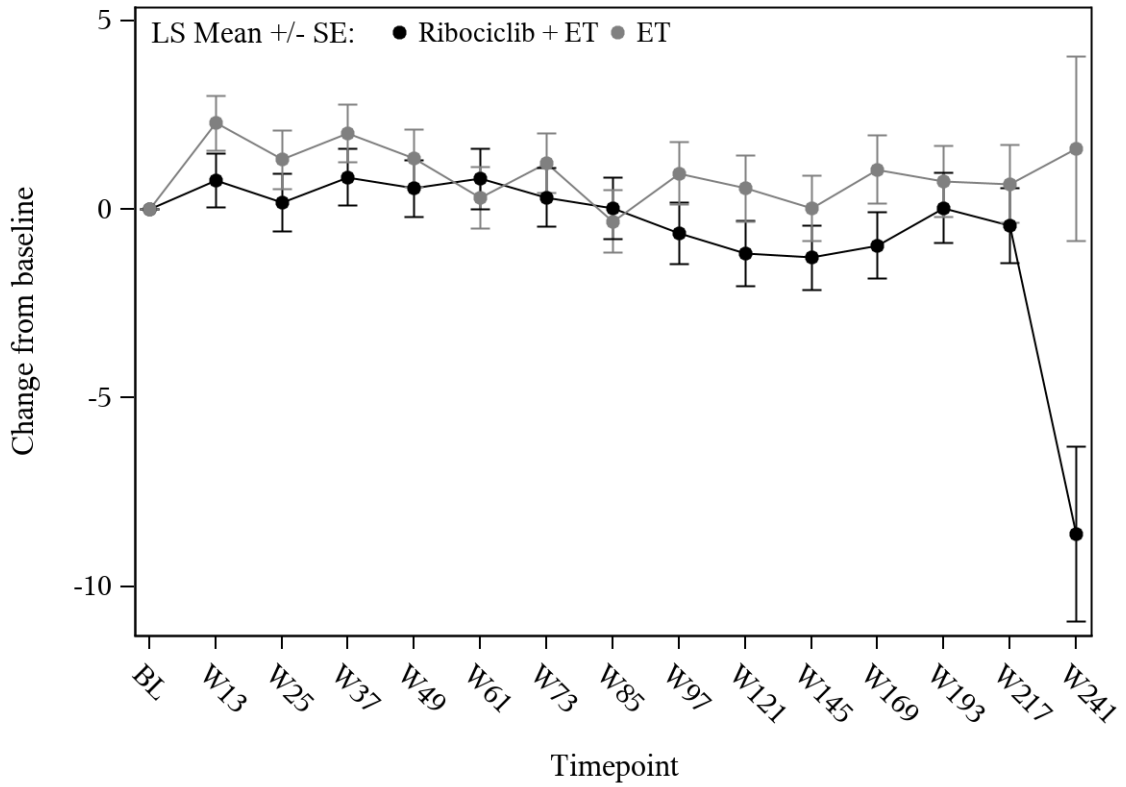
Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.905					
Grade 1	94 0.57 (1.38)	102 0.78 (1.27)	Difference	-0.21	[-3.96; 3.54]	0.912
			Hedges G	-0.02	[-0.30; 0.26]	
Grade 2	786 0.28 (0.50)	702 1.05 (0.53)	Difference	-0.76	[-2.19; 0.66]	0.293
			Hedges G	-0.05	[-0.16; 0.05]	
Grade 3	357 -0.42 (0.83)	370 -0.05 (0.82)	Difference	-0.36	[-2.66; 1.94]	0.757
			Hedges G	-0.02	[-0.17; 0.12]	
Histological subtype						
Interaction test	p = 0.322					
Ductal	956 -0.00 (0.48)	927 0.69 (0.48)	Difference	-0.69	[-2.03; 0.64]	0.306
			Hedges G	-0.05	[-0.14; 0.04]	
Lobular	278 -0.31 (0.86)	262 -0.86 (0.88)	Difference	0.55	[-1.85; 2.96]	0.652
			Hedges G	0.04	[-0.13; 0.21]	
Other	88 2.28 (1.53)	70 -1.39 (1.75)	Difference	3.67	[-0.93; 8.28]	0.117
			Hedges G	0.25	[-0.06; 0.57]	
Ki67 status from surgical specimen						
Interaction test	p = 0.013					
Ki67≤20	619 -0.68 (0.61)	590 0.99 (0.62)	Difference	-1.67	[-3.38; 0.05]	0.056
			Hedges G	-0.11	[-0.22; 0.00]	
Ki67>20	466 0.62 (0.73)	474 -1.08 (0.73)	Difference	1.70	[-0.33; 3.73]	0.101
			Hedges G	0.11	[-0.02; 0.24]	
Type of NSAI						
Interaction test	p = 0.835					
Letrozole	848 0.10 (0.52)	821 0.46 (0.53)	Difference	-0.35	[-1.81; 1.11]	0.635
			Hedges G	-0.02	[-0.12; 0.07]	
Anastrozole	475 -0.31 (0.71)	435 -0.16 (0.74)	Difference	-0.15	[-2.16; 1.86]	0.883
			Hedges G	-0.01	[-0.14; 0.12]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.449					
Yes	1129 0.54 (0.45)	1052 0.60 (0.47)	Difference	-0.07	[-1.34; 1.21]	0.920
			Hedges G	-0.00	[-0.09; 0.08]	
No	194 -2.07 (1.07)	207 -1.11 (1.05)	Difference	-0.96	[-3.91; 2.00]	0.525
			Hedges G	-0.06	[-0.26; 0.13]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.554					
Yes	656 0.50 (0.57)	632 1.08 (0.58)	Difference	-0.58	[-2.18; 1.02]	0.477
			Hedges G	-0.04	[-0.15; 0.07]	
No	667 -0.48 (0.61)	627 -0.73 (0.63)	Difference	0.24	[-1.48; 1.97]	0.782
			Hedges G	0.02	[-0.09; 0.12]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	p = 0.138					
Yes	500 0.68 (0.69)	450 -0.41 (0.73)	Difference	1.08	[-0.89; 3.06]	0.282
			Hedges G	0.07	[-0.06; 0.20]	
No	823 -0.24 (0.52)	809 0.58 (0.52)	Difference	-0.82	[-2.27; 0.63]	0.267
			Hedges G	-0.05	[-0.15; 0.04]	
Prior endocrine therapy						
Interaction test	p = 0.399					
Yes	894 -0.91 (0.52)	866 -0.30 (0.52)	Difference	-0.61	[-2.06; 0.83]	0.405
			Hedges G	-0.04	[-0.13; 0.05]	
No	429 2.20 (0.70)	393 1.54 (0.73)	Difference	0.66	[-1.33; 2.64]	0.516
			Hedges G	0.05	[-0.09; 0.18]	
Prior mastectomy						
Interaction test	p = 0.368					
Yes	808 0.10 (0.55)	776 -0.08 (0.56)	Difference	0.18	[-1.37; 1.72]	0.821
			Hedges G	0.01	[-0.09; 0.11]	
No	515 -0.27 (0.64)	483 0.88 (0.66)	Difference	-1.14	[-2.94; 0.66]	0.213
			Hedges G	-0.08	[-0.20; 0.05]	
Prior radiotherapy						
Interaction test	p = 0.607					
Yes	1177 0.14 (0.43)	1112 0.23 (0.44)	Difference	-0.08	[-1.29; 1.12]	0.892
			Hedges G	-0.01	[-0.09; 0.08]	
No	146 -0.11 (1.19)	147 0.65 (1.18)	Difference	-0.76	[-4.06; 2.55]	0.653
			Hedges G	-0.05	[-0.28; 0.18]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: $\text{change from baseline} = \text{treatment} + \text{visit} + \text{treatment} * \text{visit} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor} + \text{subgroup factor} * \text{visit} + \text{treatment} * \text{subgroup factor} * \text{visit} + \text{baseline value}$ If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: $\text{change from baseline} = \text{treatment} + \text{visit} + \text{treatment} * \text{visit} + \text{baseline value}$ ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>† The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

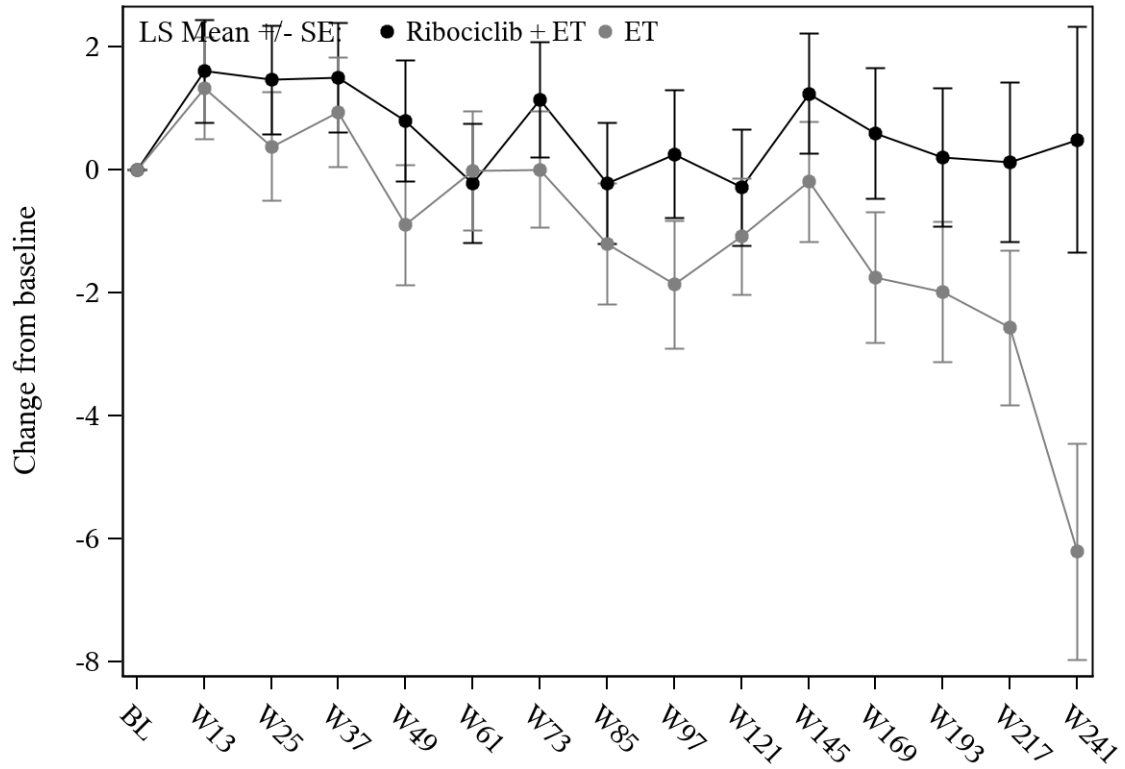
Figure 5-2.2.6.1 QLQ-C30 - Social Functioning: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-C30 - Social Functioning
Ki67 status from surgical specimen: Ki67 \leq 20



Ribociclib + ET	619	597	568	568	549	548	538	531	533	515	506	438	352	217	39
ET	590	561	538	535	536	530	523	513	507	499	483	412	343	210	35

QLQ-C30 - Social Functioning
Ki67 status from surgical specimen: Ki67>20



Ribociclib + ET	466	449	441	433	424	421	419	405	400	388	377	326	293	169	33
ET	474	455	438	429	423	416	416	405	398	386	374	325	284	189	38

5-2.3 EORTC QLQ-BR23 Symptoms

Table 5-2.3.1.1 QLQ-BR23 - Side Effects Of Systemic Therapy: change from baseline analysis - subgroup analysis (Full Analysis Set)

Treatment Groups		Comparison				
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-BR23 - Side Effects Of Systemic Therapy						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.609					
NA/WE/O	831 4.47 (0.38)	768 3.10 (0.39)	Difference	1.37	[0.29; 2.44]	0.013
			Hedges G	0.13	[0.03; 0.22]	
ROW	498 3.77 (0.50)	489 2.84 (0.50)	Difference	0.93	[-0.45; 2.31]	0.188
			Hedges G	0.08	[-0.04; 0.21]	
Geographical region						
Interaction test	p = 0.224					
Europe	787 4.41 (0.39)	771 2.89 (0.39)	Difference	1.52	[0.44; 2.61]	0.006
			Hedges G	0.14	[0.04; 0.24]	
North America/Australia	370 3.14 (0.48)	322 2.29 (0.51)	Difference	0.86	[-0.52; 2.23]	0.222
			Hedges G	0.09	[-0.06; 0.24]	
Asia	101 3.85 (0.90)	93 3.82 (1.01)	Difference	0.03	[-2.64; 2.69]	0.984
			Hedges G	0.00	[-0.28; 0.28]	
Latin America	71 7.33 (1.27)	71 3.16 (1.28)	Difference	4.17	[0.60; 7.74]	0.022
			Hedges G	0.39	[0.06; 0.72]	
Age group 1 at randomization						
Interaction test	p = 0.055					
<45	55 7.00 (1.40)	48 5.62 (1.51)	Difference	1.38	[-2.72; 5.49]	0.505
			Hedges G	0.13	[-0.26; 0.52]	
45 to 54	288 3.46 (0.60)	288 3.43 (0.60)	Difference	0.03	[-1.64; 1.70]	0.971
			Hedges G	0.00	[-0.16; 0.17]	
55 to 64	615 3.78 (0.43)	603 2.46 (0.43)	Difference	1.32	[0.12; 2.51]	0.031
			Hedges G	0.12	[0.01; 0.24]	
≥65	371 5.05 (0.53)	318 2.67 (0.57)	Difference	2.38	[0.86; 3.90]	0.002
			Hedges G	0.23	[0.08; 0.38]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.009					
<Median	602 3.57 (0.45)	577 3.67 (0.46)	Difference	-0.10	[-1.37; 1.17]	0.877
			Hedges G	-0.01	[-0.12; 0.11]	
≥Median	727 4.68 (0.41)	680 2.39 (0.42)	Difference	2.30	[1.15; 3.44]	<.001
			Hedges G	0.21	[0.11; 0.32]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.663					
Asian	125 3.47 (0.79)	116 2.38 (0.88)	Difference	1.09	[-1.25; 3.42]	0.359
			Hedges G	0.12	[-0.13; 0.37]	
Non-Asian	1128 4.28 (0.32)	1080 2.91 (0.32)	Difference	1.37	[0.48; 2.26]	0.003
			Hedges G	0.13	[0.05; 0.21]	
BMI at screening						
Interaction test	p = 0.519					
≥25	878 4.04 (0.37)	862 3.02 (0.38)	Difference	1.02	[-0.02; 2.07]	0.055
			Hedges G	0.09	[-0.00; 0.19]	
<25	440 4.53 (0.51)	384 2.80 (0.55)	Difference	1.73	[0.26; 3.20]	0.021
			Hedges G	0.16	[0.02; 0.30]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.198					
Group I/II	545 3.95 (0.45)	550 2.08 (0.44)	Difference	1.87	[0.64; 3.10]	0.003
			Hedges G	0.18	[0.06; 0.30]	
Group III	783 4.40 (0.41)	707 3.66 (0.43)	Difference	0.74	[-0.44; 1.91]	0.220
			Hedges G	0.06	[-0.04; 0.17]	
Anatomic stages						
Interaction test	p = 0.613					
IA/IB/IIA	288 4.61 (0.60)	290 2.18 (0.59)	Difference	2.43	[0.78; 4.09]	0.004
			Hedges G	0.24	[0.08; 0.40]	
IIB	257 3.15 (0.61)	260 1.80 (0.60)	Difference	1.34	[-0.34; 3.03]	0.118
			Hedges G	0.14	[-0.03; 0.31]	
IIIA	461 4.91 (0.52)	414 4.18 (0.54)	Difference	0.73	[-0.75; 2.20]	0.333
			Hedges G	0.07	[-0.07; 0.20]	
IIIB	92 2.66 (1.13)	78 1.59 (1.23)	Difference	1.08	[-2.21; 4.36]	0.518
			Hedges G	0.10	[-0.20; 0.40]	
IIIC	230 4.30 (0.67)	215 2.89 (0.70)	Difference	1.40	[-0.51; 3.31]	0.149
			Hedges G	0.14	[-0.05; 0.32]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.813					
N0	176 4.47 (0.72)	187 2.83 (0.71)	Difference	1.64	[-0.35; 3.63]	0.106
			Hedges G	0.17	[-0.04; 0.38]	
N1-N3	1150 N.E.	1070 N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	

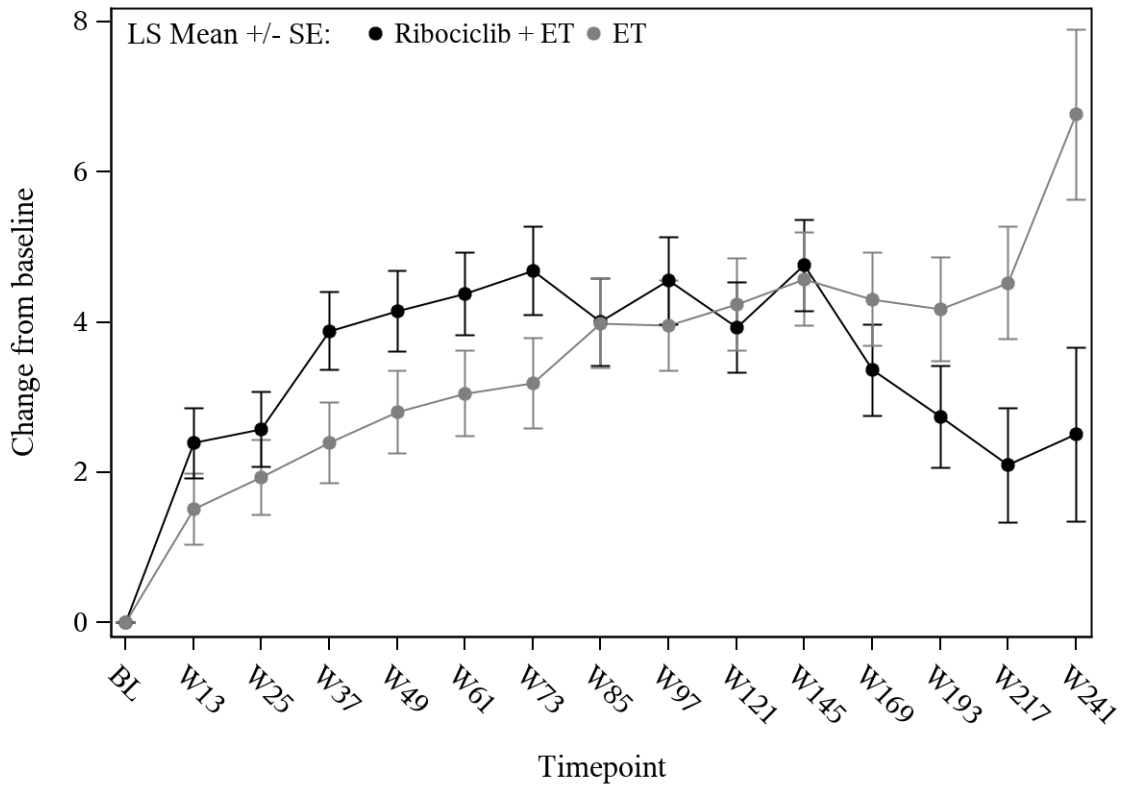
Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.739					
Grade 1	95 5.16 (0.92)	103 4.52 (0.86)	Difference	0.65	[-1.85; 3.14]	0.611
			Hedges G	0.07	[-0.21; 0.35]	
Grade 2	792 3.57 (0.38)	703 2.01 (0.40)	Difference	1.56	[0.47; 2.65]	0.005
			Hedges G	0.15	[0.04; 0.25]	
Grade 3	356 N.E.	367 N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Histological subtype						
Interaction test	N.E.					
Ductal	964 4.13 (0.34)	924 2.63 (0.35)	Difference	1.50	[0.55; 2.45]	0.002
			Hedges G	0.14	[0.05; 0.23]	
Lobular	277 4.59 (0.61)	263 3.38 (0.62)	Difference	1.21	[-0.50; 2.91]	0.165
			Hedges G	0.12	[-0.05; 0.29]	
Other	87 2.86 (1.10)	70 4.66 (1.25)	Difference	-1.80	[-5.10; 1.50]	0.282
			Hedges G	-0.17	[-0.49; 0.14]	
Ki67 status from surgical specimen						
Interaction test	p = 0.344					
Ki67≤20	621 4.90 (0.44)	590 2.96 (0.45)	Difference	1.93	[0.70; 3.17]	0.002
			Hedges G	0.18	[0.06; 0.29]	
Ki67>20	468 4.37 (0.52)	473 3.47 (0.52)	Difference	0.91	[-0.53; 2.35]	0.215
			Hedges G	0.08	[-0.05; 0.21]	
Type of NSAI						
Interaction test	p = 0.049					
Letrozole	853 4.66 (0.36)	821 2.83 (0.37)	Difference	1.83	[0.81; 2.85]	<.001
			Hedges G	0.17	[0.08; 0.27]	
Anastrozole	476 3.25 (0.46)	433 3.08 (0.48)	Difference	0.17	[-1.14; 1.48]	0.795
			Hedges G	0.02	[-0.11; 0.15]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.227					
Yes	1136 3.95 (0.34)	1052 2.93 (0.35)	Difference	1.02	[0.07; 1.96]	0.035
			Hedges G	0.09	[0.01; 0.17]	
No	193 5.70 (0.69)	205 3.22 (0.67)	Difference	2.48	[0.59; 4.37]	0.010
			Hedges G	0.26	[0.06; 0.46]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.331					
Yes	660 3.01 (0.44)	630 2.25 (0.45)	Difference	0.75	[-0.48; 1.98]	0.232
			Hedges G	0.07	[-0.04; 0.18]	
No	669 5.44 (0.41)	627 3.79 (0.42)	Difference	1.65	[0.50; 2.80]	0.005
			Hedges G	0.16	[0.05; 0.27]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test p = 0.566						
Yes	503 4.98 (0.46)	451 3.96 (0.49)	Difference	1.02	[-0.30; 2.34]	0.131
			Hedges G	0.10	[-0.03; 0.23]	
No	826 3.70 (0.36)	806 2.31 (0.37)	Difference	1.39	[0.37; 2.40]	0.007
			Hedges G	0.13	[0.04; 0.23]	
Prior endocrine therapy						
Interaction test p = 0.995						
Yes	898 5.03 (0.34)	868 3.74 (0.34)	Difference	1.29	[0.35; 2.23]	0.007
			Hedges G	0.13	[0.03; 0.22]	
No	431 2.32 (0.52)	389 1.10 (0.55)	Difference	1.23	[-0.26; 2.72]	0.105
			Hedges G	0.11	[-0.02; 0.25]	
Prior mastectomy						
Interaction test p = 0.052						
Yes	811 3.89 (0.39)	774 3.26 (0.40)	Difference	0.63	[-0.47; 1.73]	0.258
			Hedges G	0.06	[-0.04; 0.16]	
No	518 4.78 (0.47)	483 2.47 (0.49)	Difference	2.30	[0.96; 3.64]	<.001
			Hedges G	0.21	[0.09; 0.34]	
Prior radiotherapy						
Interaction test p = 0.734						
Yes	1182 4.20 (0.32)	1110 3.03 (0.33)	Difference	1.17	[0.26; 2.08]	0.012
			Hedges G	0.11	[0.02; 0.19]	
No	147 4.21 (0.89)	147 2.61 (0.88)	Difference	1.60	[-0.86; 4.06]	0.201
			Hedges G	0.15	[-0.08; 0.38]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed N.E.: Not estimable ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + baseline value ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>+ The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

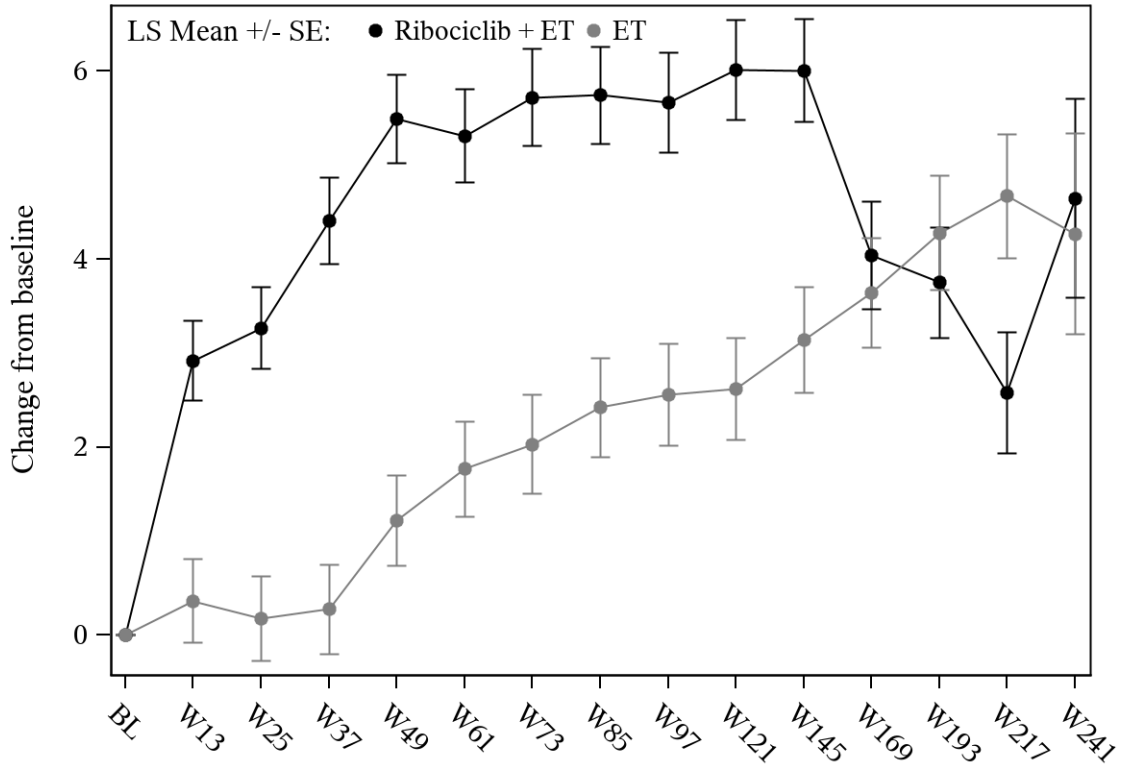
Figure 5-2.3.1.1 QLQ-BR23 - Side Effects Of Systemic Therapy: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-BR23 - Side Effects Of Systemic Therapy
Age group 2 at randomization (median for subpopulation post-menopausal female patients): <Median



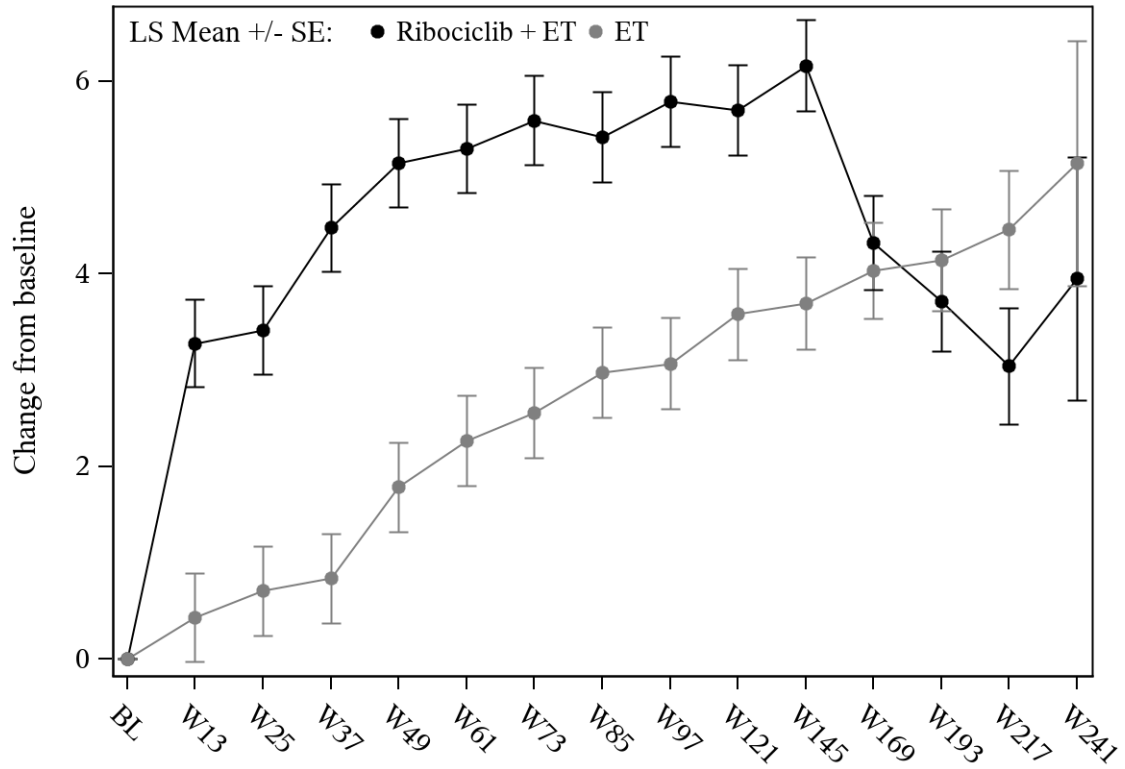
Ribociclib + ET	602	574	542	551	540	535	529	517	512	491	480	401	327	200	35
ET	577	546	526	510	510	502	497	490	482	471	464	385	322	214	39

QLQ-BR23 - Side Effects Of Systemic Therapy
Age group 2 at randomization (median for subpopulation post-menopausal female patients): \geq Median



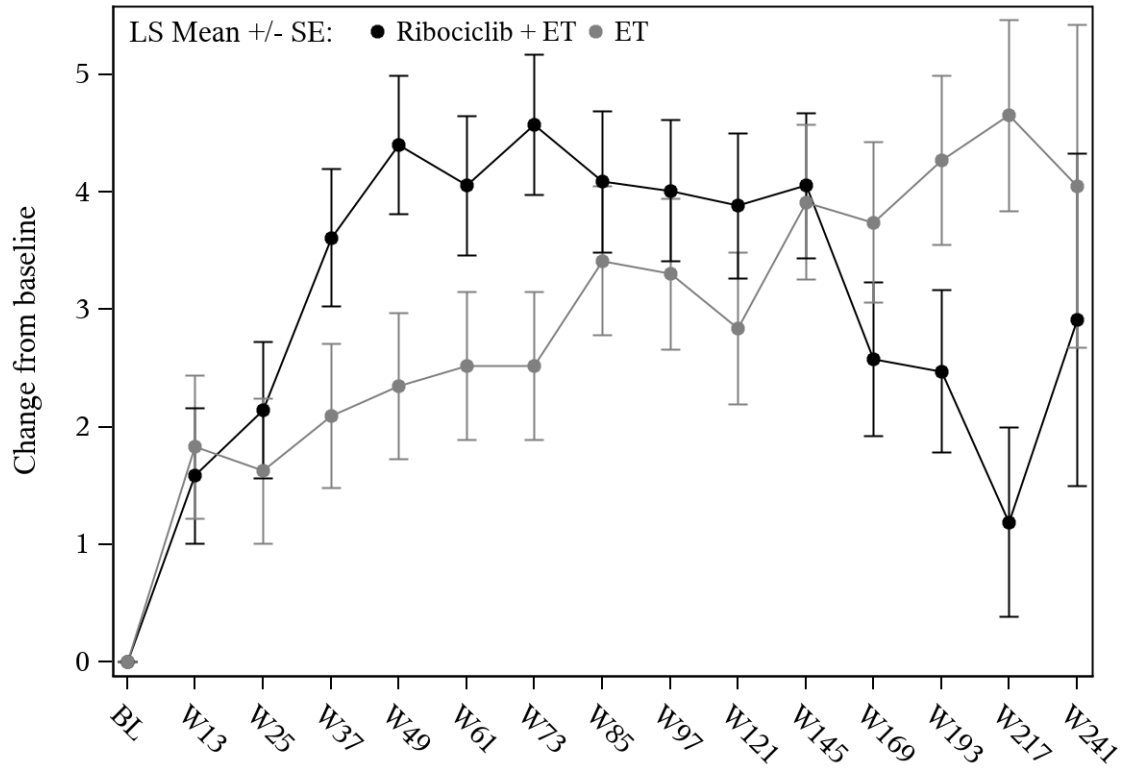
Ribociclib + ET	727	698	679	666	651	645	637	614	618	592	591	508	441	279	58
ET	680	645	622	628	630	610	608	596	590	570	547	484	408	264	57

QLQ-BR23 - Side Effects Of Systemic Therapy
Type of NSAI: Letrozole



Ribociclib + ET	853	811	778	781	765	758	750	729	728	712	701	606	513	316	52
ET	821	781	760	736	754	742	742	726	723	701	683	584	486	310	52

QLQ-BR23 - Side Effects Of Systemic Therapy
Type of NSAI: Anastrozole



Ribociclib + ET	476	461	443	436	426	422	416	402	402	371	370	303	255	163	41
ET	433	408	387	401	386	368	363	360	348	340	327	285	244	168	44

Table 5-2.3.2.1 QLQ-BR23 - Breast Symptoms: change from baseline analysis - subgroup analysis (Full Analysis Set)

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-BR23 - Breast Symptoms						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.499					
NA/WE/O	825 -5.60 (0.40)	772 -5.99 (0.41)	Difference	0.38	[-0.73; 1.50]	0.501
			Hedges G	0.03	[-0.06; 0.13]	
ROW	497 -5.35 (0.50)	487 -4.93 (0.50)	Difference	-0.43	[-1.82; 0.97]	0.549
			Hedges G	-0.04	[-0.16; 0.09]	
Geographical region						
Interaction test	p = 0.258					
Europe	785 -5.73 (0.40)	772 -6.25 (0.40)	Difference	0.52	[-0.60; 1.64]	0.366
			Hedges G	0.05	[-0.05; 0.15]	
North America/Australia	366 -5.69 (0.51)	324 -4.80 (0.53)	Difference	-0.90	[-2.34; 0.55]	0.224
			Hedges G	-0.09	[-0.24; 0.06]	
Asia	101 -1.85 (1.16)	93 -1.04 (1.29)	Difference	-0.80	[-4.22; 2.62]	0.644
			Hedges G	-0.07	[-0.35; 0.22]	
Latin America	70 -5.09 (1.71)	70 -7.47 (1.72)	Difference	2.38	[-2.42; 7.18]	0.328
			Hedges G	0.17	[-0.17; 0.50]	
Age group 1 at randomization						
Interaction test	p = 0.885					
<45	55 -3.43 (1.55)	48 -3.10 (1.67)	Difference	-0.33	[-4.84; 4.18]	0.884
			Hedges G	-0.03	[-0.42; 0.36]	
45 to 54	285 -4.64 (0.70)	288 -4.13 (0.70)	Difference	-0.51	[-2.44; 1.43]	0.606
			Hedges G	-0.04	[-0.21; 0.12]	
55 to 64	610 -6.39 (0.46)	602 -6.73 (0.45)	Difference	0.34	[-0.92; 1.61]	0.593
			Hedges G	0.03	[-0.08; 0.14]	
≥65	372 -5.05 (0.55)	321 -5.01 (0.59)	Difference	-0.03	[-1.62; 1.55]	0.968
			Hedges G	-0.00	[-0.15; 0.15]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.176					
<Median	598 -5.61 (0.48)	576 -5.12 (0.49)	Difference	-0.49	[-1.84; 0.86]	0.474
			Hedges G	-0.04	[-0.16; 0.07]	
≥Median	724 -5.37 (0.41)	683 -5.88 (0.42)	Difference	0.51	[-0.64; 1.66]	0.384
			Hedges G	0.05	[-0.06; 0.15]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.320					
Asian	125 -2.67 (0.97)	116 -1.54 (1.08)	Difference	-1.13	[-3.99; 1.73]	0.436
			Hedges G	-0.10	[-0.35; 0.15]	
Non-Asian	1120 -5.87 (0.34)	1080 -6.06 (0.34)	Difference	0.19	[-0.75; 1.13]	0.689
			Hedges G	0.02	[-0.07; 0.10]	
BMI at screening						
Interaction test	p = 0.077					
≥25	872 -5.25 (0.40)	862 -5.88 (0.40)	Difference	0.63	[-0.47; 1.73]	0.261
			Hedges G	0.05	[-0.04; 0.15]	
<25	439 -5.83 (0.50)	386 -4.79 (0.53)	Difference	-1.04	[-2.47; 0.38]	0.150
			Hedges G	-0.10	[-0.24; 0.04]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.098					
Group I/II	540 -5.65 (0.44)	549 -6.63 (0.44)	Difference	0.99	[-0.23; 2.20]	0.112
			Hedges G	0.10	[-0.02; 0.22]	
Group III	781 -5.13 (0.44)	710 -4.67 (0.46)	Difference	-0.46	[-1.71; 0.79]	0.470
			Hedges G	-0.04	[-0.14; 0.06]	
Anatomic stages						
Interaction test	p = 0.096					
IA/IB/IIA	285 -5.28 (0.58)	290 -6.91 (0.57)	Difference	1.62	[0.02; 3.22]	0.047
			Hedges G	0.17	[0.00; 0.33]	
IIB	255 -6.32 (0.66)	259 -6.33 (0.65)	Difference	0.01	[-1.81; 1.82]	0.993
			Hedges G	0.00	[-0.17; 0.17]	
IIIA	459 -4.45 (0.59)	415 -5.00 (0.60)	Difference	0.55	[-1.11; 2.21]	0.516
			Hedges G	0.04	[-0.09; 0.18]	
IIIB	92 -8.57 (1.10)	78 -7.77 (1.21)	Difference	-0.81	[-4.03; 2.42]	0.622
			Hedges G	-0.08	[-0.38; 0.23]	
IIIC	230 -5.71 (0.74)	217 -3.18 (0.78)	Difference	-2.54	[-4.65; -0.42]	0.019
			Hedges G	-0.22	[-0.41; -0.04]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.414					
N0	174 -5.24 (0.72)	188 -6.08 (0.70)	Difference	0.84	[-1.13; 2.81]	0.404
			Hedges G	0.09	[-0.12; 0.29]	
N1-N3	1145 -5.44 (0.35)	1071 -5.42 (0.36)	Difference	-0.02	[-0.99; 0.96]	0.974
			Hedges G	-0.00	[-0.08; 0.08]	

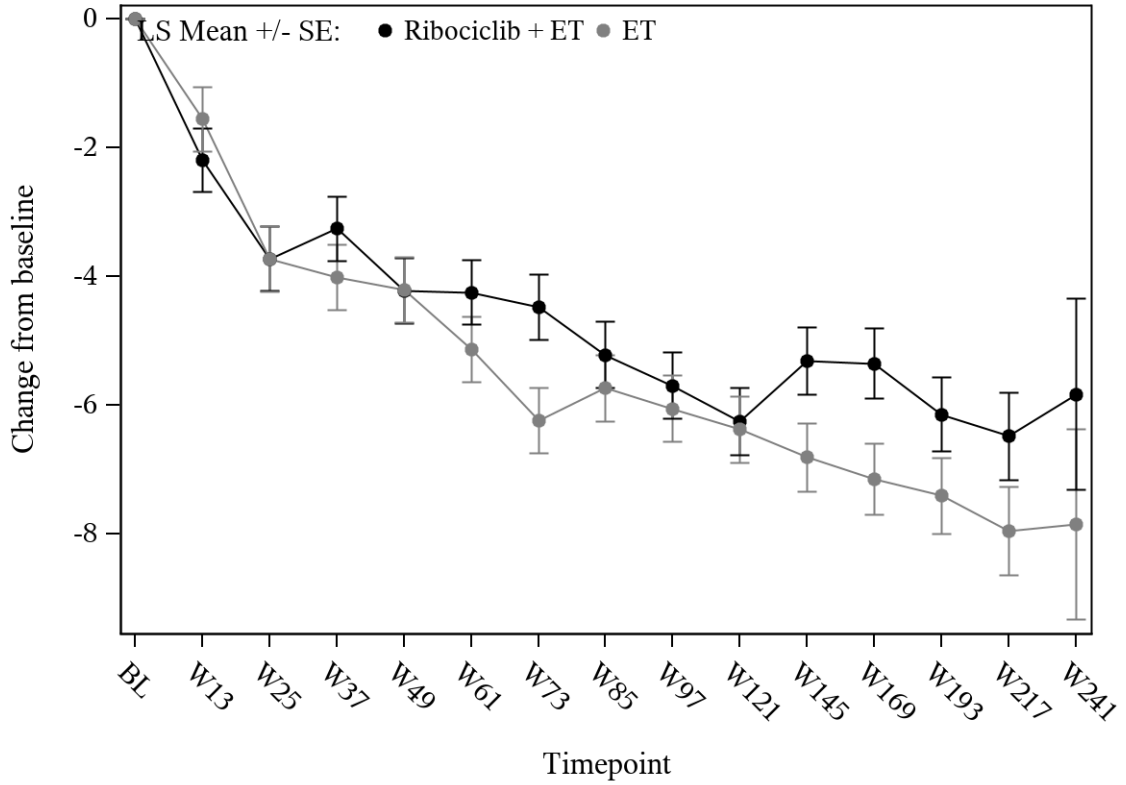
Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.992					
Grade 1	94 -6.07 (1.10)	103 -6.27 (1.02)	Difference	0.20	[-2.77; 3.17]	0.895
			Hedges G	0.02	[-0.26; 0.30]	
Grade 2	786 -5.63 (0.39)	704 -5.69 (0.42)	Difference	0.06	[-1.07; 1.18]	0.919
			Hedges G	0.01	[-0.10; 0.11]	
Grade 3	356 -4.94 (0.61)	369 -4.60 (0.60)	Difference	-0.35	[-2.03; 1.34]	0.687
			Hedges G	-0.03	[-0.18; 0.12]	
Histological subtype						
Interaction test	p = 0.398					
Ductal	957 -5.61 (0.36)	926 -5.89 (0.36)	Difference	0.28	[-0.73; 1.28]	0.589
			Hedges G	0.02	[-0.07; 0.12]	
Lobular	277 -4.14 (0.67)	264 -4.02 (0.68)	Difference	-0.12	[-1.99; 1.76]	0.902
			Hedges G	-0.01	[-0.18; 0.16]	
Other	87 -8.31 (1.32)	69 -5.98 (1.51)	Difference	-2.32	[-6.28; 1.64]	0.248
			Hedges G	-0.19	[-0.50; 0.13]	
Ki67 status from surgical specimen						
Interaction test	p = 0.857					
Ki67≤20	619 -5.29 (0.45)	591 -5.39 (0.46)	Difference	0.10	[-1.15; 1.36]	0.872
			Hedges G	0.01	[-0.10; 0.12]	
Ki67>20	467 -5.37 (0.55)	475 -5.43 (0.55)	Difference	0.06	[-1.46; 1.59]	0.937
			Hedges G	0.01	[-0.12; 0.13]	
Type of NSAI						
Interaction test	p = 0.024					
Letrozole	847 -4.89 (0.38)	822 -5.74 (0.39)	Difference	0.85	[-0.22; 1.91]	0.121
			Hedges G	0.08	[-0.02; 0.17]	
Anastrozole	475 -6.58 (0.52)	434 -5.20 (0.54)	Difference	-1.38	[-2.85; 0.09]	0.066
			Hedges G	-0.12	[-0.25; 0.01]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.569					
Yes	1129 -5.27 (0.35)	1053 -5.23 (0.36)	Difference	-0.04	[-1.02; 0.94]	0.932
			Hedges G	-0.00	[-0.09; 0.08]	
No	193 -6.38 (0.70)	206 -7.21 (0.68)	Difference	0.83	[-1.08; 2.75]	0.394
			Hedges G	0.09	[-0.11; 0.28]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.318					
Yes	657 -4.96 (0.44)	632 -4.61 (0.45)	Difference	-0.36	[-1.60; 0.88]	0.572
			Hedges G	-0.03	[-0.14; 0.08]	
No	665 -5.94 (0.44)	627 -6.44 (0.46)	Difference	0.50	[-0.75; 1.74]	0.434
			Hedges G	0.04	[-0.07; 0.15]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	p = 0.864					
Yes	499 -5.57 (0.54)	450 -5.67 (0.57)	Difference	0.10	[-1.44; 1.64]	0.898
			Hedges G	0.01	[-0.12; 0.14]	
No	823 -5.34 (0.38)	809 -5.35 (0.38)	Difference	0.01	[-1.06; 1.08]	0.983
			Hedges G	0.00	[-0.10; 0.10]	
Prior endocrine therapy						
Interaction test	p = 0.459					
Yes	895 -5.04 (0.37)	866 -5.33 (0.38)	Difference	0.29	[-0.75; 1.34]	0.578
			Hedges G	0.03	[-0.07; 0.12]	
No	427 -6.48 (0.55)	393 -6.01 (0.57)	Difference	-0.48	[-2.02; 1.07]	0.545
			Hedges G	-0.04	[-0.18; 0.09]	
Prior mastectomy						
Interaction test	p = 0.007					
Yes	807 -4.80 (0.39)	776 -3.90 (0.39)	Difference	-0.90	[-1.98; 0.19]	0.105
			Hedges G	-0.08	[-0.18; 0.02]	
No	515 -6.62 (0.51)	483 -8.08 (0.53)	Difference	1.46	[0.01; 2.91]	0.049
			Hedges G	0.13	[0.00; 0.25]	
Prior radiotherapy						
Interaction test	p = 0.323					
Yes	1175 -5.73 (0.34)	1111 -5.66 (0.35)	Difference	-0.07	[-1.03; 0.89]	0.886
			Hedges G	-0.01	[-0.09; 0.08]	
No	147 -3.52 (0.78)	148 -4.75 (0.78)	Difference	1.23	[-0.94; 3.40]	0.266
			Hedges G	0.13	[-0.10; 0.36]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: $\text{change from baseline} = \text{treatment} + \text{visit} + \text{treatment} * \text{visit} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor} + \text{subgroup factor} * \text{visit} + \text{treatment} * \text{subgroup factor} * \text{visit} + \text{baseline value}$ If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: $\text{change from baseline} = \text{treatment} + \text{visit} + \text{treatment} * \text{visit} + \text{baseline value}$ ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>† The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

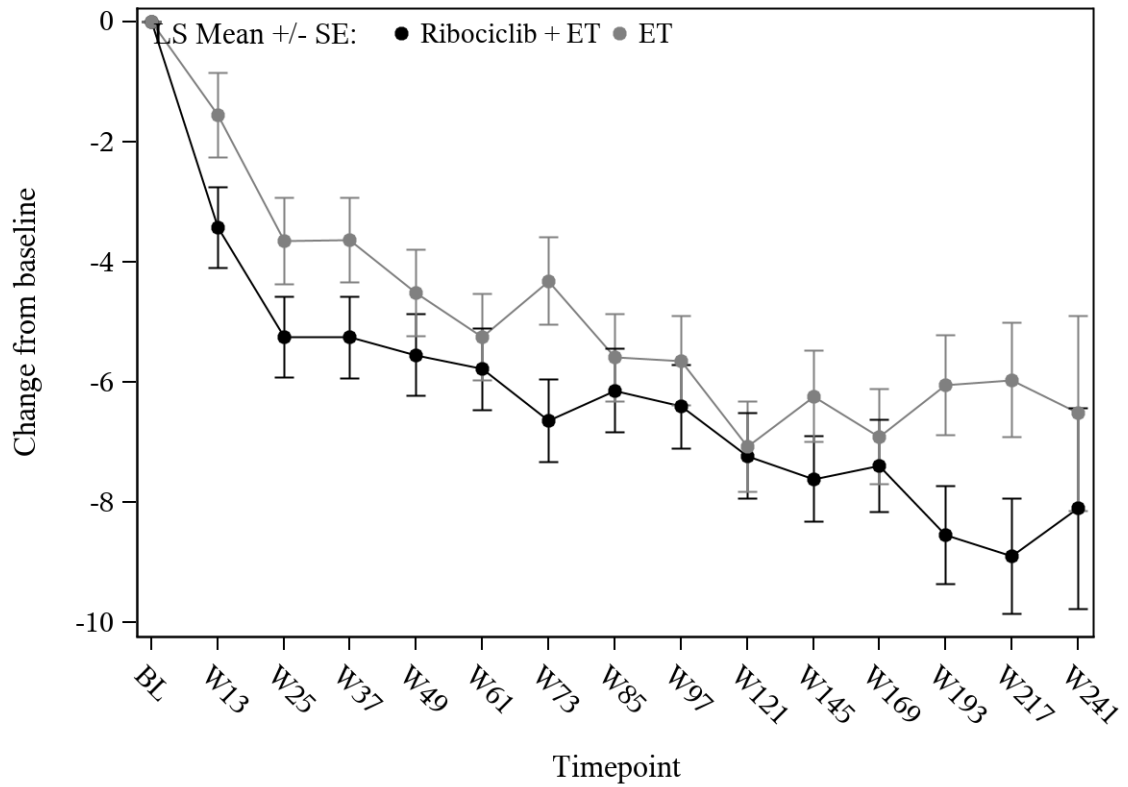
Figure 5-2.3.2.1 QLQ-BR23 - Breast Symptoms: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-BR23 - Breast Symptoms
Type of NSAI: Letrozole



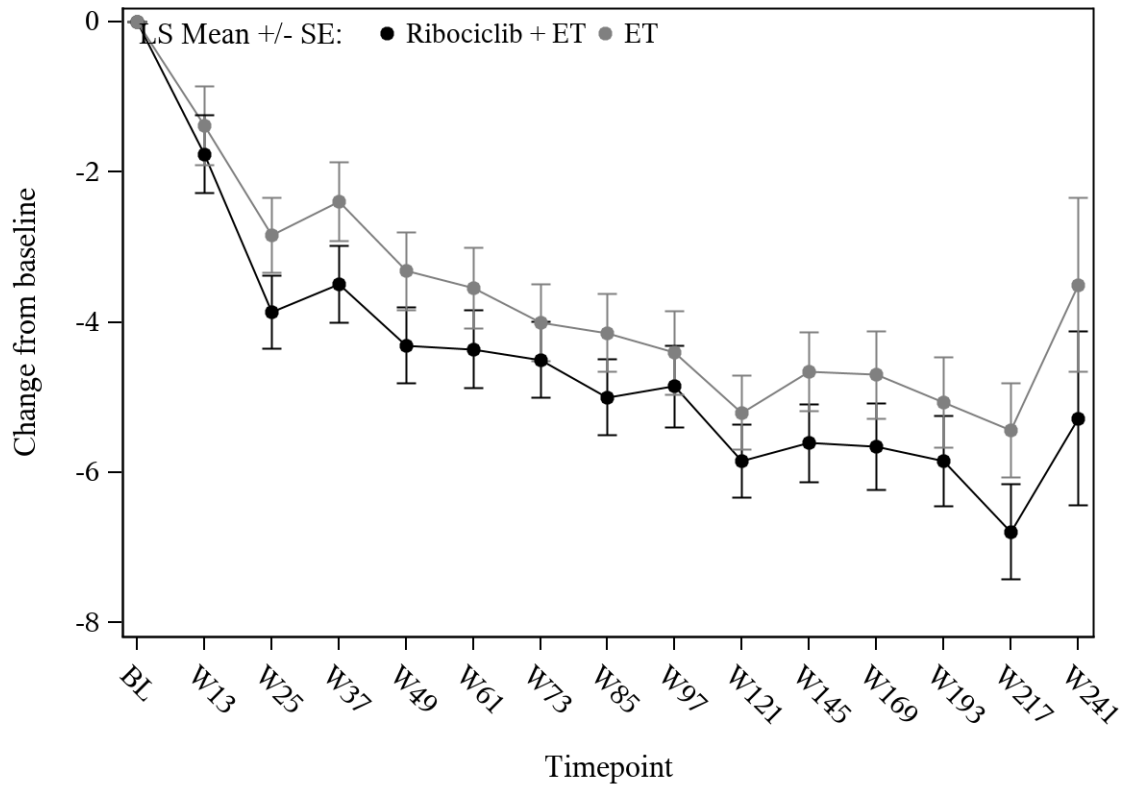
Ribociclib + ET	847	801	771	770	754	751	741	719	719	706	691	602	506	314	51
ET	822	779	758	732	747	741	739	724	721	700	679	581	484	311	52

QLQ-BR23 - Breast Symptoms
Type of NSAI: Anastrozole



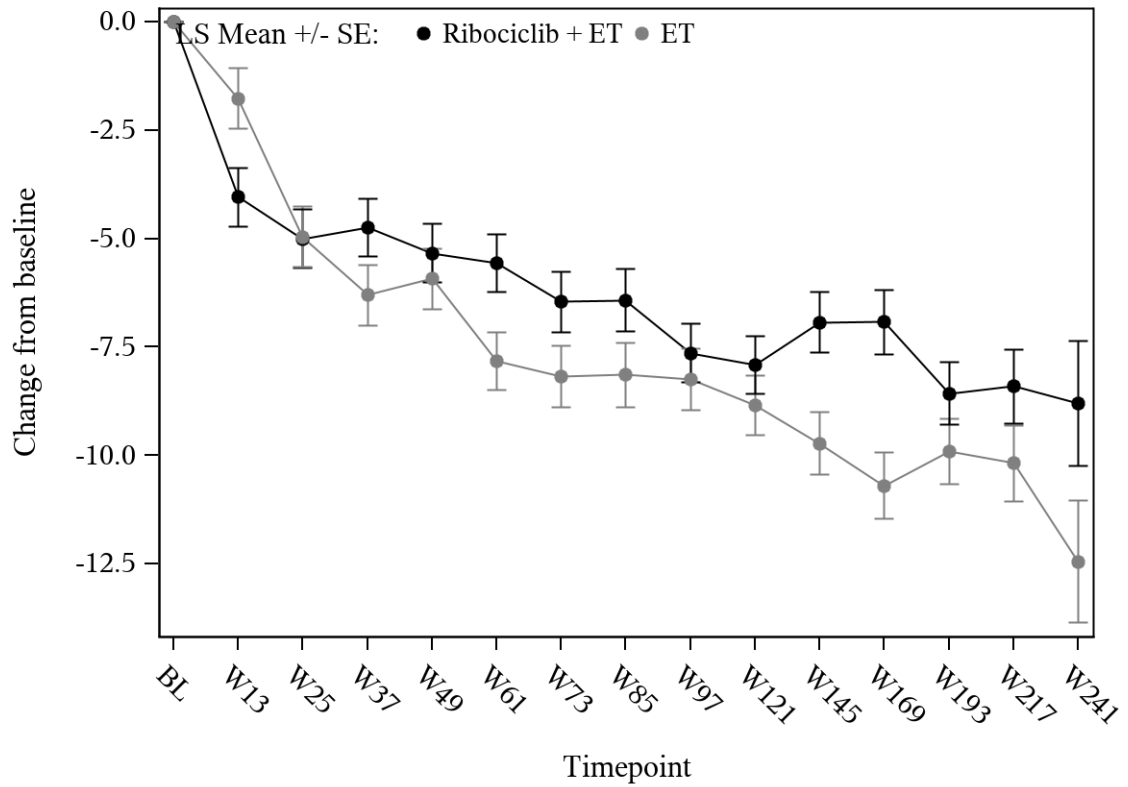
Ribociclib + ET	475	458	441	429	421	418	414	399	399	368	368	297	253	161	41
ET	434	406	386	399	384	369	362	358	347	340	327	283	240	168	44

QLQ-BR23 - Breast Symptoms
Prior mastectomy: Yes



Ribociclib + ET	807	770	753	729	717	722	707	674	676	641	630	516	411	271	58
ET	776	737	702	700	695	687	678	667	657	639	622	515	416	283	59

QLQ-BR23 - Breast Symptoms
Prior mastectomy: No



Ribociclib + ET	515	489	459	470	458	447	448	444	442	433	429	383	348	204	34
ET	483	449	443	432	436	425	423	415	411	401	385	349	308	196	37

Table 5-2.3.3.1 QLQ-BR23 - Arm Symptoms: change from baseline analysis - subgroup analysis (Full Analysis Set)

Treatment Groups		Comparison				
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-BR23 - Arm Symptoms						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.671					
NA/WE/O	826 0.54 (0.53)	773 -0.25 (0.54)	Difference	0.80	[-0.68; 2.28]	0.292
			Hedges G	0.05	[-0.05; 0.15]	
ROW	497 -0.12 (0.67)	488 -0.36 (0.68)	Difference	0.24	[-1.64; 2.11]	0.805
			Hedges G	0.02	[-0.11; 0.14]	
Geographical region						
Interaction test	p = 0.268					
Europe	786 0.37 (0.53)	773 -0.18 (0.53)	Difference	0.55	[-0.92; 2.02]	0.463
			Hedges G	0.04	[-0.06; 0.14]	
North America/Australia	366 0.72 (0.71)	325 -0.82 (0.75)	Difference	1.54	[-0.50; 3.58]	0.138
			Hedges G	0.11	[-0.04; 0.26]	
Asia	101 0.93 (1.44)	93 3.33 (1.55)	Difference	-2.40	[-6.57; 1.78]	0.259
			Hedges G	-0.16	[-0.44; 0.12]	
Latin America	70 -2.51 (1.92)	70 -4.14 (1.93)	Difference	1.63	[-3.75; 7.01]	0.550
			Hedges G	0.10	[-0.23; 0.43]	
Age group 1 at randomization						
Interaction test	p = 0.053					
<45	55 0.70 (2.33)	48 -0.48 (2.52)	Difference	1.18	[-5.62; 7.98]	0.731
			Hedges G	0.07	[-0.32; 0.46]	
45 to 54	285 -1.65 (0.92)	289 -0.10 (0.92)	Difference	-1.55	[-4.10; 1.00]	0.234
			Hedges G	-0.10	[-0.26; 0.06]	
55 to 64	611 -0.15 (0.58)	603 -0.32 (0.58)	Difference	0.17	[-1.44; 1.78]	0.834
			Hedges G	0.01	[-0.10; 0.12]	
≥65	372 2.28 (0.73)	321 -0.74 (0.78)	Difference	3.02	[0.93; 5.11]	0.005
			Hedges G	0.22	[0.07; 0.37]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.061					
<Median	599 -0.81 (0.64)	577 -0.22 (0.65)	Difference	-0.59	[-2.39; 1.21]	0.519
			Hedges G	-0.04	[-0.15; 0.08]	
≥Median	724 1.25 (0.54)	684 -0.50 (0.55)	Difference	1.75	[0.23; 3.27]	0.024
			Hedges G	0.12	[0.02; 0.23]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.176					
Asian	125 -0.37 (1.26)	116 1.57 (1.42)	Difference	-1.95	[-5.69; 1.79]	0.306
			Hedges G	-0.13	[-0.39; 0.12]	
Non-Asian	1121 0.03 (0.44)	1082 -0.70 (0.45)	Difference	0.73	[-0.50; 1.96]	0.243
			Hedges G	0.05	[-0.03; 0.13]	
BMI at screening						
Interaction test	p = 0.356					
≥25	873 0.85 (0.51)	864 -0.14 (0.52)	Difference	0.99	[-0.43; 2.42]	0.173
			Hedges G	0.07	[-0.03; 0.16]	
<25	439 -0.84 (0.70)	386 -0.60 (0.74)	Difference	-0.24	[-2.23; 1.75]	0.812
			Hedges G	-0.02	[-0.15; 0.12]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.069					
Group I/II	541 0.41 (0.61)	550 -1.36 (0.60)	Difference	1.78	[0.09; 3.46]	0.039
			Hedges G	0.13	[0.01; 0.24]	
Group III	781 -0.07 (0.57)	711 0.45 (0.59)	Difference	-0.52	[-2.13; 1.09]	0.526
			Hedges G	-0.03	[-0.13; 0.07]	
Anatomic stages						
Interaction test	p = 0.366					
IA/IB/IIA	285 0.22 (0.82)	290 -0.99 (0.81)	Difference	1.21	[-1.05; 3.47]	0.293
			Hedges G	0.09	[-0.08; 0.25]	
IIB	256 0.51 (0.88)	260 -1.90 (0.86)	Difference	2.41	[-0.01; 4.82]	0.051
			Hedges G	0.17	[-0.00; 0.35]	
IIIA	459 0.37 (0.73)	416 0.44 (0.75)	Difference	-0.07	[-2.13; 1.99]	0.948
			Hedges G	-0.00	[-0.14; 0.13]	
IIIB	92 -4.10 (1.58)	78 -3.07 (1.72)	Difference	-1.03	[-5.64; 3.59]	0.661
			Hedges G	-0.07	[-0.37; 0.23]	
IIIC	230 0.61 (0.97)	217 1.38 (1.01)	Difference	-0.77	[-3.53; 1.98]	0.582
			Hedges G	-0.05	[-0.24; 0.13]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.477					
N0	174 -0.29 (1.12)	188 0.24 (1.08)	Difference	-0.53	[-3.59; 2.53]	0.734
			Hedges G	-0.04	[-0.24; 0.17]	
N1-N3	1146 0.40 (0.45)	1073 -0.44 (0.46)	Difference	0.84	[-0.41; 2.10]	0.188
			Hedges G	0.06	[-0.03; 0.14]	

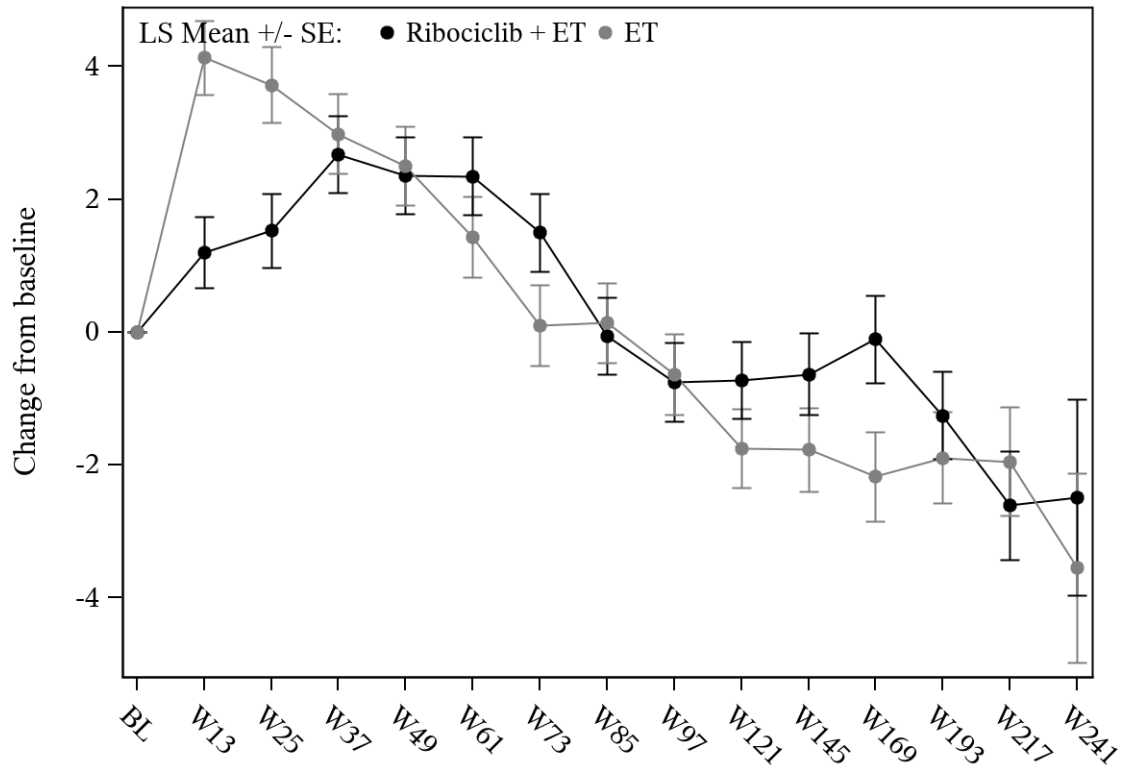
Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.581					
Grade 1	94 2.15 (1.44)	103 -0.44 (1.32)	Difference	2.58	[-1.27; 6.44]	0.188
			Hedges G	0.19	[-0.09; 0.47]	
Grade 2	787 -0.64 (0.51)	704 -0.88 (0.54)	Difference	0.23	[-1.22; 1.69]	0.753
			Hedges G	0.02	[-0.09; 0.12]	
Grade 3	356 0.64 (0.83)	370 0.59 (0.81)	Difference	0.05	[-2.23; 2.32]	0.968
			Hedges G	0.00	[-0.14; 0.15]	
Histological subtype						
Interaction test	p = 0.571					
Ductal	958 N.E.	927 N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Lobular	277 0.39 (0.89)	264 -0.14 (0.91)	Difference	0.53	[-1.97; 3.03]	0.679
			Hedges G	0.04	[-0.13; 0.20]	
Other	87 -0.56 (1.43)	70 0.88 (1.63)	Difference	-1.44	[-5.73; 2.84]	0.507
			Hedges G	-0.11	[-0.42; 0.21]	
Ki67 status from surgical specimen						
Interaction test	p = 0.430					
Ki67≤20	619 -0.16 (0.58)	591 -0.36 (0.59)	Difference	0.20	[-1.42; 1.83]	0.805
			Hedges G	0.01	[-0.10; 0.13]	
Ki67>20	467 0.81 (0.74)	476 -0.50 (0.74)	Difference	1.31	[-0.75; 3.37]	0.213
			Hedges G	0.08	[-0.05; 0.21]	
Type of NSAI						
Interaction test	p = 0.843					
Letrozole	848 0.19 (0.52)	823 -0.36 (0.53)	Difference	0.55	[-0.91; 2.01]	0.459
			Hedges G	0.04	[-0.06; 0.13]	
Anastrozole	475 0.55 (0.67)	435 -0.48 (0.71)	Difference	1.02	[-0.89; 2.94]	0.295
			Hedges G	0.07	[-0.06; 0.20]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.086					
Yes	1130 0.17 (0.46)	1055 0.02 (0.47)	Difference	0.15	[-1.14; 1.44]	0.820
			Hedges G	0.01	[-0.07; 0.09]	
No	193 0.57 (0.98)	206 -2.15 (0.95)	Difference	2.73	[0.04; 5.41]	0.047
			Hedges G	0.20	[0.00; 0.40]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.188					
Yes	657 0.25 (0.58)	634 0.34 (0.58)	Difference	-0.09	[-1.69; 1.52]	0.915
			Hedges G	-0.01	[-0.12; 0.10]	
No	666 0.32 (0.60)	627 -1.03 (0.62)	Difference	1.34	[-0.34; 3.03]	0.117
			Hedges G	0.09	[-0.02; 0.20]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	p = 0.858					
Yes	500 0.16 (0.72)	451 -0.41 (0.76)	Difference	0.57	[-1.50; 2.63]	0.590
			Hedges G	0.04	[-0.09; 0.16]	
No	823 0.35 (0.51)	810 -0.35 (0.51)	Difference	0.70	[-0.70; 2.11]	0.327
			Hedges G	0.05	[-0.05; 0.15]	
Prior endocrine therapy						
Interaction test	p = 0.581					
Yes	895 0.77 (0.50)	868 0.35 (0.50)	Difference	0.42	[-0.97; 1.81]	0.553
			Hedges G	0.03	[-0.07; 0.12]	
No	428 -0.93 (0.75)	393 -1.94 (0.77)	Difference	1.01	[-1.10; 3.12]	0.349
			Hedges G	0.07	[-0.07; 0.20]	
Prior mastectomy						
Interaction test	p = 0.705					
Yes	808 -0.07 (0.54)	778 -0.55 (0.55)	Difference	0.47	[-1.03; 1.98]	0.538
			Hedges G	0.03	[-0.07; 0.13]	
No	515 0.86 (0.65)	483 -0.14 (0.67)	Difference	0.99	[-0.85; 2.84]	0.290
			Hedges G	0.07	[-0.06; 0.19]	
Prior radiotherapy						
Interaction test	p = 0.039					
Yes	1176 0.21 (0.45)	1113 0.09 (0.46)	Difference	0.12	[-1.13; 1.37]	0.849
			Hedges G	0.01	[-0.07; 0.09]	
No	147 0.32 (1.18)	148 -3.55 (1.18)	Difference	3.87	[0.57; 7.17]	0.022
			Hedges G	0.27	[0.04; 0.50]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed N.E.: Not estimable ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + baseline value ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>+ The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

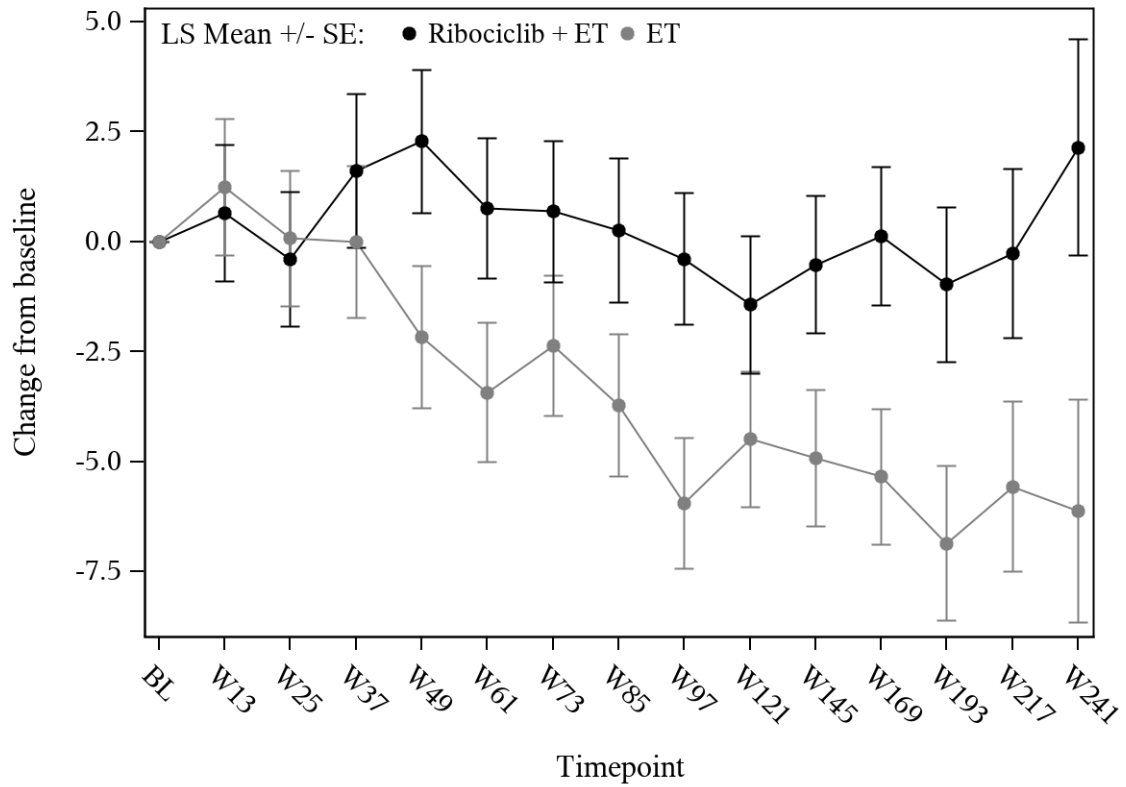
Figure 5-2.3.3.1 QLQ-BR23 - Arm Symptoms: line chart of change from baseline - subgroup analysis (Full Analysis Set)

QLQ-BR23 - Arm Symptoms
Prior radiotherapy: Yes



Ribociclib + ET	1176	1116	1072	1063	1042	1031	1019	988	986	949	935	786	649	396	69
ET	1113	1047	1009	991	994	971	967	946	933	907	878	746	617	403	75

QLQ-BR23 - Arm Symptoms
Prior radiotherapy: No



Ribociclib + ET	147	143	141	138	136	139	138	132	132	128	127	113	113	79	23
ET	148	142	138	142	139	142	135	139	137	134	130	119	110	77	21

Table 5-2.3.4.1 QLQ-BR23 - Being Upset With Hair Loss: change from baseline analysis - subgroup analysis (Full Analysis Set)

Treatment Groups		Comparison				
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-BR23 - Being Upset With Hair Loss						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.397					
NA/WE/O	197 4.98 (1.87)	181 -1.64 (1.98)	Difference	6.63	[1.28; 11.98]	0.015
			Hedges G	0.25	[0.05; 0.45]	
ROW	159 1.80 (1.76)	170 -1.49 (1.77)	Difference	3.29	[-1.63; 8.21]	0.189
			Hedges G	0.15	[-0.07; 0.36]	
Geographical region						
Interaction test	p = 0.910					
Europe	199 1.85 (1.43)	202 -3.82 (1.50)	Difference	5.67	[1.60; 9.75]	0.007
			Hedges G	0.27	[0.08; 0.47]	
North America/Australia	92 3.81 (2.25)	80 1.43 (2.44)	Difference	2.38	[-4.21; 8.98]	0.477
			Hedges G	0.11	[-0.19; 0.41]	
Asia	44 9.88 (2.90)	41 6.91 (3.17)	Difference	2.97	[-5.58; 11.52]	0.492
			Hedges G	0.15	[-0.28; 0.58]	
Latin America	21 9.17 (3.75)	28 -0.97 (3.62)	Difference	10.15	[-0.46; 20.75]	0.060
			Hedges G	0.56	[-0.02; 1.13]	
Age group 1 at randomization						
Interaction test	p = 0.508					
<45	12 -7.84 (5.15)	12 -1.74 (5.93)	Difference	-6.10	[-22.49; 10.29]	0.447
			Hedges G	-0.32	[-1.12; 0.49]	
45 to 54	66 0.25 (2.55)	70 -1.93 (2.69)	Difference	2.18	[-5.15; 9.52]	0.557
			Hedges G	0.10	[-0.24; 0.44]	
55 to 64	167 2.56 (1.58)	181 -2.33 (1.54)	Difference	4.89	[0.55; 9.23]	0.027
			Hedges G	0.24	[0.03; 0.45]	
≥65	111 9.81 (1.80)	88 2.74 (2.15)	Difference	7.08	[1.54; 12.62]	0.013
			Hedges G	0.36	[0.08; 0.64]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.396					
<Median	145 -0.31 (2.09)	145 -3.52 (2.15)	Difference	3.21	[-2.69; 9.11]	0.285
			Hedges G	0.13	[-0.10; 0.36]	
≥Median	211 6.19 (1.59)	206 -0.23 (1.65)	Difference	6.42	[1.91; 10.92]	0.005
			Hedges G	0.27	[0.08; 0.47]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.624					
Asian	50 9.78 (3.32)	50 5.66 (3.44)	Difference	4.12	[-5.41; 13.65]	0.393
			Hedges G	0.17	[-0.22; 0.56]	
Non-Asian	291 2.66 (1.41)	292 -2.45 (1.44)	Difference	5.11	[1.14; 9.08]	0.012
			Hedges G	0.21	[0.05; 0.37]	
BMI at screening						
Interaction test	p = 0.837					
≥25	248 2.20 (1.48)	237 -2.86 (1.56)	Difference	5.05	[0.83; 9.28]	0.019
			Hedges G	0.21	[0.03; 0.39]	
<25	104 7.38 (2.55)	110 1.17 (2.51)	Difference	6.21	[-0.85; 13.27]	0.084
			Hedges G	0.24	[-0.03; 0.51]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.275					
Group I/II	146 3.17 (1.93)	151 -3.99 (1.96)	Difference	7.16	[1.75; 12.58]	0.010
			Hedges G	0.30	[0.07; 0.53]	
Group III	210 3.68 (1.72)	200 0.48 (1.79)	Difference	3.20	[-1.68; 8.08]	0.198
			Hedges G	0.13	[-0.07; 0.32]	
Anatomic stages						
Interaction test	p = 0.487					
IA/IB/IIA	76 6.25 (2.28)	84 -3.78 (2.35)	Difference	10.03	[3.57; 16.49]	0.003
			Hedges G	0.49	[0.17; 0.80]	
IIB	70 0.77 (2.27)	67 -3.22 (2.34)	Difference	3.99	[-2.46; 10.45]	0.223
			Hedges G	0.21	[-0.13; 0.55]	
IIIA	130 6.13 (1.92)	107 1.68 (2.17)	Difference	4.45	[-1.26; 10.17]	0.126
			Hedges G	0.20	[-0.06; 0.46]	
IIIB	24 1.60 (3.64)	27 -1.49 (3.34)	Difference	3.09	[-6.85; 13.02]	0.535
			Hedges G	0.18	[-0.38; 0.73]	
IIIC	56 0.30 (2.75)	66 2.19 (2.70)	Difference	-1.88	[-9.52; 5.76]	0.626
			Hedges G	-0.09	[-0.44; 0.27]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.282					
N0	42 -0.04 (3.48)	56 0.77 (3.12)	Difference	-0.81	[-10.08; 8.47]	0.863
			Hedges G	-0.04	[-0.44; 0.36]	
N1-N3	314 3.85 (1.37)	295 -1.82 (1.45)	Difference	5.67	[1.75; 9.60]	0.005
			Hedges G	0.23	[0.07; 0.39]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.561					
Grade 1	23 8.95 (3.10)	23 -2.83 (3.36)	Difference	11.78	[2.47; 21.09]	0.014
			Hedges G	0.75	[0.15; 1.35]	
Grade 2	223 2.24 (1.31)	205 -1.22 (1.42)	Difference	3.46	[-0.34; 7.26]	0.074
			Hedges G	0.17	[-0.02; 0.36]	
Grade 3	90 4.01 (2.38)	99 -0.78 (2.33)	Difference	4.79	[-1.78; 11.36]	0.152
			Hedges G	0.21	[-0.08; 0.50]	
Histological subtype						
Interaction test	p = 0.618					
Ductal	252 3.81 (1.28)	263 -1.66 (1.31)	Difference	5.48	[1.88; 9.07]	0.003
			Hedges G	0.26	[0.09; 0.44]	
Lobular	74 2.63 (2.39)	60 -1.50 (2.76)	Difference	4.13	[-3.11; 11.36]	0.261
			Hedges G	0.20	[-0.15; 0.54]	
Other	30 6.36 (3.32)	28 8.37 (3.47)	Difference	-2.01	[-11.63; 7.62]	0.678
			Hedges G	-0.11	[-0.63; 0.41]	
Ki67 status from surgical specimen						
Interaction test	p = 0.185					
Ki67≤20	169 4.22 (1.83)	165 -3.66 (1.92)	Difference	7.88	[2.65; 13.11]	0.003
			Hedges G	0.32	[0.11; 0.54]	
Ki67>20	127 4.26 (2.20)	137 2.05 (2.18)	Difference	2.21	[-3.89; 8.31]	0.476
			Hedges G	0.09	[-0.15; 0.33]	
Type of NSAI						
Interaction test	p = 0.834					
Letrozole	220 5.37 (1.67)	227 -0.11 (1.67)	Difference	5.48	[0.85; 10.12]	0.021
			Hedges G	0.22	[0.03; 0.41]	
Anastrozole	136 0.32 (1.90)	123 -4.01 (2.10)	Difference	4.32	[-1.25; 9.89]	0.128
			Hedges G	0.19	[-0.05; 0.43]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.163					
Yes	283 0.84 (1.47)	278 -2.91 (1.52)	Difference	3.75	[-0.40; 7.90]	0.076
			Hedges G	0.15	[-0.02; 0.32]	
No	73 13.01 (2.37)	73 3.39 (2.47)	Difference	9.62	[2.85; 16.39]	0.006
			Hedges G	0.46	[0.14; 0.79]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.417					
Yes	173 -2.08 (1.95)	185 -5.28 (1.92)	Difference	3.20	[-2.18; 8.59]	0.243
			Hedges G	0.12	[-0.08; 0.33]	
No	183 8.82 (1.70)	166 2.42 (1.84)	Difference	6.40	[1.48; 11.32]	0.011
			Hedges G	0.27	[0.06; 0.49]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	p = 0.298					
Yes	117 4.07 (2.20)	103 1.78 (2.39)	Difference	2.29	[-4.12; 8.70]	0.483
			Hedges G	0.10	[-0.17; 0.36]	
No	239 3.42 (1.56)	248 -2.89 (1.58)	Difference	6.31	[1.94; 10.67]	0.005
			Hedges G	0.26	[0.08; 0.44]	
Prior endocrine therapy						
Interaction test	p = 0.509					
Yes	209 6.91 (1.69)	220 2.80 (1.69)	Difference	4.11	[-0.58; 8.81]	0.086
			Hedges G	0.17	[-0.02; 0.36]	
No	147 -1.68 (1.88)	131 -8.41 (2.03)	Difference	6.73	[1.28; 12.19]	0.016
			Hedges G	0.29	[0.06; 0.53]	
Prior mastectomy						
Interaction test	p = 0.141					
Yes	217 1.11 (1.59)	224 -1.31 (1.60)	Difference	2.42	[-2.01; 6.85]	0.283
			Hedges G	0.10	[-0.08; 0.29]	
No	139 6.97 (2.15)	127 -1.58 (2.31)	Difference	8.55	[2.34; 14.76]	0.007
			Hedges G	0.33	[0.09; 0.57]	
Prior radiotherapy						
Interaction test	p = 0.605					
Yes	303 3.95 (1.42)	301 -1.41 (1.46)	Difference	5.36	[1.36; 9.35]	0.009
			Hedges G	0.21	[0.05; 0.37]	
No	53 1.15 (2.85)	50 -2.37 (3.07)	Difference	3.52	[-4.89; 11.92]	0.408
			Hedges G	0.16	[-0.22; 0.55]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: $\text{change from baseline} = \text{treatment} + \text{visit} + \text{treatment} * \text{visit} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor} + \text{subgroup factor} * \text{visit} + \text{treatment} * \text{subgroup factor} * \text{visit} + \text{baseline value}$ If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: $\text{change from baseline} = \text{treatment} + \text{visit} + \text{treatment} * \text{visit} + \text{baseline value}$ ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>† The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

5-2.4 EORTC QLQ-BR23 QoL

Table 5-2.4.1.1 QLQ-BR23 - Body Image: change from baseline analysis - subgroup analysis (Full Analysis Set)

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-BR23 - Body Image						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.987					
NA/WE/O	829 2.36 (0.60)	765 1.89 (0.62)	Difference	0.47	[-1.21; 2.15]	0.581
			Hedges G	0.03	[-0.07; 0.13]	
ROW	498 2.99 (0.78)	489 2.51 (0.79)	Difference	0.47	[-1.70; 2.64]	0.670
			Hedges G	0.03	[-0.10; 0.15]	
Geographical region						
Interaction test	p = 0.841					
Europe	786 3.77 (0.60)	768 2.76 (0.60)	Difference	1.00	[-0.65; 2.66]	0.235
			Hedges G	0.06	[-0.04; 0.16]	
North America/Australia	369 1.76 (0.83)	322 1.75 (0.88)	Difference	0.00	[-2.36; 2.37]	0.999
			Hedges G	0.00	[-0.15; 0.15]	
Asia	101 -2.15 (1.58)	93 -1.61 (1.74)	Difference	-0.54	[-5.18; 4.10]	0.818
			Hedges G	-0.03	[-0.31; 0.25]	
Latin America	71 2.40 (2.25)	71 1.23 (2.26)	Difference	1.17	[-5.18; 7.52]	0.716
			Hedges G	0.06	[-0.27; 0.39]	
Age group 1 at randomization						
Interaction test	p = 0.904					
<45	55 5.16 (2.39)	48 4.63 (2.58)	Difference	0.53	[-6.45; 7.51]	0.880
			Hedges G	0.03	[-0.36; 0.42]	
45 to 54	287 4.67 (1.06)	287 2.98 (1.07)	Difference	1.70	[-1.26; 4.65]	0.261
			Hedges G	0.09	[-0.07; 0.26]	
55 to 64	615 2.54 (0.65)	602 2.21 (0.65)	Difference	0.33	[-1.48; 2.15]	0.718
			Hedges G	0.02	[-0.09; 0.13]	
≥65	370 1.17 (0.82)	317 1.04 (0.88)	Difference	0.13	[-2.23; 2.50]	0.913
			Hedges G	0.01	[-0.14; 0.16]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.166					
<Median	601 4.49 (0.74)	575 2.96 (0.76)	Difference	1.53	[-0.56; 3.62]	0.151
			Hedges G	0.08	[-0.03; 0.20]	
≥Median	726 1.24 (0.61)	679 1.51 (0.63)	Difference	-0.27	[-1.99; 1.44]	0.753
			Hedges G	-0.02	[-0.12; 0.09]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.859					
Asian	125 -2.03 (1.40)	116 -2.14 (1.52)	Difference	0.11	[-3.96; 4.18]	0.958
			Hedges G	0.01	[-0.25; 0.26]	
Non-Asian	1126 3.17 (0.50)	1077 2.67 (0.50)	Difference	0.49	[-0.89; 1.88]	0.485
			Hedges G	0.03	[-0.05; 0.11]	
BMI at screening						
Interaction test	p = 0.970					
≥25	876 2.30 (0.59)	859 1.83 (0.60)	Difference	0.47	[-1.18; 2.12]	0.577
			Hedges G	0.03	[-0.07; 0.12]	
<25	440 3.13 (0.80)	384 2.61 (0.85)	Difference	0.52	[-1.78; 2.82]	0.657
			Hedges G	0.03	[-0.11; 0.17]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.221					
Group I/II	544 3.26 (0.69)	549 1.65 (0.68)	Difference	1.61	[-0.29; 3.51]	0.097
			Hedges G	0.10	[-0.02; 0.22]	
Group III	782 2.45 (0.65)	705 2.59 (0.68)	Difference	-0.14	[-1.99; 1.70]	0.880
			Hedges G	-0.01	[-0.11; 0.09]	
Anatomic stages						
Interaction test	p = 0.587					
IA/IB/IIA	287 3.61 (0.87)	289 2.13 (0.87)	Difference	1.48	[-0.93; 3.89]	0.228
			Hedges G	0.10	[-0.06; 0.26]	
IIB	257 2.93 (0.99)	260 1.27 (0.98)	Difference	1.65	[-1.09; 4.40]	0.238
			Hedges G	0.10	[-0.07; 0.28]	
IIIA	460 1.89 (0.82)	414 2.83 (0.85)	Difference	-0.94	[-3.26; 1.38]	0.426
			Hedges G	-0.05	[-0.19; 0.08]	
IIIB	92 5.73 (1.86)	78 5.06 (2.03)	Difference	0.67	[-4.76; 6.10]	0.808
			Hedges G	0.04	[-0.26; 0.34]	
IIIC	230 2.02 (1.16)	213 0.72 (1.22)	Difference	1.29	[-2.01; 4.60]	0.442
			Hedges G	0.07	[-0.11; 0.26]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.243					
N0	175 4.76 (1.11)	187 2.15 (1.08)	Difference	2.61	[-0.42; 5.65]	0.091
			Hedges G	0.18	[-0.03; 0.38]	
N1-N3	1149 2.44 (0.50)	1067 2.17 (0.51)	Difference	0.27	[-1.14; 1.67]	0.711
			Hedges G	0.02	[-0.07; 0.10]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.219					
Grade 1	95 4.40 (1.44)	103 -0.47 (1.33)	Difference	4.88	[1.01; 8.75]	0.014
			Hedges G	0.35	[0.07; 0.63]	
Grade 2	792 2.96 (0.58)	702 2.48 (0.62)	Difference	0.48	[-1.18; 2.15]	0.569
			Hedges G	0.03	[-0.07; 0.13]	
Grade 3	354 2.29 (0.93)	365 1.95 (0.92)	Difference	0.35	[-2.21; 2.91]	0.789
			Hedges G	0.02	[-0.13; 0.17]	
Histological subtype						
Interaction test	p = 0.243					
Ductal	963 2.60 (0.54)	921 2.40 (0.55)	Difference	0.20	[-1.31; 1.71]	0.796
			Hedges G	0.01	[-0.08; 0.10]	
Lobular	276 2.40 (0.95)	263 1.53 (0.97)	Difference	0.86	[-1.80; 3.52]	0.524
			Hedges G	0.05	[-0.11; 0.22]	
Other	87 5.78 (1.84)	70 1.15 (2.09)	Difference	4.62	[-0.87; 10.12]	0.099
			Hedges G	0.27	[-0.05; 0.58]	
Ki67 status from surgical specimen						
Interaction test	p = 0.912					
Ki67≤20	620 2.23 (0.68)	589 1.32 (0.70)	Difference	0.91	[-1.00; 2.82]	0.350
			Hedges G	0.05	[-0.06; 0.17]	
Ki67>20	468 3.31 (0.81)	471 2.24 (0.81)	Difference	1.07	[-1.19; 3.33]	0.353
			Hedges G	0.06	[-0.07; 0.19]	
Type of NSAI						
Interaction test	p = 0.630					
Letrozole	852 1.97 (0.59)	819 1.83 (0.59)	Difference	0.14	[-1.50; 1.78]	0.866
			Hedges G	0.01	[-0.09; 0.10]	
Anastrozole	475 4.00 (0.80)	432 2.66 (0.84)	Difference	1.34	[-0.95; 3.62]	0.251
			Hedges G	0.08	[-0.05; 0.21]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.340					
Yes	1134 3.04 (0.52)	1049 2.79 (0.54)	Difference	0.25	[-1.23; 1.73]	0.740
			Hedges G	0.01	[-0.07; 0.10]	
No	193 1.03 (1.10)	205 -0.71 (1.07)	Difference	1.74	[-1.28; 4.77]	0.258
			Hedges G	0.11	[-0.08; 0.31]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.940					
Yes	658 3.62 (0.69)	629 2.91 (0.69)	Difference	0.70	[-1.21; 2.62]	0.471
			Hedges G	0.04	[-0.07; 0.15]	
No	669 1.79 (0.65)	625 1.22 (0.68)	Difference	0.58	[-1.27; 2.42]	0.541
			Hedges G	0.03	[-0.08; 0.14]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test p = 0.725						
Yes	503 2.71 (0.77)	449 2.25 (0.82)	Difference	0.47	[-1.75; 2.68]	0.680
			Hedges G	0.03	[-0.10; 0.15]	
No	824 2.83 (0.60)	805 2.01 (0.60)	Difference	0.82	[-0.84; 2.48]	0.334
			Hedges G	0.05	[-0.05; 0.15]	
Prior endocrine therapy						
Interaction test p = 0.323						
Yes	898 1.49 (0.56)	865 1.43 (0.57)	Difference	0.06	[-1.51; 1.63]	0.938
			Hedges G	0.00	[-0.09; 0.10]	
No	429 5.35 (0.85)	389 3.65 (0.89)	Difference	1.70	[-0.71; 4.12]	0.166
			Hedges G	0.10	[-0.04; 0.23]	
Prior mastectomy						
Interaction test p = 0.269						
Yes	809 3.22 (0.63)	774 3.28 (0.64)	Difference	-0.06	[-1.84; 1.71]	0.943
			Hedges G	-0.00	[-0.10; 0.09]	
No	518 1.99 (0.70)	480 0.55 (0.72)	Difference	1.44	[-0.53; 3.42]	0.151
			Hedges G	0.09	[-0.03; 0.22]	
Prior radiotherapy						
Interaction test p = 0.756						
Yes	1180 2.43 (0.50)	1107 1.84 (0.52)	Difference	0.59	[-0.82; 2.00]	0.413
			Hedges G	0.03	[-0.05; 0.12]	
No	147 4.18 (1.42)	147 4.55 (1.41)	Difference	-0.37	[-4.31; 3.56]	0.852
			Hedges G	-0.02	[-0.25; 0.21]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: $\text{change from baseline} = \text{treatment} + \text{visit} + \text{treatment} * \text{visit} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor} + \text{subgroup factor} * \text{visit} + \text{treatment} * \text{subgroup factor} * \text{visit} + \text{baseline value}$ If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: $\text{change from baseline} = \text{treatment} + \text{visit} + \text{treatment} * \text{visit} + \text{baseline value}$ ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>† The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

Table 5-2.4.2.1 QLQ-BR23 - Sexual Functioning: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-BR23 - Sexual Functioning						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.920					
NA/WE/O	804 -1.76 (0.47)	738 -1.84 (0.49)	Difference	0.08	[-1.25; 1.40]	0.911
			Hedges G	0.01	[-0.09; 0.11]	
ROW	493 -2.39 (0.55)	483 -2.49 (0.56)	Difference	0.10	[-1.44; 1.64]	0.900
			Hedges G	0.01	[-0.12; 0.13]	
Geographical region						
Interaction test	p = 0.962					
Europe	762 N.E.	744 N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
North America/Australia	365 -2.20 (0.65)	314 -2.34 (0.69)	Difference	0.14	[-1.71; 2.00]	0.878
			Hedges G	0.01	[-0.14; 0.16]	
Asia	100 -3.51 (1.07)	92 -3.69 (1.20)	Difference	0.19	[-2.99; 3.36]	0.908
			Hedges G	0.02	[-0.27; 0.30]	
Latin America	70 -1.93 (1.80)	71 -2.27 (1.78)	Difference	0.33	[-4.68; 5.34]	0.895
			Hedges G	0.02	[-0.31; 0.35]	
Age group 1 at randomization						
Interaction test	p = 0.071					
<45	55 -6.76 (2.26)	48 -1.24 (2.44)	Difference	-5.52	[-12.18; 1.14]	0.103
			Hedges G	-0.32	[-0.71; 0.06]	
45 to 54	282 -1.84 (0.83)	281 -2.54 (0.84)	Difference	0.70	[-1.62; 3.02]	0.554
			Hedges G	0.05	[-0.12; 0.22]	
55 to 64	599 -1.93 (0.53)	595 -2.11 (0.52)	Difference	0.18	[-1.28; 1.63]	0.811
			Hedges G	0.01	[-0.10; 0.13]	
≥65	361 -0.95 (0.56)	297 -1.78 (0.61)	Difference	0.84	[-0.78; 2.45]	0.310
			Hedges G	0.08	[-0.07; 0.23]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.295					
<Median	589 -2.20 (0.59)	566 -2.11 (0.60)	Difference	-0.09	[-1.74; 1.57]	0.916
			Hedges G	-0.01	[-0.12; 0.11]	
≥Median	708 -1.45 (0.44)	655 -2.16 (0.45)	Difference	0.70	[-0.53; 1.94]	0.263
			Hedges G	0.06	[-0.05; 0.17]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.764					
Asian	124 -3.02 (1.02)	115 -2.99 (1.13)	Difference	-0.03	[-3.02; 2.97]	0.986
			Hedges G	-0.00	[-0.26; 0.25]	
Non-Asian	1099 -1.89 (0.39)	1048 -2.06 (0.39)	Difference	0.17	[-0.92; 1.25]	0.764
			Hedges G	0.01	[-0.07; 0.10]	
BMI at screening						
Interaction test	p = 0.014					
≥25	858 -1.52 (0.42)	839 -2.51 (0.43)	Difference	0.99	[-0.19; 2.17]	0.099
			Hedges G	0.08	[-0.02; 0.18]	
<25	428 -3.15 (0.68)	371 -1.26 (0.72)	Difference	-1.89	[-3.84; 0.05]	0.056
			Hedges G	-0.14	[-0.27; 0.00]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.221					
Group I/II	529 -1.37 (0.57)	535 -2.27 (0.56)	Difference	0.89	[-0.67; 2.46]	0.263
			Hedges G	0.07	[-0.05; 0.19]	
Group III	767 -2.49 (0.47)	686 -1.89 (0.49)	Difference	-0.60	[-1.92; 0.72]	0.374
			Hedges G	-0.05	[-0.15; 0.06]	
Anatomic stages						
Interaction test	p = 0.967					
IA/IB/IIA	279 -1.49 (0.79)	283 -2.44 (0.79)	Difference	0.95	[-1.24; 3.15]	0.395
			Hedges G	0.07	[-0.09; 0.24]	
IIB	250 -1.19 (0.81)	252 -2.23 (0.80)	Difference	1.05	[-1.19; 3.28]	0.357
			Hedges G	0.08	[-0.09; 0.26]	
IIIA	451 -2.28 (0.62)	409 -1.63 (0.63)	Difference	-0.65	[-2.40; 1.09]	0.462
			Hedges G	-0.05	[-0.18; 0.08]	
IIIB	91 -4.32 (1.09)	73 -3.37 (1.22)	Difference	-0.95	[-4.18; 2.27]	0.561
			Hedges G	-0.09	[-0.40; 0.22]	
IIIC	225 -2.11 (0.89)	204 -2.00 (0.93)	Difference	-0.11	[-2.64; 2.43]	0.934
			Hedges G	-0.01	[-0.20; 0.18]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.677					
N0	169 -1.14 (0.98)	182 -1.69 (0.95)	Difference	0.54	[-2.13; 3.22]	0.690
			Hedges G	0.04	[-0.17; 0.25]	
N1-N3	1125 -2.07 (0.39)	1039 -2.15 (0.40)	Difference	0.08	[-1.00; 1.17]	0.880
			Hedges G	0.01	[-0.08; 0.09]	

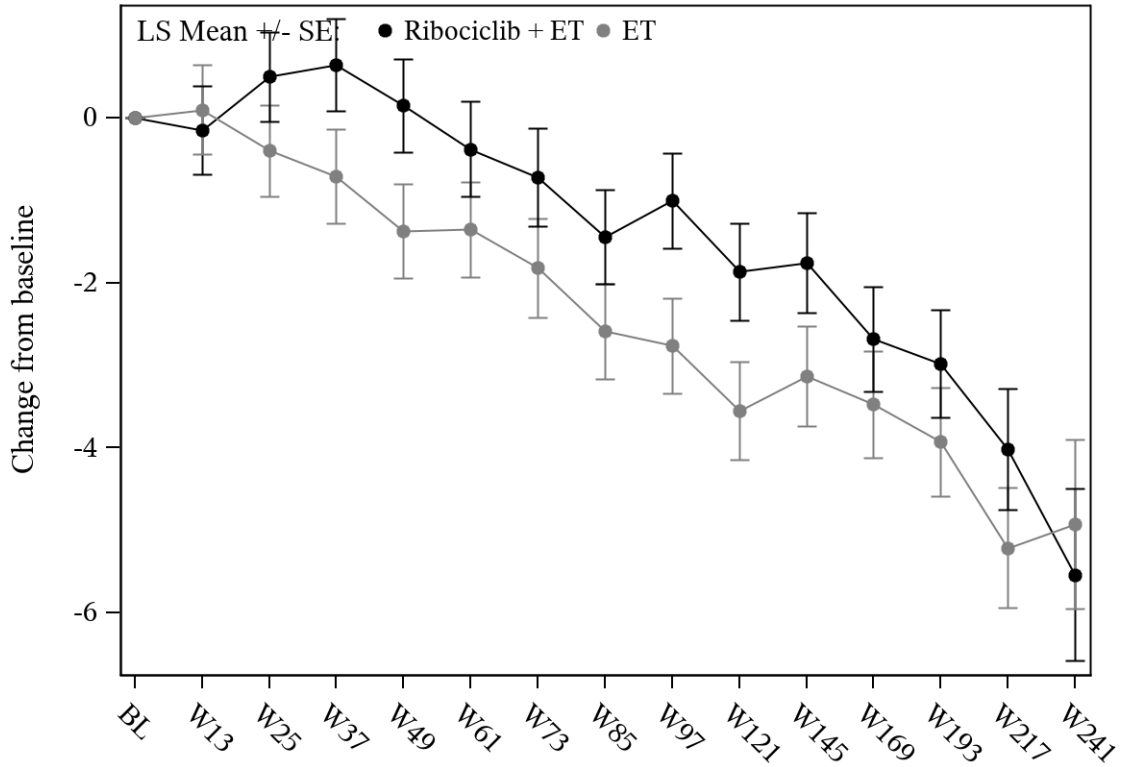
Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.395					
Grade 1	94 -0.75 (1.39)	102 -3.46 (1.28)	Difference	2.71	[-1.02; 6.43]	0.154
			Hedges G	0.20	[-0.08; 0.49]	
Grade 2	771 -2.37 (0.45)	682 -2.46 (0.48)	Difference	0.09	[-1.20; 1.39]	0.886
			Hedges G	0.01	[-0.10; 0.11]	
Grade 3	347 -0.97 (0.69)	353 -1.71 (0.68)	Difference	0.74	[-1.16; 2.65]	0.444
			Hedges G	0.06	[-0.09; 0.21]	
Histological subtype						
Interaction test	p = 0.876					
Ductal	945 -2.15 (0.42)	901 -2.20 (0.43)	Difference	0.05	[-1.13; 1.23]	0.936
			Hedges G	0.00	[-0.09; 0.10]	
Lobular	266 -1.24 (0.77)	253 -2.10 (0.78)	Difference	0.86	[-1.29; 3.01]	0.432
			Hedges G	0.07	[-0.10; 0.24]	
Other	85 -1.74 (1.43)	67 -0.37 (1.65)	Difference	-1.36	[-5.68; 2.96]	0.535
			Hedges G	-0.10	[-0.42; 0.22]	
Ki67 status from surgical specimen						
Interaction test	p = 0.239					
Ki67≤20	607 -1.95 (0.54)	577 -2.74 (0.55)	Difference	0.79	[-0.71; 2.29]	0.302
			Hedges G	0.06	[-0.05; 0.17]	
Ki67>20	455 -1.46 (0.60)	460 -0.88 (0.60)	Difference	-0.58	[-2.25; 1.10]	0.498
			Hedges G	-0.04	[-0.17; 0.08]	
Type of NSAI						
Interaction test	p = 0.713					
Letrozole	833 -1.86 (0.46)	792 -1.98 (0.47)	Difference	0.12	[-1.17; 1.40]	0.857
			Hedges G	0.01	[-0.09; 0.11]	
Anastrozole	464 -1.96 (0.58)	426 -2.36 (0.60)	Difference	0.40	[-1.25; 2.04]	0.636
			Hedges G	0.03	[-0.10; 0.16]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.213					
Yes	1107 -2.13 (0.39)	1021 -2.01 (0.41)	Difference	-0.11	[-1.22; 0.99]	0.839
			Hedges G	-0.01	[-0.09; 0.08]	
No	190 -0.75 (0.93)	200 -2.46 (0.91)	Difference	1.70	[-0.85; 4.26]	0.191
			Hedges G	0.13	[-0.07; 0.33]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.155					
Yes	641 -1.64 (0.50)	611 -2.48 (0.51)	Difference	0.84	[-0.56; 2.24]	0.240
			Hedges G	0.07	[-0.04; 0.18]	
No	656 -2.30 (0.52)	610 -1.76 (0.54)	Difference	-0.55	[-2.02; 0.92]	0.464
			Hedges G	-0.04	[-0.15; 0.07]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	p = 0.022					
Yes	493 -2.79 (0.61)	438 -1.35 (0.64)	Difference	-1.44	[-3.17; 0.30]	0.104
			Hedges G	-0.11	[-0.24; 0.02]	
No	804 -1.44 (0.45)	783 -2.45 (0.45)	Difference	1.00	[-0.25; 2.25]	0.117
			Hedges G	0.08	[-0.02; 0.18]	
Prior endocrine therapy						
Interaction test	p = 0.091					
Yes	877 -2.43 (0.44)	840 -2.02 (0.45)	Difference	-0.42	[-1.66; 0.83]	0.511
			Hedges G	-0.03	[-0.13; 0.06]	
No	420 -0.71 (0.63)	381 -2.33 (0.65)	Difference	1.62	[-0.16; 3.40]	0.074
			Hedges G	0.13	[-0.01; 0.27]	
Prior mastectomy						
Interaction test	p = 0.049					
Yes	799 -2.47 (0.44)	750 -1.76 (0.45)	Difference	-0.71	[-1.95; 0.53]	0.260
			Hedges G	-0.06	[-0.16; 0.04]	
No	498 -1.10 (0.61)	471 -2.49 (0.63)	Difference	1.39	[-0.33; 3.11]	0.113
			Hedges G	0.10	[-0.02; 0.23]	
Prior radiotherapy						
Interaction test	N.E.					
Yes	1151 -2.10 (0.38)	1075 -2.13 (0.39)	Difference	0.03	[-1.05; 1.10]	0.963
			Hedges G	0.00	[-0.08; 0.09]	
No	146 -0.89 (1.01)	146 -1.97 (1.00)	Difference	1.09	[-1.71; 3.88]	0.445
			Hedges G	0.09	[-0.14; 0.32]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed N.E.: Not estimable ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + baseline value ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>+ The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

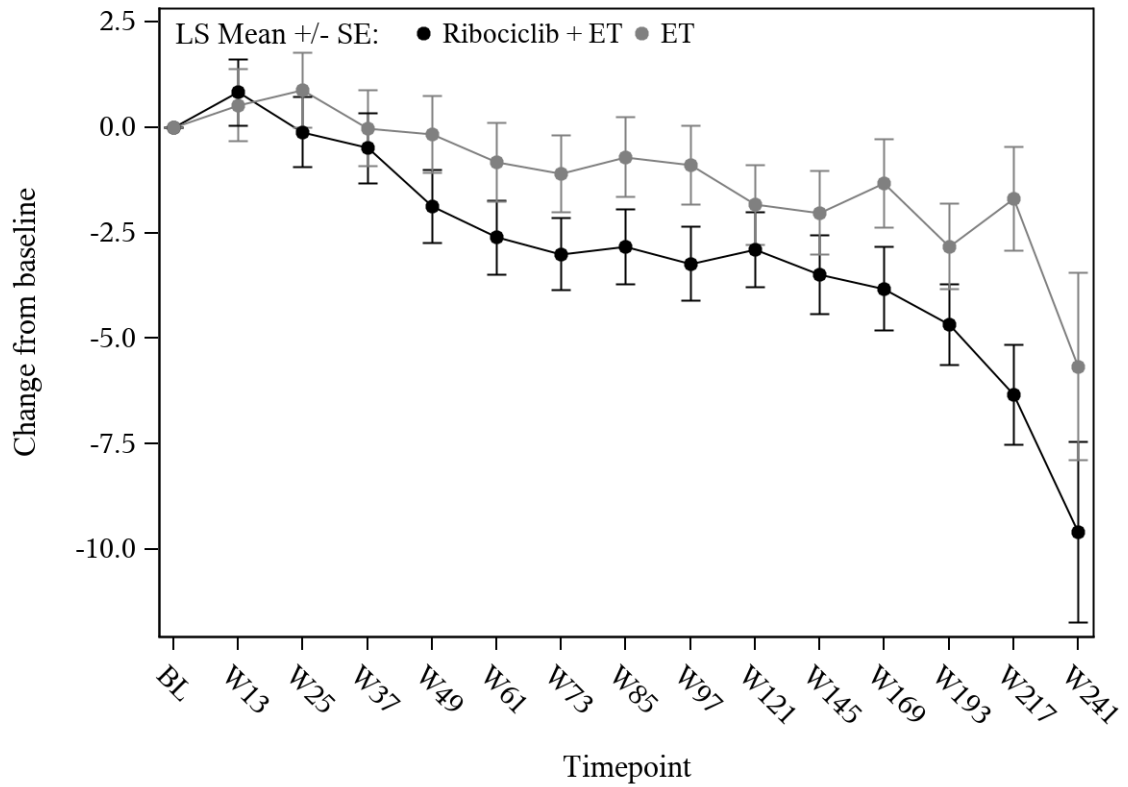
Figure 5-2.4.2.1 QLQ-BR23 - Sexual Functioning: line chart of change from baseline - subgroup analysis (Full Analysis Set)

**QLQ-BR23 - Sexual Functioning
 BMI at screening: ≥ 25**



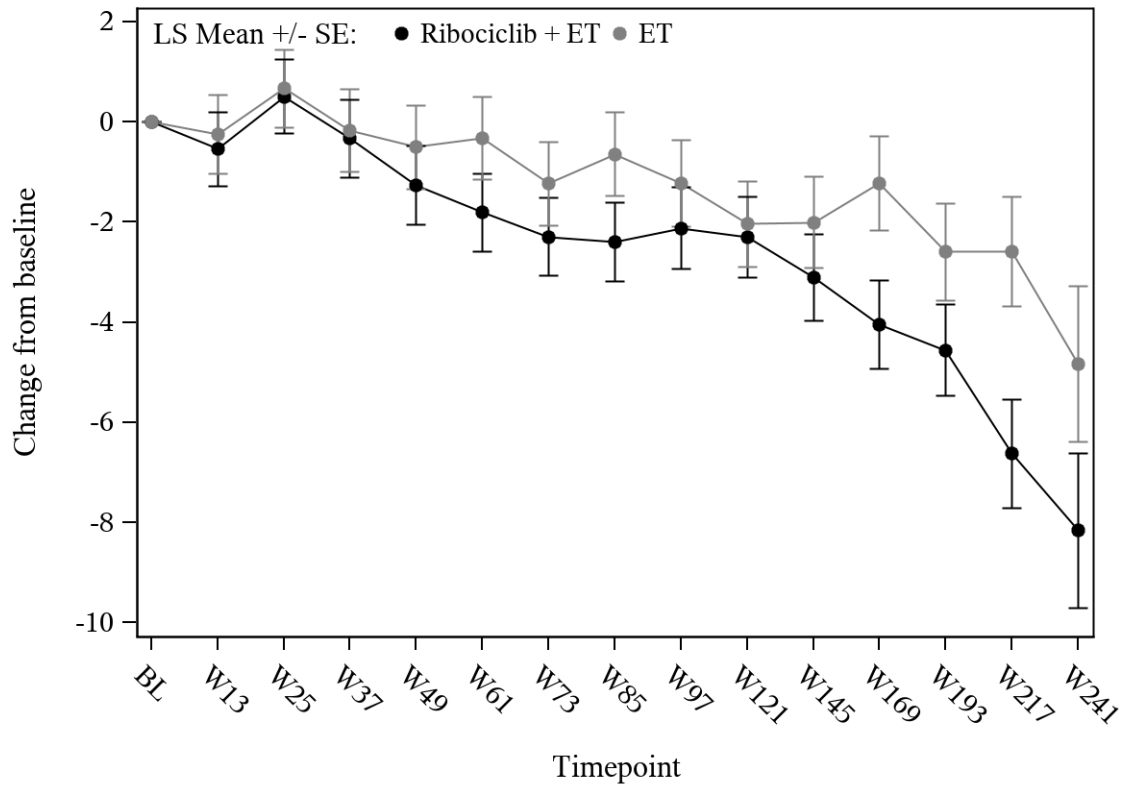
Ribociclib + ET	858	809	781	784	760	753	743	709	716	681	670	570	476	303	64
ET	839	786	757	750	758	743	727	721	710	685	671	558	470	314	66

QLQ-BR23 - Sexual Functioning
BMI at screening: <25



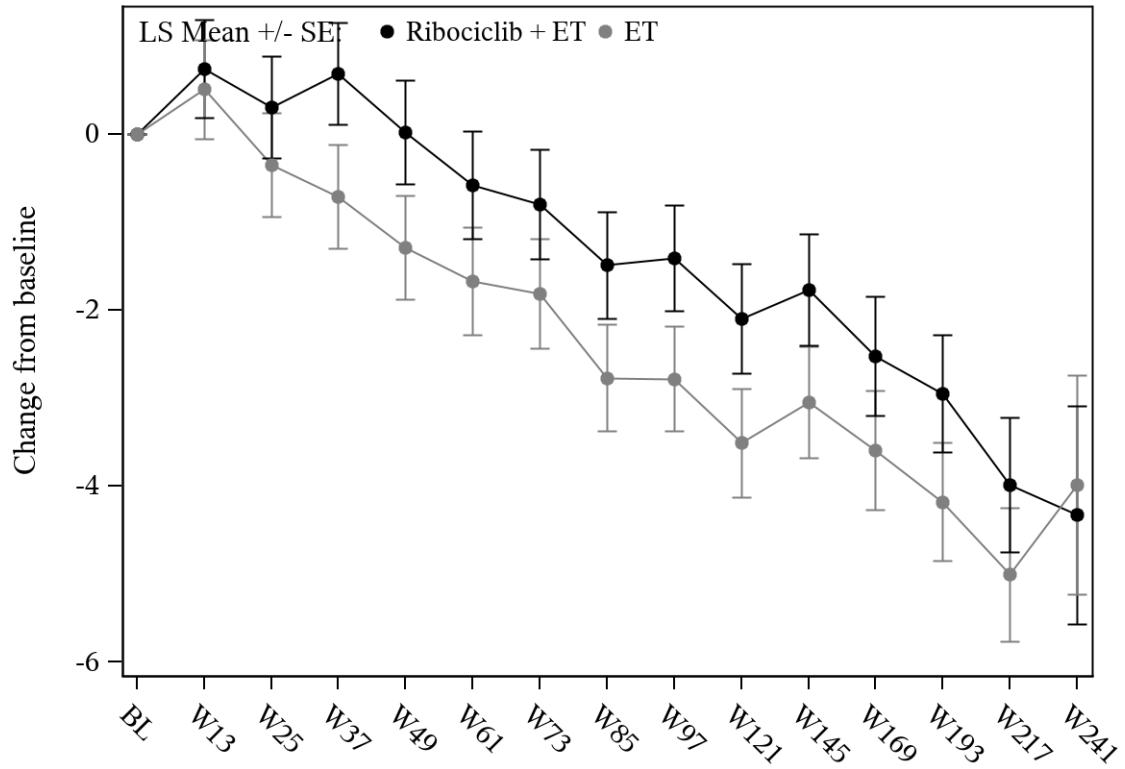
Ribociclib + ET	428	406	386	372	366	352	350	348	341	329	324	275	227	137	24
ET	371	347	334	332	328	320	318	307	300	297	280	251	210	131	24

QLQ-BR23 - Sexual Functioning
Prior neoadjuvant chemotherapy: Yes



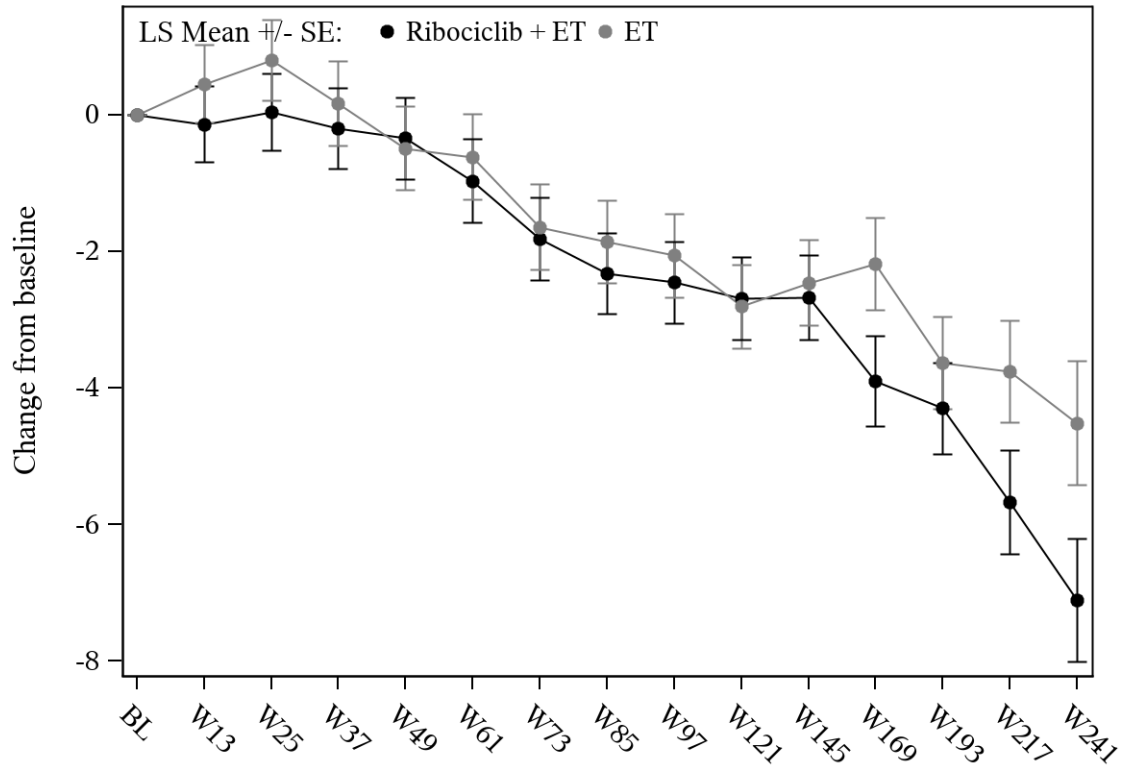
Ribociclib + ET	493	462	452	436	433	424	419	404	398	384	371	294	221	127	23
ET	438	411	398	380	384	377	370	359	351	339	330	263	203	129	25

QLQ-BR23 - Sexual Functioning
Prior neoadjuvant chemotherapy: No



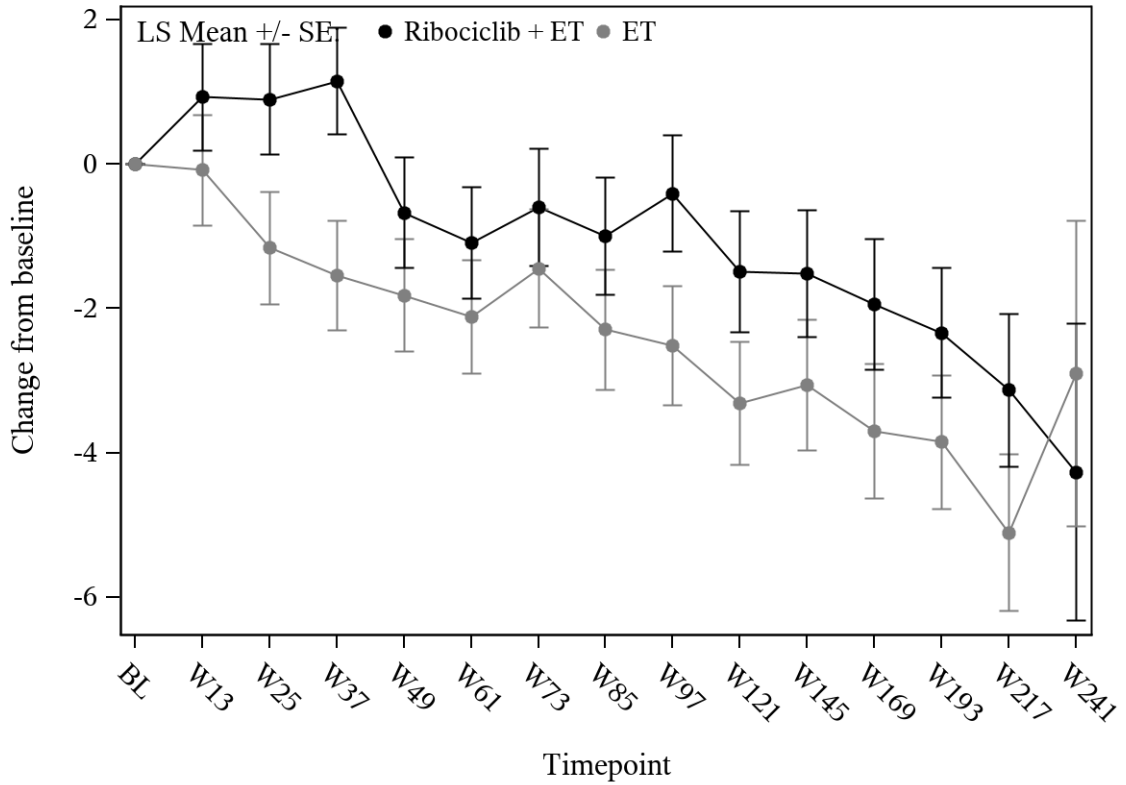
Ribociclib + ET	804	763	725	729	703	691	684	663	669	633	632	558	489	317	66
ET	783	731	701	711	713	694	684	676	670	650	629	554	483	321	65

QLQ-BR23 - Sexual Functioning
Prior mastectomy: Yes



Ribociclib + ET	799	754	744	717	702	693	688	654	659	619	606	493	392	256	55
ET	750	704	670	676	673	658	648	639	629	610	593	489	398	270	58

QLQ-BR23 - Sexual Functioning
Prior mastectomy: No



Ribociclib + ET	498	471	433	448	434	422	415	413	408	398	397	359	318	188	34
ET	471	438	429	415	424	413	406	396	392	379	366	328	288	180	32

Table 5-2.4.3.1 QLQ-BR23 - Sexual Enjoyment: change from baseline analysis - subgroup analysis (Full Analysis Set)

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-BR23 - Sexual Enjoyment						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.985					
NA/WE/O	377 -5.56 (0.94)	300 -4.91 (1.05)	Difference	-0.65	[-3.40; 2.11]	0.646
			Hedges G	-0.04	[-0.19; 0.12]	
ROW	206 -6.96 (1.33)	213 -6.36 (1.34)	Difference	-0.59	[-4.29; 3.11]	0.752
			Hedges G	-0.03	[-0.22; 0.16]	
Geographical region						
Interaction test	p = 0.094					
Europe	332 -5.58 (0.74)	301 -5.31 (0.80)	Difference	-0.27	[-2.40; 1.87]	0.807
			Hedges G	-0.02	[-0.18; 0.14]	
North America/Australia	163 -2.50 (1.09)	138 -5.65 (1.13)	Difference	3.15	[0.06; 6.24]	0.045
			Hedges G	0.23	[0.00; 0.46]	
Asia	43 -7.76 (1.85)	36 -9.78 (2.04)	Difference	2.02	[-3.47; 7.51]	0.465
			Hedges G	0.17	[-0.28; 0.61]	
Latin America	45 -7.20 (1.99)	38 0.06 (2.24)	Difference	-7.26	[-13.21; -1.30]	0.018
			Hedges G	-0.53	[-0.97; -0.09]	
Age group 1 at randomization						
Interaction test	p = 0.710					
<45	37 -9.29 (2.98)	28 -4.33 (3.52)	Difference	-4.96	[-14.35; 4.44]	0.296
			Hedges G	-0.26	[-0.76; 0.23]	
45 to 54	152 -7.46 (1.50)	137 -7.40 (1.60)	Difference	-0.06	[-4.36; 4.24]	0.978
			Hedges G	-0.00	[-0.23; 0.23]	
55 to 64	267 -5.67 (1.12)	248 -5.73 (1.17)	Difference	0.06	[-3.11; 3.24]	0.969
			Hedges G	0.00	[-0.17; 0.18]	
≥65	127 -3.47 (1.63)	100 -3.76 (1.85)	Difference	0.29	[-4.55; 5.13]	0.906
			Hedges G	0.02	[-0.25; 0.28]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.718					
<Median	314 -7.02 (1.06)	270 -6.22 (1.15)	Difference	-0.81	[-3.88; 2.26]	0.606
			Hedges G	-0.04	[-0.21; 0.12]	
≥Median	269 -4.94 (1.14)	243 -5.15 (1.22)	Difference	0.21	[-3.06; 3.47]	0.901
			Hedges G	0.01	[-0.16; 0.18]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.915					
Asian	50 -7.22 (2.61)	47 -6.71 (2.69)	Difference	-0.52	[-7.96; 6.93]	0.890
			Hedges G	-0.03	[-0.43; 0.37]	
Non-Asian	496 -5.83 (0.81)	445 -5.97 (0.87)	Difference	0.14	[-2.18; 2.47]	0.903
			Hedges G	0.01	[-0.12; 0.14]	
BMI at screening						
Interaction test	p = 0.038					
≥25	367 -5.57 (0.95)	345 -6.73 (0.99)	Difference	1.17	[-1.53; 3.87]	0.395
			Hedges G	0.06	[-0.08; 0.21]	
<25	209 -7.55 (1.33)	163 -3.44 (1.51)	Difference	-4.11	[-8.06; -0.17]	0.041
			Hedges G	-0.21	[-0.42; -0.01]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.855					
Group I/II	235 -6.51 (1.24)	232 -5.92 (1.25)	Difference	-0.59	[-4.05; 2.87]	0.738
			Hedges G	-0.03	[-0.21; 0.15]	
Group III	348 -5.40 (1.00)	281 -5.46 (1.13)	Difference	0.06	[-2.89; 3.01]	0.967
			Hedges G	0.00	[-0.15; 0.16]	
Anatomic stages						
Interaction test	p = 0.998					
IA/IB/IIA	120 -5.31 (1.36)	121 -5.05 (1.37)	Difference	-0.26	[-4.07; 3.55]	0.893
			Hedges G	-0.02	[-0.27; 0.24]	
IIB	115 -5.78 (1.25)	111 -5.44 (1.26)	Difference	-0.33	[-3.84; 3.17]	0.851
			Hedges G	-0.03	[-0.29; 0.24]	
IIIA	209 -4.91 (0.92)	165 -5.32 (1.09)	Difference	0.41	[-2.38; 3.21]	0.773
			Hedges G	0.03	[-0.17; 0.23]	
IIIB	37 -2.68 (2.43)	34 -4.66 (2.71)	Difference	1.98	[-5.29; 9.25]	0.588
			Hedges G	0.13	[-0.34; 0.60]	
IIIC	102 -5.29 (1.46)	82 -6.75 (1.63)	Difference	1.46	[-2.85; 5.78]	0.504
			Hedges G	0.10	[-0.19; 0.39]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.849					
N0	64 -5.29 (2.37)	71 -3.54 (2.27)	Difference	-1.75	[-8.25; 4.76]	0.596
			Hedges G	-0.09	[-0.43; 0.25]	
N1-N3	517 -6.09 (0.80)	442 -6.02 (0.87)	Difference	-0.07	[-2.38; 2.25]	0.955
			Hedges G	-0.00	[-0.13; 0.12]	

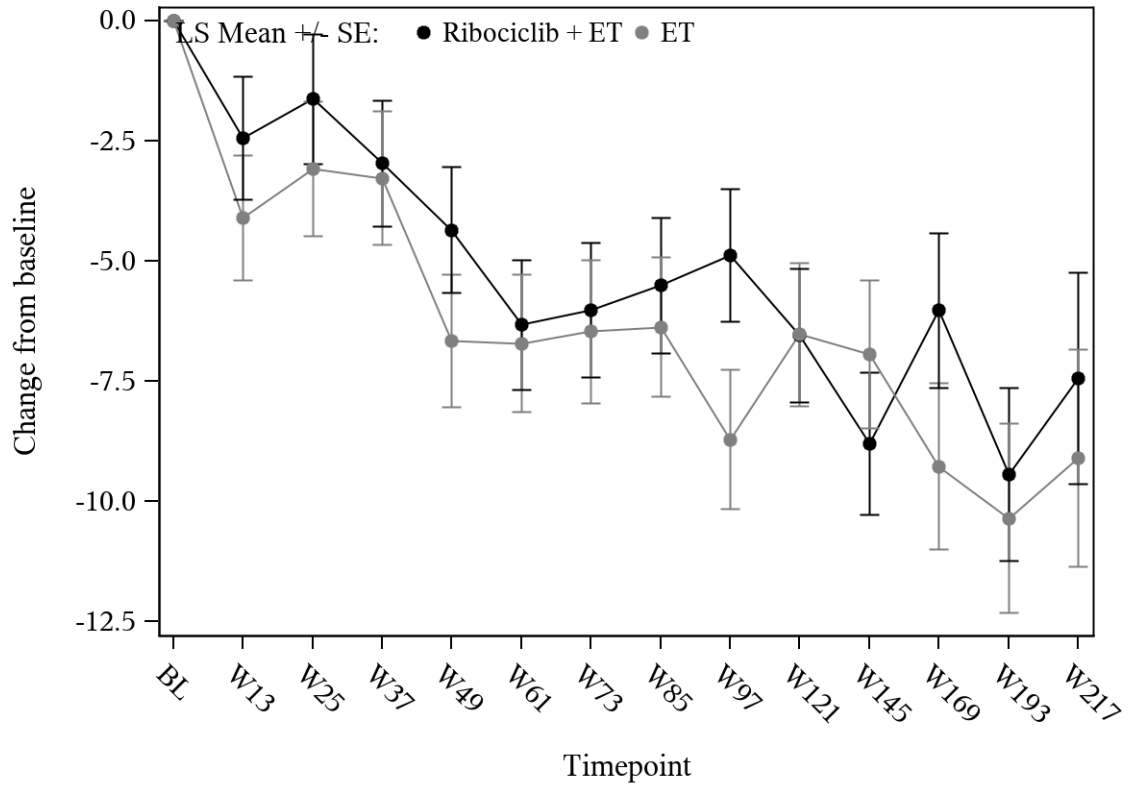
Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.148					
Grade 1	41 -1.73 (2.95)	47 -8.89 (2.84)	Difference	7.16	[-0.97; 15.29]	0.084
			Hedges G	0.37	[-0.05; 0.80]	
Grade 2	349 -7.54 (0.95)	283 -6.28 (1.07)	Difference	-1.27	[-4.07; 1.53]	0.374
			Hedges G	-0.07	[-0.23; 0.09]	
Grade 3	153 -3.22 (1.54)	141 -2.66 (1.59)	Difference	-0.56	[-4.91; 3.79]	0.801
			Hedges G	-0.03	[-0.26; 0.20]	
Histological subtype						
Interaction test	p = 0.890					
Ductal	428 -6.14 (0.91)	372 -5.80 (0.98)	Difference	-0.33	[-2.96; 2.29]	0.804
			Hedges G	-0.02	[-0.16; 0.12]	
Lobular	116 -5.51 (1.58)	105 -4.61 (1.67)	Difference	-0.90	[-5.42; 3.62]	0.696
			Hedges G	-0.05	[-0.32; 0.21]	
Other	39 -6.17 (2.70)	36 -8.45 (3.02)	Difference	2.28	[-5.83; 10.39]	0.577
			Hedges G	0.13	[-0.32; 0.58]	
Ki67 status from surgical specimen						
Interaction test	p = 0.634					
Ki67≤20	273 -6.22 (1.13)	239 -5.15 (1.22)	Difference	-1.06	[-4.33; 2.20]	0.522
			Hedges G	-0.06	[-0.23; 0.12]	
Ki67>20	209 -6.01 (1.30)	193 -6.17 (1.38)	Difference	0.16	[-3.56; 3.87]	0.934
			Hedges G	0.01	[-0.19; 0.20]	
Type of NSAI						
Interaction test	p = 0.119					
Letrozole	373 -7.02 (0.98)	340 -5.37 (1.04)	Difference	-1.65	[-4.45; 1.15]	0.247
			Hedges G	-0.09	[-0.23; 0.06]	
Anastrozole	210 -3.95 (1.26)	173 -6.34 (1.38)	Difference	2.39	[-1.28; 6.07]	0.201
			Hedges G	0.13	[-0.07; 0.33]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.937					
Yes	511 -5.57 (0.81)	432 -5.24 (0.89)	Difference	-0.33	[-2.69; 2.03]	0.785
			Hedges G	-0.02	[-0.15; 0.11]	
No	72 -8.72 (2.12)	81 -8.03 (2.03)	Difference	-0.69	[-6.46; 5.08]	0.814
			Hedges G	-0.04	[-0.36; 0.28]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.809					
Yes	284 -4.29 (1.10)	259 -4.17 (1.16)	Difference	-0.12	[-3.27; 3.03]	0.940
			Hedges G	-0.01	[-0.17; 0.16]	
No	299 -7.90 (1.10)	254 -7.43 (1.20)	Difference	-0.47	[-3.66; 2.72]	0.773
			Hedges G	-0.02	[-0.19; 0.14]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test p = 0.808						
Yes	239 -7.37 (1.25)	187 -6.56 (1.44)	Difference	-0.81	[-4.54; 2.92]	0.670
			Hedges G	-0.04	[-0.23; 0.15]	
No	344 -5.33 (1.00)	326 -5.18 (1.03)	Difference	-0.15	[-2.96; 2.66]	0.916
			Hedges G	-0.01	[-0.16; 0.14]	
Prior endocrine therapy						
Interaction test p = 0.276						
Yes	392 -6.80 (0.90)	359 -5.70 (0.95)	Difference	-1.10	[-3.65; 1.46]	0.400
			Hedges G	-0.06	[-0.20; 0.08]	
No	191 -4.19 (1.52)	154 -5.61 (1.70)	Difference	1.42	[-3.05; 5.89]	0.533
			Hedges G	0.07	[-0.14; 0.28]	
Prior mastectomy						
Interaction test p = 0.772						
Yes	359 -6.01 (1.02)	309 -5.33 (1.11)	Difference	-0.67	[-3.62; 2.27]	0.654
			Hedges G	-0.03	[-0.19; 0.12]	
No	224 -6.13 (1.19)	204 -6.18 (1.26)	Difference	0.04	[-3.35; 3.44]	0.980
			Hedges G	0.00	[-0.19; 0.19]	
Prior radiotherapy						
Interaction test p = 0.283						
Yes	523 -6.14 (0.81)	453 -5.27 (0.87)	Difference	-0.88	[-3.21; 1.45]	0.459
			Hedges G	-0.05	[-0.17; 0.08]	
No	60 -5.38 (2.70)	60 -7.94 (2.72)	Difference	2.56	[-5.00; 10.13]	0.504
			Hedges G	0.12	[-0.24; 0.48]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: $\text{change from baseline} = \text{treatment} + \text{visit} + \text{treatment} * \text{visit} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor} + \text{subgroup factor} * \text{visit} + \text{treatment} * \text{subgroup factor} * \text{visit} + \text{baseline value}$ If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: $\text{change from baseline} = \text{treatment} + \text{visit} + \text{treatment} * \text{visit} + \text{baseline value}$ ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>† The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

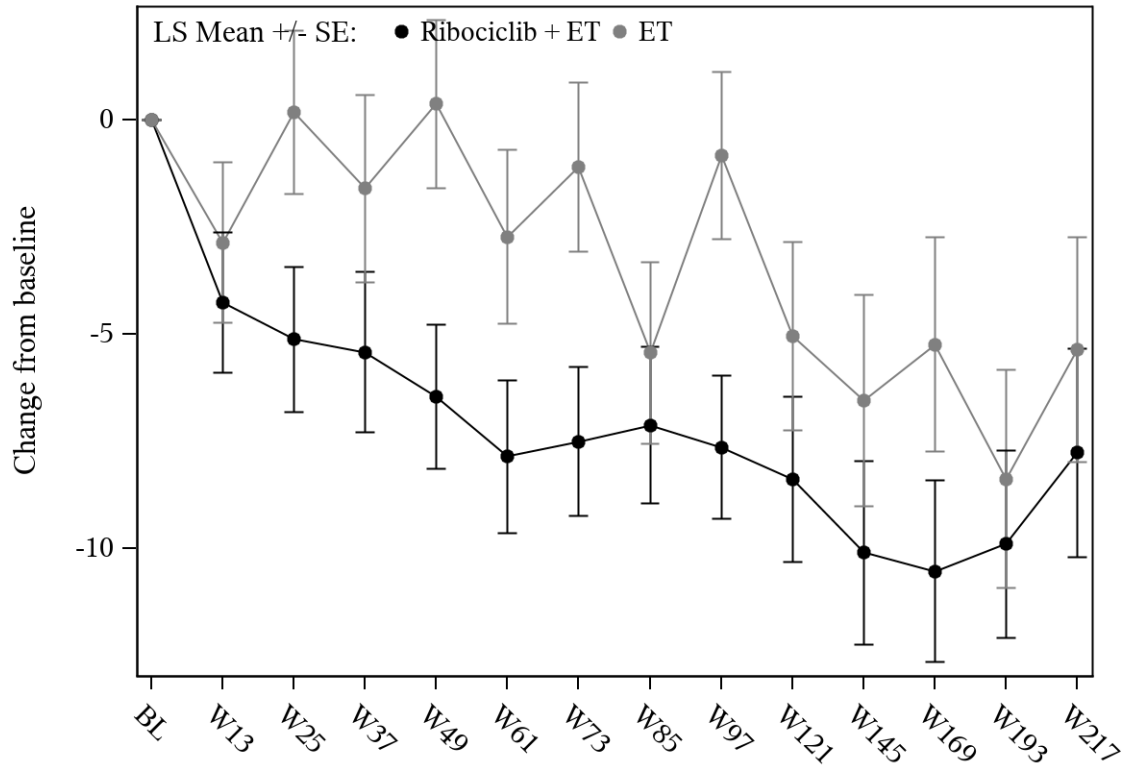
Figure 5-2.4.3.1 QLQ-BR23 - Sexual Enjoyment: line chart of change from baseline - subgroup analysis (Full Analysis Set)

**QLQ-BR23 - Sexual Enjoyment
 BMI at screening: ≥ 25**



Ribociclib + ET	367	261	260	259	265	253	245	230	229	223	213	174	149	85
ET	345	256	239	225	233	226	216	222	209	191	194	144	122	81

QLQ-BR23 - Sexual Enjoyment
BMI at screening: <25



Ribociclib + ET	209	172	149	150	147	140	138	132	137	124	116	107	79	44
ET	163	129	119	106	101	106	106	98	94	94	84	72	57	42

Table 5-2.4.4.1 QLQ-BR23 - Future Perspective: change from baseline analysis - subgroup analysis (Full Analysis Set)

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
QLQ-BR23 - Future Perspective						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.142					
NA/WE/O	829 7.25 (0.69)	763 7.43 (0.71)	Difference	-0.18	[-2.12; 1.76]	0.857
			Hedges G	-0.01	[-0.11; 0.09]	
ROW	498 11.50 (0.87)	489 9.17 (0.88)	Difference	2.33	[-0.11; 4.76]	0.061
			Hedges G	0.12	[-0.01; 0.24]	
Geographical region						
Interaction test	p = 0.673					
Europe	786 9.74 (0.72)	767 9.51 (0.72)	Difference	0.23	[-1.76; 2.22]	0.819
			Hedges G	0.01	[-0.09; 0.11]	
North America/Australia	369 6.86 (0.97)	321 5.84 (1.03)	Difference	1.02	[-1.76; 3.80]	0.471
			Hedges G	0.06	[-0.09; 0.20]	
Asia	101 N.E.	93 N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Latin America	71 13.96 (2.50)	71 9.36 (2.51)	Difference	4.60	[-2.46; 11.66]	0.200
			Hedges G	0.22	[-0.11; 0.55]	
Age group 1 at randomization						
Interaction test	N.E.					
<45	55 8.48 (2.96)	48 7.93 (3.21)	Difference	0.55	[-8.23; 9.33]	0.901
			Hedges G	0.02	[-0.36; 0.41]	
45 to 54	287 11.35 (1.21)	286 8.75 (1.21)	Difference	2.60	[-0.76; 5.96]	0.130
			Hedges G	0.13	[-0.04; 0.29]	
55 to 64	615 8.57 (0.78)	601 8.03 (0.78)	Difference	0.54	[-1.61; 2.69]	0.623
			Hedges G	0.03	[-0.08; 0.14]	
≥65	370 7.90 (0.94)	317 8.13 (1.01)	Difference	-0.23	[-2.94; 2.48]	0.869
			Hedges G	-0.01	[-0.16; 0.14]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.537					
<Median	601 10.41 (0.84)	574 9.19 (0.86)	Difference	1.23	[-1.14; 3.59]	0.310
			Hedges G	0.06	[-0.06; 0.17]	
≥Median	726 7.76 (0.70)	678 7.44 (0.72)	Difference	0.32	[-1.65; 2.29]	0.749
			Hedges G	0.02	[-0.09; 0.12]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.811					
Asian	125 5.71 (1.59)	116 4.19 (1.77)	Difference	1.52	[-3.17; 6.21]	0.523
			Hedges G	0.08	[-0.17; 0.34]	
Non-Asian	1126 9.41 (0.59)	1077 8.70 (0.60)	Difference	0.71	[-0.94; 2.35]	0.399
			Hedges G	0.04	[-0.05; 0.12]	
BMI at screening						
Interaction test	p = 0.219					
≥25	876 9.50 (0.67)	859 8.05 (0.68)	Difference	1.45	[-0.42; 3.33]	0.128
			Hedges G	0.07	[-0.02; 0.17]	
<25	440 7.81 (0.91)	382 8.52 (0.97)	Difference	-0.71	[-3.33; 1.91]	0.595
			Hedges G	-0.04	[-0.17; 0.10]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.279					
Group I/II	544 8.86 (0.80)	548 8.87 (0.80)	Difference	-0.01	[-2.23; 2.22]	0.995
			Hedges G	-0.00	[-0.12; 0.12]	
Group III	782 9.53 (0.73)	704 7.87 (0.76)	Difference	1.66	[-0.40; 3.73]	0.115
			Hedges G	0.08	[-0.02; 0.18]	
Anatomic stages						
Interaction test	p = 0.748					
IA/IB/IIA	287 9.30 (1.08)	289 9.56 (1.08)	Difference	-0.26	[-3.26; 2.74]	0.865
			Hedges G	-0.01	[-0.18; 0.15]	
IIB	257 8.36 (1.14)	259 7.91 (1.13)	Difference	0.45	[-2.70; 3.60]	0.779
			Hedges G	0.02	[-0.15; 0.20]	
IIIA	460 9.56 (0.97)	414 8.30 (0.99)	Difference	1.26	[-1.47; 3.99]	0.366
			Hedges G	0.06	[-0.07; 0.19]	
IIIB	92 13.26 (2.01)	78 8.90 (2.20)	Difference	4.36	[-1.52; 10.24]	0.145
			Hedges G	0.23	[-0.08; 0.53]	
IIIC	230 8.13 (1.33)	212 6.32 (1.42)	Difference	1.81	[-2.01; 5.63]	0.352
			Hedges G	0.09	[-0.10; 0.28]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.246					
N0	175 9.37 (1.36)	187 6.50 (1.33)	Difference	2.86	[-0.88; 6.61]	0.133
			Hedges G	0.16	[-0.05; 0.36]	
N1-N3	1149 8.94 (0.59)	1065 8.60 (0.61)	Difference	0.34	[-1.32; 2.00]	0.687
			Hedges G	0.02	[-0.07; 0.10]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test p = 0.671						
Grade 1	95 7.18 (1.93)	102 5.26 (1.79)	Difference	1.91	[-3.29; 7.11]	0.469
			Hedges G	0.10	[-0.18; 0.38]	
Grade 2	792 9.40 (0.68)	701 9.01 (0.73)	Difference	0.39	[-1.56; 2.35]	0.695
			Hedges G	0.02	[-0.08; 0.12]	
Grade 3	354 8.21 (1.05)	365 6.66 (1.03)	Difference	1.55	[-1.34; 4.44]	0.291
			Hedges G	0.08	[-0.07; 0.23]	
Histological subtype						
Interaction test p = 0.162						
Ductal	963 9.21 (0.64)	920 8.75 (0.65)	Difference	0.46	[-1.33; 2.24]	0.617
			Hedges G	0.02	[-0.07; 0.11]	
Lobular	276 7.28 (1.09)	262 6.44 (1.10)	Difference	0.85	[-2.20; 3.89]	0.586
			Hedges G	0.05	[-0.12; 0.22]	
Other	87 14.38 (2.13)	70 8.69 (2.44)	Difference	5.69	[-0.70; 12.08]	0.080
			Hedges G	0.28	[-0.03; 0.60]	
Ki67 status from surgical specimen						
Interaction test p = 0.609						
Ki67≤20	620 9.16 (0.80)	587 8.33 (0.82)	Difference	0.83	[-1.42; 3.07]	0.470
			Hedges G	0.04	[-0.07; 0.15]	
Ki67>20	468 8.44 (0.90)	471 7.67 (0.90)	Difference	0.77	[-1.73; 3.27]	0.546
			Hedges G	0.04	[-0.09; 0.17]	
Type of NSAI						
Interaction test p = 0.091						
Letrozole	852 8.42 (0.67)	819 8.79 (0.68)	Difference	-0.38	[-2.25; 1.50]	0.694
			Hedges G	-0.02	[-0.12; 0.08]	
Anastrozole	475 10.03 (0.91)	430 7.63 (0.95)	Difference	2.40	[-0.18; 4.98]	0.068
			Hedges G	0.12	[-0.01; 0.25]	
Prior neo/adjuvant chemotherapy						
Interaction test p = 0.585						
Yes	1134 9.34 (0.59)	1047 8.67 (0.61)	Difference	0.67	[-0.99; 2.32]	0.429
			Hedges G	0.03	[-0.05; 0.12]	
No	193 7.57 (1.40)	205 5.83 (1.37)	Difference	1.73	[-2.12; 5.59]	0.377
			Hedges G	0.09	[-0.11; 0.29]	
Prior adjuvant chemotherapy						
Interaction test p = 0.610						
Yes	658 9.34 (0.75)	627 8.73 (0.76)	Difference	0.62	[-1.47; 2.71]	0.562
			Hedges G	0.03	[-0.08; 0.14]	
No	669 8.65 (0.78)	625 7.48 (0.81)	Difference	1.17	[-1.04; 3.39]	0.299
			Hedges G	0.06	[-0.05; 0.17]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	p = 0.988					
Yes	503 9.39 (0.90)	449 8.84 (0.96)	Difference	0.55	[-2.03; 3.14]	0.675
			Hedges G	0.03	[-0.10; 0.15]	
No	824 8.90 (0.67)	803 7.98 (0.68)	Difference	0.93	[-0.95; 2.80]	0.333
			Hedges G	0.05	[-0.05; 0.15]	
Prior endocrine therapy						
Interaction test	p = 0.875					
Yes	898 8.72 (0.66)	864 7.88 (0.67)	Difference	0.84	[-1.01; 2.68]	0.373
			Hedges G	0.04	[-0.05; 0.14]	
No	429 9.68 (0.95)	388 8.97 (0.99)	Difference	0.71	[-1.99; 3.40]	0.607
			Hedges G	0.04	[-0.10; 0.17]	
Prior mastectomy						
Interaction test	p = 0.608					
Yes	809 8.58 (0.70)	772 8.13 (0.72)	Difference	0.45	[-1.52; 2.41]	0.655
			Hedges G	0.02	[-0.08; 0.12]	
No	518 9.74 (0.84)	480 8.32 (0.87)	Difference	1.42	[-0.95; 3.79]	0.239
			Hedges G	0.07	[-0.05; 0.20]	
Prior radiotherapy						
Interaction test	p = 0.808					
Yes	1180 8.65 (0.58)	1105 7.90 (0.59)	Difference	0.75	[-0.87; 2.38]	0.362
			Hedges G	0.04	[-0.04; 0.12]	
No	147 11.04 (1.59)	147 10.09 (1.58)	Difference	0.95	[-3.47; 5.36]	0.673
			Hedges G	0.05	[-0.18; 0.28]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed N.E.: Not estimable ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + baseline value ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>* The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

5-2.5 EQ-5D VAS

Table 5-2.5.1.1 EQ5D01-Health Today: change from baseline analysis - subgroup analysis (Full Analysis Set)

Treatment Groups		Comparison				
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
EQ5D01-Health Today						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.437					
NA/WE/O	824 -1.00 (0.40)	771 -0.87 (0.41)	Difference	-0.13	[-1.25; 1.00]	0.827
			Hedges G	-0.01	[-0.11; 0.09]	
ROW	499 -2.52 (0.52)	488 -1.76 (0.53)	Difference	-0.76	[-2.22; 0.70]	0.308
			Hedges G	-0.06	[-0.19; 0.06]	
Geographical region						
Interaction test	N.E.					
Europe	783 -2.41 (0.42)	770 -1.94 (0.42)	Difference	-0.48	[-1.63; 0.68]	0.418
			Hedges G	-0.04	[-0.14; 0.06]	
North America/Australia	367 0.15 (0.50)	326 0.11 (0.52)	Difference	0.04	[-1.38; 1.46]	0.954
			Hedges G	0.00	[-0.14; 0.15]	
Asia	101 -1.52 (1.00)	92 -0.95 (1.10)	Difference	-0.58	[-3.51; 2.36]	0.699
			Hedges G	-0.06	[-0.34; 0.23]	
Latin America	72 -1.38 (1.17)	71 0.12 (1.18)	Difference	-1.50	[-4.78; 1.78]	0.368
			Hedges G	-0.15	[-0.48; 0.18]	
Age group 1 at randomization						
Interaction test	p = 0.111					
<45	56 -2.12 (1.47)	48 -3.63 (1.61)	Difference	1.51	[-2.83; 5.84]	0.492
			Hedges G	0.14	[-0.25; 0.52]	
45 to 54	286 0.38 (0.67)	290 -0.92 (0.67)	Difference	1.30	[-0.56; 3.16]	0.171
			Hedges G	0.11	[-0.05; 0.28]	
55 to 64	612 -1.21 (0.45)	600 -0.92 (0.45)	Difference	-0.29	[-1.55; 0.97]	0.651
			Hedges G	-0.03	[-0.14; 0.09]	
≥65	369 -3.58 (0.56)	321 -1.95 (0.60)	Difference	-1.62	[-3.24; -0.01]	0.048
			Hedges G	-0.15	[-0.30; -0.00]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.008					
<Median	601 -0.56 (0.48)	577 -1.51 (0.49)	Difference	0.94	[-0.39; 2.28]	0.167
			Hedges G	0.08	[-0.03; 0.19]	
≥Median	722 -2.45 (0.43)	682 -0.98 (0.44)	Difference	-1.47	[-2.66; -0.27]	0.016
			Hedges G	-0.13	[-0.23; -0.02]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.703					
Asian	125 -1.68 (0.87)	115 -0.72 (0.96)	Difference	-0.96	[-3.52; 1.60]	0.461
			Hedges G	-0.10	[-0.35; 0.16]	
Non-Asian	1123 -1.59 (0.34)	1082 -1.24 (0.34)	Difference	-0.35	[-1.29; 0.59]	0.464
			Hedges G	-0.03	[-0.11; 0.05]	
BMI at screening						
Interaction test	p = 0.305					
≥25	874 -1.78 (0.40)	859 -1.16 (0.40)	Difference	-0.62	[-1.73; 0.48]	0.268
			Hedges G	-0.05	[-0.15; 0.04]	
<25	439 -1.37 (0.54)	389 -1.77 (0.58)	Difference	0.40	[-1.15; 1.95]	0.612
			Hedges G	0.04	[-0.10; 0.17]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.463					
Group I/II	540 -1.80 (0.49)	549 -1.11 (0.49)	Difference	-0.69	[-2.05; 0.67]	0.319
			Hedges G	-0.06	[-0.18; 0.06]	
Group III	782 -1.30 (0.42)	710 -1.42 (0.44)	Difference	0.12	[-1.06; 1.30]	0.838
			Hedges G	0.01	[-0.09; 0.11]	
Anatomic stages						
Interaction test	N.E.					
IA/IB/IIA	284 -1.57 (0.64)	290 -1.31 (0.63)	Difference	-0.26	[-2.03; 1.51]	0.774
			Hedges G	-0.02	[-0.19; 0.14]	
IIB	256 -2.07 (0.72)	259 -0.97 (0.71)	Difference	-1.10	[-3.08; 0.88]	0.276
			Hedges G	-0.10	[-0.27; 0.08]	
IIIA	462 -1.59 (0.53)	417 -1.72 (0.54)	Difference	0.13	[-1.35; 1.62]	0.859
			Hedges G	0.01	[-0.12; 0.14]	
IIIB	91 0.81 (1.25)	78 -0.21 (1.35)	Difference	1.02	[-2.62; 4.66]	0.581
			Hedges G	0.09	[-0.22; 0.39]	
IIIC	229 -1.48 (0.74)	215 -1.11 (0.77)	Difference	-0.36	[-2.47; 1.74]	0.735
			Hedges G	-0.03	[-0.22; 0.15]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.265					
N0	172 -1.44 (0.83)	186 -2.39 (0.81)	Difference	0.95	[-1.34; 3.23]	0.416
			Hedges G	0.09	[-0.12; 0.29]	
N1-N3	1148 -1.58 (0.34)	1073 -1.08 (0.35)	Difference	-0.51	[-1.47; 0.46]	0.304
			Hedges G	-0.04	[-0.13; 0.04]	

	Treatment Groups		Parameter	Comparison		
	Ribociclib + ET (N = 1424)	ET (N = 1420)		Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.691					
Grade 1	94 -0.81 (1.00)	103 -1.71 (0.92)	Difference	0.91	[-1.78; 3.59]	0.506
			Hedges G	0.10	[-0.18; 0.37]	
Grade 2	788 -1.23 (0.38)	703 -0.71 (0.41)	Difference	-0.52	[-1.62; 0.57]	0.348
			Hedges G	-0.05	[-0.15; 0.05]	
Grade 3	355 -2.27 (0.63)	368 -1.82 (0.62)	Difference	-0.46	[-2.20; 1.28]	0.605
			Hedges G	-0.04	[-0.18; 0.11]	
Histological subtype						
Interaction test	p = 0.203					
Ductal	959 -1.85 (0.37)	927 -1.15 (0.37)	Difference	-0.69	[-1.71; 0.32]	0.181
			Hedges G	-0.06	[-0.15; 0.03]	
Lobular	276 -1.32 (0.65)	262 -1.50 (0.67)	Difference	0.17	[-1.67; 2.01]	0.854
			Hedges G	0.02	[-0.15; 0.18]	
Other	87 1.12 (1.09)	70 -2.43 (1.24)	Difference	3.55	[0.28; 6.82]	0.033
			Hedges G	0.34	[0.03; 0.66]	
Ki67 status from surgical specimen						
Interaction test	p = 0.958					
Ki67≤20	618 -1.08 (0.47)	590 -0.90 (0.48)	Difference	-0.18	[-1.50; 1.15]	0.795
			Hedges G	-0.01	[-0.13; 0.10]	
Ki67>20	466 -2.83 (0.57)	475 -2.66 (0.56)	Difference	-0.17	[-1.73; 1.40]	0.833
			Hedges G	-0.01	[-0.14; 0.11]	
Type of NSAI						
Interaction test	p = 0.912					
Letrozole	846 -2.08 (0.40)	821 -1.79 (0.40)	Difference	-0.29	[-1.40; 0.82]	0.607
			Hedges G	-0.03	[-0.12; 0.07]	
Anastrozole	477 -0.82 (0.54)	435 -0.30 (0.56)	Difference	-0.52	[-2.05; 1.01]	0.503
			Hedges G	-0.04	[-0.17; 0.09]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.567					
Yes	1130 -1.50 (0.35)	1053 -1.22 (0.36)	Difference	-0.28	[-1.26; 0.70]	0.576
			Hedges G	-0.02	[-0.11; 0.06]	
No	193 -1.67 (0.76)	206 -1.63 (0.74)	Difference	-0.04	[-2.13; 2.05]	0.971
			Hedges G	-0.00	[-0.20; 0.19]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.848					
Yes	658 -0.79 (0.44)	631 -0.49 (0.45)	Difference	-0.29	[-1.53; 0.94]	0.641
			Hedges G	-0.03	[-0.14; 0.08]	
No	665 -2.40 (0.46)	628 -2.09 (0.48)	Difference	-0.32	[-1.61; 0.98]	0.632
			Hedges G	-0.03	[-0.14; 0.08]	

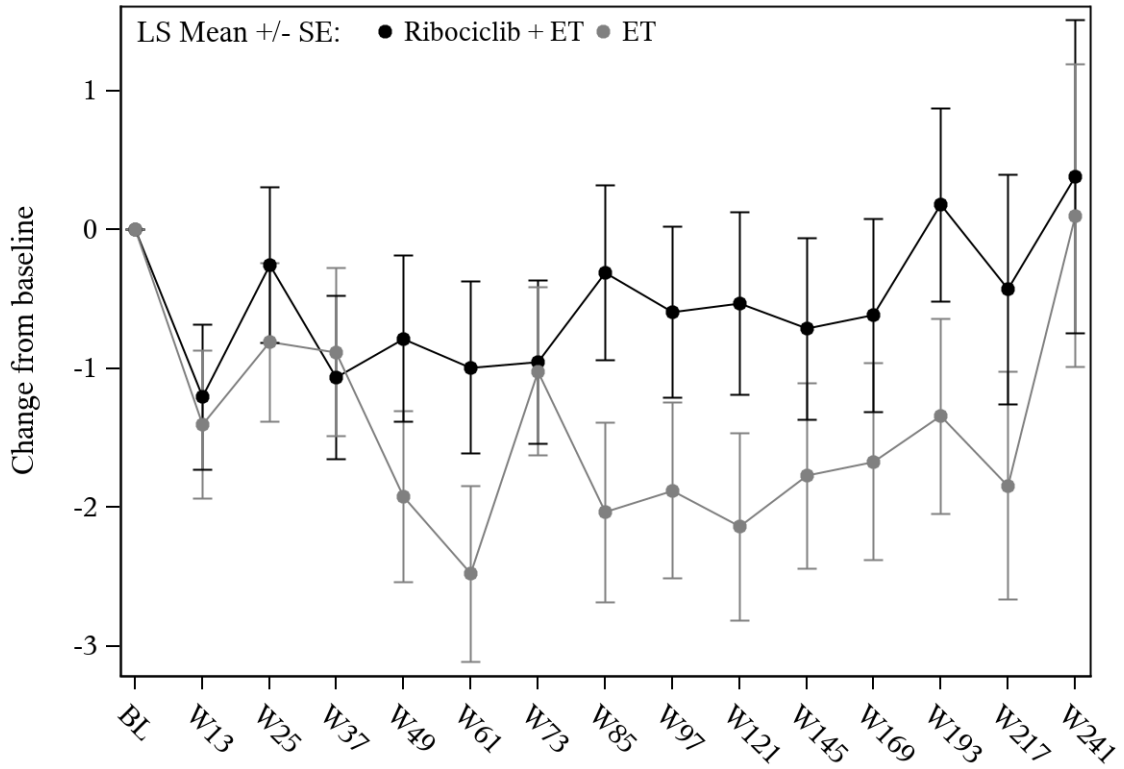
Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	p = 0.920					
Yes	499 -2.48 (0.54)	452 -2.14 (0.57)	Difference	-0.34	[-1.89; 1.21]	0.668
			Hedges G	-0.03	[-0.16; 0.10]	
No	824 -1.06 (0.39)	807 -0.82 (0.40)	Difference	-0.24	[-1.34; 0.86]	0.668
			Hedges G	-0.02	[-0.12; 0.08]	
Prior endocrine therapy						
Interaction test	p = 0.450					
Yes	895 -1.85 (0.39)	864 -1.31 (0.40)	Difference	-0.54	[-1.64; 0.56]	0.336
			Hedges G	-0.05	[-0.14; 0.05]	
No	428 -1.13 (0.55)	395 -1.29 (0.57)	Difference	0.16	[-1.39; 1.70]	0.844
			Hedges G	0.01	[-0.12; 0.15]	
Prior mastectomy						
Interaction test	p = 0.250					
Yes	806 -1.36 (0.41)	775 -1.49 (0.42)	Difference	0.13	[-1.02; 1.28]	0.826
			Hedges G	0.01	[-0.09; 0.11]	
No	517 -1.92 (0.51)	484 -0.88 (0.52)	Difference	-1.04	[-2.47; 0.39]	0.153
			Hedges G	-0.09	[-0.21; 0.03]	
Prior radiotherapy						
Interaction test	p = 0.650					
Yes	1179 -1.46 (0.33)	1112 -1.07 (0.34)	Difference	-0.39	[-1.34; 0.55]	0.412
			Hedges G	-0.03	[-0.12; 0.05]	
No	144 -2.59 (0.98)	147 -2.79 (0.97)	Difference	0.20	[-2.52; 2.92]	0.885
			Hedges G	0.02	[-0.21; 0.25]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed N.E.: Not estimable ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + baseline value ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>+ The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

Figure 5-2.5.1.1 EQ5D01-Health Today: line chart of change from baseline - subgroup analysis (Full Analysis Set)

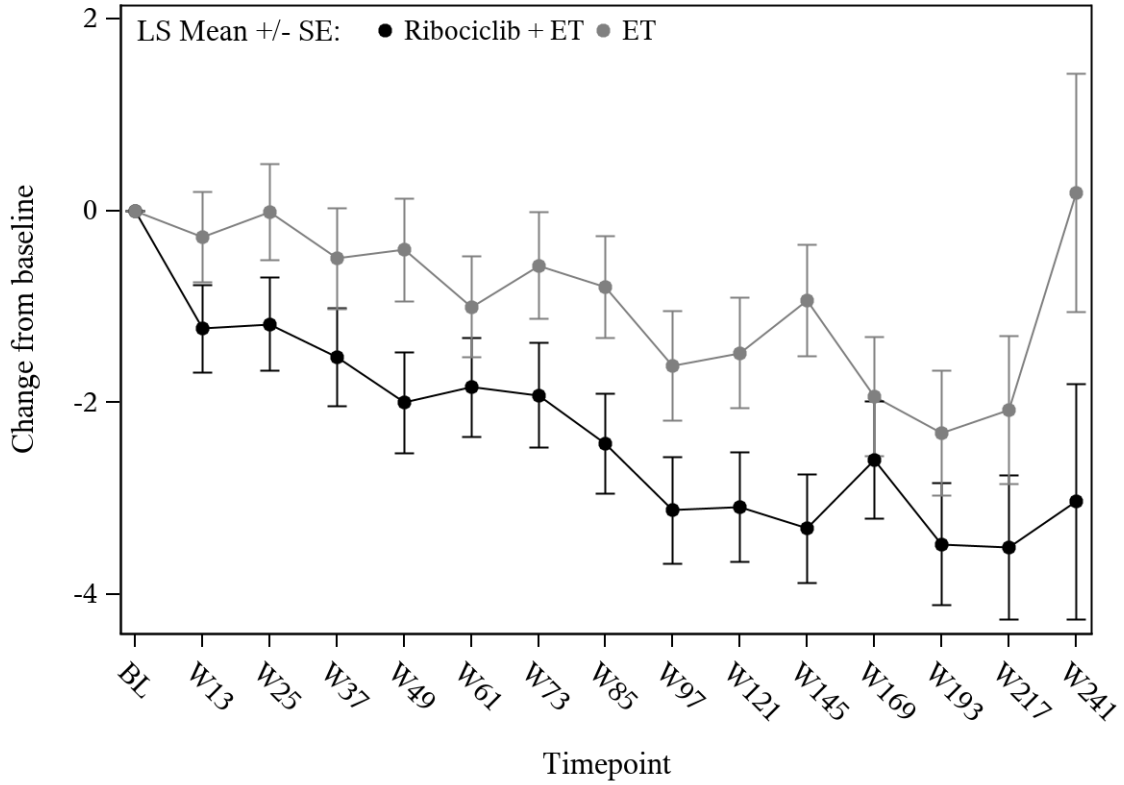
EQ5D01-Health Today

Age group 2 at randomization (median for subpopulation post-menopausal female patients): <Median



Ribociclib + ET	601	566	540	547	538	535	530	518	511	491	475	403	329	199	34
ET	577	543	524	507	507	501	494	487	477	468	462	386	322	215	39

EQ5D01-Health Today
Age group 2 at randomization (median for subpopulation post-menopausal female patients): \geq Median



Ribociclib + ET	722	688	668	653	646	633	624	606	610	587	585	505	435	278	56
ET	682	641	619	618	622	602	608	595	587	572	545	484	406	265	56

5-2.6 HADS

Table 5-2.6.1.1 HADS - Anxiety: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
HADS - Anxiety						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.791					
NA/WE/O	816 0.25 (0.10)	769 0.25 (0.10)	Difference	0.01	[-0.27; 0.28]	0.970
			Hedges G	0.00	[-0.10; 0.10]	
ROW	499 0.23 (0.12)	488 0.28 (0.12)	Difference	-0.05	[-0.37; 0.28]	0.772
			Hedges G	-0.02	[-0.14; 0.11]	
Geographical region						
Interaction test	p = 0.307					
Europe	777 0.33 (0.09)	768 0.22 (0.09)	Difference	0.11	[-0.15; 0.37]	0.394
			Hedges G	0.04	[-0.06; 0.14]	
North America/Australia	365 -0.05 (0.13)	326 0.13 (0.14)	Difference	-0.19	[-0.56; 0.19]	0.332
			Hedges G	-0.07	[-0.22; 0.08]	
Asia	101 0.43 (0.24)	92 1.17 (0.27)	Difference	-0.74	[-1.46; -0.03]	0.041
			Hedges G	-0.30	[-0.58; -0.01]	
Latin America	72 0.40 (0.36)	71 0.06 (0.36)	Difference	0.34	[-0.67; 1.35]	0.503
			Hedges G	0.11	[-0.22; 0.44]	
Age group 1 at randomization						
Interaction test	p = 0.395					
<45	56 0.21 (0.36)	48 0.81 (0.39)	Difference	-0.60	[-1.67; 0.47]	0.266
			Hedges G	-0.22	[-0.61; 0.17]	
45 to 54	284 0.23 (0.17)	286 0.39 (0.17)	Difference	-0.16	[-0.63; 0.31]	0.498
			Hedges G	-0.06	[-0.22; 0.11]	
55 to 64	611 0.20 (0.10)	600 0.21 (0.10)	Difference	-0.01	[-0.30; 0.27]	0.923
			Hedges G	-0.01	[-0.12; 0.11]	
≥65	364 0.32 (0.13)	323 0.12 (0.14)	Difference	0.19	[-0.17; 0.56]	0.300
			Hedges G	0.08	[-0.07; 0.23]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.007					
<Median	599 0.11 (0.12)	574 0.43 (0.12)	Difference	-0.32	[-0.65; 0.01]	0.056
			Hedges G	-0.11	[-0.23; 0.00]	
≥Median	716 0.37 (0.10)	683 0.11 (0.10)	Difference	0.25	[-0.02; 0.53]	0.071
			Hedges G	0.10	[-0.01; 0.20]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.073					
Asian	124 0.28 (0.21)	115 0.86 (0.23)	Difference	-0.57	[-1.19; 0.05]	0.070
			Hedges G	-0.24	[-0.49; 0.02]	
Non-Asian	1117 0.21 (0.08)	1078 0.21 (0.08)	Difference	-0.00	[-0.22; 0.22]	0.986
			Hedges G	-0.00	[-0.08; 0.08]	
BMI at screening						
Interaction test	p = 0.085					
≥25	871 0.29 (0.09)	858 0.19 (0.09)	Difference	0.11	[-0.15; 0.36]	0.421
			Hedges G	0.04	[-0.06; 0.13]	
<25	435 0.19 (0.13)	388 0.45 (0.14)	Difference	-0.26	[-0.64; 0.11]	0.172
			Hedges G	-0.10	[-0.23; 0.04]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.152					
Group I/II	538 0.25 (0.12)	551 0.09 (0.11)	Difference	0.17	[-0.15; 0.49]	0.298
			Hedges G	0.06	[-0.06; 0.18]	
Group III	777 0.23 (0.10)	706 0.40 (0.10)	Difference	-0.17	[-0.45; 0.11]	0.233
			Hedges G	-0.06	[-0.16; 0.04]	
Anatomic stages						
Interaction test	p = 0.157					
IA/IB/IIA	283 0.25 (0.15)	291 -0.08 (0.15)	Difference	0.32	[-0.10; 0.75]	0.135
			Hedges G	0.12	[-0.04; 0.29]	
IIB	255 0.21 (0.16)	260 0.26 (0.16)	Difference	-0.05	[-0.49; 0.38]	0.807
			Hedges G	-0.02	[-0.19; 0.15]	
IIIA	456 0.30 (0.13)	414 0.29 (0.13)	Difference	0.00	[-0.35; 0.36]	0.983
			Hedges G	0.00	[-0.13; 0.13]	
IIIB	91 0.05 (0.29)	78 0.58 (0.32)	Difference	-0.54	[-1.39; 0.31]	0.215
			Hedges G	-0.19	[-0.50; 0.11]	
IIIC	230 0.13 (0.16)	214 0.50 (0.17)	Difference	-0.37	[-0.84; 0.10]	0.119
			Hedges G	-0.15	[-0.33; 0.04]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.634					
N0	172 0.27 (0.20)	188 0.21 (0.19)	Difference	0.06	[-0.50; 0.61]	0.844
			Hedges G	0.02	[-0.19; 0.23]	
N1-N3	1140 0.23 (0.08)	1069 0.28 (0.08)	Difference	-0.05	[-0.28; 0.18]	0.695
			Hedges G	-0.02	[-0.10; 0.07]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.532					
Grade 1	94 0.48 (0.25)	103 0.64 (0.23)	Difference	-0.16	[-0.84; 0.51]	0.634
			Hedges G	-0.07	[-0.35; 0.21]	
Grade 2	780 0.16 (0.09)	703 0.20 (0.10)	Difference	-0.04	[-0.31; 0.22]	0.745
			Hedges G	-0.02	[-0.12; 0.09]	
Grade 3	355 0.39 (0.14)	366 0.24 (0.14)	Difference	0.16	[-0.22; 0.54]	0.423
			Hedges G	0.06	[-0.09; 0.21]	
Histological subtype						
Interaction test	p = 0.347					
Ductal	952 0.29 (0.08)	924 0.25 (0.09)	Difference	0.04	[-0.19; 0.28]	0.719
			Hedges G	0.02	[-0.07; 0.11]	
Lobular	274 0.11 (0.15)	264 0.20 (0.15)	Difference	-0.09	[-0.52; 0.34]	0.676
			Hedges G	-0.04	[-0.21; 0.13]	
Other	88 -0.23 (0.30)	69 0.34 (0.34)	Difference	-0.57	[-1.47; 0.32]	0.207
			Hedges G	-0.20	[-0.52; 0.11]	
Ki67 status from surgical specimen						
Interaction test	p = 0.710					
Ki67≤20	615 0.26 (0.11)	590 0.15 (0.11)	Difference	0.11	[-0.20; 0.41]	0.491
			Hedges G	0.04	[-0.07; 0.15]	
Ki67>20	460 0.41 (0.13)	473 0.39 (0.13)	Difference	0.02	[-0.34; 0.37]	0.931
			Hedges G	0.01	[-0.12; 0.13]	
Type of NSAI						
Interaction test	p = 0.717					
Letrozole	840 0.35 (0.09)	821 0.30 (0.09)	Difference	0.05	[-0.21; 0.31]	0.716
			Hedges G	0.02	[-0.08; 0.11]	
Anastrozole	475 0.10 (0.13)	433 0.10 (0.13)	Difference	-0.00	[-0.36; 0.36]	0.989
			Hedges G	-0.00	[-0.13; 0.13]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.578					
Yes	1123 0.28 (0.08)	1049 0.33 (0.09)	Difference	-0.05	[-0.28; 0.19]	0.681
			Hedges G	-0.02	[-0.10; 0.07]	
No	192 0.05 (0.17)	208 -0.10 (0.17)	Difference	0.14	[-0.32; 0.61]	0.547
			Hedges G	0.06	[-0.14; 0.26]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.266					
Yes	655 0.28 (0.11)	629 0.17 (0.11)	Difference	0.12	[-0.19; 0.42]	0.448
			Hedges G	0.04	[-0.07; 0.15]	
No	660 0.23 (0.10)	628 0.35 (0.11)	Difference	-0.12	[-0.42; 0.17]	0.413
			Hedges G	-0.05	[-0.15; 0.06]	

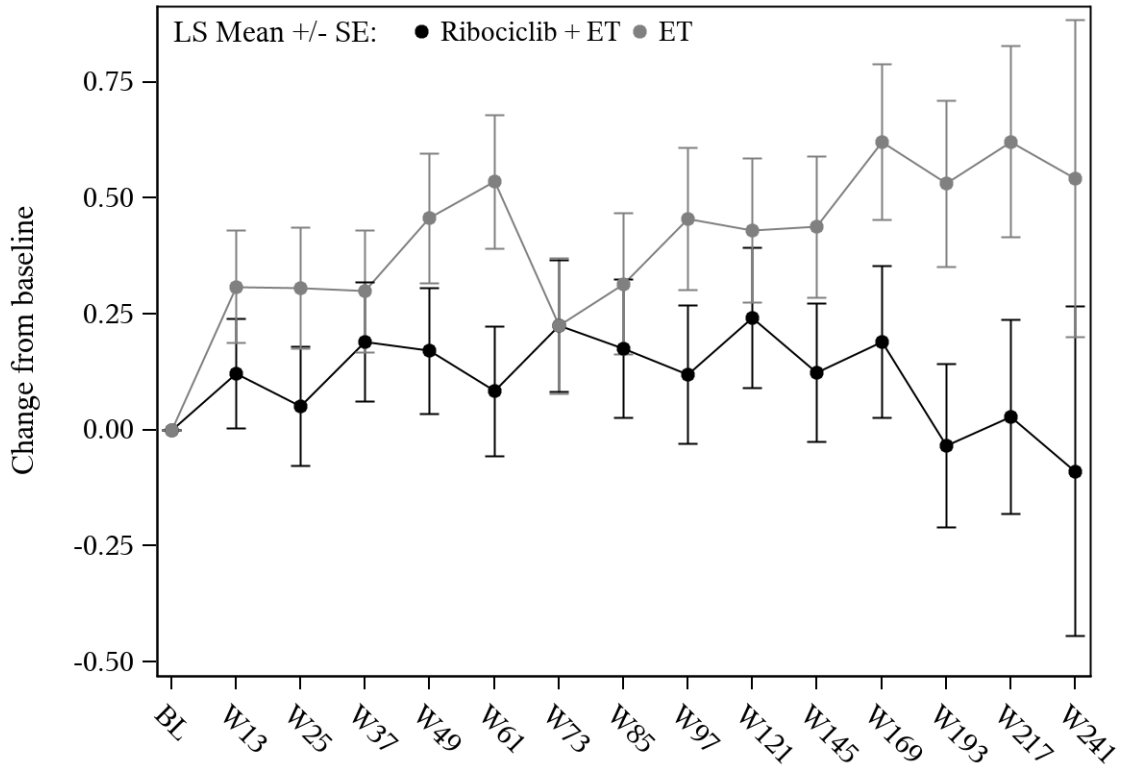
Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	p = 0.081					
Yes	494 0.32 (0.13)	450 0.61 (0.13)	Difference	-0.29	[-0.65; 0.07]	0.112
			Hedges G	-0.10	[-0.23; 0.02]	
No	821 0.21 (0.09)	807 0.09 (0.09)	Difference	0.13	[-0.13; 0.39]	0.337
			Hedges G	0.05	[-0.05; 0.14]	
Prior endocrine therapy						
Interaction test	p = 0.343					
Yes	889 0.37 (0.09)	861 0.30 (0.09)	Difference	0.07	[-0.19; 0.32]	0.616
			Hedges G	0.02	[-0.07; 0.12]	
No	426 0.01 (0.13)	396 0.14 (0.14)	Difference	-0.13	[-0.51; 0.24]	0.478
			Hedges G	-0.05	[-0.19; 0.09]	
Prior mastectomy						
Interaction test	p = 0.085					
Yes	804 0.19 (0.10)	774 0.30 (0.10)	Difference	-0.12	[-0.39; 0.16]	0.405
			Hedges G	-0.04	[-0.14; 0.06]	
No	511 0.35 (0.12)	483 0.19 (0.12)	Difference	0.16	[-0.17; 0.50]	0.336
			Hedges G	0.06	[-0.06; 0.19]	
Prior radiotherapy						
Interaction test	p = 0.447					
Yes	1174 0.19 (0.06)	1109 0.29 (0.06)	Difference	-0.10	[-0.27; 0.07]	0.232
			Hedges G	-0.05	[-0.13; 0.03]	
No	141 0.12 (0.16)	148 -0.06 (0.16)	Difference	0.17	[-0.27; 0.62]	0.444
			Hedges G	0.09	[-0.14; 0.32]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: $\text{change from baseline} = \text{treatment} + \text{visit} + \text{treatment} * \text{visit} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor} + \text{subgroup factor} * \text{visit} + \text{treatment} * \text{subgroup factor} * \text{visit} + \text{baseline value}$ If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: $\text{change from baseline} = \text{treatment} + \text{visit} + \text{treatment} * \text{visit} + \text{baseline value}$ ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>† The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

Figure 5-2.6.1.1 HADS - Anxiety: line chart of change from baseline - subgroup analysis (Full Analysis Set)

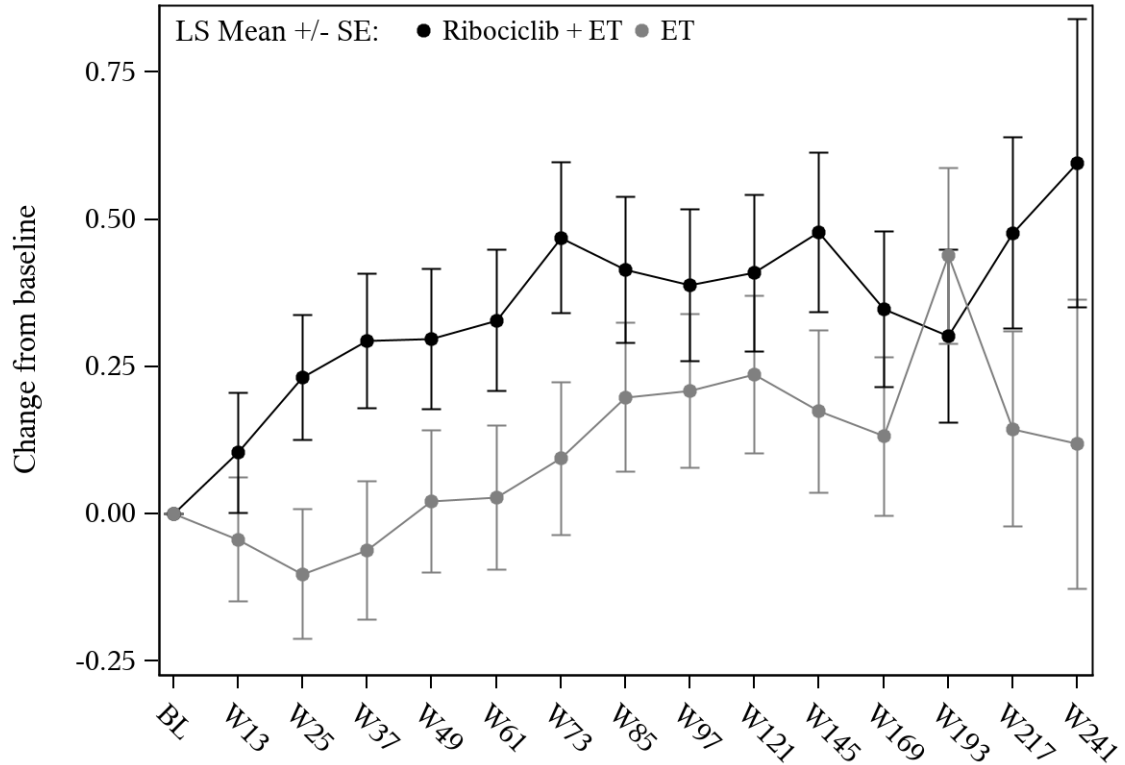
HADS - Anxiety

Age group 2 at randomization (median for subpopulation post-menopausal female patients): <Median



Ribociclib + ET	599	557	529	544	531	528	526	515	510	483	470	395	324	198	35
ET	574	537	512	502	502	494	492	486	476	465	458	382	318	212	39

HADS - Anxiety
Age group 2 at randomization (median for subpopulation post-menopausal female patients): \geq Median



Ribociclib + ET	716	675	660	646	636	625	618	603	596	576	574	495	430	277	57
ET	683	632	612	619	619	601	599	592	582	565	548	479	406	265	57

Table 5-2.6.2.1 HADS - Depression: change from baseline analysis - subgroup analysis (Full Analysis Set)

	Treatment Groups		Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
HADS - Depression						
	N' LS Mean (SE)	N' LS Mean (SE)				
Region						
Interaction test	p = 0.798					
NA/WE/O	814 0.80 (0.09)	769 0.77 (0.09)	Difference	0.02	[-0.23; 0.28]	0.848
			Hedges G	0.01	[-0.09; 0.11]	
ROW	499 0.74 (0.11)	488 0.66 (0.11)	Difference	0.08	[-0.24; 0.39]	0.631
			Hedges G	0.03	[-0.09; 0.16]	
Geographical region						
Interaction test	N.E.					
Europe	777 0.95 (0.09)	768 0.80 (0.09)	Difference	0.15	[-0.10; 0.40]	0.246
			Hedges G	0.06	[-0.04; 0.16]	
North America/Australia	363 0.45 (0.12)	326 0.61 (0.12)	Difference	-0.16	[-0.49; 0.17]	0.339
			Hedges G	-0.07	[-0.22; 0.08]	
Asia	101 0.33 (0.25)	92 0.37 (0.28)	Difference	-0.04	[-0.78; 0.70]	0.910
			Hedges G	-0.02	[-0.30; 0.27]	
Latin America	72 0.90 (0.29)	71 0.72 (0.29)	Difference	0.18	[-0.64; 1.00]	0.661
			Hedges G	0.07	[-0.25; 0.40]	
Age group 1 at randomization						
Interaction test	p = 0.297					
<45	56 0.78 (0.34)	48 0.91 (0.37)	Difference	-0.13	[-1.12; 0.86]	0.793
			Hedges G	-0.05	[-0.44; 0.33]	
45 to 54	284 0.77 (0.15)	286 0.84 (0.15)	Difference	-0.07	[-0.49; 0.36]	0.757
			Hedges G	-0.03	[-0.19; 0.14]	
55 to 64	611 0.55 (0.10)	600 0.61 (0.10)	Difference	-0.06	[-0.34; 0.22]	0.663
			Hedges G	-0.03	[-0.14; 0.09]	
≥65	362 N.E.	323 N.E.	Difference	N.E.	[N.E.]	N.E.
			Hedges G	N.E.	[N.E.]	
Age group 2 at randomization (median for subpopulation post-menopausal female patients)						
Interaction test	p = 0.041					
<Median	599 0.57 (0.11)	574 0.76 (0.11)	Difference	-0.19	[-0.49; 0.11]	0.216
			Hedges G	-0.07	[-0.19; 0.04]	
≥Median	714 0.93 (0.09)	683 0.69 (0.09)	Difference	0.24	[-0.02; 0.50]	0.074
			Hedges G	0.10	[-0.01; 0.20]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Race						
Interaction test	p = 0.822					
Asian	124 0.21 (0.21)	115 0.25 (0.24)	Difference	-0.04	[-0.67; 0.59]	0.905
			Hedges G	-0.02	[-0.27; 0.24]	
Non-Asian	1115 0.80 (0.07)	1078 0.78 (0.07)	Difference	0.03	[-0.18; 0.23]	0.797
			Hedges G	0.01	[-0.07; 0.09]	
BMI at screening						
Interaction test	p = 0.965					
≥25	869 0.83 (0.09)	858 0.78 (0.09)	Difference	0.05	[-0.19; 0.29]	0.686
			Hedges G	0.02	[-0.07; 0.11]	
<25	435 0.65 (0.12)	388 0.63 (0.13)	Difference	0.02	[-0.32; 0.36]	0.910
			Hedges G	0.01	[-0.13; 0.14]	
AJCC Anatomic Stage Group						
Interaction test	p = 0.184					
Group I/II	538 0.70 (0.11)	551 0.50 (0.11)	Difference	0.20	[-0.10; 0.50]	0.193
			Hedges G	0.08	[-0.04; 0.20]	
Group III	775 0.82 (0.09)	706 0.90 (0.10)	Difference	-0.08	[-0.34; 0.19]	0.571
			Hedges G	-0.03	[-0.13; 0.07]	
Anatomic stages						
Interaction test	p = 0.494					
IA/IB/IIA	283 0.80 (0.15)	291 0.50 (0.14)	Difference	0.30	[-0.10; 0.70]	0.142
			Hedges G	0.12	[-0.04; 0.29]	
IIB	255 0.55 (0.15)	260 0.52 (0.15)	Difference	0.03	[-0.37; 0.44]	0.870
			Hedges G	0.01	[-0.16; 0.19]	
IIIA	455 0.92 (0.12)	414 0.89 (0.12)	Difference	0.03	[-0.30; 0.37]	0.851
			Hedges G	0.01	[-0.12; 0.15]	
IIIB	91 0.80 (0.27)	78 0.87 (0.29)	Difference	-0.07	[-0.85; 0.71]	0.862
			Hedges G	-0.03	[-0.33; 0.28]	
IIIC	229 0.65 (0.16)	214 0.88 (0.16)	Difference	-0.22	[-0.67; 0.22]	0.325
			Hedges G	-0.09	[-0.28; 0.09]	
Tumor category						
N.A. ⁺						
Nodal status						
Interaction test	p = 0.427					
N0	172 0.96 (0.19)	188 0.73 (0.18)	Difference	0.23	[-0.28; 0.74]	0.384
			Hedges G	0.09	[-0.11; 0.30]	
N1-N3	1138 0.73 (0.07)	1069 0.70 (0.07)	Difference	0.03	[-0.17; 0.24]	0.764
			Hedges G	0.01	[-0.07; 0.10]	

Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Histological grade at time of surgery						
Interaction test	p = 0.134					
Grade 1	94 0.75 (0.24)	103 1.03 (0.23)	Difference	-0.29	[-0.95; 0.37]	0.392
			Hedges G	-0.12	[-0.40; 0.16]	
Grade 2	780 0.72 (0.09)	703 0.61 (0.09)	Difference	0.11	[-0.14; 0.35]	0.398
			Hedges G	0.04	[-0.06; 0.15]	
Grade 3	353 0.87 (0.13)	366 0.77 (0.13)	Difference	0.10	[-0.27; 0.47]	0.591
			Hedges G	0.04	[-0.11; 0.19]	
Histological subtype						
Interaction test	p = 0.028					
Ductal	952 0.85 (0.08)	924 0.66 (0.08)	Difference	0.19	[-0.03; 0.41]	0.095
			Hedges G	0.08	[-0.01; 0.17]	
Lobular	272 0.50 (0.14)	264 0.76 (0.14)	Difference	-0.26	[-0.66; 0.14]	0.196
			Hedges G	-0.11	[-0.28; 0.06]	
Other	88 0.56 (0.26)	69 1.39 (0.30)	Difference	-0.83	[-1.62; -0.05]	0.038
			Hedges G	-0.34	[-0.65; -0.02]	
Ki67 status from surgical specimen						
Interaction test	p = 0.554					
Ki67≤20	615 0.87 (0.10)	590 0.71 (0.11)	Difference	0.16	[-0.13; 0.45]	0.289
			Hedges G	0.06	[-0.05; 0.17]	
Ki67>20	459 0.83 (0.12)	473 0.80 (0.12)	Difference	0.02	[-0.31; 0.36]	0.898
			Hedges G	0.01	[-0.12; 0.14]	
Type of NSAI						
Interaction test	p = 0.773					
Letrozole	839 0.82 (0.09)	821 0.75 (0.09)	Difference	0.07	[-0.17; 0.31]	0.574
			Hedges G	0.03	[-0.07; 0.12]	
Anastrozole	474 0.72 (0.12)	433 0.68 (0.12)	Difference	0.05	[-0.29; 0.38]	0.774
			Hedges G	0.02	[-0.11; 0.15]	
Prior neo/adjuvant chemotherapy						
Interaction test	p = 0.668					
Yes	1122 0.79 (0.08)	1049 0.77 (0.08)	Difference	0.03	[-0.19; 0.24]	0.807
			Hedges G	0.01	[-0.07; 0.09]	
No	191 0.63 (0.17)	208 0.51 (0.17)	Difference	0.12	[-0.35; 0.59]	0.613
			Hedges G	0.05	[-0.15; 0.25]	
Prior adjuvant chemotherapy						
Interaction test	p = 0.341					
Yes	654 0.80 (0.10)	629 0.66 (0.10)	Difference	0.14	[-0.15; 0.42]	0.340
			Hedges G	0.05	[-0.06; 0.16]	
No	659 0.74 (0.10)	628 0.80 (0.10)	Difference	-0.05	[-0.33; 0.22]	0.705
			Hedges G	-0.02	[-0.13; 0.09]	

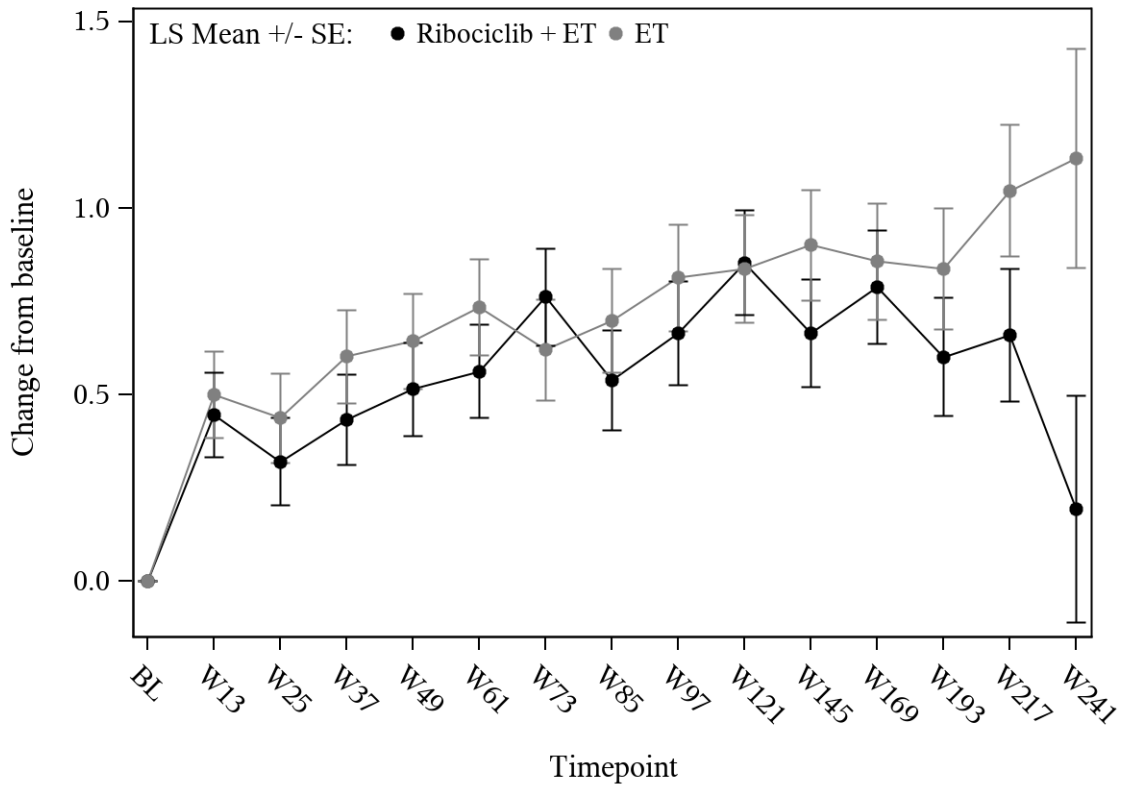
Treatment Groups			Comparison			
	Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
Prior neoadjuvant chemotherapy						
Interaction test	p = 0.074					
Yes	494 0.80 (0.11)	450 0.97 (0.12)	Difference	-0.17	[-0.49; 0.16]	0.315
			Hedges G	-0.07	[-0.19; 0.06]	
No	819 0.77 (0.09)	807 0.60 (0.09)	Difference	0.17	[-0.08; 0.42]	0.182
			Hedges G	0.07	[-0.03; 0.16]	
Prior endocrine therapy						
Interaction test	p = 0.035					
Yes	888 0.91 (0.09)	861 0.71 (0.09)	Difference	0.20	[-0.04; 0.44]	0.102
			Hedges G	0.08	[-0.02; 0.17]	
No	425 0.51 (0.12)	396 0.73 (0.13)	Difference	-0.22	[-0.57; 0.13]	0.213
			Hedges G	-0.09	[-0.22; 0.05]	
Prior mastectomy						
Interaction test	p = 0.383					
Yes	802 0.75 (0.09)	774 0.76 (0.09)	Difference	-0.01	[-0.27; 0.24]	0.913
			Hedges G	-0.01	[-0.10; 0.09]	
No	511 0.84 (0.11)	483 0.66 (0.12)	Difference	0.18	[-0.14; 0.50]	0.267
			Hedges G	0.07	[-0.05; 0.19]	
Prior radiotherapy						
Interaction test	p = 0.126					
Yes	1172 0.75 (0.07)	1109 0.76 (0.08)	Difference	-0.01	[-0.22; 0.20]	0.901
			Hedges G	-0.01	[-0.09; 0.08]	
No	141 0.94 (0.22)	148 0.48 (0.22)	Difference	0.47	[-0.15; 1.08]	0.137
			Hedges G	0.18	[-0.06; 0.41]	

Treatment Groups		Comparison			
Ribociclib + ET (N = 1424)	ET (N = 1420)	Parameter	Estimate	[95% CI]	p-value
<p>N: Number of patients N': Number of patients in the analysis CI: Confidence interval SD: Standard deviation LS Mean: Least square mean SE: Standard error MMRM: Mixed model for repeated measures N.A.: Not analyzed N.E.: Not estimable ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + subgroup factor + treatment * subgroup factor + subgroup factor * visit + treatment * subgroup factor * visit + baseline value If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry. If the model did still not converge, interactions were removed in the order treatment * subgroup factor * visit, subgroup factor * visit.</p> <p>Analysis methods for within-subgroup analysis: Adjusted mean (LS Mean) change from baseline and overall effect obtained from MMRM with unstructured covariance matrix: change from baseline = treatment + visit + treatment * visit + baseline value ET was the reference group for treatment group comparison. If the model did not converge for a parameter*subgroup factor, the covariance structure was simplified in the order Toeplitz, first-order autoregressive, compound symmetry.</p> <p>Patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis. All data collected were included in the analysis, including assessments at confirmation of first recurrence and thereafter, as long as there were at least 50 patients in each treatment group at a visit in the overall (sub-)population.</p> <p>+ The subgroup analysis is not presented as there is at least one subgroup with less than 10 patients in the analysis.</p>					

Figure 5-2.6.2.1 HADS - Depression: line chart of change from baseline - subgroup analysis (Full Analysis Set)

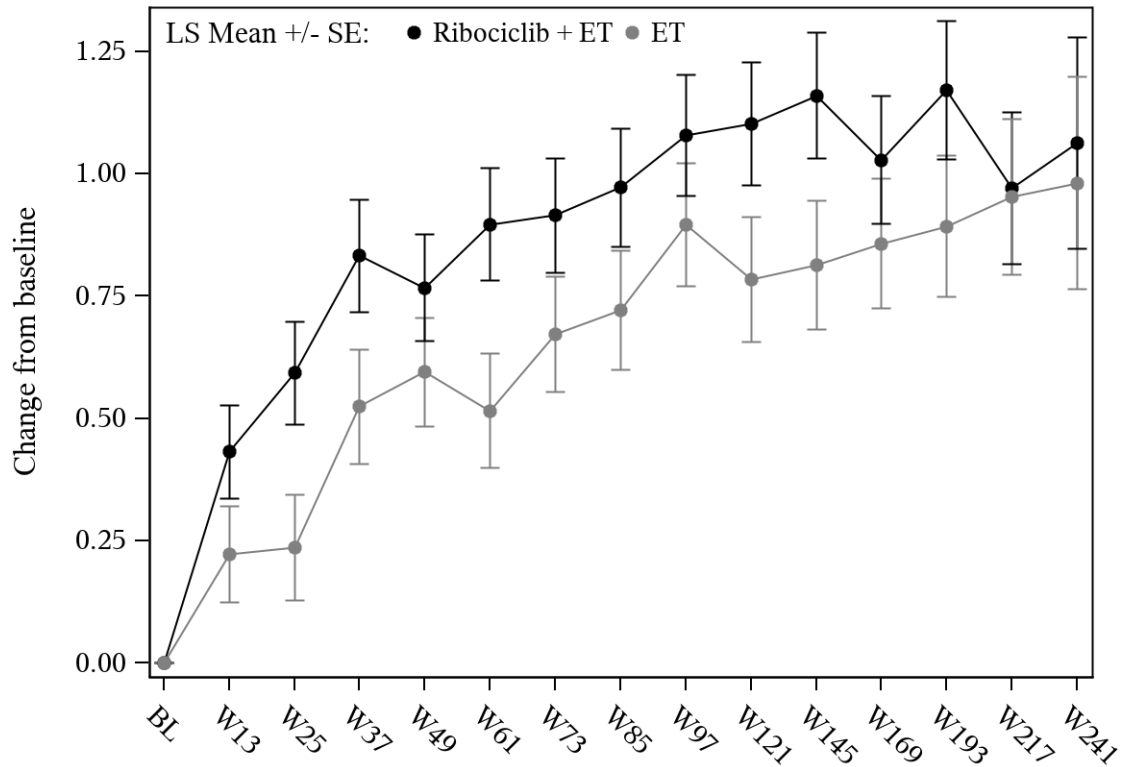
HADS - Depression

Age group 2 at randomization (median for subpopulation post-menopausal female patients): <Median



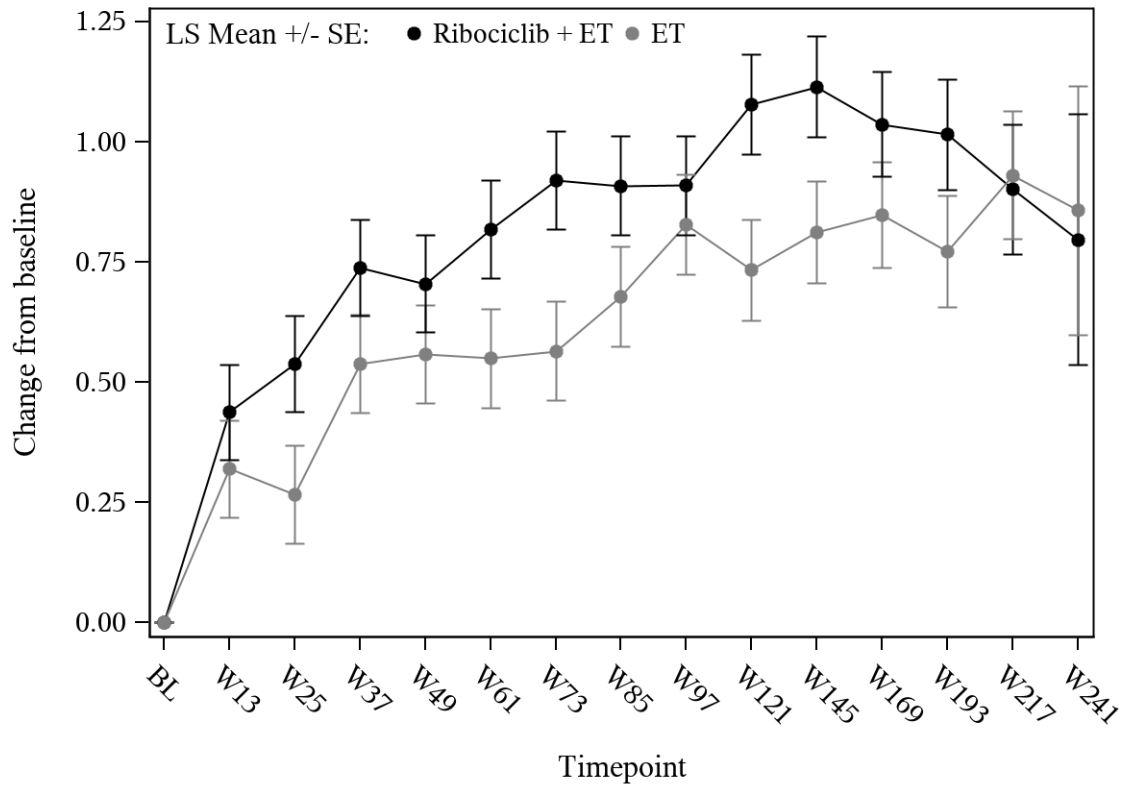
Ribociclib + ET	599	555	529	543	529	528	526	514	510	483	470	395	323	197	35
ET	574	538	511	503	502	493	492	486	476	465	457	382	319	212	39

HADS - Depression
Age group 2 at randomization (median for subpopulation post-menopausal female patients): \geq Median



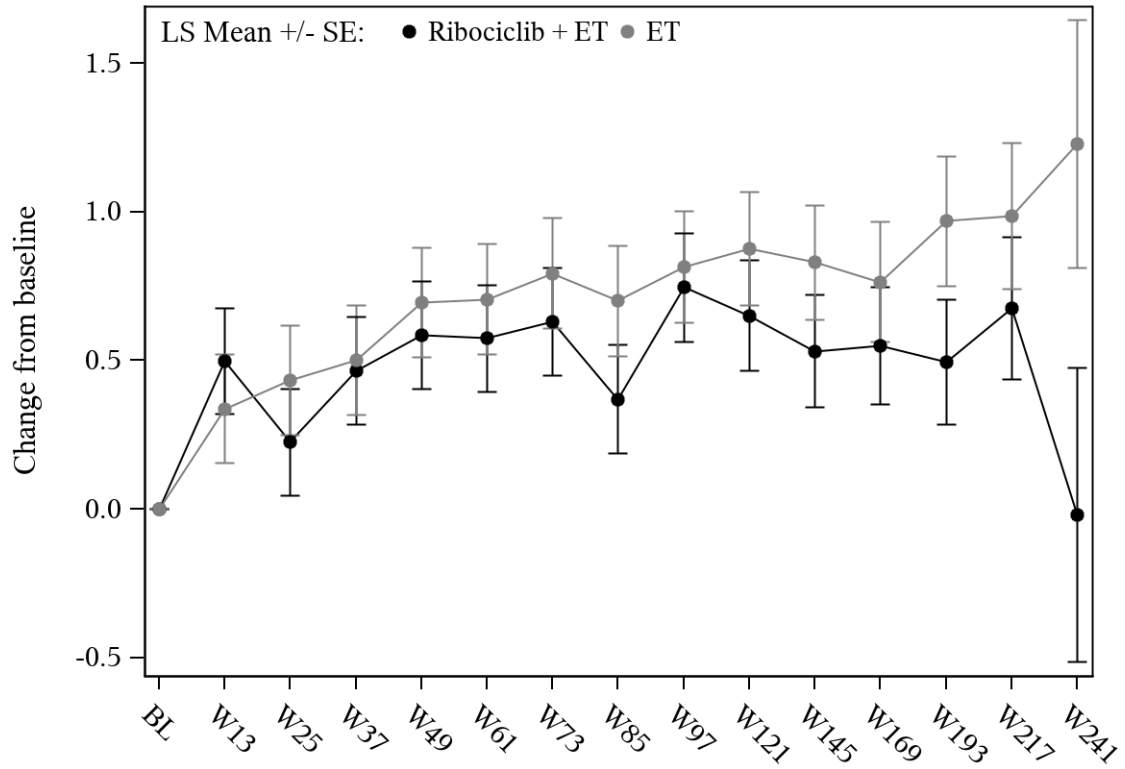
Ribociclib + ET	714	674	659	643	635	623	618	600	595	575	570	494	429	277	57
ET	683	630	609	615	617	599	601	590	581	565	546	481	405	265	57

HADS - Depression
Histological subtype: Ductal



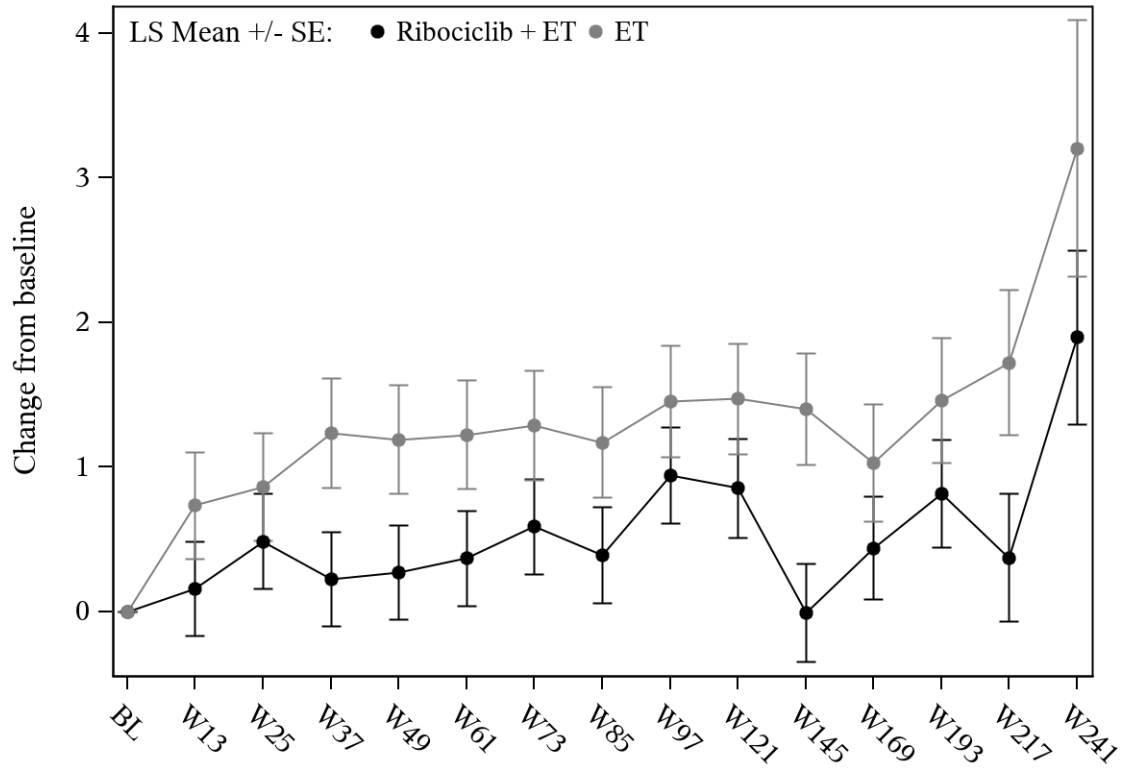
Ribociclib + ET	952	889	860	859	840	827	828	799	795	767	756	649	550	341	66
ET	924	863	833	828	827	808	805	792	777	761	742	643	551	359	67

HADS - Depression
Histological subtype: Lobular



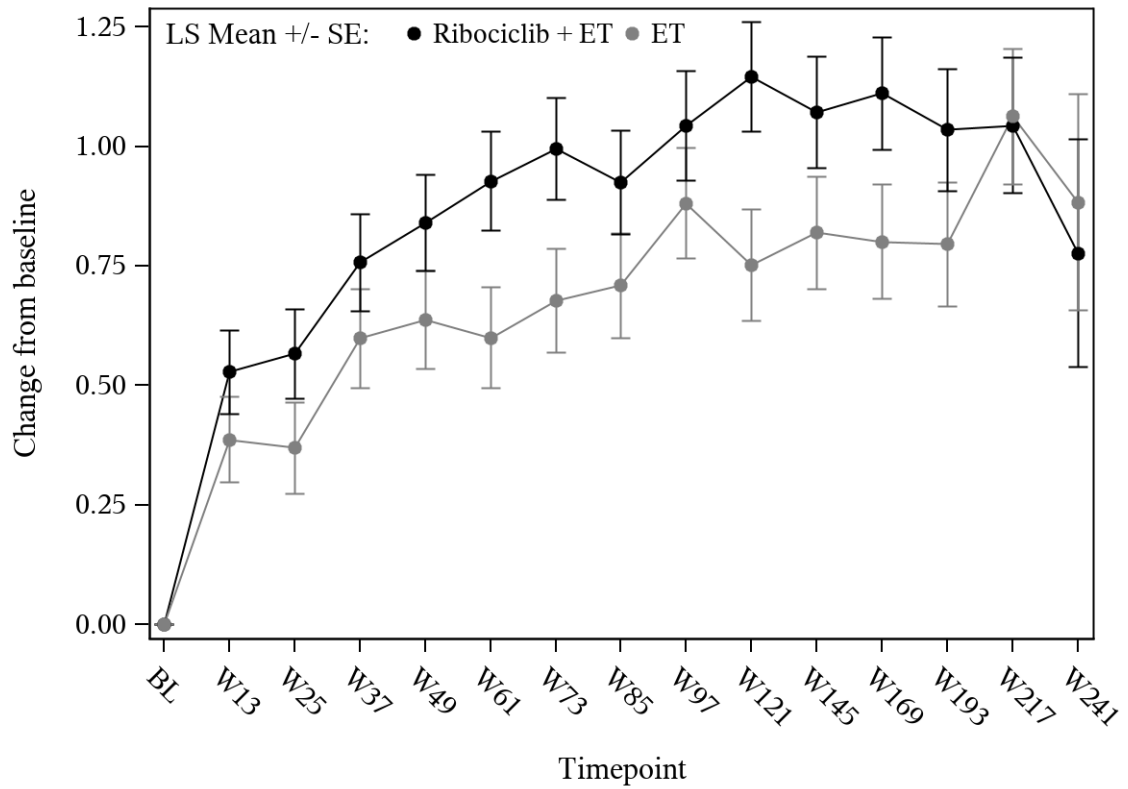
Ribociclib + ET	272	256	250	244	244	244	238	235	233	220	213	180	150	103	17
ET	264	243	227	232	232	224	228	226	226	212	205	174	136	94	25

HADS - Depression
Histological subtype: Other



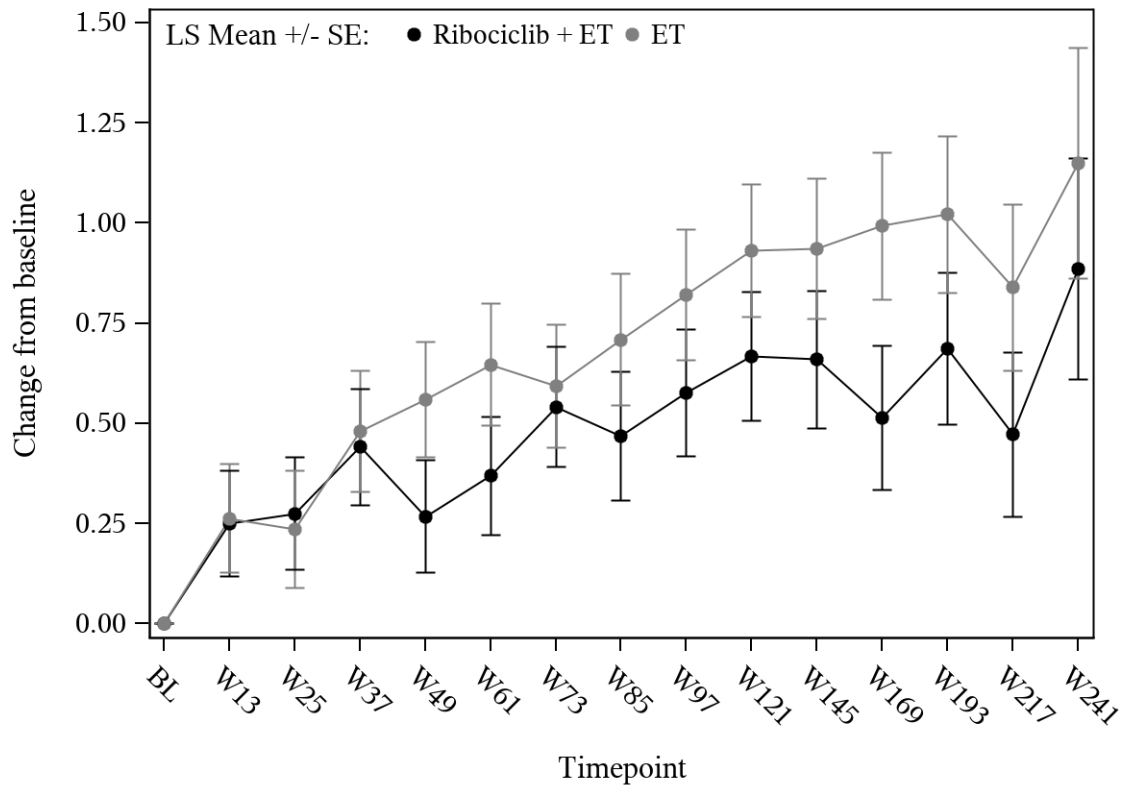
Ribociclib + ET	88	83	77	82	80	80	78	79	76	70	71	60	52	30	9
ET	69	62	60	58	60	60	60	58	54	57	56	46	37	24	4

HADS - Depression
Prior endocrine therapy: Yes



Ribociclib + ET	888	831	796	797	788	779	777	756	743	720	707	606	508	309	56
ET	861	799	762	765	757	739	736	731	714	702	683	591	494	313	64

HADS - Depression
Prior endocrine therapy: No



Ribociclib + ET	425	398	392	389	376	372	367	358	362	338	333	283	244	165	36
ET	396	369	358	353	362	353	357	345	343	328	320	272	230	164	32

5-3 Subgroup analysis for safety

5-3.1 Subgroup analysis for adverse events

Table 5-3.1.1 Any adverse event: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Any adverse event					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.770				
NA/WE/O	885 / 899 (98.4)	773 / 856 (90.3)	1.09	[1.06; 1.12]	<.001
ROW	491 / 510 (96.3)	410 / 506 (81.0)	1.19	[1.14; 1.24]	<.001
Geographical region					
Interaction test	p = 0.633				
Europe	808 / 832 (97.1)	718 / 824 (87.1)	1.11	[1.08; 1.15]	<.001
North America/Australia	393 / 400 (98.3)	323 / 364 (88.7)	1.11	[1.07; 1.15]	<.001
Asia	102 / 102 (100.0)	83 / 101 (82.2)	1.22	[1.11; 1.33]	<.001
Latin America	73 / 75 (97.3)	59 / 73 (80.8)	1.20	[1.07; 1.35]	0.002
Age group 1 at randomization					
Interaction test	p = 0.538				
<45	59 / 60 (98.3)	44 / 52 (84.6)	1.16	[1.03; 1.31]	0.015
45 to 54	296 / 300 (98.7)	281 / 322 (87.3)	1.13	[1.08; 1.18]	<.001
55 to 64	632 / 651 (97.1)	559 / 642 (87.1)	1.11	[1.08; 1.15]	<.001
≥65	389 / 398 (97.7)	299 / 346 (86.4)	1.13	[1.08; 1.18]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.693				
<Median	618 / 633 (97.6)	554 / 632 (87.7)	1.11	[1.08; 1.15]	<.001
≥Median	758 / 776 (97.7)	629 / 730 (86.2)	1.13	[1.10; 1.17]	<.001
Race					
Interaction test	N.E.				
Asian	128 / 128 (100.0)	106 / 127 (83.5)	1.20	[1.11; 1.29]	<.001
Non-Asian	1170 / 1203 (97.3)	1011 / 1167 (86.6)	1.12	[1.10; 1.15]	<.001
BMI at screening					
Interaction test	p = 0.947				
≥25	913 / 935 (97.6)	813 / 935 (87.0)	1.12	[1.09; 1.15]	<.001
<25	449 / 460 (97.6)	357 / 410 (87.1)	1.12	[1.08; 1.17]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.231				
Group I/II	568 / 585 (97.1)	514 / 589 (87.3)	1.11	[1.08; 1.15]	<.001
Group III	807 / 823 (98.1)	669 / 772 (86.7)	1.13	[1.10; 1.17]	<.001

	Treatment Groups		RR	Comparison	
	Ribociclib + ET (N = 1409)	ET (N = 1362)		[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.629				
IA/IB/IIA	302 / 310 (97.4)	269 / 311 (86.5)	1.13	[1.07; 1.18]	<.001
IIB	266 / 275 (96.7)	245 / 278 (88.1)	1.10	[1.05; 1.15]	<.001
IIIA	475 / 482 (98.5)	395 / 450 (87.8)	1.12	[1.08; 1.16]	<.001
IIIB	97 / 100 (97.0)	71 / 82 (86.6)	1.12	[1.02; 1.23]	0.015
IIIC	235 / 241 (97.5)	203 / 240 (84.6)	1.15	[1.09; 1.22]	<.001
Tumor category					
Interaction test	p = 0.982				
T0	5 / 5 (100.0)	4 / 5 (80.0)	1.25	[0.81; 1.94]	0.318
T1-T3	1257 / 1287 (97.7)	1094 / 1258 (87.0)	1.12	[1.10; 1.15]	<.001
>T3	110 / 113 (97.3)	83 / 97 (85.6)	1.14	[1.04; 1.24]	0.004
Nodal status					
Interaction test	p = 0.715				
N0	185 / 190 (97.4)	175 / 200 (87.5)	1.11	[1.05; 1.18]	<.001
N1-N3	1188 / 1216 (97.7)	1007 / 1160 (86.8)	1.13	[1.10; 1.15]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.397				
Grade 1	97 / 102 (95.1)	90 / 106 (84.9)	1.12	[1.02; 1.23]	0.015
Grade 2	822 / 842 (97.6)	668 / 768 (87.0)	1.12	[1.09; 1.16]	<.001
Grade 3	367 / 373 (98.4)	347 / 397 (87.4)	1.13	[1.08; 1.17]	<.001
Histological subtype					
Interaction test	p = 0.443				
Ductal	1002 / 1025 (97.8)	876 / 1010 (86.7)	1.13	[1.10; 1.16]	<.001
Lobular	282 / 291 (96.9)	242 / 276 (87.7)	1.11	[1.05; 1.16]	<.001
Other	91 / 92 (98.9)	65 / 76 (85.5)	1.16	[1.05; 1.27]	0.003
Ki67 status from surgical specimen					
Interaction test	p = 0.170				
Ki67≤20	640 / 660 (97.0)	547 / 629 (87.0)	1.12	[1.08; 1.15]	<.001
Ki67>20	480 / 489 (98.2)	443 / 516 (85.9)	1.14	[1.10; 1.19]	<.001
Type of NSAI					
Interaction test	p = 0.214				
Letrozole	889 / 907 (98.0)	775 / 895 (86.6)	1.13	[1.10; 1.16]	<.001
Anastrozole	487 / 502 (97.0)	408 / 467 (87.4)	1.11	[1.07; 1.15]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.092				
Yes	1171 / 1194 (98.1)	999 / 1146 (87.2)	1.13	[1.10; 1.15]	<.001
No	205 / 215 (95.3)	184 / 216 (85.2)	1.12	[1.05; 1.19]	<.001
Prior adjuvant chemotherapy					
Interaction test	p = 0.583				
Yes	678 / 694 (97.7)	594 / 673 (88.3)	1.11	[1.07; 1.14]	<.001
No	698 / 715 (97.6)	589 / 689 (85.5)	1.14	[1.11; 1.18]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.034				
Yes	521 / 528 (98.7)	431 / 503 (85.7)	1.15	[1.11; 1.20]	<.001
No	855 / 881 (97.0)	752 / 859 (87.5)	1.11	[1.08; 1.14]	<.001
Prior endocrine therapy					
Interaction test	p = 0.038				
Yes	941 / 957 (98.3)	817 / 940 (86.9)	1.13	[1.10; 1.16]	<.001
No	435 / 452 (96.2)	366 / 422 (86.7)	1.11	[1.06; 1.16]	<.001
Prior mastectomy					
Interaction test	p = 0.184				
Yes	840 / 857 (98.0)	731 / 847 (86.3)	1.14	[1.10; 1.17]	<.001
No	536 / 552 (97.1)	452 / 515 (87.8)	1.11	[1.07; 1.15]	<.001
Prior radiotherapy					
Interaction test	p = 0.879				
Yes	1223 / 1253 (97.6)	1043 / 1203 (86.7)	1.13	[1.10; 1.15]	<.001
No	153 / 156 (98.1)	140 / 159 (88.1)	1.11	[1.05; 1.18]	<.001
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.1.2 Any grade ≥ 3 adverse event: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Any grade ≥ 3 adverse event					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.962				
NA/WE/O	573 / 899 (63.7)	182 / 856 (21.3)	3.00	[2.61; 3.44]	<.001
ROW	310 / 510 (60.8)	98 / 506 (19.4)	3.14	[2.59; 3.80]	<.001
Geographical region					
Interaction test	p = 0.081				
Europe	511 / 832 (61.4)	167 / 824 (20.3)	3.03	[2.62; 3.51]	<.001
North America/Australia	250 / 400 (62.5)	81 / 364 (22.3)	2.81	[2.28; 3.45]	<.001
Asia	76 / 102 (74.5)	16 / 101 (15.8)	4.70	[2.96; 7.48]	<.001
Latin America	46 / 75 (61.3)	16 / 73 (21.9)	2.80	[1.75; 4.47]	<.001
Age group 1 at randomization					
Interaction test	p = 0.328				
<45	36 / 60 (60.0)	12 / 52 (23.1)	2.60	[1.52; 4.45]	<.001
45 to 54	190 / 300 (63.3)	64 / 322 (19.9)	3.19	[2.52; 4.03]	<.001
55 to 64	403 / 651 (61.9)	116 / 642 (18.1)	3.43	[2.87; 4.08]	<.001
≥ 65	254 / 398 (63.8)	88 / 346 (25.4)	2.51	[2.06; 3.05]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.679				
<Median	385 / 633 (60.8)	126 / 632 (19.9)	3.05	[2.58; 3.61]	<.001
\geq Median	498 / 776 (64.2)	154 / 730 (21.1)	3.04	[2.62; 3.53]	<.001
Race					
Interaction test	p = <.001				
Asian	96 / 128 (75.0)	18 / 127 (14.2)	5.29	[3.41; 8.21]	<.001
Non-Asian	733 / 1203 (60.9)	245 / 1167 (21.0)	2.90	[2.57; 3.27]	<.001
BMI at screening					
Interaction test	p = <.001				
≥ 25	561 / 935 (60.0)	206 / 935 (22.0)	2.72	[2.39; 3.11]	<.001
<25	315 / 460 (68.5)	71 / 410 (17.3)	3.95	[3.17; 4.93]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.654				
Group I/II	348 / 585 (59.5)	113 / 589 (19.2)	3.10	[2.59; 3.71]	<.001
Group III	534 / 823 (64.9)	167 / 772 (21.6)	3.00	[2.60; 3.46]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.909				
IA/IB/IIA	187 / 310 (60.3)	60 / 311 (19.3)	3.13	[2.45; 3.99]	<.001
IIB	161 / 275 (58.5)	53 / 278 (19.1)	3.07	[2.36; 3.99]	<.001
IIIA	320 / 482 (66.4)	105 / 450 (23.3)	2.85	[2.38; 3.40]	<.001
IIIB	58 / 100 (58.0)	16 / 82 (19.5)	2.97	[1.86; 4.76]	<.001
IIIC	156 / 241 (64.7)	46 / 240 (19.2)	3.38	[2.56; 4.45]	<.001
Tumor category					
Interaction test	p = 0.755				
T0	4 / 5 (80.0)	0 / 5 (0.0)	9.00	[0.61; >99.99]	0.110
T1-T3	807 / 1287 (62.7)	262 / 1258 (20.8)	3.01	[2.68; 3.38]	<.001
>T3	68 / 113 (60.2)	17 / 97 (17.5)	3.43	[2.17; 5.42]	<.001
Nodal status					
Interaction test	p = 0.515				
N0	118 / 190 (62.1)	36 / 200 (18.0)	3.45	[2.52; 4.73]	<.001
N1-N3	763 / 1216 (62.7)	244 / 1160 (21.0)	2.98	[2.65; 3.36]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.500				
Grade 1	64 / 102 (62.7)	28 / 106 (26.4)	2.38	[1.67; 3.37]	<.001
Grade 2	525 / 842 (62.4)	151 / 768 (19.7)	3.17	[2.72; 3.69]	<.001
Grade 3	235 / 373 (63.0)	79 / 397 (19.9)	3.17	[2.56; 3.91]	<.001
Histological subtype					
Interaction test	p = 0.244				
Ductal	656 / 1025 (64.0)	213 / 1010 (21.1)	3.03	[2.67; 3.45]	<.001
Lobular	165 / 291 (56.7)	55 / 276 (19.9)	2.85	[2.20; 3.68]	<.001
Other	61 / 92 (66.3)	12 / 76 (15.8)	4.20	[2.45; 7.20]	<.001
Ki67 status from surgical specimen					
Interaction test	p = 0.479				
Ki67≤20	410 / 660 (62.1)	136 / 629 (21.6)	2.87	[2.45; 3.37]	<.001
Ki67>20	305 / 489 (62.4)	101 / 516 (19.6)	3.19	[2.64; 3.85]	<.001
Type of NSAI					
Interaction test	p = 0.748				
Letrozole	567 / 907 (62.5)	186 / 895 (20.8)	3.01	[2.62; 3.45]	<.001
Anastrozole	316 / 502 (62.9)	94 / 467 (20.1)	3.13	[2.58; 3.79]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.005				
Yes	760 / 1194 (63.7)	224 / 1146 (19.5)	3.26	[2.87; 3.69]	<.001
No	123 / 215 (57.2)	56 / 216 (25.9)	2.21	[1.71; 2.84]	<.001
Prior adjuvant chemotherapy					
Interaction test	p = 0.799				
Yes	441 / 694 (63.5)	140 / 673 (20.8)	3.05	[2.61; 3.58]	<.001
No	442 / 715 (61.8)	140 / 689 (20.3)	3.04	[2.60; 3.57]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.043				
Yes	339 / 528 (64.2)	90 / 503 (17.9)	3.59	[2.94; 4.37]	<.001
No	544 / 881 (61.7)	190 / 859 (22.1)	2.79	[2.44; 3.20]	<.001
Prior endocrine therapy					
Interaction test	p = 0.061				
Yes	620 / 957 (64.8)	190 / 940 (20.2)	3.21	[2.80; 3.67]	<.001
No	263 / 452 (58.2)	90 / 422 (21.3)	2.73	[2.24; 3.33]	<.001
Prior mastectomy					
Interaction test	p = 0.908				
Yes	537 / 857 (62.7)	173 / 847 (20.4)	3.07	[2.66; 3.54]	<.001
No	346 / 552 (62.7)	107 / 515 (20.8)	3.02	[2.52; 3.61]	<.001
Prior radiotherapy					
Interaction test	p = 0.621				
Yes	785 / 1253 (62.6)	244 / 1203 (20.3)	3.09	[2.74; 3.48]	<.001
No	98 / 156 (62.8)	36 / 159 (22.6)	2.77	[2.03; 3.79]	<.001
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.1.3 Any serious adverse event: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Any serious adverse event					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.846				
NA/WE/O	147 / 899 (16.4)	101 / 856 (11.8)	1.39	[1.10; 1.75]	0.007
ROW	82 / 510 (16.1)	61 / 506 (12.1)	1.33	[0.98; 1.81]	0.067
Geographical region					
Interaction test	p = 0.629				
Europe	136 / 832 (16.3)	102 / 824 (12.4)	1.32	[1.04; 1.68]	0.022
North America/Australia	66 / 400 (16.5)	38 / 364 (10.4)	1.58	[1.09; 2.30]	0.016
Asia	15 / 102 (14.7)	15 / 101 (14.9)	0.99	[0.51; 1.92]	0.977
Latin America	12 / 75 (16.0)	7 / 73 (9.6)	1.67	[0.70; 4.00]	0.251
Age group 1 at randomization					
Interaction test	p = 0.776				
<45	10 / 60 (16.7)	9 / 52 (17.3)	0.96	[0.42; 2.19]	0.928
45 to 54	45 / 300 (15.0)	36 / 322 (11.2)	1.34	[0.89; 2.02]	0.159
55 to 64	94 / 651 (14.4)	62 / 642 (9.7)	1.50	[1.11; 2.02]	0.009
≥65	80 / 398 (20.1)	55 / 346 (15.9)	1.26	[0.93; 1.73]	0.140
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.290				
<Median	85 / 633 (13.4)	70 / 632 (11.1)	1.21	[0.90; 1.63]	0.203
≥Median	144 / 776 (18.6)	92 / 730 (12.6)	1.47	[1.16; 1.87]	0.002
Race					
Interaction test	p = 0.438				
Asian	18 / 128 (14.1)	16 / 127 (12.6)	1.12	[0.60; 2.09]	0.731
Non-Asian	201 / 1203 (16.7)	135 / 1167 (11.6)	1.44	[1.18; 1.77]	<.001
BMI at screening					
Interaction test	p = 0.301				
≥25	172 / 935 (18.4)	119 / 935 (12.7)	1.45	[1.17; 1.79]	<.001
<25	55 / 460 (12.0)	42 / 410 (10.2)	1.17	[0.80; 1.70]	0.424
AJCC Anatomic Stage Group					
Interaction test	p = 0.650				
Group I/II	94 / 585 (16.1)	66 / 589 (11.2)	1.43	[1.07; 1.92]	0.016
Group III	134 / 823 (16.3)	96 / 772 (12.4)	1.31	[1.03; 1.67]	0.030

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.069				
IA/IB/IIA	37 / 310 (11.9)	38 / 311 (12.2)	0.98	[0.64; 1.49]	0.914
IIB	57 / 275 (20.7)	28 / 278 (10.1)	2.06	[1.35; 3.13]	<.001
IIIA	72 / 482 (14.9)	60 / 450 (13.3)	1.12	[0.82; 1.54]	0.483
IIIB	22 / 100 (22.0)	10 / 82 (12.2)	1.80	[0.91; 3.59]	0.093
IIIC	40 / 241 (16.6)	26 / 240 (10.8)	1.53	[0.97; 2.43]	0.069
Tumor category					
Interaction test	p = 0.188				
T0	1 / 5 (20.0)	0 / 5 (0.0)	3.00	[0.15; 59.89]	0.472
T1-T3	201 / 1287 (15.6)	150 / 1258 (11.9)	1.31	[1.08; 1.59]	0.007
>T3	26 / 113 (23.0)	11 / 97 (11.3)	2.03	[1.06; 3.89]	0.033
Nodal status					
Interaction test	p = 0.453				
N0	26 / 190 (13.7)	24 / 200 (12.0)	1.14	[0.68; 1.91]	0.619
N1-N3	203 / 1216 (16.7)	138 / 1160 (11.9)	1.40	[1.15; 1.72]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.454				
Grade 1	18 / 102 (17.6)	17 / 106 (16.0)	1.10	[0.60; 2.01]	0.757
Grade 2	132 / 842 (15.7)	90 / 768 (11.7)	1.34	[1.04; 1.72]	0.022
Grade 3	63 / 373 (16.9)	40 / 397 (10.1)	1.68	[1.16; 2.43]	0.006
Histological subtype					
Interaction test	p = 0.436				
Ductal	176 / 1025 (17.2)	128 / 1010 (12.7)	1.35	[1.10; 1.67]	0.005
Lobular	38 / 291 (13.1)	29 / 276 (10.5)	1.24	[0.79; 1.96]	0.348
Other	15 / 92 (16.3)	5 / 76 (6.6)	2.48	[0.94; 6.51]	0.065
Ki67 status from surgical specimen					
Interaction test	p = 0.350				
Ki67≤20	105 / 660 (15.9)	82 / 629 (13.0)	1.22	[0.93; 1.59]	0.144
Ki67>20	83 / 489 (17.0)	59 / 516 (11.4)	1.48	[1.09; 2.02]	0.012
Type of NSAI					
Interaction test	p = 0.080				
Letrozole	150 / 907 (16.5)	121 / 895 (13.5)	1.22	[0.98; 1.53]	0.074
Anastrozole	79 / 502 (15.7)	41 / 467 (8.8)	1.79	[1.26; 2.56]	0.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.891				
Yes	187 / 1194 (15.7)	130 / 1146 (11.3)	1.38	[1.12; 1.70]	0.002
No	42 / 215 (19.5)	32 / 216 (14.8)	1.32	[0.87; 2.01]	0.196
Prior adjuvant chemotherapy					
Interaction test	p = 0.921				
Yes	109 / 694 (15.7)	78 / 673 (11.6)	1.36	[1.03; 1.78]	0.028
No	120 / 715 (16.8)	84 / 689 (12.2)	1.38	[1.06; 1.78]	0.015

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.308				
Yes	87 / 528 (16.5)	53 / 503 (10.5)	1.56	[1.14; 2.15]	0.006
No	142 / 881 (16.1)	109 / 859 (12.7)	1.27	[1.01; 1.60]	0.043
Prior endocrine therapy					
Interaction test	p = 0.593				
Yes	156 / 957 (16.3)	116 / 940 (12.3)	1.32	[1.06; 1.65]	0.014
No	73 / 452 (16.2)	46 / 422 (10.9)	1.48	[1.05; 2.09]	0.025
Prior mastectomy					
Interaction test	p = 0.017				
Yes	165 / 857 (19.3)	102 / 847 (12.0)	1.60	[1.27; 2.01]	<.001
No	64 / 552 (11.6)	60 / 515 (11.7)	1.00	[0.71; 1.39]	0.977
Prior radiotherapy					
Interaction test	p = 0.396				
Yes	195 / 1253 (15.6)	141 / 1203 (11.7)	1.33	[1.09; 1.62]	0.006
No	34 / 156 (21.8)	21 / 159 (13.2)	1.65	[1.00; 2.71]	0.048
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

**Table 5-3.1.4 Any adverse event leading to treatment discontinuation of ribociclib:
binary analysis - subgroup analysis (Safety Set)**

Analysis not performed as these events could not occur in treatment arm ET.

Table 5-3.1.5 Any adverse event leading to treatment discontinuation of NSAI: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Any adverse event leading to treatment discontinuation of NSAI					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.901				
NA/WE/O	73 / 899 (8.1)	53 / 856 (6.2)	1.31	[0.93; 1.84]	0.119
ROW	21 / 510 (4.1)	15 / 506 (3.0)	1.39	[0.72; 2.66]	0.323
Geographical region					
Interaction test	p = 0.245				
Europe	40 / 832 (4.8)	40 / 824 (4.9)	0.99	[0.65; 1.52]	0.965
North America/Australia	46 / 400 (11.5)	24 / 364 (6.6)	1.74	[1.09; 2.80]	0.021
Asia	4 / 102 (3.9)	3 / 101 (3.0)	1.32	[0.30; 5.75]	0.711
Latin America	4 / 75 (5.3)	1 / 73 (1.4)	3.89	[0.45; 34.01]	0.219
Age group 1 at randomization					
Interaction test	p = 0.770				
<45	1 / 60 (1.7)	2 / 52 (3.8)	0.43	[0.04; 4.64]	0.489
45 to 54	19 / 300 (6.3)	15 / 322 (4.7)	1.36	[0.70; 2.63]	0.361
55 to 64	43 / 651 (6.6)	29 / 642 (4.5)	1.46	[0.92; 2.31]	0.104
≥65	31 / 398 (7.8)	22 / 346 (6.4)	1.22	[0.72; 2.08]	0.450
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.438				
<Median	36 / 633 (5.7)	31 / 632 (4.9)	1.16	[0.73; 1.85]	0.535
≥Median	58 / 776 (7.5)	37 / 730 (5.1)	1.47	[0.99; 2.20]	0.057
Race					
Interaction test	p = 0.555				
Asian	5 / 128 (3.9)	5 / 127 (3.9)	0.99	[0.29; 3.34]	0.990
Non-Asian	86 / 1203 (7.1)	58 / 1167 (5.0)	1.44	[1.04; 1.99]	0.027
BMI at screening					
Interaction test	p = 0.841				
≥25	63 / 935 (6.7)	48 / 935 (5.1)	1.31	[0.91; 1.89]	0.144
<25	30 / 460 (6.5)	19 / 410 (4.6)	1.41	[0.80; 2.46]	0.231
AJCC Anatomic Stage Group					
Interaction test	p = 0.504				
Group I/II	40 / 585 (6.8)	34 / 589 (5.8)	1.18	[0.76; 1.84]	0.453
Group III	53 / 823 (6.4)	34 / 772 (4.4)	1.46	[0.96; 2.22]	0.076

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.416				
IA/IB/IIA	21 / 310 (6.8)	24 / 311 (7.7)	0.88	[0.50; 1.54]	0.651
IIB	19 / 275 (6.9)	10 / 278 (3.6)	1.92	[0.91; 4.06]	0.087
IIIA	34 / 482 (7.1)	22 / 450 (4.9)	1.44	[0.86; 2.43]	0.168
IIIB	3 / 100 (3.0)	3 / 82 (3.7)	0.82	[0.17; 3.96]	0.805
IIIC	16 / 241 (6.6)	9 / 240 (3.8)	1.77	[0.80; 3.93]	0.160
Tumor category					
Interaction test	p = 0.545				
T0	0 / 5 (0.0)	1 / 5 (20.0)	0.33	[0.02; 6.65]	0.472
T1-T3	90 / 1287 (7.0)	63 / 1258 (5.0)	1.40	[1.02; 1.91]	0.036
>T3	3 / 113 (2.7)	3 / 97 (3.1)	0.86	[0.18; 4.16]	0.850
Nodal status					
Interaction test	p = 0.357				
N0	13 / 190 (6.8)	14 / 200 (7.0)	0.98	[0.47; 2.02]	0.951
N1-N3	81 / 1216 (6.7)	54 / 1160 (4.7)	1.43	[1.02; 2.00]	0.036
Histological grade at time of surgery					
Interaction test	p = 0.537				
Grade 1	7 / 102 (6.9)	9 / 106 (8.5)	0.81	[0.31; 2.09]	0.660
Grade 2	55 / 842 (6.5)	36 / 768 (4.7)	1.39	[0.93; 2.10]	0.111
Grade 3	28 / 373 (7.5)	20 / 397 (5.0)	1.49	[0.85; 2.60]	0.160
Histological subtype					
Interaction test	p = 0.644				
Ductal	77 / 1025 (7.5)	54 / 1010 (5.3)	1.41	[1.00; 1.97]	0.048
Lobular	11 / 291 (3.8)	11 / 276 (4.0)	0.95	[0.42; 2.15]	0.899
Other	6 / 92 (6.5)	3 / 76 (3.9)	1.65	[0.43; 6.39]	0.467
Ki67 status from surgical specimen					
Interaction test	p = 0.293				
Ki67≤20	43 / 660 (6.5)	30 / 629 (4.8)	1.37	[0.87; 2.15]	0.177
Ki67>20	26 / 489 (5.3)	29 / 516 (5.6)	0.95	[0.57; 1.58]	0.833
Type of NSAI					
Interaction test	p = 0.367				
Letrozole	51 / 907 (5.6)	33 / 895 (3.7)	1.53	[0.99; 2.34]	0.053
Anastrozole	43 / 502 (8.6)	35 / 467 (7.5)	1.14	[0.74; 1.75]	0.541
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.374				
Yes	79 / 1194 (6.6)	53 / 1146 (4.6)	1.43	[1.02; 2.01]	0.038
No	15 / 215 (7.0)	15 / 216 (6.9)	1.00	[0.50; 2.00]	0.989
Prior adjuvant chemotherapy					
Interaction test	p = 0.318				
Yes	54 / 694 (7.8)	34 / 673 (5.1)	1.54	[1.02; 2.33]	0.042
No	40 / 715 (5.6)	34 / 689 (4.9)	1.13	[0.73; 1.77]	0.581

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.898				
Yes	26 / 528 (4.9)	19 / 503 (3.8)	1.30	[0.73; 2.33]	0.369
No	68 / 881 (7.7)	49 / 859 (5.7)	1.35	[0.95; 1.93]	0.095
Prior endocrine therapy					
Interaction test	p = 0.566				
Yes	60 / 957 (6.3)	47 / 940 (5.0)	1.25	[0.87; 1.82]	0.232
No	34 / 452 (7.5)	21 / 422 (5.0)	1.51	[0.89; 2.56]	0.125
Prior mastectomy					
Interaction test	p = 0.776				
Yes	52 / 857 (6.1)	40 / 847 (4.7)	1.28	[0.86; 1.92]	0.221
No	42 / 552 (7.6)	28 / 515 (5.4)	1.40	[0.88; 2.22]	0.155
Prior radiotherapy					
Interaction test	p = 0.267				
Yes	90 / 1253 (7.2)	62 / 1203 (5.2)	1.39	[1.02; 1.91]	0.038
No	4 / 156 (2.6)	6 / 159 (3.8)	0.68	[0.20; 2.36]	0.543
<p>N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.1.6 Any adverse event leading to treatment discontinuation of any component: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Any adverse event leading to treatment discontinuation of any component					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.093				
NA/WE/O	230 / 899 (25.6)	53 / 856 (6.2)	4.13	[3.11; 5.49]	<.001
ROW	110 / 510 (21.6)	15 / 506 (3.0)	7.28	[4.30; 12.30]	<.001
Geographical region					
Interaction test	p = 0.504				
Europe	210 / 832 (25.2)	40 / 824 (4.9)	5.20	[3.76; 7.19]	<.001
North America/Australia	99 / 400 (24.8)	24 / 364 (6.6)	3.75	[2.46; 5.73]	<.001
Asia	17 / 102 (16.7)	3 / 101 (3.0)	5.61	[1.70; 18.56]	0.005
Latin America	14 / 75 (18.7)	1 / 73 (1.4)	13.63	[1.84; >99.99]	0.011
Age group 1 at randomization					
Interaction test	p = 0.415				
<45	4 / 60 (6.7)	2 / 52 (3.8)	1.73	[0.33; 9.08]	0.515
45 to 54	58 / 300 (19.3)	15 / 322 (4.7)	4.15	[2.41; 7.16]	<.001
55 to 64	162 / 651 (24.9)	29 / 642 (4.5)	5.51	[3.77; 8.05]	<.001
≥65	116 / 398 (29.1)	22 / 346 (6.4)	4.58	[2.97; 7.06]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.062				
<Median	118 / 633 (18.6)	31 / 632 (4.9)	3.80	[2.60; 5.56]	<.001
≥Median	222 / 776 (28.6)	37 / 730 (5.1)	5.64	[4.05; 7.87]	<.001
Race					
Interaction test	p = 0.564				
Asian	21 / 128 (16.4)	5 / 127 (3.9)	4.17	[1.62; 10.71]	0.003
Non-Asian	306 / 1203 (25.4)	58 / 1167 (5.0)	5.12	[3.91; 6.70]	<.001
BMI at screening					
Interaction test	p = 0.837				
≥25	234 / 935 (25.0)	48 / 935 (5.1)	4.87	[3.62; 6.56]	<.001
<25	101 / 460 (22.0)	19 / 410 (4.6)	4.74	[2.96; 7.59]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.617				
Group I/II	150 / 585 (25.6)	34 / 589 (5.8)	4.44	[3.12; 6.33]	<.001
Group III	189 / 823 (23.0)	34 / 772 (4.4)	5.21	[3.67; 7.41]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.642				
IA/IB/IIA	85 / 310 (27.4)	24 / 311 (7.7)	3.55	[2.32; 5.43]	<.001
IIB	65 / 275 (23.6)	10 / 278 (3.6)	6.57	[3.45; 12.52]	<.001
IIIA	123 / 482 (25.5)	22 / 450 (4.9)	5.22	[3.38; 8.07]	<.001
IIIB	16 / 100 (16.0)	3 / 82 (3.7)	4.37	[1.32; 14.49]	0.016
IIIC	50 / 241 (20.7)	9 / 240 (3.8)	5.53	[2.78; 11.00]	<.001
Tumor category					
Interaction test	p = 0.513				
T0	1 / 5 (20.0)	1 / 5 (20.0)	1.00	[0.08; 11.93]	1.000
T1-T3	319 / 1287 (24.8)	63 / 1258 (5.0)	4.95	[3.82; 6.41]	<.001
>T3	18 / 113 (15.9)	3 / 97 (3.1)	5.15	[1.56; 16.96]	0.007
Nodal status					
Interaction test	p = 0.560				
N0	53 / 190 (27.9)	14 / 200 (7.0)	3.98	[2.29; 6.94]	<.001
N1-N3	287 / 1216 (23.6)	54 / 1160 (4.7)	5.07	[3.83; 6.70]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.520				
Grade 1	27 / 102 (26.5)	9 / 106 (8.5)	3.12	[1.54; 6.30]	0.002
Grade 2	195 / 842 (23.2)	36 / 768 (4.7)	4.94	[3.51; 6.95]	<.001
Grade 3	98 / 373 (26.3)	20 / 397 (5.0)	5.22	[3.29; 8.26]	<.001
Histological subtype					
Interaction test	p = 0.831				
Ductal	255 / 1025 (24.9)	54 / 1010 (5.3)	4.65	[3.52; 6.16]	<.001
Lobular	61 / 291 (21.0)	11 / 276 (4.0)	5.26	[2.83; 9.78]	<.001
Other	24 / 92 (26.1)	3 / 76 (3.9)	6.61	[2.07; 21.11]	0.001
Ki67 status from surgical specimen					
Interaction test	p = 0.559				
Ki67≤20	161 / 660 (24.4)	30 / 629 (4.8)	5.11	[3.52; 7.44]	<.001
Ki67>20	119 / 489 (24.3)	29 / 516 (5.6)	4.33	[2.94; 6.37]	<.001
Type of NSAI					
Interaction test	p = 0.015				
Letrozole	215 / 907 (23.7)	33 / 895 (3.7)	6.43	[4.51; 9.17]	<.001
Anastrozole	125 / 502 (24.9)	35 / 467 (7.5)	3.32	[2.33; 4.73]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.720				
Yes	268 / 1194 (22.4)	53 / 1146 (4.6)	4.85	[3.66; 6.44]	<.001
No	72 / 215 (33.5)	15 / 216 (6.9)	4.82	[2.86; 8.14]	<.001
Prior adjuvant chemotherapy					
Interaction test	p = 0.909				
Yes	167 / 694 (24.1)	34 / 673 (5.1)	4.76	[3.35; 6.78]	<.001
No	173 / 715 (24.2)	34 / 689 (4.9)	4.90	[3.45; 6.98]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.737				
Yes	108 / 528 (20.5)	19 / 503 (3.8)	5.42	[3.38; 8.68]	<.001
No	232 / 881 (26.3)	49 / 859 (5.7)	4.62	[3.44; 6.19]	<.001
Prior endocrine therapy					
Interaction test	p = 0.990				
Yes	231 / 957 (24.1)	47 / 940 (5.0)	4.83	[3.57; 6.52]	<.001
No	109 / 452 (24.1)	21 / 422 (5.0)	4.85	[3.10; 7.58]	<.001
Prior mastectomy					
Interaction test	p = 0.716				
Yes	204 / 857 (23.8)	40 / 847 (4.7)	5.04	[3.64; 6.98]	<.001
No	136 / 552 (24.6)	28 / 515 (5.4)	4.53	[3.07; 6.68]	<.001
Prior radiotherapy					
Interaction test	p = 0.102				
Yes	290 / 1253 (23.1)	62 / 1203 (5.2)	4.49	[3.45; 5.84]	<.001
No	50 / 156 (32.1)	6 / 159 (3.8)	8.49	[3.75; 19.24]	<.001
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

5-3.2 Subgroup analysis for adverse events by SOC and PT

Table 5-3.2.1 SOC investigations: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Investigations					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.620				
NA/WE/O	567 / 899 (63.1)	260 / 856 (30.4)	2.08	[1.85; 2.33]	<.001
ROW	335 / 510 (65.7)	157 / 506 (31.0)	2.12	[1.83; 2.45]	<.001
Geographical region					
Interaction test	p = <.001				
Europe	500 / 832 (60.1)	266 / 824 (32.3)	1.86	[1.66; 2.09]	<.001
North America/Australia	270 / 400 (67.5)	115 / 364 (31.6)	2.14	[1.81; 2.52]	<.001
Asia	89 / 102 (87.3)	24 / 101 (23.8)	3.67	[2.57; 5.25]	<.001
Latin America	43 / 75 (57.3)	12 / 73 (16.4)	3.49	[2.01; 6.06]	<.001
Age group 1 at randomization					
Interaction test	p = 0.209				
<45	44 / 60 (73.3)	12 / 52 (23.1)	3.18	[1.89; 5.34]	<.001
45 to 54	184 / 300 (61.3)	93 / 322 (28.9)	2.12	[1.75; 2.58]	<.001
55 to 64	415 / 651 (63.7)	191 / 642 (29.8)	2.14	[1.88; 2.45]	<.001
≥65	259 / 398 (65.1)	121 / 346 (35.0)	1.86	[1.58; 2.19]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.823				
<Median	402 / 633 (63.5)	188 / 632 (29.7)	2.13	[1.87; 2.44]	<.001
≥Median	500 / 776 (64.4)	229 / 730 (31.4)	2.05	[1.82; 2.31]	<.001
Race					
Interaction test	p = <.001				
Asian	107 / 128 (83.6)	33 / 127 (26.0)	3.22	[2.38; 4.36]	<.001
Non-Asian	758 / 1203 (63.0)	358 / 1167 (30.7)	2.05	[1.87; 2.26]	<.001
BMI at screening					
Interaction test	p = 0.027				
≥25	621 / 935 (66.4)	281 / 935 (30.1)	2.21	[1.98; 2.46]	<.001
<25	274 / 460 (59.6)	131 / 410 (32.0)	1.86	[1.59; 2.19]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.244				
Group I/II	371 / 585 (63.4)	191 / 589 (32.4)	1.96	[1.71; 2.23]	<.001
Group III	530 / 823 (64.4)	226 / 772 (29.3)	2.20	[1.95; 2.48]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.147				
IA/IB/IIA	194 / 310 (62.6)	101 / 311 (32.5)	1.93	[1.61; 2.31]	<.001
IIB	177 / 275 (64.4)	90 / 278 (32.4)	1.99	[1.64; 2.41]	<.001
IIIA	313 / 482 (64.9)	135 / 450 (30.0)	2.16	[1.85; 2.53]	<.001
IIIB	57 / 100 (57.0)	29 / 82 (35.4)	1.61	[1.15; 2.26]	0.006
IIIC	160 / 241 (66.4)	62 / 240 (25.8)	2.57	[2.04; 3.24]	<.001
Tumor category					
Interaction test	p = 0.166				
T0	5 / 5 (100.0)	1 / 5 (20.0)	5.00	[0.87; 28.86]	0.072
T1-T3	828 / 1287 (64.3)	383 / 1258 (30.4)	2.11	[1.93; 2.32]	<.001
>T3	66 / 113 (58.4)	33 / 97 (34.0)	1.72	[1.25; 2.36]	<.001
Nodal status					
Interaction test	p = 0.224				
N0	118 / 190 (62.1)	68 / 200 (34.0)	1.83	[1.46; 2.28]	<.001
N1-N3	783 / 1216 (64.4)	349 / 1160 (30.1)	2.14	[1.94; 2.36]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.134				
Grade 1	58 / 102 (56.9)	37 / 106 (34.9)	1.63	[1.19; 2.22]	0.002
Grade 2	551 / 842 (65.4)	227 / 768 (29.6)	2.21	[1.96; 2.50]	<.001
Grade 3	241 / 373 (64.6)	124 / 397 (31.2)	2.07	[1.76; 2.44]	<.001
Histological subtype					
Interaction test	p = 0.936				
Ductal	662 / 1025 (64.6)	311 / 1010 (30.8)	2.10	[1.89; 2.32]	<.001
Lobular	176 / 291 (60.5)	78 / 276 (28.3)	2.14	[1.74; 2.64]	<.001
Other	63 / 92 (68.5)	28 / 76 (36.8)	1.86	[1.34; 2.57]	<.001
Ki67 status from surgical specimen					
Interaction test	p = 0.290				
Ki67≤20	407 / 660 (61.7)	190 / 629 (30.2)	2.04	[1.79; 2.33]	<.001
Ki67>20	318 / 489 (65.0)	151 / 516 (29.3)	2.22	[1.91; 2.58]	<.001
Type of NSAI					
Interaction test	p = 0.648				
Letrozole	576 / 907 (63.5)	275 / 895 (30.7)	2.07	[1.85; 2.31]	<.001
Anastrozole	326 / 502 (64.9)	142 / 467 (30.4)	2.14	[1.84; 2.49]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = <.001				
Yes	777 / 1194 (65.1)	330 / 1146 (28.8)	2.26	[2.04; 2.50]	<.001
No	125 / 215 (58.1)	87 / 216 (40.3)	1.44	[1.18; 1.76]	<.001
Prior adjuvant chemotherapy					
Interaction test	p = 0.411				
Yes	455 / 694 (65.6)	206 / 673 (30.6)	2.14	[1.89; 2.43]	<.001
No	447 / 715 (62.5)	211 / 689 (30.6)	2.04	[1.80; 2.32]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.020				
Yes	346 / 528 (65.5)	135 / 503 (26.8)	2.44	[2.09; 2.86]	<.001
No	556 / 881 (63.1)	282 / 859 (32.8)	1.92	[1.73; 2.14]	<.001
Prior endocrine therapy					
Interaction test	p = 0.161				
Yes	612 / 957 (63.9)	272 / 940 (28.9)	2.21	[1.98; 2.47]	<.001
No	290 / 452 (64.2)	145 / 422 (34.4)	1.87	[1.61; 2.17]	<.001
Prior mastectomy					
Interaction test	p = 0.797				
Yes	555 / 857 (64.8)	262 / 847 (30.9)	2.09	[1.87; 2.34]	<.001
No	347 / 552 (62.9)	155 / 515 (30.1)	2.09	[1.80; 2.42]	<.001
Prior radiotherapy					
Interaction test	p = 0.028				
Yes	795 / 1253 (63.4)	343 / 1203 (28.5)	2.23	[2.02; 2.46]	<.001
No	107 / 156 (68.6)	74 / 159 (46.5)	1.47	[1.21; 1.80]	<.001
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.2 PT alanine aminotransferase increased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Alanine aminotransferase increased					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.220				
NA/WE/O	162 / 899 (18.0)	30 / 856 (3.5)	5.14	[3.52; 7.50]	<.001
ROW	140 / 510 (27.5)	41 / 506 (8.1)	3.39	[2.45; 4.69]	<.001
Geographical region					
Interaction test	p = 0.346				
Europe	187 / 832 (22.5)	51 / 824 (6.2)	3.63	[2.71; 4.87]	<.001
North America/Australia	80 / 400 (20.0)	11 / 364 (3.0)	6.62	[3.58; 12.23]	<.001
Asia	22 / 102 (21.6)	7 / 101 (6.9)	3.11	[1.39; 6.96]	0.006
Latin America	13 / 75 (17.3)	2 / 73 (2.7)	6.33	[1.48; 27.06]	0.013
Age group 1 at randomization					
Interaction test	p = 0.065				
<45	7 / 60 (11.7)	1 / 52 (1.9)	6.07	[0.77; 47.70]	0.087
45 to 54	50 / 300 (16.7)	21 / 322 (6.5)	2.56	[1.57; 4.15]	<.001
55 to 64	163 / 651 (25.0)	29 / 642 (4.5)	5.54	[3.79; 8.10]	<.001
≥65	82 / 398 (20.6)	20 / 346 (5.8)	3.56	[2.23; 5.69]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.075				
<Median	121 / 633 (19.1)	37 / 632 (5.9)	3.27	[2.30; 4.64]	<.001
≥Median	181 / 776 (23.3)	34 / 730 (4.7)	5.01	[3.52; 7.12]	<.001
Race					
Interaction test	p = 0.406				
Asian	25 / 128 (19.5)	8 / 127 (6.3)	3.10	[1.45; 6.61]	0.003
Non-Asian	267 / 1203 (22.2)	60 / 1167 (5.1)	4.32	[3.30; 5.64]	<.001
BMI at screening					
Interaction test	p = 0.067				
≥25	235 / 935 (25.1)	50 / 935 (5.3)	4.70	[3.51; 6.29]	<.001
<25	64 / 460 (13.9)	19 / 410 (4.6)	3.00	[1.83; 4.92]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.053				
Group I/II	140 / 585 (23.9)	26 / 589 (4.4)	5.42	[3.62; 8.11]	<.001
Group III	161 / 823 (19.6)	45 / 772 (5.8)	3.36	[2.45; 4.60]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.135				
IA/IB/IIA	73 / 310 (23.5)	18 / 311 (5.8)	4.07	[2.49; 6.65]	<.001
IIB	67 / 275 (24.4)	8 / 278 (2.9)	8.47	[4.15; 17.29]	<.001
IIIA	97 / 482 (20.1)	24 / 450 (5.3)	3.77	[2.46; 5.79]	<.001
IIIB	19 / 100 (19.0)	4 / 82 (4.9)	3.90	[1.38; 11.00]	0.010
IIIC	45 / 241 (18.7)	17 / 240 (7.1)	2.64	[1.55; 4.47]	<.001
Tumor category					
Interaction test	p = 0.904				
T0	0 / 5 (0.0)	1 / 5 (20.0)	0.33	[0.02; 6.65]	0.472
T1-T3	281 / 1287 (21.8)	66 / 1258 (5.2)	4.16	[3.22; 5.38]	<.001
>T3	19 / 113 (16.8)	4 / 97 (4.1)	4.08	[1.44; 11.58]	0.008
Nodal status					
Interaction test	p = 0.294				
N0	48 / 190 (25.3)	9 / 200 (4.5)	5.61	[2.83; 11.12]	<.001
N1-N3	254 / 1216 (20.9)	62 / 1160 (5.3)	3.91	[3.00; 5.10]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.441				
Grade 1	18 / 102 (17.6)	7 / 106 (6.6)	2.67	[1.17; 6.13]	0.020
Grade 2	184 / 842 (21.9)	36 / 768 (4.7)	4.66	[3.31; 6.57]	<.001
Grade 3	87 / 373 (23.3)	20 / 397 (5.0)	4.63	[2.91; 7.37]	<.001
Histological subtype					
Interaction test	p = 0.111				
Ductal	219 / 1025 (21.4)	60 / 1010 (5.9)	3.60	[2.74; 4.72]	<.001
Lobular	56 / 291 (19.2)	10 / 276 (3.6)	5.31	[2.77; 10.20]	<.001
Other	27 / 92 (29.3)	1 / 76 (1.3)	22.30	[3.10; >99.99]	0.002
Ki67 status from surgical specimen					
Interaction test	p = 0.378				
Ki67≤20	135 / 660 (20.5)	38 / 629 (6.0)	3.39	[2.40; 4.77]	<.001
Ki67>20	109 / 489 (22.3)	27 / 516 (5.2)	4.26	[2.85; 6.37]	<.001
Type of NSAI					
Interaction test	p = 0.952				
Letrozole	193 / 907 (21.3)	46 / 895 (5.1)	4.14	[3.04; 5.63]	<.001
Anastrozole	109 / 502 (21.7)	25 / 467 (5.4)	4.06	[2.68; 6.15]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.340				
Yes	235 / 1194 (19.7)	57 / 1146 (5.0)	3.96	[3.00; 5.22]	<.001
No	67 / 215 (31.2)	14 / 216 (6.5)	4.81	[2.79; 8.28]	<.001
Prior adjuvant chemotherapy					
Interaction test	p = 0.033				
Yes	131 / 694 (18.9)	40 / 673 (5.9)	3.18	[2.27; 4.45]	<.001
No	171 / 715 (23.9)	31 / 689 (4.5)	5.32	[3.68; 7.68]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.184				
Yes	112 / 528 (21.2)	20 / 503 (4.0)	5.33	[3.37; 8.45]	<.001
No	190 / 881 (21.6)	51 / 859 (5.9)	3.63	[2.71; 4.88]	<.001
Prior endocrine therapy					
Interaction test	p = 0.317				
Yes	186 / 957 (19.4)	39 / 940 (4.1)	4.68	[3.36; 6.54]	<.001
No	116 / 452 (25.7)	32 / 422 (7.6)	3.38	[2.34; 4.89]	<.001
Prior mastectomy					
Interaction test	p = 0.788				
Yes	186 / 857 (21.7)	46 / 847 (5.4)	4.00	[2.94; 5.44]	<.001
No	116 / 552 (21.0)	25 / 515 (4.9)	4.33	[2.86; 6.56]	<.001
Prior radiotherapy					
Interaction test	p = 0.369				
Yes	247 / 1253 (19.7)	59 / 1203 (4.9)	4.02	[3.06; 5.28]	<.001
No	55 / 156 (35.3)	12 / 159 (7.5)	4.67	[2.60; 8.38]	<.001
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.3 PT neutrophil count decreased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Neutrophil count decreased					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.342				
NA/WE/O	219 / 899 (24.4)	8 / 856 (0.9)	26.07	[12.95; 52.45]	<.001
ROW	83 / 510 (16.3)	5 / 506 (1.0)	16.47	[6.74; 40.27]	<.001
Geographical region					
Interaction test	p = 0.075				
Europe	113 / 832 (13.6)	2 / 824 (0.2)	55.96	[13.87; >99.99]	<.001
North America/Australia	115 / 400 (28.8)	8 / 364 (2.2)	13.08	[6.48; 26.41]	<.001
Asia	71 / 102 (69.6)	3 / 101 (3.0)	23.43	[7.63; 71.97]	<.001
Latin America	3 / 75 (4.0)	0 / 73 (0.0)	6.82	[0.36; >99.99]	0.202
Age group 1 at randomization					
Interaction test	p = 0.928				
<45	23 / 60 (38.3)	1 / 52 (1.9)	19.93	[2.79; >99.99]	0.003
45 to 54	65 / 300 (21.7)	4 / 322 (1.2)	17.44	[6.43; 47.29]	<.001
55 to 64	140 / 651 (21.5)	6 / 642 (0.9)	23.01	[10.24; 51.72]	<.001
≥65	74 / 398 (18.6)	2 / 346 (0.6)	32.17	[7.96; >99.99]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.559				
<Median	152 / 633 (24.0)	8 / 632 (1.3)	18.97	[9.40; 38.29]	<.001
≥Median	150 / 776 (19.3)	5 / 730 (0.7)	28.22	[11.64; 68.40]	<.001
Race					
Interaction test	p = 0.764				
Asian	78 / 128 (60.9)	5 / 127 (3.9)	15.48	[6.48; 36.95]	<.001
Non-Asian	216 / 1203 (18.0)	8 / 1167 (0.7)	26.19	[12.99; 52.80]	<.001
BMI at screening					
Interaction test	p = 0.054				
≥25	175 / 935 (18.7)	4 / 935 (0.4)	43.75	[16.31; >99.99]	<.001
<25	123 / 460 (26.7)	9 / 410 (2.2)	12.18	[6.27; 23.65]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.936				
Group I/II	111 / 585 (19.0)	5 / 589 (0.8)	22.35	[9.19; 54.36]	<.001
Group III	190 / 823 (23.1)	8 / 772 (1.0)	22.28	[11.06; 44.89]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.622				
IA/IB/IIA	64 / 310 (20.6)	3 / 311 (1.0)	21.40	[6.80; 67.39]	<.001
IIB	47 / 275 (17.1)	2 / 278 (0.7)	23.76	[5.83; 96.84]	<.001
IIIA	114 / 482 (23.7)	3 / 450 (0.7)	35.48	[11.36; >99.99]	<.001
IIIB	12 / 100 (12.0)	0 / 82 (0.0)	20.54	[1.23; >99.99]	0.035
IIIC	64 / 241 (26.6)	5 / 240 (2.1)	12.75	[5.22; 31.11]	<.001
Tumor category					
Interaction test	p = 0.088				
T0	1 / 5 (20.0)	0 / 5 (0.0)	3.00	[0.15; 59.89]	0.472
T1-T3	283 / 1287 (22.0)	11 / 1258 (0.9)	25.15	[13.84; 45.70]	<.001
>T3	16 / 113 (14.2)	2 / 97 (2.1)	6.87	[1.62; 29.12]	0.009
Nodal status					
Interaction test	p = 0.193				
N0	32 / 190 (16.8)	3 / 200 (1.5)	11.23	[3.50; 36.06]	<.001
N1-N3	270 / 1216 (22.2)	10 / 1160 (0.9)	25.76	[13.77; 48.17]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.826				
Grade 1	18 / 102 (17.6)	1 / 106 (0.9)	18.71	[2.54; >99.99]	0.004
Grade 2	184 / 842 (21.9)	8 / 768 (1.0)	20.98	[10.41; 42.29]	<.001
Grade 3	86 / 373 (23.1)	3 / 397 (0.8)	30.51	[9.73; 95.63]	<.001
Histological subtype					
Interaction test	p = 0.896				
Ductal	240 / 1025 (23.4)	11 / 1010 (1.1)	21.50	[11.82; 39.10]	<.001
Lobular	45 / 291 (15.5)	2 / 276 (0.7)	21.34	[5.23; 87.13]	<.001
Other	16 / 92 (17.4)	0 / 76 (0.0)	27.32	[1.67; >99.99]	0.020
Ki67 status from surgical specimen					
Interaction test	p = 0.451				
Ki67≤20	139 / 660 (21.1)	5 / 629 (0.8)	26.49	[10.93; 64.22]	<.001
Ki67>20	96 / 489 (19.6)	6 / 516 (1.2)	16.88	[7.47; 38.16]	<.001
Type of NSAI					
Interaction test	p = 0.226				
Letrozole	188 / 907 (20.7)	6 / 895 (0.7)	30.92	[13.79; 69.33]	<.001
Anastrozole	114 / 502 (22.7)	7 / 467 (1.5)	15.15	[7.14; 32.16]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.705				
Yes	284 / 1194 (23.8)	12 / 1146 (1.0)	22.72	[12.82; 40.24]	<.001
No	18 / 215 (8.4)	1 / 216 (0.5)	18.08	[2.44; >99.99]	0.005
Prior adjuvant chemotherapy					
Interaction test	p = 0.868				
Yes	165 / 694 (23.8)	7 / 673 (1.0)	22.86	[10.81; 48.34]	<.001
No	137 / 715 (19.2)	6 / 689 (0.9)	22.00	[9.78; 49.50]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.856				
Yes	129 / 528 (24.4)	6 / 503 (1.2)	20.48	[9.12; 46.01]	<.001
No	173 / 881 (19.6)	7 / 859 (0.8)	24.10	[11.39; 51.00]	<.001
Prior endocrine therapy					
Interaction test	p = 0.802				
Yes	217 / 957 (22.7)	10 / 940 (1.1)	21.31	[11.38; 39.92]	<.001
No	85 / 452 (18.8)	3 / 422 (0.7)	26.45	[8.43; 83.02]	<.001
Prior mastectomy					
Interaction test	p = 0.668				
Yes	178 / 857 (20.8)	7 / 847 (0.8)	25.13	[11.88; 53.16]	<.001
No	124 / 552 (22.5)	6 / 515 (1.2)	19.28	[8.57; 43.36]	<.001
Prior radiotherapy					
Interaction test	p = 0.794				
Yes	283 / 1253 (22.6)	12 / 1203 (1.0)	22.64	[12.78; 40.13]	<.001
No	19 / 156 (12.2)	1 / 159 (0.6)	19.37	[2.62; >99.99]	0.004
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.4 PT aspartate aminotransferase increased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Aspartate aminotransferase increased					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.167				
NA/WE/O	132 / 899 (14.7)	30 / 856 (3.5)	4.19	[2.85; 6.16]	<.001
ROW	129 / 510 (25.3)	48 / 506 (9.5)	2.67	[1.96; 3.63]	<.001
Geographical region					
Interaction test	p = 0.722				
Europe	165 / 832 (19.8)	54 / 824 (6.6)	3.03	[2.26; 4.05]	<.001
North America/Australia	65 / 400 (16.3)	14 / 364 (3.8)	4.23	[2.41; 7.39]	<.001
Asia	18 / 102 (17.6)	7 / 101 (6.9)	2.55	[1.11; 5.83]	0.027
Latin America	13 / 75 (17.3)	3 / 73 (4.1)	4.22	[1.25; 14.19]	0.020
Age group 1 at randomization					
Interaction test	p = <.001				
<45	9 / 60 (15.0)	2 / 52 (3.8)	3.90	[0.88; 17.24]	0.073
45 to 54	35 / 300 (11.7)	26 / 322 (8.1)	1.44	[0.89; 2.34]	0.135
55 to 64	143 / 651 (22.0)	27 / 642 (4.2)	5.22	[3.51; 7.77]	<.001
≥65	74 / 398 (18.6)	23 / 346 (6.6)	2.80	[1.79; 4.37]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.018				
<Median	103 / 633 (16.3)	43 / 632 (6.8)	2.39	[1.71; 3.35]	<.001
≥Median	158 / 776 (20.4)	35 / 730 (4.8)	4.25	[2.99; 6.04]	<.001
Race					
Interaction test	p = 0.478				
Asian	20 / 128 (15.6)	8 / 127 (6.3)	2.48	[1.13; 5.42]	0.023
Non-Asian	233 / 1203 (19.4)	69 / 1167 (5.9)	3.28	[2.54; 4.23]	<.001
BMI at screening					
Interaction test	p = 0.009				
≥25	204 / 935 (21.8)	52 / 935 (5.6)	3.92	[2.93; 5.25]	<.001
<25	54 / 460 (11.7)	24 / 410 (5.9)	2.01	[1.26; 3.18]	0.003
AJCC Anatomic Stage Group					
Interaction test	p = 0.324				
Group I/II	117 / 585 (20.0)	32 / 589 (5.4)	3.68	[2.53; 5.35]	<.001
Group III	143 / 823 (17.4)	46 / 772 (6.0)	2.92	[2.12; 4.01]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.842				
IA/IB/IIA	64 / 310 (20.6)	17 / 311 (5.5)	3.78	[2.27; 6.30]	<.001
IIB	53 / 275 (19.3)	15 / 278 (5.4)	3.57	[2.06; 6.18]	<.001
IIIA	89 / 482 (18.5)	29 / 450 (6.4)	2.87	[1.92; 4.27]	<.001
IIIB	17 / 100 (17.0)	6 / 82 (7.3)	2.32	[0.96; 5.62]	0.062
IIIC	37 / 241 (15.4)	11 / 240 (4.6)	3.35	[1.75; 6.41]	<.001
Tumor category					
Interaction test	p = 0.479				
T0	0 / 5 (0.0)	1 / 5 (20.0)	0.33	[0.02; 6.65]	0.472
T1-T3	242 / 1287 (18.8)	71 / 1258 (5.6)	3.33	[2.59; 4.29]	<.001
>T3	17 / 113 (15.0)	6 / 97 (6.2)	2.43	[1.00; 5.92]	0.050
Nodal status					
Interaction test	p = 0.089				
N0	43 / 190 (22.6)	8 / 200 (4.0)	5.66	[2.73; 11.72]	<.001
N1-N3	218 / 1216 (17.9)	70 / 1160 (6.0)	2.97	[2.30; 3.84]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.407				
Grade 1	16 / 102 (15.7)	8 / 106 (7.5)	2.08	[0.93; 4.64]	0.074
Grade 2	157 / 842 (18.6)	39 / 768 (5.1)	3.67	[2.62; 5.14]	<.001
Grade 3	77 / 373 (20.6)	22 / 397 (5.5)	3.73	[2.37; 5.86]	<.001
Histological subtype					
Interaction test	p = 0.221				
Ductal	196 / 1025 (19.1)	66 / 1010 (6.5)	2.93	[2.24; 3.81]	<.001
Lobular	43 / 291 (14.8)	10 / 276 (3.6)	4.08	[2.09; 7.95]	<.001
Other	22 / 92 (23.9)	2 / 76 (2.6)	9.09	[2.21; 37.42]	0.002
Ki67 status from surgical specimen					
Interaction test	p = 0.773				
Ki67≤20	114 / 660 (17.3)	36 / 629 (5.7)	3.02	[2.11; 4.32]	<.001
Ki67>20	97 / 489 (19.8)	32 / 516 (6.2)	3.20	[2.19; 4.68]	<.001
Type of NSAI					
Interaction test	p = 0.462				
Letrozole	172 / 907 (19.0)	56 / 895 (6.3)	3.03	[2.27; 4.04]	<.001
Anastrozole	89 / 502 (17.7)	22 / 467 (4.7)	3.76	[2.40; 5.90]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.964				
Yes	203 / 1194 (17.0)	59 / 1146 (5.1)	3.30	[2.50; 4.36]	<.001
No	58 / 215 (27.0)	19 / 216 (8.8)	3.07	[1.89; 4.97]	<.001
Prior adjuvant chemotherapy					
Interaction test	p = 0.365				
Yes	114 / 694 (16.4)	38 / 673 (5.6)	2.91	[2.05; 4.13]	<.001
No	147 / 715 (20.6)	40 / 689 (5.8)	3.54	[2.54; 4.94]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.148				
Yes	98 / 528 (18.6)	22 / 503 (4.4)	4.24	[2.72; 6.63]	<.001
No	163 / 881 (18.5)	56 / 859 (6.5)	2.84	[2.13; 3.79]	<.001
Prior endocrine therapy					
Interaction test	p = 0.189				
Yes	156 / 957 (16.3)	40 / 940 (4.3)	3.83	[2.74; 5.36]	<.001
No	105 / 452 (23.2)	38 / 422 (9.0)	2.58	[1.82; 3.65]	<.001
Prior mastectomy					
Interaction test	p = 0.392				
Yes	163 / 857 (19.0)	54 / 847 (6.4)	2.98	[2.23; 4.00]	<.001
No	98 / 552 (17.8)	24 / 515 (4.7)	3.81	[2.48; 5.86]	<.001
Prior radiotherapy					
Interaction test	p = 0.876				
Yes	209 / 1253 (16.7)	59 / 1203 (4.9)	3.40	[2.58; 4.49]	<.001
No	52 / 156 (33.3)	19 / 159 (11.9)	2.79	[1.73; 4.49]	<.001
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.5 PT sars-cov-2 test positive: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
SARS-CoV-2 test positive					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.248				
NA/WE/O	175 / 899 (19.5)	116 / 856 (13.6)	1.44	[1.16; 1.78]	<.001
ROW	81 / 510 (15.9)	43 / 506 (8.5)	1.87	[1.32; 2.65]	<.001
Geographical region					
Interaction test	p = 0.153				
Europe	145 / 832 (17.4)	96 / 824 (11.7)	1.50	[1.18; 1.90]	<.001
North America/Australia	78 / 400 (19.5)	52 / 364 (14.3)	1.37	[0.99; 1.88]	0.057
Asia	17 / 102 (16.7)	8 / 101 (7.9)	2.10	[0.95; 4.65]	0.066
Latin America	16 / 75 (21.3)	3 / 73 (4.1)	5.19	[1.58; 17.07]	0.007
Age group 1 at randomization					
Interaction test	p = 0.565				
<45	15 / 60 (25.0)	7 / 52 (13.5)	1.86	[0.82; 4.20]	0.137
45 to 54	69 / 300 (23.0)	41 / 322 (12.7)	1.81	[1.27; 2.57]	0.001
55 to 64	107 / 651 (16.4)	77 / 642 (12.0)	1.37	[1.04; 1.80]	0.023
≥65	65 / 398 (16.3)	34 / 346 (9.8)	1.66	[1.13; 2.45]	0.010
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.677				
<Median	129 / 633 (20.4)	80 / 632 (12.7)	1.61	[1.25; 2.08]	<.001
≥Median	127 / 776 (16.4)	79 / 730 (10.8)	1.51	[1.16; 1.97]	0.002
Race					
Interaction test	p = 0.949				
Asian	23 / 128 (18.0)	14 / 127 (11.0)	1.63	[0.88; 3.02]	0.121
Non-Asian	220 / 1203 (18.3)	134 / 1167 (11.5)	1.59	[1.31; 1.94]	<.001
BMI at screening					
Interaction test	p = 0.186				
≥25	177 / 935 (18.9)	105 / 935 (11.2)	1.69	[1.35; 2.11]	<.001
<25	77 / 460 (16.7)	53 / 410 (12.9)	1.29	[0.94; 1.79]	0.117
AJCC Anatomic Stage Group					
Interaction test	p = 0.012				
Group I/II	96 / 585 (16.4)	81 / 589 (13.8)	1.19	[0.91; 1.57]	0.204
Group III	160 / 823 (19.4)	78 / 772 (10.1)	1.92	[1.50; 2.48]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.111				
IA/IB/IIA	48 / 310 (15.5)	40 / 311 (12.9)	1.20	[0.82; 1.78]	0.350
IIB	48 / 275 (17.5)	41 / 278 (14.7)	1.18	[0.81; 1.73]	0.387
IIIA	101 / 482 (21.0)	54 / 450 (12.0)	1.75	[1.29; 2.37]	<.001
IIIB	19 / 100 (19.0)	5 / 82 (6.1)	3.12	[1.22; 7.98]	0.018
IIIC	40 / 241 (16.6)	19 / 240 (7.9)	2.10	[1.25; 3.51]	0.005
Tumor category					
Interaction test	p = 0.066				
T0	2 / 5 (40.0)	0 / 5 (0.0)	5.00	[0.30; 83.69]	0.263
T1-T3	233 / 1287 (18.1)	154 / 1258 (12.2)	1.48	[1.23; 1.79]	<.001
>T3	21 / 113 (18.6)	5 / 97 (5.2)	3.61	[1.41; 9.20]	0.007
Nodal status					
Interaction test	p = 0.662				
N0	33 / 190 (17.4)	20 / 200 (10.0)	1.74	[1.03; 2.92]	0.037
N1-N3	222 / 1216 (18.3)	139 / 1160 (12.0)	1.52	[1.25; 1.85]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.500				
Grade 1	16 / 102 (15.7)	15 / 106 (14.2)	1.11	[0.58; 2.12]	0.756
Grade 2	158 / 842 (18.8)	86 / 768 (11.2)	1.68	[1.31; 2.14]	<.001
Grade 3	68 / 373 (18.2)	47 / 397 (11.8)	1.54	[1.09; 2.17]	0.014
Histological subtype					
Interaction test	p = 0.529				
Ductal	178 / 1025 (17.4)	117 / 1010 (11.6)	1.50	[1.21; 1.86]	<.001
Lobular	61 / 291 (21.0)	31 / 276 (11.2)	1.87	[1.25; 2.78]	0.002
Other	17 / 92 (18.5)	11 / 76 (14.5)	1.28	[0.64; 2.56]	0.491
Ki67 status from surgical specimen					
Interaction test	p = 0.670				
Ki67≤20	123 / 660 (18.6)	71 / 629 (11.3)	1.65	[1.26; 2.16]	<.001
Ki67>20	88 / 489 (18.0)	51 / 516 (9.9)	1.82	[1.32; 2.51]	<.001
Type of NSAI					
Interaction test	p = 0.202				
Letrozole	156 / 907 (17.2)	108 / 895 (12.1)	1.43	[1.14; 1.79]	0.002
Anastrozole	100 / 502 (19.9)	51 / 467 (10.9)	1.82	[1.33; 2.49]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.010				
Yes	229 / 1194 (19.2)	128 / 1146 (11.2)	1.72	[1.41; 2.10]	<.001
No	27 / 215 (12.6)	31 / 216 (14.4)	0.88	[0.54; 1.41]	0.586
Prior adjuvant chemotherapy					
Interaction test	p = 0.328				
Yes	129 / 694 (18.6)	88 / 673 (13.1)	1.42	[1.11; 1.82]	0.006
No	127 / 715 (17.8)	71 / 689 (10.3)	1.72	[1.31; 2.26]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.003				
Yes	107 / 528 (20.3)	44 / 503 (8.7)	2.32	[1.67; 3.22]	<.001
No	149 / 881 (16.9)	115 / 859 (13.4)	1.26	[1.01; 1.58]	0.041
Prior endocrine therapy					
Interaction test	p = 0.523				
Yes	172 / 957 (18.0)	113 / 940 (12.0)	1.50	[1.20; 1.86]	<.001
No	84 / 452 (18.6)	46 / 422 (10.9)	1.70	[1.22; 2.38]	0.002
Prior mastectomy					
Interaction test	p = 0.746				
Yes	158 / 857 (18.4)	98 / 847 (11.6)	1.59	[1.26; 2.01]	<.001
No	98 / 552 (17.8)	61 / 515 (11.8)	1.50	[1.11; 2.02]	0.007
Prior radiotherapy					
Interaction test	p = 0.154				
Yes	234 / 1253 (18.7)	138 / 1203 (11.5)	1.63	[1.34; 1.98]	<.001
No	22 / 156 (14.1)	21 / 159 (13.2)	1.07	[0.61; 1.86]	0.817
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.6 PT white blood cell count decreased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
White blood cell count decreased					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.161				
NA/WE/O	78 / 899 (8.7)	12 / 856 (1.4)	6.19	[3.39; 11.28]	<.001
ROW	38 / 510 (7.5)	2 / 506 (0.4)	18.85	[4.57; 77.72]	<.001
Geographical region					
Interaction test	p = 0.049				
Europe	28 / 832 (3.4)	1 / 824 (0.1)	27.73	[3.78; >99.99]	0.001
North America/Australia	52 / 400 (13.0)	11 / 364 (3.0)	4.30	[2.28; 8.12]	<.001
Asia	34 / 102 (33.3)	2 / 101 (2.0)	16.83	[4.15; 68.21]	<.001
Latin America	2 / 75 (2.7)	0 / 73 (0.0)	4.87	[0.24; 99.70]	0.304
Age group 1 at randomization					
Interaction test	p = 0.483				
<45	13 / 60 (21.7)	1 / 52 (1.9)	11.27	[1.53; 83.23]	0.018
45 to 54	20 / 300 (6.7)	3 / 322 (0.9)	7.16	[2.15; 23.83]	0.001
55 to 64	58 / 651 (8.9)	5 / 642 (0.8)	11.44	[4.62; 28.33]	<.001
≥65	25 / 398 (6.3)	5 / 346 (1.4)	4.35	[1.68; 11.23]	0.002
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.286				
<Median	57 / 633 (9.0)	5 / 632 (0.8)	11.38	[4.59; 28.21]	<.001
≥Median	59 / 776 (7.6)	9 / 730 (1.2)	6.17	[3.08; 12.35]	<.001
Race					
Interaction test	p = 0.426				
Asian	38 / 128 (29.7)	4 / 127 (3.1)	9.43	[3.47; 25.64]	<.001
Non-Asian	76 / 1203 (6.3)	10 / 1167 (0.9)	7.37	[3.83; 14.18]	<.001
BMI at screening					
Interaction test	p = 0.010				
≥25	67 / 935 (7.2)	3 / 935 (0.3)	22.33	[7.05; 70.75]	<.001
<25	47 / 460 (10.2)	11 / 410 (2.7)	3.81	[2.00; 7.24]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.382				
Group I/II	37 / 585 (6.3)	3 / 589 (0.5)	12.42	[3.85; 40.05]	<.001
Group III	78 / 823 (9.5)	11 / 772 (1.4)	6.65	[3.57; 12.41]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.841				
IA/IB/IIA	22 / 310 (7.1)	2 / 311 (0.6)	11.04	[2.62; 46.53]	0.001
IIB	15 / 275 (5.5)	1 / 278 (0.4)	15.16	[2.02; >99.99]	0.008
IIIA	42 / 482 (8.7)	6 / 450 (1.3)	6.54	[2.81; 15.22]	<.001
IIIB	4 / 100 (4.0)	1 / 82 (1.2)	3.28	[0.37; 28.78]	0.284
IIIC	32 / 241 (13.3)	4 / 240 (1.7)	7.97	[2.86; 22.18]	<.001
Tumor category					
Interaction test	p = 0.150				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	108 / 1287 (8.4)	12 / 1258 (1.0)	8.80	[4.87; 15.89]	<.001
>T3	6 / 113 (5.3)	2 / 97 (2.1)	2.58	[0.53; 12.47]	0.240
Nodal status					
Interaction test	N.E.				
N0	15 / 190 (7.9)	0 / 200 (0.0)	32.62	[1.97; >99.99]	0.015
N1-N3	101 / 1216 (8.3)	14 / 1160 (1.2)	6.88	[3.96; 11.97]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.193				
Grade 1	8 / 102 (7.8)	1 / 106 (0.9)	8.31	[1.06; 65.29]	0.044
Grade 2	66 / 842 (7.8)	10 / 768 (1.3)	6.02	[3.12; 11.62]	<.001
Grade 3	38 / 373 (10.2)	1 / 397 (0.3)	40.45	[5.58; >99.99]	<.001
Histological subtype					
Interaction test	p = 0.549				
Ductal	94 / 1025 (9.2)	11 / 1010 (1.1)	8.42	[4.54; 15.63]	<.001
Lobular	18 / 291 (6.2)	3 / 276 (1.1)	5.69	[1.70; 19.10]	0.005
Other	4 / 92 (4.3)	0 / 76 (0.0)	7.45	[0.41; >99.99]	0.176
Ki67 status from surgical specimen					
Interaction test	p = 0.033				
Ki67≤20	49 / 660 (7.4)	2 / 629 (0.3)	23.35	[5.70; 95.61]	<.001
Ki67>20	31 / 489 (6.3)	8 / 516 (1.6)	4.09	[1.90; 8.81]	<.001
Type of NSAI					
Interaction test	p = 0.265				
Letrozole	67 / 907 (7.4)	6 / 895 (0.7)	11.02	[4.80; 25.27]	<.001
Anastrozole	49 / 502 (9.8)	8 / 467 (1.7)	5.70	[2.73; 11.90]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.625				
Yes	111 / 1194 (9.3)	13 / 1146 (1.1)	8.20	[4.64; 14.47]	<.001
No	5 / 215 (2.3)	1 / 216 (0.5)	5.02	[0.59; 42.64]	0.139
Prior adjuvant chemotherapy					
Interaction test	p = 0.268				
Yes	67 / 694 (9.7)	6 / 673 (0.9)	10.83	[4.73; 24.80]	<.001
No	49 / 715 (6.9)	8 / 689 (1.2)	5.90	[2.82; 12.37]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.258				
Yes	48 / 528 (9.1)	8 / 503 (1.6)	5.72	[2.73; 11.96]	<.001
No	68 / 881 (7.7)	6 / 859 (0.7)	11.05	[4.82; 25.33]	<.001
Prior endocrine therapy					
Interaction test	p = 0.981				
Yes	74 / 957 (7.7)	9 / 940 (1.0)	8.08	[4.07; 16.04]	<.001
No	42 / 452 (9.3)	5 / 422 (1.2)	7.84	[3.13; 19.63]	<.001
Prior mastectomy					
Interaction test	p = 0.375				
Yes	78 / 857 (9.1)	8 / 847 (0.9)	9.64	[4.68; 19.82]	<.001
No	38 / 552 (6.9)	6 / 515 (1.2)	5.91	[2.52; 13.86]	<.001
Prior radiotherapy					
Interaction test	p = 0.885				
Yes	109 / 1253 (8.7)	13 / 1203 (1.1)	8.05	[4.55; 14.23]	<.001
No	7 / 156 (4.5)	1 / 159 (0.6)	7.13	[0.89; 57.32]	0.065
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.7 PT sars-cov-2 test negative: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
SARS-CoV-2 test negative					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.292				
NA/WE/O	53 / 899 (5.9)	22 / 856 (2.6)	2.29	[1.41; 3.74]	<.001
ROW	31 / 510 (6.1)	20 / 506 (4.0)	1.54	[0.89; 2.66]	0.124
Geographical region					
Interaction test	p = 0.870				
Europe	58 / 832 (7.0)	30 / 824 (3.6)	1.91	[1.25; 2.94]	0.003
North America/Australia	25 / 400 (6.3)	11 / 364 (3.0)	2.07	[1.03; 4.14]	0.040
Asia	1 / 102 (1.0)	1 / 101 (1.0)	0.99	[0.06; 15.62]	0.994
Latin America	0 / 75 (0.0)	0 / 73 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	p = 0.619				
<45	6 / 60 (10.0)	1 / 52 (1.9)	5.20	[0.65; 41.80]	0.121
45 to 54	20 / 300 (6.7)	10 / 322 (3.1)	2.15	[1.02; 4.51]	0.044
55 to 64	31 / 651 (4.8)	20 / 642 (3.1)	1.53	[0.88; 2.65]	0.132
≥65	27 / 398 (6.8)	11 / 346 (3.2)	2.13	[1.07; 4.24]	0.030
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.873				
<Median	38 / 633 (6.0)	19 / 632 (3.0)	2.00	[1.16; 3.43]	0.012
≥Median	46 / 776 (5.9)	23 / 730 (3.2)	1.88	[1.15; 3.07]	0.012
Race					
Interaction test	p = 0.726				
Asian	3 / 128 (2.3)	2 / 127 (1.6)	1.49	[0.25; 8.76]	0.660
Non-Asian	79 / 1203 (6.6)	38 / 1167 (3.3)	2.02	[1.38; 2.94]	<.001
BMI at screening					
Interaction test	p = 0.084				
≥25	65 / 935 (7.0)	28 / 935 (3.0)	2.32	[1.50; 3.58]	<.001
<25	18 / 460 (3.9)	14 / 410 (3.4)	1.15	[0.58; 2.27]	0.697
AJCC Anatomic Stage Group					
Interaction test	p = 0.337				
Group I/II	35 / 585 (6.0)	22 / 589 (3.7)	1.60	[0.95; 2.70]	0.076
Group III	49 / 823 (6.0)	20 / 772 (2.6)	2.30	[1.38; 3.83]	0.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.056				
IA/IB/IIA	14 / 310 (4.5)	14 / 311 (4.5)	1.00	[0.49; 2.07]	0.993
IIB	21 / 275 (7.6)	8 / 278 (2.9)	2.65	[1.20; 5.89]	0.016
IIIA	22 / 482 (4.6)	15 / 450 (3.3)	1.37	[0.72; 2.61]	0.338
IIIB	9 / 100 (9.0)	3 / 82 (3.7)	2.46	[0.69; 8.79]	0.166
IIIC	18 / 241 (7.5)	2 / 240 (0.8)	8.96	[2.10; 38.20]	0.003
Tumor category					
Interaction test	p = 0.303				
T0	1 / 5 (20.0)	0 / 5 (0.0)	3.00	[0.15; 59.89]	0.472
T1-T3	71 / 1287 (5.5)	39 / 1258 (3.1)	1.78	[1.21; 2.61]	0.003
>T3	12 / 113 (10.6)	3 / 97 (3.1)	3.43	[1.00; 11.81]	0.050
Nodal status					
Interaction test	p = 0.254				
N0	11 / 190 (5.8)	3 / 200 (1.5)	3.86	[1.09; 13.62]	0.036
N1-N3	73 / 1216 (6.0)	39 / 1160 (3.4)	1.79	[1.22; 2.61]	0.003
Histological grade at time of surgery					
Interaction test	p = 0.245				
Grade 1	4 / 102 (3.9)	6 / 106 (5.7)	0.69	[0.20; 2.38]	0.560
Grade 2	52 / 842 (6.2)	22 / 768 (2.9)	2.16	[1.32; 3.51]	0.002
Grade 3	20 / 373 (5.4)	11 / 397 (2.8)	1.94	[0.94; 3.98]	0.073
Histological subtype					
Interaction test	p = 0.503				
Ductal	64 / 1025 (6.2)	31 / 1010 (3.1)	2.03	[1.34; 3.10]	<.001
Lobular	14 / 291 (4.8)	6 / 276 (2.2)	2.21	[0.86; 5.68]	0.098
Other	6 / 92 (6.5)	5 / 76 (6.6)	0.99	[0.31; 3.12]	0.988
Ki67 status from surgical specimen					
Interaction test	p = 0.955				
Ki67≤20	40 / 660 (6.1)	20 / 629 (3.2)	1.91	[1.13; 3.22]	0.016
Ki67>20	26 / 489 (5.3)	14 / 516 (2.7)	1.96	[1.04; 3.71]	0.039
Type of NSAI					
Interaction test	p = 0.437				
Letrozole	49 / 907 (5.4)	22 / 895 (2.5)	2.20	[1.34; 3.60]	0.002
Anastrozole	35 / 502 (7.0)	20 / 467 (4.3)	1.63	[0.95; 2.78]	0.074
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.152				
Yes	73 / 1194 (6.1)	32 / 1146 (2.8)	2.19	[1.46; 3.29]	<.001
No	11 / 215 (5.1)	10 / 216 (4.6)	1.11	[0.48; 2.55]	0.815
Prior adjuvant chemotherapy					
Interaction test	p = 0.795				
Yes	38 / 694 (5.5)	18 / 673 (2.7)	2.05	[1.18; 3.55]	0.011
No	46 / 715 (6.4)	24 / 689 (3.5)	1.85	[1.14; 2.99]	0.013

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.319				
Yes	38 / 528 (7.2)	15 / 503 (3.0)	2.41	[1.34; 4.33]	0.003
No	46 / 881 (5.2)	27 / 859 (3.1)	1.66	[1.04; 2.65]	0.033
Prior endocrine therapy					
Interaction test	p = 0.881				
Yes	56 / 957 (5.9)	29 / 940 (3.1)	1.90	[1.22; 2.94]	0.004
No	28 / 452 (6.2)	13 / 422 (3.1)	2.01	[1.06; 3.83]	0.034
Prior mastectomy					
Interaction test	p = 0.558				
Yes	59 / 857 (6.9)	28 / 847 (3.3)	2.08	[1.34; 3.23]	0.001
No	25 / 552 (4.5)	14 / 515 (2.7)	1.67	[0.88; 3.17]	0.120
Prior radiotherapy					
Interaction test	p = 0.303				
Yes	68 / 1253 (5.4)	30 / 1203 (2.5)	2.18	[1.43; 3.32]	<.001
No	16 / 156 (10.3)	12 / 159 (7.5)	1.36	[0.66; 2.78]	0.401
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.8 PT gamma-glutamyltransferase increased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Gamma-glutamyltransferase increased					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.769				
NA/WE/O	33 / 899 (3.7)	17 / 856 (2.0)	1.85	[1.04; 3.29]	0.037
ROW	44 / 510 (8.6)	27 / 506 (5.3)	1.62	[1.02; 2.57]	0.042
Geographical region					
Interaction test	p = 0.240				
Europe	54 / 832 (6.5)	36 / 824 (4.4)	1.49	[0.99; 2.24]	0.059
North America/Australia	15 / 400 (3.8)	2 / 364 (0.5)	6.83	[1.57; 29.64]	0.010
Asia	3 / 102 (2.9)	3 / 101 (3.0)	0.99	[0.20; 4.79]	0.990
Latin America	5 / 75 (6.7)	3 / 73 (4.1)	1.62	[0.40; 6.54]	0.497
Age group 1 at randomization					
Interaction test	p = 0.037				
<45	3 / 60 (5.0)	0 / 52 (0.0)	6.08	[0.32; >99.99]	0.229
45 to 54	10 / 300 (3.3)	16 / 322 (5.0)	0.67	[0.31; 1.46]	0.312
55 to 64	37 / 651 (5.7)	17 / 642 (2.6)	2.15	[1.22; 3.77]	0.008
≥65	27 / 398 (6.8)	11 / 346 (3.2)	2.13	[1.07; 4.24]	0.030
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.025				
<Median	30 / 633 (4.7)	27 / 632 (4.3)	1.11	[0.67; 1.84]	0.689
≥Median	47 / 776 (6.1)	17 / 730 (2.3)	2.60	[1.51; 4.49]	<.001
Race					
Interaction test	p = 0.410				
Asian	3 / 128 (2.3)	3 / 127 (2.4)	0.99	[0.20; 4.82]	0.992
Non-Asian	74 / 1203 (6.2)	37 / 1167 (3.2)	1.94	[1.32; 2.86]	<.001
BMI at screening					
Interaction test	p = 0.048				
≥25	66 / 935 (7.1)	32 / 935 (3.4)	2.06	[1.37; 3.12]	<.001
<25	10 / 460 (2.2)	11 / 410 (2.7)	0.81	[0.35; 1.89]	0.626
AJCC Anatomic Stage Group					
Interaction test	p = 0.984				
Group I/II	27 / 585 (4.6)	16 / 589 (2.7)	1.70	[0.93; 3.12]	0.087
Group III	50 / 823 (6.1)	28 / 772 (3.6)	1.68	[1.07; 2.63]	0.025

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.367				
IA/IB/IIA	13 / 310 (4.2)	11 / 311 (3.5)	1.19	[0.54; 2.61]	0.672
IIB	14 / 275 (5.1)	5 / 278 (1.8)	2.83	[1.03; 7.75]	0.043
IIIA	23 / 482 (4.8)	17 / 450 (3.8)	1.26	[0.68; 2.33]	0.456
IIIB	13 / 100 (13.0)	7 / 82 (8.5)	1.52	[0.64; 3.64]	0.344
IIIC	14 / 241 (5.8)	4 / 240 (1.7)	3.49	[1.16; 10.44]	0.026
Tumor category					
Interaction test	p = 0.951				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	64 / 1287 (5.0)	37 / 1258 (2.9)	1.69	[1.14; 2.52]	0.010
>T3	13 / 113 (11.5)	7 / 97 (7.2)	1.59	[0.66; 3.84]	0.298
Nodal status					
Interaction test	p = 0.198				
N0	7 / 190 (3.7)	8 / 200 (4.0)	0.92	[0.34; 2.49]	0.871
N1-N3	70 / 1216 (5.8)	36 / 1160 (3.1)	1.85	[1.25; 2.75]	0.002
Histological grade at time of surgery					
Interaction test	p = 0.701				
Grade 1	6 / 102 (5.9)	2 / 106 (1.9)	3.12	[0.64; 15.09]	0.158
Grade 2	48 / 842 (5.7)	28 / 768 (3.6)	1.56	[0.99; 2.47]	0.055
Grade 3	17 / 373 (4.6)	10 / 397 (2.5)	1.81	[0.84; 3.90]	0.130
Histological subtype					
Interaction test	p = 0.024				
Ductal	55 / 1025 (5.4)	41 / 1010 (4.1)	1.32	[0.89; 1.96]	0.166
Lobular	18 / 291 (6.2)	3 / 276 (1.1)	5.69	[1.70; 19.10]	0.005
Other	4 / 92 (4.3)	0 / 76 (0.0)	7.45	[0.41; >99.99]	0.176
Ki67 status from surgical specimen					
Interaction test	p = 0.126				
Ki67≤20	43 / 660 (6.5)	21 / 629 (3.3)	1.95	[1.17; 3.25]	0.010
Ki67>20	20 / 489 (4.1)	20 / 516 (3.9)	1.06	[0.57; 1.94]	0.862
Type of NSAI					
Interaction test	p = 0.426				
Letrozole	46 / 907 (5.1)	30 / 895 (3.4)	1.51	[0.96; 2.37]	0.072
Anastrozole	31 / 502 (6.2)	14 / 467 (3.0)	2.06	[1.11; 3.82]	0.022
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.400				
Yes	57 / 1194 (4.8)	35 / 1146 (3.1)	1.56	[1.03; 2.36]	0.034
No	20 / 215 (9.3)	9 / 216 (4.2)	2.23	[1.04; 4.79]	0.039
Prior adjuvant chemotherapy					
Interaction test	p = 0.389				
Yes	29 / 694 (4.2)	20 / 673 (3.0)	1.41	[0.80; 2.46]	0.233
No	48 / 715 (6.7)	24 / 689 (3.5)	1.93	[1.19; 3.11]	0.007

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.629				
Yes	30 / 528 (5.7)	15 / 503 (3.0)	1.91	[1.04; 3.50]	0.038
No	47 / 881 (5.3)	29 / 859 (3.4)	1.58	[1.00; 2.49]	0.048
Prior endocrine therapy					
Interaction test	p = 0.929				
Yes	39 / 957 (4.1)	23 / 940 (2.4)	1.67	[1.00; 2.77]	0.049
No	38 / 452 (8.4)	21 / 422 (5.0)	1.69	[1.01; 2.83]	0.046
Prior mastectomy					
Interaction test	p = 0.259				
Yes	53 / 857 (6.2)	35 / 847 (4.1)	1.50	[0.99; 2.27]	0.058
No	24 / 552 (4.3)	9 / 515 (1.7)	2.49	[1.17; 5.30]	0.018
Prior radiotherapy					
Interaction test	p = 0.529				
Yes	57 / 1253 (4.5)	34 / 1203 (2.8)	1.61	[1.06; 2.44]	0.025
No	20 / 156 (12.8)	10 / 159 (6.3)	2.04	[0.99; 4.21]	0.055
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.9 PT blood creatinine increased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Blood creatinine increased					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.136				
NA/WE/O	46 / 899 (5.1)	15 / 856 (1.8)	2.92	[1.64; 5.19]	<.001
ROW	29 / 510 (5.7)	4 / 506 (0.8)	7.19	[2.55; 20.31]	<.001
Geographical region					
Interaction test	p = 0.871				
Europe	48 / 832 (5.8)	13 / 824 (1.6)	3.66	[2.00; 6.70]	<.001
North America/Australia	21 / 400 (5.3)	5 / 364 (1.4)	3.82	[1.46; 10.03]	0.006
Asia	2 / 102 (2.0)	1 / 101 (1.0)	1.98	[0.18; 21.50]	0.574
Latin America	4 / 75 (5.3)	0 / 73 (0.0)	8.76	[0.48; >99.99]	0.143
Age group 1 at randomization					
Interaction test	p = 0.463				
<45	2 / 60 (3.3)	0 / 52 (0.0)	4.34	[0.21; 88.48]	0.339
45 to 54	9 / 300 (3.0)	4 / 322 (1.2)	2.42	[0.75; 7.76]	0.139
55 to 64	37 / 651 (5.7)	7 / 642 (1.1)	5.21	[2.34; 11.61]	<.001
≥65	27 / 398 (6.8)	8 / 346 (2.3)	2.93	[1.35; 6.37]	0.007
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.653				
<Median	23 / 633 (3.6)	7 / 632 (1.1)	3.28	[1.42; 7.59]	0.006
≥Median	52 / 776 (6.7)	12 / 730 (1.6)	4.08	[2.19; 7.57]	<.001
Race					
Interaction test	p = 0.736				
Asian	3 / 128 (2.3)	1 / 127 (0.8)	2.98	[0.31; 28.24]	0.342
Non-Asian	67 / 1203 (5.6)	15 / 1167 (1.3)	4.33	[2.49; 7.54]	<.001
BMI at screening					
Interaction test	p = 0.505				
≥25	58 / 935 (6.2)	14 / 935 (1.5)	4.14	[2.33; 7.37]	<.001
<25	16 / 460 (3.5)	5 / 410 (1.2)	2.85	[1.05; 7.72]	0.039
AJCC Anatomic Stage Group					
Interaction test	p = 0.346				
Group I/II	39 / 585 (6.7)	8 / 589 (1.4)	4.91	[2.31; 10.41]	<.001
Group III	36 / 823 (4.4)	11 / 772 (1.4)	3.07	[1.57; 5.99]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.226				
IA/IB/IIA	25 / 310 (8.1)	4 / 311 (1.3)	6.27	[2.21; 17.81]	<.001
IIB	14 / 275 (5.1)	4 / 278 (1.4)	3.54	[1.18; 10.61]	0.024
IIIA	21 / 482 (4.4)	3 / 450 (0.7)	6.54	[1.96; 21.76]	0.002
IIIB	7 / 100 (7.0)	2 / 82 (2.4)	2.87	[0.61; 13.44]	0.181
IIIC	8 / 241 (3.3)	6 / 240 (2.5)	1.33	[0.47; 3.77]	0.594
Tumor category					
Interaction test	p = 0.118				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	68 / 1287 (5.3)	15 / 1258 (1.2)	4.43	[2.55; 7.71]	<.001
>T3	7 / 113 (6.2)	4 / 97 (4.1)	1.50	[0.45; 4.98]	0.506
Nodal status					
Interaction test	p = 0.819				
N0	16 / 190 (8.4)	4 / 200 (2.0)	4.21	[1.43; 12.37]	0.009
N1-N3	59 / 1216 (4.9)	15 / 1160 (1.3)	3.75	[2.14; 6.58]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.571				
Grade 1	7 / 102 (6.9)	0 / 106 (0.0)	15.58	[0.90; >99.99]	0.059
Grade 2	48 / 842 (5.7)	12 / 768 (1.6)	3.65	[1.95; 6.82]	<.001
Grade 3	15 / 373 (4.0)	6 / 397 (1.5)	2.66	[1.04; 6.79]	0.040
Histological subtype					
Interaction test	p = 0.740				
Ductal	56 / 1025 (5.5)	14 / 1010 (1.4)	3.94	[2.21; 7.03]	<.001
Lobular	14 / 291 (4.8)	3 / 276 (1.1)	4.43	[1.29; 15.23]	0.018
Other	5 / 92 (5.4)	2 / 76 (2.6)	2.07	[0.41; 10.35]	0.378
Ki67 status from surgical specimen					
Interaction test	p = 0.318				
Ki67≤20	37 / 660 (5.6)	6 / 629 (1.0)	5.88	[2.50; 13.83]	<.001
Ki67>20	28 / 489 (5.7)	9 / 516 (1.7)	3.28	[1.57; 6.89]	0.002
Type of NSAI					
Interaction test	p = 0.799				
Letrozole	48 / 907 (5.3)	13 / 895 (1.5)	3.64	[1.99; 6.68]	<.001
Anastrozole	27 / 502 (5.4)	6 / 467 (1.3)	4.19	[1.74; 10.05]	0.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.227				
Yes	54 / 1194 (4.5)	16 / 1146 (1.4)	3.24	[1.87; 5.63]	<.001
No	21 / 215 (9.8)	3 / 216 (1.4)	7.03	[2.13; 23.23]	0.001
Prior adjuvant chemotherapy					
Interaction test	p = 0.090				
Yes	31 / 694 (4.5)	12 / 673 (1.8)	2.51	[1.30; 4.84]	0.006
No	44 / 715 (6.2)	7 / 689 (1.0)	6.06	[2.75; 13.36]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.383				
Yes	24 / 528 (4.5)	4 / 503 (0.8)	5.72	[2.00; 16.36]	0.001
No	51 / 881 (5.8)	15 / 859 (1.7)	3.32	[1.88; 5.85]	<.001
Prior endocrine therapy					
Interaction test	p = 0.616				
Yes	46 / 957 (4.8)	13 / 940 (1.4)	3.48	[1.89; 6.39]	<.001
No	29 / 452 (6.4)	6 / 422 (1.4)	4.51	[1.89; 10.76]	<.001
Prior mastectomy					
Interaction test	p = 0.272				
Yes	44 / 857 (5.1)	14 / 847 (1.7)	3.11	[1.72; 5.63]	<.001
No	31 / 552 (5.6)	5 / 515 (1.0)	5.78	[2.27; 14.76]	<.001
Prior radiotherapy					
Interaction test	p = 0.349				
Yes	57 / 1253 (4.5)	16 / 1203 (1.3)	3.42	[1.98; 5.92]	<.001
No	18 / 156 (11.5)	3 / 159 (1.9)	6.12	[1.84; 20.35]	0.003
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.10 PT electrocardiogram qt prolonged: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Electrocardiogram QT prolonged					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.091				
NA/WE/O	23 / 899 (2.6)	7 / 856 (0.8)	3.13	[1.35; 7.25]	0.008
ROW	32 / 510 (6.3)	3 / 506 (0.6)	10.58	[3.26; 34.34]	<.001
Geographical region					
Interaction test	p = 0.360				
Europe	32 / 832 (3.8)	6 / 824 (0.7)	5.28	[2.22; 12.57]	<.001
North America/Australia	12 / 400 (3.0)	4 / 364 (1.1)	2.73	[0.89; 8.39]	0.080
Asia	5 / 102 (4.9)	0 / 101 (0.0)	10.89	[0.61; >99.99]	0.104
Latin America	6 / 75 (8.0)	0 / 73 (0.0)	12.66	[0.73; >99.99]	0.082
Age group 1 at randomization					
Interaction test	p = 0.329				
<45	3 / 60 (5.0)	0 / 52 (0.0)	6.08	[0.32; >99.99]	0.229
45 to 54	9 / 300 (3.0)	1 / 322 (0.3)	9.66	[1.23; 75.79]	0.031
55 to 64	22 / 651 (3.4)	7 / 642 (1.1)	3.10	[1.33; 7.20]	0.009
≥65	21 / 398 (5.3)	2 / 346 (0.6)	9.13	[2.16; 38.65]	0.003
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.532				
<Median	21 / 633 (3.3)	5 / 632 (0.8)	4.19	[1.59; 11.05]	0.004
≥Median	34 / 776 (4.4)	5 / 730 (0.7)	6.40	[2.52; 16.27]	<.001
Race					
Interaction test	N.E.				
Asian	7 / 128 (5.5)	0 / 127 (0.0)	14.88	[0.86; >99.99]	0.064
Non-Asian	47 / 1203 (3.9)	9 / 1167 (0.8)	5.07	[2.49; 10.29]	<.001
BMI at screening					
Interaction test	p = 0.623				
≥25	36 / 935 (3.9)	6 / 935 (0.6)	6.00	[2.54; 14.17]	<.001
<25	19 / 460 (4.1)	4 / 410 (1.0)	4.23	[1.45; 12.34]	0.008
AJCC Anatomic Stage Group					
Interaction test	p = 0.046				
Group I/II	26 / 585 (4.4)	1 / 589 (0.2)	26.18	[3.56; >99.99]	0.001
Group III	29 / 823 (3.5)	9 / 772 (1.2)	3.02	[1.44; 6.34]	0.003

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.255				
IA/IB/IIA	11 / 310 (3.5)	1 / 311 (0.3)	11.04	[1.43; 84.96]	0.021
IIB	15 / 275 (5.5)	0 / 278 (0.0)	31.34	[1.88; >99.99]	0.016
IIIA	19 / 482 (3.9)	6 / 450 (1.3)	2.96	[1.19; 7.34]	0.019
IIIB	6 / 100 (6.0)	0 / 82 (0.0)	10.68	[0.61; >99.99]	0.105
IIIC	4 / 241 (1.7)	3 / 240 (1.3)	1.33	[0.30; 5.87]	0.708
Tumor category					
Interaction test	N.E.				
T0	1 / 5 (20.0)	0 / 5 (0.0)	3.00	[0.15; 59.89]	0.472
T1-T3	48 / 1287 (3.7)	10 / 1258 (0.8)	4.69	[2.38; 9.23]	<.001
>T3	6 / 113 (5.3)	0 / 97 (0.0)	11.18	[0.64; >99.99]	0.099
Nodal status					
Interaction test	N.E.				
N0	6 / 190 (3.2)	0 / 200 (0.0)	13.68	[0.78; >99.99]	0.074
N1-N3	49 / 1216 (4.0)	10 / 1160 (0.9)	4.67	[2.38; 9.18]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.822				
Grade 1	5 / 102 (4.9)	1 / 106 (0.9)	5.20	[0.62; 43.71]	0.129
Grade 2	29 / 842 (3.4)	7 / 768 (0.9)	3.78	[1.67; 8.58]	0.001
Grade 3	12 / 373 (3.2)	2 / 397 (0.5)	6.39	[1.44; 28.34]	0.015
Histological subtype					
Interaction test	p = 0.086				
Ductal	41 / 1025 (4.0)	4 / 1010 (0.4)	10.10	[3.63; 28.09]	<.001
Lobular	10 / 291 (3.4)	4 / 276 (1.4)	2.37	[0.75; 7.47]	0.140
Other	4 / 92 (4.3)	2 / 76 (2.6)	1.65	[0.31; 8.78]	0.556
Ki67 status from surgical specimen					
Interaction test	p = 0.139				
Ki67≤20	23 / 660 (3.5)	5 / 629 (0.8)	4.38	[1.68; 11.46]	0.003
Ki67>20	22 / 489 (4.5)	1 / 516 (0.2)	23.21	[3.14; >99.99]	0.002
Type of NSAI					
Interaction test	p = 0.511				
Letrozole	38 / 907 (4.2)	6 / 895 (0.7)	6.25	[2.66; 14.71]	<.001
Anastrozole	17 / 502 (3.4)	4 / 467 (0.9)	3.95	[1.34; 11.66]	0.013
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.335				
Yes	50 / 1194 (4.2)	8 / 1146 (0.7)	6.00	[2.86; 12.60]	<.001
No	5 / 215 (2.3)	2 / 216 (0.9)	2.51	[0.49; 12.81]	0.268
Prior adjuvant chemotherapy					
Interaction test	p = 0.060				
Yes	25 / 694 (3.6)	8 / 673 (1.2)	3.03	[1.38; 6.67]	0.006
No	30 / 715 (4.2)	2 / 689 (0.3)	14.45	[3.47; 60.25]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.040				
Yes	28 / 528 (5.3)	1 / 503 (0.2)	26.67	[3.64; >99.99]	0.001
No	27 / 881 (3.1)	9 / 859 (1.0)	2.93	[1.38; 6.18]	0.005
Prior endocrine therapy					
Interaction test	p = 0.107				
Yes	33 / 957 (3.4)	9 / 940 (1.0)	3.60	[1.73; 7.48]	<.001
No	22 / 452 (4.9)	1 / 422 (0.2)	20.54	[2.78; >99.99]	0.003
Prior mastectomy					
Interaction test	p = 0.196				
Yes	37 / 857 (4.3)	9 / 847 (1.1)	4.06	[1.97; 8.37]	<.001
No	18 / 552 (3.3)	1 / 515 (0.2)	16.79	[2.25; >99.99]	0.006
Prior radiotherapy					
Interaction test	p = 0.765				
Yes	48 / 1253 (3.8)	9 / 1203 (0.7)	5.12	[2.52; 10.39]	<.001
No	7 / 156 (4.5)	1 / 159 (0.6)	7.13	[0.89; 57.32]	0.065
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.11 PT blood magnesium decreased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Blood magnesium decreased					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.088				
NA/WE/O	15 / 899 (1.7)	1 / 856 (0.1)	14.28	[1.89; >99.99]	0.010
ROW	38 / 510 (7.5)	17 / 506 (3.4)	2.22	[1.27; 3.88]	0.005
Geographical region					
Interaction test	N.E.				
Europe	48 / 832 (5.8)	17 / 824 (2.1)	2.80	[1.62; 4.82]	<.001
North America/Australia	4 / 400 (1.0)	0 / 364 (0.0)	8.19	[0.44; >99.99]	0.158
Asia	1 / 102 (1.0)	0 / 101 (0.0)	2.97	[0.12; 72.08]	0.503
Latin America	0 / 75 (0.0)	1 / 73 (1.4)	0.32	[0.01; 7.84]	0.489
Age group 1 at randomization					
Interaction test	p = 0.697				
<45	1 / 60 (1.7)	0 / 52 (0.0)	2.61	[0.11; 62.64]	0.555
45 to 54	5 / 300 (1.7)	3 / 322 (0.9)	1.79	[0.43; 7.42]	0.423
55 to 64	23 / 651 (3.5)	9 / 642 (1.4)	2.52	[1.18; 5.40]	0.018
≥65	24 / 398 (6.0)	6 / 346 (1.7)	3.48	[1.44; 8.41]	0.006
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.910				
<Median	15 / 633 (2.4)	5 / 632 (0.8)	3.00	[1.10; 8.19]	0.033
≥Median	38 / 776 (4.9)	13 / 730 (1.8)	2.75	[1.48; 5.12]	0.001
Race					
Interaction test	N.E.				
Asian	1 / 128 (0.8)	0 / 127 (0.0)	2.98	[0.12; 72.39]	0.503
Non-Asian	51 / 1203 (4.2)	18 / 1167 (1.5)	2.75	[1.62; 4.68]	<.001
BMI at screening					
Interaction test	p = 0.879				
≥25	44 / 935 (4.7)	15 / 935 (1.6)	2.93	[1.64; 5.23]	<.001
<25	9 / 460 (2.0)	3 / 410 (0.7)	2.67	[0.73; 9.81]	0.138
AJCC Anatomic Stage Group					
Interaction test	p = 0.112				
Group I/II	31 / 585 (5.3)	7 / 589 (1.2)	4.46	[1.98; 10.04]	<.001
Group III	22 / 823 (2.7)	11 / 772 (1.4)	1.88	[0.92; 3.84]	0.085

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.188				
IA/IB/IIA	19 / 310 (6.1)	4 / 311 (1.3)	4.77	[1.64; 13.85]	0.004
IIB	12 / 275 (4.4)	3 / 278 (1.1)	4.04	[1.15; 14.17]	0.029
IIIA	9 / 482 (1.9)	5 / 450 (1.1)	1.68	[0.57; 4.98]	0.349
IIIB	8 / 100 (8.0)	6 / 82 (7.3)	1.09	[0.40; 3.02]	0.864
IIIC	5 / 241 (2.1)	0 / 240 (0.0)	10.95	[0.61; >99.99]	0.104
Tumor category					
Interaction test	p = 0.068				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	45 / 1287 (3.5)	12 / 1258 (1.0)	3.67	[1.95; 6.90]	<.001
>T3	8 / 113 (7.1)	6 / 97 (6.2)	1.14	[0.41; 3.18]	0.796
Nodal status					
Interaction test	p = 0.341				
N0	13 / 190 (6.8)	7 / 200 (3.5)	1.95	[0.80; 4.79]	0.143
N1-N3	40 / 1216 (3.3)	11 / 1160 (0.9)	3.47	[1.79; 6.73]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.541				
Grade 1	4 / 102 (3.9)	2 / 106 (1.9)	2.08	[0.39; 11.10]	0.392
Grade 2	33 / 842 (3.9)	13 / 768 (1.7)	2.32	[1.23; 4.37]	0.009
Grade 3	14 / 373 (3.8)	3 / 397 (0.8)	4.97	[1.44; 17.15]	0.011
Histological subtype					
Interaction test	p = 0.670				
Ductal	39 / 1025 (3.8)	15 / 1010 (1.5)	2.56	[1.42; 4.62]	0.002
Lobular	11 / 291 (3.8)	3 / 276 (1.1)	3.48	[0.98; 12.33]	0.054
Other	3 / 92 (3.3)	0 / 76 (0.0)	5.80	[0.30; >99.99]	0.243
Ki67 status from surgical specimen					
Interaction test	p = 0.184				
Ki67≤20	25 / 660 (3.8)	12 / 629 (1.9)	1.99	[1.01; 3.92]	0.048
Ki67>20	24 / 489 (4.9)	6 / 516 (1.2)	4.22	[1.74; 10.24]	0.001
Type of NSAI					
Interaction test	p = 0.787				
Letrozole	45 / 907 (5.0)	15 / 895 (1.7)	2.96	[1.66; 5.27]	<.001
Anastrozole	8 / 502 (1.6)	3 / 467 (0.6)	2.48	[0.66; 9.29]	0.178
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.181				
Yes	33 / 1194 (2.8)	14 / 1146 (1.2)	2.26	[1.22; 4.21]	0.010
No	20 / 215 (9.3)	4 / 216 (1.9)	5.02	[1.75; 14.45]	0.003
Prior adjuvant chemotherapy					
Interaction test	p = 0.374				
Yes	24 / 694 (3.5)	6 / 673 (0.9)	3.88	[1.60; 9.43]	0.003
No	29 / 715 (4.1)	12 / 689 (1.7)	2.33	[1.20; 4.53]	0.013

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.046				
Yes	11 / 528 (2.1)	8 / 503 (1.6)	1.31	[0.53; 3.23]	0.558
No	42 / 881 (4.8)	10 / 859 (1.2)	4.10	[2.07; 8.11]	<.001
Prior endocrine therapy					
Interaction test	p = 0.108				
Yes	23 / 957 (2.4)	4 / 940 (0.4)	5.65	[1.96; 16.27]	0.001
No	30 / 452 (6.6)	14 / 422 (3.3)	2.00	[1.08; 3.72]	0.028
Prior mastectomy					
Interaction test	p = 0.313				
Yes	37 / 857 (4.3)	15 / 847 (1.8)	2.44	[1.35; 4.41]	0.003
No	16 / 552 (2.9)	3 / 515 (0.6)	4.98	[1.46; 16.98]	0.010
Prior radiotherapy					
Interaction test	p = 0.557				
Yes	27 / 1253 (2.2)	7 / 1203 (0.6)	3.70	[1.62; 8.47]	0.002
No	26 / 156 (16.7)	11 / 159 (6.9)	2.41	[1.23; 4.71]	0.010
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.12 PT blood bilirubin increased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Blood bilirubin increased					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.040				
NA/WE/O	17 / 899 (1.9)	2 / 856 (0.2)	8.09	[1.88; 34.93]	0.005
ROW	21 / 510 (4.1)	14 / 506 (2.8)	1.49	[0.77; 2.89]	0.241
Geographical region					
Interaction test	N.E.				
Europe	23 / 832 (2.8)	16 / 824 (1.9)	1.42	[0.76; 2.68]	0.272
North America/Australia	10 / 400 (2.5)	0 / 364 (0.0)	19.11	[1.12; >99.99]	0.041
Asia	3 / 102 (2.9)	0 / 101 (0.0)	6.93	[0.36; >99.99]	0.198
Latin America	2 / 75 (2.7)	0 / 73 (0.0)	4.87	[0.24; 99.70]	0.304
Age group 1 at randomization					
Interaction test	p = 0.502				
<45	1 / 60 (1.7)	0 / 52 (0.0)	2.61	[0.11; 62.64]	0.555
45 to 54	4 / 300 (1.3)	3 / 322 (0.9)	1.43	[0.32; 6.34]	0.637
55 to 64	22 / 651 (3.4)	7 / 642 (1.1)	3.10	[1.33; 7.20]	0.009
≥65	11 / 398 (2.8)	6 / 346 (1.7)	1.59	[0.60; 4.26]	0.353
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.205				
<Median	16 / 633 (2.5)	4 / 632 (0.6)	3.99	[1.34; 11.88]	0.013
≥Median	22 / 776 (2.8)	12 / 730 (1.6)	1.72	[0.86; 3.46]	0.125
Race					
Interaction test	N.E.				
Asian	3 / 128 (2.3)	0 / 127 (0.0)	6.95	[0.36; >99.99]	0.198
Non-Asian	33 / 1203 (2.7)	15 / 1167 (1.3)	2.13	[1.17; 3.91]	0.014
BMI at screening					
Interaction test	p = 0.903				
≥25	27 / 935 (2.9)	12 / 935 (1.3)	2.25	[1.15; 4.41]	0.018
<25	11 / 460 (2.4)	4 / 410 (1.0)	2.45	[0.79; 7.64]	0.122
AJCC Anatomic Stage Group					
Interaction test	p = 0.078				
Group I/II	11 / 585 (1.9)	9 / 589 (1.5)	1.23	[0.51; 2.95]	0.642
Group III	27 / 823 (3.3)	7 / 772 (0.9)	3.62	[1.58; 8.26]	0.002

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.160				
IA/IB/IIA	5 / 310 (1.6)	5 / 311 (1.6)	1.00	[0.29; 3.43]	0.996
IIB	6 / 275 (2.2)	4 / 278 (1.4)	1.52	[0.43; 5.31]	0.515
IIIA	17 / 482 (3.5)	3 / 450 (0.7)	5.29	[1.56; 17.93]	0.007
IIIB	4 / 100 (4.0)	4 / 82 (4.9)	0.82	[0.21; 3.18]	0.774
IIIC	6 / 241 (2.5)	0 / 240 (0.0)	12.95	[0.73; >99.99]	0.080
Tumor category					
Interaction test	p = 0.134				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	34 / 1287 (2.6)	12 / 1258 (1.0)	2.77	[1.44; 5.32]	0.002
>T3	4 / 113 (3.5)	4 / 97 (4.1)	0.86	[0.22; 3.34]	0.826
Nodal status					
Interaction test	p = 0.164				
N0	5 / 190 (2.6)	5 / 200 (2.5)	1.05	[0.31; 3.58]	0.935
N1-N3	33 / 1216 (2.7)	11 / 1160 (0.9)	2.86	[1.45; 5.64]	0.002
Histological grade at time of surgery					
Interaction test	p = 0.701				
Grade 1	2 / 102 (2.0)	2 / 106 (1.9)	1.04	[0.15; 7.24]	0.969
Grade 2	25 / 842 (3.0)	9 / 768 (1.2)	2.53	[1.19; 5.39]	0.016
Grade 3	9 / 373 (2.4)	4 / 397 (1.0)	2.39	[0.74; 7.71]	0.143
Histological subtype					
Interaction test	p = 0.613				
Ductal	26 / 1025 (2.5)	15 / 1010 (1.5)	1.71	[0.91; 3.21]	0.096
Lobular	11 / 291 (3.8)	0 / 276 (0.0)	21.82	[1.29; >99.99]	0.033
Other	1 / 92 (1.1)	1 / 76 (1.3)	0.83	[0.05; 12.99]	0.892
Ki67 status from surgical specimen					
Interaction test	p = 0.583				
Ki67≤20	18 / 660 (2.7)	8 / 629 (1.3)	2.14	[0.94; 4.90]	0.070
Ki67>20	10 / 489 (2.0)	7 / 516 (1.4)	1.51	[0.58; 3.93]	0.401
Type of NSAI					
Interaction test	p = 0.515				
Letrozole	30 / 907 (3.3)	14 / 895 (1.6)	2.11	[1.13; 3.96]	0.019
Anastrozole	8 / 502 (1.6)	2 / 467 (0.4)	3.72	[0.79; 17.43]	0.095
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.242				
Yes	30 / 1194 (2.5)	10 / 1146 (0.9)	2.88	[1.41; 5.86]	0.004
No	8 / 215 (3.7)	6 / 216 (2.8)	1.34	[0.47; 3.80]	0.582
Prior adjuvant chemotherapy					
Interaction test	p = 0.812				
Yes	13 / 694 (1.9)	6 / 673 (0.9)	2.10	[0.80; 5.50]	0.130
No	25 / 715 (3.5)	10 / 689 (1.5)	2.41	[1.17; 4.98]	0.018

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.374				
Yes	17 / 528 (3.2)	5 / 503 (1.0)	3.24	[1.20; 8.71]	0.020
No	21 / 881 (2.4)	11 / 859 (1.3)	1.86	[0.90; 3.84]	0.092
Prior endocrine therapy					
Interaction test	p = 0.165				
Yes	24 / 957 (2.5)	7 / 940 (0.7)	3.37	[1.46; 7.78]	0.004
No	14 / 452 (3.1)	9 / 422 (2.1)	1.45	[0.64; 3.32]	0.376
Prior mastectomy					
Interaction test	p = 0.515				
Yes	30 / 857 (3.5)	14 / 847 (1.7)	2.12	[1.13; 3.97]	0.019
No	8 / 552 (1.4)	2 / 515 (0.4)	3.73	[0.80; 17.49]	0.095
Prior radiotherapy					
Interaction test	p = 0.021				
Yes	28 / 1253 (2.2)	6 / 1203 (0.5)	4.48	[1.86; 10.78]	<.001
No	10 / 156 (6.4)	10 / 159 (6.3)	1.02	[0.44; 2.38]	0.965
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.13 PT glomerular filtration rate decreased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Glomerular filtration rate decreased					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.277				
NA/WE/O	12 / 899 (1.3)	2 / 856 (0.2)	5.71	[1.28; 25.45]	0.022
ROW	20 / 510 (3.9)	9 / 506 (1.8)	2.20	[1.01; 4.80]	0.046
Geographical region					
Interaction test	p = 0.979				
Europe	24 / 832 (2.9)	9 / 824 (1.1)	2.64	[1.24; 5.65]	0.012
North America/Australia	6 / 400 (1.5)	2 / 364 (0.5)	2.73	[0.55; 13.44]	0.217
Asia	0 / 102 (0.0)	0 / 101 (0.0)	N.E.	N.E.	N.E.
Latin America	2 / 75 (2.7)	0 / 73 (0.0)	4.87	[0.24; 99.70]	0.304
Age group 1 at randomization					
Interaction test	p = 0.353				
<45	1 / 60 (1.7)	0 / 52 (0.0)	2.61	[0.11; 62.64]	0.555
45 to 54	1 / 300 (0.3)	2 / 322 (0.6)	0.54	[0.05; 5.89]	0.611
55 to 64	10 / 651 (1.5)	4 / 642 (0.6)	2.47	[0.78; 7.82]	0.126
≥65	20 / 398 (5.0)	5 / 346 (1.4)	3.48	[1.32; 9.17]	0.012
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.283				
<Median	4 / 633 (0.6)	3 / 632 (0.5)	1.33	[0.30; 5.92]	0.707
≥Median	28 / 776 (3.6)	8 / 730 (1.1)	3.29	[1.51; 7.18]	0.003
Race					
Interaction test	N.E.				
Asian	0 / 128 (0.0)	0 / 127 (0.0)	N.E.	N.E.	N.E.
Non-Asian	32 / 1203 (2.7)	11 / 1167 (0.9)	2.82	[1.43; 5.57]	0.003
BMI at screening					
Interaction test	p = 0.295				
≥25	24 / 935 (2.6)	7 / 935 (0.7)	3.43	[1.48; 7.92]	0.004
<25	7 / 460 (1.5)	4 / 410 (1.0)	1.56	[0.46; 5.29]	0.476
AJCC Anatomic Stage Group					
Interaction test	p = 0.872				
Group I/II	12 / 585 (2.1)	4 / 589 (0.7)	3.02	[0.98; 9.31]	0.054
Group III	20 / 823 (2.4)	7 / 772 (0.9)	2.68	[1.14; 6.30]	0.024

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.911				
IA/IB/IIA	6 / 310 (1.9)	2 / 311 (0.6)	3.01	[0.61; 14.80]	0.175
IIB	6 / 275 (2.2)	2 / 278 (0.7)	3.03	[0.62; 14.90]	0.172
IIIA	9 / 482 (1.9)	3 / 450 (0.7)	2.80	[0.76; 10.28]	0.121
IIIB	8 / 100 (8.0)	4 / 82 (4.9)	1.64	[0.51; 5.25]	0.405
IIIC	3 / 241 (1.2)	0 / 240 (0.0)	6.97	[0.36; >99.99]	0.198
Tumor category					
Interaction test	p = 0.525				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	23 / 1287 (1.8)	7 / 1258 (0.6)	3.21	[1.38; 7.46]	0.007
>T3	9 / 113 (8.0)	4 / 97 (4.1)	1.93	[0.61; 6.08]	0.260
Nodal status					
Interaction test	p = 0.497				
N0	3 / 190 (1.6)	2 / 200 (1.0)	1.58	[0.27; 9.35]	0.615
N1-N3	29 / 1216 (2.4)	9 / 1160 (0.8)	3.07	[1.46; 6.47]	0.003
Histological grade at time of surgery					
Interaction test	p = 0.402				
Grade 1	4 / 102 (3.9)	0 / 106 (0.0)	9.35	[0.51; >99.99]	0.132
Grade 2	20 / 842 (2.4)	9 / 768 (1.2)	2.03	[0.93; 4.42]	0.076
Grade 3	8 / 373 (2.1)	2 / 397 (0.5)	4.26	[0.91; 19.92]	0.066
Histological subtype					
Interaction test	p = 0.890				
Ductal	23 / 1025 (2.2)	8 / 1010 (0.8)	2.83	[1.27; 6.30]	0.011
Lobular	7 / 291 (2.4)	2 / 276 (0.7)	3.32	[0.70; 15.84]	0.132
Other	2 / 92 (2.2)	1 / 76 (1.3)	1.65	[0.15; 17.87]	0.679
Ki67 status from surgical specimen					
Interaction test	p = 0.746				
Ki67≤20	21 / 660 (3.2)	6 / 629 (1.0)	3.34	[1.36; 8.21]	0.009
Ki67>20	10 / 489 (2.0)	4 / 516 (0.8)	2.64	[0.83; 8.36]	0.099
Type of NSAI					
Interaction test	N.E.				
Letrozole	26 / 907 (2.9)	11 / 895 (1.2)	2.33	[1.16; 4.69]	0.018
Anastrozole	6 / 502 (1.2)	0 / 467 (0.0)	12.10	[0.68; >99.99]	0.089
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.716				
Yes	20 / 1194 (1.7)	6 / 1146 (0.5)	3.20	[1.29; 7.94]	0.012
No	12 / 215 (5.6)	5 / 216 (2.3)	2.41	[0.86; 6.73]	0.093
Prior adjuvant chemotherapy					
Interaction test	p = 0.809				
Yes	10 / 694 (1.4)	3 / 673 (0.4)	3.23	[0.89; 11.69]	0.074
No	22 / 715 (3.1)	8 / 689 (1.2)	2.65	[1.19; 5.91]	0.017

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.560				
Yes	12 / 528 (2.3)	3 / 503 (0.6)	3.81	[1.08; 13.42]	0.037
No	20 / 881 (2.3)	8 / 859 (0.9)	2.44	[1.08; 5.50]	0.032
Prior endocrine therapy					
Interaction test	p = 0.317				
Yes	14 / 957 (1.5)	3 / 940 (0.3)	4.58	[1.32; 15.90]	0.016
No	18 / 452 (4.0)	8 / 422 (1.9)	2.10	[0.92; 4.78]	0.077
Prior mastectomy					
Interaction test	p = 0.192				
Yes	22 / 857 (2.6)	10 / 847 (1.2)	2.17	[1.04; 4.56]	0.040
No	10 / 552 (1.8)	1 / 515 (0.2)	9.33	[1.20; 72.63]	0.033
Prior radiotherapy					
Interaction test	p = 0.179				
Yes	20 / 1253 (1.6)	4 / 1203 (0.3)	4.80	[1.65; 14.00]	0.004
No	12 / 156 (7.7)	7 / 159 (4.4)	1.75	[0.71; 4.32]	0.227
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.14 PT platelet count decreased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Platelet count decreased					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.318				
NA/WE/O	23 / 899 (2.6)	3 / 856 (0.4)	7.30	[2.20; 24.22]	0.001
ROW	9 / 510 (1.8)	3 / 506 (0.6)	2.98	[0.81; 10.93]	0.100
Geographical region					
Interaction test	p = 0.793				
Europe	9 / 832 (1.1)	2 / 824 (0.2)	4.46	[0.97; 20.56]	0.055
North America/Australia	16 / 400 (4.0)	2 / 364 (0.5)	7.28	[1.69; 31.44]	0.008
Asia	7 / 102 (6.9)	2 / 101 (2.0)	3.47	[0.74; 16.28]	0.115
Latin America	0 / 75 (0.0)	0 / 73 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	p = 0.069				
<45	2 / 60 (3.3)	0 / 52 (0.0)	4.34	[0.21; 88.48]	0.339
45 to 54	2 / 300 (0.7)	3 / 322 (0.9)	0.72	[0.12; 4.25]	0.713
55 to 64	12 / 651 (1.8)	2 / 642 (0.3)	5.92	[1.33; 26.33]	0.020
≥65	16 / 398 (4.0)	1 / 346 (0.3)	13.91	[1.85; >99.99]	0.010
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.095				
<Median	9 / 633 (1.4)	4 / 632 (0.6)	2.25	[0.70; 7.26]	0.176
≥Median	23 / 776 (3.0)	2 / 730 (0.3)	10.82	[2.56; 45.72]	0.001
Race					
Interaction test	p = 0.981				
Asian	10 / 128 (7.8)	2 / 127 (1.6)	4.96	[1.11; 22.19]	0.036
Non-Asian	22 / 1203 (1.8)	4 / 1167 (0.3)	5.34	[1.84; 15.44]	0.002
BMI at screening					
Interaction test	p = 0.748				
≥25	13 / 935 (1.4)	3 / 935 (0.3)	4.33	[1.24; 15.16]	0.022
<25	19 / 460 (4.1)	3 / 410 (0.7)	5.64	[1.68; 18.94]	0.005
AJCC Anatomic Stage Group					
Interaction test	p = 0.422				
Group I/II	10 / 585 (1.7)	1 / 589 (0.2)	10.07	[1.29; 78.40]	0.027
Group III	21 / 823 (2.6)	5 / 772 (0.6)	3.94	[1.49; 10.40]	0.006

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.192				
IA/IB/IIA	2 / 310 (0.6)	0 / 311 (0.0)	5.02	[0.24; >99.99]	0.297
IIB	8 / 275 (2.9)	1 / 278 (0.4)	8.09	[1.02; 64.23]	0.048
IIIA	13 / 482 (2.7)	1 / 450 (0.2)	12.14	[1.59; 92.40]	0.016
IIIB	1 / 100 (1.0)	0 / 82 (0.0)	2.47	[0.10; 59.72]	0.579
IIIC	7 / 241 (2.9)	4 / 240 (1.7)	1.74	[0.52; 5.88]	0.370
Tumor category					
Interaction test	p = 0.196				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	30 / 1287 (2.3)	5 / 1258 (0.4)	5.86	[2.28; 15.07]	<.001
>T3	1 / 113 (0.9)	1 / 97 (1.0)	0.86	[0.05; 13.54]	0.914
Nodal status					
Interaction test	N.E.				
N0	1 / 190 (0.5)	0 / 200 (0.0)	3.16	[0.13; 77.02]	0.481
N1-N3	31 / 1216 (2.5)	6 / 1160 (0.5)	4.93	[2.06; 11.77]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.558				
Grade 1	2 / 102 (2.0)	1 / 106 (0.9)	2.08	[0.19; 22.57]	0.548
Grade 2	18 / 842 (2.1)	3 / 768 (0.4)	5.47	[1.62; 18.51]	0.006
Grade 3	11 / 373 (2.9)	1 / 397 (0.3)	11.71	[1.52; 90.24]	0.018
Histological subtype					
Interaction test	p = 0.610				
Ductal	27 / 1025 (2.6)	5 / 1010 (0.5)	5.32	[2.06; 13.76]	<.001
Lobular	3 / 291 (1.0)	1 / 276 (0.4)	2.85	[0.30; 27.19]	0.364
Other	2 / 92 (2.2)	0 / 76 (0.0)	4.14	[0.20; 84.94]	0.357
Ki67 status from surgical specimen					
Interaction test	p = 0.862				
Ki67≤20	13 / 660 (2.0)	3 / 629 (0.5)	4.13	[1.18; 14.42]	0.026
Ki67>20	10 / 489 (2.0)	3 / 516 (0.6)	3.52	[0.97; 12.70]	0.055
Type of NSAI					
Interaction test	p = 0.894				
Letrozole	20 / 907 (2.2)	4 / 895 (0.4)	4.93	[1.69; 14.38]	0.003
Anastrozole	12 / 502 (2.4)	2 / 467 (0.4)	5.58	[1.26; 24.81]	0.024
Prior neo/adjuvant chemotherapy					
Interaction test	N.E.				
Yes	30 / 1194 (2.5)	6 / 1146 (0.5)	4.80	[2.00; 11.49]	<.001
No	2 / 215 (0.9)	0 / 216 (0.0)	5.02	[0.24; >99.99]	0.297
Prior adjuvant chemotherapy					
Interaction test	p = 0.780				
Yes	14 / 694 (2.0)	3 / 673 (0.4)	4.53	[1.31; 15.68]	0.017
No	18 / 715 (2.5)	3 / 689 (0.4)	5.78	[1.71; 19.54]	0.005

Treatment Groups			Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.450				
Yes	16 / 528 (3.0)	4 / 503 (0.8)	3.81	[1.28; 11.32]	0.016
No	16 / 881 (1.8)	2 / 859 (0.2)	7.80	[1.80; 33.82]	0.006
Prior endocrine therapy					
Interaction test	p = 0.533				
Yes	20 / 957 (2.1)	3 / 940 (0.3)	6.55	[1.95; 21.96]	0.002
No	12 / 452 (2.7)	3 / 422 (0.7)	3.73	[1.06; 13.14]	0.040
Prior mastectomy					
Interaction test	p = 0.866				
Yes	22 / 857 (2.6)	4 / 847 (0.5)	5.44	[1.88; 15.71]	0.002
No	10 / 552 (1.8)	2 / 515 (0.4)	4.66	[1.03; 21.19]	0.046
Prior radiotherapy					
Interaction test	p = 0.630				
Yes	29 / 1253 (2.3)	5 / 1203 (0.4)	5.57	[2.16; 14.34]	<.001
No	3 / 156 (1.9)	1 / 159 (0.6)	3.06	[0.32; 29.08]	0.331
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.15 PT lymphocyte count decreased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Lymphocyte count decreased					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.720				
NA/WE/O	26 / 899 (2.9)	9 / 856 (1.1)	2.75	[1.30; 5.84]	0.008
ROW	4 / 510 (0.8)	2 / 506 (0.4)	1.98	[0.37; 10.79]	0.428
Geographical region					
Interaction test	p = 0.492				
Europe	8 / 832 (1.0)	1 / 824 (0.1)	7.92	[0.99; 63.21]	0.051
North America/Australia	18 / 400 (4.5)	8 / 364 (2.2)	2.05	[0.90; 4.65]	0.087
Asia	4 / 102 (3.9)	2 / 101 (2.0)	1.98	[0.37; 10.57]	0.424
Latin America	0 / 75 (0.0)	0 / 73 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	p = 0.452				
<45	3 / 60 (5.0)	2 / 52 (3.8)	1.30	[0.23; 7.48]	0.769
45 to 54	5 / 300 (1.7)	2 / 322 (0.6)	2.68	[0.52; 13.73]	0.236
55 to 64	18 / 651 (2.8)	4 / 642 (0.6)	4.44	[1.51; 13.04]	0.007
≥65	4 / 398 (1.0)	3 / 346 (0.9)	1.16	[0.26; 5.14]	0.846
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.580				
<Median	13 / 633 (2.1)	6 / 632 (0.9)	2.16	[0.83; 5.66]	0.116
≥Median	17 / 776 (2.2)	5 / 730 (0.7)	3.20	[1.19; 8.62]	0.022
Race					
Interaction test	p = 0.632				
Asian	4 / 128 (3.1)	2 / 127 (1.6)	1.98	[0.37; 10.64]	0.424
Non-Asian	26 / 1203 (2.2)	8 / 1167 (0.7)	3.15	[1.43; 6.94]	0.004
BMI at screening					
Interaction test	p = 0.016				
≥25	22 / 935 (2.4)	4 / 935 (0.4)	5.50	[1.90; 15.90]	0.002
<25	7 / 460 (1.5)	7 / 410 (1.7)	0.89	[0.32; 2.52]	0.828
AJCC Anatomic Stage Group					
Interaction test	p = 0.403				
Group I/II	12 / 585 (2.1)	3 / 589 (0.5)	4.03	[1.14; 14.20]	0.030
Group III	18 / 823 (2.2)	8 / 772 (1.0)	2.11	[0.92; 4.83]	0.077

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.698				
IA/IB/IIA	6 / 310 (1.9)	1 / 311 (0.3)	6.02	[0.73; 49.71]	0.096
IIB	6 / 275 (2.2)	2 / 278 (0.7)	3.03	[0.62; 14.90]	0.172
IIIA	10 / 482 (2.1)	3 / 450 (0.7)	3.11	[0.86; 11.24]	0.083
IIIB	0 / 100 (0.0)	0 / 82 (0.0)	N.E.	N.E.	N.E.
IIIC	8 / 241 (3.3)	5 / 240 (2.1)	1.59	[0.53; 4.80]	0.408
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	30 / 1287 (2.3)	10 / 1258 (0.8)	2.93	[1.44; 5.97]	0.003
>T3	0 / 113 (0.0)	1 / 97 (1.0)	0.29	[0.01; 6.95]	0.442
Nodal status					
Interaction test	N.E.				
N0	1 / 190 (0.5)	0 / 200 (0.0)	3.16	[0.13; 77.02]	0.481
N1-N3	29 / 1216 (2.4)	11 / 1160 (0.9)	2.51	[1.26; 5.01]	0.009
Histological grade at time of surgery					
Interaction test	p = 0.149				
Grade 1	1 / 102 (1.0)	0 / 106 (0.0)	3.12	[0.13; 75.63]	0.485
Grade 2	16 / 842 (1.9)	8 / 768 (1.0)	1.82	[0.79; 4.24]	0.162
Grade 3	12 / 373 (3.2)	2 / 397 (0.5)	6.39	[1.44; 28.34]	0.015
Histological subtype					
Interaction test	p = 0.443				
Ductal	24 / 1025 (2.3)	10 / 1010 (1.0)	2.36	[1.14; 4.92]	0.021
Lobular	6 / 291 (2.1)	1 / 276 (0.4)	5.69	[0.69; 46.97]	0.106
Other	0 / 92 (0.0)	0 / 76 (0.0)	N.E.	N.E.	N.E.
Ki67 status from surgical specimen					
Interaction test	p = 0.327				
Ki67≤20	7 / 660 (1.1)	5 / 629 (0.8)	1.33	[0.43; 4.18]	0.621
Ki67>20	9 / 489 (1.8)	3 / 516 (0.6)	3.17	[0.86; 11.62]	0.083
Type of NSAI					
Interaction test	p = 0.364				
Letrozole	18 / 907 (2.0)	5 / 895 (0.6)	3.55	[1.32; 9.53]	0.012
Anastrozole	12 / 502 (2.4)	6 / 467 (1.3)	1.86	[0.70; 4.92]	0.211
Prior neo/adjuvant chemotherapy					
Interaction test	N.E.				
Yes	28 / 1194 (2.3)	11 / 1146 (1.0)	2.44	[1.22; 4.88]	0.011
No	2 / 215 (0.9)	0 / 216 (0.0)	5.02	[0.24; >99.99]	0.297
Prior adjuvant chemotherapy					
Interaction test	p = 0.398				
Yes	18 / 694 (2.6)	5 / 673 (0.7)	3.49	[1.30; 9.35]	0.013
No	12 / 715 (1.7)	6 / 689 (0.9)	1.93	[0.73; 5.11]	0.187

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.082				
Yes	10 / 528 (1.9)	7 / 503 (1.4)	1.36	[0.52; 3.55]	0.528
No	20 / 881 (2.3)	4 / 859 (0.5)	4.88	[1.67; 14.20]	0.004
Prior endocrine therapy					
Interaction test	p = 0.124				
Yes	19 / 957 (2.0)	10 / 940 (1.1)	1.87	[0.87; 3.99]	0.108
No	11 / 452 (2.4)	1 / 422 (0.2)	10.27	[1.33; 79.20]	0.025
Prior mastectomy					
Interaction test	p = 0.950				
Yes	19 / 857 (2.2)	7 / 847 (0.8)	2.68	[1.13; 6.35]	0.025
No	11 / 552 (2.0)	4 / 515 (0.8)	2.57	[0.82; 8.01]	0.105
Prior radiotherapy					
Interaction test	N.E.				
Yes	30 / 1253 (2.4)	11 / 1203 (0.9)	2.62	[1.32; 5.20]	0.006
No	0 / 156 (0.0)	0 / 159 (0.0)	N.E.	N.E.	N.E.
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.16 PT adjusted calcium decreased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Adjusted calcium decreased					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.895				
NA/WE/O	4 / 899 (0.4)	1 / 856 (0.1)	3.81	[0.43; 34.01]	0.231
ROW	16 / 510 (3.1)	5 / 506 (1.0)	3.17	[1.17; 8.60]	0.023
Geographical region					
Interaction test	p = 0.403				
Europe	16 / 832 (1.9)	5 / 824 (0.6)	3.17	[1.17; 8.61]	0.024
North America/Australia	1 / 400 (0.3)	1 / 364 (0.3)	0.91	[0.06; 14.50]	0.947
Asia	2 / 102 (2.0)	0 / 101 (0.0)	4.95	[0.24; >99.99]	0.300
Latin America	1 / 75 (1.3)	0 / 73 (0.0)	2.92	[0.12; 70.56]	0.509
Age group 1 at randomization					
Interaction test	p = 0.671				
<45	1 / 60 (1.7)	0 / 52 (0.0)	2.61	[0.11; 62.64]	0.555
45 to 54	1 / 300 (0.3)	1 / 322 (0.3)	1.07	[0.07; 17.08]	0.960
55 to 64	12 / 651 (1.8)	4 / 642 (0.6)	2.96	[0.96; 9.12]	0.059
≥65	6 / 398 (1.5)	1 / 346 (0.3)	5.22	[0.63; 43.11]	0.125
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.201				
<Median	7 / 633 (1.1)	4 / 632 (0.6)	1.75	[0.51; 5.94]	0.371
≥Median	13 / 776 (1.7)	2 / 730 (0.3)	6.11	[1.38; 27.00]	0.017
Race					
Interaction test	N.E.				
Asian	3 / 128 (2.3)	0 / 127 (0.0)	6.95	[0.36; >99.99]	0.198
Non-Asian	16 / 1203 (1.3)	6 / 1167 (0.5)	2.59	[1.02; 6.59]	0.046
BMI at screening					
Interaction test	p = 0.603				
≥25	15 / 935 (1.6)	4 / 935 (0.4)	3.75	[1.25; 11.26]	0.018
<25	5 / 460 (1.1)	2 / 410 (0.5)	2.23	[0.43; 11.42]	0.337
AJCC Anatomic Stage Group					
Interaction test	p = 0.142				
Group I/II	9 / 585 (1.5)	5 / 589 (0.8)	1.81	[0.61; 5.38]	0.284
Group III	11 / 823 (1.3)	1 / 772 (0.1)	10.32	[1.34; 79.73]	0.025

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.559				
IA/IB/IIA	6 / 310 (1.9)	4 / 311 (1.3)	1.50	[0.43; 5.28]	0.523
IIB	3 / 275 (1.1)	1 / 278 (0.4)	3.03	[0.32; 28.98]	0.335
IIIA	6 / 482 (1.2)	1 / 450 (0.2)	5.60	[0.68; 46.35]	0.110
IIIB	4 / 100 (4.0)	0 / 82 (0.0)	7.40	[0.40; >99.99]	0.177
IIIC	1 / 241 (0.4)	0 / 240 (0.0)	2.99	[0.12; 72.97]	0.502
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	16 / 1287 (1.2)	6 / 1258 (0.5)	2.61	[1.02; 6.64]	0.045
>T3	4 / 113 (3.5)	0 / 97 (0.0)	7.74	[0.42; >99.99]	0.168
Nodal status					
Interaction test	N.E.				
N0	6 / 190 (3.2)	0 / 200 (0.0)	13.68	[0.78; >99.99]	0.074
N1-N3	14 / 1216 (1.2)	6 / 1160 (0.5)	2.23	[0.86; 5.77]	0.100
Histological grade at time of surgery					
Interaction test	p = 0.398				
Grade 1	2 / 102 (2.0)	2 / 106 (1.9)	1.04	[0.15; 7.24]	0.969
Grade 2	12 / 842 (1.4)	2 / 768 (0.3)	5.47	[1.23; 24.37]	0.026
Grade 3	4 / 373 (1.1)	2 / 397 (0.5)	2.13	[0.39; 11.55]	0.381
Histological subtype					
Interaction test	p = 0.664				
Ductal	17 / 1025 (1.7)	5 / 1010 (0.5)	3.35	[1.24; 9.05]	0.017
Lobular	2 / 291 (0.7)	1 / 276 (0.4)	1.90	[0.17; 20.80]	0.600
Other	1 / 92 (1.1)	0 / 76 (0.0)	2.48	[0.10; 60.11]	0.576
Ki67 status from surgical specimen					
Interaction test	p = 0.418				
Ki67≤20	9 / 660 (1.4)	4 / 629 (0.6)	2.14	[0.66; 6.93]	0.202
Ki67>20	9 / 489 (1.8)	2 / 516 (0.4)	4.75	[1.03; 21.87]	0.046
Type of NSAI					
Interaction test	p = 0.988				
Letrozole	13 / 907 (1.4)	4 / 895 (0.4)	3.21	[1.05; 9.80]	0.041
Anastrozole	7 / 502 (1.4)	2 / 467 (0.4)	3.26	[0.68; 15.59]	0.140
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.278				
Yes	15 / 1194 (1.3)	3 / 1146 (0.3)	4.80	[1.39; 16.53]	0.013
No	5 / 215 (2.3)	3 / 216 (1.4)	1.67	[0.41; 6.92]	0.476
Prior adjuvant chemotherapy					
Interaction test	p = 0.994				
Yes	10 / 694 (1.4)	3 / 673 (0.4)	3.23	[0.89; 11.69]	0.074
No	10 / 715 (1.4)	3 / 689 (0.4)	3.21	[0.89; 11.62]	0.075

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	N.E.				
Yes	6 / 528 (1.1)	0 / 503 (0.0)	12.39	[0.70; >99.99]	0.086
No	14 / 881 (1.6)	6 / 859 (0.7)	2.28	[0.88; 5.89]	0.090
Prior endocrine therapy					
Interaction test	p = 0.535				
Yes	7 / 957 (0.7)	3 / 940 (0.3)	2.29	[0.59; 8.84]	0.228
No	13 / 452 (2.9)	3 / 422 (0.7)	4.05	[1.16; 14.10]	0.028
Prior mastectomy					
Interaction test	p = 0.461				
Yes	16 / 857 (1.9)	4 / 847 (0.5)	3.95	[1.33; 11.78]	0.014
No	4 / 552 (0.7)	2 / 515 (0.4)	1.87	[0.34; 10.14]	0.470
Prior radiotherapy					
Interaction test	p = 0.914				
Yes	10 / 1253 (0.8)	3 / 1203 (0.2)	3.20	[0.88; 11.60]	0.077
No	10 / 156 (6.4)	3 / 159 (1.9)	3.40	[0.95; 12.11]	0.059
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.17 PT blood potassium increased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Blood potassium increased					
	n / N (%)	n / N (%)			
Region					
Interaction test	N.E.				
NA/WE/O	7 / 899 (0.8)	0 / 856 (0.0)	14.28	[0.82; >99.99]	0.069
ROW	8 / 510 (1.6)	2 / 506 (0.4)	3.97	[0.85; 18.60]	0.080
Geographical region					
Interaction test	N.E.				
Europe	10 / 832 (1.2)	2 / 824 (0.2)	4.95	[1.09; 22.53]	0.039
North America/Australia	1 / 400 (0.3)	0 / 364 (0.0)	2.73	[0.11; 66.82]	0.538
Asia	1 / 102 (1.0)	0 / 101 (0.0)	2.97	[0.12; 72.08]	0.503
Latin America	3 / 75 (4.0)	0 / 73 (0.0)	6.82	[0.36; >99.99]	0.202
Age group 1 at randomization					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	N.E.				
<Median	4 / 633 (0.6)	0 / 632 (0.0)	8.99	[0.48; >99.99]	0.141
≥Median	11 / 776 (1.4)	2 / 730 (0.3)	5.17	[1.15; 23.26]	0.032
Race					
Interaction test	N.E.				
Asian	1 / 128 (0.8)	0 / 127 (0.0)	2.98	[0.12; 72.39]	0.503
Non-Asian	13 / 1203 (1.1)	2 / 1167 (0.2)	6.31	[1.43; 27.88]	0.015
BMI at screening					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
AJCC Anatomic Stage Group					
Interaction test	p = 0.824				
Group I/II	6 / 585 (1.0)	1 / 589 (0.2)	6.04	[0.73; 50.02]	0.095
Group III	9 / 823 (1.1)	1 / 772 (0.1)	8.44	[1.07; 66.48]	0.043
Anatomic stages					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Tumor category					
Interaction test	p = 0.114				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	14 / 1287 (1.1)	1 / 1258 (0.1)	13.68	[1.80; >99.99]	0.011
>T3	1 / 113 (0.9)	1 / 97 (1.0)	0.86	[0.05; 13.54]	0.914
Nodal status					
Interaction test	p = 0.269				
N0	2 / 190 (1.1)	1 / 200 (0.5)	2.11	[0.19; 23.03]	0.542
N1-N3	13 / 1216 (1.1)	1 / 1160 (0.1)	12.40	[1.62; 94.65]	0.015
Histological grade at time of surgery					
Interaction test	N.E.				
Grade 1	1 / 102 (1.0)	0 / 106 (0.0)	3.12	[0.13; 75.63]	0.485
Grade 2	10 / 842 (1.2)	0 / 768 (0.0)	19.16	[1.12; >99.99]	0.041
Grade 3	4 / 373 (1.1)	2 / 397 (0.5)	2.13	[0.39; 11.55]	0.381
Histological subtype					
Interaction test	N.E.				
Ductal	11 / 1025 (1.1)	2 / 1010 (0.2)	5.42	[1.20; 24.39]	0.028
Lobular	3 / 291 (1.0)	0 / 276 (0.0)	6.64	[0.34; >99.99]	0.210
Other	1 / 92 (1.1)	0 / 76 (0.0)	2.48	[0.10; 60.11]	0.576
Ki67 status from surgical specimen					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Type of NSAI					
Interaction test	N.E.				
Letrozole	5 / 907 (0.6)	2 / 895 (0.2)	2.47	[0.48; 12.68]	0.280
Anastrozole	10 / 502 (2.0)	0 / 467 (0.0)	19.54	[1.15; >99.99]	0.040
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.138				
Yes	14 / 1194 (1.2)	1 / 1146 (0.1)	13.44	[1.77; >99.99]	0.012
No	1 / 215 (0.5)	1 / 216 (0.5)	1.00	[0.06; 15.96]	0.997
Prior adjuvant chemotherapy					
Interaction test	N.E.				
Yes	10 / 694 (1.4)	0 / 673 (0.0)	20.37	[1.20; >99.99]	0.037
No	5 / 715 (0.7)	2 / 689 (0.3)	2.41	[0.47; 12.38]	0.292
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.497				
Yes	4 / 528 (0.8)	1 / 503 (0.2)	3.81	[0.43; 33.98]	0.231
No	11 / 881 (1.2)	1 / 859 (0.1)	10.73	[1.39; 82.89]	0.023

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior endocrine therapy					
Interaction test	N.E.				
Yes	12 / 957 (1.3)	0 / 940 (0.0)	24.56	[1.46; >99.99]	0.026
No	3 / 452 (0.7)	2 / 422 (0.5)	1.40	[0.24; 8.34]	0.711
Prior mastectomy					
Interaction test	N.E.				
Yes	9 / 857 (1.1)	2 / 847 (0.2)	4.45	[0.96; 20.52]	0.056
No	6 / 552 (1.1)	0 / 515 (0.0)	12.13	[0.69; >99.99]	0.089
Prior radiotherapy					
Interaction test	N.E.				
Yes	13 / 1253 (1.0)	0 / 1203 (0.0)	25.92	[1.54; >99.99]	0.024
No	2 / 156 (1.3)	2 / 159 (1.3)	1.02	[0.15; 7.15]	0.985
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.18 SOC musculoskeletal and connective tissue disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Musculoskeletal and connective tissue disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.953				
NA/WE/O	606 / 899 (67.4)	613 / 856 (71.6)	0.94	[0.88; 1.00]	0.056
ROW	226 / 510 (44.3)	248 / 506 (49.0)	0.90	[0.79; 1.03]	0.134
Geographical region					
Interaction test	p = 0.370				
Europe	475 / 832 (57.1)	515 / 824 (62.5)	0.91	[0.84; 0.99]	0.025
North America/Australia	272 / 400 (68.0)	248 / 364 (68.1)	1.00	[0.91; 1.10]	0.969
Asia	41 / 102 (40.2)	54 / 101 (53.5)	0.75	[0.56; 1.01]	0.061
Latin America	44 / 75 (58.7)	44 / 73 (60.3)	0.97	[0.75; 1.27]	0.842
Age group 1 at randomization					
Interaction test	p = 0.681				
<45	43 / 60 (71.7)	35 / 52 (67.3)	1.06	[0.83; 1.36]	0.619
45 to 54	183 / 300 (61.0)	216 / 322 (67.1)	0.91	[0.81; 1.02]	0.116
55 to 64	378 / 651 (58.1)	404 / 642 (62.9)	0.92	[0.84; 1.01]	0.074
≥65	228 / 398 (57.3)	206 / 346 (59.5)	0.96	[0.85; 1.09]	0.534
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.958				
<Median	395 / 633 (62.4)	420 / 632 (66.5)	0.94	[0.87; 1.02]	0.132
≥Median	437 / 776 (56.3)	441 / 730 (60.4)	0.93	[0.86; 1.02]	0.107
Race					
Interaction test	p = 0.331				
Asian	62 / 128 (48.4)	74 / 127 (58.3)	0.83	[0.66; 1.05]	0.118
Non-Asian	711 / 1203 (59.1)	728 / 1167 (62.4)	0.95	[0.89; 1.01]	0.102
BMI at screening					
Interaction test	p = 0.472				
≥25	565 / 935 (60.4)	596 / 935 (63.7)	0.95	[0.88; 1.02]	0.140
<25	257 / 460 (55.9)	255 / 410 (62.2)	0.90	[0.80; 1.00]	0.058
AJCC Anatomic Stage Group					
Interaction test	p = 0.285				
Group I/II	346 / 585 (59.1)	386 / 589 (65.5)	0.90	[0.83; 0.99]	0.024
Group III	486 / 823 (59.1)	475 / 772 (61.5)	0.96	[0.89; 1.04]	0.312

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.121				
IA/IB/IIA	182 / 310 (58.7)	208 / 311 (66.9)	0.88	[0.78; 0.99]	0.036
IIB	164 / 275 (59.6)	178 / 278 (64.0)	0.93	[0.82; 1.06]	0.288
IIIA	291 / 482 (60.4)	285 / 450 (63.3)	0.95	[0.86; 1.05]	0.352
IIIB	48 / 100 (48.0)	53 / 82 (64.6)	0.74	[0.57; 0.96]	0.025
IIIC	147 / 241 (61.0)	137 / 240 (57.1)	1.07	[0.92; 1.24]	0.383
Tumor category					
Interaction test	p = 0.107				
T0	5 / 5 (100.0)	2 / 5 (40.0)	2.50	[0.85; 7.31]	0.094
T1-T3	772 / 1287 (60.0)	797 / 1258 (63.4)	0.95	[0.89; 1.01]	0.081
>T3	54 / 113 (47.8)	61 / 97 (62.9)	0.76	[0.59; 0.97]	0.029
Nodal status					
Interaction test	p = 0.325				
N0	111 / 190 (58.4)	134 / 200 (67.0)	0.87	[0.75; 1.02]	0.082
N1-N3	719 / 1216 (59.1)	726 / 1160 (62.6)	0.94	[0.89; 1.01]	0.084
Histological grade at time of surgery					
Interaction test	p = 0.030				
Grade 1	60 / 102 (58.8)	67 / 106 (63.2)	0.93	[0.75; 1.16]	0.518
Grade 2	483 / 842 (57.4)	493 / 768 (64.2)	0.89	[0.83; 0.97]	0.005
Grade 3	244 / 373 (65.4)	242 / 397 (61.0)	1.07	[0.96; 1.20]	0.200
Histological subtype					
Interaction test	p = 0.398				
Ductal	606 / 1025 (59.1)	627 / 1010 (62.1)	0.95	[0.89; 1.02]	0.172
Lobular	164 / 291 (56.4)	181 / 276 (65.6)	0.86	[0.75; 0.98]	0.025
Other	61 / 92 (66.3)	53 / 76 (69.7)	0.95	[0.77; 1.17]	0.634
Ki67 status from surgical specimen					
Interaction test	p = 0.246				
Ki67≤20	368 / 660 (55.8)	402 / 629 (63.9)	0.87	[0.80; 0.95]	0.003
Ki67>20	278 / 489 (56.9)	311 / 516 (60.3)	0.94	[0.85; 1.05]	0.272
Type of NSAI					
Interaction test	p = 0.169				
Letrozole	515 / 907 (56.8)	563 / 895 (62.9)	0.90	[0.84; 0.97]	0.008
Anastrozole	317 / 502 (63.1)	298 / 467 (63.8)	0.99	[0.90; 1.09]	0.830
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.906				
Yes	714 / 1194 (59.8)	732 / 1146 (63.9)	0.94	[0.88; 1.00]	0.043
No	118 / 215 (54.9)	129 / 216 (59.7)	0.92	[0.78; 1.08]	0.311
Prior adjuvant chemotherapy					
Interaction test	p = 0.131				
Yes	414 / 694 (59.7)	448 / 673 (66.6)	0.90	[0.83; 0.97]	0.008
No	418 / 715 (58.5)	413 / 689 (59.9)	0.98	[0.89; 1.06]	0.573

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.057				
Yes	318 / 528 (60.2)	301 / 503 (59.8)	1.01	[0.91; 1.11]	0.899
No	514 / 881 (58.3)	560 / 859 (65.2)	0.89	[0.83; 0.96]	0.003
Prior endocrine therapy					
Interaction test	p = 0.917				
Yes	576 / 957 (60.2)	603 / 940 (64.1)	0.94	[0.87; 1.01]	0.075
No	256 / 452 (56.6)	258 / 422 (61.1)	0.93	[0.83; 1.04]	0.177
Prior mastectomy					
Interaction test	p = 0.117				
Yes	503 / 857 (58.7)	514 / 847 (60.7)	0.97	[0.89; 1.05]	0.402
No	329 / 552 (59.6)	347 / 515 (67.4)	0.88	[0.81; 0.97]	0.008
Prior radiotherapy					
Interaction test	p = 0.507				
Yes	749 / 1253 (59.8)	764 / 1203 (63.5)	0.94	[0.88; 1.00]	0.057
No	83 / 156 (53.2)	97 / 159 (61.0)	0.87	[0.72; 1.06]	0.164
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.19 PT arthralgia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Arthralgia					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.869				
NA/WE/O	390 / 899 (43.4)	432 / 856 (50.5)	0.86	[0.78; 0.95]	0.003
ROW	114 / 510 (22.4)	143 / 506 (28.3)	0.79	[0.64; 0.98]	0.031
Geographical region					
Interaction test	p = 0.431				
Europe	295 / 832 (35.5)	346 / 824 (42.0)	0.84	[0.75; 0.95]	0.007
North America/Australia	167 / 400 (41.8)	166 / 364 (45.6)	0.92	[0.78; 1.08]	0.283
Asia	22 / 102 (21.6)	32 / 101 (31.7)	0.68	[0.43; 1.09]	0.107
Latin America	20 / 75 (26.7)	31 / 73 (42.5)	0.63	[0.40; 1.00]	0.048
Age group 1 at randomization					
Interaction test	p = 0.891				
<45	26 / 60 (43.3)	28 / 52 (53.8)	0.80	[0.55; 1.18]	0.267
45 to 54	120 / 300 (40.0)	143 / 322 (44.4)	0.90	[0.75; 1.08]	0.267
55 to 64	224 / 651 (34.4)	268 / 642 (41.7)	0.82	[0.72; 0.95]	0.007
≥65	134 / 398 (33.7)	136 / 346 (39.3)	0.86	[0.71; 1.04]	0.111
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.872				
<Median	250 / 633 (39.5)	289 / 632 (45.7)	0.86	[0.76; 0.98]	0.025
≥Median	254 / 776 (32.7)	286 / 730 (39.2)	0.84	[0.73; 0.96]	0.009
Race					
Interaction test	p = 0.592				
Asian	34 / 128 (26.6)	45 / 127 (35.4)	0.75	[0.52; 1.09]	0.129
Non-Asian	429 / 1203 (35.7)	489 / 1167 (41.9)	0.85	[0.77; 0.94]	0.002
BMI at screening					
Interaction test	p = 0.715				
≥25	343 / 935 (36.7)	401 / 935 (42.9)	0.86	[0.76; 0.96]	0.006
<25	153 / 460 (33.3)	167 / 410 (40.7)	0.82	[0.69; 0.97]	0.023
AJCC Anatomic Stage Group					
Interaction test	p = 0.463				
Group I/II	212 / 585 (36.2)	261 / 589 (44.3)	0.82	[0.71; 0.94]	0.005
Group III	292 / 823 (35.5)	314 / 772 (40.7)	0.87	[0.77; 0.99]	0.033

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.480				
IA/IB/IIA	118 / 310 (38.1)	146 / 311 (46.9)	0.81	[0.67; 0.98]	0.026
IIB	94 / 275 (34.2)	115 / 278 (41.4)	0.83	[0.67; 1.03]	0.083
IIIA	178 / 482 (36.9)	188 / 450 (41.8)	0.88	[0.75; 1.04]	0.130
IIIB	22 / 100 (22.0)	30 / 82 (36.6)	0.60	[0.38; 0.96]	0.033
IIIC	92 / 241 (38.2)	96 / 240 (40.0)	0.95	[0.76; 1.19]	0.682
Tumor category					
Interaction test	p = 0.169				
T0	2 / 5 (40.0)	2 / 5 (40.0)	1.00	[0.22; 4.56]	1.000
T1-T3	478 / 1287 (37.1)	535 / 1258 (42.5)	0.87	[0.79; 0.96]	0.006
>T3	24 / 113 (21.2)	37 / 97 (38.1)	0.56	[0.36; 0.86]	0.009
Nodal status					
Interaction test	p = 0.728				
N0	71 / 190 (37.4)	91 / 200 (45.5)	0.82	[0.65; 1.04]	0.106
N1-N3	432 / 1216 (35.5)	483 / 1160 (41.6)	0.85	[0.77; 0.94]	0.002
Histological grade at time of surgery					
Interaction test	p = 0.249				
Grade 1	40 / 102 (39.2)	43 / 106 (40.6)	0.97	[0.69; 1.35]	0.842
Grade 2	284 / 842 (33.7)	320 / 768 (41.7)	0.81	[0.71; 0.92]	0.001
Grade 3	153 / 373 (41.0)	169 / 397 (42.6)	0.96	[0.82; 1.14]	0.663
Histological subtype					
Interaction test	p = 0.131				
Ductal	375 / 1025 (36.6)	418 / 1010 (41.4)	0.88	[0.79; 0.99]	0.027
Lobular	87 / 291 (29.9)	120 / 276 (43.5)	0.69	[0.55; 0.86]	<.001
Other	42 / 92 (45.7)	37 / 76 (48.7)	0.94	[0.68; 1.29]	0.695
Ki67 status from surgical specimen					
Interaction test	p = 0.460				
Ki67≤20	232 / 660 (35.2)	257 / 629 (40.9)	0.86	[0.75; 0.99]	0.035
Ki67>20	164 / 489 (33.5)	218 / 516 (42.2)	0.79	[0.68; 0.93]	0.005
Type of NSAI					
Interaction test	p = 0.302				
Letrozole	309 / 907 (34.1)	375 / 895 (41.9)	0.81	[0.72; 0.92]	<.001
Anastrozole	195 / 502 (38.8)	200 / 467 (42.8)	0.91	[0.78; 1.06]	0.208
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.937				
Yes	435 / 1194 (36.4)	493 / 1146 (43.0)	0.85	[0.77; 0.94]	0.001
No	69 / 215 (32.1)	82 / 216 (38.0)	0.85	[0.65; 1.09]	0.203
Prior adjuvant chemotherapy					
Interaction test	p = 0.554				
Yes	266 / 694 (38.3)	310 / 673 (46.1)	0.83	[0.73; 0.94]	0.004
No	238 / 715 (33.3)	265 / 689 (38.5)	0.87	[0.75; 1.00]	0.044

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.409				
Yes	179 / 528 (33.9)	192 / 503 (38.2)	0.89	[0.75; 1.05]	0.154
No	325 / 881 (36.9)	383 / 859 (44.6)	0.83	[0.74; 0.93]	0.001
Prior endocrine therapy					
Interaction test	p = 0.530				
Yes	341 / 957 (35.6)	403 / 940 (42.9)	0.83	[0.74; 0.93]	0.001
No	163 / 452 (36.1)	172 / 422 (40.8)	0.88	[0.75; 1.05]	0.154
Prior mastectomy					
Interaction test	p = 0.387				
Yes	291 / 857 (34.0)	331 / 847 (39.1)	0.87	[0.77; 0.99]	0.028
No	213 / 552 (38.6)	244 / 515 (47.4)	0.81	[0.71; 0.94]	0.004
Prior radiotherapy					
Interaction test	p = 0.389				
Yes	450 / 1253 (35.9)	517 / 1203 (43.0)	0.84	[0.76; 0.92]	<.001
No	54 / 156 (34.6)	58 / 159 (36.5)	0.95	[0.70; 1.28]	0.730
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.20 PT joint swelling: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Joint swelling					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.862				
NA/WE/O	15 / 899 (1.7)	6 / 856 (0.7)	2.38	[0.93; 6.11]	0.071
ROW	3 / 510 (0.6)	1 / 506 (0.2)	2.98	[0.31; 28.52]	0.344
Geographical region					
Interaction test	p = 0.578				
Europe	5 / 832 (0.6)	3 / 824 (0.4)	1.65	[0.40; 6.88]	0.492
North America/Australia	12 / 400 (3.0)	4 / 364 (1.1)	2.73	[0.89; 8.39]	0.080
Asia	0 / 102 (0.0)	0 / 101 (0.0)	N.E.	N.E.	N.E.
Latin America	1 / 75 (1.3)	0 / 73 (0.0)	2.92	[0.12; 70.56]	0.509
Age group 1 at randomization					
Interaction test	p = 0.646				
<45	1 / 60 (1.7)	1 / 52 (1.9)	0.87	[0.06; 13.51]	0.919
45 to 54	4 / 300 (1.3)	1 / 322 (0.3)	4.29	[0.48; 38.20]	0.191
55 to 64	8 / 651 (1.2)	2 / 642 (0.3)	3.94	[0.84; 18.50]	0.082
≥65	5 / 398 (1.3)	3 / 346 (0.9)	1.45	[0.35; 6.02]	0.610
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.310				
<Median	6 / 633 (0.9)	4 / 632 (0.6)	1.50	[0.42; 5.28]	0.530
≥Median	12 / 776 (1.5)	3 / 730 (0.4)	3.76	[1.07; 13.28]	0.039
Race					
Interaction test	N.E.				
Asian	0 / 128 (0.0)	1 / 127 (0.8)	0.33	[0.01; 8.04]	0.497
Non-Asian	18 / 1203 (1.5)	6 / 1167 (0.5)	2.91	[1.16; 7.31]	0.023
BMI at screening					
Interaction test	p = 0.397				
≥25	13 / 935 (1.4)	4 / 935 (0.4)	3.25	[1.06; 9.93]	0.039
<25	5 / 460 (1.1)	3 / 410 (0.7)	1.49	[0.36; 6.18]	0.586
AJCC Anatomic Stage Group					
Interaction test	p = 0.711				
Group I/II	6 / 585 (1.0)	3 / 589 (0.5)	2.01	[0.51; 8.01]	0.321
Group III	12 / 823 (1.5)	4 / 772 (0.5)	2.81	[0.91; 8.69]	0.072
Anatomic stages					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Tumor category					
Interaction test	p = 0.431				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	17 / 1287 (1.3)	6 / 1258 (0.5)	2.77	[1.10; 7.00]	0.031
>T3	1 / 113 (0.9)	1 / 97 (1.0)	0.86	[0.05; 13.54]	0.914
Nodal status					
Interaction test	N.E.				
N0	3 / 190 (1.6)	0 / 200 (0.0)	7.37	[0.38; >99.99]	0.186
N1-N3	15 / 1216 (1.2)	7 / 1160 (0.6)	2.04	[0.84; 5.00]	0.117
Histological grade at time of surgery					
Interaction test	p = 0.947				
Grade 1	2 / 102 (2.0)	0 / 106 (0.0)	5.19	[0.25; >99.99]	0.286
Grade 2	10 / 842 (1.2)	4 / 768 (0.5)	2.28	[0.72; 7.24]	0.162
Grade 3	4 / 373 (1.1)	2 / 397 (0.5)	2.13	[0.39; 11.55]	0.381
Histological subtype					
Interaction test	p = 0.630				
Ductal	12 / 1025 (1.2)	4 / 1010 (0.4)	2.96	[0.96; 9.14]	0.060
Lobular	6 / 291 (2.1)	3 / 276 (1.1)	1.90	[0.48; 7.51]	0.362
Other	0 / 92 (0.0)	0 / 76 (0.0)	N.E.	N.E.	N.E.
Ki67 status from surgical specimen					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Type of NSAI					
Interaction test	p = 0.992				
Letrozole	10 / 907 (1.1)	4 / 895 (0.4)	2.47	[0.78; 7.84]	0.126
Anastrozole	8 / 502 (1.6)	3 / 467 (0.6)	2.48	[0.66; 9.29]	0.178
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.197				
Yes	15 / 1194 (1.3)	4 / 1146 (0.3)	3.60	[1.20; 10.81]	0.022
No	3 / 215 (1.4)	3 / 216 (1.4)	1.00	[0.21; 4.92]	0.995
Prior adjuvant chemotherapy					
Interaction test	p = 0.232				
Yes	10 / 694 (1.4)	2 / 673 (0.3)	4.85	[1.07; 22.05]	0.041
No	8 / 715 (1.1)	5 / 689 (0.7)	1.54	[0.51; 4.69]	0.446
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.947				
Yes	5 / 528 (0.9)	2 / 503 (0.4)	2.38	[0.46; 12.22]	0.298
No	13 / 881 (1.5)	5 / 859 (0.6)	2.54	[0.91; 7.08]	0.076

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior endocrine therapy					
Interaction test	p = 0.283				
Yes	14 / 957 (1.5)	4 / 940 (0.4)	3.44	[1.14; 10.41]	0.029
No	4 / 452 (0.9)	3 / 422 (0.7)	1.24	[0.28; 5.53]	0.773
Prior mastectomy					
Interaction test	p = 0.140				
Yes	9 / 857 (1.1)	6 / 847 (0.7)	1.48	[0.53; 4.15]	0.453
No	9 / 552 (1.6)	1 / 515 (0.2)	8.40	[1.07; 66.04]	0.043
Prior radiotherapy					
Interaction test	N.E.				
Yes	18 / 1253 (1.4)	5 / 1203 (0.4)	3.46	[1.29; 9.28]	0.014
No	0 / 156 (0.0)	2 / 159 (1.3)	0.20	[<0.01; 4.21]	0.303
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.21 SOC general disorders and administration site conditions: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
General disorders and administration site conditions					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.024				
NA/WE/O	585 / 899 (65.1)	366 / 856 (42.8)	1.52	[1.39; 1.67]	<.001
ROW	189 / 510 (37.1)	130 / 506 (25.7)	1.44	[1.20; 1.74]	<.001
Geographical region					
Interaction test	p = 0.209				
Europe	447 / 832 (53.7)	313 / 824 (38.0)	1.41	[1.27; 1.58]	<.001
North America/Australia	261 / 400 (65.3)	147 / 364 (40.4)	1.62	[1.40; 1.87]	<.001
Asia	34 / 102 (33.3)	18 / 101 (17.8)	1.87	[1.13; 3.09]	0.014
Latin America	32 / 75 (42.7)	18 / 73 (24.7)	1.73	[1.07; 2.79]	0.025
Age group 1 at randomization					
Interaction test	p = 0.543				
<45	44 / 60 (73.3)	23 / 52 (44.2)	1.66	[1.18; 2.33]	0.004
45 to 54	159 / 300 (53.0)	116 / 322 (36.0)	1.47	[1.23; 1.76]	<.001
55 to 64	343 / 651 (52.7)	215 / 642 (33.5)	1.57	[1.38; 1.79]	<.001
≥65	228 / 398 (57.3)	142 / 346 (41.0)	1.40	[1.20; 1.63]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.730				
<Median	344 / 633 (54.3)	231 / 632 (36.6)	1.49	[1.31; 1.68]	<.001
≥Median	430 / 776 (55.4)	265 / 730 (36.3)	1.53	[1.36; 1.71]	<.001
Race					
Interaction test	p = 0.454				
Asian	51 / 128 (39.8)	26 / 127 (20.5)	1.95	[1.30; 2.91]	0.001
Non-Asian	660 / 1203 (54.9)	433 / 1167 (37.1)	1.48	[1.35; 1.62]	<.001
BMI at screening					
Interaction test	p = 0.676				
≥25	508 / 935 (54.3)	340 / 935 (36.4)	1.49	[1.35; 1.66]	<.001
<25	259 / 460 (56.3)	150 / 410 (36.6)	1.54	[1.32; 1.79]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.378				
Group I/II	312 / 585 (53.3)	217 / 589 (36.8)	1.45	[1.27; 1.65]	<.001
Group III	461 / 823 (56.0)	279 / 772 (36.1)	1.55	[1.39; 1.73]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.682				
IA/IB/IIA	164 / 310 (52.9)	116 / 311 (37.3)	1.42	[1.19; 1.70]	<.001
IIB	148 / 275 (53.8)	101 / 278 (36.3)	1.48	[1.22; 1.79]	<.001
IIIA	269 / 482 (55.8)	170 / 450 (37.8)	1.48	[1.28; 1.70]	<.001
IIIB	51 / 100 (51.0)	27 / 82 (32.9)	1.55	[1.08; 2.23]	0.018
IIIC	141 / 241 (58.5)	82 / 240 (34.2)	1.71	[1.39; 2.10]	<.001
Tumor category					
Interaction test	p = 0.703				
T0	3 / 5 (60.0)	1 / 5 (20.0)	3.00	[0.45; 19.93]	0.255
T1-T3	710 / 1287 (55.2)	463 / 1258 (36.8)	1.50	[1.37; 1.64]	<.001
>T3	60 / 113 (53.1)	31 / 97 (32.0)	1.66	[1.18; 2.33]	0.003
Nodal status					
Interaction test	p = 0.516				
N0	103 / 190 (54.2)	66 / 200 (33.0)	1.64	[1.30; 2.08]	<.001
N1-N3	669 / 1216 (55.0)	430 / 1160 (37.1)	1.48	[1.36; 1.62]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.353				
Grade 1	54 / 102 (52.9)	34 / 106 (32.1)	1.65	[1.18; 2.30]	0.003
Grade 2	452 / 842 (53.7)	283 / 768 (36.8)	1.46	[1.30; 1.63]	<.001
Grade 3	224 / 373 (60.1)	147 / 397 (37.0)	1.62	[1.39; 1.89]	<.001
Histological subtype					
Interaction test	p = 0.121				
Ductal	560 / 1025 (54.6)	348 / 1010 (34.5)	1.59	[1.43; 1.76]	<.001
Lobular	166 / 291 (57.0)	112 / 276 (40.6)	1.41	[1.18; 1.67]	<.001
Other	48 / 92 (52.2)	36 / 76 (47.4)	1.10	[0.81; 1.50]	0.538
Ki67 status from surgical specimen					
Interaction test	p = 0.879				
Ki67≤20	337 / 660 (51.1)	216 / 629 (34.3)	1.49	[1.30; 1.70]	<.001
Ki67>20	262 / 489 (53.6)	186 / 516 (36.0)	1.49	[1.29; 1.71]	<.001
Type of NSAI					
Interaction test	p = 0.092				
Letrozole	499 / 907 (55.0)	307 / 895 (34.3)	1.60	[1.44; 1.79]	<.001
Anastrozole	275 / 502 (54.8)	189 / 467 (40.5)	1.35	[1.18; 1.55]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.202				
Yes	669 / 1194 (56.0)	418 / 1146 (36.5)	1.54	[1.40; 1.68]	<.001
No	105 / 215 (48.8)	78 / 216 (36.1)	1.35	[1.08; 1.69]	0.008
Prior adjuvant chemotherapy					
Interaction test	p = 0.733				
Yes	392 / 694 (56.5)	259 / 673 (38.5)	1.47	[1.31; 1.65]	<.001
No	382 / 715 (53.4)	237 / 689 (34.4)	1.55	[1.37; 1.76]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.179				
Yes	293 / 528 (55.5)	170 / 503 (33.8)	1.64	[1.42; 1.90]	<.001
No	481 / 881 (54.6)	326 / 859 (38.0)	1.44	[1.30; 1.60]	<.001
Prior endocrine therapy					
Interaction test	p = 0.171				
Yes	536 / 957 (56.0)	336 / 940 (35.7)	1.57	[1.41; 1.74]	<.001
No	238 / 452 (52.7)	160 / 422 (37.9)	1.39	[1.20; 1.61]	<.001
Prior mastectomy					
Interaction test	p = 0.462				
Yes	474 / 857 (55.3)	320 / 847 (37.8)	1.46	[1.32; 1.63]	<.001
No	300 / 552 (54.3)	176 / 515 (34.2)	1.59	[1.38; 1.83]	<.001
Prior radiotherapy					
Interaction test	p = 0.575				
Yes	694 / 1253 (55.4)	439 / 1203 (36.5)	1.52	[1.39; 1.66]	<.001
No	80 / 156 (51.3)	57 / 159 (35.8)	1.43	[1.11; 1.85]	0.007
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.22 PT fatigue: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Fatigue					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.390				
NA/WE/O	287 / 899 (31.9)	153 / 856 (17.9)	1.79	[1.50; 2.12]	<.001
ROW	48 / 510 (9.4)	29 / 506 (5.7)	1.64	[1.05; 2.56]	0.029
Geographical region					
Interaction test	p = 0.126				
Europe	137 / 832 (16.5)	89 / 824 (10.8)	1.52	[1.19; 1.96]	<.001
North America/Australia	176 / 400 (44.0)	82 / 364 (22.5)	1.95	[1.57; 2.43]	<.001
Asia	10 / 102 (9.8)	6 / 101 (5.9)	1.65	[0.62; 4.37]	0.313
Latin America	12 / 75 (16.0)	5 / 73 (6.8)	2.34	[0.87; 6.30]	0.094
Age group 1 at randomization					
Interaction test	p = 0.606				
<45	21 / 60 (35.0)	15 / 52 (28.8)	1.21	[0.70; 2.10]	0.490
45 to 54	63 / 300 (21.0)	41 / 322 (12.7)	1.65	[1.15; 2.37]	0.007
55 to 64	145 / 651 (22.3)	72 / 642 (11.2)	1.99	[1.53; 2.58]	<.001
≥65	106 / 398 (26.6)	54 / 346 (15.6)	1.71	[1.27; 2.29]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.543				
<Median	150 / 633 (23.7)	89 / 632 (14.1)	1.68	[1.33; 2.13]	<.001
≥Median	185 / 776 (23.8)	93 / 730 (12.7)	1.87	[1.49; 2.35]	<.001
Race					
Interaction test	p = 0.507				
Asian	22 / 128 (17.2)	9 / 127 (7.1)	2.43	[1.16; 5.06]	0.018
Non-Asian	306 / 1203 (25.4)	167 / 1167 (14.3)	1.78	[1.50; 2.11]	<.001
BMI at screening					
Interaction test	p = 0.448				
≥25	221 / 935 (23.6)	129 / 935 (13.8)	1.71	[1.41; 2.09]	<.001
<25	111 / 460 (24.1)	50 / 410 (12.2)	1.98	[1.46; 2.69]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.834				
Group I/II	137 / 585 (23.4)	76 / 589 (12.9)	1.81	[1.41; 2.34]	<.001
Group III	197 / 823 (23.9)	106 / 772 (13.7)	1.74	[1.41; 2.16]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.953				
IA/IB/IIA	66 / 310 (21.3)	32 / 311 (10.3)	2.07	[1.40; 3.06]	<.001
IIB	71 / 275 (25.8)	44 / 278 (15.8)	1.63	[1.16; 2.29]	0.004
IIIA	115 / 482 (23.9)	61 / 450 (13.6)	1.76	[1.33; 2.33]	<.001
IIIB	20 / 100 (20.0)	10 / 82 (12.2)	1.64	[0.81; 3.30]	0.166
IIIC	62 / 241 (25.7)	35 / 240 (14.6)	1.76	[1.21; 2.56]	0.003
Tumor category					
Interaction test	p = 0.844				
T0	2 / 5 (40.0)	1 / 5 (20.0)	2.00	[0.26; 15.62]	0.509
T1-T3	309 / 1287 (24.0)	168 / 1258 (13.4)	1.80	[1.52; 2.13]	<.001
>T3	23 / 113 (20.4)	13 / 97 (13.4)	1.52	[0.81; 2.83]	0.189
Nodal status					
Interaction test	p = 0.831				
N0	49 / 190 (25.8)	28 / 200 (14.0)	1.84	[1.21; 2.80]	0.004
N1-N3	286 / 1216 (23.5)	154 / 1160 (13.3)	1.77	[1.48; 2.12]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.079				
Grade 1	26 / 102 (25.5)	6 / 106 (5.7)	4.50	[1.93; 10.48]	<.001
Grade 2	192 / 842 (22.8)	101 / 768 (13.2)	1.73	[1.39; 2.16]	<.001
Grade 3	97 / 373 (26.0)	64 / 397 (16.1)	1.61	[1.22; 2.14]	<.001
Histological subtype					
Interaction test	p = 0.253				
Ductal	249 / 1025 (24.3)	130 / 1010 (12.9)	1.89	[1.56; 2.29]	<.001
Lobular	66 / 291 (22.7)	37 / 276 (13.4)	1.69	[1.17; 2.44]	0.005
Other	20 / 92 (21.7)	15 / 76 (19.7)	1.10	[0.61; 2.00]	0.751
Ki67 status from surgical specimen					
Interaction test	p = 0.975				
Ki67≤20	121 / 660 (18.3)	67 / 629 (10.7)	1.72	[1.30; 2.27]	<.001
Ki67>20	105 / 489 (21.5)	65 / 516 (12.6)	1.70	[1.28; 2.26]	<.001
Type of NSAI					
Interaction test	p = 0.378				
Letrozole	197 / 907 (21.7)	115 / 895 (12.8)	1.69	[1.37; 2.09]	<.001
Anastrozole	138 / 502 (27.5)	67 / 467 (14.3)	1.92	[1.47; 2.49]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.948				
Yes	289 / 1194 (24.2)	156 / 1146 (13.6)	1.78	[1.49; 2.12]	<.001
No	46 / 215 (21.4)	26 / 216 (12.0)	1.78	[1.14; 2.77]	0.011
Prior adjuvant chemotherapy					
Interaction test	p = 0.875				
Yes	172 / 694 (24.8)	93 / 673 (13.8)	1.79	[1.43; 2.25]	<.001
No	163 / 715 (22.8)	89 / 689 (12.9)	1.76	[1.39; 2.24]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.612				
Yes	125 / 528 (23.7)	63 / 503 (12.5)	1.89	[1.43; 2.49]	<.001
No	210 / 881 (23.8)	119 / 859 (13.9)	1.72	[1.40; 2.11]	<.001
Prior endocrine therapy					
Interaction test	p = 0.115				
Yes	231 / 957 (24.1)	116 / 940 (12.3)	1.96	[1.59; 2.40]	<.001
No	104 / 452 (23.0)	66 / 422 (15.6)	1.47	[1.11; 1.94]	0.007
Prior mastectomy					
Interaction test	p = 0.268				
Yes	206 / 857 (24.0)	123 / 847 (14.5)	1.66	[1.35; 2.03]	<.001
No	129 / 552 (23.4)	59 / 515 (11.5)	2.04	[1.54; 2.71]	<.001
Prior radiotherapy					
Interaction test	p = 0.703				
Yes	305 / 1253 (24.3)	167 / 1203 (13.9)	1.75	[1.48; 2.08]	<.001
No	30 / 156 (19.2)	15 / 159 (9.4)	2.04	[1.14; 3.64]	0.016
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.23 PT asthenia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Asthenia					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.261				
NA/WE/O	171 / 899 (19.0)	104 / 856 (12.1)	1.57	[1.25; 1.96]	<.001
ROW	70 / 510 (13.7)	55 / 506 (10.9)	1.26	[0.91; 1.76]	0.167
Geographical region					
Interaction test	p = 0.709				
Europe	220 / 832 (26.4)	148 / 824 (18.0)	1.47	[1.22; 1.77]	<.001
North America/Australia	10 / 400 (2.5)	5 / 364 (1.4)	1.82	[0.63; 5.27]	0.270
Asia	5 / 102 (4.9)	1 / 101 (1.0)	4.95	[0.59; 41.63]	0.141
Latin America	6 / 75 (8.0)	5 / 73 (6.8)	1.17	[0.37; 3.66]	0.790
Age group 1 at randomization					
Interaction test	p = 0.305				
<45	7 / 60 (11.7)	1 / 52 (1.9)	6.07	[0.77; 47.70]	0.087
45 to 54	56 / 300 (18.7)	35 / 322 (10.9)	1.72	[1.16; 2.54]	0.007
55 to 64	107 / 651 (16.4)	72 / 642 (11.2)	1.47	[1.11; 1.94]	0.007
≥65	71 / 398 (17.8)	51 / 346 (14.7)	1.21	[0.87; 1.68]	0.257
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.946				
<Median	98 / 633 (15.5)	66 / 632 (10.4)	1.48	[1.11; 1.99]	0.008
≥Median	143 / 776 (18.4)	93 / 730 (12.7)	1.45	[1.14; 1.84]	0.003
Race					
Interaction test	p = 0.246				
Asian	5 / 128 (3.9)	1 / 127 (0.8)	4.96	[0.59; 41.87]	0.141
Non-Asian	185 / 1203 (15.4)	133 / 1167 (11.4)	1.35	[1.10; 1.66]	0.005
BMI at screening					
Interaction test	p = 0.399				
≥25	155 / 935 (16.6)	113 / 935 (12.1)	1.37	[1.10; 1.72]	0.006
<25	84 / 460 (18.3)	46 / 410 (11.2)	1.63	[1.17; 2.27]	0.004
AJCC Anatomic Stage Group					
Interaction test	p = 0.425				
Group I/II	96 / 585 (16.4)	72 / 589 (12.2)	1.34	[1.01; 1.78]	0.042
Group III	145 / 823 (17.6)	87 / 772 (11.3)	1.56	[1.22; 2.00]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.859				
IA/IB/IIA	59 / 310 (19.0)	43 / 311 (13.8)	1.38	[0.96; 1.97]	0.082
IIB	37 / 275 (13.5)	29 / 278 (10.4)	1.29	[0.82; 2.04]	0.275
IIIA	85 / 482 (17.6)	54 / 450 (12.0)	1.47	[1.07; 2.02]	0.017
IIIB	19 / 100 (19.0)	11 / 82 (13.4)	1.42	[0.72; 2.80]	0.318
IIIC	41 / 241 (17.0)	22 / 240 (9.2)	1.86	[1.14; 3.02]	0.013
Tumor category					
Interaction test	p = 0.438				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	217 / 1287 (16.9)	147 / 1258 (11.7)	1.44	[1.19; 1.75]	<.001
>T3	24 / 113 (21.2)	11 / 97 (11.3)	1.87	[0.97; 3.62]	0.062
Nodal status					
Interaction test	p = 0.489				
N0	30 / 190 (15.8)	18 / 200 (9.0)	1.75	[1.01; 3.04]	0.045
N1-N3	209 / 1216 (17.2)	141 / 1160 (12.2)	1.41	[1.16; 1.72]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.228				
Grade 1	16 / 102 (15.7)	18 / 106 (17.0)	0.92	[0.50; 1.71]	0.801
Grade 2	143 / 842 (17.0)	85 / 768 (11.1)	1.53	[1.20; 1.97]	<.001
Grade 3	70 / 373 (18.8)	43 / 397 (10.8)	1.73	[1.22; 2.46]	0.002
Histological subtype					
Interaction test	p = 0.356				
Ductal	175 / 1025 (17.1)	113 / 1010 (11.2)	1.53	[1.22; 1.90]	<.001
Lobular	52 / 291 (17.9)	33 / 276 (12.0)	1.49	[1.00; 2.24]	0.051
Other	14 / 92 (15.2)	13 / 76 (17.1)	0.89	[0.45; 1.78]	0.740
Ki67 status from surgical specimen					
Interaction test	p = 0.304				
Ki67≤20	136 / 660 (20.6)	79 / 629 (12.6)	1.64	[1.27; 2.12]	<.001
Ki67>20	88 / 489 (18.0)	69 / 516 (13.4)	1.35	[1.01; 1.80]	0.045
Type of NSAI					
Interaction test	p = 0.008				
Letrozole	176 / 907 (19.4)	100 / 895 (11.2)	1.74	[1.38; 2.18]	<.001
Anastrozole	65 / 502 (12.9)	59 / 467 (12.6)	1.02	[0.74; 1.42]	0.884
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.214				
Yes	210 / 1194 (17.6)	131 / 1146 (11.4)	1.54	[1.26; 1.88]	<.001
No	31 / 215 (14.4)	28 / 216 (13.0)	1.11	[0.69; 1.79]	0.660
Prior adjuvant chemotherapy					
Interaction test	p = 0.916				
Yes	121 / 694 (17.4)	81 / 673 (12.0)	1.45	[1.12; 1.88]	0.005
No	120 / 715 (16.8)	78 / 689 (11.3)	1.48	[1.14; 1.93]	0.004

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.327				
Yes	94 / 528 (17.8)	54 / 503 (10.7)	1.66	[1.21; 2.26]	0.001
No	147 / 881 (16.7)	105 / 859 (12.2)	1.37	[1.08; 1.72]	0.009
Prior endocrine therapy					
Interaction test	p = 0.121				
Yes	181 / 957 (18.9)	111 / 940 (11.8)	1.60	[1.29; 1.99]	<.001
No	60 / 452 (13.3)	48 / 422 (11.4)	1.17	[0.82; 1.67]	0.395
Prior mastectomy					
Interaction test	p = 0.864				
Yes	140 / 857 (16.3)	93 / 847 (11.0)	1.49	[1.17; 1.90]	0.001
No	101 / 552 (18.3)	66 / 515 (12.8)	1.43	[1.07; 1.90]	0.015
Prior radiotherapy					
Interaction test	p = 0.748				
Yes	206 / 1253 (16.4)	136 / 1203 (11.3)	1.45	[1.19; 1.78]	<.001
No	35 / 156 (22.4)	23 / 159 (14.5)	1.55	[0.96; 2.50]	0.072
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.24 PT pyrexia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Pyrexia					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.445				
NA/WE/O	91 / 899 (10.1)	51 / 856 (6.0)	1.70	[1.22; 2.36]	0.002
ROW	42 / 510 (8.2)	19 / 506 (3.8)	2.19	[1.29; 3.72]	0.004
Geographical region					
Interaction test	p = 0.915				
Europe	75 / 832 (9.0)	41 / 824 (5.0)	1.81	[1.25; 2.62]	0.002
North America/Australia	41 / 400 (10.3)	20 / 364 (5.5)	1.87	[1.11; 3.12]	0.018
Asia	13 / 102 (12.7)	8 / 101 (7.9)	1.61	[0.70; 3.71]	0.265
Latin America	4 / 75 (5.3)	1 / 73 (1.4)	3.89	[0.45; 34.01]	0.219
Age group 1 at randomization					
Interaction test	p = 0.157				
<45	6 / 60 (10.0)	2 / 52 (3.8)	2.60	[0.55; 12.33]	0.229
45 to 54	34 / 300 (11.3)	12 / 322 (3.7)	3.04	[1.61; 5.76]	<.001
55 to 64	58 / 651 (8.9)	42 / 642 (6.5)	1.36	[0.93; 2.00]	0.113
≥65	35 / 398 (8.8)	14 / 346 (4.0)	2.17	[1.19; 3.97]	0.012
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.940				
<Median	60 / 633 (9.5)	33 / 632 (5.2)	1.82	[1.20; 2.74]	0.004
≥Median	73 / 776 (9.4)	37 / 730 (5.1)	1.86	[1.27; 2.72]	0.002
Race					
Interaction test	p = 0.621				
Asian	18 / 128 (14.1)	8 / 127 (6.3)	2.23	[1.01; 4.95]	0.048
Non-Asian	110 / 1203 (9.1)	58 / 1167 (5.0)	1.84	[1.35; 2.50]	<.001
BMI at screening					
Interaction test	p = 0.101				
≥25	86 / 935 (9.2)	39 / 935 (4.2)	2.21	[1.53; 3.18]	<.001
<25	47 / 460 (10.2)	31 / 410 (7.6)	1.35	[0.88; 2.08]	0.173
AJCC Anatomic Stage Group					
Interaction test	p = 0.178				
Group I/II	48 / 585 (8.2)	33 / 589 (5.6)	1.46	[0.95; 2.25]	0.081
Group III	85 / 823 (10.3)	37 / 772 (4.8)	2.15	[1.48; 3.13]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.058				
IA/IB/IIA	22 / 310 (7.1)	24 / 311 (7.7)	0.92	[0.53; 1.60]	0.768
IIB	26 / 275 (9.5)	9 / 278 (3.2)	2.92	[1.39; 6.12]	0.005
IIIA	48 / 482 (10.0)	19 / 450 (4.2)	2.36	[1.41; 3.95]	0.001
IIIB	9 / 100 (9.0)	2 / 82 (2.4)	3.69	[0.82; 16.61]	0.089
IIIC	28 / 241 (11.6)	16 / 240 (6.7)	1.74	[0.97; 3.14]	0.064
Tumor category					
Interaction test	p = 0.149				
T0	1 / 5 (20.0)	0 / 5 (0.0)	3.00	[0.15; 59.89]	0.472
T1-T3	120 / 1287 (9.3)	68 / 1258 (5.4)	1.72	[1.29; 2.30]	<.001
>T3	12 / 113 (10.6)	2 / 97 (2.1)	5.15	[1.18; 22.45]	0.029
Nodal status					
Interaction test	p = 0.946				
N0	12 / 190 (6.3)	7 / 200 (3.5)	1.80	[0.73; 4.49]	0.204
N1-N3	121 / 1216 (10.0)	63 / 1160 (5.4)	1.83	[1.37; 2.46]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.052				
Grade 1	7 / 102 (6.9)	10 / 106 (9.4)	0.73	[0.29; 1.84]	0.501
Grade 2	76 / 842 (9.0)	36 / 768 (4.7)	1.93	[1.31; 2.83]	<.001
Grade 3	44 / 373 (11.8)	17 / 397 (4.3)	2.75	[1.60; 4.73]	<.001
Histological subtype					
Interaction test	p = 0.078				
Ductal	102 / 1025 (10.0)	45 / 1010 (4.5)	2.23	[1.59; 3.14]	<.001
Lobular	23 / 291 (7.9)	21 / 276 (7.6)	1.04	[0.59; 1.83]	0.896
Other	8 / 92 (8.7)	4 / 76 (5.3)	1.65	[0.52; 5.28]	0.397
Ki67 status from surgical specimen					
Interaction test	p = 0.991				
Ki67≤20	62 / 660 (9.4)	32 / 629 (5.1)	1.85	[1.22; 2.79]	0.004
Ki67>20	44 / 489 (9.0)	25 / 516 (4.8)	1.86	[1.15; 2.99]	0.011
Type of NSAI					
Interaction test	p = 0.843				
Letrozole	82 / 907 (9.0)	45 / 895 (5.0)	1.80	[1.26; 2.56]	0.001
Anastrozole	51 / 502 (10.2)	25 / 467 (5.4)	1.90	[1.20; 3.01]	0.007
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.042				
Yes	119 / 1194 (10.0)	55 / 1146 (4.8)	2.08	[1.52; 2.83]	<.001
No	14 / 215 (6.5)	15 / 216 (6.9)	0.94	[0.46; 1.89]	0.858
Prior adjuvant chemotherapy					
Interaction test	p = 0.476				
Yes	71 / 694 (10.2)	34 / 673 (5.1)	2.03	[1.36; 3.01]	<.001
No	62 / 715 (8.7)	36 / 689 (5.2)	1.66	[1.12; 2.47]	0.012

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.474				
Yes	51 / 528 (9.7)	23 / 503 (4.6)	2.11	[1.31; 3.40]	0.002
No	82 / 881 (9.3)	47 / 859 (5.5)	1.70	[1.20; 2.40]	0.003
Prior endocrine therapy					
Interaction test	p = 0.404				
Yes	92 / 957 (9.6)	53 / 940 (5.6)	1.71	[1.23; 2.36]	0.001
No	41 / 452 (9.1)	17 / 422 (4.0)	2.25	[1.30; 3.90]	0.004
Prior mastectomy					
Interaction test	p = 0.732				
Yes	83 / 857 (9.7)	43 / 847 (5.1)	1.91	[1.34; 2.72]	<.001
No	50 / 552 (9.1)	27 / 515 (5.2)	1.73	[1.10; 2.72]	0.018
Prior radiotherapy					
Interaction test	p = 0.171				
Yes	124 / 1253 (9.9)	61 / 1203 (5.1)	1.95	[1.45; 2.62]	<.001
No	9 / 156 (5.8)	9 / 159 (5.7)	1.02	[0.42; 2.50]	0.967
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.25 PT oedema peripheral: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Oedema peripheral					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.669				
NA/WE/O	74 / 899 (8.2)	40 / 856 (4.7)	1.76	[1.21; 2.56]	0.003
ROW	15 / 510 (2.9)	10 / 506 (2.0)	1.49	[0.67; 3.28]	0.324
Geographical region					
Interaction test	p = 0.729				
Europe	45 / 832 (5.4)	25 / 824 (3.0)	1.78	[1.10; 2.88]	0.018
North America/Australia	36 / 400 (9.0)	20 / 364 (5.5)	1.64	[0.97; 2.78]	0.067
Asia	1 / 102 (1.0)	2 / 101 (2.0)	0.50	[0.05; 5.37]	0.563
Latin America	7 / 75 (9.3)	3 / 73 (4.1)	2.27	[0.61; 8.45]	0.221
Age group 1 at randomization					
Interaction test	p = 0.496				
<45	6 / 60 (10.0)	1 / 52 (1.9)	5.20	[0.65; 41.80]	0.121
45 to 54	16 / 300 (5.3)	14 / 322 (4.3)	1.23	[0.61; 2.47]	0.567
55 to 64	33 / 651 (5.1)	16 / 642 (2.5)	2.03	[1.13; 3.66]	0.018
≥65	34 / 398 (8.5)	19 / 346 (5.5)	1.56	[0.90; 2.68]	0.110
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.753				
<Median	39 / 633 (6.2)	24 / 632 (3.8)	1.62	[0.99; 2.67]	0.056
≥Median	50 / 776 (6.4)	26 / 730 (3.6)	1.81	[1.14; 2.87]	0.012
Race					
Interaction test	p = 0.151				
Asian	1 / 128 (0.8)	3 / 127 (2.4)	0.33	[0.03; 3.14]	0.335
Non-Asian	78 / 1203 (6.5)	44 / 1167 (3.8)	1.72	[1.20; 2.47]	0.003
BMI at screening					
Interaction test	p = 0.461				
≥25	64 / 935 (6.8)	34 / 935 (3.6)	1.88	[1.25; 2.82]	0.002
<25	24 / 460 (5.2)	15 / 410 (3.7)	1.43	[0.76; 2.68]	0.270
AJCC Anatomic Stage Group					
Interaction test	p = 0.251				
Group I/II	41 / 585 (7.0)	19 / 589 (3.2)	2.17	[1.28; 3.70]	0.004
Group III	48 / 823 (5.8)	31 / 772 (4.0)	1.45	[0.93; 2.26]	0.097

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.293				
IA/IB/IIA	22 / 310 (7.1)	10 / 311 (3.2)	2.21	[1.06; 4.58]	0.034
IIB	19 / 275 (6.9)	9 / 278 (3.2)	2.13	[0.98; 4.63]	0.055
IIIA	23 / 482 (4.8)	21 / 450 (4.7)	1.02	[0.57; 1.82]	0.940
IIIB	5 / 100 (5.0)	1 / 82 (1.2)	4.10	[0.49; 34.40]	0.194
IIIC	20 / 241 (8.3)	9 / 240 (3.8)	2.21	[1.03; 4.76]	0.042
Tumor category					
Interaction test	p = 0.397				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	84 / 1287 (6.5)	49 / 1258 (3.9)	1.68	[1.19; 2.36]	0.003
>T3	5 / 113 (4.4)	1 / 97 (1.0)	4.29	[0.51; 36.11]	0.180
Nodal status					
Interaction test	p = 0.340				
N0	11 / 190 (5.8)	4 / 200 (2.0)	2.89	[0.94; 8.93]	0.065
N1-N3	78 / 1216 (6.4)	46 / 1160 (4.0)	1.62	[1.13; 2.31]	0.008
Histological grade at time of surgery					
Interaction test	p = 0.579				
Grade 1	7 / 102 (6.9)	5 / 106 (4.7)	1.45	[0.48; 4.44]	0.510
Grade 2	45 / 842 (5.3)	27 / 768 (3.5)	1.52	[0.95; 2.42]	0.079
Grade 3	33 / 373 (8.8)	16 / 397 (4.0)	2.20	[1.23; 3.92]	0.008
Histological subtype					
Interaction test	p = 0.779				
Ductal	65 / 1025 (6.3)	36 / 1010 (3.6)	1.78	[1.20; 2.65]	0.005
Lobular	17 / 291 (5.8)	9 / 276 (3.3)	1.79	[0.81; 3.95]	0.149
Other	7 / 92 (7.6)	5 / 76 (6.6)	1.16	[0.38; 3.50]	0.797
Ki67 status from surgical specimen					
Interaction test	p = 0.515				
Ki67≤20	37 / 660 (5.6)	18 / 629 (2.9)	1.96	[1.13; 3.40]	0.017
Ki67>20	30 / 489 (6.1)	21 / 516 (4.1)	1.51	[0.88; 2.60]	0.139
Type of NSAI					
Interaction test	p = 0.895				
Letrozole	55 / 907 (6.1)	31 / 895 (3.5)	1.75	[1.14; 2.69]	0.011
Anastrozole	34 / 502 (6.8)	19 / 467 (4.1)	1.66	[0.96; 2.88]	0.068
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.516				
Yes	68 / 1194 (5.7)	40 / 1146 (3.5)	1.63	[1.11; 2.39]	0.012
No	21 / 215 (9.8)	10 / 216 (4.6)	2.11	[1.02; 4.37]	0.045
Prior adjuvant chemotherapy					
Interaction test	p = 0.783				
Yes	44 / 694 (6.3)	26 / 673 (3.9)	1.64	[1.02; 2.63]	0.040
No	45 / 715 (6.3)	24 / 689 (3.5)	1.81	[1.11; 2.93]	0.017

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.561				
Yes	25 / 528 (4.7)	16 / 503 (3.2)	1.49	[0.80; 2.75]	0.205
No	64 / 881 (7.3)	34 / 859 (4.0)	1.84	[1.22; 2.75]	0.003
Prior endocrine therapy					
Interaction test	p = 0.912				
Yes	57 / 957 (6.0)	33 / 940 (3.5)	1.70	[1.12; 2.58]	0.013
No	32 / 452 (7.1)	17 / 422 (4.0)	1.76	[0.99; 3.12]	0.054
Prior mastectomy					
Interaction test	p = 0.328				
Yes	52 / 857 (6.1)	34 / 847 (4.0)	1.51	[0.99; 2.30]	0.055
No	37 / 552 (6.7)	16 / 515 (3.1)	2.16	[1.22; 3.83]	0.009
Prior radiotherapy					
Interaction test	p = 0.477				
Yes	79 / 1253 (6.3)	46 / 1203 (3.8)	1.65	[1.16; 2.35]	0.006
No	10 / 156 (6.4)	4 / 159 (2.5)	2.55	[0.82; 7.95]	0.107
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.26 PT influenza like illness: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Influenza like illness					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.992				
NA/WE/O	38 / 899 (4.2)	22 / 856 (2.6)	1.64	[0.98; 2.76]	0.059
ROW	5 / 510 (1.0)	3 / 506 (0.6)	1.65	[0.40; 6.88]	0.489
Geographical region					
Interaction test	p = 0.883				
Europe	13 / 832 (1.6)	9 / 824 (1.1)	1.43	[0.61; 3.33]	0.406
North America/Australia	28 / 400 (7.0)	15 / 364 (4.1)	1.70	[0.92; 3.13]	0.089
Asia	1 / 102 (1.0)	1 / 101 (1.0)	0.99	[0.06; 15.62]	0.994
Latin America	1 / 75 (1.3)	0 / 73 (0.0)	2.92	[0.12; 70.56]	0.509
Age group 1 at randomization					
Interaction test	p = 0.223				
<45	3 / 60 (5.0)	4 / 52 (7.7)	0.65	[0.15; 2.77]	0.560
45 to 54	13 / 300 (4.3)	4 / 322 (1.2)	3.49	[1.15; 10.58]	0.027
55 to 64	19 / 651 (2.9)	10 / 642 (1.6)	1.87	[0.88; 4.00]	0.104
≥65	8 / 398 (2.0)	7 / 346 (2.0)	0.99	[0.36; 2.71]	0.990
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.571				
<Median	23 / 633 (3.6)	12 / 632 (1.9)	1.91	[0.96; 3.81]	0.065
≥Median	20 / 776 (2.6)	13 / 730 (1.8)	1.45	[0.73; 2.89]	0.294
Race					
Interaction test	p = 0.890				
Asian	2 / 128 (1.6)	1 / 127 (0.8)	1.98	[0.18; 21.61]	0.574
Non-Asian	41 / 1203 (3.4)	24 / 1167 (2.1)	1.66	[1.01; 2.72]	0.046
BMI at screening					
Interaction test	p = 0.014				
≥25	37 / 935 (4.0)	14 / 935 (1.5)	2.64	[1.44; 4.86]	0.002
<25	6 / 460 (1.3)	9 / 410 (2.2)	0.59	[0.21; 1.66]	0.319
AJCC Anatomic Stage Group					
Interaction test	p = 0.018				
Group I/II	14 / 585 (2.4)	16 / 589 (2.7)	0.88	[0.43; 1.79]	0.726
Group III	29 / 823 (3.5)	9 / 772 (1.2)	3.02	[1.44; 6.34]	0.003

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.168				
IA/IB/IIA	7 / 310 (2.3)	10 / 311 (3.2)	0.70	[0.27; 1.82]	0.467
IIB	7 / 275 (2.5)	6 / 278 (2.2)	1.18	[0.40; 3.46]	0.764
IIIA	16 / 482 (3.3)	5 / 450 (1.1)	2.99	[1.10; 8.09]	0.031
IIIB	4 / 100 (4.0)	2 / 82 (2.4)	1.64	[0.31; 8.73]	0.562
IIIC	9 / 241 (3.7)	2 / 240 (0.8)	4.48	[0.98; 20.52]	0.053
Tumor category					
Interaction test	p = 0.944				
T0	1 / 5 (20.0)	0 / 5 (0.0)	3.00	[0.15; 59.89]	0.472
T1-T3	38 / 1287 (3.0)	23 / 1258 (1.8)	1.61	[0.97; 2.69]	0.066
>T3	4 / 113 (3.5)	2 / 97 (2.1)	1.72	[0.32; 9.17]	0.527
Nodal status					
Interaction test	p = 0.426				
N0	5 / 190 (2.6)	5 / 200 (2.5)	1.05	[0.31; 3.58]	0.935
N1-N3	38 / 1216 (3.1)	20 / 1160 (1.7)	1.81	[1.06; 3.10]	0.029
Histological grade at time of surgery					
Interaction test	p = 0.318				
Grade 1	1 / 102 (1.0)	1 / 106 (0.9)	1.04	[0.07; 16.39]	0.978
Grade 2	28 / 842 (3.3)	19 / 768 (2.5)	1.34	[0.76; 2.39]	0.313
Grade 3	13 / 373 (3.5)	4 / 397 (1.0)	3.46	[1.14; 10.51]	0.029
Histological subtype					
Interaction test	p = 0.806				
Ductal	33 / 1025 (3.2)	20 / 1010 (2.0)	1.63	[0.94; 2.81]	0.082
Lobular	9 / 291 (3.1)	4 / 276 (1.4)	2.13	[0.66; 6.85]	0.203
Other	1 / 92 (1.1)	1 / 76 (1.3)	0.83	[0.05; 12.99]	0.892
Ki67 status from surgical specimen					
Interaction test	p = 0.166				
Ki67≤20	17 / 660 (2.6)	8 / 629 (1.3)	2.03	[0.88; 4.66]	0.097
Ki67>20	9 / 489 (1.8)	11 / 516 (2.1)	0.86	[0.36; 2.07]	0.741
Type of NSAI					
Interaction test	p = 0.209				
Letrozole	22 / 907 (2.4)	17 / 895 (1.9)	1.28	[0.68; 2.39]	0.444
Anastrozole	21 / 502 (4.2)	8 / 467 (1.7)	2.44	[1.09; 5.46]	0.030
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.310				
Yes	36 / 1194 (3.0)	23 / 1146 (2.0)	1.50	[0.90; 2.52]	0.123
No	7 / 215 (3.3)	2 / 216 (0.9)	3.52	[0.74; 16.73]	0.114
Prior adjuvant chemotherapy					
Interaction test	p = 0.230				
Yes	21 / 694 (3.0)	16 / 673 (2.4)	1.27	[0.67; 2.42]	0.461
No	22 / 715 (3.1)	9 / 689 (1.3)	2.36	[1.09; 5.08]	0.029

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.888				
Yes	15 / 528 (2.8)	9 / 503 (1.8)	1.59	[0.70; 3.60]	0.268
No	28 / 881 (3.2)	16 / 859 (1.9)	1.71	[0.93; 3.13]	0.084
Prior endocrine therapy					
Interaction test	p = 0.179				
Yes	32 / 957 (3.3)	15 / 940 (1.6)	2.10	[1.14; 3.84]	0.017
No	11 / 452 (2.4)	10 / 422 (2.4)	1.03	[0.44; 2.39]	0.951
Prior mastectomy					
Interaction test	p = 0.777				
Yes	29 / 857 (3.4)	18 / 847 (2.1)	1.59	[0.89; 2.85]	0.116
No	14 / 552 (2.5)	7 / 515 (1.4)	1.87	[0.76; 4.59]	0.174
Prior radiotherapy					
Interaction test	p = 0.275				
Yes	40 / 1253 (3.2)	21 / 1203 (1.7)	1.83	[1.08; 3.08]	0.023
No	3 / 156 (1.9)	4 / 159 (2.5)	0.76	[0.17; 3.36]	0.722
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.27 PT pain: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Pain					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.535				
NA/WE/O	36 / 899 (4.0)	17 / 856 (2.0)	2.02	[1.14; 3.56]	0.016
ROW	7 / 510 (1.4)	2 / 506 (0.4)	3.47	[0.72; 16.64]	0.119
Geographical region					
Interaction test	p = 0.419				
Europe	18 / 832 (2.2)	11 / 824 (1.3)	1.62	[0.77; 3.41]	0.203
North America/Australia	22 / 400 (5.5)	8 / 364 (2.2)	2.50	[1.13; 5.55]	0.024
Asia	1 / 102 (1.0)	0 / 101 (0.0)	2.97	[0.12; 72.08]	0.503
Latin America	2 / 75 (2.7)	0 / 73 (0.0)	4.87	[0.24; 99.70]	0.304
Age group 1 at randomization					
Interaction test	p = 0.773				
<45	2 / 60 (3.3)	0 / 52 (0.0)	4.34	[0.21; 88.48]	0.339
45 to 54	11 / 300 (3.7)	6 / 322 (1.9)	1.97	[0.74; 5.25]	0.177
55 to 64	23 / 651 (3.5)	9 / 642 (1.4)	2.52	[1.18; 5.40]	0.018
≥65	7 / 398 (1.8)	4 / 346 (1.2)	1.52	[0.45; 5.15]	0.500
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.993				
<Median	22 / 633 (3.5)	10 / 632 (1.6)	2.20	[1.05; 4.60]	0.037
≥Median	21 / 776 (2.7)	9 / 730 (1.2)	2.20	[1.01; 4.76]	0.047
Race					
Interaction test	N.E.				
Asian	2 / 128 (1.6)	0 / 127 (0.0)	4.96	[0.24; >99.99]	0.300
Non-Asian	37 / 1203 (3.1)	19 / 1167 (1.6)	1.89	[1.09; 3.27]	0.023
BMI at screening					
Interaction test	p = 0.728				
≥25	28 / 935 (3.0)	12 / 935 (1.3)	2.33	[1.19; 4.56]	0.013
<25	15 / 460 (3.3)	7 / 410 (1.7)	1.91	[0.79; 4.64]	0.153
AJCC Anatomic Stage Group					
Interaction test	p = 0.999				
Group I/II	13 / 585 (2.2)	6 / 589 (1.0)	2.18	[0.83; 5.70]	0.111
Group III	30 / 823 (3.6)	13 / 772 (1.7)	2.16	[1.14; 4.12]	0.019

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.664				
IA/IB/IIA	7 / 310 (2.3)	4 / 311 (1.3)	1.76	[0.52; 5.94]	0.365
IIB	6 / 275 (2.2)	2 / 278 (0.7)	3.03	[0.62; 14.90]	0.172
IIIA	14 / 482 (2.9)	9 / 450 (2.0)	1.45	[0.63; 3.32]	0.377
IIIB	3 / 100 (3.0)	1 / 82 (1.2)	2.46	[0.26; 23.21]	0.432
IIIC	13 / 241 (5.4)	3 / 240 (1.3)	4.32	[1.25; 14.95]	0.021
Tumor category					
Interaction test	p = 0.853				
T0	2 / 5 (40.0)	0 / 5 (0.0)	5.00	[0.30; 83.69]	0.263
T1-T3	38 / 1287 (3.0)	18 / 1258 (1.4)	2.06	[1.18; 3.60]	0.011
>T3	3 / 113 (2.7)	1 / 97 (1.0)	2.58	[0.27; 24.36]	0.409
Nodal status					
Interaction test	p = 0.742				
N0	5 / 190 (2.6)	3 / 200 (1.5)	1.75	[0.43; 7.24]	0.437
N1-N3	38 / 1216 (3.1)	16 / 1160 (1.4)	2.27	[1.27; 4.04]	0.006
Histological grade at time of surgery					
Interaction test	p = 0.326				
Grade 1	3 / 102 (2.9)	3 / 106 (2.8)	1.04	[0.21; 5.03]	0.962
Grade 2	22 / 842 (2.6)	11 / 768 (1.4)	1.82	[0.89; 3.74]	0.100
Grade 3	15 / 373 (4.0)	4 / 397 (1.0)	3.99	[1.34; 11.92]	0.013
Histological subtype					
Interaction test	p = 0.365				
Ductal	29 / 1025 (2.8)	12 / 1010 (1.2)	2.38	[1.22; 4.64]	0.011
Lobular	13 / 291 (4.5)	5 / 276 (1.8)	2.47	[0.89; 6.83]	0.082
Other	1 / 92 (1.1)	2 / 76 (2.6)	0.41	[0.04; 4.47]	0.467
Ki67 status from surgical specimen					
Interaction test	p = 0.398				
Ki67≤20	16 / 660 (2.4)	6 / 629 (1.0)	2.54	[1.00; 6.45]	0.050
Ki67>20	11 / 489 (2.2)	8 / 516 (1.6)	1.45	[0.59; 3.58]	0.419
Type of NSAI					
Interaction test	p = 0.477				
Letrozole	24 / 907 (2.6)	9 / 895 (1.0)	2.63	[1.23; 5.63]	0.013
Anastrozole	19 / 502 (3.8)	10 / 467 (2.1)	1.77	[0.83; 3.76]	0.139
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.414				
Yes	41 / 1194 (3.4)	17 / 1146 (1.5)	2.31	[1.32; 4.05]	0.003
No	2 / 215 (0.9)	2 / 216 (0.9)	1.00	[0.14; 7.07]	0.996
Prior adjuvant chemotherapy					
Interaction test	p = 0.489				
Yes	23 / 694 (3.3)	12 / 673 (1.8)	1.86	[0.93; 3.71]	0.078
No	20 / 715 (2.8)	7 / 689 (1.0)	2.75	[1.17; 6.47]	0.020

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.107				
Yes	21 / 528 (4.0)	5 / 503 (1.0)	4.00	[1.52; 10.53]	0.005
No	22 / 881 (2.5)	14 / 859 (1.6)	1.53	[0.79; 2.97]	0.207
Prior endocrine therapy					
Interaction test	p = 0.314				
Yes	28 / 957 (2.9)	15 / 940 (1.6)	1.83	[0.99; 3.41]	0.056
No	15 / 452 (3.3)	4 / 422 (0.9)	3.50	[1.17; 10.46]	0.025
Prior mastectomy					
Interaction test	p = 0.390				
Yes	27 / 857 (3.2)	10 / 847 (1.2)	2.67	[1.30; 5.48]	0.007
No	16 / 552 (2.9)	9 / 515 (1.7)	1.66	[0.74; 3.72]	0.220
Prior radiotherapy					
Interaction test	p = 0.089				
Yes	42 / 1253 (3.4)	16 / 1203 (1.3)	2.52	[1.42; 4.46]	0.001
No	1 / 156 (0.6)	3 / 159 (1.9)	0.34	[0.04; 3.23]	0.348
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.28 PT mucosal inflammation: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Mucosal inflammation					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.124				
NA/WE/O	31 / 899 (3.4)	3 / 856 (0.4)	9.84	[3.02; 32.06]	<.001
ROW	4 / 510 (0.8)	2 / 506 (0.4)	1.98	[0.37; 10.79]	0.428
Geographical region					
Interaction test	p = 0.408				
Europe	24 / 832 (2.9)	4 / 824 (0.5)	5.94	[2.07; 17.05]	<.001
North America/Australia	7 / 400 (1.8)	0 / 364 (0.0)	13.65	[0.78; >99.99]	0.073
Asia	2 / 102 (2.0)	1 / 101 (1.0)	1.98	[0.18; 21.50]	0.574
Latin America	2 / 75 (2.7)	0 / 73 (0.0)	4.87	[0.24; 99.70]	0.304
Age group 1 at randomization					
Interaction test	p = 0.250				
<45	1 / 60 (1.7)	0 / 52 (0.0)	2.61	[0.11; 62.64]	0.555
45 to 54	7 / 300 (2.3)	3 / 322 (0.9)	2.50	[0.65; 9.60]	0.180
55 to 64	19 / 651 (2.9)	1 / 642 (0.2)	18.74	[2.52; >99.99]	0.004
≥65	8 / 398 (2.0)	1 / 346 (0.3)	6.95	[0.87; 55.33]	0.067
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.279				
<Median	18 / 633 (2.8)	4 / 632 (0.6)	4.49	[1.53; 13.20]	0.006
≥Median	17 / 776 (2.2)	1 / 730 (0.1)	15.99	[2.13; >99.99]	0.007
Race					
Interaction test	p = 0.215				
Asian	2 / 128 (1.6)	1 / 127 (0.8)	1.98	[0.18; 21.61]	0.574
Non-Asian	33 / 1203 (2.7)	3 / 1167 (0.3)	10.67	[3.28; 34.70]	<.001
BMI at screening					
Interaction test	p = 0.749				
≥25	22 / 935 (2.4)	3 / 935 (0.3)	7.33	[2.20; 24.42]	0.001
<25	12 / 460 (2.6)	2 / 410 (0.5)	5.35	[1.20; 23.75]	0.028
AJCC Anatomic Stage Group					
Interaction test	p = 0.956				
Group I/II	13 / 585 (2.2)	2 / 589 (0.3)	6.54	[1.48; 28.87]	0.013
Group III	22 / 823 (2.7)	3 / 772 (0.4)	6.88	[2.07; 22.89]	0.002

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.352				
IA/IB/IIA	8 / 310 (2.6)	0 / 311 (0.0)	17.05	[0.99; >99.99]	0.051
IIB	5 / 275 (1.8)	2 / 278 (0.7)	2.53	[0.49; 12.92]	0.265
IIIA	15 / 482 (3.1)	2 / 450 (0.4)	7.00	[1.61; 30.45]	0.009
IIIB	1 / 100 (1.0)	1 / 82 (1.2)	0.82	[0.05; 12.91]	0.888
IIIC	6 / 241 (2.5)	0 / 240 (0.0)	12.95	[0.73; >99.99]	0.080
Tumor category					
Interaction test	p = 0.130				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	34 / 1287 (2.6)	4 / 1258 (0.3)	8.31	[2.96; 23.34]	<.001
>T3	1 / 113 (0.9)	1 / 97 (1.0)	0.86	[0.05; 13.54]	0.914
Nodal status					
Interaction test	N.E.				
N0	7 / 190 (3.7)	0 / 200 (0.0)	15.79	[0.91; >99.99]	0.058
N1-N3	28 / 1216 (2.3)	5 / 1160 (0.4)	5.34	[2.07; 13.79]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.933				
Grade 1	2 / 102 (2.0)	0 / 106 (0.0)	5.19	[0.25; >99.99]	0.286
Grade 2	21 / 842 (2.5)	3 / 768 (0.4)	6.38	[1.91; 21.32]	0.003
Grade 3	11 / 373 (2.9)	2 / 397 (0.5)	5.85	[1.31; 26.24]	0.021
Histological subtype					
Interaction test	N.E.				
Ductal	29 / 1025 (2.8)	5 / 1010 (0.5)	5.72	[2.22; 14.71]	<.001
Lobular	4 / 291 (1.4)	0 / 276 (0.0)	8.54	[0.46; >99.99]	0.150
Other	2 / 92 (2.2)	0 / 76 (0.0)	4.14	[0.20; 84.94]	0.357
Ki67 status from surgical specimen					
Interaction test	p = 0.183				
Ki67≤20	16 / 660 (2.4)	1 / 629 (0.2)	15.25	[2.03; >99.99]	0.008
Ki67>20	12 / 489 (2.5)	4 / 516 (0.8)	3.17	[1.03; 9.75]	0.045
Type of NSAI					
Interaction test	p = 0.121				
Letrozole	26 / 907 (2.9)	2 / 895 (0.2)	12.83	[3.05; 53.89]	<.001
Anastrozole	9 / 502 (1.8)	3 / 467 (0.6)	2.79	[0.76; 10.25]	0.122
Prior neo/adjuvant chemotherapy					
Interaction test	N.E.				
Yes	34 / 1194 (2.8)	5 / 1146 (0.4)	6.53	[2.56; 16.63]	<.001
No	1 / 215 (0.5)	0 / 216 (0.0)	3.01	[0.12; 73.57]	0.499
Prior adjuvant chemotherapy					
Interaction test	p = 0.331				
Yes	22 / 694 (3.2)	2 / 673 (0.3)	10.67	[2.52; 45.19]	0.001
No	13 / 715 (1.8)	3 / 689 (0.4)	4.18	[1.20; 14.59]	0.025

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.269				
Yes	12 / 528 (2.3)	3 / 503 (0.6)	3.81	[1.08; 13.42]	0.037
No	23 / 881 (2.6)	2 / 859 (0.2)	11.21	[2.65; 47.41]	0.001
Prior endocrine therapy					
Interaction test	p = 0.820				
Yes	26 / 957 (2.7)	4 / 940 (0.4)	6.38	[2.24; 18.22]	<.001
No	9 / 452 (2.0)	1 / 422 (0.2)	8.40	[1.07; 66.04]	0.043
Prior mastectomy					
Interaction test	p = 0.968				
Yes	14 / 857 (1.6)	2 / 847 (0.2)	6.92	[1.58; 30.35]	0.010
No	21 / 552 (3.8)	3 / 515 (0.6)	6.53	[1.96; 21.76]	0.002
Prior radiotherapy					
Interaction test	N.E.				
Yes	32 / 1253 (2.6)	5 / 1203 (0.4)	6.14	[2.40; 15.72]	<.001
No	3 / 156 (1.9)	0 / 159 (0.0)	7.13	[0.37; >99.99]	0.192
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.29 PT chills: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Chills					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.227				
NA/WE/O	22 / 899 (2.4)	7 / 856 (0.8)	2.99	[1.29; 6.97]	0.011
ROW	3 / 510 (0.6)	3 / 506 (0.6)	0.99	[0.20; 4.89]	0.992
Geographical region					
Interaction test	p = 0.828				
Europe	7 / 832 (0.8)	3 / 824 (0.4)	2.31	[0.60; 8.91]	0.224
North America/Australia	16 / 400 (4.0)	6 / 364 (1.6)	2.43	[0.96; 6.13]	0.061
Asia	1 / 102 (1.0)	1 / 101 (1.0)	0.99	[0.06; 15.62]	0.994
Latin America	1 / 75 (1.3)	0 / 73 (0.0)	2.92	[0.12; 70.56]	0.509
Age group 1 at randomization					
Interaction test	p = 0.662				
<45	2 / 60 (3.3)	1 / 52 (1.9)	1.73	[0.16; 18.57]	0.649
45 to 54	6 / 300 (2.0)	0 / 322 (0.0)	13.95	[0.79; >99.99]	0.072
55 to 64	12 / 651 (1.8)	8 / 642 (1.2)	1.48	[0.61; 3.59]	0.387
≥65	5 / 398 (1.3)	1 / 346 (0.3)	4.35	[0.51; 37.03]	0.179
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.576				
<Median	12 / 633 (1.9)	6 / 632 (0.9)	2.00	[0.75; 5.29]	0.164
≥Median	13 / 776 (1.7)	4 / 730 (0.5)	3.06	[1.00; 9.33]	0.050
Race					
Interaction test	p = 0.889				
Asian	2 / 128 (1.6)	1 / 127 (0.8)	1.98	[0.18; 21.61]	0.574
Non-Asian	22 / 1203 (1.8)	9 / 1167 (0.8)	2.37	[1.10; 5.13]	0.028
BMI at screening					
Interaction test	p = 0.978				
≥25	17 / 935 (1.8)	7 / 935 (0.7)	2.43	[1.01; 5.83]	0.047
<25	8 / 460 (1.7)	3 / 410 (0.7)	2.38	[0.63; 8.90]	0.199
AJCC Anatomic Stage Group					
Interaction test	p = 0.843				
Group I/II	8 / 585 (1.4)	3 / 589 (0.5)	2.68	[0.72; 10.07]	0.143
Group III	17 / 823 (2.1)	7 / 772 (0.9)	2.28	[0.95; 5.46]	0.065

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.742				
IA/IB/IIA	5 / 310 (1.6)	2 / 311 (0.6)	2.51	[0.49; 12.83]	0.270
IIB	3 / 275 (1.1)	1 / 278 (0.4)	3.03	[0.32; 28.98]	0.335
IIIA	10 / 482 (2.1)	5 / 450 (1.1)	1.87	[0.64; 5.42]	0.251
IIIB	0 / 100 (0.0)	1 / 82 (1.2)	0.27	[0.01; 6.64]	0.426
IIIC	7 / 241 (2.9)	1 / 240 (0.4)	6.97	[0.86; 56.23]	0.068
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	25 / 1287 (1.9)	9 / 1258 (0.7)	2.72	[1.27; 5.79]	0.010
>T3	0 / 113 (0.0)	1 / 97 (1.0)	0.29	[0.01; 6.95]	0.442
Nodal status					
Interaction test	p = 0.905				
N0	2 / 190 (1.1)	1 / 200 (0.5)	2.11	[0.19; 23.03]	0.542
N1-N3	23 / 1216 (1.9)	9 / 1160 (0.8)	2.44	[1.13; 5.25]	0.023
Histological grade at time of surgery					
Interaction test	p = 0.349				
Grade 1	1 / 102 (1.0)	2 / 106 (1.9)	0.52	[0.05; 5.64]	0.591
Grade 2	19 / 842 (2.3)	7 / 768 (0.9)	2.48	[1.05; 5.86]	0.039
Grade 3	5 / 373 (1.3)	1 / 397 (0.3)	5.32	[0.62; 45.34]	0.126
Histological subtype					
Interaction test	p = 0.728				
Ductal	18 / 1025 (1.8)	7 / 1010 (0.7)	2.53	[1.06; 6.04]	0.036
Lobular	6 / 291 (2.1)	2 / 276 (0.7)	2.85	[0.58; 13.98]	0.198
Other	1 / 92 (1.1)	1 / 76 (1.3)	0.83	[0.05; 12.99]	0.892
Ki67 status from surgical specimen					
Interaction test	p = 0.567				
Ki67≤20	8 / 660 (1.2)	6 / 629 (1.0)	1.27	[0.44; 3.64]	0.656
Ki67>20	6 / 489 (1.2)	3 / 516 (0.6)	2.11	[0.53; 8.39]	0.289
Type of NSAI					
Interaction test	p = 0.950				
Letrozole	10 / 907 (1.1)	4 / 895 (0.4)	2.47	[0.78; 7.84]	0.126
Anastrozole	15 / 502 (3.0)	6 / 467 (1.3)	2.33	[0.91; 5.94]	0.078
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.346				
Yes	23 / 1194 (1.9)	8 / 1146 (0.7)	2.76	[1.24; 6.14]	0.013
No	2 / 215 (0.9)	2 / 216 (0.9)	1.00	[0.14; 7.07]	0.996
Prior adjuvant chemotherapy					
Interaction test	p = 0.811				
Yes	16 / 694 (2.3)	6 / 673 (0.9)	2.59	[1.02; 6.57]	0.046
No	9 / 715 (1.3)	4 / 689 (0.6)	2.17	[0.67; 7.01]	0.196

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.600				
Yes	10 / 528 (1.9)	3 / 503 (0.6)	3.18	[0.88; 11.47]	0.078
No	15 / 881 (1.7)	7 / 859 (0.8)	2.09	[0.86; 5.10]	0.106
Prior endocrine therapy					
Interaction test	p = 0.043				
Yes	19 / 957 (2.0)	4 / 940 (0.4)	4.67	[1.59; 13.66]	0.005
No	6 / 452 (1.3)	6 / 422 (1.4)	0.93	[0.30; 2.87]	0.905
Prior mastectomy					
Interaction test	p = 0.192				
Yes	18 / 857 (2.1)	5 / 847 (0.6)	3.56	[1.33; 9.54]	0.012
No	7 / 552 (1.3)	5 / 515 (1.0)	1.31	[0.42; 4.09]	0.646
Prior radiotherapy					
Interaction test	N.E.				
Yes	22 / 1253 (1.8)	10 / 1203 (0.8)	2.11	[1.00; 4.44]	0.049
No	3 / 156 (1.9)	0 / 159 (0.0)	7.13	[0.37; >99.99]	0.192
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.30 SOC gastrointestinal disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Gastrointestinal disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = <.001				
NA/WE/O	598 / 899 (66.5)	290 / 856 (33.9)	1.96	[1.77; 2.18]	<.001
ROW	162 / 510 (31.8)	94 / 506 (18.6)	1.71	[1.37; 2.14]	<.001
Geographical region					
Interaction test	p = 0.425				
Europe	411 / 832 (49.4)	209 / 824 (25.4)	1.95	[1.70; 2.23]	<.001
North America/Australia	280 / 400 (70.0)	140 / 364 (38.5)	1.82	[1.57; 2.10]	<.001
Asia	37 / 102 (36.3)	17 / 101 (16.8)	2.16	[1.30; 3.57]	0.003
Latin America	32 / 75 (42.7)	18 / 73 (24.7)	1.73	[1.07; 2.79]	0.025
Age group 1 at randomization					
Interaction test	p = 0.653				
<45	40 / 60 (66.7)	17 / 52 (32.7)	2.04	[1.33; 3.13]	0.001
45 to 54	166 / 300 (55.3)	86 / 322 (26.7)	2.07	[1.68; 2.55]	<.001
55 to 64	340 / 651 (52.2)	179 / 642 (27.9)	1.87	[1.62; 2.16]	<.001
≥65	214 / 398 (53.8)	102 / 346 (29.5)	1.82	[1.51; 2.20]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.734				
<Median	351 / 633 (55.5)	182 / 632 (28.8)	1.93	[1.67; 2.22]	<.001
≥Median	409 / 776 (52.7)	202 / 730 (27.7)	1.90	[1.66; 2.18]	<.001
Race					
Interaction test	p = 0.974				
Asian	54 / 128 (42.2)	25 / 127 (19.7)	2.14	[1.43; 3.22]	<.001
Non-Asian	653 / 1203 (54.3)	335 / 1167 (28.7)	1.89	[1.70; 2.10]	<.001
BMI at screening					
Interaction test	p = 0.920				
≥25	502 / 935 (53.7)	263 / 935 (28.1)	1.91	[1.70; 2.15]	<.001
<25	250 / 460 (54.3)	119 / 410 (29.0)	1.87	[1.58; 2.23]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.698				
Group I/II	323 / 585 (55.2)	168 / 589 (28.5)	1.94	[1.67; 2.24]	<.001
Group III	436 / 823 (53.0)	216 / 772 (28.0)	1.89	[1.66; 2.16]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.506				
IA/IB/IIA	165 / 310 (53.2)	94 / 311 (30.2)	1.76	[1.44; 2.15]	<.001
IIB	158 / 275 (57.5)	74 / 278 (26.6)	2.16	[1.73; 2.69]	<.001
IIIA	264 / 482 (54.8)	141 / 450 (31.3)	1.75	[1.49; 2.05]	<.001
IIIB	47 / 100 (47.0)	17 / 82 (20.7)	2.27	[1.41; 3.63]	<.001
IIIC	125 / 241 (51.9)	58 / 240 (24.2)	2.15	[1.66; 2.77]	<.001
Tumor category					
Interaction test	p = 0.916				
T0	2 / 5 (40.0)	1 / 5 (20.0)	2.00	[0.26; 15.62]	0.509
T1-T3	704 / 1287 (54.7)	363 / 1258 (28.9)	1.90	[1.72; 2.10]	<.001
>T3	53 / 113 (46.9)	20 / 97 (20.6)	2.27	[1.47; 3.52]	<.001
Nodal status					
Interaction test	p = 0.718				
N0	98 / 190 (51.6)	50 / 200 (25.0)	2.06	[1.56; 2.72]	<.001
N1-N3	660 / 1216 (54.3)	334 / 1160 (28.8)	1.89	[1.70; 2.09]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.895				
Grade 1	57 / 102 (55.9)	34 / 106 (32.1)	1.74	[1.26; 2.41]	<.001
Grade 2	456 / 842 (54.2)	212 / 768 (27.6)	1.96	[1.72; 2.23]	<.001
Grade 3	208 / 373 (55.8)	117 / 397 (29.5)	1.89	[1.59; 2.26]	<.001
Histological subtype					
Interaction test	p = 0.186				
Ductal	531 / 1025 (51.8)	285 / 1010 (28.2)	1.84	[1.64; 2.06]	<.001
Lobular	167 / 291 (57.4)	76 / 276 (27.5)	2.08	[1.68; 2.59]	<.001
Other	61 / 92 (66.3)	23 / 76 (30.3)	2.19	[1.51; 3.18]	<.001
Ki67 status from surgical specimen					
Interaction test	p = 0.978				
Ki67≤20	346 / 660 (52.4)	174 / 629 (27.7)	1.90	[1.64; 2.19]	<.001
Ki67>20	226 / 489 (46.2)	119 / 516 (23.1)	2.00	[1.67; 2.41]	<.001
Type of NSAI					
Interaction test	p = 0.710				
Letrozole	476 / 907 (52.5)	238 / 895 (26.6)	1.97	[1.74; 2.24]	<.001
Anastrozole	284 / 502 (56.6)	146 / 467 (31.3)	1.81	[1.55; 2.11]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.240				
Yes	657 / 1194 (55.0)	324 / 1146 (28.3)	1.95	[1.75; 2.16]	<.001
No	103 / 215 (47.9)	60 / 216 (27.8)	1.72	[1.33; 2.23]	<.001
Prior adjuvant chemotherapy					
Interaction test	p = 0.598				
Yes	399 / 694 (57.5)	215 / 673 (31.9)	1.80	[1.58; 2.04]	<.001
No	361 / 715 (50.5)	169 / 689 (24.5)	2.06	[1.77; 2.39]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.096				
Yes	274 / 528 (51.9)	116 / 503 (23.1)	2.25	[1.88; 2.69]	<.001
No	486 / 881 (55.2)	268 / 859 (31.2)	1.77	[1.57; 1.99]	<.001
Prior endocrine therapy					
Interaction test	p = 0.409				
Yes	535 / 957 (55.9)	271 / 940 (28.8)	1.94	[1.73; 2.18]	<.001
No	225 / 452 (49.8)	113 / 422 (26.8)	1.86	[1.55; 2.23]	<.001
Prior mastectomy					
Interaction test	p = 0.352				
Yes	460 / 857 (53.7)	227 / 847 (26.8)	2.00	[1.76; 2.28]	<.001
No	300 / 552 (54.3)	157 / 515 (30.5)	1.78	[1.53; 2.07]	<.001
Prior radiotherapy					
Interaction test	p = 0.195				
Yes	687 / 1253 (54.8)	339 / 1203 (28.2)	1.95	[1.75; 2.16]	<.001
No	73 / 156 (46.8)	45 / 159 (28.3)	1.65	[1.23; 2.23]	<.001
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.31 PT nausea: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Nausea					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.138				
NA/WE/O	293 / 899 (32.6)	80 / 856 (9.3)	3.49	[2.77; 4.38]	<.001
ROW	53 / 510 (10.4)	19 / 506 (3.8)	2.77	[1.66; 4.61]	<.001
Geographical region					
Interaction test	p = 0.956				
Europe	164 / 832 (19.7)	45 / 824 (5.5)	3.61	[2.63; 4.95]	<.001
North America/Australia	163 / 400 (40.8)	48 / 364 (13.2)	3.09	[2.31; 4.13]	<.001
Asia	7 / 102 (6.9)	2 / 101 (2.0)	3.47	[0.74; 16.28]	0.115
Latin America	12 / 75 (16.0)	4 / 73 (5.5)	2.92	[0.99; 8.64]	0.053
Age group 1 at randomization					
Interaction test	p = 0.770				
<45	21 / 60 (35.0)	4 / 52 (7.7)	4.55	[1.67; 12.40]	0.003
45 to 54	73 / 300 (24.3)	21 / 322 (6.5)	3.73	[2.36; 5.91]	<.001
55 to 64	153 / 651 (23.5)	49 / 642 (7.6)	3.08	[2.28; 4.17]	<.001
≥65	99 / 398 (24.9)	25 / 346 (7.2)	3.44	[2.27; 5.21]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.647				
<Median	160 / 633 (25.3)	45 / 632 (7.1)	3.55	[2.60; 4.85]	<.001
≥Median	186 / 776 (24.0)	54 / 730 (7.4)	3.24	[2.44; 4.31]	<.001
Race					
Interaction test	p = 0.153				
Asian	20 / 128 (15.6)	2 / 127 (1.6)	9.92	[2.37; 41.57]	0.002
Non-Asian	308 / 1203 (25.6)	95 / 1167 (8.1)	3.15	[2.54; 3.90]	<.001
BMI at screening					
Interaction test	p = 0.663				
≥25	234 / 935 (25.0)	68 / 935 (7.3)	3.44	[2.67; 4.44]	<.001
<25	109 / 460 (23.7)	31 / 410 (7.6)	3.13	[2.15; 4.56]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.982				
Group I/II	135 / 585 (23.1)	40 / 589 (6.8)	3.40	[2.43; 4.74]	<.001
Group III	210 / 823 (25.5)	59 / 772 (7.6)	3.34	[2.54; 4.38]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.953				
IA/IB/IIA	76 / 310 (24.5)	22 / 311 (7.1)	3.47	[2.21; 5.42]	<.001
IIB	59 / 275 (21.5)	18 / 278 (6.5)	3.31	[2.01; 5.47]	<.001
IIIA	124 / 482 (25.7)	38 / 450 (8.4)	3.05	[2.17; 4.28]	<.001
IIIB	23 / 100 (23.0)	5 / 82 (6.1)	3.77	[1.50; 9.48]	0.005
IIIC	63 / 241 (26.1)	16 / 240 (6.7)	3.92	[2.33; 6.59]	<.001
Tumor category					
Interaction test	p = 0.776				
T0	1 / 5 (20.0)	0 / 5 (0.0)	3.00	[0.15; 59.89]	0.472
T1-T3	319 / 1287 (24.8)	92 / 1258 (7.3)	3.39	[2.72; 4.22]	<.001
>T3	25 / 113 (22.1)	7 / 97 (7.2)	3.07	[1.39; 6.78]	0.006
Nodal status					
Interaction test	p = 0.696				
N0	41 / 190 (21.6)	14 / 200 (7.0)	3.08	[1.74; 5.47]	<.001
N1-N3	303 / 1216 (24.9)	85 / 1160 (7.3)	3.40	[2.71; 4.27]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.913				
Grade 1	18 / 102 (17.6)	6 / 106 (5.7)	3.12	[1.29; 7.54]	0.012
Grade 2	212 / 842 (25.2)	54 / 768 (7.0)	3.58	[2.70; 4.75]	<.001
Grade 3	102 / 373 (27.3)	32 / 397 (8.1)	3.39	[2.34; 4.92]	<.001
Histological subtype					
Interaction test	p = 0.605				
Ductal	235 / 1025 (22.9)	71 / 1010 (7.0)	3.26	[2.54; 4.19]	<.001
Lobular	87 / 291 (29.9)	21 / 276 (7.6)	3.93	[2.51; 6.14]	<.001
Other	24 / 92 (26.1)	7 / 76 (9.2)	2.83	[1.29; 6.21]	0.009
Ki67 status from surgical specimen					
Interaction test	p = 0.077				
Ki67≤20	147 / 660 (22.3)	37 / 629 (5.9)	3.79	[2.69; 5.34]	<.001
Ki67>20	84 / 489 (17.2)	36 / 516 (7.0)	2.46	[1.70; 3.57]	<.001
Type of NSAI					
Interaction test	p = 0.673				
Letrozole	198 / 907 (21.8)	54 / 895 (6.0)	3.62	[2.72; 4.82]	<.001
Anastrozole	148 / 502 (29.5)	45 / 467 (9.6)	3.06	[2.25; 4.17]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.867				
Yes	297 / 1194 (24.9)	84 / 1146 (7.3)	3.39	[2.70; 4.26]	<.001
No	49 / 215 (22.8)	15 / 216 (6.9)	3.28	[1.90; 5.67]	<.001
Prior adjuvant chemotherapy					
Interaction test	p = 0.983				
Yes	176 / 694 (25.4)	51 / 673 (7.6)	3.35	[2.50; 4.49]	<.001
No	170 / 715 (23.8)	48 / 689 (7.0)	3.41	[2.52; 4.62]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.990				
Yes	125 / 528 (23.7)	35 / 503 (7.0)	3.40	[2.39; 4.85]	<.001
No	221 / 881 (25.1)	64 / 859 (7.5)	3.37	[2.59; 4.37]	<.001
Prior endocrine therapy					
Interaction test	p = 0.553				
Yes	243 / 957 (25.4)	74 / 940 (7.9)	3.23	[2.53; 4.12]	<.001
No	103 / 452 (22.8)	25 / 422 (5.9)	3.85	[2.54; 5.83]	<.001
Prior mastectomy					
Interaction test	p = 0.269				
Yes	212 / 857 (24.7)	68 / 847 (8.0)	3.08	[2.39; 3.98]	<.001
No	134 / 552 (24.3)	31 / 515 (6.0)	4.03	[2.78; 5.85]	<.001
Prior radiotherapy					
Interaction test	p = 0.254				
Yes	317 / 1253 (25.3)	87 / 1203 (7.2)	3.50	[2.80; 4.38]	<.001
No	29 / 156 (18.6)	12 / 159 (7.5)	2.46	[1.30; 4.65]	0.005
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.32 PT diarrhoea: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Diarrhoea					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.791				
NA/WE/O	205 / 899 (22.8)	73 / 856 (8.5)	2.67	[2.08; 3.43]	<.001
ROW	36 / 510 (7.1)	13 / 506 (2.6)	2.75	[1.47; 5.12]	0.001
Geographical region					
Interaction test	p = 0.320				
Europe	128 / 832 (15.4)	46 / 824 (5.6)	2.76	[2.00; 3.81]	<.001
North America/Australia	101 / 400 (25.3)	35 / 364 (9.6)	2.63	[1.84; 3.75]	<.001
Asia	6 / 102 (5.9)	0 / 101 (0.0)	12.87	[0.73; >99.99]	0.080
Latin America	6 / 75 (8.0)	5 / 73 (6.8)	1.17	[0.37; 3.66]	0.790
Age group 1 at randomization					
Interaction test	p = 0.800				
<45	14 / 60 (23.3)	7 / 52 (13.5)	1.73	[0.76; 3.97]	0.193
45 to 54	46 / 300 (15.3)	19 / 322 (5.9)	2.60	[1.56; 4.33]	<.001
55 to 64	106 / 651 (16.3)	38 / 642 (5.9)	2.75	[1.93; 3.92]	<.001
≥65	75 / 398 (18.8)	22 / 346 (6.4)	2.96	[1.88; 4.66]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.308				
<Median	105 / 633 (16.6)	44 / 632 (7.0)	2.38	[1.71; 3.33]	<.001
≥Median	136 / 776 (17.5)	42 / 730 (5.8)	3.05	[2.19; 4.24]	<.001
Race					
Interaction test	p = 0.192				
Asian	11 / 128 (8.6)	1 / 127 (0.8)	10.91	[1.43; 83.30]	0.021
Non-Asian	213 / 1203 (17.7)	79 / 1167 (6.8)	2.62	[2.05; 3.34]	<.001
BMI at screening					
Interaction test	p = 0.484				
≥25	173 / 935 (18.5)	61 / 935 (6.5)	2.84	[2.15; 3.74]	<.001
<25	65 / 460 (14.1)	24 / 410 (5.9)	2.41	[1.54; 3.78]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.166				
Group I/II	108 / 585 (18.5)	48 / 589 (8.1)	2.27	[1.64; 3.12]	<.001
Group III	132 / 823 (16.0)	38 / 772 (4.9)	3.26	[2.30; 4.61]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.207				
IA/IB/IIA	54 / 310 (17.4)	30 / 311 (9.6)	1.81	[1.19; 2.74]	0.006
IIB	54 / 275 (19.6)	18 / 278 (6.5)	3.03	[1.83; 5.03]	<.001
IIIA	71 / 482 (14.7)	24 / 450 (5.3)	2.76	[1.77; 4.31]	<.001
IIIB	13 / 100 (13.0)	3 / 82 (3.7)	3.55	[1.05; 12.05]	0.042
IIIC	48 / 241 (19.9)	11 / 240 (4.6)	4.35	[2.31; 8.16]	<.001
Tumor category					
Interaction test	p = 0.784				
T0	1 / 5 (20.0)	0 / 5 (0.0)	3.00	[0.15; 59.89]	0.472
T1-T3	224 / 1287 (17.4)	82 / 1258 (6.5)	2.67	[2.10; 3.40]	<.001
>T3	15 / 113 (13.3)	4 / 97 (4.1)	3.22	[1.11; 9.38]	0.032
Nodal status					
Interaction test	p = 0.568				
N0	35 / 190 (18.4)	16 / 200 (8.0)	2.30	[1.32; 4.02]	0.003
N1-N3	206 / 1216 (16.9)	70 / 1160 (6.0)	2.81	[2.17; 3.64]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.250				
Grade 1	17 / 102 (16.7)	2 / 106 (1.9)	8.83	[2.09; 37.27]	0.003
Grade 2	139 / 842 (16.5)	50 / 768 (6.5)	2.54	[1.86; 3.45]	<.001
Grade 3	74 / 373 (19.8)	29 / 397 (7.3)	2.72	[1.81; 4.07]	<.001
Histological subtype					
Interaction test	p = 0.181				
Ductal	156 / 1025 (15.2)	64 / 1010 (6.3)	2.40	[1.82; 3.17]	<.001
Lobular	70 / 291 (24.1)	17 / 276 (6.2)	3.91	[2.36; 6.46]	<.001
Other	15 / 92 (16.3)	5 / 76 (6.6)	2.48	[0.94; 6.51]	0.065
Ki67 status from surgical specimen					
Interaction test	p = 0.700				
Ki67≤20	96 / 660 (14.5)	34 / 629 (5.4)	2.69	[1.85; 3.92]	<.001
Ki67>20	75 / 489 (15.3)	33 / 516 (6.4)	2.40	[1.62; 3.54]	<.001
Type of NSAI					
Interaction test	p = 0.839				
Letrozole	144 / 907 (15.9)	51 / 895 (5.7)	2.79	[2.05; 3.78]	<.001
Anastrozole	97 / 502 (19.3)	35 / 467 (7.5)	2.58	[1.79; 3.72]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.638				
Yes	210 / 1194 (17.6)	73 / 1146 (6.4)	2.76	[2.14; 3.56]	<.001
No	31 / 215 (14.4)	13 / 216 (6.0)	2.40	[1.29; 4.45]	0.006
Prior adjuvant chemotherapy					
Interaction test	p = 0.960				
Yes	138 / 694 (19.9)	50 / 673 (7.4)	2.68	[1.97; 3.63]	<.001
No	103 / 715 (14.4)	36 / 689 (5.2)	2.76	[1.91; 3.97]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.668				
Yes	76 / 528 (14.4)	24 / 503 (4.8)	3.02	[1.94; 4.70]	<.001
No	165 / 881 (18.7)	62 / 859 (7.2)	2.59	[1.97; 3.42]	<.001
Prior endocrine therapy					
Interaction test	p = 0.298				
Yes	168 / 957 (17.6)	66 / 940 (7.0)	2.50	[1.91; 3.28]	<.001
No	73 / 452 (16.2)	20 / 422 (4.7)	3.41	[2.12; 5.49]	<.001
Prior mastectomy					
Interaction test	p = 0.021				
Yes	153 / 857 (17.9)	44 / 847 (5.2)	3.44	[2.49; 4.74]	<.001
No	88 / 552 (15.9)	42 / 515 (8.2)	1.95	[1.38; 2.77]	<.001
Prior radiotherapy					
Interaction test	p = 0.472				
Yes	216 / 1253 (17.2)	79 / 1203 (6.6)	2.63	[2.05; 3.35]	<.001
No	25 / 156 (16.0)	7 / 159 (4.4)	3.64	[1.62; 8.17]	0.002
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.33 PT constipation: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Constipation					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.702				
NA/WE/O	153 / 899 (17.0)	59 / 856 (6.9)	2.47	[1.86; 3.28]	<.001
ROW	34 / 510 (6.7)	11 / 506 (2.2)	3.07	[1.57; 5.98]	0.001
Geographical region					
Interaction test	p = 0.261				
Europe	90 / 832 (10.8)	26 / 824 (3.2)	3.43	[2.24; 5.25]	<.001
North America/Australia	73 / 400 (18.3)	36 / 364 (9.9)	1.85	[1.27; 2.68]	0.001
Asia	14 / 102 (13.7)	4 / 101 (4.0)	3.47	[1.18; 10.17]	0.024
Latin America	10 / 75 (13.3)	4 / 73 (5.5)	2.43	[0.80; 7.41]	0.118
Age group 1 at randomization					
Interaction test	p = 0.520				
<45	11 / 60 (18.3)	6 / 52 (11.5)	1.59	[0.63; 4.00]	0.325
45 to 54	43 / 300 (14.3)	13 / 322 (4.0)	3.55	[1.95; 6.47]	<.001
55 to 64	82 / 651 (12.6)	31 / 642 (4.8)	2.61	[1.75; 3.89]	<.001
≥65	51 / 398 (12.8)	20 / 346 (5.8)	2.22	[1.35; 3.64]	0.002
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.980				
<Median	88 / 633 (13.9)	34 / 632 (5.4)	2.58	[1.77; 3.78]	<.001
≥Median	99 / 776 (12.8)	36 / 730 (4.9)	2.59	[1.79; 3.74]	<.001
Race					
Interaction test	p = 0.887				
Asian	17 / 128 (13.3)	6 / 127 (4.7)	2.81	[1.15; 6.90]	0.024
Non-Asian	157 / 1203 (13.1)	58 / 1167 (5.0)	2.63	[1.96; 3.51]	<.001
BMI at screening					
Interaction test	p = 0.227				
≥25	109 / 935 (11.7)	48 / 935 (5.1)	2.27	[1.64; 3.15]	<.001
<25	77 / 460 (16.7)	22 / 410 (5.4)	3.12	[1.98; 4.92]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.208				
Group I/II	77 / 585 (13.2)	24 / 589 (4.1)	3.23	[2.07; 5.03]	<.001
Group III	110 / 823 (13.4)	46 / 772 (6.0)	2.24	[1.61; 3.12]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.616				
IA/IB/IIA	37 / 310 (11.9)	13 / 311 (4.2)	2.86	[1.55; 5.27]	<.001
IIB	40 / 275 (14.5)	11 / 278 (4.0)	3.68	[1.93; 7.01]	<.001
IIIA	67 / 482 (13.9)	31 / 450 (6.9)	2.02	[1.34; 3.03]	<.001
IIIB	6 / 100 (6.0)	2 / 82 (2.4)	2.46	[0.51; 11.87]	0.262
IIIC	37 / 241 (15.4)	13 / 240 (5.4)	2.83	[1.55; 5.20]	<.001
Tumor category					
Interaction test	p = 0.638				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	178 / 1287 (13.8)	68 / 1258 (5.4)	2.56	[1.96; 3.35]	<.001
>T3	9 / 113 (8.0)	2 / 97 (2.1)	3.86	[0.86; 17.45]	0.079
Nodal status					
Interaction test	p = 0.429				
N0	21 / 190 (11.1)	6 / 200 (3.0)	3.68	[1.52; 8.93]	0.004
N1-N3	166 / 1216 (13.7)	64 / 1160 (5.5)	2.47	[1.88; 3.26]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.651				
Grade 1	16 / 102 (15.7)	9 / 106 (8.5)	1.85	[0.86; 3.99]	0.118
Grade 2	108 / 842 (12.8)	37 / 768 (4.8)	2.66	[1.86; 3.82]	<.001
Grade 3	57 / 373 (15.3)	21 / 397 (5.3)	2.89	[1.79; 4.67]	<.001
Histological subtype					
Interaction test	p = 0.918				
Ductal	130 / 1025 (12.7)	51 / 1010 (5.0)	2.51	[1.84; 3.43]	<.001
Lobular	41 / 291 (14.1)	15 / 276 (5.4)	2.59	[1.47; 4.58]	0.001
Other	15 / 92 (16.3)	4 / 76 (5.3)	3.10	[1.07; 8.94]	0.037
Ki67 status from surgical specimen					
Interaction test	p = 0.828				
Ki67≤20	81 / 660 (12.3)	27 / 629 (4.3)	2.86	[1.88; 4.36]	<.001
Ki67>20	51 / 489 (10.4)	20 / 516 (3.9)	2.69	[1.63; 4.45]	<.001
Type of NSAI					
Interaction test	p = 0.670				
Letrozole	113 / 907 (12.5)	41 / 895 (4.6)	2.72	[1.93; 3.84]	<.001
Anastrozole	74 / 502 (14.7)	29 / 467 (6.2)	2.37	[1.57; 3.58]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.780				
Yes	161 / 1194 (13.5)	59 / 1146 (5.1)	2.62	[1.97; 3.49]	<.001
No	26 / 215 (12.1)	11 / 216 (5.1)	2.37	[1.20; 4.68]	0.013
Prior adjuvant chemotherapy					
Interaction test	p = 0.576				
Yes	107 / 694 (15.4)	38 / 673 (5.6)	2.73	[1.92; 3.89]	<.001
No	80 / 715 (11.2)	32 / 689 (4.6)	2.41	[1.62; 3.58]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.587				
Yes	57 / 528 (10.8)	23 / 503 (4.6)	2.36	[1.48; 3.77]	<.001
No	130 / 881 (14.8)	47 / 859 (5.5)	2.70	[1.96; 3.71]	<.001
Prior endocrine therapy					
Interaction test	p = 0.979				
Yes	136 / 957 (14.2)	52 / 940 (5.5)	2.57	[1.89; 3.49]	<.001
No	51 / 452 (11.3)	18 / 422 (4.3)	2.65	[1.57; 4.45]	<.001
Prior mastectomy					
Interaction test	p = 0.202				
Yes	110 / 857 (12.8)	48 / 847 (5.7)	2.26	[1.64; 3.14]	<.001
No	77 / 552 (13.9)	22 / 515 (4.3)	3.27	[2.06; 5.16]	<.001
Prior radiotherapy					
Interaction test	p = 0.686				
Yes	174 / 1253 (13.9)	64 / 1203 (5.3)	2.61	[1.98; 3.44]	<.001
No	13 / 156 (8.3)	6 / 159 (3.8)	2.21	[0.86; 5.66]	0.099
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.34 PT vomiting: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Vomiting					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.670				
NA/WE/O	101 / 899 (11.2)	42 / 856 (4.9)	2.29	[1.62; 3.24]	<.001
ROW	18 / 510 (3.5)	9 / 506 (1.8)	1.98	[0.90; 4.38]	0.089
Geographical region					
Interaction test	p = 0.527				
Europe	56 / 832 (6.7)	19 / 824 (2.3)	2.92	[1.75; 4.87]	<.001
North America/Australia	55 / 400 (13.8)	29 / 364 (8.0)	1.73	[1.13; 2.64]	0.012
Asia	4 / 102 (3.9)	2 / 101 (2.0)	1.98	[0.37; 10.57]	0.424
Latin America	4 / 75 (5.3)	1 / 73 (1.4)	3.89	[0.45; 34.01]	0.219
Age group 1 at randomization					
Interaction test	p = 0.480				
<45	6 / 60 (10.0)	2 / 52 (3.8)	2.60	[0.55; 12.33]	0.229
45 to 54	26 / 300 (8.7)	8 / 322 (2.5)	3.49	[1.60; 7.58]	0.002
55 to 64	50 / 651 (7.7)	28 / 642 (4.4)	1.76	[1.12; 2.76]	0.014
≥65	37 / 398 (9.3)	13 / 346 (3.8)	2.47	[1.34; 4.58]	0.004
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.425				
<Median	55 / 633 (8.7)	21 / 632 (3.3)	2.61	[1.60; 4.27]	<.001
≥Median	64 / 776 (8.2)	30 / 730 (4.1)	2.01	[1.32; 3.06]	0.001
Race					
Interaction test	p = 0.769				
Asian	6 / 128 (4.7)	2 / 127 (1.6)	2.98	[0.61; 14.47]	0.176
Non-Asian	110 / 1203 (9.1)	47 / 1167 (4.0)	2.27	[1.63; 3.16]	<.001
BMI at screening					
Interaction test	p = 0.296				
≥25	87 / 935 (9.3)	35 / 935 (3.7)	2.49	[1.70; 3.64]	<.001
<25	31 / 460 (6.7)	16 / 410 (3.9)	1.73	[0.96; 3.11]	0.069
AJCC Anatomic Stage Group					
Interaction test	p = 0.184				
Group I/II	55 / 585 (9.4)	19 / 589 (3.2)	2.91	[1.75; 4.85]	<.001
Group III	64 / 823 (7.8)	32 / 772 (4.1)	1.88	[1.24; 2.83]	0.003

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.429				
IA/IB/IIA	29 / 310 (9.4)	10 / 311 (3.2)	2.91	[1.44; 5.87]	0.003
IIB	26 / 275 (9.5)	9 / 278 (3.2)	2.92	[1.39; 6.12]	0.005
IIIA	40 / 482 (8.3)	18 / 450 (4.0)	2.07	[1.21; 3.56]	0.008
IIIB	5 / 100 (5.0)	5 / 82 (6.1)	0.82	[0.25; 2.74]	0.747
IIIC	19 / 241 (7.9)	9 / 240 (3.8)	2.10	[0.97; 4.55]	0.059
Tumor category					
Interaction test	p = 0.255				
T0	1 / 5 (20.0)	0 / 5 (0.0)	3.00	[0.15; 59.89]	0.472
T1-T3	111 / 1287 (8.6)	46 / 1258 (3.7)	2.36	[1.69; 3.30]	<.001
>T3	7 / 113 (6.2)	5 / 97 (5.2)	1.20	[0.39; 3.67]	0.747
Nodal status					
Interaction test	p = 0.179				
N0	17 / 190 (8.9)	4 / 200 (2.0)	4.47	[1.53; 13.05]	0.006
N1-N3	102 / 1216 (8.4)	47 / 1160 (4.1)	2.07	[1.48; 2.90]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.017				
Grade 1	6 / 102 (5.9)	4 / 106 (3.8)	1.56	[0.45; 5.36]	0.481
Grade 2	63 / 842 (7.5)	35 / 768 (4.6)	1.64	[1.10; 2.45]	0.015
Grade 3	46 / 373 (12.3)	10 / 397 (2.5)	4.90	[2.51; 9.56]	<.001
Histological subtype					
Interaction test	p = 0.417				
Ductal	86 / 1025 (8.4)	39 / 1010 (3.9)	2.17	[1.50; 3.14]	<.001
Lobular	27 / 291 (9.3)	8 / 276 (2.9)	3.20	[1.48; 6.92]	0.003
Other	6 / 92 (6.5)	4 / 76 (5.3)	1.24	[0.36; 4.23]	0.732
Ki67 status from surgical specimen					
Interaction test	p = 0.724				
Ki67≤20	51 / 660 (7.7)	25 / 629 (4.0)	1.94	[1.22; 3.10]	0.005
Ki67>20	28 / 489 (5.7)	13 / 516 (2.5)	2.27	[1.19; 4.34]	0.013
Type of NSAI					
Interaction test	p = 0.442				
Letrozole	67 / 907 (7.4)	26 / 895 (2.9)	2.54	[1.63; 3.96]	<.001
Anastrozole	52 / 502 (10.4)	25 / 467 (5.4)	1.93	[1.22; 3.07]	0.005
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.598				
Yes	102 / 1194 (8.5)	45 / 1146 (3.9)	2.18	[1.55; 3.06]	<.001
No	17 / 215 (7.9)	6 / 216 (2.8)	2.85	[1.14; 7.08]	0.024
Prior adjuvant chemotherapy					
Interaction test	p = 0.919				
Yes	68 / 694 (9.8)	29 / 673 (4.3)	2.27	[1.49; 3.47]	<.001
No	51 / 715 (7.1)	22 / 689 (3.2)	2.23	[1.37; 3.64]	0.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.445				
Yes	36 / 528 (6.8)	18 / 503 (3.6)	1.91	[1.10; 3.31]	0.022
No	83 / 881 (9.4)	33 / 859 (3.8)	2.45	[1.66; 3.63]	<.001
Prior endocrine therapy					
Interaction test	p = 0.417				
Yes	83 / 957 (8.7)	33 / 940 (3.5)	2.47	[1.67; 3.66]	<.001
No	36 / 452 (8.0)	18 / 422 (4.3)	1.87	[1.08; 3.24]	0.026
Prior mastectomy					
Interaction test	p = 0.976				
Yes	75 / 857 (8.8)	33 / 847 (3.9)	2.25	[1.51; 3.35]	<.001
No	44 / 552 (8.0)	18 / 515 (3.5)	2.28	[1.34; 3.89]	0.003
Prior radiotherapy					
Interaction test	p = 0.838				
Yes	111 / 1253 (8.9)	47 / 1203 (3.9)	2.27	[1.63; 3.16]	<.001
No	8 / 156 (5.1)	4 / 159 (2.5)	2.04	[0.63; 6.63]	0.237
<p>N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.35 PT abdominal pain: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Abdominal pain					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.743				
NA/WE/O	68 / 899 (7.6)	33 / 856 (3.9)	1.96	[1.31; 2.94]	0.001
ROW	21 / 510 (4.1)	9 / 506 (1.8)	2.32	[1.07; 5.01]	0.033
Geographical region					
Interaction test	p = 0.794				
Europe	46 / 832 (5.5)	21 / 824 (2.5)	2.17	[1.31; 3.60]	0.003
North America/Australia	33 / 400 (8.3)	18 / 364 (4.9)	1.67	[0.96; 2.91]	0.071
Asia	4 / 102 (3.9)	1 / 101 (1.0)	3.96	[0.45; 34.83]	0.215
Latin America	6 / 75 (8.0)	2 / 73 (2.7)	2.92	[0.61; 14.00]	0.180
Age group 1 at randomization					
Interaction test	p = 0.769				
<45	3 / 60 (5.0)	2 / 52 (3.8)	1.30	[0.23; 7.48]	0.769
45 to 54	18 / 300 (6.0)	10 / 322 (3.1)	1.93	[0.91; 4.12]	0.088
55 to 64	43 / 651 (6.6)	17 / 642 (2.6)	2.49	[1.44; 4.33]	0.001
≥65	25 / 398 (6.3)	13 / 346 (3.8)	1.67	[0.87; 3.22]	0.124
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.599				
<Median	37 / 633 (5.8)	16 / 632 (2.5)	2.31	[1.30; 4.11]	0.004
≥Median	52 / 776 (6.7)	26 / 730 (3.6)	1.88	[1.19; 2.98]	0.007
Race					
Interaction test	p = 0.302				
Asian	6 / 128 (4.7)	1 / 127 (0.8)	5.95	[0.73; 48.75]	0.096
Non-Asian	75 / 1203 (6.2)	38 / 1167 (3.3)	1.91	[1.31; 2.80]	<.001
BMI at screening					
Interaction test	p = 0.292				
≥25	57 / 935 (6.1)	31 / 935 (3.3)	1.84	[1.20; 2.82]	0.005
<25	32 / 460 (7.0)	10 / 410 (2.4)	2.85	[1.42; 5.73]	0.003
AJCC Anatomic Stage Group					
Interaction test	p = 0.504				
Group I/II	39 / 585 (6.7)	22 / 589 (3.7)	1.78	[1.07; 2.97]	0.026
Group III	49 / 823 (6.0)	20 / 772 (2.6)	2.30	[1.38; 3.83]	0.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.615				
IA/IB/IIA	24 / 310 (7.7)	14 / 311 (4.5)	1.72	[0.91; 3.26]	0.097
IIB	15 / 275 (5.5)	8 / 278 (2.9)	1.90	[0.82; 4.40]	0.136
IIIA	26 / 482 (5.4)	12 / 450 (2.7)	2.02	[1.03; 3.96]	0.040
IIIB	6 / 100 (6.0)	4 / 82 (4.9)	1.23	[0.36; 4.21]	0.742
IIIC	17 / 241 (7.1)	4 / 240 (1.7)	4.23	[1.45; 12.39]	0.008
Tumor category					
Interaction test	p = 0.614				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	81 / 1287 (6.3)	38 / 1258 (3.0)	2.08	[1.43; 3.04]	<.001
>T3	7 / 113 (6.2)	4 / 97 (4.1)	1.50	[0.45; 4.98]	0.506
Nodal status					
Interaction test	p = 0.545				
N0	13 / 190 (6.8)	5 / 200 (2.5)	2.74	[0.99; 7.53]	0.051
N1-N3	76 / 1216 (6.3)	37 / 1160 (3.2)	1.96	[1.33; 2.88]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.048				
Grade 1	4 / 102 (3.9)	8 / 106 (7.5)	0.52	[0.16; 1.67]	0.272
Grade 2	58 / 842 (6.9)	21 / 768 (2.7)	2.52	[1.54; 4.11]	<.001
Grade 3	24 / 373 (6.4)	11 / 397 (2.8)	2.32	[1.15; 4.67]	0.018
Histological subtype					
Interaction test	p = 0.601				
Ductal	59 / 1025 (5.8)	32 / 1010 (3.2)	1.82	[1.19; 2.77]	0.005
Lobular	21 / 291 (7.2)	7 / 276 (2.5)	2.85	[1.23; 6.59]	0.015
Other	9 / 92 (9.8)	3 / 76 (3.9)	2.48	[0.70; 8.83]	0.162
Ki67 status from surgical specimen					
Interaction test	p = 0.024				
Ki67≤20	35 / 660 (5.3)	25 / 629 (4.0)	1.33	[0.81; 2.20]	0.260
Ki67>20	27 / 489 (5.5)	7 / 516 (1.4)	4.07	[1.79; 9.26]	<.001
Type of NSAI					
Interaction test	p = 0.249				
Letrozole	49 / 907 (5.4)	28 / 895 (3.1)	1.73	[1.10; 2.72]	0.019
Anastrozole	40 / 502 (8.0)	14 / 467 (3.0)	2.66	[1.47; 4.82]	0.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.142				
Yes	79 / 1194 (6.6)	33 / 1146 (2.9)	2.30	[1.54; 3.42]	<.001
No	10 / 215 (4.7)	9 / 216 (4.2)	1.12	[0.46; 2.69]	0.807
Prior adjuvant chemotherapy					
Interaction test	p = 0.339				
Yes	47 / 694 (6.8)	26 / 673 (3.9)	1.75	[1.10; 2.80]	0.019
No	42 / 715 (5.9)	16 / 689 (2.3)	2.53	[1.44; 4.46]	0.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.146				
Yes	33 / 528 (6.3)	10 / 503 (2.0)	3.14	[1.57; 6.31]	0.001
No	56 / 881 (6.4)	32 / 859 (3.7)	1.71	[1.12; 2.61]	0.014
Prior endocrine therapy					
Interaction test	p = 0.844				
Yes	64 / 957 (6.7)	30 / 940 (3.2)	2.10	[1.37; 3.20]	<.001
No	25 / 452 (5.5)	12 / 422 (2.8)	1.95	[0.99; 3.82]	0.054
Prior mastectomy					
Interaction test	p = 0.290				
Yes	54 / 857 (6.3)	22 / 847 (2.6)	2.43	[1.49; 3.95]	<.001
No	35 / 552 (6.3)	20 / 515 (3.9)	1.63	[0.96; 2.79]	0.073
Prior radiotherapy					
Interaction test	p = 0.849				
Yes	74 / 1253 (5.9)	35 / 1203 (2.9)	2.03	[1.37; 3.01]	<.001
No	15 / 156 (9.6)	7 / 159 (4.4)	2.18	[0.92; 5.21]	0.078
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.36 PT abdominal pain upper: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Abdominal pain upper					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.759				
NA/WE/O	49 / 899 (5.5)	30 / 856 (3.5)	1.56	[1.00; 2.43]	0.052
ROW	18 / 510 (3.5)	13 / 506 (2.6)	1.37	[0.68; 2.77]	0.376
Geographical region					
Interaction test	p = 0.352				
Europe	45 / 832 (5.4)	30 / 824 (3.6)	1.49	[0.95; 2.33]	0.086
North America/Australia	17 / 400 (4.3)	8 / 364 (2.2)	1.93	[0.84; 4.43]	0.119
Asia	2 / 102 (2.0)	0 / 101 (0.0)	4.95	[0.24; >99.99]	0.300
Latin America	3 / 75 (4.0)	5 / 73 (6.8)	0.58	[0.14; 2.36]	0.450
Age group 1 at randomization					
Interaction test	p = 0.442				
<45	4 / 60 (6.7)	0 / 52 (0.0)	7.82	[0.43; >99.99]	0.164
45 to 54	14 / 300 (4.7)	11 / 322 (3.4)	1.37	[0.63; 2.96]	0.430
55 to 64	27 / 651 (4.1)	23 / 642 (3.6)	1.16	[0.67; 2.00]	0.599
≥65	22 / 398 (5.5)	9 / 346 (2.6)	2.13	[0.99; 4.55]	0.053
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.287				
<Median	28 / 633 (4.4)	23 / 632 (3.6)	1.22	[0.71; 2.09]	0.479
≥Median	39 / 776 (5.0)	20 / 730 (2.7)	1.83	[1.08; 3.11]	0.025
Race					
Interaction test	N.E.				
Asian	5 / 128 (3.9)	0 / 127 (0.0)	10.91	[0.61; >99.99]	0.104
Non-Asian	55 / 1203 (4.6)	38 / 1167 (3.3)	1.40	[0.94; 2.11]	0.101
BMI at screening					
Interaction test	p = 0.396				
≥25	42 / 935 (4.5)	31 / 935 (3.3)	1.35	[0.86; 2.14]	0.191
<25	24 / 460 (5.2)	11 / 410 (2.7)	1.94	[0.96; 3.92]	0.063
AJCC Anatomic Stage Group					
Interaction test	p = 0.554				
Group I/II	26 / 585 (4.4)	15 / 589 (2.5)	1.75	[0.93; 3.26]	0.081
Group III	41 / 823 (5.0)	28 / 772 (3.6)	1.37	[0.86; 2.20]	0.186

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.962				
IA/IB/IIA	13 / 310 (4.2)	8 / 311 (2.6)	1.63	[0.69; 3.88]	0.269
IIB	13 / 275 (4.7)	7 / 278 (2.5)	1.88	[0.76; 4.63]	0.172
IIIA	31 / 482 (6.4)	20 / 450 (4.4)	1.45	[0.84; 2.50]	0.186
IIIB	4 / 100 (4.0)	3 / 82 (3.7)	1.09	[0.25; 4.75]	0.905
IIIC	6 / 241 (2.5)	5 / 240 (2.1)	1.20	[0.37; 3.86]	0.766
Tumor category					
Interaction test	p = 0.911				
T0	0 / 5 (0.0)	1 / 5 (20.0)	0.33	[0.02; 6.65]	0.472
T1-T3	62 / 1287 (4.8)	39 / 1258 (3.1)	1.55	[1.05; 2.30]	0.028
>T3	5 / 113 (4.4)	3 / 97 (3.1)	1.43	[0.35; 5.83]	0.617
Nodal status					
Interaction test	p = 0.326				
N0	8 / 190 (4.2)	3 / 200 (1.5)	2.81	[0.76; 10.42]	0.123
N1-N3	59 / 1216 (4.9)	40 / 1160 (3.4)	1.41	[0.95; 2.09]	0.089
Histological grade at time of surgery					
Interaction test	p = 0.705				
Grade 1	6 / 102 (5.9)	6 / 106 (5.7)	1.04	[0.35; 3.12]	0.945
Grade 2	40 / 842 (4.8)	24 / 768 (3.1)	1.52	[0.93; 2.50]	0.098
Grade 3	19 / 373 (5.1)	11 / 397 (2.8)	1.84	[0.89; 3.81]	0.102
Histological subtype					
Interaction test	p = 0.650				
Ductal	45 / 1025 (4.4)	30 / 1010 (3.0)	1.48	[0.94; 2.33]	0.091
Lobular	15 / 291 (5.2)	11 / 276 (4.0)	1.29	[0.60; 2.77]	0.507
Other	7 / 92 (7.6)	2 / 76 (2.6)	2.89	[0.62; 13.51]	0.177
Ki67 status from surgical specimen					
Interaction test	p = 0.389				
Ki67≤20	33 / 660 (5.0)	25 / 629 (4.0)	1.26	[0.76; 2.09]	0.376
Ki67>20	21 / 489 (4.3)	12 / 516 (2.3)	1.85	[0.92; 3.71]	0.085
Type of NSAI					
Interaction test	p = 0.289				
Letrozole	49 / 907 (5.4)	28 / 895 (3.1)	1.73	[1.10; 2.72]	0.019
Anastrozole	18 / 502 (3.6)	15 / 467 (3.2)	1.12	[0.57; 2.19]	0.749
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.914				
Yes	53 / 1194 (4.4)	34 / 1146 (3.0)	1.50	[0.98; 2.28]	0.062
No	14 / 215 (6.5)	9 / 216 (4.2)	1.56	[0.69; 3.53]	0.283
Prior adjuvant chemotherapy					
Interaction test	p = 0.312				
Yes	36 / 694 (5.2)	19 / 673 (2.8)	1.84	[1.06; 3.17]	0.029
No	31 / 715 (4.3)	24 / 689 (3.5)	1.24	[0.74; 2.10]	0.412

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.423				
Yes	19 / 528 (3.6)	15 / 503 (3.0)	1.21	[0.62; 2.35]	0.580
No	48 / 881 (5.4)	28 / 859 (3.3)	1.67	[1.06; 2.64]	0.027
Prior endocrine therapy					
Interaction test	p = 0.927				
Yes	45 / 957 (4.7)	29 / 940 (3.1)	1.52	[0.96; 2.41]	0.071
No	22 / 452 (4.9)	14 / 422 (3.3)	1.47	[0.76; 2.83]	0.253
Prior mastectomy					
Interaction test	p = 0.453				
Yes	38 / 857 (4.4)	28 / 847 (3.3)	1.34	[0.83; 2.17]	0.229
No	29 / 552 (5.3)	15 / 515 (2.9)	1.80	[0.98; 3.33]	0.059
Prior radiotherapy					
Interaction test	p = 0.557				
Yes	63 / 1253 (5.0)	39 / 1203 (3.2)	1.55	[1.05; 2.29]	0.028
No	4 / 156 (2.6)	4 / 159 (2.5)	1.02	[0.26; 4.00]	0.978
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.37 PT dyspepsia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Dyspepsia					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.740				
NA/WE/O	52 / 899 (5.8)	26 / 856 (3.0)	1.90	[1.20; 3.02]	0.006
ROW	14 / 510 (2.7)	6 / 506 (1.2)	2.32	[0.90; 5.98]	0.083
Geographical region					
Interaction test	p = 0.419				
Europe	36 / 832 (4.3)	18 / 824 (2.2)	1.98	[1.13; 3.46]	0.016
North America/Australia	24 / 400 (6.0)	10 / 364 (2.7)	2.18	[1.06; 4.50]	0.034
Asia	3 / 102 (2.9)	4 / 101 (4.0)	0.74	[0.17; 3.23]	0.692
Latin America	3 / 75 (4.0)	0 / 73 (0.0)	6.82	[0.36; >99.99]	0.202
Age group 1 at randomization					
Interaction test	p = 0.811				
<45	2 / 60 (3.3)	2 / 52 (3.8)	0.87	[0.13; 5.94]	0.884
45 to 54	14 / 300 (4.7)	6 / 322 (1.9)	2.50	[0.98; 6.43]	0.056
55 to 64	37 / 651 (5.7)	18 / 642 (2.8)	2.03	[1.17; 3.52]	0.012
≥65	13 / 398 (3.3)	6 / 346 (1.7)	1.88	[0.72; 4.90]	0.195
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.245				
<Median	32 / 633 (5.1)	20 / 632 (3.2)	1.60	[0.92; 2.76]	0.094
≥Median	34 / 776 (4.4)	12 / 730 (1.6)	2.67	[1.39; 5.11]	0.003
Race					
Interaction test	p = 0.063				
Asian	4 / 128 (3.1)	6 / 127 (4.7)	0.66	[0.19; 2.29]	0.514
Non-Asian	62 / 1203 (5.2)	26 / 1167 (2.2)	2.31	[1.47; 3.63]	<.001
BMI at screening					
Interaction test	p = 0.854				
≥25	47 / 935 (5.0)	23 / 935 (2.5)	2.04	[1.25; 3.34]	0.004
<25	19 / 460 (4.1)	9 / 410 (2.2)	1.88	[0.86; 4.11]	0.113
AJCC Anatomic Stage Group					
Interaction test	p = 0.247				
Group I/II	22 / 585 (3.8)	15 / 589 (2.5)	1.48	[0.77; 2.82]	0.237
Group III	44 / 823 (5.3)	17 / 772 (2.2)	2.43	[1.40; 4.21]	0.002

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.663				
IA/IB/IIA	13 / 310 (4.2)	9 / 311 (2.9)	1.45	[0.63; 3.34]	0.384
IIB	9 / 275 (3.3)	6 / 278 (2.2)	1.52	[0.55; 4.20]	0.423
IIIA	29 / 482 (6.0)	13 / 450 (2.9)	2.08	[1.10; 3.96]	0.025
IIIB	2 / 100 (2.0)	0 / 82 (0.0)	4.11	[0.20; 84.40]	0.359
IIIC	13 / 241 (5.4)	4 / 240 (1.7)	3.24	[1.07; 9.78]	0.037
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	63 / 1287 (4.9)	32 / 1258 (2.5)	1.92	[1.27; 2.92]	0.002
>T3	3 / 113 (2.7)	0 / 97 (0.0)	6.02	[0.31; >99.99]	0.233
Nodal status					
Interaction test	p = 0.413				
N0	6 / 190 (3.2)	5 / 200 (2.5)	1.26	[0.39; 4.07]	0.696
N1-N3	60 / 1216 (4.9)	27 / 1160 (2.3)	2.12	[1.36; 3.31]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.948				
Grade 1	9 / 102 (8.8)	5 / 106 (4.7)	1.87	[0.65; 5.39]	0.246
Grade 2	40 / 842 (4.8)	19 / 768 (2.5)	1.92	[1.12; 3.29]	0.017
Grade 3	15 / 373 (4.0)	7 / 397 (1.8)	2.28	[0.94; 5.53]	0.068
Histological subtype					
Interaction test	p = 0.425				
Ductal	46 / 1025 (4.5)	26 / 1010 (2.6)	1.74	[1.09; 2.80]	0.021
Lobular	16 / 291 (5.5)	4 / 276 (1.4)	3.79	[1.28; 11.21]	0.016
Other	4 / 92 (4.3)	2 / 76 (2.6)	1.65	[0.31; 8.78]	0.556
Ki67 status from surgical specimen					
Interaction test	p = 0.512				
Ki67≤20	28 / 660 (4.2)	17 / 629 (2.7)	1.57	[0.87; 2.84]	0.136
Ki67>20	15 / 489 (3.1)	7 / 516 (1.4)	2.26	[0.93; 5.50]	0.072
Type of NSAI					
Interaction test	p = 0.062				
Letrozole	38 / 907 (4.2)	25 / 895 (2.8)	1.50	[0.91; 2.46]	0.109
Anastrozole	28 / 502 (5.6)	7 / 467 (1.5)	3.72	[1.64; 8.44]	0.002
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.424				
Yes	54 / 1194 (4.5)	28 / 1146 (2.4)	1.85	[1.18; 2.90]	0.007
No	12 / 215 (5.6)	4 / 216 (1.9)	3.01	[0.99; 9.20]	0.053
Prior adjuvant chemotherapy					
Interaction test	p = 0.312				
Yes	34 / 694 (4.9)	20 / 673 (3.0)	1.65	[0.96; 2.83]	0.071
No	32 / 715 (4.5)	12 / 689 (1.7)	2.57	[1.33; 4.95]	0.005

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.643				
Yes	22 / 528 (4.2)	9 / 503 (1.8)	2.33	[1.08; 5.01]	0.031
No	44 / 881 (5.0)	23 / 859 (2.7)	1.87	[1.14; 3.06]	0.014
Prior endocrine therapy					
Interaction test	p = 0.023				
Yes	56 / 957 (5.9)	21 / 940 (2.2)	2.62	[1.60; 4.29]	<.001
No	10 / 452 (2.2)	11 / 422 (2.6)	0.85	[0.36; 1.98]	0.704
Prior mastectomy					
Interaction test	p = 0.690				
Yes	43 / 857 (5.0)	20 / 847 (2.4)	2.12	[1.26; 3.58]	0.005
No	23 / 552 (4.2)	12 / 515 (2.3)	1.79	[0.90; 3.56]	0.098
Prior radiotherapy					
Interaction test	p = 0.592				
Yes	62 / 1253 (4.9)	29 / 1203 (2.4)	2.05	[1.33; 3.17]	0.001
No	4 / 156 (2.6)	3 / 159 (1.9)	1.36	[0.31; 5.97]	0.685
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.38 PT dry mouth: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Dry mouth					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.619				
NA/WE/O	42 / 899 (4.7)	23 / 856 (2.7)	1.74	[1.05; 2.87]	0.030
ROW	16 / 510 (3.1)	7 / 506 (1.4)	2.27	[0.94; 5.47]	0.068
Geographical region					
Interaction test	p = 0.611				
Europe	32 / 832 (3.8)	16 / 824 (1.9)	1.98	[1.10; 3.58]	0.024
North America/Australia	24 / 400 (6.0)	14 / 364 (3.8)	1.56	[0.82; 2.97]	0.176
Asia	2 / 102 (2.0)	0 / 101 (0.0)	4.95	[0.24; >99.99]	0.300
Latin America	0 / 75 (0.0)	0 / 73 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	p = 0.363				
<45	4 / 60 (6.7)	0 / 52 (0.0)	7.82	[0.43; >99.99]	0.164
45 to 54	13 / 300 (4.3)	4 / 322 (1.2)	3.49	[1.15; 10.58]	0.027
55 to 64	24 / 651 (3.7)	17 / 642 (2.6)	1.39	[0.76; 2.57]	0.289
≥65	17 / 398 (4.3)	9 / 346 (2.6)	1.64	[0.74; 3.64]	0.221
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.038				
<Median	28 / 633 (4.4)	8 / 632 (1.3)	3.49	[1.61; 7.61]	0.002
≥Median	30 / 776 (3.9)	22 / 730 (3.0)	1.28	[0.75; 2.20]	0.367
Race					
Interaction test	p = 0.457				
Asian	4 / 128 (3.1)	1 / 127 (0.8)	3.97	[0.45; 35.02]	0.215
Non-Asian	49 / 1203 (4.1)	28 / 1167 (2.4)	1.70	[1.07; 2.68]	0.023
BMI at screening					
Interaction test	p = 0.062				
≥25	38 / 935 (4.1)	26 / 935 (2.8)	1.46	[0.89; 2.39]	0.129
<25	20 / 460 (4.3)	4 / 410 (1.0)	4.46	[1.54; 12.93]	0.006
AJCC Anatomic Stage Group					
Interaction test	p = 0.019				
Group I/II	17 / 585 (2.9)	17 / 589 (2.9)	1.01	[0.52; 1.95]	0.984
Group III	41 / 823 (5.0)	13 / 772 (1.7)	2.96	[1.60; 5.48]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.136				
IA/IB/IIA	8 / 310 (2.6)	11 / 311 (3.5)	0.73	[0.30; 1.79]	0.491
IIB	9 / 275 (3.3)	6 / 278 (2.2)	1.52	[0.55; 4.20]	0.423
IIIA	22 / 482 (4.6)	7 / 450 (1.6)	2.93	[1.27; 6.80]	0.012
IIIB	5 / 100 (5.0)	0 / 82 (0.0)	9.04	[0.51; >99.99]	0.134
IIIC	14 / 241 (5.8)	6 / 240 (2.5)	2.32	[0.91; 5.95]	0.079
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	51 / 1287 (4.0)	30 / 1258 (2.4)	1.66	[1.07; 2.59]	0.025
>T3	7 / 113 (6.2)	0 / 97 (0.0)	12.89	[0.75; >99.99]	0.079
Nodal status					
Interaction test	p = 0.124				
N0	7 / 190 (3.7)	8 / 200 (4.0)	0.92	[0.34; 2.49]	0.871
N1-N3	51 / 1216 (4.2)	22 / 1160 (1.9)	2.21	[1.35; 3.62]	0.002
Histological grade at time of surgery					
Interaction test	p = 0.735				
Grade 1	6 / 102 (5.9)	0 / 106 (0.0)	13.50	[0.77; >99.99]	0.075
Grade 2	34 / 842 (4.0)	19 / 768 (2.5)	1.63	[0.94; 2.84]	0.082
Grade 3	18 / 373 (4.8)	10 / 397 (2.5)	1.92	[0.90; 4.10]	0.094
Histological subtype					
Interaction test	p = 0.648				
Ductal	38 / 1025 (3.7)	19 / 1010 (1.9)	1.97	[1.14; 3.39]	0.014
Lobular	11 / 291 (3.8)	8 / 276 (2.9)	1.30	[0.53; 3.19]	0.561
Other	9 / 92 (9.8)	3 / 76 (3.9)	2.48	[0.70; 8.83]	0.162
Ki67 status from surgical specimen					
Interaction test	p = 0.049				
Ki67≤20	25 / 660 (3.8)	18 / 629 (2.9)	1.32	[0.73; 2.40]	0.356
Ki67>20	15 / 489 (3.1)	3 / 516 (0.6)	5.28	[1.54; 18.11]	0.008
Type of NSAI					
Interaction test	p = 0.064				
Letrozole	26 / 907 (2.9)	20 / 895 (2.2)	1.28	[0.72; 2.28]	0.396
Anastrozole	32 / 502 (6.4)	10 / 467 (2.1)	2.98	[1.48; 5.99]	0.002
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.238				
Yes	52 / 1194 (4.4)	24 / 1146 (2.1)	2.08	[1.29; 3.35]	0.003
No	6 / 215 (2.8)	6 / 216 (2.8)	1.00	[0.33; 3.07]	0.993
Prior adjuvant chemotherapy					
Interaction test	p = 0.961				
Yes	33 / 694 (4.8)	17 / 673 (2.5)	1.88	[1.06; 3.35]	0.031
No	25 / 715 (3.5)	13 / 689 (1.9)	1.85	[0.96; 3.59]	0.068

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.392				
Yes	21 / 528 (4.0)	8 / 503 (1.6)	2.50	[1.12; 5.59]	0.026
No	37 / 881 (4.2)	22 / 859 (2.6)	1.64	[0.98; 2.76]	0.062
Prior endocrine therapy					
Interaction test	p = 0.517				
Yes	36 / 957 (3.8)	21 / 940 (2.2)	1.68	[0.99; 2.86]	0.054
No	22 / 452 (4.9)	9 / 422 (2.1)	2.28	[1.06; 4.90]	0.034
Prior mastectomy					
Interaction test	p = 0.355				
Yes	36 / 857 (4.2)	16 / 847 (1.9)	2.22	[1.24; 3.98]	0.007
No	22 / 552 (4.0)	14 / 515 (2.7)	1.47	[0.76; 2.83]	0.255
Prior radiotherapy					
Interaction test	p = 0.273				
Yes	57 / 1253 (4.5)	28 / 1203 (2.3)	1.95	[1.25; 3.05]	0.003
No	1 / 156 (0.6)	2 / 159 (1.3)	0.51	[0.05; 5.56]	0.580
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.39 PT stomatitis: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Stomatitis					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.002				
NA/WE/O	44 / 899 (4.9)	1 / 856 (0.1)	41.90	[5.79; >99.99]	<.001
ROW	5 / 510 (1.0)	5 / 506 (1.0)	0.99	[0.29; 3.41]	0.990
Geographical region					
Interaction test	p = 0.013				
Europe	25 / 832 (3.0)	3 / 824 (0.4)	8.25	[2.50; 27.23]	<.001
North America/Australia	23 / 400 (5.8)	0 / 364 (0.0)	42.78	[2.61; >99.99]	0.009
Asia	1 / 102 (1.0)	3 / 101 (3.0)	0.33	[0.03; 3.12]	0.333
Latin America	0 / 75 (0.0)	0 / 73 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	p = 0.294				
<45	1 / 60 (1.7)	1 / 52 (1.9)	0.87	[0.06; 13.51]	0.919
45 to 54	8 / 300 (2.7)	2 / 322 (0.6)	4.29	[0.92; 20.06]	0.064
55 to 64	30 / 651 (4.6)	2 / 642 (0.3)	14.79	[3.55; 61.64]	<.001
≥65	10 / 398 (2.5)	1 / 346 (0.3)	8.69	[1.12; 67.57]	0.039
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.978				
<Median	24 / 633 (3.8)	3 / 632 (0.5)	7.99	[2.42; 26.39]	<.001
≥Median	25 / 776 (3.2)	3 / 730 (0.4)	7.84	[2.38; 25.85]	<.001
Race					
Interaction test	p = 0.011				
Asian	3 / 128 (2.3)	3 / 127 (2.4)	0.99	[0.20; 4.82]	0.992
Non-Asian	40 / 1203 (3.3)	3 / 1167 (0.3)	12.93	[4.01; 41.69]	<.001
BMI at screening					
Interaction test	p = 0.413				
≥25	31 / 935 (3.3)	3 / 935 (0.3)	10.33	[3.17; 33.68]	<.001
<25	17 / 460 (3.7)	3 / 410 (0.7)	5.05	[1.49; 17.11]	0.009
AJCC Anatomic Stage Group					
Interaction test	p = 0.537				
Group I/II	22 / 585 (3.8)	2 / 589 (0.3)	11.08	[2.62; 46.89]	0.001
Group III	27 / 823 (3.3)	4 / 772 (0.5)	6.33	[2.23; 18.01]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.768				
IA/IB/IIA	10 / 310 (3.2)	1 / 311 (0.3)	10.03	[1.29; 77.90]	0.027
IIB	12 / 275 (4.4)	1 / 278 (0.4)	12.13	[1.59; 92.66]	0.016
IIIA	13 / 482 (2.7)	3 / 450 (0.7)	4.05	[1.16; 14.10]	0.028
IIIB	6 / 100 (6.0)	0 / 82 (0.0)	10.68	[0.61; >99.99]	0.105
IIIC	8 / 241 (3.3)	1 / 240 (0.4)	7.97	[1.00; 63.21]	0.050
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	43 / 1287 (3.3)	6 / 1258 (0.5)	7.01	[2.99; 16.40]	<.001
>T3	6 / 113 (5.3)	0 / 97 (0.0)	11.18	[0.64; >99.99]	0.099
Nodal status					
Interaction test	N.E.				
N0	8 / 190 (4.2)	0 / 200 (0.0)	17.89	[1.04; >99.99]	0.047
N1-N3	41 / 1216 (3.4)	6 / 1160 (0.5)	6.52	[2.78; 15.30]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.651				
Grade 1	6 / 102 (5.9)	1 / 106 (0.9)	6.24	[0.76; 50.89]	0.088
Grade 2	25 / 842 (3.0)	2 / 768 (0.3)	11.40	[2.71; 47.98]	<.001
Grade 3	13 / 373 (3.5)	3 / 397 (0.8)	4.61	[1.32; 16.06]	0.016
Histological subtype					
Interaction test	N.E.				
Ductal	36 / 1025 (3.5)	6 / 1010 (0.6)	5.91	[2.50; 13.97]	<.001
Lobular	9 / 291 (3.1)	0 / 276 (0.0)	18.02	[1.05; >99.99]	0.046
Other	4 / 92 (4.3)	0 / 76 (0.0)	7.45	[0.41; >99.99]	0.176
Ki67 status from surgical specimen					
Interaction test	p = 0.913				
Ki67≤20	22 / 660 (3.3)	3 / 629 (0.5)	6.99	[2.10; 23.23]	0.002
Ki67>20	18 / 489 (3.7)	3 / 516 (0.6)	6.33	[1.88; 21.36]	0.003
Type of NSAI					
Interaction test	N.E.				
Letrozole	34 / 907 (3.7)	6 / 895 (0.7)	5.59	[2.36; 13.25]	<.001
Anastrozole	15 / 502 (3.0)	0 / 467 (0.0)	28.84	[1.73; >99.99]	0.019
Prior neo/adjuvant chemotherapy					
Interaction test	N.E.				
Yes	45 / 1194 (3.8)	6 / 1146 (0.5)	7.20	[3.08; 16.81]	<.001
No	4 / 215 (1.9)	0 / 216 (0.0)	9.04	[0.49; >99.99]	0.139
Prior adjuvant chemotherapy					
Interaction test	p = 0.146				
Yes	24 / 694 (3.5)	5 / 673 (0.7)	4.65	[1.79; 12.13]	0.002
No	25 / 715 (3.5)	1 / 689 (0.1)	24.09	[3.27; >99.99]	0.002

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.219				
Yes	22 / 528 (4.2)	1 / 503 (0.2)	20.96	[2.84; >99.99]	0.003
No	27 / 881 (3.1)	5 / 859 (0.6)	5.27	[2.04; 13.61]	<.001
Prior endocrine therapy					
Interaction test	p = 0.267				
Yes	35 / 957 (3.7)	3 / 940 (0.3)	11.46	[3.54; 37.13]	<.001
No	14 / 452 (3.1)	3 / 422 (0.7)	4.36	[1.26; 15.05]	0.020
Prior mastectomy					
Interaction test	p = 0.154				
Yes	24 / 857 (2.8)	1 / 847 (0.1)	23.72	[3.22; >99.99]	0.002
No	25 / 552 (4.5)	5 / 515 (1.0)	4.66	[1.80; 12.09]	0.002
Prior radiotherapy					
Interaction test	N.E.				
Yes	44 / 1253 (3.5)	6 / 1203 (0.5)	7.04	[3.01; 16.46]	<.001
No	5 / 156 (3.2)	0 / 159 (0.0)	11.21	[0.63; >99.99]	0.101
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.40 PT toothache: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Toothache					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.312				
NA/WE/O	21 / 899 (2.3)	5 / 856 (0.6)	4.00	[1.51; 10.56]	0.005
ROW	5 / 510 (1.0)	3 / 506 (0.6)	1.65	[0.40; 6.88]	0.489
Geographical region					
Interaction test	p = 0.936				
Europe	15 / 832 (1.8)	5 / 824 (0.6)	2.97	[1.08; 8.14]	0.034
North America/Australia	6 / 400 (1.5)	1 / 364 (0.3)	5.46	[0.66; 45.14]	0.115
Asia	3 / 102 (2.9)	1 / 101 (1.0)	2.97	[0.31; 28.08]	0.342
Latin America	2 / 75 (2.7)	1 / 73 (1.4)	1.95	[0.18; 21.01]	0.583
Age group 1 at randomization					
Interaction test	p = 0.477				
<45	2 / 60 (3.3)	0 / 52 (0.0)	4.34	[0.21; 88.48]	0.339
45 to 54	6 / 300 (2.0)	1 / 322 (0.3)	6.44	[0.78; 53.18]	0.084
55 to 64	13 / 651 (2.0)	4 / 642 (0.6)	3.21	[1.05; 9.78]	0.041
≥65	5 / 398 (1.3)	3 / 346 (0.9)	1.45	[0.35; 6.02]	0.610
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.145				
<Median	14 / 633 (2.2)	2 / 632 (0.3)	6.99	[1.59; 30.63]	0.010
≥Median	12 / 776 (1.5)	6 / 730 (0.8)	1.88	[0.71; 4.99]	0.204
Race					
Interaction test	p = 0.859				
Asian	4 / 128 (3.1)	1 / 127 (0.8)	3.97	[0.45; 35.02]	0.215
Non-Asian	20 / 1203 (1.7)	6 / 1167 (0.5)	3.23	[1.30; 8.02]	0.011
BMI at screening					
Interaction test	p = 0.180				
≥25	15 / 935 (1.6)	7 / 935 (0.7)	2.14	[0.88; 5.23]	0.094
<25	11 / 460 (2.4)	1 / 410 (0.2)	9.80	[1.27; 75.61]	0.029
AJCC Anatomic Stage Group					
Interaction test	N.E.				
Group I/II	9 / 585 (1.5)	0 / 589 (0.0)	19.13	[1.12; >99.99]	0.042
Group III	17 / 823 (2.1)	8 / 772 (1.0)	1.99	[0.87; 4.59]	0.105

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.986				
IA/IB/IIA	4 / 310 (1.3)	0 / 311 (0.0)	9.03	[0.49; >99.99]	0.139
IIB	5 / 275 (1.8)	0 / 278 (0.0)	11.12	[0.62; >99.99]	0.102
IIIA	11 / 482 (2.3)	5 / 450 (1.1)	2.05	[0.72; 5.87]	0.179
IIIB	2 / 100 (2.0)	1 / 82 (1.2)	1.64	[0.15; 17.77]	0.684
IIIC	4 / 241 (1.7)	2 / 240 (0.8)	1.99	[0.37; 10.77]	0.424
Tumor category					
Interaction test	p = 0.606				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	24 / 1287 (1.9)	7 / 1258 (0.6)	3.35	[1.45; 7.75]	0.005
>T3	2 / 113 (1.8)	1 / 97 (1.0)	1.72	[0.16; 18.64]	0.657
Nodal status					
Interaction test	N.E.				
N0	1 / 190 (0.5)	0 / 200 (0.0)	3.16	[0.13; 77.02]	0.481
N1-N3	25 / 1216 (2.1)	8 / 1160 (0.7)	2.98	[1.35; 6.58]	0.007
Histological grade at time of surgery					
Interaction test	p = 0.431				
Grade 1	2 / 102 (2.0)	2 / 106 (1.9)	1.04	[0.15; 7.24]	0.969
Grade 2	18 / 842 (2.1)	4 / 768 (0.5)	4.10	[1.40; 12.07]	0.010
Grade 3	5 / 373 (1.3)	1 / 397 (0.3)	5.32	[0.62; 45.34]	0.126
Histological subtype					
Interaction test	p = 0.371				
Ductal	19 / 1025 (1.9)	6 / 1010 (0.6)	3.12	[1.25; 7.78]	0.015
Lobular	4 / 291 (1.4)	0 / 276 (0.0)	8.54	[0.46; >99.99]	0.150
Other	3 / 92 (3.3)	2 / 76 (2.6)	1.24	[0.21; 7.23]	0.812
Ki67 status from surgical specimen					
Interaction test	p = 0.722				
Ki67≤20	15 / 660 (2.3)	5 / 629 (0.8)	2.86	[1.05; 7.82]	0.041
Ki67>20	6 / 489 (1.2)	3 / 516 (0.6)	2.11	[0.53; 8.39]	0.289
Type of NSAI					
Interaction test	p = 0.165				
Letrozole	15 / 907 (1.7)	7 / 895 (0.8)	2.11	[0.87; 5.16]	0.100
Anastrozole	11 / 502 (2.2)	1 / 467 (0.2)	10.23	[1.33; 78.95]	0.026
Prior neo/adjuvant chemotherapy					
Interaction test	N.E.				
Yes	25 / 1194 (2.1)	8 / 1146 (0.7)	3.00	[1.36; 6.62]	0.007
No	1 / 215 (0.5)	0 / 216 (0.0)	3.01	[0.12; 73.57]	0.499
Prior adjuvant chemotherapy					
Interaction test	p = 0.973				
Yes	16 / 694 (2.3)	5 / 673 (0.7)	3.10	[1.14; 8.42]	0.026
No	10 / 715 (1.4)	3 / 689 (0.4)	3.21	[0.89; 11.62]	0.075

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.983				
Yes	10 / 528 (1.9)	3 / 503 (0.6)	3.18	[0.88; 11.47]	0.078
No	16 / 881 (1.8)	5 / 859 (0.6)	3.12	[1.15; 8.48]	0.026
Prior endocrine therapy					
Interaction test	p = 0.023				
Yes	21 / 957 (2.2)	3 / 940 (0.3)	6.88	[2.06; 22.97]	0.002
No	5 / 452 (1.1)	5 / 422 (1.2)	0.93	[0.27; 3.20]	0.913
Prior mastectomy					
Interaction test	p = 0.517				
Yes	19 / 857 (2.2)	5 / 847 (0.6)	3.76	[1.41; 10.01]	0.008
No	7 / 552 (1.3)	3 / 515 (0.6)	2.18	[0.57; 8.37]	0.258
Prior radiotherapy					
Interaction test	N.E.				
Yes	24 / 1253 (1.9)	8 / 1203 (0.7)	2.88	[1.30; 6.39]	0.009
No	2 / 156 (1.3)	0 / 159 (0.0)	5.10	[0.25; >99.99]	0.292
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.41 PT abdominal distension: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Abdominal distension					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.054				
NA/WE/O	22 / 899 (2.4)	3 / 856 (0.4)	6.98	[2.10; 23.24]	0.002
ROW	3 / 510 (0.6)	3 / 506 (0.6)	0.99	[0.20; 4.89]	0.992
Geographical region					
Interaction test	p = 0.178				
Europe	12 / 832 (1.4)	3 / 824 (0.4)	3.96	[1.12; 13.99]	0.032
North America/Australia	10 / 400 (2.5)	1 / 364 (0.3)	9.10	[1.17; 70.74]	0.035
Asia	1 / 102 (1.0)	2 / 101 (2.0)	0.50	[0.05; 5.37]	0.563
Latin America	2 / 75 (2.7)	0 / 73 (0.0)	4.87	[0.24; 99.70]	0.304
Age group 1 at randomization					
Interaction test	p = 0.347				
<45	2 / 60 (3.3)	0 / 52 (0.0)	4.34	[0.21; 88.48]	0.339
45 to 54	6 / 300 (2.0)	2 / 322 (0.6)	3.22	[0.65; 15.83]	0.150
55 to 64	11 / 651 (1.7)	1 / 642 (0.2)	10.85	[1.40; 83.78]	0.022
≥65	6 / 398 (1.5)	3 / 346 (0.9)	1.74	[0.44; 6.90]	0.432
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.875				
<Median	13 / 633 (2.1)	3 / 632 (0.5)	4.33	[1.24; 15.11]	0.022
≥Median	12 / 776 (1.5)	3 / 730 (0.4)	3.76	[1.07; 13.28]	0.039
Race					
Interaction test	p = 0.291				
Asian	3 / 128 (2.3)	2 / 127 (1.6)	1.49	[0.25; 8.76]	0.660
Non-Asian	19 / 1203 (1.6)	4 / 1167 (0.3)	4.61	[1.57; 13.50]	0.005
BMI at screening					
Interaction test	p = 0.027				
≥25	20 / 935 (2.1)	2 / 935 (0.2)	10.00	[2.34; 42.66]	0.002
<25	5 / 460 (1.1)	4 / 410 (1.0)	1.11	[0.30; 4.12]	0.871
AJCC Anatomic Stage Group					
Interaction test	p = 0.072				
Group I/II	15 / 585 (2.6)	1 / 589 (0.2)	15.10	[2.00; >99.99]	0.008
Group III	10 / 823 (1.2)	5 / 772 (0.6)	1.88	[0.64; 5.46]	0.249
Anatomic stages					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	24 / 1287 (1.9)	6 / 1258 (0.5)	3.91	[1.60; 9.53]	0.003
>T3	1 / 113 (0.9)	0 / 97 (0.0)	2.58	[0.11; 62.59]	0.560
Nodal status					
Interaction test	N.E.				
N0	3 / 190 (1.6)	0 / 200 (0.0)	7.37	[0.38; >99.99]	0.186
N1-N3	22 / 1216 (1.8)	6 / 1160 (0.5)	3.50	[1.42; 8.60]	0.006
Histological grade at time of surgery					
Interaction test	p = 0.925				
Grade 1	3 / 102 (2.9)	1 / 106 (0.9)	3.12	[0.33; 29.48]	0.321
Grade 2	11 / 842 (1.3)	2 / 768 (0.3)	5.02	[1.12; 22.56]	0.036
Grade 3	10 / 373 (2.7)	2 / 397 (0.5)	5.32	[1.17; 24.13]	0.030
Histological subtype					
Interaction test	p = 0.527				
Ductal	18 / 1025 (1.8)	3 / 1010 (0.3)	5.91	[1.75; 20.01]	0.004
Lobular	4 / 291 (1.4)	2 / 276 (0.7)	1.90	[0.35; 10.27]	0.458
Other	3 / 92 (3.3)	1 / 76 (1.3)	2.48	[0.26; 23.34]	0.428
Ki67 status from surgical specimen					
Interaction test	p = 0.942				
Ki67≤20	12 / 660 (1.8)	4 / 629 (0.6)	2.86	[0.93; 8.82]	0.068
Ki67>20	3 / 489 (0.6)	1 / 516 (0.2)	3.17	[0.33; 30.33]	0.318
Type of NSAI					
Interaction test	p = 0.746				
Letrozole	14 / 907 (1.5)	3 / 895 (0.3)	4.60	[1.33; 15.97]	0.016
Anastrozole	11 / 502 (2.2)	3 / 467 (0.6)	3.41	[0.96; 12.15]	0.058
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.998				
Yes	21 / 1194 (1.8)	5 / 1146 (0.4)	4.03	[1.53; 10.65]	0.005
No	4 / 215 (1.9)	1 / 216 (0.5)	4.02	[0.45; 35.66]	0.212
Prior adjuvant chemotherapy					
Interaction test	p = 0.525				
Yes	13 / 694 (1.9)	4 / 673 (0.6)	3.15	[1.03; 9.62]	0.044
No	12 / 715 (1.7)	2 / 689 (0.3)	5.78	[1.30; 25.74]	0.021
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.397				
Yes	8 / 528 (1.5)	3 / 503 (0.6)	2.54	[0.68; 9.52]	0.167
No	17 / 881 (1.9)	3 / 859 (0.3)	5.53	[1.63; 18.79]	0.006

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior endocrine therapy					
Interaction test	p = 0.668				
Yes	14 / 957 (1.5)	4 / 940 (0.4)	3.44	[1.14; 10.41]	0.029
No	11 / 452 (2.4)	2 / 422 (0.5)	5.13	[1.14; 23.03]	0.033
Prior mastectomy					
Interaction test	p = 0.952				
Yes	16 / 857 (1.9)	4 / 847 (0.5)	3.95	[1.33; 11.78]	0.014
No	9 / 552 (1.6)	2 / 515 (0.4)	4.20	[0.91; 19.34]	0.066
Prior radiotherapy					
Interaction test	N.E.				
Yes	25 / 1253 (2.0)	6 / 1203 (0.5)	4.00	[1.65; 9.72]	0.002
No	0 / 156 (0.0)	0 / 159 (0.0)	N.E.	N.E.	N.E.
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.42 PT haemorrhoids: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Haemorrhoids					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.922				
NA/WE/O	16 / 899 (1.8)	4 / 856 (0.5)	3.81	[1.28; 11.35]	0.016
ROW	7 / 510 (1.4)	2 / 506 (0.4)	3.47	[0.72; 16.64]	0.119
Geographical region					
Interaction test	p = 0.533				
Europe	12 / 832 (1.4)	5 / 824 (0.6)	2.38	[0.84; 6.72]	0.102
North America/Australia	5 / 400 (1.3)	0 / 364 (0.0)	10.01	[0.56; >99.99]	0.118
Asia	5 / 102 (4.9)	1 / 101 (1.0)	4.95	[0.59; 41.63]	0.141
Latin America	1 / 75 (1.3)	0 / 73 (0.0)	2.92	[0.12; 70.56]	0.509
Age group 1 at randomization					
Interaction test	p = 0.933				
<45	3 / 60 (5.0)	0 / 52 (0.0)	6.08	[0.32; >99.99]	0.229
45 to 54	5 / 300 (1.7)	2 / 322 (0.6)	2.68	[0.52; 13.73]	0.236
55 to 64	10 / 651 (1.5)	4 / 642 (0.6)	2.47	[0.78; 7.82]	0.126
≥65	5 / 398 (1.3)	0 / 346 (0.0)	9.57	[0.53; >99.99]	0.126
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.487				
<Median	11 / 633 (1.7)	2 / 632 (0.3)	5.49	[1.22; 24.67]	0.026
≥Median	12 / 776 (1.5)	4 / 730 (0.5)	2.82	[0.91; 8.71]	0.071
Race					
Interaction test	p = 0.829				
Asian	5 / 128 (3.9)	1 / 127 (0.8)	4.96	[0.59; 41.87]	0.141
Non-Asian	16 / 1203 (1.3)	4 / 1167 (0.3)	3.88	[1.30; 11.57]	0.015
BMI at screening					
Interaction test	p = 0.268				
≥25	13 / 935 (1.4)	2 / 935 (0.2)	6.50	[1.47; 28.72]	0.014
<25	10 / 460 (2.2)	4 / 410 (1.0)	2.23	[0.70; 7.05]	0.173
AJCC Anatomic Stage Group					
Interaction test	p = 0.462				
Group I/II	11 / 585 (1.9)	4 / 589 (0.7)	2.77	[0.89; 8.65]	0.080
Group III	12 / 823 (1.5)	2 / 772 (0.3)	5.63	[1.26; 25.07]	0.023

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.654				
IA/IB/IIA	6 / 310 (1.9)	3 / 311 (1.0)	2.01	[0.51; 7.95]	0.322
IIB	5 / 275 (1.8)	1 / 278 (0.4)	5.05	[0.59; 42.98]	0.138
IIIA	10 / 482 (2.1)	2 / 450 (0.4)	4.67	[1.03; 21.19]	0.046
IIIB	1 / 100 (1.0)	0 / 82 (0.0)	2.47	[0.10; 59.72]	0.579
IIIC	1 / 241 (0.4)	0 / 240 (0.0)	2.99	[0.12; 72.97]	0.502
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	22 / 1287 (1.7)	6 / 1258 (0.5)	3.58	[1.46; 8.81]	0.005
>T3	1 / 113 (0.9)	0 / 97 (0.0)	2.58	[0.11; 62.59]	0.560
Nodal status					
Interaction test	N.E.				
N0	2 / 190 (1.1)	0 / 200 (0.0)	5.26	[0.25; >99.99]	0.283
N1-N3	21 / 1216 (1.7)	6 / 1160 (0.5)	3.34	[1.35; 8.24]	0.009
Histological grade at time of surgery					
Interaction test	N.E.				
Grade 1	0 / 102 (0.0)	1 / 106 (0.9)	0.35	[0.01; 8.40]	0.515
Grade 2	15 / 842 (1.8)	5 / 768 (0.7)	2.74	[1.00; 7.49]	0.050
Grade 3	7 / 373 (1.9)	0 / 397 (0.0)	15.96	[0.91; >99.99]	0.058
Histological subtype					
Interaction test	p = 0.489				
Ductal	17 / 1025 (1.7)	3 / 1010 (0.3)	5.58	[1.64; 18.99]	0.006
Lobular	4 / 291 (1.4)	2 / 276 (0.7)	1.90	[0.35; 10.27]	0.458
Other	2 / 92 (2.2)	1 / 76 (1.3)	1.65	[0.15; 17.87]	0.679
Ki67 status from surgical specimen					
Interaction test	N.E.				
Ki67≤20	14 / 660 (2.1)	5 / 629 (0.8)	2.67	[0.97; 7.37]	0.058
Ki67>20	3 / 489 (0.6)	0 / 516 (0.0)	7.39	[0.38; >99.99]	0.186
Type of NSAI					
Interaction test	N.E.				
Letrozole	18 / 907 (2.0)	6 / 895 (0.7)	2.96	[1.18; 7.42]	0.021
Anastrozole	5 / 502 (1.0)	0 / 467 (0.0)	10.23	[0.57; >99.99]	0.115
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.595				
Yes	21 / 1194 (1.8)	5 / 1146 (0.4)	4.03	[1.53; 10.65]	0.005
No	2 / 215 (0.9)	1 / 216 (0.5)	2.01	[0.18; 21.99]	0.568
Prior adjuvant chemotherapy					
Interaction test	p = 0.076				
Yes	17 / 694 (2.4)	2 / 673 (0.3)	8.24	[1.91; 35.54]	0.005
No	6 / 715 (0.8)	4 / 689 (0.6)	1.45	[0.41; 5.10]	0.567

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.106				
Yes	4 / 528 (0.8)	3 / 503 (0.6)	1.27	[0.29; 5.65]	0.753
No	19 / 881 (2.2)	3 / 859 (0.3)	6.18	[1.83; 20.79]	0.003
Prior endocrine therapy					
Interaction test	p = 0.429				
Yes	15 / 957 (1.6)	5 / 940 (0.5)	2.95	[1.08; 8.08]	0.036
No	8 / 452 (1.8)	1 / 422 (0.2)	7.47	[0.94; 59.46]	0.057
Prior mastectomy					
Interaction test	p = 0.841				
Yes	16 / 857 (1.9)	4 / 847 (0.5)	3.95	[1.33; 11.78]	0.014
No	7 / 552 (1.3)	2 / 515 (0.4)	3.27	[0.68; 15.65]	0.139
Prior radiotherapy					
Interaction test	N.E.				
Yes	21 / 1253 (1.7)	6 / 1203 (0.5)	3.36	[1.36; 8.30]	0.009
No	2 / 156 (1.3)	0 / 159 (0.0)	5.10	[0.25; >99.99]	0.292
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.43 PT mouth ulceration: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Mouth ulceration					
	n / N (%)	n / N (%)			
Region					
Interaction test	N.E.				
NA/WE/O	18 / 899 (2.0)	1 / 856 (0.1)	17.14	[2.29; >99.99]	0.006
ROW	0 / 510 (0.0)	1 / 506 (0.2)	0.33	[0.01; 8.10]	0.498
Geographical region					
Interaction test	N.E.				
Europe	12 / 832 (1.4)	1 / 824 (0.1)	11.88	[1.55; 91.19]	0.017
North America/Australia	6 / 400 (1.5)	0 / 364 (0.0)	11.83	[0.67; >99.99]	0.092
Asia	0 / 102 (0.0)	1 / 101 (1.0)	0.33	[0.01; 8.01]	0.496
Latin America	0 / 75 (0.0)	0 / 73 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	N.E.				
<45	0 / 60 (0.0)	0 / 52 (0.0)	N.E.	N.E.	N.E.
45 to 54	6 / 300 (2.0)	2 / 322 (0.6)	3.22	[0.65; 15.83]	0.150
55 to 64	10 / 651 (1.5)	0 / 642 (0.0)	20.71	[1.22; >99.99]	0.036
≥65	2 / 398 (0.5)	0 / 346 (0.0)	4.35	[0.21; 90.27]	0.342
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	N.E.				
<Median	14 / 633 (2.2)	2 / 632 (0.3)	6.99	[1.59; 30.63]	0.010
≥Median	4 / 776 (0.5)	0 / 730 (0.0)	8.47	[0.46; >99.99]	0.152
Race					
Interaction test	p = 0.115				
Asian	1 / 128 (0.8)	1 / 127 (0.8)	0.99	[0.06; 15.69]	0.996
Non-Asian	16 / 1203 (1.3)	1 / 1167 (0.1)	15.52	[2.06; >99.99]	0.008
BMI at screening					
Interaction test	N.E.				
≥25	11 / 935 (1.2)	2 / 935 (0.2)	5.50	[1.22; 24.75]	0.026
<25	7 / 460 (1.5)	0 / 410 (0.0)	13.37	[0.77; >99.99]	0.076
AJCC Anatomic Stage Group					
Interaction test	N.E.				
Group I/II	4 / 585 (0.7)	0 / 589 (0.0)	9.06	[0.49; >99.99]	0.139
Group III	14 / 823 (1.7)	2 / 772 (0.3)	6.57	[1.50; 28.80]	0.013

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.732				
IA/IB/IIA	1 / 310 (0.3)	0 / 311 (0.0)	3.01	[0.12; 73.59]	0.499
IIB	3 / 275 (1.1)	0 / 278 (0.0)	7.08	[0.37; >99.99]	0.195
IIIA	9 / 482 (1.9)	1 / 450 (0.2)	8.40	[1.07; 66.06]	0.043
IIIB	0 / 100 (0.0)	0 / 82 (0.0)	N.E.	N.E.	N.E.
IIIC	5 / 241 (2.1)	1 / 240 (0.4)	4.98	[0.59; 42.30]	0.141
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	18 / 1287 (1.4)	2 / 1258 (0.2)	8.80	[2.05; 37.84]	0.003
>T3	0 / 113 (0.0)	0 / 97 (0.0)	N.E.	N.E.	N.E.
Nodal status					
Interaction test	N.E.				
N0	0 / 190 (0.0)	0 / 200 (0.0)	N.E.	N.E.	N.E.
N1-N3	18 / 1216 (1.5)	2 / 1160 (0.2)	8.59	[2.00; 36.92]	0.004
Histological grade at time of surgery					
Interaction test	p = 0.720				
Grade 1	0 / 102 (0.0)	0 / 106 (0.0)	N.E.	N.E.	N.E.
Grade 2	12 / 842 (1.4)	1 / 768 (0.1)	10.95	[1.43; 83.98]	0.021
Grade 3	6 / 373 (1.6)	1 / 397 (0.3)	6.39	[0.77; 52.79]	0.085
Histological subtype					
Interaction test	p = 0.270				
Ductal	10 / 1025 (1.0)	1 / 1010 (0.1)	9.85	[1.26; 76.83]	0.029
Lobular	6 / 291 (2.1)	0 / 276 (0.0)	12.33	[0.70; >99.99]	0.086
Other	2 / 92 (2.2)	1 / 76 (1.3)	1.65	[0.15; 17.87]	0.679
Ki67 status from surgical specimen					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Type of NSAI					
Interaction test	p = 0.733				
Letrozole	11 / 907 (1.2)	1 / 895 (0.1)	10.85	[1.40; 83.90]	0.022
Anastrozole	7 / 502 (1.4)	1 / 467 (0.2)	6.51	[0.80; 52.73]	0.079
Prior neo/adjuvant chemotherapy					
Interaction test	N.E.				
Yes	18 / 1194 (1.5)	2 / 1146 (0.2)	8.64	[2.01; 37.14]	0.004
No	0 / 215 (0.0)	0 / 216 (0.0)	N.E.	N.E.	N.E.
Prior adjuvant chemotherapy					
Interaction test	p = 0.756				
Yes	11 / 694 (1.6)	1 / 673 (0.1)	10.67	[1.38; 82.40]	0.023
No	7 / 715 (1.0)	1 / 689 (0.1)	6.75	[0.83; 54.68]	0.074

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.751				
Yes	7 / 528 (1.3)	1 / 503 (0.2)	6.67	[0.82; 54.01]	0.075
No	11 / 881 (1.2)	1 / 859 (0.1)	10.73	[1.39; 82.89]	0.023
Prior endocrine therapy					
Interaction test	p = 0.620				
Yes	12 / 957 (1.3)	1 / 940 (0.1)	11.79	[1.54; 90.47]	0.018
No	6 / 452 (1.3)	1 / 422 (0.2)	5.60	[0.68; 46.34]	0.110
Prior mastectomy					
Interaction test	N.E.				
Yes	12 / 857 (1.4)	2 / 847 (0.2)	5.93	[1.33; 26.42]	0.020
No	6 / 552 (1.1)	0 / 515 (0.0)	12.13	[0.69; >99.99]	0.089
Prior radiotherapy					
Interaction test	N.E.				
Yes	18 / 1253 (1.4)	2 / 1203 (0.2)	8.64	[2.01; 37.16]	0.004
No	0 / 156 (0.0)	0 / 159 (0.0)	N.E.	N.E.	N.E.
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.44 SOC infections and infestations: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Infections and infestations					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.882				
NA/WE/O	504 / 899 (56.1)	351 / 856 (41.0)	1.37	[1.24; 1.51]	<.001
ROW	190 / 510 (37.3)	126 / 506 (24.9)	1.50	[1.24; 1.81]	<.001
Geographical region					
Interaction test	p = 0.463				
Europe	385 / 832 (46.3)	272 / 824 (33.0)	1.40	[1.24; 1.58]	<.001
North America/Australia	230 / 400 (57.5)	159 / 364 (43.7)	1.32	[1.14; 1.52]	<.001
Asia	41 / 102 (40.2)	28 / 101 (27.7)	1.45	[0.98; 2.15]	0.065
Latin America	38 / 75 (50.7)	18 / 73 (24.7)	2.05	[1.30; 3.25]	0.002
Age group 1 at randomization					
Interaction test	p = 0.013				
<45	37 / 60 (61.7)	19 / 52 (36.5)	1.69	[1.12; 2.54]	0.012
45 to 54	170 / 300 (56.7)	105 / 322 (32.6)	1.74	[1.44; 2.09]	<.001
55 to 64	298 / 651 (45.8)	236 / 642 (36.8)	1.25	[1.09; 1.42]	0.001
≥65	189 / 398 (47.5)	117 / 346 (33.8)	1.40	[1.17; 1.68]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.013				
<Median	344 / 633 (54.3)	220 / 632 (34.8)	1.56	[1.37; 1.78]	<.001
≥Median	350 / 776 (45.1)	257 / 730 (35.2)	1.28	[1.13; 1.45]	<.001
Race					
Interaction test	p = 0.535				
Asian	56 / 128 (43.8)	42 / 127 (33.1)	1.32	[0.96; 1.81]	0.083
Non-Asian	601 / 1203 (50.0)	407 / 1167 (34.9)	1.43	[1.30; 1.58]	<.001
BMI at screening					
Interaction test	p = 0.545				
≥25	469 / 935 (50.2)	328 / 935 (35.1)	1.43	[1.28; 1.59]	<.001
<25	218 / 460 (47.4)	143 / 410 (34.9)	1.36	[1.15; 1.60]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.015				
Group I/II	262 / 585 (44.8)	212 / 589 (36.0)	1.24	[1.08; 1.43]	0.002
Group III	432 / 823 (52.5)	265 / 772 (34.3)	1.53	[1.36; 1.72]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.055				
IA/IB/IIA	135 / 310 (43.5)	108 / 311 (34.7)	1.25	[1.03; 1.53]	0.025
IIB	127 / 275 (46.2)	104 / 278 (37.4)	1.23	[1.01; 1.51]	0.038
IIIA	253 / 482 (52.5)	170 / 450 (37.8)	1.39	[1.20; 1.61]	<.001
IIIB	48 / 100 (48.0)	21 / 82 (25.6)	1.87	[1.23; 2.86]	0.003
IIIC	131 / 241 (54.4)	74 / 240 (30.8)	1.76	[1.41; 2.20]	<.001
Tumor category					
Interaction test	p = 0.217				
T0	2 / 5 (40.0)	1 / 5 (20.0)	2.00	[0.26; 15.62]	0.509
T1-T3	635 / 1287 (49.3)	451 / 1258 (35.9)	1.38	[1.25; 1.51]	<.001
>T3	56 / 113 (49.6)	24 / 97 (24.7)	2.00	[1.35; 2.97]	<.001
Nodal status					
Interaction test	p = 0.947				
N0	83 / 190 (43.7)	61 / 200 (30.5)	1.43	[1.10; 1.87]	0.008
N1-N3	609 / 1216 (50.1)	416 / 1160 (35.9)	1.40	[1.27; 1.54]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.436				
Grade 1	50 / 102 (49.0)	44 / 106 (41.5)	1.18	[0.87; 1.59]	0.278
Grade 2	413 / 842 (49.0)	265 / 768 (34.5)	1.42	[1.26; 1.60]	<.001
Grade 3	196 / 373 (52.5)	140 / 397 (35.3)	1.49	[1.26; 1.76]	<.001
Histological subtype					
Interaction test	p = 0.920				
Ductal	497 / 1025 (48.5)	344 / 1010 (34.1)	1.42	[1.28; 1.58]	<.001
Lobular	154 / 291 (52.9)	106 / 276 (38.4)	1.38	[1.15; 1.66]	<.001
Other	43 / 92 (46.7)	27 / 76 (35.5)	1.32	[0.91; 1.91]	0.150
Ki67 status from surgical specimen					
Interaction test	p = 0.232				
Ki67≤20	321 / 660 (48.6)	230 / 629 (36.6)	1.33	[1.17; 1.51]	<.001
Ki67>20	224 / 489 (45.8)	152 / 516 (29.5)	1.56	[1.32; 1.83]	<.001
Type of NSAI					
Interaction test	p = 0.414				
Letrozole	432 / 907 (47.6)	310 / 895 (34.6)	1.38	[1.23; 1.54]	<.001
Anastrozole	262 / 502 (52.2)	167 / 467 (35.8)	1.46	[1.26; 1.69]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.035				
Yes	605 / 1194 (50.7)	398 / 1146 (34.7)	1.46	[1.32; 1.61]	<.001
No	89 / 215 (41.4)	79 / 216 (36.6)	1.13	[0.89; 1.43]	0.306
Prior adjuvant chemotherapy					
Interaction test	p = 0.638				
Yes	363 / 694 (52.3)	260 / 673 (38.6)	1.35	[1.20; 1.52]	<.001
No	331 / 715 (46.3)	217 / 689 (31.5)	1.47	[1.28; 1.68]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.027				
Yes	257 / 528 (48.7)	148 / 503 (29.4)	1.65	[1.41; 1.94]	<.001
No	437 / 881 (49.6)	329 / 859 (38.3)	1.30	[1.16; 1.44]	<.001
Prior endocrine therapy					
Interaction test	p = 0.857				
Yes	484 / 957 (50.6)	342 / 940 (36.4)	1.39	[1.25; 1.54]	<.001
No	210 / 452 (46.5)	135 / 422 (32.0)	1.45	[1.22; 1.72]	<.001
Prior mastectomy					
Interaction test	p = 0.467				
Yes	430 / 857 (50.2)	295 / 847 (34.8)	1.44	[1.29; 1.61]	<.001
No	264 / 552 (47.8)	182 / 515 (35.3)	1.35	[1.17; 1.57]	<.001
Prior radiotherapy					
Interaction test	p = 0.353				
Yes	628 / 1253 (50.1)	424 / 1203 (35.2)	1.42	[1.29; 1.56]	<.001
No	66 / 156 (42.3)	53 / 159 (33.3)	1.27	[0.95; 1.69]	0.103
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.45 PT covid-19: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
COVID-19					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.185				
NA/WE/O	182 / 899 (20.2)	125 / 856 (14.6)	1.39	[1.13; 1.71]	0.002
ROW	81 / 510 (15.9)	43 / 506 (8.5)	1.87	[1.32; 2.65]	<.001
Geographical region					
Interaction test	p = 0.147				
Europe	148 / 832 (17.8)	103 / 824 (12.5)	1.42	[1.13; 1.80]	0.003
North America/Australia	82 / 400 (20.5)	53 / 364 (14.6)	1.41	[1.03; 1.93]	0.033
Asia	16 / 102 (15.7)	9 / 101 (8.9)	1.76	[0.82; 3.80]	0.149
Latin America	17 / 75 (22.7)	3 / 73 (4.1)	5.52	[1.69; 18.03]	0.005
Age group 1 at randomization					
Interaction test	p = 0.749				
<45	17 / 60 (28.3)	8 / 52 (15.4)	1.84	[0.87; 3.91]	0.112
45 to 54	69 / 300 (23.0)	46 / 322 (14.3)	1.61	[1.15; 2.26]	0.006
55 to 64	109 / 651 (16.7)	78 / 642 (12.1)	1.38	[1.05; 1.80]	0.020
≥65	68 / 398 (17.1)	36 / 346 (10.4)	1.64	[1.13; 2.40]	0.010
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.713				
<Median	134 / 633 (21.2)	86 / 632 (13.6)	1.56	[1.21; 1.99]	<.001
≥Median	129 / 776 (16.6)	82 / 730 (11.2)	1.48	[1.14; 1.91]	0.003
Race					
Interaction test	p = 0.711				
Asian	21 / 128 (16.4)	15 / 127 (11.8)	1.39	[0.75; 2.57]	0.295
Non-Asian	228 / 1203 (19.0)	142 / 1167 (12.2)	1.56	[1.28; 1.89]	<.001
BMI at screening					
Interaction test	p = 0.192				
≥25	178 / 935 (19.0)	108 / 935 (11.6)	1.65	[1.32; 2.06]	<.001
<25	83 / 460 (18.0)	58 / 410 (14.1)	1.28	[0.94; 1.74]	0.121
AJCC Anatomic Stage Group					
Interaction test	p = 0.010				
Group I/II	98 / 585 (16.8)	85 / 589 (14.4)	1.16	[0.89; 1.52]	0.274
Group III	165 / 823 (20.0)	83 / 772 (10.8)	1.86	[1.46; 2.38]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.068				
IA/IB/IIA	49 / 310 (15.8)	42 / 311 (13.5)	1.17	[0.80; 1.71]	0.418
IIB	49 / 275 (17.8)	43 / 278 (15.5)	1.15	[0.79; 1.67]	0.459
IIIA	103 / 482 (21.4)	58 / 450 (12.9)	1.66	[1.23; 2.23]	<.001
IIIB	19 / 100 (19.0)	4 / 82 (4.9)	3.90	[1.38; 11.00]	0.010
IIIC	43 / 241 (17.8)	21 / 240 (8.8)	2.04	[1.25; 3.33]	0.004
Tumor category					
Interaction test	p = 0.093				
T0	2 / 5 (40.0)	1 / 5 (20.0)	2.00	[0.26; 15.62]	0.509
T1-T3	240 / 1287 (18.6)	163 / 1258 (13.0)	1.44	[1.20; 1.73]	<.001
>T3	21 / 113 (18.6)	4 / 97 (4.1)	4.51	[1.60; 12.68]	0.004
Nodal status					
Interaction test	p = 0.422				
N0	35 / 190 (18.4)	20 / 200 (10.0)	1.84	[1.10; 3.07]	0.019
N1-N3	227 / 1216 (18.7)	148 / 1160 (12.8)	1.46	[1.21; 1.77]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.672				
Grade 1	17 / 102 (16.7)	15 / 106 (14.2)	1.18	[0.62; 2.23]	0.616
Grade 2	159 / 842 (18.9)	92 / 768 (12.0)	1.58	[1.24; 2.00]	<.001
Grade 3	73 / 373 (19.6)	48 / 397 (12.1)	1.62	[1.16; 2.26]	0.005
Histological subtype					
Interaction test	p = 0.634				
Ductal	181 / 1025 (17.7)	124 / 1010 (12.3)	1.44	[1.16; 1.78]	<.001
Lobular	63 / 291 (21.6)	34 / 276 (12.3)	1.76	[1.20; 2.58]	0.004
Other	19 / 92 (20.7)	10 / 76 (13.2)	1.57	[0.78; 3.17]	0.209
Ki67 status from surgical specimen					
Interaction test	p = 0.501				
Ki67≤20	127 / 660 (19.2)	77 / 629 (12.2)	1.57	[1.21; 2.04]	<.001
Ki67>20	90 / 489 (18.4)	52 / 516 (10.1)	1.83	[1.33; 2.51]	<.001
Type of NSAI					
Interaction test	p = 0.046				
Letrozole	160 / 907 (17.6)	119 / 895 (13.3)	1.33	[1.07; 1.65]	0.011
Anastrozole	103 / 502 (20.5)	49 / 467 (10.5)	1.96	[1.43; 2.68]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.081				
Yes	232 / 1194 (19.4)	138 / 1146 (12.0)	1.61	[1.33; 1.96]	<.001
No	31 / 215 (14.4)	30 / 216 (13.9)	1.04	[0.65; 1.65]	0.875
Prior adjuvant chemotherapy					
Interaction test	p = 0.254				
Yes	131 / 694 (18.9)	93 / 673 (13.8)	1.37	[1.07; 1.74]	0.012
No	132 / 715 (18.5)	75 / 689 (10.9)	1.70	[1.30; 2.21]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.010				
Yes	108 / 528 (20.5)	49 / 503 (9.7)	2.10	[1.53; 2.88]	<.001
No	155 / 881 (17.6)	119 / 859 (13.9)	1.27	[1.02; 1.58]	0.033
Prior endocrine therapy					
Interaction test	p = 0.449				
Yes	175 / 957 (18.3)	119 / 940 (12.7)	1.44	[1.17; 1.79]	<.001
No	88 / 452 (19.5)	49 / 422 (11.6)	1.68	[1.21; 2.32]	0.002
Prior mastectomy					
Interaction test	p = 0.678				
Yes	162 / 857 (18.9)	109 / 847 (12.9)	1.47	[1.17; 1.84]	<.001
No	101 / 552 (18.3)	59 / 515 (11.5)	1.60	[1.19; 2.15]	0.002
Prior radiotherapy					
Interaction test	p = 0.121				
Yes	240 / 1253 (19.2)	145 / 1203 (12.1)	1.59	[1.31; 1.92]	<.001
No	23 / 156 (14.7)	23 / 159 (14.5)	1.02	[0.60; 1.74]	0.944
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.46 PT urinary tract infection: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Urinary tract infection					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.610				
NA/WE/O	96 / 899 (10.7)	64 / 856 (7.5)	1.43	[1.06; 1.93]	0.021
ROW	13 / 510 (2.5)	11 / 506 (2.2)	1.17	[0.53; 2.59]	0.694
Geographical region					
Interaction test	p = 0.416				
Europe	43 / 832 (5.2)	25 / 824 (3.0)	1.70	[1.05; 2.76]	0.031
North America/Australia	59 / 400 (14.8)	40 / 364 (11.0)	1.34	[0.92; 1.95]	0.124
Asia	3 / 102 (2.9)	4 / 101 (4.0)	0.74	[0.17; 3.23]	0.692
Latin America	4 / 75 (5.3)	6 / 73 (8.2)	0.65	[0.19; 2.21]	0.488
Age group 1 at randomization					
Interaction test	p = 0.368				
<45	5 / 60 (8.3)	3 / 52 (5.8)	1.44	[0.36; 5.76]	0.602
45 to 54	20 / 300 (6.7)	19 / 322 (5.9)	1.13	[0.62; 2.07]	0.694
55 to 64	40 / 651 (6.1)	34 / 642 (5.3)	1.16	[0.74; 1.81]	0.512
≥65	44 / 398 (11.1)	19 / 346 (5.5)	2.01	[1.20; 3.38]	0.008
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.328				
<Median	39 / 633 (6.2)	33 / 632 (5.2)	1.18	[0.75; 1.85]	0.471
≥Median	70 / 776 (9.0)	42 / 730 (5.8)	1.57	[1.08; 2.27]	0.017
Race					
Interaction test	p = 0.106				
Asian	5 / 128 (3.9)	8 / 127 (6.3)	0.62	[0.21; 1.84]	0.390
Non-Asian	103 / 1203 (8.6)	64 / 1167 (5.5)	1.56	[1.15; 2.11]	0.004
BMI at screening					
Interaction test	p = 0.393				
≥25	73 / 935 (7.8)	56 / 935 (6.0)	1.30	[0.93; 1.82]	0.122
<25	35 / 460 (7.6)	18 / 410 (4.4)	1.73	[1.00; 3.01]	0.051
AJCC Anatomic Stage Group					
Interaction test	p = 0.879				
Group I/II	43 / 585 (7.4)	30 / 589 (5.1)	1.44	[0.92; 2.27]	0.112
Group III	66 / 823 (8.0)	45 / 772 (5.8)	1.38	[0.95; 1.98]	0.088

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.020				
IA/IB/IIA	30 / 310 (9.7)	13 / 311 (4.2)	2.32	[1.23; 4.35]	0.009
IIB	13 / 275 (4.7)	17 / 278 (6.1)	0.77	[0.38; 1.56]	0.473
IIIA	36 / 482 (7.5)	32 / 450 (7.1)	1.05	[0.66; 1.66]	0.834
IIIB	5 / 100 (5.0)	5 / 82 (6.1)	0.82	[0.25; 2.74]	0.747
IIIC	25 / 241 (10.4)	8 / 240 (3.3)	3.11	[1.43; 6.76]	0.004
Tumor category					
Interaction test	p = 0.577				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	103 / 1287 (8.0)	70 / 1258 (5.6)	1.44	[1.07; 1.93]	0.015
>T3	6 / 113 (5.3)	5 / 97 (5.2)	1.03	[0.32; 3.27]	0.960
Nodal status					
Interaction test	p = 0.784				
N0	16 / 190 (8.4)	11 / 200 (5.5)	1.53	[0.73; 3.21]	0.260
N1-N3	92 / 1216 (7.6)	64 / 1160 (5.5)	1.37	[1.01; 1.87]	0.045
Histological grade at time of surgery					
Interaction test	p = 0.506				
Grade 1	11 / 102 (10.8)	5 / 106 (4.7)	2.29	[0.82; 6.35]	0.113
Grade 2	63 / 842 (7.5)	44 / 768 (5.7)	1.31	[0.90; 1.90]	0.160
Grade 3	33 / 373 (8.8)	21 / 397 (5.3)	1.67	[0.99; 2.84]	0.056
Histological subtype					
Interaction test	p = 0.466				
Ductal	80 / 1025 (7.8)	50 / 1010 (5.0)	1.58	[1.12; 2.22]	0.009
Lobular	23 / 291 (7.9)	21 / 276 (7.6)	1.04	[0.59; 1.83]	0.896
Other	6 / 92 (6.5)	4 / 76 (5.3)	1.24	[0.36; 4.23]	0.732
Ki67 status from surgical specimen					
Interaction test	p = 0.276				
Ki67≤20	52 / 660 (7.9)	35 / 629 (5.6)	1.42	[0.94; 2.14]	0.100
Ki67>20	34 / 489 (7.0)	17 / 516 (3.3)	2.11	[1.19; 3.73]	0.010
Type of NSAI					
Interaction test	p = 0.337				
Letrozole	58 / 907 (6.4)	46 / 895 (5.1)	1.24	[0.85; 1.81]	0.254
Anastrozole	51 / 502 (10.2)	29 / 467 (6.2)	1.64	[1.06; 2.54]	0.028
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.336				
Yes	88 / 1194 (7.4)	64 / 1146 (5.6)	1.32	[0.97; 1.80]	0.081
No	21 / 215 (9.8)	11 / 216 (5.1)	1.92	[0.95; 3.88]	0.070
Prior adjuvant chemotherapy					
Interaction test	p = 0.728				
Yes	58 / 694 (8.4)	42 / 673 (6.2)	1.34	[0.91; 1.96]	0.135
No	51 / 715 (7.1)	33 / 689 (4.8)	1.49	[0.97; 2.28]	0.066

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.664				
Yes	31 / 528 (5.9)	23 / 503 (4.6)	1.28	[0.76; 2.17]	0.351
No	78 / 881 (8.9)	52 / 859 (6.1)	1.46	[1.04; 2.05]	0.028
Prior endocrine therapy					
Interaction test	p = 0.321				
Yes	73 / 957 (7.6)	56 / 940 (6.0)	1.28	[0.91; 1.79]	0.150
No	36 / 452 (8.0)	19 / 422 (4.5)	1.77	[1.03; 3.03]	0.038
Prior mastectomy					
Interaction test	p = 0.507				
Yes	69 / 857 (8.1)	45 / 847 (5.3)	1.52	[1.05; 2.18]	0.025
No	40 / 552 (7.2)	30 / 515 (5.8)	1.24	[0.79; 1.97]	0.350
Prior radiotherapy					
Interaction test	p = 0.943				
Yes	99 / 1253 (7.9)	68 / 1203 (5.7)	1.40	[1.04; 1.88]	0.028
No	10 / 156 (6.4)	7 / 159 (4.4)	1.46	[0.57; 3.73]	0.434
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.47 PT upper respiratory tract infection: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Upper respiratory tract infection					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.049				
NA/WE/O	45 / 899 (5.0)	21 / 856 (2.5)	2.04	[1.23; 3.40]	0.006
ROW	16 / 510 (3.1)	18 / 506 (3.6)	0.88	[0.45; 1.71]	0.710
Geographical region					
Interaction test	p = 0.344				
Europe	18 / 832 (2.2)	12 / 824 (1.5)	1.49	[0.72; 3.06]	0.284
North America/Australia	31 / 400 (7.8)	15 / 364 (4.1)	1.88	[1.03; 3.43]	0.039
Asia	10 / 102 (9.8)	7 / 101 (6.9)	1.41	[0.56; 3.57]	0.463
Latin America	2 / 75 (2.7)	5 / 73 (6.8)	0.39	[0.08; 1.94]	0.250
Age group 1 at randomization					
Interaction test	p = 0.875				
<45	6 / 60 (10.0)	2 / 52 (3.8)	2.60	[0.55; 12.33]	0.229
45 to 54	10 / 300 (3.3)	7 / 322 (2.2)	1.53	[0.59; 3.98]	0.379
55 to 64	27 / 651 (4.1)	20 / 642 (3.1)	1.33	[0.75; 2.35]	0.323
≥65	18 / 398 (4.5)	10 / 346 (2.9)	1.56	[0.73; 3.34]	0.248
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.345				
<Median	33 / 633 (5.2)	18 / 632 (2.8)	1.83	[1.04; 3.22]	0.036
≥Median	28 / 776 (3.6)	21 / 730 (2.9)	1.25	[0.72; 2.19]	0.425
Race					
Interaction test	p = 0.734				
Asian	12 / 128 (9.4)	7 / 127 (5.5)	1.70	[0.69; 4.18]	0.247
Non-Asian	48 / 1203 (4.0)	32 / 1167 (2.7)	1.46	[0.94; 2.26]	0.095
BMI at screening					
Interaction test	p = 0.423				
≥25	41 / 935 (4.4)	30 / 935 (3.2)	1.37	[0.86; 2.17]	0.185
<25	20 / 460 (4.3)	9 / 410 (2.2)	1.98	[0.91; 4.30]	0.084
AJCC Anatomic Stage Group					
Interaction test	p = 0.797				
Group I/II	21 / 585 (3.6)	15 / 589 (2.5)	1.41	[0.73; 2.71]	0.303
Group III	40 / 823 (4.9)	24 / 772 (3.1)	1.56	[0.95; 2.57]	0.078

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.091				
IA/IB/IIA	12 / 310 (3.9)	4 / 311 (1.3)	3.01	[0.98; 9.23]	0.054
IIB	9 / 275 (3.3)	11 / 278 (4.0)	0.83	[0.35; 1.96]	0.667
IIIA	25 / 482 (5.2)	9 / 450 (2.0)	2.59	[1.22; 5.50]	0.013
IIIB	2 / 100 (2.0)	4 / 82 (4.9)	0.41	[0.08; 2.18]	0.296
IIIC	13 / 241 (5.4)	11 / 240 (4.6)	1.18	[0.54; 2.57]	0.683
Tumor category					
Interaction test	p = 0.236				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	58 / 1287 (4.5)	35 / 1258 (2.8)	1.62	[1.07; 2.45]	0.022
>T3	3 / 113 (2.7)	4 / 97 (4.1)	0.64	[0.15; 2.81]	0.558
Nodal status					
Interaction test	p = 0.621				
N0	6 / 190 (3.2)	3 / 200 (1.5)	2.11	[0.53; 8.30]	0.287
N1-N3	55 / 1216 (4.5)	36 / 1160 (3.1)	1.46	[0.96; 2.20]	0.073
Histological grade at time of surgery					
Interaction test	p = 0.555				
Grade 1	6 / 102 (5.9)	2 / 106 (1.9)	3.12	[0.64; 15.09]	0.158
Grade 2	34 / 842 (4.0)	24 / 768 (3.1)	1.29	[0.77; 2.16]	0.328
Grade 3	18 / 373 (4.8)	12 / 397 (3.0)	1.60	[0.78; 3.27]	0.201
Histological subtype					
Interaction test	p = 0.468				
Ductal	48 / 1025 (4.7)	27 / 1010 (2.7)	1.75	[1.10; 2.78]	0.018
Lobular	11 / 291 (3.8)	10 / 276 (3.6)	1.04	[0.45; 2.42]	0.921
Other	2 / 92 (2.2)	2 / 76 (2.6)	0.83	[0.12; 5.73]	0.847
Ki67 status from surgical specimen					
Interaction test	p = 0.643				
Ki67≤20	29 / 660 (4.4)	20 / 629 (3.2)	1.38	[0.79; 2.42]	0.257
Ki67>20	18 / 489 (3.7)	11 / 516 (2.1)	1.73	[0.82; 3.62]	0.148
Type of NSAI					
Interaction test	p = 0.042				
Letrozole	34 / 907 (3.7)	30 / 895 (3.4)	1.12	[0.69; 1.81]	0.649
Anastrozole	27 / 502 (5.4)	9 / 467 (1.9)	2.79	[1.33; 5.87]	0.007
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.675				
Yes	55 / 1194 (4.6)	36 / 1146 (3.1)	1.47	[0.97; 2.21]	0.069
No	6 / 215 (2.8)	3 / 216 (1.4)	2.01	[0.51; 7.93]	0.319
Prior adjuvant chemotherapy					
Interaction test	p = 0.135				
Yes	33 / 694 (4.8)	27 / 673 (4.0)	1.19	[0.72; 1.95]	0.503
No	28 / 715 (3.9)	12 / 689 (1.7)	2.25	[1.15; 4.39]	0.017

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.321				
Yes	25 / 528 (4.7)	12 / 503 (2.4)	1.98	[1.01; 3.91]	0.047
No	36 / 881 (4.1)	27 / 859 (3.1)	1.30	[0.80; 2.12]	0.294
Prior endocrine therapy					
Interaction test	p = 0.359				
Yes	48 / 957 (5.0)	28 / 940 (3.0)	1.68	[1.07; 2.66]	0.026
No	13 / 452 (2.9)	11 / 422 (2.6)	1.10	[0.50; 2.44]	0.808
Prior mastectomy					
Interaction test	p = 0.639				
Yes	41 / 857 (4.8)	25 / 847 (3.0)	1.62	[0.99; 2.64]	0.053
No	20 / 552 (3.6)	14 / 515 (2.7)	1.33	[0.68; 2.61]	0.402
Prior radiotherapy					
Interaction test	p = 0.880				
Yes	57 / 1253 (4.5)	36 / 1203 (3.0)	1.52	[1.01; 2.29]	0.045
No	4 / 156 (2.6)	3 / 159 (1.9)	1.36	[0.31; 5.97]	0.685
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.48 PT suspected covid-19: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Suspected COVID-19					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.774				
NA/WE/O	15 / 899 (1.7)	5 / 856 (0.6)	2.86	[1.04; 7.83]	0.041
ROW	14 / 510 (2.7)	6 / 506 (1.2)	2.32	[0.90; 5.98]	0.083
Geographical region					
Interaction test	p = 0.921				
Europe	14 / 832 (1.7)	5 / 824 (0.6)	2.77	[1.00; 7.66]	0.049
North America/Australia	7 / 400 (1.8)	3 / 364 (0.8)	2.12	[0.55; 8.15]	0.273
Asia	6 / 102 (5.9)	3 / 101 (3.0)	1.98	[0.51; 7.70]	0.324
Latin America	2 / 75 (2.7)	0 / 73 (0.0)	4.87	[0.24; 99.70]	0.304
Age group 1 at randomization					
Interaction test	p = 0.676				
<45	2 / 60 (3.3)	2 / 52 (3.8)	0.87	[0.13; 5.94]	0.884
45 to 54	6 / 300 (2.0)	3 / 322 (0.9)	2.15	[0.54; 8.51]	0.277
55 to 64	13 / 651 (2.0)	4 / 642 (0.6)	3.21	[1.05; 9.78]	0.041
≥65	8 / 398 (2.0)	2 / 346 (0.6)	3.48	[0.74; 16.27]	0.113
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.556				
<Median	15 / 633 (2.4)	7 / 632 (1.1)	2.14	[0.88; 5.21]	0.094
≥Median	14 / 776 (1.8)	4 / 730 (0.5)	3.29	[1.09; 9.96]	0.035
Race					
Interaction test	p = 0.928				
Asian	7 / 128 (5.5)	3 / 127 (2.4)	2.32	[0.61; 8.75]	0.216
Non-Asian	21 / 1203 (1.7)	8 / 1167 (0.7)	2.55	[1.13; 5.73]	0.024
BMI at screening					
Interaction test	p = 0.698				
≥25	17 / 935 (1.8)	6 / 935 (0.6)	2.83	[1.12; 7.15]	0.028
<25	12 / 460 (2.6)	5 / 410 (1.2)	2.14	[0.76; 6.02]	0.150
AJCC Anatomic Stage Group					
Interaction test	p = 0.603				
Group I/II	10 / 585 (1.7)	3 / 589 (0.5)	3.36	[0.93; 12.13]	0.065
Group III	19 / 823 (2.3)	8 / 772 (1.0)	2.23	[0.98; 5.06]	0.056

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.608				
IA/IB/IIA	2 / 310 (0.6)	2 / 311 (0.6)	1.00	[0.14; 7.08]	0.997
IIB	8 / 275 (2.9)	1 / 278 (0.4)	8.09	[1.02; 64.23]	0.048
IIIA	11 / 482 (2.3)	4 / 450 (0.9)	2.57	[0.82; 8.00]	0.104
IIIB	1 / 100 (1.0)	1 / 82 (1.2)	0.82	[0.05; 12.91]	0.888
IIIC	7 / 241 (2.9)	3 / 240 (1.3)	2.32	[0.61; 8.88]	0.218
Tumor category					
Interaction test	p = 0.735				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	27 / 1287 (2.1)	10 / 1258 (0.8)	2.64	[1.28; 5.43]	0.008
>T3	2 / 113 (1.8)	1 / 97 (1.0)	1.72	[0.16; 18.64]	0.657
Nodal status					
Interaction test	N.E.				
N0	0 / 190 (0.0)	2 / 200 (1.0)	0.21	[0.01; 4.36]	0.313
N1-N3	29 / 1216 (2.4)	9 / 1160 (0.8)	3.07	[1.46; 6.47]	0.003
Histological grade at time of surgery					
Interaction test	p = 0.105				
Grade 1	1 / 102 (1.0)	3 / 106 (2.8)	0.35	[0.04; 3.28]	0.355
Grade 2	15 / 842 (1.8)	5 / 768 (0.7)	2.74	[1.00; 7.49]	0.050
Grade 3	12 / 373 (3.2)	2 / 397 (0.5)	6.39	[1.44; 28.34]	0.015
Histological subtype					
Interaction test	p = 0.671				
Ductal	21 / 1025 (2.0)	7 / 1010 (0.7)	2.96	[1.26; 6.92]	0.013
Lobular	7 / 291 (2.4)	3 / 276 (1.1)	2.21	[0.58; 8.47]	0.246
Other	1 / 92 (1.1)	1 / 76 (1.3)	0.83	[0.05; 12.99]	0.892
Ki67 status from surgical specimen					
Interaction test	p = 0.978				
Ki67≤20	17 / 660 (2.6)	7 / 629 (1.1)	2.31	[0.97; 5.54]	0.060
Ki67>20	9 / 489 (1.8)	4 / 516 (0.8)	2.37	[0.74; 7.66]	0.148
Type of NSAI					
Interaction test	p = 0.721				
Letrozole	19 / 907 (2.1)	8 / 895 (0.9)	2.34	[1.03; 5.33]	0.042
Anastrozole	10 / 502 (2.0)	3 / 467 (0.6)	3.10	[0.86; 11.20]	0.084
Prior neo/adjuvant chemotherapy					
Interaction test	N.E.				
Yes	29 / 1194 (2.4)	11 / 1146 (1.0)	2.53	[1.27; 5.04]	0.008
No	0 / 215 (0.0)	0 / 216 (0.0)	N.E.	N.E.	N.E.
Prior adjuvant chemotherapy					
Interaction test	p = 0.383				
Yes	20 / 694 (2.9)	6 / 673 (0.9)	3.23	[1.31; 8.00]	0.011
No	9 / 715 (1.3)	5 / 689 (0.7)	1.73	[0.58; 5.15]	0.321

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.238				
Yes	10 / 528 (1.9)	6 / 503 (1.2)	1.59	[0.58; 4.34]	0.367
No	19 / 881 (2.2)	5 / 859 (0.6)	3.71	[1.39; 9.88]	0.009
Prior endocrine therapy					
Interaction test	p = 0.290				
Yes	25 / 957 (2.6)	8 / 940 (0.9)	3.07	[1.39; 6.77]	0.005
No	4 / 452 (0.9)	3 / 422 (0.7)	1.24	[0.28; 5.53]	0.773
Prior mastectomy					
Interaction test	p = 0.721				
Yes	19 / 857 (2.2)	8 / 847 (0.9)	2.35	[1.03; 5.33]	0.042
No	10 / 552 (1.8)	3 / 515 (0.6)	3.11	[0.86; 11.24]	0.083
Prior radiotherapy					
Interaction test	N.E.				
Yes	23 / 1253 (1.8)	11 / 1203 (0.9)	2.01	[0.98; 4.10]	0.056
No	6 / 156 (3.8)	0 / 159 (0.0)	13.25	[0.75; >99.99]	0.077
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.49 SOC blood and lymphatic system disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Blood and lymphatic system disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.211				
NA/WE/O	383 / 899 (42.6)	47 / 856 (5.5)	7.76	[5.82; 10.35]	<.001
ROW	303 / 510 (59.4)	67 / 506 (13.2)	4.49	[3.55; 5.67]	<.001
Geographical region					
Interaction test	p = 0.955				
Europe	461 / 832 (55.4)	82 / 824 (10.0)	5.57	[4.49; 6.90]	<.001
North America/Australia	154 / 400 (38.5)	21 / 364 (5.8)	6.67	[4.33; 10.29]	<.001
Asia	23 / 102 (22.5)	2 / 101 (2.0)	11.39	[2.76; 47.04]	<.001
Latin America	48 / 75 (64.0)	9 / 73 (12.3)	5.19	[2.75; 9.79]	<.001
Age group 1 at randomization					
Interaction test	p = 0.501				
<45	30 / 60 (50.0)	7 / 52 (13.5)	3.71	[1.78; 7.74]	<.001
45 to 54	143 / 300 (47.7)	20 / 322 (6.2)	7.67	[4.94; 11.92]	<.001
55 to 64	303 / 651 (46.5)	53 / 642 (8.3)	5.64	[4.30; 7.39]	<.001
≥65	210 / 398 (52.8)	34 / 346 (9.8)	5.37	[3.85; 7.49]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.828				
<Median	284 / 633 (44.9)	47 / 632 (7.4)	6.03	[4.52; 8.05]	<.001
≥Median	402 / 776 (51.8)	67 / 730 (9.2)	5.64	[4.45; 7.16]	<.001
Race					
Interaction test	p = 0.374				
Asian	37 / 128 (28.9)	3 / 127 (2.4)	12.24	[3.87; 38.67]	<.001
Non-Asian	596 / 1203 (49.5)	108 / 1167 (9.3)	5.35	[4.43; 6.46]	<.001
BMI at screening					
Interaction test	p = 0.374				
≥25	438 / 935 (46.8)	78 / 935 (8.3)	5.62	[4.49; 7.02]	<.001
<25	243 / 460 (52.8)	35 / 410 (8.5)	6.19	[4.46; 8.59]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.893				
Group I/II	276 / 585 (47.2)	46 / 589 (7.8)	6.04	[4.52; 8.08]	<.001
Group III	409 / 823 (49.7)	68 / 772 (8.8)	5.64	[4.45; 7.15]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.542				
IA/IB/IIA	147 / 310 (47.4)	20 / 311 (6.4)	7.37	[4.75; 11.45]	<.001
IIB	129 / 275 (46.9)	26 / 278 (9.4)	5.02	[3.41; 7.39]	<.001
IIIA	231 / 482 (47.9)	42 / 450 (9.3)	5.13	[3.79; 6.95]	<.001
IIIB	62 / 100 (62.0)	11 / 82 (13.4)	4.62	[2.61; 8.18]	<.001
IIIC	116 / 241 (48.1)	15 / 240 (6.3)	7.70	[4.64; 12.79]	<.001
Tumor category					
Interaction test	p = 0.931				
T0	4 / 5 (80.0)	0 / 5 (0.0)	9.00	[0.61; >99.99]	0.110
T1-T3	611 / 1287 (47.5)	101 / 1258 (8.0)	5.91	[4.86; 7.19]	<.001
>T3	68 / 113 (60.2)	12 / 97 (12.4)	4.86	[2.81; 8.44]	<.001
Nodal status					
Interaction test	p = 1.000				
N0	90 / 190 (47.4)	16 / 200 (8.0)	5.92	[3.62; 9.70]	<.001
N1-N3	594 / 1216 (48.8)	98 / 1160 (8.4)	5.78	[4.74; 7.05]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.769				
Grade 1	55 / 102 (53.9)	11 / 106 (10.4)	5.20	[2.89; 9.35]	<.001
Grade 2	400 / 842 (47.5)	68 / 768 (8.9)	5.37	[4.23; 6.81]	<.001
Grade 3	172 / 373 (46.1)	28 / 397 (7.1)	6.54	[4.50; 9.50]	<.001
Histological subtype					
Interaction test	p = 0.796				
Ductal	487 / 1025 (47.5)	84 / 1010 (8.3)	5.71	[4.61; 7.08]	<.001
Lobular	150 / 291 (51.5)	24 / 276 (8.7)	5.93	[3.98; 8.83]	<.001
Other	49 / 92 (53.3)	6 / 76 (7.9)	6.75	[3.06; 14.89]	<.001
Ki67 status from surgical specimen					
Interaction test	p = 0.770				
Ki67≤20	331 / 660 (50.2)	56 / 629 (8.9)	5.63	[4.34; 7.32]	<.001
Ki67>20	254 / 489 (51.9)	46 / 516 (8.9)	5.83	[4.37; 7.78]	<.001
Type of NSAI					
Interaction test	p = 0.891				
Letrozole	455 / 907 (50.2)	78 / 895 (8.7)	5.76	[4.61; 7.19]	<.001
Anastrozole	231 / 502 (46.0)	36 / 467 (7.7)	5.97	[4.30; 8.28]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.007				
Yes	575 / 1194 (48.2)	81 / 1146 (7.1)	6.81	[5.48; 8.47]	<.001
No	111 / 215 (51.6)	33 / 216 (15.3)	3.38	[2.41; 4.75]	<.001
Prior adjuvant chemotherapy					
Interaction test	p = 0.223				
Yes	320 / 694 (46.1)	44 / 673 (6.5)	7.05	[5.24; 9.49]	<.001
No	366 / 715 (51.2)	70 / 689 (10.2)	5.04	[3.99; 6.36]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.486				
Yes	270 / 528 (51.1)	42 / 503 (8.3)	6.12	[4.53; 8.28]	<.001
No	416 / 881 (47.2)	72 / 859 (8.4)	5.63	[4.47; 7.10]	<.001
Prior endocrine therapy					
Interaction test	p = 0.005				
Yes	459 / 957 (48.0)	61 / 940 (6.5)	7.39	[5.75; 9.50]	<.001
No	227 / 452 (50.2)	53 / 422 (12.6)	4.00	[3.06; 5.23]	<.001
Prior mastectomy					
Interaction test	p = 0.077				
Yes	418 / 857 (48.8)	81 / 847 (9.6)	5.10	[4.10; 6.34]	<.001
No	268 / 552 (48.6)	33 / 515 (6.4)	7.58	[5.39; 10.66]	<.001
Prior radiotherapy					
Interaction test	p = 0.009				
Yes	603 / 1253 (48.1)	87 / 1203 (7.2)	6.65	[5.39; 8.21]	<.001
No	83 / 156 (53.2)	27 / 159 (17.0)	3.13	[2.16; 4.55]	<.001
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.50 PT neutropenia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Neutropenia					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.297				
NA/WE/O	323 / 899 (35.9)	12 / 856 (1.4)	25.63	[14.51; 45.25]	<.001
ROW	258 / 510 (50.6)	19 / 506 (3.8)	13.47	[8.60; 21.12]	<.001
Geographical region					
Interaction test	p = 0.895				
Europe	409 / 832 (49.2)	25 / 824 (3.0)	16.20	[10.95; 23.98]	<.001
North America/Australia	122 / 400 (30.5)	4 / 364 (1.1)	27.76	[10.36; 74.38]	<.001
Asia	12 / 102 (11.8)	0 / 101 (0.0)	24.76	[1.49; >99.99]	0.025
Latin America	38 / 75 (50.7)	2 / 73 (2.7)	18.49	[4.63; 73.87]	<.001
Age group 1 at randomization					
Interaction test	p = 0.173				
<45	25 / 60 (41.7)	4 / 52 (7.7)	5.42	[2.02; 14.55]	<.001
45 to 54	124 / 300 (41.3)	6 / 322 (1.9)	22.18	[9.93; 49.57]	<.001
55 to 64	265 / 651 (40.7)	14 / 642 (2.2)	18.67	[11.03; 31.60]	<.001
≥65	167 / 398 (42.0)	7 / 346 (2.0)	20.74	[9.87; 43.57]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.067				
<Median	253 / 633 (40.0)	19 / 632 (3.0)	13.29	[8.45; 20.91]	<.001
≥Median	328 / 776 (42.3)	12 / 730 (1.6)	25.71	[14.58; 45.34]	<.001
Race					
Interaction test	N.E.				
Asian	26 / 128 (20.3)	0 / 127 (0.0)	52.59	[3.24; >99.99]	0.005
Non-Asian	508 / 1203 (42.2)	30 / 1167 (2.6)	16.43	[11.47; 23.53]	<.001
BMI at screening					
Interaction test	p = 0.351				
≥25	362 / 935 (38.7)	16 / 935 (1.7)	22.63	[13.83; 37.02]	<.001
<25	217 / 460 (47.2)	14 / 410 (3.4)	13.82	[8.18; 23.33]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.275				
Group I/II	238 / 585 (40.7)	10 / 589 (1.7)	23.96	[12.86; 44.65]	<.001
Group III	343 / 823 (41.7)	21 / 772 (2.7)	15.32	[9.97; 23.54]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.346				
IA/IB/IIA	127 / 310 (41.0)	6 / 311 (1.9)	21.23	[9.51; 47.43]	<.001
IIB	111 / 275 (40.4)	4 / 278 (1.4)	28.05	[10.49; 75.00]	<.001
IIIA	200 / 482 (41.5)	16 / 450 (3.6)	11.67	[7.13; 19.10]	<.001
IIIB	49 / 100 (49.0)	1 / 82 (1.2)	40.18	[5.67; >99.99]	<.001
IIIC	94 / 241 (39.0)	4 / 240 (1.7)	23.40	[8.74; 62.64]	<.001
Tumor category					
Interaction test	p = 0.626				
T0	4 / 5 (80.0)	0 / 5 (0.0)	9.00	[0.61; >99.99]	0.110
T1-T3	522 / 1287 (40.6)	29 / 1258 (2.3)	17.59	[12.20; 25.36]	<.001
>T3	53 / 113 (46.9)	2 / 97 (2.1)	22.75	[5.69; 90.92]	<.001
Nodal status					
Interaction test	p = 0.792				
N0	78 / 190 (41.1)	4 / 200 (2.0)	20.53	[7.67; 54.96]	<.001
N1-N3	501 / 1216 (41.2)	27 / 1160 (2.3)	17.70	[12.12; 25.85]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.634				
Grade 1	48 / 102 (47.1)	2 / 106 (1.9)	24.94	[6.22; 99.95]	<.001
Grade 2	333 / 842 (39.5)	19 / 768 (2.5)	15.99	[10.17; 25.12]	<.001
Grade 3	146 / 373 (39.1)	7 / 397 (1.8)	22.20	[10.54; 46.76]	<.001
Histological subtype					
Interaction test	p = 0.585				
Ductal	405 / 1025 (39.5)	21 / 1010 (2.1)	19.00	[12.36; 29.21]	<.001
Lobular	131 / 291 (45.0)	9 / 276 (3.3)	13.81	[7.17; 26.58]	<.001
Other	45 / 92 (48.9)	1 / 76 (1.3)	37.17	[5.25; >99.99]	<.001
Ki67 status from surgical specimen					
Interaction test	p = 0.539				
Ki67≤20	282 / 660 (42.7)	17 / 629 (2.7)	15.81	[9.81; 25.48]	<.001
Ki67>20	220 / 489 (45.0)	12 / 516 (2.3)	19.35	[10.97; 34.13]	<.001
Type of NSAI					
Interaction test	p = 0.545				
Letrozole	386 / 907 (42.6)	23 / 895 (2.6)	16.56	[10.99; 24.96]	<.001
Anastrozole	195 / 502 (38.8)	8 / 467 (1.7)	22.68	[11.31; 45.47]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.688				
Yes	490 / 1194 (41.0)	25 / 1146 (2.2)	18.81	[12.69; 27.89]	<.001
No	91 / 215 (42.3)	6 / 216 (2.8)	15.24	[6.82; 34.06]	<.001
Prior adjuvant chemotherapy					
Interaction test	p = 0.101				
Yes	280 / 694 (40.3)	10 / 673 (1.5)	27.15	[14.58; 50.57]	<.001
No	301 / 715 (42.1)	21 / 689 (3.0)	13.81	[8.99; 21.23]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.029				
Yes	221 / 528 (41.9)	18 / 503 (3.6)	11.70	[7.35; 18.61]	<.001
No	360 / 881 (40.9)	13 / 859 (1.5)	27.00	[15.65; 46.58]	<.001
Prior endocrine therapy					
Interaction test	p = 0.664				
Yes	392 / 957 (41.0)	20 / 940 (2.1)	19.25	[12.40; 29.90]	<.001
No	189 / 452 (41.8)	11 / 422 (2.6)	16.04	[8.86; 29.03]	<.001
Prior mastectomy					
Interaction test	p = 0.762				
Yes	352 / 857 (41.1)	20 / 847 (2.4)	17.39	[11.20; 27.02]	<.001
No	229 / 552 (41.5)	11 / 515 (2.1)	19.42	[10.73; 35.14]	<.001
Prior radiotherapy					
Interaction test	p = 0.367				
Yes	516 / 1253 (41.2)	29 / 1203 (2.4)	17.08	[11.85; 24.62]	<.001
No	65 / 156 (41.7)	2 / 159 (1.3)	33.13	[8.25; >99.99]	<.001
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.51 PT leukopenia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Leukopenia					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.185				
NA/WE/O	83 / 899 (9.2)	4 / 856 (0.5)	19.76	[7.28; 53.65]	<.001
ROW	132 / 510 (25.9)	17 / 506 (3.4)	7.70	[4.72; 12.57]	<.001
Geographical region					
Interaction test	p = 0.815				
Europe	174 / 832 (20.9)	18 / 824 (2.2)	9.57	[5.95; 15.40]	<.001
North America/Australia	22 / 400 (5.5)	2 / 364 (0.5)	10.01	[2.37; 42.27]	0.002
Asia	1 / 102 (1.0)	0 / 101 (0.0)	2.97	[0.12; 72.08]	0.503
Latin America	18 / 75 (24.0)	1 / 73 (1.4)	17.52	[2.40; >99.99]	0.005
Age group 1 at randomization					
Interaction test	p = 0.610				
<45	11 / 60 (18.3)	0 / 52 (0.0)	19.98	[1.21; >99.99]	0.037
45 to 54	40 / 300 (13.3)	5 / 322 (1.6)	8.59	[3.43; 21.47]	<.001
55 to 64	89 / 651 (13.7)	11 / 642 (1.7)	7.98	[4.31; 14.79]	<.001
≥65	75 / 398 (18.8)	5 / 346 (1.4)	13.04	[5.34; 31.87]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.625				
<Median	80 / 633 (12.6)	9 / 632 (1.4)	8.87	[4.50; 17.52]	<.001
≥Median	135 / 776 (17.4)	12 / 730 (1.6)	10.58	[5.92; 18.93]	<.001
Race					
Interaction test	N.E.				
Asian	2 / 128 (1.6)	0 / 127 (0.0)	4.96	[0.24; >99.99]	0.300
Non-Asian	192 / 1203 (16.0)	21 / 1167 (1.8)	8.87	[5.69; 13.82]	<.001
BMI at screening					
Interaction test	p = 0.375				
≥25	148 / 935 (15.8)	17 / 935 (1.8)	8.71	[5.31; 14.26]	<.001
<25	66 / 460 (14.3)	4 / 410 (1.0)	14.71	[5.41; 39.99]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.362				
Group I/II	81 / 585 (13.8)	6 / 589 (1.0)	13.59	[5.98; 30.90]	<.001
Group III	134 / 823 (16.3)	15 / 772 (1.9)	8.38	[4.96; 14.16]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.345				
IA/IB/IIA	49 / 310 (15.8)	3 / 311 (1.0)	16.39	[5.16; 52.01]	<.001
IIB	32 / 275 (11.6)	3 / 278 (1.1)	10.78	[3.34; 34.80]	<.001
IIIA	76 / 482 (15.8)	12 / 450 (2.7)	5.91	[3.26; 10.72]	<.001
IIIB	29 / 100 (29.0)	2 / 82 (2.4)	11.89	[2.92; 48.35]	<.001
IIIC	29 / 241 (12.0)	1 / 240 (0.4)	28.88	[3.97; >99.99]	<.001
Tumor category					
Interaction test	p = 0.566				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	185 / 1287 (14.4)	19 / 1258 (1.5)	9.52	[5.97; 15.16]	<.001
>T3	30 / 113 (26.5)	2 / 97 (2.1)	12.88	[3.16; 52.50]	<.001
Nodal status					
Interaction test	p = 0.611				
N0	29 / 190 (15.3)	4 / 200 (2.0)	7.63	[2.73; 21.30]	<.001
N1-N3	184 / 1216 (15.1)	17 / 1160 (1.5)	10.33	[6.32; 16.86]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.325				
Grade 1	16 / 102 (15.7)	1 / 106 (0.9)	16.63	[2.25; >99.99]	0.006
Grade 2	136 / 842 (16.2)	11 / 768 (1.4)	11.28	[6.15; 20.68]	<.001
Grade 3	51 / 373 (13.7)	9 / 397 (2.3)	6.03	[3.01; 12.08]	<.001
Histological subtype					
Interaction test	p = 0.879				
Ductal	155 / 1025 (15.1)	16 / 1010 (1.6)	9.55	[5.75; 15.85]	<.001
Lobular	46 / 291 (15.8)	5 / 276 (1.8)	8.73	[3.52; 21.64]	<.001
Other	14 / 92 (15.2)	0 / 76 (0.0)	24.01	[1.46; >99.99]	0.026
Ki67 status from surgical specimen					
Interaction test	p = 0.225				
Ki67≤20	116 / 660 (17.6)	9 / 629 (1.4)	12.28	[6.29; 23.99]	<.001
Ki67>20	74 / 489 (15.1)	11 / 516 (2.1)	7.10	[3.81; 13.21]	<.001
Type of NSAI					
Interaction test	p = 0.566				
Letrozole	147 / 907 (16.2)	16 / 895 (1.8)	9.07	[5.46; 15.06]	<.001
Anastrozole	68 / 502 (13.5)	5 / 467 (1.1)	12.65	[5.15; 31.10]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.397				
Yes	167 / 1194 (14.0)	14 / 1146 (1.2)	11.45	[6.68; 19.63]	<.001
No	48 / 215 (22.3)	7 / 216 (3.2)	6.89	[3.19; 14.88]	<.001
Prior adjuvant chemotherapy					
Interaction test	p = 0.880				
Yes	88 / 694 (12.7)	8 / 673 (1.2)	10.67	[5.21; 21.83]	<.001
No	127 / 715 (17.8)	13 / 689 (1.9)	9.41	[5.37; 16.50]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.498				
Yes	88 / 528 (16.7)	7 / 503 (1.4)	11.98	[5.60; 25.61]	<.001
No	127 / 881 (14.4)	14 / 859 (1.6)	8.84	[5.13; 15.24]	<.001
Prior endocrine therapy					
Interaction test	p = 0.891				
Yes	127 / 957 (13.3)	12 / 940 (1.3)	10.40	[5.79; 18.66]	<.001
No	88 / 452 (19.5)	9 / 422 (2.1)	9.13	[4.66; 17.89]	<.001
Prior mastectomy					
Interaction test	p = 0.693				
Yes	131 / 857 (15.3)	14 / 847 (1.7)	9.25	[5.37; 15.91]	<.001
No	84 / 552 (15.2)	7 / 515 (1.4)	11.20	[5.23; 23.98]	<.001
Prior radiotherapy					
Interaction test	p = 0.943				
Yes	180 / 1253 (14.4)	17 / 1203 (1.4)	10.17	[6.22; 16.61]	<.001
No	35 / 156 (22.4)	4 / 159 (2.5)	8.92	[3.25; 24.50]	<.001
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.52 PT anaemia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anaemia					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.905				
NA/WE/O	69 / 899 (7.7)	20 / 856 (2.3)	3.28	[2.01; 5.36]	<.001
ROW	67 / 510 (13.1)	22 / 506 (4.3)	3.02	[1.90; 4.81]	<.001
Geographical region					
Interaction test	p = 0.878				
Europe	87 / 832 (10.5)	28 / 824 (3.4)	3.08	[2.03; 4.66]	<.001
North America/Australia	32 / 400 (8.0)	9 / 364 (2.5)	3.24	[1.57; 6.69]	0.002
Asia	7 / 102 (6.9)	1 / 101 (1.0)	6.93	[0.87; 55.32]	0.068
Latin America	10 / 75 (13.3)	4 / 73 (5.5)	2.43	[0.80; 7.41]	0.118
Age group 1 at randomization					
Interaction test	p = 0.981				
<45	7 / 60 (11.7)	2 / 52 (3.8)	3.03	[0.66; 13.97]	0.154
45 to 54	16 / 300 (5.3)	5 / 322 (1.6)	3.43	[1.27; 9.26]	0.015
55 to 64	49 / 651 (7.5)	17 / 642 (2.6)	2.84	[1.66; 4.88]	<.001
≥65	64 / 398 (16.1)	18 / 346 (5.2)	3.09	[1.87; 5.11]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.959				
<Median	35 / 633 (5.5)	11 / 632 (1.7)	3.18	[1.63; 6.20]	<.001
≥Median	101 / 776 (13.0)	31 / 730 (4.2)	3.06	[2.08; 4.52]	<.001
Race					
Interaction test	p = 0.370				
Asian	8 / 128 (6.3)	1 / 127 (0.8)	7.94	[1.01; 62.55]	0.049
Non-Asian	122 / 1203 (10.1)	40 / 1167 (3.4)	2.96	[2.09; 4.19]	<.001
BMI at screening					
Interaction test	p = 0.980				
≥25	95 / 935 (10.2)	31 / 935 (3.3)	3.06	[2.06; 4.55]	<.001
<25	38 / 460 (8.3)	11 / 410 (2.7)	3.08	[1.60; 5.94]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.182				
Group I/II	50 / 585 (8.5)	21 / 589 (3.6)	2.40	[1.46; 3.94]	<.001
Group III	85 / 823 (10.3)	21 / 772 (2.7)	3.80	[2.38; 6.06]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.275				
IA/IB/IIA	28 / 310 (9.0)	7 / 311 (2.3)	4.01	[1.78; 9.05]	<.001
IIB	22 / 275 (8.0)	14 / 278 (5.0)	1.59	[0.83; 3.04]	0.162
IIIA	43 / 482 (8.9)	11 / 450 (2.4)	3.65	[1.91; 6.99]	<.001
IIIB	20 / 100 (20.0)	5 / 82 (6.1)	3.28	[1.29; 8.36]	0.013
IIIC	22 / 241 (9.1)	5 / 240 (2.1)	4.38	[1.69; 11.38]	0.002
Tumor category					
Interaction test	p = 0.663				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	114 / 1287 (8.9)	36 / 1258 (2.9)	3.10	[2.15; 4.47]	<.001
>T3	21 / 113 (18.6)	5 / 97 (5.2)	3.61	[1.41; 9.20]	0.007
Nodal status					
Interaction test	p = 0.852				
N0	19 / 190 (10.0)	6 / 200 (3.0)	3.33	[1.36; 8.17]	0.008
N1-N3	115 / 1216 (9.5)	36 / 1160 (3.1)	3.05	[2.11; 4.39]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.947				
Grade 1	9 / 102 (8.8)	3 / 106 (2.8)	3.12	[0.87; 11.19]	0.081
Grade 2	83 / 842 (9.9)	23 / 768 (3.0)	3.29	[2.10; 5.17]	<.001
Grade 3	38 / 373 (10.2)	14 / 397 (3.5)	2.89	[1.59; 5.24]	<.001
Histological subtype					
Interaction test	p = 0.695				
Ductal	101 / 1025 (9.9)	34 / 1010 (3.4)	2.93	[2.00; 4.28]	<.001
Lobular	28 / 291 (9.6)	6 / 276 (2.2)	4.43	[1.86; 10.52]	<.001
Other	7 / 92 (7.6)	2 / 76 (2.6)	2.89	[0.62; 13.51]	0.177
Ki67 status from surgical specimen					
Interaction test	p = 0.756				
Ki67≤20	68 / 660 (10.3)	22 / 629 (3.5)	2.95	[1.84; 4.70]	<.001
Ki67>20	53 / 489 (10.8)	17 / 516 (3.3)	3.29	[1.93; 5.60]	<.001
Type of NSAI					
Interaction test	p = 0.370				
Letrozole	98 / 907 (10.8)	28 / 895 (3.1)	3.45	[2.29; 5.20]	<.001
Anastrozole	38 / 502 (7.6)	14 / 467 (3.0)	2.53	[1.39; 4.60]	0.002
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.065				
Yes	106 / 1194 (8.9)	26 / 1146 (2.3)	3.91	[2.57; 5.96]	<.001
No	30 / 215 (14.0)	16 / 216 (7.4)	1.88	[1.06; 3.35]	0.031
Prior adjuvant chemotherapy					
Interaction test	p = 0.756				
Yes	56 / 694 (8.1)	16 / 673 (2.4)	3.39	[1.97; 5.86]	<.001
No	80 / 715 (11.2)	26 / 689 (3.8)	2.97	[1.93; 4.56]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.144				
Yes	53 / 528 (10.0)	11 / 503 (2.2)	4.59	[2.43; 8.69]	<.001
No	83 / 881 (9.4)	31 / 859 (3.6)	2.61	[1.75; 3.90]	<.001
Prior endocrine therapy					
Interaction test	p = 0.598				
Yes	80 / 957 (8.4)	23 / 940 (2.4)	3.42	[2.17; 5.38]	<.001
No	56 / 452 (12.4)	19 / 422 (4.5)	2.75	[1.66; 4.55]	<.001
Prior mastectomy					
Interaction test	p = 0.557				
Yes	95 / 857 (11.1)	32 / 847 (3.8)	2.93	[1.99; 4.33]	<.001
No	41 / 552 (7.4)	10 / 515 (1.9)	3.83	[1.94; 7.56]	<.001
Prior radiotherapy					
Interaction test	p = 0.568				
Yes	104 / 1253 (8.3)	29 / 1203 (2.4)	3.44	[2.30; 5.16]	<.001
No	32 / 156 (20.5)	13 / 159 (8.2)	2.51	[1.37; 4.60]	0.003
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.53 PT thrombocytopenia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Thrombocytopenia					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.434				
NA/WE/O	31 / 899 (3.4)	7 / 856 (0.8)	4.22	[1.87; 9.52]	<.001
ROW	44 / 510 (8.6)	16 / 506 (3.2)	2.73	[1.56; 4.77]	<.001
Geographical region					
Interaction test	p = 0.682				
Europe	54 / 832 (6.5)	20 / 824 (2.4)	2.67	[1.62; 4.43]	<.001
North America/Australia	12 / 400 (3.0)	3 / 364 (0.8)	3.64	[1.04; 12.80]	0.044
Asia	3 / 102 (2.9)	0 / 101 (0.0)	6.93	[0.36; >99.99]	0.198
Latin America	6 / 75 (8.0)	0 / 73 (0.0)	12.66	[0.73; >99.99]	0.082
Age group 1 at randomization					
Interaction test	p = 0.993				
<45	3 / 60 (5.0)	1 / 52 (1.9)	2.60	[0.28; 24.24]	0.402
45 to 54	9 / 300 (3.0)	3 / 322 (0.9)	3.22	[0.88; 11.78]	0.077
55 to 64	36 / 651 (5.5)	12 / 642 (1.9)	2.96	[1.55; 5.63]	<.001
≥65	27 / 398 (6.8)	7 / 346 (2.0)	3.35	[1.48; 7.60]	0.004
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.974				
<Median	22 / 633 (3.5)	7 / 632 (1.1)	3.14	[1.35; 7.29]	0.008
≥Median	53 / 776 (6.8)	16 / 730 (2.2)	3.12	[1.80; 5.40]	<.001
Race					
Interaction test	p = 0.600				
Asian	5 / 128 (3.9)	1 / 127 (0.8)	4.96	[0.59; 41.87]	0.141
Non-Asian	62 / 1203 (5.2)	22 / 1167 (1.9)	2.73	[1.69; 4.42]	<.001
BMI at screening					
Interaction test	p = 0.524				
≥25	47 / 935 (5.0)	17 / 935 (1.8)	2.76	[1.60; 4.78]	<.001
<25	26 / 460 (5.7)	6 / 410 (1.5)	3.86	[1.61; 9.29]	0.003
AJCC Anatomic Stage Group					
Interaction test	p = 0.971				
Group I/II	31 / 585 (5.3)	10 / 589 (1.7)	3.12	[1.54; 6.31]	0.002
Group III	44 / 823 (5.3)	13 / 772 (1.7)	3.17	[1.72; 5.85]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.385				
IA/IB/IIA	15 / 310 (4.8)	6 / 311 (1.9)	2.51	[0.99; 6.38]	0.054
IIB	16 / 275 (5.8)	4 / 278 (1.4)	4.04	[1.37; 11.94]	0.011
IIIA	20 / 482 (4.1)	11 / 450 (2.4)	1.70	[0.82; 3.50]	0.152
IIIB	13 / 100 (13.0)	2 / 82 (2.4)	5.33	[1.24; 22.95]	0.025
IIIC	11 / 241 (4.6)	0 / 240 (0.0)	22.90	[1.36; >99.99]	0.030
Tumor category					
Interaction test	p = 0.360				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	61 / 1287 (4.7)	21 / 1258 (1.7)	2.84	[1.74; 4.63]	<.001
>T3	13 / 113 (11.5)	2 / 97 (2.1)	5.58	[1.29; 24.12]	0.021
Nodal status					
Interaction test	p = 0.316				
N0	9 / 190 (4.7)	5 / 200 (2.5)	1.89	[0.65; 5.55]	0.244
N1-N3	66 / 1216 (5.4)	18 / 1160 (1.6)	3.50	[2.09; 5.85]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.225				
Grade 1	6 / 102 (5.9)	2 / 106 (1.9)	3.12	[0.64; 15.09]	0.158
Grade 2	48 / 842 (5.7)	19 / 768 (2.5)	2.30	[1.37; 3.88]	0.002
Grade 3	17 / 373 (4.6)	2 / 397 (0.5)	9.05	[2.10; 38.89]	0.003
Histological subtype					
Interaction test	p = 0.454				
Ductal	59 / 1025 (5.8)	16 / 1010 (1.6)	3.63	[2.11; 6.27]	<.001
Lobular	13 / 291 (4.5)	5 / 276 (1.8)	2.47	[0.89; 6.83]	0.082
Other	3 / 92 (3.3)	2 / 76 (2.6)	1.24	[0.21; 7.23]	0.812
Ki67 status from surgical specimen					
Interaction test	p = 0.600				
Ki67≤20	36 / 660 (5.5)	10 / 629 (1.6)	3.43	[1.72; 6.85]	<.001
Ki67>20	30 / 489 (6.1)	12 / 516 (2.3)	2.64	[1.37; 5.09]	0.004
Type of NSAI					
Interaction test	p = 0.828				
Letrozole	56 / 907 (6.2)	18 / 895 (2.0)	3.07	[1.82; 5.18]	<.001
Anastrozole	19 / 502 (3.8)	5 / 467 (1.1)	3.54	[1.33; 9.39]	0.011
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.003				
Yes	63 / 1194 (5.3)	12 / 1146 (1.0)	5.04	[2.73; 9.29]	<.001
No	12 / 215 (5.6)	11 / 216 (5.1)	1.10	[0.49; 2.43]	0.821
Prior adjuvant chemotherapy					
Interaction test	p = 0.772				
Yes	24 / 694 (3.5)	8 / 673 (1.2)	2.91	[1.32; 6.43]	0.008
No	51 / 715 (7.1)	15 / 689 (2.2)	3.28	[1.86; 5.77]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.003				
Yes	41 / 528 (7.8)	4 / 503 (0.8)	9.76	[3.52; 27.06]	<.001
No	34 / 881 (3.9)	19 / 859 (2.2)	1.74	[1.00; 3.03]	0.049
Prior endocrine therapy					
Interaction test	p = 0.112				
Yes	46 / 957 (4.8)	10 / 940 (1.1)	4.52	[2.29; 8.90]	<.001
No	29 / 452 (6.4)	13 / 422 (3.1)	2.08	[1.10; 3.95]	0.025
Prior mastectomy					
Interaction test	p = 0.114				
Yes	44 / 857 (5.1)	18 / 847 (2.1)	2.42	[1.41; 4.15]	0.001
No	31 / 552 (5.6)	5 / 515 (1.0)	5.78	[2.27; 14.76]	<.001
Prior radiotherapy					
Interaction test	p = 0.134				
Yes	59 / 1253 (4.7)	14 / 1203 (1.2)	4.05	[2.27; 7.21]	<.001
No	16 / 156 (10.3)	9 / 159 (5.7)	1.81	[0.83; 3.98]	0.138
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.54 PT lymphopenia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Lymphopenia					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.769				
NA/WE/O	32 / 899 (3.6)	4 / 856 (0.5)	7.62	[2.71; 21.45]	<.001
ROW	20 / 510 (3.9)	2 / 506 (0.4)	9.92	[2.33; 42.23]	0.002
Geographical region					
Interaction test	p = 0.948				
Europe	31 / 832 (3.7)	4 / 824 (0.5)	7.68	[2.72; 21.65]	<.001
North America/Australia	11 / 400 (2.8)	1 / 364 (0.3)	10.01	[1.30; 77.15]	0.027
Asia	0 / 102 (0.0)	0 / 101 (0.0)	N.E.	N.E.	N.E.
Latin America	10 / 75 (13.3)	1 / 73 (1.4)	9.73	[1.28; 74.13]	0.028
Age group 1 at randomization					
Interaction test	p = 0.543				
<45	4 / 60 (6.7)	0 / 52 (0.0)	7.82	[0.43; >99.99]	0.164
45 to 54	13 / 300 (4.3)	1 / 322 (0.3)	13.95	[1.84; >99.99]	0.011
55 to 64	20 / 651 (3.1)	2 / 642 (0.3)	9.86	[2.31; 42.02]	0.002
≥65	15 / 398 (3.8)	3 / 346 (0.9)	4.35	[1.27; 14.89]	0.019
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.260				
<Median	21 / 633 (3.3)	1 / 632 (0.2)	20.97	[2.83; >99.99]	0.003
≥Median	31 / 776 (4.0)	5 / 730 (0.7)	5.83	[2.28; 14.92]	<.001
Race					
Interaction test	N.E.				
Asian	0 / 128 (0.0)	0 / 127 (0.0)	N.E.	N.E.	N.E.
Non-Asian	38 / 1203 (3.2)	5 / 1167 (0.4)	7.37	[2.91; 18.67]	<.001
BMI at screening					
Interaction test	p = 0.641				
≥25	38 / 935 (4.1)	4 / 935 (0.4)	9.50	[3.40; 26.51]	<.001
<25	14 / 460 (3.0)	2 / 410 (0.5)	6.24	[1.43; 27.29]	0.015
AJCC Anatomic Stage Group					
Interaction test	p = 0.361				
Group I/II	18 / 585 (3.1)	1 / 589 (0.2)	18.12	[2.43; >99.99]	0.005
Group III	34 / 823 (4.1)	5 / 772 (0.6)	6.38	[2.51; 16.23]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.835				
IA/IB/IIA	11 / 310 (3.5)	0 / 311 (0.0)	23.07	[1.37; >99.99]	0.030
IIB	7 / 275 (2.5)	1 / 278 (0.4)	7.08	[0.88; 57.13]	0.066
IIIA	21 / 482 (4.4)	2 / 450 (0.4)	9.80	[2.31; 41.57]	0.002
IIIB	5 / 100 (5.0)	1 / 82 (1.2)	4.10	[0.49; 34.40]	0.194
IIIC	8 / 241 (3.3)	2 / 240 (0.8)	3.98	[0.85; 18.57]	0.078
Tumor category					
Interaction test	p = 0.527				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	47 / 1287 (3.7)	5 / 1258 (0.4)	9.19	[3.67; 23.03]	<.001
>T3	5 / 113 (4.4)	1 / 97 (1.0)	4.29	[0.51; 36.11]	0.180
Nodal status					
Interaction test	N.E.				
N0	6 / 190 (3.2)	0 / 200 (0.0)	13.68	[0.78; >99.99]	0.074
N1-N3	45 / 1216 (3.7)	6 / 1160 (0.5)	7.15	[3.06; 16.71]	<.001
Histological grade at time of surgery					
Interaction test	N.E.				
Grade 1	4 / 102 (3.9)	0 / 106 (0.0)	9.35	[0.51; >99.99]	0.132
Grade 2	33 / 842 (3.9)	6 / 768 (0.8)	5.02	[2.11; 11.91]	<.001
Grade 3	14 / 373 (3.8)	0 / 397 (0.0)	30.86	[1.85; >99.99]	0.017
Histological subtype					
Interaction test	p = 0.217				
Ductal	36 / 1025 (3.5)	3 / 1010 (0.3)	11.82	[3.65; 38.27]	<.001
Lobular	15 / 291 (5.2)	2 / 276 (0.7)	7.11	[1.64; 30.82]	0.009
Other	1 / 92 (1.1)	1 / 76 (1.3)	0.83	[0.05; 12.99]	0.892
Ki67 status from surgical specimen					
Interaction test	p = 0.569				
Ki67≤20	25 / 660 (3.8)	3 / 629 (0.5)	7.94	[2.41; 26.17]	<.001
Ki67>20	15 / 489 (3.1)	1 / 516 (0.2)	15.83	[2.10; >99.99]	0.007
Type of NSAI					
Interaction test	p = 0.961				
Letrozole	25 / 907 (2.8)	3 / 895 (0.3)	8.22	[2.49; 27.14]	<.001
Anastrozole	27 / 502 (5.4)	3 / 467 (0.6)	8.37	[2.56; 27.41]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.933				
Yes	43 / 1194 (3.6)	5 / 1146 (0.4)	8.25	[3.28; 20.76]	<.001
No	9 / 215 (4.2)	1 / 216 (0.5)	9.04	[1.16; 70.75]	0.036
Prior adjuvant chemotherapy					
Interaction test	p = 0.920				
Yes	27 / 694 (3.9)	3 / 673 (0.4)	8.73	[2.66; 28.63]	<.001
No	25 / 715 (3.5)	3 / 689 (0.4)	8.03	[2.44; 26.47]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.974				
Yes	18 / 528 (3.4)	2 / 503 (0.4)	8.57	[2.00; 36.76]	0.004
No	34 / 881 (3.9)	4 / 859 (0.5)	8.29	[2.95; 23.26]	<.001
Prior endocrine therapy					
Interaction test	p = 0.431				
Yes	34 / 957 (3.6)	3 / 940 (0.3)	11.13	[3.43; 36.12]	<.001
No	18 / 452 (4.0)	3 / 422 (0.7)	5.60	[1.66; 18.88]	0.005
Prior mastectomy					
Interaction test	p = 0.815				
Yes	28 / 857 (3.3)	3 / 847 (0.4)	9.22	[2.82; 30.23]	<.001
No	24 / 552 (4.3)	3 / 515 (0.6)	7.46	[2.26; 24.64]	<.001
Prior radiotherapy					
Interaction test	N.E.				
Yes	51 / 1253 (4.1)	6 / 1203 (0.5)	8.16	[3.52; 18.95]	<.001
No	1 / 156 (0.6)	0 / 159 (0.0)	3.06	[0.13; 74.48]	0.493
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.55 SOC nervous system disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Nervous system disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.303				
NA/WE/O	416 / 899 (46.3)	304 / 856 (35.5)	1.30	[1.16; 1.46]	<.001
ROW	132 / 510 (25.9)	107 / 506 (21.1)	1.22	[0.98; 1.53]	0.076
Geographical region					
Interaction test	p = 0.069				
Europe	297 / 832 (35.7)	246 / 824 (29.9)	1.20	[1.04; 1.37]	0.012
North America/Australia	208 / 400 (52.0)	132 / 364 (36.3)	1.43	[1.22; 1.69]	<.001
Asia	23 / 102 (22.5)	12 / 101 (11.9)	1.90	[1.00; 3.60]	0.050
Latin America	20 / 75 (26.7)	21 / 73 (28.8)	0.93	[0.55; 1.56]	0.775
Age group 1 at randomization					
Interaction test	p = 0.719				
<45	29 / 60 (48.3)	17 / 52 (32.7)	1.48	[0.92; 2.36]	0.103
45 to 54	127 / 300 (42.3)	106 / 322 (32.9)	1.29	[1.05; 1.58]	0.016
55 to 64	229 / 651 (35.2)	184 / 642 (28.7)	1.23	[1.05; 1.44]	0.012
≥65	163 / 398 (41.0)	104 / 346 (30.1)	1.36	[1.12; 1.66]	0.002
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.929				
<Median	257 / 633 (40.6)	199 / 632 (31.5)	1.29	[1.11; 1.50]	<.001
≥Median	291 / 776 (37.5)	212 / 730 (29.0)	1.29	[1.12; 1.49]	<.001
Race					
Interaction test	p = 0.442				
Asian	37 / 128 (28.9)	23 / 127 (18.1)	1.60	[1.01; 2.53]	0.046
Non-Asian	476 / 1203 (39.6)	364 / 1167 (31.2)	1.27	[1.14; 1.42]	<.001
BMI at screening					
Interaction test	p = 0.421				
≥25	372 / 935 (39.8)	281 / 935 (30.1)	1.32	[1.17; 1.50]	<.001
<25	170 / 460 (37.0)	125 / 410 (30.5)	1.21	[1.00; 1.46]	0.046
AJCC Anatomic Stage Group					
Interaction test	p = 0.339				
Group I/II	201 / 585 (34.4)	166 / 589 (28.2)	1.22	[1.03; 1.45]	0.023
Group III	346 / 823 (42.0)	245 / 772 (31.7)	1.32	[1.16; 1.51]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.003				
IA/IB/IIA	113 / 310 (36.5)	76 / 311 (24.4)	1.49	[1.17; 1.90]	0.001
IIB	88 / 275 (32.0)	90 / 278 (32.4)	0.99	[0.78; 1.26]	0.925
IIIA	178 / 482 (36.9)	148 / 450 (32.9)	1.12	[0.94; 1.34]	0.197
IIIB	47 / 100 (47.0)	27 / 82 (32.9)	1.43	[0.98; 2.07]	0.061
IIIC	121 / 241 (50.2)	70 / 240 (29.2)	1.72	[1.36; 2.17]	<.001
Tumor category					
Interaction test	p = 0.334				
T0	3 / 5 (60.0)	1 / 5 (20.0)	3.00	[0.45; 19.93]	0.255
T1-T3	491 / 1287 (38.2)	380 / 1258 (30.2)	1.26	[1.13; 1.41]	<.001
>T3	52 / 113 (46.0)	29 / 97 (29.9)	1.54	[1.07; 2.22]	0.020
Nodal status					
Interaction test	p = 0.003				
N0	75 / 190 (39.5)	38 / 200 (19.0)	2.08	[1.48; 2.91]	<.001
N1-N3	473 / 1216 (38.9)	373 / 1160 (32.2)	1.21	[1.08; 1.35]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.211				
Grade 1	36 / 102 (35.3)	38 / 106 (35.8)	0.98	[0.68; 1.42]	0.933
Grade 2	329 / 842 (39.1)	230 / 768 (29.9)	1.30	[1.14; 1.50]	<.001
Grade 3	159 / 373 (42.6)	119 / 397 (30.0)	1.42	[1.17; 1.72]	<.001
Histological subtype					
Interaction test	p = 0.784				
Ductal	389 / 1025 (38.0)	295 / 1010 (29.2)	1.30	[1.15; 1.47]	<.001
Lobular	115 / 291 (39.5)	83 / 276 (30.1)	1.31	[1.04; 1.65]	0.020
Other	44 / 92 (47.8)	33 / 76 (43.4)	1.10	[0.79; 1.54]	0.570
Ki67 status from surgical specimen					
Interaction test	p = 0.455				
Ki67≤20	247 / 660 (37.4)	194 / 629 (30.8)	1.21	[1.04; 1.41]	0.013
Ki67>20	169 / 489 (34.6)	132 / 516 (25.6)	1.35	[1.12; 1.64]	0.002
Type of NSAI					
Interaction test	p = 0.762				
Letrozole	344 / 907 (37.9)	266 / 895 (29.7)	1.28	[1.12; 1.45]	<.001
Anastrozole	204 / 502 (40.6)	145 / 467 (31.0)	1.31	[1.10; 1.55]	0.002
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.813				
Yes	475 / 1194 (39.8)	357 / 1146 (31.2)	1.28	[1.14; 1.43]	<.001
No	73 / 215 (34.0)	54 / 216 (25.0)	1.36	[1.01; 1.83]	0.043
Prior adjuvant chemotherapy					
Interaction test	p = 0.436				
Yes	271 / 694 (39.0)	213 / 673 (31.6)	1.23	[1.07; 1.43]	0.004
No	277 / 715 (38.7)	198 / 689 (28.7)	1.35	[1.16; 1.57]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.927				
Yes	215 / 528 (40.7)	159 / 503 (31.6)	1.29	[1.09; 1.52]	0.003
No	333 / 881 (37.8)	252 / 859 (29.3)	1.29	[1.13; 1.47]	<.001
Prior endocrine therapy					
Interaction test	p = 0.625				
Yes	370 / 957 (38.7)	287 / 940 (30.5)	1.27	[1.12; 1.44]	<.001
No	178 / 452 (39.4)	124 / 422 (29.4)	1.34	[1.11; 1.62]	0.002
Prior mastectomy					
Interaction test	p = 0.336				
Yes	350 / 857 (40.8)	259 / 847 (30.6)	1.34	[1.17; 1.52]	<.001
No	198 / 552 (35.9)	152 / 515 (29.5)	1.22	[1.02; 1.45]	0.028
Prior radiotherapy					
Interaction test	p = 0.361				
Yes	483 / 1253 (38.5)	366 / 1203 (30.4)	1.27	[1.13; 1.41]	<.001
No	65 / 156 (41.7)	45 / 159 (28.3)	1.47	[1.08; 2.01]	0.014
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.56 PT headache: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Headache					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.073				
NA/WE/O	208 / 899 (23.1)	135 / 856 (15.8)	1.47	[1.21; 1.78]	<.001
ROW	57 / 510 (11.2)	54 / 506 (10.7)	1.05	[0.74; 1.49]	0.797
Geographical region					
Interaction test	p = 0.599				
Europe	135 / 832 (16.2)	98 / 824 (11.9)	1.36	[1.07; 1.74]	0.012
North America/Australia	110 / 400 (27.5)	72 / 364 (19.8)	1.39	[1.07; 1.80]	0.013
Asia	10 / 102 (9.8)	7 / 101 (6.9)	1.41	[0.56; 3.57]	0.463
Latin America	10 / 75 (13.3)	12 / 73 (16.4)	0.81	[0.37; 1.76]	0.596
Age group 1 at randomization					
Interaction test	p = 0.703				
<45	16 / 60 (26.7)	7 / 52 (13.5)	1.98	[0.88; 4.44]	0.097
45 to 54	71 / 300 (23.7)	54 / 322 (16.8)	1.41	[1.03; 1.94]	0.033
55 to 64	118 / 651 (18.1)	92 / 642 (14.3)	1.26	[0.99; 1.62]	0.065
≥65	60 / 398 (15.1)	36 / 346 (10.4)	1.45	[0.98; 2.13]	0.061
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.309				
<Median	140 / 633 (22.1)	95 / 632 (15.0)	1.47	[1.16; 1.86]	0.001
≥Median	125 / 776 (16.1)	94 / 730 (12.9)	1.25	[0.98; 1.60]	0.077
Race					
Interaction test	p = 0.892				
Asian	20 / 128 (15.6)	14 / 127 (11.0)	1.42	[0.75; 2.68]	0.283
Non-Asian	229 / 1203 (19.0)	166 / 1167 (14.2)	1.34	[1.11; 1.61]	0.002
BMI at screening					
Interaction test	p = 0.713				
≥25	177 / 935 (18.9)	127 / 935 (13.6)	1.39	[1.13; 1.72]	0.002
<25	86 / 460 (18.7)	59 / 410 (14.4)	1.30	[0.96; 1.76]	0.091
AJCC Anatomic Stage Group					
Interaction test	p = 0.145				
Group I/II	92 / 585 (15.7)	80 / 589 (13.6)	1.16	[0.88; 1.53]	0.300
Group III	173 / 823 (21.0)	109 / 772 (14.1)	1.49	[1.20; 1.85]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.052				
IA/IB/IIA	58 / 310 (18.7)	37 / 311 (11.9)	1.57	[1.07; 2.30]	0.020
IIB	34 / 275 (12.4)	43 / 278 (15.5)	0.80	[0.53; 1.21]	0.293
IIIA	95 / 482 (19.7)	67 / 450 (14.9)	1.32	[1.00; 1.76]	0.054
IIIB	21 / 100 (21.0)	9 / 82 (11.0)	1.91	[0.93; 3.95]	0.079
IIIC	57 / 241 (23.7)	33 / 240 (13.8)	1.72	[1.16; 2.54]	0.006
Tumor category					
Interaction test	p = 0.266				
T0	2 / 5 (40.0)	0 / 5 (0.0)	5.00	[0.30; 83.69]	0.263
T1-T3	240 / 1287 (18.6)	178 / 1258 (14.1)	1.32	[1.10; 1.57]	0.002
>T3	23 / 113 (20.4)	10 / 97 (10.3)	1.97	[0.99; 3.94]	0.054
Nodal status					
Interaction test	p = 0.056				
N0	36 / 190 (18.9)	17 / 200 (8.5)	2.23	[1.30; 3.83]	0.004
N1-N3	229 / 1216 (18.8)	172 / 1160 (14.8)	1.27	[1.06; 1.52]	0.009
Histological grade at time of surgery					
Interaction test	p = 0.551				
Grade 1	17 / 102 (16.7)	17 / 106 (16.0)	1.04	[0.56; 1.92]	0.902
Grade 2	163 / 842 (19.4)	107 / 768 (13.9)	1.39	[1.11; 1.74]	0.004
Grade 3	76 / 373 (20.4)	53 / 397 (13.4)	1.53	[1.11; 2.10]	0.010
Histological subtype					
Interaction test	p = 0.469				
Ductal	186 / 1025 (18.1)	130 / 1010 (12.9)	1.41	[1.15; 1.73]	0.001
Lobular	61 / 291 (21.0)	43 / 276 (15.6)	1.35	[0.94; 1.92]	0.100
Other	18 / 92 (19.6)	16 / 76 (21.1)	0.93	[0.51; 1.70]	0.811
Ki67 status from surgical specimen					
Interaction test	p = 0.805				
Ki67≤20	118 / 660 (17.9)	82 / 629 (13.0)	1.37	[1.06; 1.78]	0.017
Ki67>20	77 / 489 (15.7)	62 / 516 (12.0)	1.31	[0.96; 1.79]	0.088
Type of NSAI					
Interaction test	p = 0.718				
Letrozole	157 / 907 (17.3)	117 / 895 (13.1)	1.32	[1.06; 1.65]	0.013
Anastrozole	108 / 502 (21.5)	72 / 467 (15.4)	1.40	[1.06; 1.83]	0.016
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.923				
Yes	233 / 1194 (19.5)	165 / 1146 (14.4)	1.36	[1.13; 1.63]	0.001
No	32 / 215 (14.9)	24 / 216 (11.1)	1.34	[0.82; 2.20]	0.247
Prior adjuvant chemotherapy					
Interaction test	p = 0.249				
Yes	129 / 694 (18.6)	102 / 673 (15.2)	1.23	[0.97; 1.55]	0.091
No	136 / 715 (19.0)	87 / 689 (12.6)	1.51	[1.18; 1.93]	0.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.355				
Yes	111 / 528 (21.0)	71 / 503 (14.1)	1.49	[1.14; 1.95]	0.004
No	154 / 881 (17.5)	118 / 859 (13.7)	1.27	[1.02; 1.59]	0.032
Prior endocrine therapy					
Interaction test	p = 0.406				
Yes	183 / 957 (19.1)	139 / 940 (14.8)	1.29	[1.06; 1.58]	0.012
No	82 / 452 (18.1)	50 / 422 (11.8)	1.53	[1.11; 2.12]	0.010
Prior mastectomy					
Interaction test	p = 0.655				
Yes	168 / 857 (19.6)	119 / 847 (14.0)	1.40	[1.13; 1.73]	0.002
No	97 / 552 (17.6)	70 / 515 (13.6)	1.29	[0.97; 1.72]	0.075
Prior radiotherapy					
Interaction test	p = 0.744				
Yes	240 / 1253 (19.2)	172 / 1203 (14.3)	1.34	[1.12; 1.60]	0.001
No	25 / 156 (16.0)	17 / 159 (10.7)	1.50	[0.84; 2.66]	0.168
<p>N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.57 PT dizziness: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Dizziness					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.842				
NA/WE/O	101 / 899 (11.2)	50 / 856 (5.8)	1.92	[1.39; 2.66]	<.001
ROW	28 / 510 (5.5)	13 / 506 (2.6)	2.14	[1.12; 4.08]	0.021
Geographical region					
Interaction test	p = 0.199				
Europe	57 / 832 (6.9)	22 / 824 (2.7)	2.57	[1.58; 4.16]	<.001
North America/Australia	57 / 400 (14.3)	34 / 364 (9.3)	1.53	[1.02; 2.28]	0.039
Asia	7 / 102 (6.9)	0 / 101 (0.0)	14.85	[0.86; >99.99]	0.063
Latin America	8 / 75 (10.7)	7 / 73 (9.6)	1.11	[0.43; 2.91]	0.828
Age group 1 at randomization					
Interaction test	p = 0.423				
<45	6 / 60 (10.0)	5 / 52 (9.6)	1.04	[0.34; 3.21]	0.946
45 to 54	24 / 300 (8.0)	9 / 322 (2.8)	2.86	[1.35; 6.06]	0.006
55 to 64	59 / 651 (9.1)	34 / 642 (5.3)	1.71	[1.14; 2.57]	0.010
≥65	40 / 398 (10.1)	15 / 346 (4.3)	2.32	[1.30; 4.12]	0.004
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.433				
<Median	53 / 633 (8.4)	23 / 632 (3.6)	2.30	[1.43; 3.71]	<.001
≥Median	76 / 776 (9.8)	40 / 730 (5.5)	1.79	[1.24; 2.59]	0.002
Race					
Interaction test	p = 0.180				
Asian	13 / 128 (10.2)	3 / 127 (2.4)	4.30	[1.26; 14.73]	0.020
Non-Asian	110 / 1203 (9.1)	59 / 1167 (5.1)	1.81	[1.33; 2.46]	<.001
BMI at screening					
Interaction test	p = 0.800				
≥25	86 / 935 (9.2)	46 / 935 (4.9)	1.87	[1.32; 2.64]	<.001
<25	39 / 460 (8.5)	17 / 410 (4.1)	2.04	[1.18; 3.56]	0.011
AJCC Anatomic Stage Group					
Interaction test	p = 0.324				
Group I/II	48 / 585 (8.2)	20 / 589 (3.4)	2.42	[1.45; 4.02]	<.001
Group III	80 / 823 (9.7)	43 / 772 (5.6)	1.75	[1.22; 2.49]	0.002

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.117				
IA/IB/IIA	25 / 310 (8.1)	8 / 311 (2.6)	3.14	[1.44; 6.84]	0.004
IIB	23 / 275 (8.4)	12 / 278 (4.3)	1.94	[0.98; 3.82]	0.056
IIIA	34 / 482 (7.1)	26 / 450 (5.8)	1.22	[0.74; 2.00]	0.429
IIIB	9 / 100 (9.0)	5 / 82 (6.1)	1.48	[0.51; 4.23]	0.469
IIIC	37 / 241 (15.4)	12 / 240 (5.0)	3.07	[1.64; 5.74]	<.001
Tumor category					
Interaction test	p = 0.660				
T0	1 / 5 (20.0)	0 / 5 (0.0)	3.00	[0.15; 59.89]	0.472
T1-T3	116 / 1287 (9.0)	57 / 1258 (4.5)	1.99	[1.46; 2.71]	<.001
>T3	11 / 113 (9.7)	6 / 97 (6.2)	1.57	[0.60; 4.10]	0.353
Nodal status					
Interaction test	p = 0.058				
N0	17 / 190 (8.9)	3 / 200 (1.5)	5.96	[1.78; 20.03]	0.004
N1-N3	112 / 1216 (9.2)	60 / 1160 (5.2)	1.78	[1.32; 2.41]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.737				
Grade 1	10 / 102 (9.8)	5 / 106 (4.7)	2.08	[0.74; 5.87]	0.167
Grade 2	78 / 842 (9.3)	39 / 768 (5.1)	1.82	[1.26; 2.65]	0.002
Grade 3	36 / 373 (9.7)	16 / 397 (4.0)	2.39	[1.35; 4.24]	0.003
Histological subtype					
Interaction test	p = 0.293				
Ductal	88 / 1025 (8.6)	46 / 1010 (4.6)	1.89	[1.33; 2.66]	<.001
Lobular	29 / 291 (10.0)	9 / 276 (3.3)	3.06	[1.47; 6.34]	0.003
Other	12 / 92 (13.0)	8 / 76 (10.5)	1.24	[0.53; 2.87]	0.617
Ki67 status from surgical specimen					
Interaction test	p = 0.334				
Ki67≤20	44 / 660 (6.7)	23 / 629 (3.7)	1.82	[1.11; 2.98]	0.017
Ki67>20	42 / 489 (8.6)	17 / 516 (3.3)	2.61	[1.50; 4.52]	<.001
Type of NSAI					
Interaction test	p = 0.185				
Letrozole	68 / 907 (7.5)	40 / 895 (4.5)	1.68	[1.15; 2.45]	0.008
Anastrozole	61 / 502 (12.2)	23 / 467 (4.9)	2.47	[1.55; 3.92]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.462				
Yes	117 / 1194 (9.8)	59 / 1146 (5.1)	1.90	[1.41; 2.58]	<.001
No	12 / 215 (5.6)	4 / 216 (1.9)	3.01	[0.99; 9.20]	0.053
Prior adjuvant chemotherapy					
Interaction test	p = 0.244				
Yes	76 / 694 (11.0)	32 / 673 (4.8)	2.30	[1.55; 3.43]	<.001
No	53 / 715 (7.4)	31 / 689 (4.5)	1.65	[1.07; 2.53]	0.023

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.052				
Yes	42 / 528 (8.0)	29 / 503 (5.8)	1.38	[0.87; 2.18]	0.168
No	87 / 881 (9.9)	34 / 859 (4.0)	2.49	[1.70; 3.67]	<.001
Prior endocrine therapy					
Interaction test	p = 0.747				
Yes	94 / 957 (9.8)	48 / 940 (5.1)	1.92	[1.37; 2.69]	<.001
No	35 / 452 (7.7)	15 / 422 (3.6)	2.18	[1.21; 3.93]	0.010
Prior mastectomy					
Interaction test	p = 0.651				
Yes	82 / 857 (9.6)	43 / 847 (5.1)	1.88	[1.32; 2.69]	<.001
No	47 / 552 (8.5)	20 / 515 (3.9)	2.19	[1.32; 3.65]	0.003
Prior radiotherapy					
Interaction test	p = 0.671				
Yes	119 / 1253 (9.5)	59 / 1203 (4.9)	1.94	[1.43; 2.62]	<.001
No	10 / 156 (6.4)	4 / 159 (2.5)	2.55	[0.82; 7.95]	0.107
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.58 PT dysgeusia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Dysgeusia					
	n / N (%)	n / N (%)			
Region					
Interaction test	N.E.				
NA/WE/O	27 / 899 (3.0)	7 / 856 (0.8)	3.67	[1.61; 8.39]	0.002
ROW	3 / 510 (0.6)	0 / 506 (0.0)	6.95	[0.36; >99.99]	0.199
Geographical region					
Interaction test	p = 0.052				
Europe	20 / 832 (2.4)	2 / 824 (0.2)	9.90	[2.32; 42.24]	0.002
North America/Australia	9 / 400 (2.3)	5 / 364 (1.4)	1.64	[0.55; 4.84]	0.372
Asia	1 / 102 (1.0)	0 / 101 (0.0)	2.97	[0.12; 72.08]	0.503
Latin America	0 / 75 (0.0)	0 / 73 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	p = 0.579				
<45	0 / 60 (0.0)	2 / 52 (3.8)	0.17	[<0.01; 3.54]	0.255
45 to 54	5 / 300 (1.7)	2 / 322 (0.6)	2.68	[0.52; 13.73]	0.236
55 to 64	15 / 651 (2.3)	2 / 642 (0.3)	7.40	[1.70; 32.21]	0.008
≥65	10 / 398 (2.5)	1 / 346 (0.3)	8.69	[1.12; 67.57]	0.039
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.064				
<Median	9 / 633 (1.4)	5 / 632 (0.8)	1.80	[0.61; 5.33]	0.291
≥Median	21 / 776 (2.7)	2 / 730 (0.3)	9.88	[2.32; 41.98]	0.002
Race					
Interaction test	N.E.				
Asian	2 / 128 (1.6)	0 / 127 (0.0)	4.96	[0.24; >99.99]	0.300
Non-Asian	27 / 1203 (2.2)	6 / 1167 (0.5)	4.37	[1.81; 10.53]	0.001
BMI at screening					
Interaction test	p = 0.661				
≥25	18 / 935 (1.9)	5 / 935 (0.5)	3.60	[1.34; 9.66]	0.011
<25	12 / 460 (2.6)	2 / 410 (0.5)	5.35	[1.20; 23.75]	0.028
AJCC Anatomic Stage Group					
Interaction test	p = 0.213				
Group I/II	9 / 585 (1.5)	4 / 589 (0.7)	2.27	[0.70; 7.32]	0.172
Group III	21 / 823 (2.6)	3 / 772 (0.4)	6.57	[1.97; 21.93]	0.002

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.331				
IA/IB/IIA	5 / 310 (1.6)	4 / 311 (1.3)	1.25	[0.34; 4.63]	0.734
IIB	4 / 275 (1.5)	0 / 278 (0.0)	9.10	[0.49; >99.99]	0.138
IIIA	10 / 482 (2.1)	3 / 450 (0.7)	3.11	[0.86; 11.24]	0.083
IIIB	3 / 100 (3.0)	0 / 82 (0.0)	5.75	[0.30; >99.99]	0.245
IIIC	8 / 241 (3.3)	0 / 240 (0.0)	16.93	[0.98; >99.99]	0.051
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	1 / 5 (20.0)	0.33	[0.02; 6.65]	0.472
T1-T3	26 / 1287 (2.0)	6 / 1258 (0.5)	4.24	[1.75; 10.26]	0.001
>T3	4 / 113 (3.5)	0 / 97 (0.0)	7.74	[0.42; >99.99]	0.168
Nodal status					
Interaction test	p = 0.801				
N0	3 / 190 (1.6)	1 / 200 (0.5)	3.16	[0.33; 30.09]	0.317
N1-N3	27 / 1216 (2.2)	6 / 1160 (0.5)	4.29	[1.78; 10.36]	0.001
Histological grade at time of surgery					
Interaction test	p = 0.122				
Grade 1	1 / 102 (1.0)	2 / 106 (1.9)	0.52	[0.05; 5.64]	0.591
Grade 2	18 / 842 (2.1)	4 / 768 (0.5)	4.10	[1.40; 12.07]	0.010
Grade 3	10 / 373 (2.7)	0 / 397 (0.0)	22.35	[1.31; >99.99]	0.032
Histological subtype					
Interaction test	p = 0.387				
Ductal	24 / 1025 (2.3)	4 / 1010 (0.4)	5.91	[2.06; 16.98]	<.001
Lobular	2 / 291 (0.7)	1 / 276 (0.4)	1.90	[0.17; 20.80]	0.600
Other	4 / 92 (4.3)	2 / 76 (2.6)	1.65	[0.31; 8.78]	0.556
Ki67 status from surgical specimen					
Interaction test	p = 0.512				
Ki67≤20	18 / 660 (2.7)	3 / 629 (0.5)	5.72	[1.69; 19.32]	0.005
Ki67>20	9 / 489 (1.8)	3 / 516 (0.6)	3.17	[0.86; 11.62]	0.083
Type of NSAI					
Interaction test	p = 0.299				
Letrozole	19 / 907 (2.1)	6 / 895 (0.7)	3.12	[1.25; 7.79]	0.014
Anastrozole	11 / 502 (2.2)	1 / 467 (0.2)	10.23	[1.33; 78.95]	0.026
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.976				
Yes	26 / 1194 (2.2)	6 / 1146 (0.5)	4.16	[1.72; 10.07]	0.002
No	4 / 215 (1.9)	1 / 216 (0.5)	4.02	[0.45; 35.66]	0.212
Prior adjuvant chemotherapy					
Interaction test	p = 0.728				
Yes	15 / 694 (2.2)	3 / 673 (0.4)	4.85	[1.41; 16.67]	0.012
No	15 / 715 (2.1)	4 / 689 (0.6)	3.61	[1.21; 10.83]	0.022

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.870				
Yes	12 / 528 (2.3)	3 / 503 (0.6)	3.81	[1.08; 13.42]	0.037
No	18 / 881 (2.0)	4 / 859 (0.5)	4.39	[1.49; 12.91]	0.007
Prior endocrine therapy					
Interaction test	p = 0.725				
Yes	23 / 957 (2.4)	5 / 940 (0.5)	4.52	[1.72; 11.83]	0.002
No	7 / 452 (1.5)	2 / 422 (0.5)	3.27	[0.68; 15.64]	0.138
Prior mastectomy					
Interaction test	p = 0.735				
Yes	19 / 857 (2.2)	5 / 847 (0.6)	3.76	[1.41; 10.01]	0.008
No	11 / 552 (2.0)	2 / 515 (0.4)	5.13	[1.14; 23.04]	0.033
Prior radiotherapy					
Interaction test	p = 0.519				
Yes	25 / 1253 (2.0)	5 / 1203 (0.4)	4.80	[1.84; 12.50]	0.001
No	5 / 156 (3.2)	2 / 159 (1.3)	2.55	[0.50; 12.94]	0.259
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.59 PT migraine: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Migraine					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.243				
NA/WE/O	19 / 899 (2.1)	5 / 856 (0.6)	3.62	[1.36; 9.65]	0.010
ROW	2 / 510 (0.4)	2 / 506 (0.4)	0.99	[0.14; 7.02]	0.994
Geographical region					
Interaction test	p = 0.439				
Europe	10 / 832 (1.2)	2 / 824 (0.2)	4.95	[1.09; 22.53]	0.039
North America/Australia	9 / 400 (2.3)	3 / 364 (0.8)	2.73	[0.74; 10.01]	0.130
Asia	0 / 102 (0.0)	0 / 101 (0.0)	N.E.	N.E.	N.E.
Latin America	2 / 75 (2.7)	2 / 73 (2.7)	0.97	[0.14; 6.73]	0.978
Age group 1 at randomization					
Interaction test	p = 0.520				
<45	0 / 60 (0.0)	0 / 52 (0.0)	N.E.	N.E.	N.E.
45 to 54	7 / 300 (2.3)	2 / 322 (0.6)	3.76	[0.79; 17.94]	0.097
55 to 64	9 / 651 (1.4)	2 / 642 (0.3)	4.44	[0.96; 20.46]	0.056
≥65	5 / 398 (1.3)	3 / 346 (0.9)	1.45	[0.35; 6.02]	0.610
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.179				
<Median	12 / 633 (1.9)	2 / 632 (0.3)	5.99	[1.35; 26.66]	0.019
≥Median	9 / 776 (1.2)	5 / 730 (0.7)	1.69	[0.57; 5.03]	0.343
Race					
Interaction test	N.E.				
Asian	0 / 128 (0.0)	0 / 127 (0.0)	N.E.	N.E.	N.E.
Non-Asian	20 / 1203 (1.7)	6 / 1167 (0.5)	3.23	[1.30; 8.02]	0.011
BMI at screening					
Interaction test	p = 0.560				
≥25	14 / 935 (1.5)	4 / 935 (0.4)	3.50	[1.16; 10.59]	0.027
<25	7 / 460 (1.5)	3 / 410 (0.7)	2.08	[0.54; 7.99]	0.286
AJCC Anatomic Stage Group					
Interaction test	p = 0.131				
Group I/II	5 / 585 (0.9)	4 / 589 (0.7)	1.26	[0.34; 4.66]	0.731
Group III	16 / 823 (1.9)	3 / 772 (0.4)	5.00	[1.46; 17.10]	0.010
Anatomic stages					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Tumor category					
Interaction test	p = 0.519				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	17 / 1287 (1.3)	5 / 1258 (0.4)	3.32	[1.23; 8.98]	0.018
>T3	4 / 113 (3.5)	2 / 97 (2.1)	1.72	[0.32; 9.17]	0.527
Nodal status					
Interaction test	p = 0.153				
N0	3 / 190 (1.6)	3 / 200 (1.5)	1.05	[0.22; 5.15]	0.950
N1-N3	18 / 1216 (1.5)	4 / 1160 (0.3)	4.29	[1.46; 12.65]	0.008
Histological grade at time of surgery					
Interaction test	p = 0.818				
Grade 1	1 / 102 (1.0)	0 / 106 (0.0)	3.12	[0.13; 75.63]	0.485
Grade 2	14 / 842 (1.7)	5 / 768 (0.7)	2.55	[0.92; 7.06]	0.071
Grade 3	6 / 373 (1.6)	2 / 397 (0.5)	3.19	[0.65; 15.72]	0.153
Histological subtype					
Interaction test	p = 0.608				
Ductal	15 / 1025 (1.5)	5 / 1010 (0.5)	2.96	[1.08; 8.10]	0.035
Lobular	5 / 291 (1.7)	1 / 276 (0.4)	4.74	[0.56; 40.34]	0.154
Other	1 / 92 (1.1)	1 / 76 (1.3)	0.83	[0.05; 12.99]	0.892
Ki67 status from surgical specimen					
Interaction test	p = 0.033				
Ki67≤20	10 / 660 (1.5)	1 / 629 (0.2)	9.53	[1.22; 74.23]	0.031
Ki67>20	3 / 489 (0.6)	5 / 516 (1.0)	0.63	[0.15; 2.64]	0.530
Type of NSAI					
Interaction test	p = 0.875				
Letrozole	11 / 907 (1.2)	4 / 895 (0.4)	2.71	[0.87; 8.49]	0.086
Anastrozole	10 / 502 (2.0)	3 / 467 (0.6)	3.10	[0.86; 11.20]	0.084
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.433				
Yes	20 / 1194 (1.7)	6 / 1146 (0.5)	3.20	[1.29; 7.94]	0.012
No	1 / 215 (0.5)	1 / 216 (0.5)	1.00	[0.06; 15.96]	0.997
Prior adjuvant chemotherapy					
Interaction test	p = 0.375				
Yes	13 / 694 (1.9)	3 / 673 (0.4)	4.20	[1.20; 14.68]	0.024
No	8 / 715 (1.1)	4 / 689 (0.6)	1.93	[0.58; 6.37]	0.282
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.803				
Yes	8 / 528 (1.5)	3 / 503 (0.6)	2.54	[0.68; 9.52]	0.167
No	13 / 881 (1.5)	4 / 859 (0.5)	3.17	[1.04; 9.68]	0.043

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior endocrine therapy					
Interaction test	p = 0.558				
Yes	17 / 957 (1.8)	5 / 940 (0.5)	3.34	[1.24; 9.02]	0.017
No	4 / 452 (0.9)	2 / 422 (0.5)	1.87	[0.34; 10.14]	0.470
Prior mastectomy					
Interaction test	p = 0.552				
Yes	17 / 857 (2.0)	5 / 847 (0.6)	3.36	[1.25; 9.07]	0.017
No	4 / 552 (0.7)	2 / 515 (0.4)	1.87	[0.34; 10.14]	0.470
Prior radiotherapy					
Interaction test	p = 0.439				
Yes	20 / 1253 (1.6)	6 / 1203 (0.5)	3.20	[1.29; 7.94]	0.012
No	1 / 156 (0.6)	1 / 159 (0.6)	1.02	[0.06; 16.15]	0.989
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.60 PT taste disorder: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Taste disorder					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.376				
NA/WE/O	10 / 899 (1.1)	2 / 856 (0.2)	4.76	[1.05; 21.67]	0.044
ROW	8 / 510 (1.6)	4 / 506 (0.8)	1.98	[0.60; 6.55]	0.261
Geographical region					
Interaction test	N.E.				
Europe	14 / 832 (1.7)	6 / 824 (0.7)	2.31	[0.89; 5.98]	0.084
North America/Australia	4 / 400 (1.0)	0 / 364 (0.0)	8.19	[0.44; >99.99]	0.158
Asia	0 / 102 (0.0)	0 / 101 (0.0)	N.E.	N.E.	N.E.
Latin America	0 / 75 (0.0)	0 / 73 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	p = 0.969				
<45	0 / 60 (0.0)	0 / 52 (0.0)	N.E.	N.E.	N.E.
45 to 54	6 / 300 (2.0)	2 / 322 (0.6)	3.22	[0.65; 15.83]	0.150
55 to 64	8 / 651 (1.2)	3 / 642 (0.5)	2.63	[0.70; 9.87]	0.152
≥65	4 / 398 (1.0)	1 / 346 (0.3)	3.48	[0.39; 30.96]	0.264
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.859				
<Median	11 / 633 (1.7)	4 / 632 (0.6)	2.75	[0.88; 8.58]	0.082
≥Median	7 / 776 (0.9)	2 / 730 (0.3)	3.29	[0.69; 15.80]	0.136
Race					
Interaction test	N.E.				
Asian	1 / 128 (0.8)	0 / 127 (0.0)	2.98	[0.12; 72.39]	0.503
Non-Asian	17 / 1203 (1.4)	6 / 1167 (0.5)	2.75	[1.09; 6.95]	0.033
BMI at screening					
Interaction test	p = 0.658				
≥25	13 / 935 (1.4)	5 / 935 (0.5)	2.60	[0.93; 7.26]	0.068
<25	5 / 460 (1.1)	1 / 410 (0.2)	4.46	[0.52; 37.99]	0.172
AJCC Anatomic Stage Group					
Interaction test	p = 0.221				
Group I/II	8 / 585 (1.4)	1 / 589 (0.2)	8.05	[1.01; 64.20]	0.049
Group III	10 / 823 (1.2)	5 / 772 (0.6)	1.88	[0.64; 5.46]	0.249
Anatomic stages					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	15 / 1287 (1.2)	6 / 1258 (0.5)	2.44	[0.95; 6.28]	0.063
>T3	3 / 113 (2.7)	0 / 97 (0.0)	6.02	[0.31; >99.99]	0.233
Nodal status					
Interaction test	N.E.				
N0	3 / 190 (1.6)	0 / 200 (0.0)	7.37	[0.38; >99.99]	0.186
N1-N3	15 / 1216 (1.2)	6 / 1160 (0.5)	2.38	[0.93; 6.13]	0.071
Histological grade at time of surgery					
Interaction test	p = 0.115				
Grade 1	2 / 102 (2.0)	0 / 106 (0.0)	5.19	[0.25; >99.99]	0.286
Grade 2	12 / 842 (1.4)	2 / 768 (0.3)	5.47	[1.23; 24.37]	0.026
Grade 3	4 / 373 (1.1)	4 / 397 (1.0)	1.06	[0.27; 4.23]	0.929
Histological subtype					
Interaction test	p = 0.918				
Ductal	10 / 1025 (1.0)	3 / 1010 (0.3)	3.28	[0.91; 11.90]	0.070
Lobular	2 / 291 (0.7)	1 / 276 (0.4)	1.90	[0.17; 20.80]	0.600
Other	6 / 92 (6.5)	2 / 76 (2.6)	2.48	[0.51; 11.93]	0.258
Ki67 status from surgical specimen					
Interaction test	p = 0.721				
Ki67≤20	8 / 660 (1.2)	3 / 629 (0.5)	2.54	[0.68; 9.54]	0.167
Ki67>20	7 / 489 (1.4)	2 / 516 (0.4)	3.69	[0.77; 17.69]	0.102
Type of NSAI					
Interaction test	p = 0.061				
Letrozole	6 / 907 (0.7)	5 / 895 (0.6)	1.18	[0.36; 3.87]	0.780
Anastrozole	12 / 502 (2.4)	1 / 467 (0.2)	11.16	[1.46; 85.52]	0.020
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.971				
Yes	15 / 1194 (1.3)	5 / 1146 (0.4)	2.88	[1.05; 7.90]	0.040
No	3 / 215 (1.4)	1 / 216 (0.5)	3.01	[0.32; 28.75]	0.338
Prior adjuvant chemotherapy					
Interaction test	p = 0.994				
Yes	9 / 694 (1.3)	3 / 673 (0.4)	2.91	[0.79; 10.70]	0.108
No	9 / 715 (1.3)	3 / 689 (0.4)	2.89	[0.79; 10.63]	0.110
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.826				
Yes	7 / 528 (1.3)	2 / 503 (0.4)	3.33	[0.70; 15.97]	0.132
No	11 / 881 (1.2)	4 / 859 (0.5)	2.68	[0.86; 8.39]	0.090

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior endocrine therapy					
Interaction test	p = 0.510				
Yes	9 / 957 (0.9)	4 / 940 (0.4)	2.21	[0.68; 7.15]	0.186
No	9 / 452 (2.0)	2 / 422 (0.5)	4.20	[0.91; 19.33]	0.065
Prior mastectomy					
Interaction test	p = 0.954				
Yes	9 / 857 (1.1)	3 / 847 (0.4)	2.96	[0.81; 10.91]	0.102
No	9 / 552 (1.6)	3 / 515 (0.6)	2.80	[0.76; 10.28]	0.121
Prior radiotherapy					
Interaction test	N.E.				
Yes	18 / 1253 (1.4)	6 / 1203 (0.5)	2.88	[1.15; 7.23]	0.024
No	0 / 156 (0.0)	0 / 159 (0.0)	N.E.	N.E.	N.E.
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.61 SOC skin and subcutaneous tissue disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Skin and subcutaneous tissue disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.255				
NA/WE/O	418 / 899 (46.5)	211 / 856 (24.6)	1.89	[1.65; 2.16]	<.001
ROW	118 / 510 (23.1)	63 / 506 (12.5)	1.86	[1.40; 2.46]	<.001
Geographical region					
Interaction test	p = 0.998				
Europe	297 / 832 (35.7)	151 / 824 (18.3)	1.95	[1.64; 2.31]	<.001
North America/Australia	186 / 400 (46.5)	97 / 364 (26.6)	1.74	[1.43; 2.13]	<.001
Asia	35 / 102 (34.3)	18 / 101 (17.8)	1.93	[1.17; 3.17]	0.010
Latin America	18 / 75 (24.0)	8 / 73 (11.0)	2.19	[1.02; 4.72]	0.045
Age group 1 at randomization					
Interaction test	p = 0.908				
<45	28 / 60 (46.7)	13 / 52 (25.0)	1.87	[1.08; 3.21]	0.024
45 to 54	108 / 300 (36.0)	58 / 322 (18.0)	2.00	[1.51; 2.64]	<.001
55 to 64	236 / 651 (36.3)	129 / 642 (20.1)	1.80	[1.50; 2.17]	<.001
≥65	164 / 398 (41.2)	74 / 346 (21.4)	1.93	[1.53; 2.43]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.467				
<Median	245 / 633 (38.7)	123 / 632 (19.5)	1.99	[1.65; 2.40]	<.001
≥Median	291 / 776 (37.5)	151 / 730 (20.7)	1.81	[1.53; 2.15]	<.001
Race					
Interaction test	p = 0.551				
Asian	48 / 128 (37.5)	29 / 127 (22.8)	1.64	[1.11; 2.43]	0.013
Non-Asian	448 / 1203 (37.2)	230 / 1167 (19.7)	1.89	[1.65; 2.17]	<.001
BMI at screening					
Interaction test	p = 0.091				
≥25	341 / 935 (36.5)	193 / 935 (20.6)	1.77	[1.52; 2.06]	<.001
<25	190 / 460 (41.3)	77 / 410 (18.8)	2.20	[1.75; 2.76]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.295				
Group I/II	223 / 585 (38.1)	129 / 589 (21.9)	1.74	[1.45; 2.09]	<.001
Group III	312 / 823 (37.9)	145 / 772 (18.8)	2.02	[1.70; 2.39]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.612				
IA/IB/IIA	113 / 310 (36.5)	64 / 311 (20.6)	1.77	[1.36; 2.30]	<.001
IIB	110 / 275 (40.0)	65 / 278 (23.4)	1.71	[1.32; 2.21]	<.001
IIIA	183 / 482 (38.0)	84 / 450 (18.7)	2.03	[1.63; 2.54]	<.001
IIIB	32 / 100 (32.0)	17 / 82 (20.7)	1.54	[0.93; 2.57]	0.096
IIIC	97 / 241 (40.2)	44 / 240 (18.3)	2.20	[1.61; 2.99]	<.001
Tumor category					
Interaction test	p = 0.271				
T0	4 / 5 (80.0)	1 / 5 (20.0)	4.00	[0.66; 24.37]	0.133
T1-T3	496 / 1287 (38.5)	253 / 1258 (20.1)	1.92	[1.68; 2.18]	<.001
>T3	35 / 113 (31.0)	20 / 97 (20.6)	1.50	[0.93; 2.42]	0.095
Nodal status					
Interaction test	p = 0.075				
N0	58 / 190 (30.5)	42 / 200 (21.0)	1.45	[1.03; 2.05]	0.033
N1-N3	478 / 1216 (39.3)	232 / 1160 (20.0)	1.97	[1.72; 2.25]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.106				
Grade 1	31 / 102 (30.4)	22 / 106 (20.8)	1.46	[0.91; 2.35]	0.115
Grade 2	315 / 842 (37.4)	159 / 768 (20.7)	1.81	[1.53; 2.13]	<.001
Grade 3	164 / 373 (44.0)	78 / 397 (19.6)	2.24	[1.78; 2.82]	<.001
Histological subtype					
Interaction test	p = 0.203				
Ductal	381 / 1025 (37.2)	204 / 1010 (20.2)	1.84	[1.59; 2.13]	<.001
Lobular	112 / 291 (38.5)	58 / 276 (21.0)	1.83	[1.40; 2.40]	<.001
Other	43 / 92 (46.7)	12 / 76 (15.8)	2.96	[1.69; 5.20]	<.001
Ki67 status from surgical specimen					
Interaction test	p = 0.850				
Ki67≤20	239 / 660 (36.2)	123 / 629 (19.6)	1.85	[1.53; 2.24]	<.001
Ki67>20	170 / 489 (34.8)	93 / 516 (18.0)	1.93	[1.55; 2.40]	<.001
Type of NSAI					
Interaction test	p = 0.350				
Letrozole	335 / 907 (36.9)	182 / 895 (20.3)	1.82	[1.56; 2.12]	<.001
Anastrozole	201 / 502 (40.0)	92 / 467 (19.7)	2.03	[1.64; 2.51]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.808				
Yes	453 / 1194 (37.9)	228 / 1146 (19.9)	1.91	[1.66; 2.19]	<.001
No	83 / 215 (38.6)	46 / 216 (21.3)	1.81	[1.33; 2.46]	<.001
Prior adjuvant chemotherapy					
Interaction test	p = 0.465				
Yes	277 / 694 (39.9)	137 / 673 (20.4)	1.96	[1.65; 2.34]	<.001
No	259 / 715 (36.2)	137 / 689 (19.9)	1.82	[1.52; 2.18]	<.001

Treatment Groups			Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.841				
Yes	187 / 528 (35.4)	94 / 503 (18.7)	1.90	[1.53; 2.35]	<.001
No	349 / 881 (39.6)	180 / 859 (21.0)	1.89	[1.62; 2.20]	<.001
Prior endocrine therapy					
Interaction test	p = 0.035				
Yes	383 / 957 (40.0)	183 / 940 (19.5)	2.06	[1.77; 2.39]	<.001
No	153 / 452 (33.8)	91 / 422 (21.6)	1.57	[1.26; 1.96]	<.001
Prior mastectomy					
Interaction test	p = 0.561				
Yes	308 / 857 (35.9)	164 / 847 (19.4)	1.86	[1.58; 2.19]	<.001
No	228 / 552 (41.3)	110 / 515 (21.4)	1.93	[1.59; 2.35]	<.001
Prior radiotherapy					
Interaction test	p = 0.575				
Yes	486 / 1253 (38.8)	245 / 1203 (20.4)	1.90	[1.67; 2.17]	<.001
No	50 / 156 (32.1)	29 / 159 (18.2)	1.76	[1.18; 2.62]	0.006
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.62 PT alopecia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Alopecia					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.125				
NA/WE/O	183 / 899 (20.4)	47 / 856 (5.5)	3.71	[2.73; 5.04]	<.001
ROW	48 / 510 (9.4)	19 / 506 (3.8)	2.51	[1.49; 4.20]	<.001
Geographical region					
Interaction test	p = 0.177				
Europe	137 / 832 (16.5)	38 / 824 (4.6)	3.57	[2.53; 5.05]	<.001
North America/Australia	75 / 400 (18.8)	20 / 364 (5.5)	3.41	[2.13; 5.47]	<.001
Asia	7 / 102 (6.9)	6 / 101 (5.9)	1.16	[0.40; 3.32]	0.789
Latin America	12 / 75 (16.0)	2 / 73 (2.7)	5.84	[1.35; 25.19]	0.018
Age group 1 at randomization					
Interaction test	p = 0.984				
<45	11 / 60 (18.3)	3 / 52 (5.8)	3.18	[0.94; 10.78]	0.064
45 to 54	39 / 300 (13.0)	11 / 322 (3.4)	3.81	[1.99; 7.29]	<.001
55 to 64	107 / 651 (16.4)	33 / 642 (5.1)	3.20	[2.20; 4.65]	<.001
≥65	74 / 398 (18.6)	19 / 346 (5.5)	3.39	[2.09; 5.49]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.814				
<Median	99 / 633 (15.6)	28 / 632 (4.4)	3.53	[2.36; 5.29]	<.001
≥Median	132 / 776 (17.0)	38 / 730 (5.2)	3.27	[2.31; 4.62]	<.001
Race					
Interaction test	p = 0.009				
Asian	12 / 128 (9.4)	10 / 127 (7.9)	1.19	[0.53; 2.66]	0.670
Non-Asian	203 / 1203 (16.9)	54 / 1167 (4.6)	3.65	[2.73; 4.87]	<.001
BMI at screening					
Interaction test	p = 0.812				
≥25	145 / 935 (15.5)	44 / 935 (4.7)	3.30	[2.38; 4.56]	<.001
<25	85 / 460 (18.5)	22 / 410 (5.4)	3.44	[2.20; 5.40]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.030				
Group I/II	97 / 585 (16.6)	39 / 589 (6.6)	2.50	[1.76; 3.57]	<.001
Group III	133 / 823 (16.2)	27 / 772 (3.5)	4.62	[3.09; 6.91]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.186				
IA/IB/IIA	55 / 310 (17.7)	19 / 311 (6.1)	2.90	[1.77; 4.77]	<.001
IIB	42 / 275 (15.3)	20 / 278 (7.2)	2.12	[1.28; 3.52]	0.004
IIIA	80 / 482 (16.6)	14 / 450 (3.1)	5.33	[3.07; 9.28]	<.001
IIIB	17 / 100 (17.0)	3 / 82 (3.7)	4.65	[1.41; 15.31]	0.012
IIIC	36 / 241 (14.9)	10 / 240 (4.2)	3.59	[1.82; 7.06]	<.001
Tumor category					
Interaction test	p = 0.761				
T0	2 / 5 (40.0)	1 / 5 (20.0)	2.00	[0.26; 15.62]	0.509
T1-T3	210 / 1287 (16.3)	62 / 1258 (4.9)	3.31	[2.52; 4.35]	<.001
>T3	18 / 113 (15.9)	3 / 97 (3.1)	5.15	[1.56; 16.96]	0.007
Nodal status					
Interaction test	p = 0.032				
N0	26 / 190 (13.7)	15 / 200 (7.5)	1.82	[1.00; 3.34]	0.051
N1-N3	205 / 1216 (16.9)	51 / 1160 (4.4)	3.83	[2.85; 5.16]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.953				
Grade 1	13 / 102 (12.7)	3 / 106 (2.8)	4.50	[1.32; 15.34]	0.016
Grade 2	137 / 842 (16.3)	35 / 768 (4.6)	3.57	[2.50; 5.11]	<.001
Grade 3	69 / 373 (18.5)	21 / 397 (5.3)	3.50	[2.19; 5.58]	<.001
Histological subtype					
Interaction test	p = 0.163				
Ductal	162 / 1025 (15.8)	52 / 1010 (5.1)	3.07	[2.27; 4.14]	<.001
Lobular	52 / 291 (17.9)	8 / 276 (2.9)	6.16	[2.98; 12.74]	<.001
Other	17 / 92 (18.5)	6 / 76 (7.9)	2.34	[0.97; 5.64]	0.058
Ki67 status from surgical specimen					
Interaction test	p = 0.878				
Ki67≤20	118 / 660 (17.9)	33 / 629 (5.2)	3.41	[2.35; 4.93]	<.001
Ki67>20	64 / 489 (13.1)	20 / 516 (3.9)	3.38	[2.08; 5.49]	<.001
Type of NSAI					
Interaction test	p = 0.125				
Letrozole	149 / 907 (16.4)	50 / 895 (5.6)	2.94	[2.16; 4.00]	<.001
Anastrozole	82 / 502 (16.3)	16 / 467 (3.4)	4.77	[2.83; 8.02]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.888				
Yes	187 / 1194 (15.7)	52 / 1146 (4.5)	3.45	[2.57; 4.64]	<.001
No	44 / 215 (20.5)	14 / 216 (6.5)	3.16	[1.78; 5.59]	<.001
Prior adjuvant chemotherapy					
Interaction test	p = 0.411				
Yes	108 / 694 (15.6)	27 / 673 (4.0)	3.88	[2.58; 5.83]	<.001
No	123 / 715 (17.2)	39 / 689 (5.7)	3.04	[2.15; 4.29]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.479				
Yes	82 / 528 (15.5)	26 / 503 (5.2)	3.00	[1.97; 4.59]	<.001
No	149 / 881 (16.9)	40 / 859 (4.7)	3.63	[2.60; 5.08]	<.001
Prior endocrine therapy					
Interaction test	p = 0.905				
Yes	163 / 957 (17.0)	47 / 940 (5.0)	3.41	[2.49; 4.65]	<.001
No	68 / 452 (15.0)	19 / 422 (4.5)	3.34	[2.05; 5.46]	<.001
Prior mastectomy					
Interaction test	p = 0.125				
Yes	134 / 857 (15.6)	32 / 847 (3.8)	4.14	[2.85; 6.01]	<.001
No	97 / 552 (17.6)	34 / 515 (6.6)	2.66	[1.84; 3.86]	<.001
Prior radiotherapy					
Interaction test	p = 0.073				
Yes	211 / 1253 (16.8)	55 / 1203 (4.6)	3.68	[2.77; 4.90]	<.001
No	20 / 156 (12.8)	11 / 159 (6.9)	1.85	[0.92; 3.74]	0.085
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.63 PT pruritus: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Pruritus					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.954				
NA/WE/O	90 / 899 (10.0)	36 / 856 (4.2)	2.38	[1.64; 3.46]	<.001
ROW	18 / 510 (3.5)	7 / 506 (1.4)	2.55	[1.07; 6.06]	0.034
Geographical region					
Interaction test	p = 0.659				
Europe	48 / 832 (5.8)	23 / 824 (2.8)	2.07	[1.27; 3.37]	0.004
North America/Australia	46 / 400 (11.5)	15 / 364 (4.1)	2.79	[1.59; 4.91]	<.001
Asia	10 / 102 (9.8)	5 / 101 (5.0)	1.98	[0.70; 5.59]	0.197
Latin America	4 / 75 (5.3)	0 / 73 (0.0)	8.76	[0.48; >99.99]	0.143
Age group 1 at randomization					
Interaction test	p = 0.934				
<45	7 / 60 (11.7)	2 / 52 (3.8)	3.03	[0.66; 13.97]	0.154
45 to 54	21 / 300 (7.0)	10 / 322 (3.1)	2.25	[1.08; 4.71]	0.031
55 to 64	45 / 651 (6.9)	20 / 642 (3.1)	2.22	[1.33; 3.71]	0.002
≥65	35 / 398 (8.8)	11 / 346 (3.2)	2.77	[1.43; 5.36]	0.003
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.881				
<Median	50 / 633 (7.9)	20 / 632 (3.2)	2.50	[1.50; 4.14]	<.001
≥Median	58 / 776 (7.5)	23 / 730 (3.2)	2.37	[1.48; 3.80]	<.001
Race					
Interaction test	p = 0.778				
Asian	13 / 128 (10.2)	6 / 127 (4.7)	2.15	[0.84; 5.48]	0.109
Non-Asian	89 / 1203 (7.4)	34 / 1167 (2.9)	2.54	[1.72; 3.74]	<.001
BMI at screening					
Interaction test	p = 0.430				
≥25	68 / 935 (7.3)	31 / 935 (3.3)	2.19	[1.45; 3.32]	<.001
<25	37 / 460 (8.0)	11 / 410 (2.7)	3.00	[1.55; 5.80]	0.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.363				
Group I/II	40 / 585 (6.8)	20 / 589 (3.4)	2.01	[1.19; 3.40]	0.009
Group III	68 / 823 (8.3)	23 / 772 (3.0)	2.77	[1.75; 4.40]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.758				
IA/IB/IIA	20 / 310 (6.5)	11 / 311 (3.5)	1.82	[0.89; 3.74]	0.101
IIB	20 / 275 (7.3)	9 / 278 (3.2)	2.25	[1.04; 4.85]	0.039
IIIA	43 / 482 (8.9)	17 / 450 (3.8)	2.36	[1.37; 4.08]	0.002
IIIB	6 / 100 (6.0)	1 / 82 (1.2)	4.92	[0.60; 40.05]	0.136
IIIC	19 / 241 (7.9)	5 / 240 (2.1)	3.78	[1.44; 9.97]	0.007
Tumor category					
Interaction test	p = 0.768				
T0	1 / 5 (20.0)	0 / 5 (0.0)	3.00	[0.15; 59.89]	0.472
T1-T3	100 / 1287 (7.8)	40 / 1258 (3.2)	2.44	[1.71; 3.50]	<.001
>T3	7 / 113 (6.2)	3 / 97 (3.1)	2.00	[0.53; 7.54]	0.304
Nodal status					
Interaction test	p = 0.617				
N0	9 / 190 (4.7)	5 / 200 (2.5)	1.89	[0.65; 5.55]	0.244
N1-N3	99 / 1216 (8.1)	38 / 1160 (3.3)	2.49	[1.72; 3.58]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.062				
Grade 1	10 / 102 (9.8)	3 / 106 (2.8)	3.46	[0.98; 12.23]	0.054
Grade 2	58 / 842 (6.9)	30 / 768 (3.9)	1.76	[1.15; 2.71]	0.010
Grade 3	33 / 373 (8.8)	7 / 397 (1.8)	5.02	[2.25; 11.20]	<.001
Histological subtype					
Interaction test	p = 0.372				
Ductal	79 / 1025 (7.7)	29 / 1010 (2.9)	2.68	[1.77; 4.07]	<.001
Lobular	20 / 291 (6.9)	12 / 276 (4.3)	1.58	[0.79; 3.17]	0.198
Other	9 / 92 (9.8)	2 / 76 (2.6)	3.72	[0.83; 16.69]	0.087
Ki67 status from surgical specimen					
Interaction test	p = 0.266				
Ki67≤20	40 / 660 (6.1)	24 / 629 (3.8)	1.59	[0.97; 2.60]	0.066
Ki67>20	29 / 489 (5.9)	12 / 516 (2.3)	2.55	[1.32; 4.94]	0.006
Type of NSAI					
Interaction test	p = 0.090				
Letrozole	66 / 907 (7.3)	33 / 895 (3.7)	1.97	[1.31; 2.97]	0.001
Anastrozole	42 / 502 (8.4)	10 / 467 (2.1)	3.91	[1.98; 7.70]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.926				
Yes	94 / 1194 (7.9)	37 / 1146 (3.2)	2.44	[1.68; 3.54]	<.001
No	14 / 215 (6.5)	6 / 216 (2.8)	2.34	[0.92; 5.99]	0.075
Prior adjuvant chemotherapy					
Interaction test	p = 0.983				
Yes	62 / 694 (8.9)	25 / 673 (3.7)	2.40	[1.53; 3.78]	<.001
No	46 / 715 (6.4)	18 / 689 (2.6)	2.46	[1.44; 4.20]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.732				
Yes	34 / 528 (6.4)	12 / 503 (2.4)	2.70	[1.41; 5.15]	0.003
No	74 / 881 (8.4)	31 / 859 (3.6)	2.33	[1.55; 3.50]	<.001
Prior endocrine therapy					
Interaction test	p = 0.161				
Yes	81 / 957 (8.5)	28 / 940 (3.0)	2.84	[1.87; 4.33]	<.001
No	27 / 452 (6.0)	15 / 422 (3.6)	1.68	[0.91; 3.11]	0.099
Prior mastectomy					
Interaction test	p = 0.884				
Yes	65 / 857 (7.6)	27 / 847 (3.2)	2.38	[1.53; 3.69]	<.001
No	43 / 552 (7.8)	16 / 515 (3.1)	2.51	[1.43; 4.40]	0.001
Prior radiotherapy					
Interaction test	p = 0.192				
Yes	99 / 1253 (7.9)	42 / 1203 (3.5)	2.26	[1.59; 3.22]	<.001
No	9 / 156 (5.8)	1 / 159 (0.6)	9.17	[1.18; 71.55]	0.034
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.64 PT rash: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Rash					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.142				
NA/WE/O	74 / 899 (8.2)	32 / 856 (3.7)	2.20	[1.47; 3.30]	<.001
ROW	28 / 510 (5.5)	6 / 506 (1.2)	4.63	[1.93; 11.09]	<.001
Geographical region					
Interaction test	p = 0.501				
Europe	49 / 832 (5.9)	18 / 824 (2.2)	2.70	[1.58; 4.59]	<.001
North America/Australia	40 / 400 (10.0)	18 / 364 (4.9)	2.02	[1.18; 3.46]	0.010
Asia	10 / 102 (9.8)	1 / 101 (1.0)	9.90	[1.29; 75.93]	0.027
Latin America	3 / 75 (4.0)	1 / 73 (1.4)	2.92	[0.31; 27.43]	0.348
Age group 1 at randomization					
Interaction test	p = 0.446				
<45	3 / 60 (5.0)	3 / 52 (5.8)	0.87	[0.18; 4.11]	0.857
45 to 54	24 / 300 (8.0)	12 / 322 (3.7)	2.15	[1.09; 4.22]	0.027
55 to 64	47 / 651 (7.2)	15 / 642 (2.3)	3.09	[1.75; 5.47]	<.001
≥65	28 / 398 (7.0)	8 / 346 (2.3)	3.04	[1.41; 6.59]	0.005
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.447				
<Median	50 / 633 (7.9)	22 / 632 (3.5)	2.27	[1.39; 3.70]	0.001
≥Median	52 / 776 (6.7)	16 / 730 (2.2)	3.06	[1.76; 5.31]	<.001
Race					
Interaction test	p = 0.349				
Asian	13 / 128 (10.2)	3 / 127 (2.4)	4.30	[1.26; 14.73]	0.020
Non-Asian	85 / 1203 (7.1)	35 / 1167 (3.0)	2.36	[1.60; 3.46]	<.001
BMI at screening					
Interaction test	p = 0.502				
≥25	67 / 935 (7.2)	23 / 935 (2.5)	2.91	[1.83; 4.64]	<.001
<25	35 / 460 (7.6)	14 / 410 (3.4)	2.23	[1.22; 4.08]	0.009
AJCC Anatomic Stage Group					
Interaction test	p = 0.302				
Group I/II	42 / 585 (7.2)	20 / 589 (3.4)	2.11	[1.26; 3.56]	0.005
Group III	60 / 823 (7.3)	18 / 772 (2.3)	3.13	[1.86; 5.25]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.217				
IA/IB/IIA	22 / 310 (7.1)	6 / 311 (1.9)	3.68	[1.51; 8.95]	0.004
IIB	20 / 275 (7.3)	14 / 278 (5.0)	1.44	[0.74; 2.80]	0.277
IIIA	25 / 482 (5.2)	6 / 450 (1.3)	3.89	[1.61; 9.39]	0.003
IIIB	7 / 100 (7.0)	4 / 82 (4.9)	1.44	[0.44; 4.73]	0.553
IIIC	28 / 241 (11.6)	8 / 240 (3.3)	3.49	[1.62; 7.49]	0.001
Tumor category					
Interaction test	p = 0.349				
T0	2 / 5 (40.0)	0 / 5 (0.0)	5.00	[0.30; 83.69]	0.263
T1-T3	91 / 1287 (7.1)	33 / 1258 (2.6)	2.70	[1.82; 3.98]	<.001
>T3	9 / 113 (8.0)	5 / 97 (5.2)	1.55	[0.54; 4.46]	0.421
Nodal status					
Interaction test	p = 0.853				
N0	9 / 190 (4.7)	4 / 200 (2.0)	2.37	[0.74; 7.56]	0.145
N1-N3	93 / 1216 (7.6)	34 / 1160 (2.9)	2.61	[1.78; 3.83]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.796				
Grade 1	3 / 102 (2.9)	2 / 106 (1.9)	1.56	[0.27; 9.14]	0.623
Grade 2	61 / 842 (7.2)	20 / 768 (2.6)	2.78	[1.70; 4.57]	<.001
Grade 3	32 / 373 (8.6)	14 / 397 (3.5)	2.43	[1.32; 4.49]	0.004
Histological subtype					
Interaction test	p = 0.930				
Ductal	69 / 1025 (6.7)	25 / 1010 (2.5)	2.72	[1.74; 4.26]	<.001
Lobular	22 / 291 (7.6)	9 / 276 (3.3)	2.32	[1.09; 4.95]	0.030
Other	11 / 92 (12.0)	4 / 76 (5.3)	2.27	[0.75; 6.85]	0.145
Ki67 status from surgical specimen					
Interaction test	p = 0.980				
Ki67≤20	36 / 660 (5.5)	13 / 629 (2.1)	2.64	[1.41; 4.93]	0.002
Ki67>20	35 / 489 (7.2)	14 / 516 (2.7)	2.64	[1.44; 4.84]	0.002
Type of NSAI					
Interaction test	p = 0.369				
Letrozole	61 / 907 (6.7)	20 / 895 (2.2)	3.01	[1.83; 4.94]	<.001
Anastrozole	41 / 502 (8.2)	18 / 467 (3.9)	2.12	[1.24; 3.63]	0.006
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.258				
Yes	81 / 1194 (6.8)	33 / 1146 (2.9)	2.36	[1.58; 3.50]	<.001
No	21 / 215 (9.8)	5 / 216 (2.3)	4.22	[1.62; 10.99]	0.003
Prior adjuvant chemotherapy					
Interaction test	p = 0.978				
Yes	48 / 694 (6.9)	18 / 673 (2.7)	2.59	[1.52; 4.40]	<.001
No	54 / 715 (7.6)	20 / 689 (2.9)	2.60	[1.57; 4.30]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.595				
Yes	36 / 528 (6.8)	15 / 503 (3.0)	2.29	[1.27; 4.12]	0.006
No	66 / 881 (7.5)	23 / 859 (2.7)	2.80	[1.76; 4.46]	<.001
Prior endocrine therapy					
Interaction test	p = 0.033				
Yes	72 / 957 (7.5)	34 / 940 (3.6)	2.08	[1.40; 3.10]	<.001
No	30 / 452 (6.6)	4 / 422 (0.9)	7.00	[2.49; 19.71]	<.001
Prior mastectomy					
Interaction test	p = 0.039				
Yes	60 / 857 (7.0)	30 / 847 (3.5)	1.98	[1.29; 3.03]	0.002
No	42 / 552 (7.6)	8 / 515 (1.6)	4.90	[2.32; 10.33]	<.001
Prior radiotherapy					
Interaction test	p = 0.695				
Yes	95 / 1253 (7.6)	36 / 1203 (3.0)	2.53	[1.74; 3.69]	<.001
No	7 / 156 (4.5)	2 / 159 (1.3)	3.57	[0.75; 16.91]	0.109
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.65 PT dry skin: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Dry skin					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.876				
NA/WE/O	43 / 899 (4.8)	17 / 856 (2.0)	2.41	[1.38; 4.19]	0.002
ROW	3 / 510 (0.6)	1 / 506 (0.2)	2.98	[0.31; 28.52]	0.344
Geographical region					
Interaction test	p = 0.356				
Europe	32 / 832 (3.8)	11 / 824 (1.3)	2.88	[1.46; 5.68]	0.002
North America/Australia	13 / 400 (3.3)	7 / 364 (1.9)	1.69	[0.68; 4.19]	0.257
Asia	0 / 102 (0.0)	0 / 101 (0.0)	N.E.	N.E.	N.E.
Latin America	1 / 75 (1.3)	0 / 73 (0.0)	2.92	[0.12; 70.56]	0.509
Age group 1 at randomization					
Interaction test	p = 0.208				
<45	5 / 60 (8.3)	0 / 52 (0.0)	9.56	[0.54; >99.99]	0.123
45 to 54	10 / 300 (3.3)	6 / 322 (1.9)	1.79	[0.66; 4.86]	0.254
55 to 64	21 / 651 (3.2)	5 / 642 (0.8)	4.14	[1.57; 10.92]	0.004
≥65	10 / 398 (2.5)	7 / 346 (2.0)	1.24	[0.48; 3.23]	0.657
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.284				
<Median	24 / 633 (3.8)	7 / 632 (1.1)	3.42	[1.49; 7.89]	0.004
≥Median	22 / 776 (2.8)	11 / 730 (1.5)	1.88	[0.92; 3.85]	0.084
Race					
Interaction test	N.E.				
Asian	1 / 128 (0.8)	0 / 127 (0.0)	2.98	[0.12; 72.39]	0.503
Non-Asian	40 / 1203 (3.3)	16 / 1167 (1.4)	2.43	[1.37; 4.31]	0.002
BMI at screening					
Interaction test	p = 0.846				
≥25	30 / 935 (3.2)	12 / 935 (1.3)	2.50	[1.29; 4.85]	0.007
<25	15 / 460 (3.3)	6 / 410 (1.5)	2.23	[0.87; 5.69]	0.094
AJCC Anatomic Stage Group					
Interaction test	p = 0.614				
Group I/II	19 / 585 (3.2)	9 / 589 (1.5)	2.13	[0.97; 4.66]	0.060
Group III	27 / 823 (3.3)	9 / 772 (1.2)	2.81	[1.33; 5.95]	0.007

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.948				
IA/IB/IIA	11 / 310 (3.5)	6 / 311 (1.9)	1.84	[0.69; 4.91]	0.224
IIB	8 / 275 (2.9)	3 / 278 (1.1)	2.70	[0.72; 10.05]	0.140
IIIA	17 / 482 (3.5)	5 / 450 (1.1)	3.17	[1.18; 8.53]	0.022
IIIB	2 / 100 (2.0)	1 / 82 (1.2)	1.64	[0.15; 17.77]	0.684
IIIC	8 / 241 (3.3)	3 / 240 (1.3)	2.66	[0.71; 9.89]	0.145
Tumor category					
Interaction test	p = 0.976				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	43 / 1287 (3.3)	17 / 1258 (1.4)	2.47	[1.42; 4.31]	0.001
>T3	3 / 113 (2.7)	1 / 97 (1.0)	2.58	[0.27; 24.36]	0.409
Nodal status					
Interaction test	p = 0.466				
N0	5 / 190 (2.6)	1 / 200 (0.5)	5.26	[0.62; 44.64]	0.128
N1-N3	41 / 1216 (3.4)	17 / 1160 (1.5)	2.30	[1.31; 4.03]	0.004
Histological grade at time of surgery					
Interaction test	p = 0.654				
Grade 1	6 / 102 (5.9)	2 / 106 (1.9)	3.12	[0.64; 15.09]	0.158
Grade 2	26 / 842 (3.1)	12 / 768 (1.6)	1.98	[1.00; 3.89]	0.049
Grade 3	13 / 373 (3.5)	4 / 397 (1.0)	3.46	[1.14; 10.51]	0.029
Histological subtype					
Interaction test	p = 0.516				
Ductal	32 / 1025 (3.1)	10 / 1010 (1.0)	3.15	[1.56; 6.38]	0.001
Lobular	12 / 291 (4.1)	7 / 276 (2.5)	1.63	[0.65; 4.07]	0.299
Other	2 / 92 (2.2)	1 / 76 (1.3)	1.65	[0.15; 17.87]	0.679
Ki67 status from surgical specimen					
Interaction test	p = 0.324				
Ki67≤20	21 / 660 (3.2)	9 / 629 (1.4)	2.22	[1.03; 4.82]	0.043
Ki67>20	10 / 489 (2.0)	2 / 516 (0.4)	5.28	[1.16; 23.96]	0.031
Type of NSAI					
Interaction test	p = 0.372				
Letrozole	28 / 907 (3.1)	9 / 895 (1.0)	3.07	[1.46; 6.47]	0.003
Anastrozole	18 / 502 (3.6)	9 / 467 (1.9)	1.86	[0.84; 4.10]	0.124
Prior neo/adjuvant chemotherapy					
Interaction test	p = <.001				
Yes	43 / 1194 (3.6)	9 / 1146 (0.8)	4.59	[2.25; 9.36]	<.001
No	3 / 215 (1.4)	9 / 216 (4.2)	0.33	[0.09; 1.22]	0.097
Prior adjuvant chemotherapy					
Interaction test	p = 0.003				
Yes	28 / 694 (4.0)	3 / 673 (0.4)	9.05	[2.76; 29.63]	<.001
No	18 / 715 (2.5)	15 / 689 (2.2)	1.16	[0.59; 2.28]	0.674

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.947				
Yes	16 / 528 (3.0)	6 / 503 (1.2)	2.54	[1.00; 6.44]	0.049
No	30 / 881 (3.4)	12 / 859 (1.4)	2.44	[1.26; 4.73]	0.008
Prior endocrine therapy					
Interaction test	p = 0.589				
Yes	38 / 957 (4.0)	14 / 940 (1.5)	2.67	[1.45; 4.89]	0.002
No	8 / 452 (1.8)	4 / 422 (0.9)	1.87	[0.57; 6.16]	0.305
Prior mastectomy					
Interaction test	p = 0.112				
Yes	25 / 857 (2.9)	6 / 847 (0.7)	4.12	[1.70; 9.99]	0.002
No	21 / 552 (3.8)	12 / 515 (2.3)	1.63	[0.81; 3.28]	0.169
Prior radiotherapy					
Interaction test	N.E.				
Yes	45 / 1253 (3.6)	18 / 1203 (1.5)	2.40	[1.40; 4.12]	0.002
No	1 / 156 (0.6)	0 / 159 (0.0)	3.06	[0.13; 74.48]	0.493
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.66 SOC metabolism and nutrition disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Metabolism and nutrition disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.069				
NA/WE/O	271 / 899 (30.1)	148 / 856 (17.3)	1.74	[1.46; 2.08]	<.001
ROW	189 / 510 (37.1)	85 / 506 (16.8)	2.21	[1.76; 2.76]	<.001
Geographical region					
Interaction test	p = 0.003				
Europe	258 / 832 (31.0)	132 / 824 (16.0)	1.94	[1.61; 2.33]	<.001
North America/Australia	129 / 400 (32.3)	70 / 364 (19.2)	1.68	[1.30; 2.16]	<.001
Asia	49 / 102 (48.0)	11 / 101 (10.9)	4.41	[2.44; 7.98]	<.001
Latin America	24 / 75 (32.0)	20 / 73 (27.4)	1.17	[0.71; 1.92]	0.541
Age group 1 at randomization					
Interaction test	p = 0.647				
<45	16 / 60 (26.7)	9 / 52 (17.3)	1.54	[0.74; 3.19]	0.244
45 to 54	81 / 300 (27.0)	48 / 322 (14.9)	1.81	[1.31; 2.50]	<.001
55 to 64	221 / 651 (33.9)	105 / 642 (16.4)	2.08	[1.69; 2.55]	<.001
≥65	142 / 398 (35.7)	71 / 346 (20.5)	1.74	[1.36; 2.22]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.826				
<Median	189 / 633 (29.9)	99 / 632 (15.7)	1.91	[1.53; 2.37]	<.001
≥Median	271 / 776 (34.9)	134 / 730 (18.4)	1.90	[1.59; 2.28]	<.001
Race					
Interaction test	p = 0.002				
Asian	56 / 128 (43.8)	14 / 127 (11.0)	3.97	[2.33; 6.75]	<.001
Non-Asian	372 / 1203 (30.9)	206 / 1167 (17.7)	1.75	[1.51; 2.04]	<.001
BMI at screening					
Interaction test	p = 0.388				
≥25	321 / 935 (34.3)	177 / 935 (18.9)	1.81	[1.55; 2.13]	<.001
<25	133 / 460 (28.9)	54 / 410 (13.2)	2.20	[1.65; 2.92]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.179				
Group I/II	191 / 585 (32.6)	89 / 589 (15.1)	2.16	[1.73; 2.70]	<.001
Group III	269 / 823 (32.7)	144 / 772 (18.7)	1.75	[1.47; 2.09]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.656				
IA/IB/IIA	101 / 310 (32.6)	49 / 311 (15.8)	2.07	[1.53; 2.80]	<.001
IIB	90 / 275 (32.7)	40 / 278 (14.4)	2.27	[1.63; 3.17]	<.001
IIIA	148 / 482 (30.7)	80 / 450 (17.8)	1.73	[1.36; 2.20]	<.001
IIIB	29 / 100 (29.0)	15 / 82 (18.3)	1.59	[0.91; 2.75]	0.101
IIIC	92 / 241 (38.2)	49 / 240 (20.4)	1.87	[1.39; 2.52]	<.001
Tumor category					
Interaction test	p = 0.241				
T0	1 / 5 (20.0)	0 / 5 (0.0)	3.00	[0.15; 59.89]	0.472
T1-T3	426 / 1287 (33.1)	213 / 1258 (16.9)	1.95	[1.69; 2.26]	<.001
>T3	32 / 113 (28.3)	19 / 97 (19.6)	1.45	[0.88; 2.38]	0.147
Nodal status					
Interaction test	p = 0.978				
N0	59 / 190 (31.1)	32 / 200 (16.0)	1.94	[1.32; 2.84]	<.001
N1-N3	401 / 1216 (33.0)	201 / 1160 (17.3)	1.90	[1.64; 2.21]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.514				
Grade 1	36 / 102 (35.3)	15 / 106 (14.2)	2.49	[1.46; 4.27]	<.001
Grade 2	276 / 842 (32.8)	139 / 768 (18.1)	1.81	[1.51; 2.17]	<.001
Grade 3	123 / 373 (33.0)	66 / 397 (16.6)	1.98	[1.52; 2.58]	<.001
Histological subtype					
Interaction test	p = 0.472				
Ductal	341 / 1025 (33.3)	168 / 1010 (16.6)	2.00	[1.70; 2.35]	<.001
Lobular	94 / 291 (32.3)	51 / 276 (18.5)	1.75	[1.30; 2.36]	<.001
Other	25 / 92 (27.2)	14 / 76 (18.4)	1.48	[0.83; 2.63]	0.189
Ki67 status from surgical specimen					
Interaction test	p = 0.561				
Ki67≤20	218 / 660 (33.0)	110 / 629 (17.5)	1.89	[1.54; 2.31]	<.001
Ki67>20	165 / 489 (33.7)	84 / 516 (16.3)	2.07	[1.64; 2.61]	<.001
Type of NSAI					
Interaction test	p = 0.429				
Letrozole	297 / 907 (32.7)	147 / 895 (16.4)	1.99	[1.67; 2.37]	<.001
Anastrozole	163 / 502 (32.5)	86 / 467 (18.4)	1.76	[1.40; 2.22]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.910				
Yes	394 / 1194 (33.0)	198 / 1146 (17.3)	1.91	[1.64; 2.22]	<.001
No	66 / 215 (30.7)	35 / 216 (16.2)	1.89	[1.32; 2.73]	<.001
Prior adjuvant chemotherapy					
Interaction test	p = 0.999				
Yes	244 / 694 (35.2)	126 / 673 (18.7)	1.88	[1.56; 2.26]	<.001
No	216 / 715 (30.2)	107 / 689 (15.5)	1.95	[1.58; 2.39]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.984				
Yes	159 / 528 (30.1)	78 / 503 (15.5)	1.94	[1.52; 2.47]	<.001
No	301 / 881 (34.2)	155 / 859 (18.0)	1.89	[1.60; 2.24]	<.001
Prior endocrine therapy					
Interaction test	p = 0.786				
Yes	318 / 957 (33.2)	162 / 940 (17.2)	1.93	[1.63; 2.28]	<.001
No	142 / 452 (31.4)	71 / 422 (16.8)	1.87	[1.45; 2.40]	<.001
Prior mastectomy					
Interaction test	p = 0.910				
Yes	280 / 857 (32.7)	146 / 847 (17.2)	1.90	[1.59; 2.26]	<.001
No	180 / 552 (32.6)	87 / 515 (16.9)	1.93	[1.54; 2.42]	<.001
Prior radiotherapy					
Interaction test	p = 0.174				
Yes	418 / 1253 (33.4)	204 / 1203 (17.0)	1.97	[1.70; 2.28]	<.001
No	42 / 156 (26.9)	29 / 159 (18.2)	1.48	[0.97; 2.24]	0.068
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.67 PT hypomagnesaemia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Hypomagnesaemia					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.860				
NA/WE/O	51 / 899 (5.7)	13 / 856 (1.5)	3.74	[2.05; 6.82]	<.001
ROW	57 / 510 (11.2)	17 / 506 (3.4)	3.33	[1.96; 5.64]	<.001
Geographical region					
Interaction test	p = 0.375				
Europe	65 / 832 (7.8)	22 / 824 (2.7)	2.93	[1.82; 4.70]	<.001
North America/Australia	25 / 400 (6.3)	6 / 364 (1.6)	3.79	[1.57; 9.14]	0.003
Asia	16 / 102 (15.7)	1 / 101 (1.0)	15.84	[2.14; >99.99]	0.007
Latin America	2 / 75 (2.7)	1 / 73 (1.4)	1.95	[0.18; 21.01]	0.583
Age group 1 at randomization					
Interaction test	p = 0.235				
<45	3 / 60 (5.0)	3 / 52 (5.8)	0.87	[0.18; 4.11]	0.857
45 to 54	18 / 300 (6.0)	3 / 322 (0.9)	6.44	[1.92; 21.64]	0.003
55 to 64	50 / 651 (7.7)	16 / 642 (2.5)	3.08	[1.77; 5.35]	<.001
≥65	37 / 398 (9.3)	8 / 346 (2.3)	4.02	[1.90; 8.52]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.814				
<Median	43 / 633 (6.8)	13 / 632 (2.1)	3.30	[1.79; 6.08]	<.001
≥Median	65 / 776 (8.4)	17 / 730 (2.3)	3.60	[2.13; 6.08]	<.001
Race					
Interaction test	p = 0.203				
Asian	16 / 128 (12.5)	2 / 127 (1.6)	7.94	[1.86; 33.82]	0.005
Non-Asian	86 / 1203 (7.1)	27 / 1167 (2.3)	3.09	[2.02; 4.73]	<.001
BMI at screening					
Interaction test	p = 0.312				
≥25	73 / 935 (7.8)	24 / 935 (2.6)	3.04	[1.94; 4.78]	<.001
<25	34 / 460 (7.4)	6 / 410 (1.5)	5.05	[2.14; 11.91]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.120				
Group I/II	44 / 585 (7.5)	8 / 589 (1.4)	5.54	[2.63; 11.66]	<.001
Group III	64 / 823 (7.8)	22 / 772 (2.8)	2.73	[1.70; 4.39]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.396				
IA/IB/IIA	23 / 310 (7.4)	3 / 311 (1.0)	7.69	[2.33; 25.35]	<.001
IIB	21 / 275 (7.6)	5 / 278 (1.8)	4.25	[1.62; 11.10]	0.003
IIIA	36 / 482 (7.5)	11 / 450 (2.4)	3.06	[1.57; 5.93]	<.001
IIIB	7 / 100 (7.0)	4 / 82 (4.9)	1.44	[0.44; 4.73]	0.553
IIIC	21 / 241 (8.7)	7 / 240 (2.9)	2.99	[1.29; 6.90]	0.010
Tumor category					
Interaction test	p = 0.160				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	100 / 1287 (7.8)	26 / 1258 (2.1)	3.76	[2.46; 5.75]	<.001
>T3	7 / 113 (6.2)	4 / 97 (4.1)	1.50	[0.45; 4.98]	0.506
Nodal status					
Interaction test	p = 0.720				
N0	11 / 190 (5.8)	4 / 200 (2.0)	2.89	[0.94; 8.93]	0.065
N1-N3	97 / 1216 (8.0)	26 / 1160 (2.2)	3.56	[2.33; 5.45]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.560				
Grade 1	9 / 102 (8.8)	5 / 106 (4.7)	1.87	[0.65; 5.39]	0.246
Grade 2	62 / 842 (7.4)	16 / 768 (2.1)	3.53	[2.06; 6.07]	<.001
Grade 3	28 / 373 (7.5)	8 / 397 (2.0)	3.73	[1.72; 8.07]	<.001
Histological subtype					
Interaction test	p = 0.770				
Ductal	79 / 1025 (7.7)	21 / 1010 (2.1)	3.71	[2.31; 5.95]	<.001
Lobular	21 / 291 (7.2)	6 / 276 (2.2)	3.32	[1.36; 8.10]	0.008
Other	8 / 92 (8.7)	3 / 76 (3.9)	2.20	[0.61; 8.02]	0.231
Ki67 status from surgical specimen					
Interaction test	p = 0.185				
Ki67≤20	53 / 660 (8.0)	17 / 629 (2.7)	2.97	[1.74; 5.07]	<.001
Ki67>20	42 / 489 (8.6)	8 / 516 (1.6)	5.54	[2.63; 11.68]	<.001
Type of NSAI					
Interaction test	p = 0.364				
Letrozole	72 / 907 (7.9)	23 / 895 (2.6)	3.09	[1.95; 4.89]	<.001
Anastrozole	36 / 502 (7.2)	7 / 467 (1.5)	4.78	[2.15; 10.65]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.458				
Yes	96 / 1194 (8.0)	28 / 1146 (2.4)	3.29	[2.18; 4.97]	<.001
No	12 / 215 (5.6)	2 / 216 (0.9)	6.03	[1.37; 26.61]	0.018
Prior adjuvant chemotherapy					
Interaction test	p = 0.159				
Yes	56 / 694 (8.1)	20 / 673 (3.0)	2.72	[1.65; 4.47]	<.001
No	52 / 715 (7.3)	10 / 689 (1.5)	5.01	[2.57; 9.78]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.201				
Yes	43 / 528 (8.1)	8 / 503 (1.6)	5.12	[2.43; 10.78]	<.001
No	65 / 881 (7.4)	22 / 859 (2.6)	2.88	[1.79; 4.63]	<.001
Prior endocrine therapy					
Interaction test	p = 0.626				
Yes	79 / 957 (8.3)	21 / 940 (2.2)	3.70	[2.30; 5.93]	<.001
No	29 / 452 (6.4)	9 / 422 (2.1)	3.01	[1.44; 6.28]	0.003
Prior mastectomy					
Interaction test	p = 0.744				
Yes	67 / 857 (7.8)	20 / 847 (2.4)	3.31	[2.03; 5.41]	<.001
No	41 / 552 (7.4)	10 / 515 (1.9)	3.83	[1.94; 7.56]	<.001
Prior radiotherapy					
Interaction test	p = 0.449				
Yes	99 / 1253 (7.9)	26 / 1203 (2.2)	3.66	[2.39; 5.59]	<.001
No	9 / 156 (5.8)	4 / 159 (2.5)	2.29	[0.72; 7.29]	0.160
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.68 PT hyperkalaemia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Hyperkalaemia					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.226				
NA/WE/O	43 / 899 (4.8)	12 / 856 (1.4)	3.41	[1.81; 6.43]	<.001
ROW	39 / 510 (7.6)	6 / 506 (1.2)	6.45	[2.75; 15.10]	<.001
Geographical region					
Interaction test	p = 0.635				
Europe	53 / 832 (6.4)	9 / 824 (1.1)	5.83	[2.90; 11.74]	<.001
North America/Australia	15 / 400 (3.8)	5 / 364 (1.4)	2.73	[1.00; 7.44]	0.050
Asia	7 / 102 (6.9)	2 / 101 (2.0)	3.47	[0.74; 16.28]	0.115
Latin America	7 / 75 (9.3)	2 / 73 (2.7)	3.41	[0.73; 15.86]	0.118
Age group 1 at randomization					
Interaction test	p = 0.368				
<45	0 / 60 (0.0)	2 / 52 (3.8)	0.17	[<0.01; 3.54]	0.255
45 to 54	13 / 300 (4.3)	5 / 322 (1.6)	2.79	[1.01; 7.73]	0.048
55 to 64	38 / 651 (5.8)	5 / 642 (0.8)	7.49	[2.97; 18.92]	<.001
≥65	31 / 398 (7.8)	6 / 346 (1.7)	4.49	[1.90; 10.64]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.199				
<Median	27 / 633 (4.3)	9 / 632 (1.4)	3.00	[1.42; 6.32]	0.004
≥Median	55 / 776 (7.1)	9 / 730 (1.2)	5.75	[2.86; 11.55]	<.001
Race					
Interaction test	p = 0.865				
Asian	8 / 128 (6.3)	2 / 127 (1.6)	3.97	[0.86; 18.33]	0.077
Non-Asian	71 / 1203 (5.9)	15 / 1167 (1.3)	4.59	[2.65; 7.97]	<.001
BMI at screening					
Interaction test	p = 0.829				
≥25	46 / 935 (4.9)	10 / 935 (1.1)	4.60	[2.34; 9.06]	<.001
<25	36 / 460 (7.8)	8 / 410 (2.0)	4.01	[1.89; 8.53]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.014				
Group I/II	48 / 585 (8.2)	5 / 589 (0.8)	9.67	[3.88; 24.11]	<.001
Group III	34 / 823 (4.1)	13 / 772 (1.7)	2.45	[1.30; 4.61]	0.005

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.411				
IA/IB/IIA	25 / 310 (8.1)	5 / 311 (1.6)	5.02	[1.95; 12.93]	<.001
IIB	23 / 275 (8.4)	0 / 278 (0.0)	47.51	[2.90; >99.99]	0.007
IIIA	19 / 482 (3.9)	5 / 450 (1.1)	3.55	[1.34; 9.42]	0.011
IIIB	5 / 100 (5.0)	2 / 82 (2.4)	2.05	[0.41; 10.29]	0.383
IIIC	10 / 241 (4.1)	6 / 240 (2.5)	1.66	[0.61; 4.49]	0.319
Tumor category					
Interaction test	p = 0.162				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	76 / 1287 (5.9)	15 / 1258 (1.2)	4.95	[2.86; 8.57]	<.001
>T3	6 / 113 (5.3)	3 / 97 (3.1)	1.72	[0.44; 6.68]	0.436
Nodal status					
Interaction test	p = 0.080				
N0	20 / 190 (10.5)	1 / 200 (0.5)	21.05	[2.85; >99.99]	0.003
N1-N3	62 / 1216 (5.1)	17 / 1160 (1.5)	3.48	[2.05; 5.91]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.337				
Grade 1	12 / 102 (11.8)	2 / 106 (1.9)	6.24	[1.43; 27.17]	0.015
Grade 2	45 / 842 (5.3)	13 / 768 (1.7)	3.16	[1.72; 5.81]	<.001
Grade 3	17 / 373 (4.6)	2 / 397 (0.5)	9.05	[2.10; 38.89]	0.003
Histological subtype					
Interaction test	p = 0.293				
Ductal	60 / 1025 (5.9)	16 / 1010 (1.6)	3.70	[2.14; 6.37]	<.001
Lobular	19 / 291 (6.5)	1 / 276 (0.4)	18.02	[2.43; >99.99]	0.005
Other	3 / 92 (3.3)	1 / 76 (1.3)	2.48	[0.26; 23.34]	0.428
Ki67 status from surgical specimen					
Interaction test	p = 0.534				
Ki67≤20	41 / 660 (6.2)	9 / 629 (1.4)	4.34	[2.13; 8.86]	<.001
Ki67>20	30 / 489 (6.1)	5 / 516 (1.0)	6.33	[2.48; 16.19]	<.001
Type of NSAI					
Interaction test	p = 0.755				
Letrozole	55 / 907 (6.1)	13 / 895 (1.5)	4.17	[2.30; 7.59]	<.001
Anastrozole	27 / 502 (5.4)	5 / 467 (1.1)	5.02	[1.95; 12.94]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.547				
Yes	64 / 1194 (5.4)	15 / 1146 (1.3)	4.10	[2.35; 7.14]	<.001
No	18 / 215 (8.4)	3 / 216 (1.4)	6.03	[1.80; 20.17]	0.004
Prior adjuvant chemotherapy					
Interaction test	p = 0.260				
Yes	38 / 694 (5.5)	11 / 673 (1.6)	3.35	[1.73; 6.50]	<.001
No	44 / 715 (6.2)	7 / 689 (1.0)	6.06	[2.75; 13.36]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.927				
Yes	27 / 528 (5.1)	6 / 503 (1.2)	4.29	[1.79; 10.30]	0.001
No	55 / 881 (6.2)	12 / 859 (1.4)	4.47	[2.41; 8.29]	<.001
Prior endocrine therapy					
Interaction test	p = 0.278				
Yes	57 / 957 (6.0)	15 / 940 (1.6)	3.73	[2.13; 6.54]	<.001
No	25 / 452 (5.5)	3 / 422 (0.7)	7.78	[2.37; 25.58]	<.001
Prior mastectomy					
Interaction test	p = 0.998				
Yes	49 / 857 (5.7)	11 / 847 (1.3)	4.40	[2.31; 8.41]	<.001
No	33 / 552 (6.0)	7 / 515 (1.4)	4.40	[1.96; 9.85]	<.001
Prior radiotherapy					
Interaction test	p = 0.392				
Yes	72 / 1253 (5.7)	17 / 1203 (1.4)	4.07	[2.41; 6.86]	<.001
No	10 / 156 (6.4)	1 / 159 (0.6)	10.19	[1.32; 78.68]	0.026
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.69 PT decreased appetite: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Decreased appetite					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.951				
NA/WE/O	57 / 899 (6.3)	27 / 856 (3.2)	2.01	[1.28; 3.15]	0.002
ROW	14 / 510 (2.7)	7 / 506 (1.4)	1.98	[0.81; 4.88]	0.135
Geographical region					
Interaction test	p = 0.678				
Europe	42 / 832 (5.0)	18 / 824 (2.2)	2.31	[1.34; 3.98]	0.003
North America/Australia	26 / 400 (6.5)	15 / 364 (4.1)	1.58	[0.85; 2.93]	0.149
Asia	2 / 102 (2.0)	1 / 101 (1.0)	1.98	[0.18; 21.50]	0.574
Latin America	1 / 75 (1.3)	0 / 73 (0.0)	2.92	[0.12; 70.56]	0.509
Age group 1 at randomization					
Interaction test	p = 0.789				
<45	1 / 60 (1.7)	0 / 52 (0.0)	2.61	[0.11; 62.64]	0.555
45 to 54	12 / 300 (4.0)	5 / 322 (1.6)	2.58	[0.92; 7.23]	0.072
55 to 64	35 / 651 (5.4)	17 / 642 (2.6)	2.03	[1.15; 3.59]	0.015
≥65	23 / 398 (5.8)	12 / 346 (3.5)	1.67	[0.84; 3.30]	0.143
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.802				
<Median	26 / 633 (4.1)	12 / 632 (1.9)	2.16	[1.10; 4.25]	0.025
≥Median	45 / 776 (5.8)	22 / 730 (3.0)	1.92	[1.17; 3.17]	0.010
Race					
Interaction test	p = 0.512				
Asian	2 / 128 (1.6)	2 / 127 (1.6)	0.99	[0.14; 6.94]	0.994
Non-Asian	59 / 1203 (4.9)	30 / 1167 (2.6)	1.91	[1.24; 2.94]	0.003
BMI at screening					
Interaction test	p = 0.759				
≥25	47 / 935 (5.0)	22 / 935 (2.4)	2.14	[1.30; 3.52]	0.003
<25	23 / 460 (5.0)	11 / 410 (2.7)	1.86	[0.92; 3.78]	0.084
AJCC Anatomic Stage Group					
Interaction test	p = 0.089				
Group I/II	32 / 585 (5.5)	10 / 589 (1.7)	3.22	[1.60; 6.49]	0.001
Group III	39 / 823 (4.7)	24 / 772 (3.1)	1.52	[0.93; 2.51]	0.098

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.213				
IA/IB/IIA	16 / 310 (5.2)	5 / 311 (1.6)	3.21	[1.19; 8.66]	0.021
IIB	16 / 275 (5.8)	5 / 278 (1.8)	3.23	[1.20; 8.71]	0.020
IIIA	18 / 482 (3.7)	16 / 450 (3.6)	1.05	[0.54; 2.03]	0.884
IIIB	4 / 100 (4.0)	1 / 82 (1.2)	3.28	[0.37; 28.78]	0.284
IIIC	17 / 241 (7.1)	7 / 240 (2.9)	2.42	[1.02; 5.73]	0.045
Tumor category					
Interaction test	p = 0.755				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	65 / 1287 (5.1)	32 / 1258 (2.5)	1.99	[1.31; 3.01]	0.001
>T3	6 / 113 (5.3)	2 / 97 (2.1)	2.58	[0.53; 12.47]	0.240
Nodal status					
Interaction test	p = 0.775				
N0	9 / 190 (4.7)	4 / 200 (2.0)	2.37	[0.74; 7.56]	0.145
N1-N3	62 / 1216 (5.1)	30 / 1160 (2.6)	1.97	[1.28; 3.03]	0.002
Histological grade at time of surgery					
Interaction test	p = 0.622				
Grade 1	5 / 102 (4.9)	1 / 106 (0.9)	5.20	[0.62; 43.71]	0.129
Grade 2	44 / 842 (5.2)	18 / 768 (2.3)	2.23	[1.30; 3.82]	0.004
Grade 3	20 / 373 (5.4)	12 / 397 (3.0)	1.77	[0.88; 3.58]	0.109
Histological subtype					
Interaction test	p = 0.107				
Ductal	53 / 1025 (5.2)	19 / 1010 (1.9)	2.75	[1.64; 4.61]	<.001
Lobular	13 / 291 (4.5)	11 / 276 (4.0)	1.12	[0.51; 2.46]	0.776
Other	5 / 92 (5.4)	4 / 76 (5.3)	1.03	[0.29; 3.71]	0.961
Ki67 status from surgical specimen					
Interaction test	p = 0.269				
Ki67≤20	36 / 660 (5.5)	12 / 629 (1.9)	2.86	[1.50; 5.44]	0.001
Ki67>20	19 / 489 (3.9)	12 / 516 (2.3)	1.67	[0.82; 3.41]	0.158
Type of NSAI					
Interaction test	p = 0.414				
Letrozole	33 / 907 (3.6)	19 / 895 (2.1)	1.71	[0.98; 2.99]	0.058
Anastrozole	38 / 502 (7.6)	15 / 467 (3.2)	2.36	[1.31; 4.23]	0.004
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.207				
Yes	61 / 1194 (5.1)	32 / 1146 (2.8)	1.83	[1.20; 2.78]	0.005
No	10 / 215 (4.7)	2 / 216 (0.9)	5.02	[1.11; 22.66]	0.036
Prior adjuvant chemotherapy					
Interaction test	p = 0.934				
Yes	45 / 694 (6.5)	22 / 673 (3.3)	1.98	[1.20; 3.27]	0.007
No	26 / 715 (3.6)	12 / 689 (1.7)	2.09	[1.06; 4.10]	0.033

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.394				
Yes	16 / 528 (3.0)	10 / 503 (2.0)	1.52	[0.70; 3.33]	0.290
No	55 / 881 (6.2)	24 / 859 (2.8)	2.23	[1.40; 3.58]	<.001
Prior endocrine therapy					
Interaction test	p = 0.792				
Yes	47 / 957 (4.9)	22 / 940 (2.3)	2.10	[1.27; 3.45]	0.004
No	24 / 452 (5.3)	12 / 422 (2.8)	1.87	[0.95; 3.69]	0.072
Prior mastectomy					
Interaction test	p = 0.162				
Yes	37 / 857 (4.3)	23 / 847 (2.7)	1.59	[0.95; 2.65]	0.076
No	34 / 552 (6.2)	11 / 515 (2.1)	2.88	[1.48; 5.63]	0.002
Prior radiotherapy					
Interaction test	p = 0.303				
Yes	67 / 1253 (5.3)	30 / 1203 (2.5)	2.14	[1.40; 3.27]	<.001
No	4 / 156 (2.6)	4 / 159 (2.5)	1.02	[0.26; 4.00]	0.978
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.70 PT hypocalcaemia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Hypocalcaemia					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.687				
NA/WE/O	29 / 899 (3.2)	3 / 856 (0.4)	9.20	[2.81; 30.10]	<.001
ROW	33 / 510 (6.5)	5 / 506 (1.0)	6.55	[2.58; 16.64]	<.001
Geographical region					
Interaction test	p = 0.885				
Europe	30 / 832 (3.6)	5 / 824 (0.6)	5.94	[2.32; 15.24]	<.001
North America/Australia	10 / 400 (2.5)	1 / 364 (0.3)	9.10	[1.17; 70.74]	0.035
Asia	13 / 102 (12.7)	0 / 101 (0.0)	26.74	[1.61; >99.99]	0.022
Latin America	9 / 75 (12.0)	2 / 73 (2.7)	4.38	[0.98; 19.59]	0.053
Age group 1 at randomization					
Interaction test	p = 0.208				
<45	3 / 60 (5.0)	0 / 52 (0.0)	6.08	[0.32; >99.99]	0.229
45 to 54	11 / 300 (3.7)	3 / 322 (0.9)	3.94	[1.11; 13.97]	0.034
55 to 64	35 / 651 (5.4)	2 / 642 (0.3)	17.26	[4.17; 71.45]	<.001
≥65	13 / 398 (3.3)	3 / 346 (0.9)	3.77	[1.08; 13.11]	0.037
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.627				
<Median	28 / 633 (4.4)	3 / 632 (0.5)	9.32	[2.85; 30.50]	<.001
≥Median	34 / 776 (4.4)	5 / 730 (0.7)	6.40	[2.52; 16.27]	<.001
Race					
Interaction test	N.E.				
Asian	14 / 128 (10.9)	0 / 127 (0.0)	28.78	[1.73; >99.99]	0.019
Non-Asian	44 / 1203 (3.7)	7 / 1167 (0.6)	6.10	[2.76; 13.48]	<.001
BMI at screening					
Interaction test	p = 0.727				
≥25	41 / 935 (4.4)	5 / 935 (0.5)	8.20	[3.25; 20.66]	<.001
<25	21 / 460 (4.6)	3 / 410 (0.7)	6.24	[1.87; 20.76]	0.003
AJCC Anatomic Stage Group					
Interaction test	p = 0.876				
Group I/II	28 / 585 (4.8)	4 / 589 (0.7)	7.05	[2.49; 19.97]	<.001
Group III	34 / 823 (4.1)	4 / 772 (0.5)	7.97	[2.84; 22.36]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.917				
IA/IB/IIA	18 / 310 (5.8)	3 / 311 (1.0)	6.02	[1.79; 20.23]	0.004
IIB	10 / 275 (3.6)	1 / 278 (0.4)	10.11	[1.30; 78.44]	0.027
IIIA	18 / 482 (3.7)	2 / 450 (0.4)	8.40	[1.96; 36.01]	0.004
IIIB	4 / 100 (4.0)	1 / 82 (1.2)	3.28	[0.37; 28.78]	0.284
IIIC	12 / 241 (5.0)	1 / 240 (0.4)	11.95	[1.57; 91.19]	0.017
Tumor category					
Interaction test	p = 0.597				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	57 / 1287 (4.4)	7 / 1258 (0.6)	7.96	[3.64; 17.38]	<.001
>T3	5 / 113 (4.4)	1 / 97 (1.0)	4.29	[0.51; 36.11]	0.180
Nodal status					
Interaction test	p = 0.257				
N0	11 / 190 (5.8)	3 / 200 (1.5)	3.86	[1.09; 13.62]	0.036
N1-N3	51 / 1216 (4.2)	5 / 1160 (0.4)	9.73	[3.90; 24.29]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.507				
Grade 1	4 / 102 (3.9)	0 / 106 (0.0)	9.35	[0.51; >99.99]	0.132
Grade 2	42 / 842 (5.0)	7 / 768 (0.9)	5.47	[2.47; 12.11]	<.001
Grade 3	11 / 373 (2.9)	1 / 397 (0.3)	11.71	[1.52; 90.24]	0.018
Histological subtype					
Interaction test	p = 0.277				
Ductal	53 / 1025 (5.2)	6 / 1010 (0.6)	8.70	[3.76; 20.16]	<.001
Lobular	7 / 291 (2.4)	2 / 276 (0.7)	3.32	[0.70; 15.84]	0.132
Other	2 / 92 (2.2)	0 / 76 (0.0)	4.14	[0.20; 84.94]	0.357
Ki67 status from surgical specimen					
Interaction test	p = 0.205				
Ki67≤20	37 / 660 (5.6)	3 / 629 (0.5)	11.75	[3.64; 37.93]	<.001
Ki67>20	21 / 489 (4.3)	5 / 516 (1.0)	4.43	[1.68; 11.66]	0.003
Type of NSAI					
Interaction test	p = 0.496				
Letrozole	38 / 907 (4.2)	4 / 895 (0.4)	9.37	[3.36; 26.16]	<.001
Anastrozole	24 / 502 (4.8)	4 / 467 (0.9)	5.58	[1.95; 15.97]	0.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.480				
Yes	53 / 1194 (4.4)	6 / 1146 (0.5)	8.48	[3.66; 19.65]	<.001
No	9 / 215 (4.2)	2 / 216 (0.9)	4.52	[0.99; 20.68]	0.052
Prior adjuvant chemotherapy					
Interaction test	p = 0.449				
Yes	32 / 694 (4.6)	3 / 673 (0.4)	10.34	[3.18; 33.62]	<.001
No	30 / 715 (4.2)	5 / 689 (0.7)	5.78	[2.26; 14.82]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.884				
Yes	22 / 528 (4.2)	3 / 503 (0.6)	6.99	[2.10; 23.20]	0.001
No	40 / 881 (4.5)	5 / 859 (0.6)	7.80	[3.09; 19.67]	<.001
Prior endocrine therapy					
Interaction test	p = 0.295				
Yes	42 / 957 (4.4)	7 / 940 (0.7)	5.89	[2.66; 13.05]	<.001
No	20 / 452 (4.4)	1 / 422 (0.2)	18.67	[2.52; >99.99]	0.004
Prior mastectomy					
Interaction test	p = 0.447				
Yes	37 / 857 (4.3)	6 / 847 (0.7)	6.09	[2.59; 14.36]	<.001
No	25 / 552 (4.5)	2 / 515 (0.4)	11.66	[2.78; 48.99]	<.001
Prior radiotherapy					
Interaction test	p = 0.068				
Yes	59 / 1253 (4.7)	6 / 1203 (0.5)	9.44	[4.09; 21.78]	<.001
No	3 / 156 (1.9)	2 / 159 (1.3)	1.53	[0.26; 9.03]	0.639
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.71 PT hypokalaemia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Hypokalaemia					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.545				
NA/WE/O	28 / 899 (3.1)	14 / 856 (1.6)	1.90	[1.01; 3.59]	0.047
ROW	21 / 510 (4.1)	8 / 506 (1.6)	2.60	[1.16; 5.83]	0.020
Geographical region					
Interaction test	p = 0.202				
Europe	24 / 832 (2.9)	7 / 824 (0.8)	3.40	[1.47; 7.84]	0.004
North America/Australia	17 / 400 (4.3)	10 / 364 (2.7)	1.55	[0.72; 3.33]	0.266
Asia	8 / 102 (7.8)	1 / 101 (1.0)	7.92	[1.01; 62.19]	0.049
Latin America	0 / 75 (0.0)	4 / 73 (5.5)	0.11	[<0.01; 1.97]	0.133
Age group 1 at randomization					
Interaction test	p = 0.280				
<45	3 / 60 (5.0)	0 / 52 (0.0)	6.08	[0.32; >99.99]	0.229
45 to 54	6 / 300 (2.0)	7 / 322 (2.2)	0.92	[0.31; 2.71]	0.880
55 to 64	21 / 651 (3.2)	8 / 642 (1.2)	2.59	[1.16; 5.80]	0.021
≥65	19 / 398 (4.8)	7 / 346 (2.0)	2.36	[1.00; 5.55]	0.049
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.552				
<Median	18 / 633 (2.8)	10 / 632 (1.6)	1.80	[0.84; 3.86]	0.133
≥Median	31 / 776 (4.0)	12 / 730 (1.6)	2.43	[1.26; 4.70]	0.008
Race					
Interaction test	p = 0.159				
Asian	8 / 128 (6.3)	1 / 127 (0.8)	7.94	[1.01; 62.55]	0.049
Non-Asian	36 / 1203 (3.0)	20 / 1167 (1.7)	1.75	[1.02; 3.00]	0.043
BMI at screening					
Interaction test	p = 0.522				
≥25	33 / 935 (3.5)	14 / 935 (1.5)	2.36	[1.27; 4.38]	0.007
<25	15 / 460 (3.3)	8 / 410 (2.0)	1.67	[0.72; 3.90]	0.235
AJCC Anatomic Stage Group					
Interaction test	p = 0.654				
Group I/II	23 / 585 (3.9)	12 / 589 (2.0)	1.93	[0.97; 3.84]	0.061
Group III	26 / 823 (3.2)	10 / 772 (1.3)	2.44	[1.18; 5.02]	0.016

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.334				
IA/IB/IIA	10 / 310 (3.2)	5 / 311 (1.6)	2.01	[0.69; 5.80]	0.199
IIB	13 / 275 (4.7)	7 / 278 (2.5)	1.88	[0.76; 4.63]	0.172
IIIA	15 / 482 (3.1)	4 / 450 (0.9)	3.50	[1.17; 10.47]	0.025
IIIB	1 / 100 (1.0)	3 / 82 (3.7)	0.27	[0.03; 2.58]	0.257
IIIC	10 / 241 (4.1)	3 / 240 (1.3)	3.32	[0.93; 11.91]	0.066
Tumor category					
Interaction test	p = 0.125				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	47 / 1287 (3.7)	19 / 1258 (1.5)	2.42	[1.43; 4.10]	0.001
>T3	2 / 113 (1.8)	3 / 97 (3.1)	0.57	[0.10; 3.35]	0.536
Nodal status					
Interaction test	p = 0.159				
N0	3 / 190 (1.6)	4 / 200 (2.0)	0.79	[0.18; 3.48]	0.755
N1-N3	46 / 1216 (3.8)	18 / 1160 (1.6)	2.44	[1.42; 4.18]	0.001
Histological grade at time of surgery					
Interaction test	p = 0.923				
Grade 1	4 / 102 (3.9)	0 / 106 (0.0)	9.35	[0.51; >99.99]	0.132
Grade 2	31 / 842 (3.7)	13 / 768 (1.7)	2.18	[1.15; 4.13]	0.017
Grade 3	13 / 373 (3.5)	6 / 397 (1.5)	2.31	[0.89; 6.00]	0.087
Histological subtype					
Interaction test	p = 0.373				
Ductal	36 / 1025 (3.5)	15 / 1010 (1.5)	2.36	[1.30; 4.29]	0.005
Lobular	12 / 291 (4.1)	5 / 276 (1.8)	2.28	[0.81; 6.38]	0.118
Other	1 / 92 (1.1)	2 / 76 (2.6)	0.41	[0.04; 4.47]	0.467
Ki67 status from surgical specimen					
Interaction test	p = 0.674				
Ki67≤20	26 / 660 (3.9)	8 / 629 (1.3)	3.10	[1.41; 6.79]	0.005
Ki67>20	16 / 489 (3.3)	7 / 516 (1.4)	2.41	[1.00; 5.81]	0.050
Type of NSAI					
Interaction test	p = 0.061				
Letrozole	37 / 907 (4.1)	12 / 895 (1.3)	3.04	[1.60; 5.80]	<.001
Anastrozole	12 / 502 (2.4)	10 / 467 (2.1)	1.12	[0.49; 2.56]	0.795
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.588				
Yes	37 / 1194 (3.1)	15 / 1146 (1.3)	2.37	[1.31; 4.29]	0.004
No	12 / 215 (5.6)	7 / 216 (3.2)	1.72	[0.69; 4.29]	0.243
Prior adjuvant chemotherapy					
Interaction test	p = 0.131				
Yes	25 / 694 (3.6)	7 / 673 (1.0)	3.46	[1.51; 7.95]	0.003
No	24 / 715 (3.4)	15 / 689 (2.2)	1.54	[0.82; 2.91]	0.183

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.278				
Yes	14 / 528 (2.7)	9 / 503 (1.8)	1.48	[0.65; 3.39]	0.352
No	35 / 881 (4.0)	13 / 859 (1.5)	2.63	[1.40; 4.93]	0.003
Prior endocrine therapy					
Interaction test	p = 0.811				
Yes	27 / 957 (2.8)	13 / 940 (1.4)	2.04	[1.06; 3.93]	0.033
No	22 / 452 (4.9)	9 / 422 (2.1)	2.28	[1.06; 4.90]	0.034
Prior mastectomy					
Interaction test	p = 0.063				
Yes	35 / 857 (4.1)	11 / 847 (1.3)	3.14	[1.61; 6.15]	<.001
No	14 / 552 (2.5)	11 / 515 (2.1)	1.19	[0.54; 2.59]	0.666
Prior radiotherapy					
Interaction test	p = 0.493				
Yes	42 / 1253 (3.4)	20 / 1203 (1.7)	2.02	[1.19; 3.41]	0.009
No	7 / 156 (4.5)	2 / 159 (1.3)	3.57	[0.75; 16.91]	0.109
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.72 PT hypercalcaemia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Hypercalcaemia					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.219				
NA/WE/O	20 / 899 (2.2)	13 / 856 (1.5)	1.46	[0.73; 2.93]	0.280
ROW	11 / 510 (2.2)	3 / 506 (0.6)	3.64	[1.02; 12.96]	0.046
Geographical region					
Interaction test	p = 0.331				
Europe	17 / 832 (2.0)	6 / 824 (0.7)	2.81	[1.11; 7.08]	0.029
North America/Australia	11 / 400 (2.8)	9 / 364 (2.5)	1.11	[0.47; 2.65]	0.811
Asia	0 / 102 (0.0)	0 / 101 (0.0)	N.E.	N.E.	N.E.
Latin America	3 / 75 (4.0)	1 / 73 (1.4)	2.92	[0.31; 27.43]	0.348
Age group 1 at randomization					
Interaction test	p = 0.500				
<45	1 / 60 (1.7)	0 / 52 (0.0)	2.61	[0.11; 62.64]	0.555
45 to 54	7 / 300 (2.3)	3 / 322 (0.9)	2.50	[0.65; 9.60]	0.180
55 to 64	14 / 651 (2.2)	6 / 642 (0.9)	2.30	[0.89; 5.95]	0.086
≥65	9 / 398 (2.3)	7 / 346 (2.0)	1.12	[0.42; 2.97]	0.823
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.224				
<Median	15 / 633 (2.4)	5 / 632 (0.8)	3.00	[1.10; 8.19]	0.033
≥Median	16 / 776 (2.1)	11 / 730 (1.5)	1.37	[0.64; 2.93]	0.419
Race					
Interaction test	N.E.				
Asian	1 / 128 (0.8)	0 / 127 (0.0)	2.98	[0.12; 72.39]	0.503
Non-Asian	28 / 1203 (2.3)	15 / 1167 (1.3)	1.81	[0.97; 3.37]	0.061
BMI at screening					
Interaction test	p = 0.278				
≥25	22 / 935 (2.4)	9 / 935 (1.0)	2.44	[1.13; 5.28]	0.023
<25	8 / 460 (1.7)	6 / 410 (1.5)	1.19	[0.42; 3.40]	0.747
AJCC Anatomic Stage Group					
Interaction test	p = 0.824				
Group I/II	12 / 585 (2.1)	7 / 589 (1.2)	1.73	[0.68; 4.35]	0.248
Group III	19 / 823 (2.3)	9 / 772 (1.2)	1.98	[0.90; 4.35]	0.089

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.754				
IA/IB/IIA	5 / 310 (1.6)	4 / 311 (1.3)	1.25	[0.34; 4.63]	0.734
IIB	7 / 275 (2.5)	3 / 278 (1.1)	2.36	[0.62; 9.03]	0.210
IIIA	9 / 482 (1.9)	3 / 450 (0.7)	2.80	[0.76; 10.28]	0.121
IIIB	2 / 100 (2.0)	0 / 82 (0.0)	4.11	[0.20; 84.40]	0.359
IIIC	8 / 241 (3.3)	6 / 240 (2.5)	1.33	[0.47; 3.77]	0.594
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	29 / 1287 (2.3)	16 / 1258 (1.3)	1.77	[0.97; 3.25]	0.064
>T3	2 / 113 (1.8)	0 / 97 (0.0)	4.30	[0.21; 88.46]	0.345
Nodal status					
Interaction test	p = 0.920				
N0	2 / 190 (1.1)	1 / 200 (0.5)	2.11	[0.19; 23.03]	0.542
N1-N3	29 / 1216 (2.4)	15 / 1160 (1.3)	1.84	[0.99; 3.42]	0.052
Histological grade at time of surgery					
Interaction test	p = 0.471				
Grade 1	1 / 102 (1.0)	0 / 106 (0.0)	3.12	[0.13; 75.63]	0.485
Grade 2	20 / 842 (2.4)	9 / 768 (1.2)	2.03	[0.93; 4.42]	0.076
Grade 3	7 / 373 (1.9)	6 / 397 (1.5)	1.24	[0.42; 3.66]	0.695
Histological subtype					
Interaction test	p = 0.918				
Ductal	25 / 1025 (2.4)	12 / 1010 (1.2)	2.05	[1.04; 4.06]	0.039
Lobular	6 / 291 (2.1)	3 / 276 (1.1)	1.90	[0.48; 7.51]	0.362
Other	0 / 92 (0.0)	1 / 76 (1.3)	0.28	[0.01; 6.68]	0.428
Ki67 status from surgical specimen					
Interaction test	p = 0.851				
Ki67≤20	10 / 660 (1.5)	4 / 629 (0.6)	2.38	[0.75; 7.56]	0.140
Ki67>20	13 / 489 (2.7)	5 / 516 (1.0)	2.74	[0.99; 7.64]	0.053
Type of NSAI					
Interaction test	p = 0.426				
Letrozole	15 / 907 (1.7)	6 / 895 (0.7)	2.47	[0.96; 6.33]	0.060
Anastrozole	16 / 502 (3.2)	10 / 467 (2.1)	1.49	[0.68; 3.25]	0.318
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.931				
Yes	27 / 1194 (2.3)	14 / 1146 (1.2)	1.85	[0.98; 3.51]	0.059
No	4 / 215 (1.9)	2 / 216 (0.9)	2.01	[0.37; 10.86]	0.417
Prior adjuvant chemotherapy					
Interaction test	p = 0.081				
Yes	11 / 694 (1.6)	10 / 673 (1.5)	1.07	[0.46; 2.50]	0.882
No	20 / 715 (2.8)	6 / 689 (0.9)	3.21	[1.30; 7.95]	0.012

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.195				
Yes	16 / 528 (3.0)	5 / 503 (1.0)	3.05	[1.13; 8.26]	0.028
No	15 / 881 (1.7)	11 / 859 (1.3)	1.33	[0.61; 2.88]	0.470
Prior endocrine therapy					
Interaction test	p = 0.468				
Yes	24 / 957 (2.5)	11 / 940 (1.2)	2.14	[1.06; 4.35]	0.035
No	7 / 452 (1.5)	5 / 422 (1.2)	1.31	[0.42; 4.09]	0.645
Prior mastectomy					
Interaction test	p = 0.838				
Yes	18 / 857 (2.1)	10 / 847 (1.2)	1.78	[0.83; 3.83]	0.141
No	13 / 552 (2.4)	6 / 515 (1.2)	2.02	[0.77; 5.28]	0.151
Prior radiotherapy					
Interaction test	p = 0.267				
Yes	30 / 1253 (2.4)	14 / 1203 (1.2)	2.06	[1.10; 3.86]	0.025
No	1 / 156 (0.6)	2 / 159 (1.3)	0.51	[0.05; 5.56]	0.580
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.73 PT hypermagnesaemia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Hypermagnesaemia					
	n / N (%)	n / N (%)			
Region					
Interaction test	N.E.				
NA/WE/O	11 / 899 (1.2)	2 / 856 (0.2)	5.24	[1.16; 23.56]	0.031
ROW	7 / 510 (1.4)	0 / 506 (0.0)	14.88	[0.85; >99.99]	0.064
Geographical region					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Age group 1 at randomization					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.670				
<Median	6 / 633 (0.9)	1 / 632 (0.2)	5.99	[0.72; 49.62]	0.097
≥Median	12 / 776 (1.5)	1 / 730 (0.1)	11.29	[1.47; 86.60]	0.020
Race					
Interaction test	N.E.				
Asian	3 / 128 (2.3)	0 / 127 (0.0)	6.95	[0.36; >99.99]	0.198
Non-Asian	13 / 1203 (1.1)	2 / 1167 (0.2)	6.31	[1.43; 27.88]	0.015
BMI at screening					
Interaction test	N.E.				
≥25	13 / 935 (1.4)	1 / 935 (0.1)	13.00	[1.70; 99.17]	0.013
<25	5 / 460 (1.1)	0 / 410 (0.0)	9.81	[0.54; >99.99]	0.122
AJCC Anatomic Stage Group					
Interaction test	N.E.				
Group I/II	4 / 585 (0.7)	0 / 589 (0.0)	9.06	[0.49; >99.99]	0.139
Group III	14 / 823 (1.7)	2 / 772 (0.3)	6.57	[1.50; 28.80]	0.013
Anatomic stages					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	14 / 1287 (1.1)	2 / 1258 (0.2)	6.84	[1.56; 30.04]	0.011
>T3	4 / 113 (3.5)	0 / 97 (0.0)	7.74	[0.42; >99.99]	0.168
Nodal status					
Interaction test	N.E.				
N0	3 / 190 (1.6)	0 / 200 (0.0)	7.37	[0.38; >99.99]	0.186
N1-N3	15 / 1216 (1.2)	2 / 1160 (0.2)	7.15	[1.64; 31.22]	0.009
Histological grade at time of surgery					
Interaction test	p = 0.723				
Grade 1	2 / 102 (2.0)	0 / 106 (0.0)	5.19	[0.25; >99.99]	0.286
Grade 2	10 / 842 (1.2)	1 / 768 (0.1)	9.12	[1.17; 71.09]	0.035
Grade 3	5 / 373 (1.3)	1 / 397 (0.3)	5.32	[0.62; 45.34]	0.126
Histological subtype					
Interaction test	p = 0.468				
Ductal	9 / 1025 (0.9)	1 / 1010 (0.1)	8.87	[1.13; 69.87]	0.038
Lobular	3 / 291 (1.0)	1 / 276 (0.4)	2.85	[0.30; 27.19]	0.364
Other	6 / 92 (6.5)	0 / 76 (0.0)	10.76	[0.62; >99.99]	0.104
Ki67 status from surgical specimen					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Type of NSAI					
Interaction test	p = 0.907				
Letrozole	8 / 907 (0.9)	1 / 895 (0.1)	7.89	[0.99; 62.99]	0.051
Anastrozole	10 / 502 (2.0)	1 / 467 (0.2)	9.30	[1.20; 72.39]	0.033
Prior neo/adjuvant chemotherapy					
Interaction test	N.E.				
Yes	15 / 1194 (1.3)	2 / 1146 (0.2)	7.20	[1.65; 31.41]	0.009
No	3 / 215 (1.4)	0 / 216 (0.0)	7.03	[0.37; >99.99]	0.196
Prior adjuvant chemotherapy					
Interaction test	N.E.				
Yes	5 / 694 (0.7)	0 / 673 (0.0)	10.67	[0.59; >99.99]	0.109
No	13 / 715 (1.8)	2 / 689 (0.3)	6.26	[1.42; 27.65]	0.015
Prior neoadjuvant chemotherapy					
Interaction test	N.E.				
Yes	10 / 528 (1.9)	2 / 503 (0.4)	4.76	[1.05; 21.63]	0.043
No	8 / 881 (0.9)	0 / 859 (0.0)	16.58	[0.96; >99.99]	0.054

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior endocrine therapy					
Interaction test	N.E.				
Yes	15 / 957 (1.6)	2 / 940 (0.2)	7.37	[1.69; 32.13]	0.008
No	3 / 452 (0.7)	0 / 422 (0.0)	6.54	[0.34; >99.99]	0.214
Prior mastectomy					
Interaction test	N.E.				
Yes	12 / 857 (1.4)	2 / 847 (0.2)	5.93	[1.33; 26.42]	0.020
No	6 / 552 (1.1)	0 / 515 (0.0)	12.13	[0.69; >99.99]	0.089
Prior radiotherapy					
Interaction test	N.E.				
Yes	17 / 1253 (1.4)	2 / 1203 (0.2)	8.16	[1.89; 35.25]	0.005
No	1 / 156 (0.6)	0 / 159 (0.0)	3.06	[0.13; 74.48]	0.493
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.74 SOC respiratory, thoracic and mediastinal disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Respiratory, thoracic and mediastinal disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.307				
NA/WE/O	318 / 899 (35.4)	190 / 856 (22.2)	1.59	[1.37; 1.86]	<.001
ROW	98 / 510 (19.2)	67 / 506 (13.2)	1.45	[1.09; 1.93]	0.011
Geographical region					
Interaction test	p = 0.066				
Europe	196 / 832 (23.6)	143 / 824 (17.4)	1.36	[1.12; 1.65]	0.002
North America/Australia	171 / 400 (42.8)	93 / 364 (25.5)	1.67	[1.36; 2.06]	<.001
Asia	32 / 102 (31.4)	12 / 101 (11.9)	2.64	[1.44; 4.83]	0.002
Latin America	17 / 75 (22.7)	9 / 73 (12.3)	1.84	[0.88; 3.86]	0.107
Age group 1 at randomization					
Interaction test	p = 0.814				
<45	20 / 60 (33.3)	11 / 52 (21.2)	1.58	[0.83; 2.97]	0.161
45 to 54	76 / 300 (25.3)	56 / 322 (17.4)	1.46	[1.07; 1.98]	0.016
55 to 64	192 / 651 (29.5)	113 / 642 (17.6)	1.68	[1.36; 2.06]	<.001
≥65	128 / 398 (32.2)	77 / 346 (22.3)	1.45	[1.13; 1.84]	0.003
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.972				
<Median	180 / 633 (28.4)	114 / 632 (18.0)	1.58	[1.28; 1.94]	<.001
≥Median	236 / 776 (30.4)	143 / 730 (19.6)	1.55	[1.29; 1.86]	<.001
Race					
Interaction test	p = 0.065				
Asian	46 / 128 (35.9)	20 / 127 (15.7)	2.28	[1.43; 3.63]	<.001
Non-Asian	339 / 1203 (28.2)	223 / 1167 (19.1)	1.47	[1.27; 1.71]	<.001
BMI at screening					
Interaction test	p = 0.513				
≥25	260 / 935 (27.8)	173 / 935 (18.5)	1.50	[1.27; 1.78]	<.001
<25	148 / 460 (32.2)	81 / 410 (19.8)	1.63	[1.29; 2.06]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.657				
Group I/II	164 / 585 (28.0)	109 / 589 (18.5)	1.51	[1.22; 1.88]	<.001
Group III	252 / 823 (30.6)	148 / 772 (19.2)	1.60	[1.34; 1.91]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.487				
IA/IB/IIA	80 / 310 (25.8)	60 / 311 (19.3)	1.34	[1.00; 1.80]	0.054
IIB	84 / 275 (30.5)	49 / 278 (17.6)	1.73	[1.27; 2.36]	<.001
IIIA	147 / 482 (30.5)	79 / 450 (17.6)	1.74	[1.36; 2.21]	<.001
IIIB	26 / 100 (26.0)	18 / 82 (22.0)	1.18	[0.70; 2.00]	0.528
IIIC	79 / 241 (32.8)	51 / 240 (21.3)	1.54	[1.14; 2.09]	0.005
Tumor category					
Interaction test	p = 0.632				
T0	1 / 5 (20.0)	1 / 5 (20.0)	1.00	[0.08; 11.93]	1.000
T1-T3	383 / 1287 (29.8)	235 / 1258 (18.7)	1.59	[1.38; 1.84]	<.001
>T3	31 / 113 (27.4)	21 / 97 (21.6)	1.27	[0.78; 2.05]	0.337
Nodal status					
Interaction test	p = 0.811				
N0	49 / 190 (25.8)	34 / 200 (17.0)	1.52	[1.03; 2.24]	0.036
N1-N3	366 / 1216 (30.1)	223 / 1160 (19.2)	1.57	[1.35; 1.81]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.102				
Grade 1	26 / 102 (25.5)	28 / 106 (26.4)	0.96	[0.61; 1.53]	0.879
Grade 2	245 / 842 (29.1)	139 / 768 (18.1)	1.61	[1.34; 1.93]	<.001
Grade 3	122 / 373 (32.7)	77 / 397 (19.4)	1.69	[1.32; 2.16]	<.001
Histological subtype					
Interaction test	p = 0.848				
Ductal	302 / 1025 (29.5)	194 / 1010 (19.2)	1.53	[1.31; 1.80]	<.001
Lobular	86 / 291 (29.6)	48 / 276 (17.4)	1.70	[1.24; 2.32]	<.001
Other	27 / 92 (29.3)	15 / 76 (19.7)	1.49	[0.86; 2.59]	0.160
Ki67 status from surgical specimen					
Interaction test	p = 0.906				
Ki67≤20	177 / 660 (26.8)	111 / 629 (17.6)	1.52	[1.23; 1.88]	<.001
Ki67>20	130 / 489 (26.6)	92 / 516 (17.8)	1.49	[1.18; 1.89]	<.001
Type of NSAI					
Interaction test	p = 0.912				
Letrozole	258 / 907 (28.4)	161 / 895 (18.0)	1.58	[1.33; 1.88]	<.001
Anastrozole	158 / 502 (31.5)	96 / 467 (20.6)	1.53	[1.23; 1.91]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.168				
Yes	361 / 1194 (30.2)	213 / 1146 (18.6)	1.63	[1.40; 1.89]	<.001
No	55 / 215 (25.6)	44 / 216 (20.4)	1.26	[0.89; 1.78]	0.200
Prior adjuvant chemotherapy					
Interaction test	p = 0.477				
Yes	227 / 694 (32.7)	136 / 673 (20.2)	1.62	[1.35; 1.95]	<.001
No	189 / 715 (26.4)	121 / 689 (17.6)	1.51	[1.23; 1.84]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.579				
Yes	146 / 528 (27.7)	83 / 503 (16.5)	1.68	[1.32; 2.13]	<.001
No	270 / 881 (30.6)	174 / 859 (20.3)	1.51	[1.28; 1.79]	<.001
Prior endocrine therapy					
Interaction test	p = 0.184				
Yes	297 / 957 (31.0)	176 / 940 (18.7)	1.66	[1.41; 1.95]	<.001
No	119 / 452 (26.3)	81 / 422 (19.2)	1.37	[1.07; 1.76]	0.013
Prior mastectomy					
Interaction test	p = 0.250				
Yes	271 / 857 (31.6)	162 / 847 (19.1)	1.65	[1.39; 1.96]	<.001
No	145 / 552 (26.3)	95 / 515 (18.4)	1.42	[1.13; 1.79]	0.003
Prior radiotherapy					
Interaction test	p = 0.079				
Yes	380 / 1253 (30.3)	224 / 1203 (18.6)	1.63	[1.41; 1.88]	<.001
No	36 / 156 (23.1)	33 / 159 (20.8)	1.11	[0.73; 1.69]	0.619
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.75 PT cough: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Cough					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.941				
NA/WE/O	137 / 899 (15.2)	91 / 856 (10.6)	1.43	[1.12; 1.84]	0.004
ROW	35 / 510 (6.9)	23 / 506 (4.5)	1.51	[0.91; 2.52]	0.114
Geographical region					
Interaction test	p = 0.813				
Europe	73 / 832 (8.8)	54 / 824 (6.6)	1.34	[0.95; 1.88]	0.091
North America/Australia	79 / 400 (19.8)	50 / 364 (13.7)	1.44	[1.04; 1.99]	0.028
Asia	14 / 102 (13.7)	7 / 101 (6.9)	1.98	[0.83; 4.70]	0.121
Latin America	6 / 75 (8.0)	3 / 73 (4.1)	1.95	[0.51; 7.49]	0.333
Age group 1 at randomization					
Interaction test	p = 0.710				
<45	9 / 60 (15.0)	7 / 52 (13.5)	1.11	[0.45; 2.78]	0.817
45 to 54	30 / 300 (10.0)	23 / 322 (7.1)	1.40	[0.83; 2.35]	0.205
55 to 64	81 / 651 (12.4)	48 / 642 (7.5)	1.66	[1.18; 2.34]	0.003
≥65	52 / 398 (13.1)	36 / 346 (10.4)	1.26	[0.84; 1.87]	0.264
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.608				
<Median	78 / 633 (12.3)	50 / 632 (7.9)	1.56	[1.11; 2.18]	0.010
≥Median	94 / 776 (12.1)	64 / 730 (8.8)	1.38	[1.02; 1.87]	0.035
Race					
Interaction test	p = 0.319				
Asian	23 / 128 (18.0)	12 / 127 (9.4)	1.90	[0.99; 3.66]	0.054
Non-Asian	137 / 1203 (11.4)	98 / 1167 (8.4)	1.36	[1.06; 1.74]	0.015
BMI at screening					
Interaction test	p = 0.173				
≥25	95 / 935 (10.2)	75 / 935 (8.0)	1.27	[0.95; 1.69]	0.109
<25	72 / 460 (15.7)	37 / 410 (9.0)	1.73	[1.19; 2.52]	0.004
AJCC Anatomic Stage Group					
Interaction test	p = 0.123				
Group I/II	65 / 585 (11.1)	55 / 589 (9.3)	1.19	[0.85; 1.67]	0.317
Group III	107 / 823 (13.0)	59 / 772 (7.6)	1.70	[1.26; 2.30]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.405				
IA/IB/IIA	33 / 310 (10.6)	32 / 311 (10.3)	1.03	[0.65; 1.64]	0.885
IIB	32 / 275 (11.6)	23 / 278 (8.3)	1.41	[0.85; 2.34]	0.189
IIIA	64 / 482 (13.3)	32 / 450 (7.1)	1.87	[1.25; 2.80]	0.002
IIIB	7 / 100 (7.0)	5 / 82 (6.1)	1.15	[0.38; 3.48]	0.807
IIIC	36 / 241 (14.9)	22 / 240 (9.2)	1.63	[0.99; 2.69]	0.055
Tumor category					
Interaction test	p = 0.670				
T0	0 / 5 (0.0)	1 / 5 (20.0)	0.33	[0.02; 6.65]	0.472
T1-T3	162 / 1287 (12.6)	106 / 1258 (8.4)	1.49	[1.18; 1.88]	<.001
>T3	10 / 113 (8.8)	7 / 97 (7.2)	1.23	[0.49; 3.10]	0.666
Nodal status					
Interaction test	p = 0.474				
N0	19 / 190 (10.0)	17 / 200 (8.5)	1.18	[0.63; 2.19]	0.609
N1-N3	152 / 1216 (12.5)	97 / 1160 (8.4)	1.49	[1.17; 1.90]	0.001
Histological grade at time of surgery					
Interaction test	p = 0.022				
Grade 1	6 / 102 (5.9)	12 / 106 (11.3)	0.52	[0.20; 1.33]	0.173
Grade 2	106 / 842 (12.6)	66 / 768 (8.6)	1.46	[1.09; 1.96]	0.010
Grade 3	56 / 373 (15.0)	28 / 397 (7.1)	2.13	[1.38; 3.28]	<.001
Histological subtype					
Interaction test	p = 0.422				
Ductal	119 / 1025 (11.6)	88 / 1010 (8.7)	1.33	[1.03; 1.73]	0.031
Lobular	38 / 291 (13.1)	20 / 276 (7.2)	1.80	[1.08; 3.02]	0.025
Other	15 / 92 (16.3)	6 / 76 (7.9)	2.07	[0.84; 5.06]	0.113
Ki67 status from surgical specimen					
Interaction test	p = 0.083				
Ki67≤20	78 / 660 (11.8)	45 / 629 (7.2)	1.65	[1.16; 2.34]	0.005
Ki67>20	42 / 489 (8.6)	43 / 516 (8.3)	1.03	[0.69; 1.55]	0.884
Type of NSAI					
Interaction test	p = 0.177				
Letrozole	116 / 907 (12.8)	70 / 895 (7.8)	1.64	[1.23; 2.17]	<.001
Anastrozole	56 / 502 (11.2)	44 / 467 (9.4)	1.18	[0.81; 1.72]	0.376
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.536				
Yes	146 / 1194 (12.2)	93 / 1146 (8.1)	1.51	[1.18; 1.93]	0.001
No	26 / 215 (12.1)	21 / 216 (9.7)	1.24	[0.72; 2.14]	0.431
Prior adjuvant chemotherapy					
Interaction test	p = 0.503				
Yes	95 / 694 (13.7)	59 / 673 (8.8)	1.56	[1.15; 2.12]	0.004
No	77 / 715 (10.8)	55 / 689 (8.0)	1.35	[0.97; 1.88]	0.075

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.786				
Yes	56 / 528 (10.6)	38 / 503 (7.6)	1.40	[0.95; 2.08]	0.091
No	116 / 881 (13.2)	76 / 859 (8.8)	1.49	[1.13; 1.96]	0.004
Prior endocrine therapy					
Interaction test	p = 0.128				
Yes	125 / 957 (13.1)	75 / 940 (8.0)	1.64	[1.25; 2.15]	<.001
No	47 / 452 (10.4)	39 / 422 (9.2)	1.13	[0.75; 1.68]	0.567
Prior mastectomy					
Interaction test	p = 0.496				
Yes	114 / 857 (13.3)	73 / 847 (8.6)	1.54	[1.17; 2.04]	0.002
No	58 / 552 (10.5)	41 / 515 (8.0)	1.32	[0.90; 1.93]	0.154
Prior radiotherapy					
Interaction test	p = 0.338				
Yes	155 / 1253 (12.4)	98 / 1203 (8.1)	1.52	[1.19; 1.93]	<.001
No	17 / 156 (10.9)	16 / 159 (10.1)	1.08	[0.57; 2.07]	0.809
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.76 PT dyspnoea: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Dyspnoea					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.803				
NA/WE/O	91 / 899 (10.1)	51 / 856 (6.0)	1.70	[1.22; 2.36]	0.002
ROW	24 / 510 (4.7)	15 / 506 (3.0)	1.59	[0.84; 2.99]	0.153
Geographical region					
Interaction test	p = 0.788				
Europe	66 / 832 (7.9)	42 / 824 (5.1)	1.56	[1.07; 2.26]	0.021
North America/Australia	39 / 400 (9.8)	20 / 364 (5.5)	1.77	[1.05; 2.98]	0.031
Asia	3 / 102 (2.9)	2 / 101 (2.0)	1.49	[0.25; 8.70]	0.661
Latin America	7 / 75 (9.3)	2 / 73 (2.7)	3.41	[0.73; 15.86]	0.118
Age group 1 at randomization					
Interaction test	p = 0.441				
<45	4 / 60 (6.7)	5 / 52 (9.6)	0.69	[0.20; 2.45]	0.569
45 to 54	19 / 300 (6.3)	14 / 322 (4.3)	1.46	[0.74; 2.85]	0.273
55 to 64	48 / 651 (7.4)	23 / 642 (3.6)	2.06	[1.27; 3.34]	0.004
≥65	44 / 398 (11.1)	24 / 346 (6.9)	1.59	[0.99; 2.57]	0.055
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.548				
<Median	44 / 633 (7.0)	29 / 632 (4.6)	1.51	[0.96; 2.39]	0.074
≥Median	71 / 776 (9.1)	37 / 730 (5.1)	1.81	[1.23; 2.65]	0.003
Race					
Interaction test	p = 0.232				
Asian	4 / 128 (3.1)	5 / 127 (3.9)	0.79	[0.22; 2.89]	0.726
Non-Asian	98 / 1203 (8.1)	54 / 1167 (4.6)	1.76	[1.28; 2.43]	<.001
BMI at screening					
Interaction test	p = 0.967				
≥25	74 / 935 (7.9)	44 / 935 (4.7)	1.68	[1.17; 2.42]	0.005
<25	39 / 460 (8.5)	21 / 410 (5.1)	1.66	[0.99; 2.77]	0.054
AJCC Anatomic Stage Group					
Interaction test	p = 0.613				
Group I/II	46 / 585 (7.9)	25 / 589 (4.2)	1.85	[1.15; 2.97]	0.011
Group III	69 / 823 (8.4)	41 / 772 (5.3)	1.58	[1.09; 2.29]	0.017

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.941				
IA/IB/IIA	26 / 310 (8.4)	16 / 311 (5.1)	1.63	[0.89; 2.98]	0.112
IIB	20 / 275 (7.3)	9 / 278 (3.2)	2.25	[1.04; 4.85]	0.039
IIIA	35 / 482 (7.3)	21 / 450 (4.7)	1.56	[0.92; 2.63]	0.099
IIIB	10 / 100 (10.0)	6 / 82 (7.3)	1.37	[0.52; 3.60]	0.528
IIIC	24 / 241 (10.0)	14 / 240 (5.8)	1.71	[0.91; 3.22]	0.098
Tumor category					
Interaction test	p = 0.781				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	103 / 1287 (8.0)	59 / 1258 (4.7)	1.71	[1.25; 2.33]	<.001
>T3	12 / 113 (10.6)	7 / 97 (7.2)	1.47	[0.60; 3.59]	0.396
Nodal status					
Interaction test	p = 0.488				
N0	15 / 190 (7.9)	7 / 200 (3.5)	2.26	[0.94; 5.41]	0.068
N1-N3	100 / 1216 (8.2)	59 / 1160 (5.1)	1.62	[1.18; 2.21]	0.003
Histological grade at time of surgery					
Interaction test	p = 0.813				
Grade 1	8 / 102 (7.8)	5 / 106 (4.7)	1.66	[0.56; 4.91]	0.358
Grade 2	66 / 842 (7.8)	32 / 768 (4.2)	1.88	[1.25; 2.84]	0.003
Grade 3	34 / 373 (9.1)	24 / 397 (6.0)	1.51	[0.91; 2.49]	0.110
Histological subtype					
Interaction test	p = 0.342				
Ductal	83 / 1025 (8.1)	53 / 1010 (5.2)	1.54	[1.11; 2.15]	0.011
Lobular	24 / 291 (8.2)	8 / 276 (2.9)	2.85	[1.30; 6.23]	0.009
Other	8 / 92 (8.7)	5 / 76 (6.6)	1.32	[0.45; 3.87]	0.611
Ki67 status from surgical specimen					
Interaction test	p = 0.148				
Ki67≤20	48 / 660 (7.3)	24 / 629 (3.8)	1.91	[1.18; 3.07]	0.008
Ki67>20	34 / 489 (7.0)	31 / 516 (6.0)	1.16	[0.72; 1.85]	0.543
Type of NSAI					
Interaction test	p = 0.756				
Letrozole	64 / 907 (7.1)	39 / 895 (4.4)	1.62	[1.10; 2.39]	0.015
Anastrozole	51 / 502 (10.2)	27 / 467 (5.8)	1.76	[1.12; 2.75]	0.014
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.840				
Yes	97 / 1194 (8.1)	56 / 1146 (4.9)	1.66	[1.21; 2.29]	0.002
No	18 / 215 (8.4)	10 / 216 (4.6)	1.81	[0.85; 3.83]	0.121
Prior adjuvant chemotherapy					
Interaction test	p = 0.338				
Yes	62 / 694 (8.9)	31 / 673 (4.6)	1.94	[1.28; 2.95]	0.002
No	53 / 715 (7.4)	35 / 689 (5.1)	1.46	[0.96; 2.21]	0.074

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.309				
Yes	36 / 528 (6.8)	25 / 503 (5.0)	1.37	[0.84; 2.25]	0.211
No	79 / 881 (9.0)	41 / 859 (4.8)	1.88	[1.30; 2.71]	<.001
Prior endocrine therapy					
Interaction test	p = 0.308				
Yes	76 / 957 (7.9)	49 / 940 (5.2)	1.52	[1.08; 2.16]	0.018
No	39 / 452 (8.6)	17 / 422 (4.0)	2.14	[1.23; 3.73]	0.007
Prior mastectomy					
Interaction test	p = 0.382				
Yes	72 / 857 (8.4)	38 / 847 (4.5)	1.87	[1.28; 2.74]	0.001
No	43 / 552 (7.8)	28 / 515 (5.4)	1.43	[0.90; 2.27]	0.126
Prior radiotherapy					
Interaction test	p = 0.944				
Yes	108 / 1253 (8.6)	62 / 1203 (5.2)	1.67	[1.24; 2.26]	<.001
No	7 / 156 (4.5)	4 / 159 (2.5)	1.78	[0.53; 5.97]	0.348
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.77 PT oropharyngeal pain: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Oropharyngeal pain					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.546				
NA/WE/O	57 / 899 (6.3)	25 / 856 (2.9)	2.17	[1.37; 3.44]	<.001
ROW	15 / 510 (2.9)	9 / 506 (1.8)	1.65	[0.73; 3.74]	0.228
Geographical region					
Interaction test	p = 0.344				
Europe	23 / 832 (2.8)	16 / 824 (1.9)	1.42	[0.76; 2.68]	0.272
North America/Australia	38 / 400 (9.5)	13 / 364 (3.6)	2.66	[1.44; 4.91]	0.002
Asia	10 / 102 (9.8)	5 / 101 (5.0)	1.98	[0.70; 5.59]	0.197
Latin America	1 / 75 (1.3)	0 / 73 (0.0)	2.92	[0.12; 70.56]	0.509
Age group 1 at randomization					
Interaction test	p = 0.847				
<45	2 / 60 (3.3)	1 / 52 (1.9)	1.73	[0.16; 18.57]	0.649
45 to 54	20 / 300 (6.7)	12 / 322 (3.7)	1.79	[0.89; 3.60]	0.103
55 to 64	34 / 651 (5.2)	13 / 642 (2.0)	2.58	[1.37; 4.84]	0.003
≥65	16 / 398 (4.0)	8 / 346 (2.3)	1.74	[0.75; 4.01]	0.195
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.888				
<Median	40 / 633 (6.3)	19 / 632 (3.0)	2.10	[1.23; 3.59]	0.006
≥Median	32 / 776 (4.1)	15 / 730 (2.1)	2.01	[1.10; 3.67]	0.024
Race					
Interaction test	p = 0.176				
Asian	18 / 128 (14.1)	5 / 127 (3.9)	3.57	[1.37; 9.33]	0.009
Non-Asian	52 / 1203 (4.3)	28 / 1167 (2.4)	1.80	[1.15; 2.83]	0.011
BMI at screening					
Interaction test	p = 0.576				
≥25	36 / 935 (3.9)	20 / 935 (2.1)	1.80	[1.05; 3.09]	0.033
<25	35 / 460 (7.6)	14 / 410 (3.4)	2.23	[1.22; 4.08]	0.009
AJCC Anatomic Stage Group					
Interaction test	p = 0.016				
Group I/II	18 / 585 (3.1)	17 / 589 (2.9)	1.07	[0.55; 2.05]	0.848
Group III	54 / 823 (6.6)	17 / 772 (2.2)	2.98	[1.74; 5.09]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.036				
IA/IB/IIA	13 / 310 (4.2)	8 / 311 (2.6)	1.63	[0.69; 3.88]	0.269
IIB	5 / 275 (1.8)	9 / 278 (3.2)	0.56	[0.19; 1.65]	0.295
IIIA	33 / 482 (6.8)	8 / 450 (1.8)	3.85	[1.80; 8.25]	<.001
IIIB	2 / 100 (2.0)	0 / 82 (0.0)	4.11	[0.20; 84.40]	0.359
IIIC	19 / 241 (7.9)	9 / 240 (3.8)	2.10	[0.97; 4.55]	0.059
Tumor category					
Interaction test	N.E.				
T0	1 / 5 (20.0)	0 / 5 (0.0)	3.00	[0.15; 59.89]	0.472
T1-T3	68 / 1287 (5.3)	34 / 1258 (2.7)	1.95	[1.30; 2.93]	0.001
>T3	3 / 113 (2.7)	0 / 97 (0.0)	6.02	[0.31; >99.99]	0.233
Nodal status					
Interaction test	p = 0.769				
N0	7 / 190 (3.7)	3 / 200 (1.5)	2.46	[0.64; 9.36]	0.188
N1-N3	64 / 1216 (5.3)	31 / 1160 (2.7)	1.97	[1.29; 3.00]	0.002
Histological grade at time of surgery					
Interaction test	p = 0.990				
Grade 1	7 / 102 (6.9)	4 / 106 (3.8)	1.82	[0.55; 6.03]	0.328
Grade 2	44 / 842 (5.2)	20 / 768 (2.6)	2.01	[1.19; 3.37]	0.009
Grade 3	19 / 373 (5.1)	10 / 397 (2.5)	2.02	[0.95; 4.29]	0.067
Histological subtype					
Interaction test	p = 0.226				
Ductal	55 / 1025 (5.4)	23 / 1010 (2.3)	2.36	[1.46; 3.80]	<.001
Lobular	13 / 291 (4.5)	7 / 276 (2.5)	1.76	[0.71; 4.35]	0.220
Other	3 / 92 (3.3)	4 / 76 (5.3)	0.62	[0.14; 2.68]	0.522
Ki67 status from surgical specimen					
Interaction test	p = 0.133				
Ki67≤20	25 / 660 (3.8)	15 / 629 (2.4)	1.59	[0.85; 2.98]	0.150
Ki67>20	21 / 489 (4.3)	6 / 516 (1.2)	3.69	[1.50; 9.07]	0.004
Type of NSAI					
Interaction test	p = 0.817				
Letrozole	44 / 907 (4.9)	22 / 895 (2.5)	1.97	[1.19; 3.26]	0.008
Anastrozole	28 / 502 (5.6)	12 / 467 (2.6)	2.17	[1.12; 4.22]	0.022
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.966				
Yes	64 / 1194 (5.4)	30 / 1146 (2.6)	2.05	[1.34; 3.14]	<.001
No	8 / 215 (3.7)	4 / 216 (1.9)	2.01	[0.61; 6.57]	0.249
Prior adjuvant chemotherapy					
Interaction test	p = 0.100				
Yes	43 / 694 (6.2)	26 / 673 (3.9)	1.60	[1.00; 2.58]	0.051
No	29 / 715 (4.1)	8 / 689 (1.2)	3.49	[1.61; 7.59]	0.002

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.047				
Yes	22 / 528 (4.2)	4 / 503 (0.8)	5.24	[1.82; 15.10]	0.002
No	50 / 881 (5.7)	30 / 859 (3.5)	1.63	[1.04; 2.53]	0.032
Prior endocrine therapy					
Interaction test	p = 0.199				
Yes	58 / 957 (6.1)	24 / 940 (2.6)	2.37	[1.49; 3.79]	<.001
No	14 / 452 (3.1)	10 / 422 (2.4)	1.31	[0.59; 2.91]	0.512
Prior mastectomy					
Interaction test	p = 0.218				
Yes	48 / 857 (5.6)	19 / 847 (2.2)	2.50	[1.48; 4.21]	<.001
No	24 / 552 (4.3)	15 / 515 (2.9)	1.49	[0.79; 2.81]	0.215
Prior radiotherapy					
Interaction test	p = 0.611				
Yes	66 / 1253 (5.3)	32 / 1203 (2.7)	1.98	[1.31; 3.00]	0.001
No	6 / 156 (3.8)	2 / 159 (1.3)	3.06	[0.63; 14.92]	0.167
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.78 PT rhinorrhoea: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Rhinorrhoea					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.646				
NA/WE/O	30 / 899 (3.3)	12 / 856 (1.4)	2.38	[1.23; 4.62]	0.010
ROW	7 / 510 (1.4)	4 / 506 (0.8)	1.74	[0.51; 5.89]	0.376
Geographical region					
Interaction test	p = 0.210				
Europe	13 / 832 (1.6)	10 / 824 (1.2)	1.29	[0.57; 2.92]	0.545
North America/Australia	18 / 400 (4.5)	4 / 364 (1.1)	4.10	[1.40; 11.99]	0.010
Asia	6 / 102 (5.9)	2 / 101 (2.0)	2.97	[0.61; 14.37]	0.176
Latin America	0 / 75 (0.0)	0 / 73 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	p = 0.056				
<45	1 / 60 (1.7)	0 / 52 (0.0)	2.61	[0.11; 62.64]	0.555
45 to 54	3 / 300 (1.0)	6 / 322 (1.9)	0.54	[0.14; 2.13]	0.376
55 to 64	24 / 651 (3.7)	6 / 642 (0.9)	3.94	[1.62; 9.59]	0.002
≥65	9 / 398 (2.3)	4 / 346 (1.2)	1.96	[0.61; 6.30]	0.261
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.338				
<Median	15 / 633 (2.4)	9 / 632 (1.4)	1.66	[0.73; 3.77]	0.223
≥Median	22 / 776 (2.8)	7 / 730 (1.0)	2.96	[1.27; 6.88]	0.012
Race					
Interaction test	p = 0.362				
Asian	8 / 128 (6.3)	2 / 127 (1.6)	3.97	[0.86; 18.33]	0.077
Non-Asian	25 / 1203 (2.1)	13 / 1167 (1.1)	1.87	[0.96; 3.63]	0.066
BMI at screening					
Interaction test	p = 0.586				
≥25	25 / 935 (2.7)	10 / 935 (1.1)	2.50	[1.21; 5.18]	0.014
<25	12 / 460 (2.6)	6 / 410 (1.5)	1.78	[0.68; 4.71]	0.243
AJCC Anatomic Stage Group					
Interaction test	p = 0.453				
Group I/II	16 / 585 (2.7)	9 / 589 (1.5)	1.79	[0.80; 4.02]	0.158
Group III	21 / 823 (2.6)	7 / 772 (0.9)	2.81	[1.20; 6.58]	0.017

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.258				
IA/IB/IIA	8 / 310 (2.6)	3 / 311 (1.0)	2.68	[0.72; 9.99]	0.143
IIB	8 / 275 (2.9)	6 / 278 (2.2)	1.35	[0.47; 3.83]	0.576
IIIA	12 / 482 (2.5)	1 / 450 (0.2)	11.20	[1.46; 85.81]	0.020
IIIB	1 / 100 (1.0)	0 / 82 (0.0)	2.47	[0.10; 59.72]	0.579
IIIC	8 / 241 (3.3)	6 / 240 (2.5)	1.33	[0.47; 3.77]	0.594
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	36 / 1287 (2.8)	16 / 1258 (1.3)	2.20	[1.23; 3.94]	0.008
>T3	1 / 113 (0.9)	0 / 97 (0.0)	2.58	[0.11; 62.59]	0.560
Nodal status					
Interaction test	N.E.				
N0	7 / 190 (3.7)	0 / 200 (0.0)	15.79	[0.91; >99.99]	0.058
N1-N3	30 / 1216 (2.5)	16 / 1160 (1.4)	1.79	[0.98; 3.26]	0.058
Histological grade at time of surgery					
Interaction test	p = 0.364				
Grade 1	1 / 102 (1.0)	2 / 106 (1.9)	0.52	[0.05; 5.64]	0.591
Grade 2	23 / 842 (2.7)	8 / 768 (1.0)	2.62	[1.18; 5.83]	0.018
Grade 3	13 / 373 (3.5)	4 / 397 (1.0)	3.46	[1.14; 10.51]	0.029
Histological subtype					
Interaction test	p = 0.449				
Ductal	26 / 1025 (2.5)	13 / 1010 (1.3)	1.97	[1.02; 3.81]	0.044
Lobular	10 / 291 (3.4)	2 / 276 (0.7)	4.74	[1.05; 21.45]	0.043
Other	1 / 92 (1.1)	1 / 76 (1.3)	0.83	[0.05; 12.99]	0.892
Ki67 status from surgical specimen					
Interaction test	p = 0.255				
Ki67≤20	13 / 660 (2.0)	9 / 629 (1.4)	1.38	[0.59; 3.20]	0.457
Ki67>20	14 / 489 (2.9)	5 / 516 (1.0)	2.95	[1.07; 8.14]	0.036
Type of NSAI					
Interaction test	p = 0.511				
Letrozole	26 / 907 (2.9)	10 / 895 (1.1)	2.57	[1.24; 5.29]	0.011
Anastrozole	11 / 502 (2.2)	6 / 467 (1.3)	1.71	[0.64; 4.57]	0.289
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.790				
Yes	34 / 1194 (2.8)	15 / 1146 (1.3)	2.18	[1.19; 3.97]	0.011
No	3 / 215 (1.4)	1 / 216 (0.5)	3.01	[0.32; 28.75]	0.338
Prior adjuvant chemotherapy					
Interaction test	p = 0.427				
Yes	27 / 694 (3.9)	10 / 673 (1.5)	2.62	[1.28; 5.37]	0.009
No	10 / 715 (1.4)	6 / 689 (0.9)	1.61	[0.59; 4.40]	0.356

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.426				
Yes	8 / 528 (1.5)	5 / 503 (1.0)	1.52	[0.50; 4.63]	0.457
No	29 / 881 (3.3)	11 / 859 (1.3)	2.57	[1.29; 5.11]	0.007
Prior endocrine therapy					
Interaction test	p = 0.784				
Yes	26 / 957 (2.7)	12 / 940 (1.3)	2.13	[1.08; 4.19]	0.029
No	11 / 452 (2.4)	4 / 422 (0.9)	2.57	[0.82; 8.00]	0.104
Prior mastectomy					
Interaction test	p = 0.465				
Yes	21 / 857 (2.5)	11 / 847 (1.3)	1.89	[0.92; 3.89]	0.085
No	16 / 552 (2.9)	5 / 515 (1.0)	2.99	[1.10; 8.09]	0.032
Prior radiotherapy					
Interaction test	N.E.				
Yes	36 / 1253 (2.9)	16 / 1203 (1.3)	2.16	[1.21; 3.87]	0.010
No	1 / 156 (0.6)	0 / 159 (0.0)	3.06	[0.13; 74.48]	0.493
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.79 PT nasal congestion: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Nasal congestion					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.717				
NA/WE/O	26 / 899 (2.9)	13 / 856 (1.5)	1.90	[0.99; 3.68]	0.055
ROW	3 / 510 (0.6)	1 / 506 (0.2)	2.98	[0.31; 28.52]	0.344
Geographical region					
Interaction test	p = 0.293				
Europe	5 / 832 (0.6)	5 / 824 (0.6)	0.99	[0.29; 3.41]	0.988
North America/Australia	21 / 400 (5.3)	9 / 364 (2.5)	2.12	[0.99; 4.58]	0.055
Asia	2 / 102 (2.0)	0 / 101 (0.0)	4.95	[0.24; >99.99]	0.300
Latin America	1 / 75 (1.3)	0 / 73 (0.0)	2.92	[0.12; 70.56]	0.509
Age group 1 at randomization					
Interaction test	p = 0.938				
<45	2 / 60 (3.3)	1 / 52 (1.9)	1.73	[0.16; 18.57]	0.649
45 to 54	6 / 300 (2.0)	2 / 322 (0.6)	3.22	[0.65; 15.83]	0.150
55 to 64	17 / 651 (2.6)	9 / 642 (1.4)	1.86	[0.84; 4.15]	0.128
≥65	4 / 398 (1.0)	2 / 346 (0.6)	1.74	[0.32; 9.43]	0.522
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.526				
<Median	17 / 633 (2.7)	7 / 632 (1.1)	2.42	[1.01; 5.81]	0.047
≥Median	12 / 776 (1.5)	7 / 730 (1.0)	1.61	[0.64; 4.07]	0.312
Race					
Interaction test	p = 0.453				
Asian	2 / 128 (1.6)	2 / 127 (1.6)	0.99	[0.14; 6.94]	0.994
Non-Asian	27 / 1203 (2.2)	12 / 1167 (1.0)	2.18	[1.11; 4.29]	0.023
BMI at screening					
Interaction test	p = 0.475				
≥25	21 / 935 (2.2)	9 / 935 (1.0)	2.33	[1.07; 5.07]	0.032
<25	8 / 460 (1.7)	5 / 410 (1.2)	1.43	[0.47; 4.32]	0.531
AJCC Anatomic Stage Group					
Interaction test	p = 0.276				
Group I/II	17 / 585 (2.9)	6 / 589 (1.0)	2.85	[1.13; 7.18]	0.026
Group III	12 / 823 (1.5)	8 / 772 (1.0)	1.41	[0.58; 3.42]	0.452

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.734				
IA/IB/IIA	9 / 310 (2.9)	4 / 311 (1.3)	2.26	[0.70; 7.25]	0.172
IIB	8 / 275 (2.9)	2 / 278 (0.7)	4.04	[0.87; 18.87]	0.075
IIIA	8 / 482 (1.7)	4 / 450 (0.9)	1.87	[0.57; 6.16]	0.305
IIIB	1 / 100 (1.0)	1 / 82 (1.2)	0.82	[0.05; 12.91]	0.888
IIIC	3 / 241 (1.2)	3 / 240 (1.3)	1.00	[0.20; 4.88]	0.996
Tumor category					
Interaction test	p = 0.533				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	28 / 1287 (2.2)	13 / 1258 (1.0)	2.11	[1.10; 4.05]	0.025
>T3	1 / 113 (0.9)	1 / 97 (1.0)	0.86	[0.05; 13.54]	0.914
Nodal status					
Interaction test	p = 0.719				
N0	5 / 190 (2.6)	2 / 200 (1.0)	2.63	[0.52; 13.40]	0.244
N1-N3	24 / 1216 (2.0)	12 / 1160 (1.0)	1.91	[0.96; 3.80]	0.066
Histological grade at time of surgery					
Interaction test	p = 0.933				
Grade 1	2 / 102 (2.0)	1 / 106 (0.9)	2.08	[0.19; 22.57]	0.548
Grade 2	16 / 842 (1.9)	8 / 768 (1.0)	1.82	[0.79; 4.24]	0.162
Grade 3	11 / 373 (2.9)	5 / 397 (1.3)	2.34	[0.82; 6.68]	0.111
Histological subtype					
Interaction test	p = 0.232				
Ductal	25 / 1025 (2.4)	9 / 1010 (0.9)	2.74	[1.28; 5.83]	0.009
Lobular	3 / 291 (1.0)	4 / 276 (1.4)	0.71	[0.16; 3.15]	0.654
Other	1 / 92 (1.1)	1 / 76 (1.3)	0.83	[0.05; 12.99]	0.892
Ki67 status from surgical specimen					
Interaction test	p = 0.967				
Ki67≤20	12 / 660 (1.8)	6 / 629 (1.0)	1.91	[0.72; 5.05]	0.194
Ki67>20	7 / 489 (1.4)	4 / 516 (0.8)	1.85	[0.54; 6.27]	0.325
Type of NSAI					
Interaction test	p = 0.640				
Letrozole	14 / 907 (1.5)	8 / 895 (0.9)	1.73	[0.73; 4.10]	0.215
Anastrozole	15 / 502 (3.0)	6 / 467 (1.3)	2.33	[0.91; 5.94]	0.078
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.362				
Yes	24 / 1194 (2.0)	13 / 1146 (1.1)	1.77	[0.91; 3.46]	0.094
No	5 / 215 (2.3)	1 / 216 (0.5)	5.02	[0.59; 42.64]	0.139
Prior adjuvant chemotherapy					
Interaction test	p = 0.018				
Yes	13 / 694 (1.9)	12 / 673 (1.8)	1.05	[0.48; 2.29]	0.901
No	16 / 715 (2.2)	2 / 689 (0.3)	7.71	[1.78; 33.40]	0.006

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.033				
Yes	13 / 528 (2.5)	1 / 503 (0.2)	12.38	[1.63; 94.32]	0.015
No	16 / 881 (1.8)	13 / 859 (1.5)	1.20	[0.58; 2.48]	0.622
Prior endocrine therapy					
Interaction test	p = 0.750				
Yes	19 / 957 (2.0)	10 / 940 (1.1)	1.87	[0.87; 3.99]	0.108
No	10 / 452 (2.2)	4 / 422 (0.9)	2.33	[0.74; 7.39]	0.149
Prior mastectomy					
Interaction test	p = 0.979				
Yes	14 / 857 (1.6)	7 / 847 (0.8)	1.98	[0.80; 4.87]	0.139
No	15 / 552 (2.7)	7 / 515 (1.4)	2.00	[0.82; 4.86]	0.127
Prior radiotherapy					
Interaction test	N.E.				
Yes	28 / 1253 (2.2)	14 / 1203 (1.2)	1.92	[1.02; 3.63]	0.045
No	1 / 156 (0.6)	0 / 159 (0.0)	3.06	[0.13; 74.48]	0.493
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.80 PT epistaxis: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Epistaxis					
	n / N (%)	n / N (%)			
Region					
Interaction test	N.E.				
NA/WE/O	21 / 899 (2.3)	7 / 856 (0.8)	2.86	[1.22; 6.68]	0.016
ROW	2 / 510 (0.4)	0 / 506 (0.0)	4.96	[0.24; >99.99]	0.301
Geographical region					
Interaction test	p = 0.402				
Europe	13 / 832 (1.6)	3 / 824 (0.4)	4.29	[1.23; 15.00]	0.023
North America/Australia	9 / 400 (2.3)	4 / 364 (1.1)	2.05	[0.64; 6.59]	0.230
Asia	0 / 102 (0.0)	0 / 101 (0.0)	N.E.	N.E.	N.E.
Latin America	1 / 75 (1.3)	0 / 73 (0.0)	2.92	[0.12; 70.56]	0.509
Age group 1 at randomization					
Interaction test	p = 0.780				
<45	0 / 60 (0.0)	0 / 52 (0.0)	N.E.	N.E.	N.E.
45 to 54	6 / 300 (2.0)	3 / 322 (0.9)	2.15	[0.54; 8.51]	0.277
55 to 64	9 / 651 (1.4)	2 / 642 (0.3)	4.44	[0.96; 20.46]	0.056
≥65	8 / 398 (2.0)	2 / 346 (0.6)	3.48	[0.74; 16.27]	0.113
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.480				
<Median	13 / 633 (2.1)	3 / 632 (0.5)	4.33	[1.24; 15.11]	0.022
≥Median	10 / 776 (1.3)	4 / 730 (0.5)	2.35	[0.74; 7.47]	0.147
Race					
Interaction test	p = 0.446				
Asian	1 / 128 (0.8)	1 / 127 (0.8)	0.99	[0.06; 15.69]	0.996
Non-Asian	19 / 1203 (1.6)	6 / 1167 (0.5)	3.07	[1.23; 7.66]	0.016
BMI at screening					
Interaction test	p = 0.220				
≥25	13 / 935 (1.4)	6 / 935 (0.6)	2.17	[0.83; 5.68]	0.116
<25	10 / 460 (2.2)	1 / 410 (0.2)	8.91	[1.15; 69.33]	0.037
AJCC Anatomic Stage Group					
Interaction test	p = 0.706				
Group I/II	8 / 585 (1.4)	2 / 589 (0.3)	4.03	[0.86; 18.88]	0.077
Group III	15 / 823 (1.8)	5 / 772 (0.6)	2.81	[1.03; 7.71]	0.044

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.412				
IA/IB/IIA	2 / 310 (0.6)	0 / 311 (0.0)	5.02	[0.24; >99.99]	0.297
IIB	6 / 275 (2.2)	2 / 278 (0.7)	3.03	[0.62; 14.90]	0.172
IIIA	9 / 482 (1.9)	2 / 450 (0.4)	4.20	[0.91; 19.34]	0.065
IIIB	3 / 100 (3.0)	0 / 82 (0.0)	5.75	[0.30; >99.99]	0.245
IIIC	3 / 241 (1.2)	3 / 240 (1.3)	1.00	[0.20; 4.88]	0.996
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	18 / 1287 (1.4)	7 / 1258 (0.6)	2.51	[1.05; 6.00]	0.038
>T3	5 / 113 (4.4)	0 / 97 (0.0)	9.46	[0.53; >99.99]	0.127
Nodal status					
Interaction test	p = 0.781				
N0	4 / 190 (2.1)	1 / 200 (0.5)	4.21	[0.47; 37.33]	0.197
N1-N3	19 / 1216 (1.6)	6 / 1160 (0.5)	3.02	[1.21; 7.54]	0.018
Histological grade at time of surgery					
Interaction test	p = 0.153				
Grade 1	5 / 102 (4.9)	0 / 106 (0.0)	11.43	[0.64; >99.99]	0.098
Grade 2	9 / 842 (1.1)	6 / 768 (0.8)	1.37	[0.49; 3.83]	0.550
Grade 3	7 / 373 (1.9)	1 / 397 (0.3)	7.45	[0.92; 60.27]	0.060
Histological subtype					
Interaction test	p = 0.054				
Ductal	15 / 1025 (1.5)	4 / 1010 (0.4)	3.70	[1.23; 11.10]	0.020
Lobular	1 / 291 (0.3)	3 / 276 (1.1)	0.32	[0.03; 3.02]	0.317
Other	7 / 92 (7.6)	0 / 76 (0.0)	12.42	[0.72; >99.99]	0.083
Ki67 status from surgical specimen					
Interaction test	p = 0.185				
Ki67≤20	9 / 660 (1.4)	4 / 629 (0.6)	2.14	[0.66; 6.93]	0.202
Ki67>20	10 / 489 (2.0)	1 / 516 (0.2)	10.55	[1.36; 82.12]	0.024
Type of NSAI					
Interaction test	p = 0.659				
Letrozole	18 / 907 (2.0)	5 / 895 (0.6)	3.55	[1.32; 9.53]	0.012
Anastrozole	5 / 502 (1.0)	2 / 467 (0.4)	2.33	[0.45; 11.93]	0.312
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.367				
Yes	20 / 1194 (1.7)	5 / 1146 (0.4)	3.84	[1.45; 10.19]	0.007
No	3 / 215 (1.4)	2 / 216 (0.9)	1.51	[0.25; 8.93]	0.651
Prior adjuvant chemotherapy					
Interaction test	p = 0.698				
Yes	8 / 694 (1.2)	3 / 673 (0.4)	2.59	[0.69; 9.71]	0.159
No	15 / 715 (2.1)	4 / 689 (0.6)	3.61	[1.21; 10.83]	0.022

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.290				
Yes	12 / 528 (2.3)	2 / 503 (0.4)	5.72	[1.29; 25.41]	0.022
No	11 / 881 (1.2)	5 / 859 (0.6)	2.15	[0.75; 6.15]	0.155
Prior endocrine therapy					
Interaction test	p = 0.782				
Yes	11 / 957 (1.1)	3 / 940 (0.3)	3.60	[1.01; 12.87]	0.049
No	12 / 452 (2.7)	4 / 422 (0.9)	2.80	[0.91; 8.62]	0.072
Prior mastectomy					
Interaction test	p = 0.185				
Yes	16 / 857 (1.9)	3 / 847 (0.4)	5.27	[1.54; 18.02]	0.008
No	7 / 552 (1.3)	4 / 515 (0.8)	1.63	[0.48; 5.54]	0.432
Prior radiotherapy					
Interaction test	N.E.				
Yes	22 / 1253 (1.8)	7 / 1203 (0.6)	3.02	[1.29; 7.04]	0.011
No	1 / 156 (0.6)	0 / 159 (0.0)	3.06	[0.13; 74.48]	0.493
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.81 SOC psychiatric disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Psychiatric disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.350				
NA/WE/O	254 / 899 (28.3)	197 / 856 (23.0)	1.23	[1.05; 1.44]	0.012
ROW	62 / 510 (12.2)	58 / 506 (11.5)	1.06	[0.76; 1.48]	0.732
Geographical region					
Interaction test	p = 0.101				
Europe	169 / 832 (20.3)	149 / 824 (18.1)	1.12	[0.92; 1.37]	0.250
North America/Australia	122 / 400 (30.5)	76 / 364 (20.9)	1.46	[1.14; 1.87]	0.003
Asia	10 / 102 (9.8)	15 / 101 (14.9)	0.66	[0.31; 1.40]	0.279
Latin America	15 / 75 (20.0)	15 / 73 (20.5)	0.97	[0.51; 1.84]	0.934
Age group 1 at randomization					
Interaction test	p = 0.994				
<45	20 / 60 (33.3)	14 / 52 (26.9)	1.24	[0.70; 2.20]	0.465
45 to 54	81 / 300 (27.0)	73 / 322 (22.7)	1.19	[0.91; 1.57]	0.212
55 to 64	131 / 651 (20.1)	109 / 642 (17.0)	1.19	[0.94; 1.49]	0.147
≥65	84 / 398 (21.1)	59 / 346 (17.1)	1.24	[0.92; 1.67]	0.164
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.137				
<Median	148 / 633 (23.4)	138 / 632 (21.8)	1.07	[0.87; 1.31]	0.511
≥Median	168 / 776 (21.6)	117 / 730 (16.0)	1.35	[1.09; 1.67]	0.006
Race					
Interaction test	p = 0.137				
Asian	17 / 128 (13.3)	21 / 127 (16.5)	0.80	[0.45; 1.45]	0.467
Non-Asian	274 / 1203 (22.8)	211 / 1167 (18.1)	1.26	[1.07; 1.48]	0.005
BMI at screening					
Interaction test	p = 0.272				
≥25	213 / 935 (22.8)	169 / 935 (18.1)	1.26	[1.05; 1.51]	0.012
<25	97 / 460 (21.1)	82 / 410 (20.0)	1.05	[0.81; 1.37]	0.692
AJCC Anatomic Stage Group					
Interaction test	p = 0.455				
Group I/II	146 / 585 (25.0)	116 / 589 (19.7)	1.27	[1.02; 1.57]	0.031
Group III	169 / 823 (20.5)	139 / 772 (18.0)	1.14	[0.93; 1.40]	0.202

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.541				
IA/IB/IIA	78 / 310 (25.2)	57 / 311 (18.3)	1.37	[1.01; 1.86]	0.040
IIB	68 / 275 (24.7)	59 / 278 (21.2)	1.17	[0.86; 1.58]	0.328
IIIA	103 / 482 (21.4)	89 / 450 (19.8)	1.08	[0.84; 1.39]	0.549
IIIB	19 / 100 (19.0)	8 / 82 (9.8)	1.95	[0.90; 4.22]	0.091
IIIC	47 / 241 (19.5)	42 / 240 (17.5)	1.11	[0.77; 1.62]	0.572
Tumor category					
Interaction test	p = 0.316				
T0	3 / 5 (60.0)	1 / 5 (20.0)	3.00	[0.45; 19.93]	0.255
T1-T3	290 / 1287 (22.5)	242 / 1258 (19.2)	1.17	[1.01; 1.36]	0.041
>T3	22 / 113 (19.5)	11 / 97 (11.3)	1.72	[0.88; 3.36]	0.114
Nodal status					
Interaction test	p = 0.218				
N0	46 / 190 (24.2)	32 / 200 (16.0)	1.51	[1.01; 2.27]	0.045
N1-N3	269 / 1216 (22.1)	223 / 1160 (19.2)	1.15	[0.98; 1.35]	0.082
Histological grade at time of surgery					
Interaction test	p = 0.702				
Grade 1	21 / 102 (20.6)	22 / 106 (20.8)	0.99	[0.58; 1.69]	0.976
Grade 2	197 / 842 (23.4)	144 / 768 (18.8)	1.25	[1.03; 1.51]	0.023
Grade 3	85 / 373 (22.8)	71 / 397 (17.9)	1.27	[0.96; 1.69]	0.092
Histological subtype					
Interaction test	p = 0.955				
Ductal	226 / 1025 (22.0)	188 / 1010 (18.6)	1.18	[1.00; 1.41]	0.055
Lobular	71 / 291 (24.4)	54 / 276 (19.6)	1.25	[0.91; 1.71]	0.167
Other	19 / 92 (20.7)	13 / 76 (17.1)	1.21	[0.64; 2.28]	0.562
Ki67 status from surgical specimen					
Interaction test	p = 0.333				
Ki67≤20	141 / 660 (21.4)	110 / 629 (17.5)	1.22	[0.98; 1.53]	0.080
Ki67>20	91 / 489 (18.6)	93 / 516 (18.0)	1.03	[0.80; 1.34]	0.810
Type of NSAI					
Interaction test	p = 0.418				
Letrozole	184 / 907 (20.3)	159 / 895 (17.8)	1.14	[0.94; 1.38]	0.173
Anastrozole	132 / 502 (26.3)	96 / 467 (20.6)	1.28	[1.02; 1.61]	0.037
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.387				
Yes	267 / 1194 (22.4)	220 / 1146 (19.2)	1.16	[0.99; 1.37]	0.060
No	49 / 215 (22.8)	35 / 216 (16.2)	1.41	[0.95; 2.08]	0.087
Prior adjuvant chemotherapy					
Interaction test	p = 0.544				
Yes	164 / 694 (23.6)	139 / 673 (20.7)	1.14	[0.94; 1.40]	0.186
No	152 / 715 (21.3)	116 / 689 (16.8)	1.26	[1.02; 1.57]	0.036

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.782				
Yes	108 / 528 (20.5)	88 / 503 (17.5)	1.17	[0.91; 1.51]	0.227
No	208 / 881 (23.6)	167 / 859 (19.4)	1.21	[1.01; 1.45]	0.035
Prior endocrine therapy					
Interaction test	p = 0.562				
Yes	223 / 957 (23.3)	188 / 940 (20.0)	1.17	[0.98; 1.38]	0.082
No	93 / 452 (20.6)	67 / 422 (15.9)	1.30	[0.97; 1.72]	0.074
Prior mastectomy					
Interaction test	p = 0.880				
Yes	185 / 857 (21.6)	154 / 847 (18.2)	1.19	[0.98; 1.44]	0.079
No	131 / 552 (23.7)	101 / 515 (19.6)	1.21	[0.96; 1.52]	0.104
Prior radiotherapy					
Interaction test	p = 0.914				
Yes	288 / 1253 (23.0)	232 / 1203 (19.3)	1.19	[1.02; 1.39]	0.025
No	28 / 156 (17.9)	23 / 159 (14.5)	1.24	[0.75; 2.06]	0.403
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.82 PT depression: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Depression					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.140				
NA/WE/O	56 / 899 (6.2)	37 / 856 (4.3)	1.44	[0.96; 2.16]	0.077
ROW	12 / 510 (2.4)	3 / 506 (0.6)	3.97	[1.13; 13.98]	0.032
Geographical region					
Interaction test	p = 0.226				
Europe	39 / 832 (4.7)	19 / 824 (2.3)	2.03	[1.18; 3.49]	0.010
North America/Australia	24 / 400 (6.0)	19 / 364 (5.2)	1.15	[0.64; 2.06]	0.641
Asia	0 / 102 (0.0)	1 / 101 (1.0)	0.33	[0.01; 8.01]	0.496
Latin America	5 / 75 (6.7)	1 / 73 (1.4)	4.87	[0.58; 40.65]	0.144
Age group 1 at randomization					
Interaction test	p = 0.830				
<45	5 / 60 (8.3)	3 / 52 (5.8)	1.44	[0.36; 5.76]	0.602
45 to 54	17 / 300 (5.7)	12 / 322 (3.7)	1.52	[0.74; 3.13]	0.255
55 to 64	31 / 651 (4.8)	15 / 642 (2.3)	2.04	[1.11; 3.74]	0.021
≥65	15 / 398 (3.8)	10 / 346 (2.9)	1.30	[0.59; 2.86]	0.509
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.480				
<Median	35 / 633 (5.5)	24 / 632 (3.8)	1.46	[0.88; 2.42]	0.147
≥Median	33 / 776 (4.3)	16 / 730 (2.2)	1.94	[1.08; 3.49]	0.027
Race					
Interaction test	p = 0.711				
Asian	1 / 128 (0.8)	1 / 127 (0.8)	0.99	[0.06; 15.69]	0.996
Non-Asian	63 / 1203 (5.2)	37 / 1167 (3.2)	1.65	[1.11; 2.46]	0.013
BMI at screening					
Interaction test	p = 0.094				
≥25	43 / 935 (4.6)	33 / 935 (3.5)	1.30	[0.84; 2.03]	0.243
<25	23 / 460 (5.0)	7 / 410 (1.7)	2.93	[1.27; 6.75]	0.012
AJCC Anatomic Stage Group					
Interaction test	p = 0.980				
Group I/II	39 / 585 (6.7)	24 / 589 (4.1)	1.64	[1.00; 2.69]	0.051
Group III	28 / 823 (3.4)	16 / 772 (2.1)	1.64	[0.90; 3.01]	0.109

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.303				
IA/IB/IIA	22 / 310 (7.1)	8 / 311 (2.6)	2.76	[1.25; 6.10]	0.012
IIB	17 / 275 (6.2)	16 / 278 (5.8)	1.07	[0.55; 2.08]	0.832
IIIA	19 / 482 (3.9)	9 / 450 (2.0)	1.97	[0.90; 4.31]	0.089
IIIB	0 / 100 (0.0)	0 / 82 (0.0)	N.E.	N.E.	N.E.
IIIC	9 / 241 (3.7)	7 / 240 (2.9)	1.28	[0.48; 3.38]	0.618
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	1 / 5 (20.0)	0.33	[0.02; 6.65]	0.472
T1-T3	67 / 1287 (5.2)	38 / 1258 (3.0)	1.72	[1.17; 2.55]	0.006
>T3	0 / 113 (0.0)	1 / 97 (1.0)	0.29	[0.01; 6.95]	0.442
Nodal status					
Interaction test	p = 0.852				
N0	15 / 190 (7.9)	9 / 200 (4.5)	1.75	[0.79; 3.91]	0.170
N1-N3	53 / 1216 (4.4)	31 / 1160 (2.7)	1.63	[1.05; 2.52]	0.028
Histological grade at time of surgery					
Interaction test	p = 0.847				
Grade 1	6 / 102 (5.9)	4 / 106 (3.8)	1.56	[0.45; 5.36]	0.481
Grade 2	34 / 842 (4.0)	20 / 768 (2.6)	1.55	[0.90; 2.67]	0.114
Grade 3	24 / 373 (6.4)	13 / 397 (3.3)	1.96	[1.02; 3.80]	0.045
Histological subtype					
Interaction test	p = 0.269				
Ductal	50 / 1025 (4.9)	25 / 1010 (2.5)	1.97	[1.23; 3.16]	0.005
Lobular	15 / 291 (5.2)	11 / 276 (4.0)	1.29	[0.60; 2.77]	0.507
Other	3 / 92 (3.3)	4 / 76 (5.3)	0.62	[0.14; 2.68]	0.522
Ki67 status from surgical specimen					
Interaction test	p = 0.935				
Ki67≤20	27 / 660 (4.1)	16 / 629 (2.5)	1.61	[0.88; 2.96]	0.126
Ki67>20	22 / 489 (4.5)	15 / 516 (2.9)	1.55	[0.81; 2.95]	0.184
Type of NSAI					
Interaction test	p = 0.705				
Letrozole	44 / 907 (4.9)	25 / 895 (2.8)	1.74	[1.07; 2.81]	0.025
Anastrozole	24 / 502 (4.8)	15 / 467 (3.2)	1.49	[0.79; 2.80]	0.218
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.908				
Yes	56 / 1194 (4.7)	33 / 1146 (2.9)	1.63	[1.07; 2.48]	0.024
No	12 / 215 (5.6)	7 / 216 (3.2)	1.72	[0.69; 4.29]	0.243
Prior adjuvant chemotherapy					
Interaction test	p = 0.598				
Yes	39 / 694 (5.6)	21 / 673 (3.1)	1.80	[1.07; 3.03]	0.027
No	29 / 715 (4.1)	19 / 689 (2.8)	1.47	[0.83; 2.60]	0.184

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.232				
Yes	17 / 528 (3.2)	14 / 503 (2.8)	1.16	[0.58; 2.32]	0.682
No	51 / 881 (5.8)	26 / 859 (3.0)	1.91	[1.20; 3.04]	0.006
Prior endocrine therapy					
Interaction test	p = 0.116				
Yes	46 / 957 (4.8)	33 / 940 (3.5)	1.37	[0.88; 2.12]	0.160
No	22 / 452 (4.9)	7 / 422 (1.7)	2.93	[1.27; 6.80]	0.012
Prior mastectomy					
Interaction test	p = 0.584				
Yes	38 / 857 (4.4)	25 / 847 (3.0)	1.50	[0.92; 2.47]	0.108
No	30 / 552 (5.4)	15 / 515 (2.9)	1.87	[1.02; 3.43]	0.044
Prior radiotherapy					
Interaction test	p = 0.990				
Yes	60 / 1253 (4.8)	35 / 1203 (2.9)	1.65	[1.09; 2.48]	0.017
No	8 / 156 (5.1)	5 / 159 (3.1)	1.63	[0.55; 4.88]	0.382
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.83 PT fall: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Fall					
	n / N (%)	n / N (%)			
Region					
Interaction test	N.E.				
NA/WE/O	18 / 899 (2.0)	31 / 856 (3.6)	0.55	[0.31; 0.98]	0.043
ROW	0 / 510 (0.0)	3 / 506 (0.6)	0.14	[<0.01; 2.74]	0.196
Geographical region					
Interaction test	p = 0.897				
Europe	4 / 832 (0.5)	7 / 824 (0.8)	0.57	[0.17; 1.93]	0.362
North America/Australia	14 / 400 (3.5)	24 / 364 (6.6)	0.53	[0.28; 1.01]	0.054
Asia	0 / 102 (0.0)	0 / 101 (0.0)	N.E.	N.E.	N.E.
Latin America	0 / 75 (0.0)	3 / 73 (4.1)	0.14	[<0.01; 2.65]	0.189
Age group 1 at randomization					
Interaction test	p = 0.462				
<45	0 / 60 (0.0)	0 / 52 (0.0)	N.E.	N.E.	N.E.
45 to 54	3 / 300 (1.0)	7 / 322 (2.2)	0.46	[0.12; 1.76]	0.257
55 to 64	6 / 651 (0.9)	17 / 642 (2.6)	0.35	[0.14; 0.88]	0.025
≥65	9 / 398 (2.3)	10 / 346 (2.9)	0.78	[0.32; 1.90]	0.589
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.070				
<Median	4 / 633 (0.6)	17 / 632 (2.7)	0.23	[0.08; 0.69]	0.009
≥Median	14 / 776 (1.8)	17 / 730 (2.3)	0.77	[0.38; 1.56]	0.475
Race					
Interaction test	p = 0.645				
Asian	1 / 128 (0.8)	1 / 127 (0.8)	0.99	[0.06; 15.69]	0.996
Non-Asian	17 / 1203 (1.4)	32 / 1167 (2.7)	0.52	[0.29; 0.92]	0.026
BMI at screening					
Interaction test	p = 0.304				
≥25	13 / 935 (1.4)	22 / 935 (2.4)	0.59	[0.30; 1.17]	0.129
<25	4 / 460 (0.9)	12 / 410 (2.9)	0.30	[0.10; 0.91]	0.034
AJCC Anatomic Stage Group					
Interaction test	p = 0.789				
Group I/II	8 / 585 (1.4)	17 / 589 (2.9)	0.47	[0.21; 1.09]	0.079
Group III	10 / 823 (1.2)	17 / 772 (2.2)	0.55	[0.25; 1.20]	0.133

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.816				
IA/IB/IIA	5 / 310 (1.6)	8 / 311 (2.6)	0.63	[0.21; 1.90]	0.408
IIB	3 / 275 (1.1)	9 / 278 (3.2)	0.34	[0.09; 1.23]	0.100
IIIA	6 / 482 (1.2)	11 / 450 (2.4)	0.51	[0.19; 1.37]	0.180
IIIB	0 / 100 (0.0)	1 / 82 (1.2)	0.27	[0.01; 6.64]	0.426
IIIC	4 / 241 (1.7)	5 / 240 (2.1)	0.80	[0.22; 2.93]	0.732
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	18 / 1287 (1.4)	33 / 1258 (2.6)	0.53	[0.30; 0.94]	0.030
>T3	0 / 113 (0.0)	1 / 97 (1.0)	0.29	[0.01; 6.95]	0.442
Nodal status					
Interaction test	N.E.				
N0	0 / 190 (0.0)	4 / 200 (2.0)	0.12	[<0.01; 2.16]	0.149
N1-N3	18 / 1216 (1.5)	30 / 1160 (2.6)	0.57	[0.32; 1.02]	0.059
Histological grade at time of surgery					
Interaction test	p = 0.156				
Grade 1	0 / 102 (0.0)	2 / 106 (1.9)	0.21	[0.01; 4.28]	0.309
Grade 2	9 / 842 (1.1)	21 / 768 (2.7)	0.39	[0.18; 0.85]	0.017
Grade 3	8 / 373 (2.1)	9 / 397 (2.3)	0.95	[0.37; 2.43]	0.908
Histological subtype					
Interaction test	p = 0.646				
Ductal	14 / 1025 (1.4)	24 / 1010 (2.4)	0.57	[0.30; 1.10]	0.097
Lobular	4 / 291 (1.4)	9 / 276 (3.3)	0.42	[0.13; 1.35]	0.147
Other	0 / 92 (0.0)	1 / 76 (1.3)	0.28	[0.01; 6.68]	0.428
Ki67 status from surgical specimen					
Interaction test	p = 0.193				
Ki67≤20	1 / 660 (0.2)	7 / 629 (1.1)	0.14	[0.02; 1.10]	0.062
Ki67>20	5 / 489 (1.0)	8 / 516 (1.6)	0.66	[0.22; 2.00]	0.463
Type of NSAI					
Interaction test	p = 0.475				
Letrozole	9 / 907 (1.0)	21 / 895 (2.3)	0.42	[0.19; 0.92]	0.030
Anastrozole	9 / 502 (1.8)	13 / 467 (2.8)	0.64	[0.28; 1.49]	0.305
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.757				
Yes	16 / 1194 (1.3)	29 / 1146 (2.5)	0.53	[0.29; 0.97]	0.039
No	2 / 215 (0.9)	5 / 216 (2.3)	0.40	[0.08; 2.05]	0.273
Prior adjuvant chemotherapy					
Interaction test	p = 0.176				
Yes	14 / 694 (2.0)	20 / 673 (3.0)	0.68	[0.35; 1.33]	0.260
No	4 / 715 (0.6)	14 / 689 (2.0)	0.28	[0.09; 0.83]	0.022

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.201				
Yes	2 / 528 (0.4)	9 / 503 (1.8)	0.21	[0.05; 0.98]	0.046
No	16 / 881 (1.8)	25 / 859 (2.9)	0.62	[0.34; 1.16]	0.136
Prior endocrine therapy					
Interaction test	p = 0.659				
Yes	12 / 957 (1.3)	21 / 940 (2.2)	0.56	[0.28; 1.13]	0.108
No	6 / 452 (1.3)	13 / 422 (3.1)	0.43	[0.17; 1.12]	0.085
Prior mastectomy					
Interaction test	p = 0.736				
Yes	10 / 857 (1.2)	21 / 847 (2.5)	0.47	[0.22; 0.99]	0.048
No	8 / 552 (1.4)	13 / 515 (2.5)	0.57	[0.24; 1.37]	0.213
Prior radiotherapy					
Interaction test	p = 0.715				
Yes	17 / 1253 (1.4)	31 / 1203 (2.6)	0.53	[0.29; 0.95]	0.032
No	1 / 156 (0.6)	3 / 159 (1.9)	0.34	[0.04; 3.23]	0.348
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.84 SOC reproductive system and breast disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Reproductive system and breast disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.967				
NA/WE/O	125 / 899 (13.9)	146 / 856 (17.1)	0.82	[0.65; 1.02]	0.068
ROW	40 / 510 (7.8)	49 / 506 (9.7)	0.81	[0.54; 1.21]	0.301
Geographical region					
Interaction test	p = 0.419				
Europe	99 / 832 (11.9)	108 / 824 (13.1)	0.91	[0.70; 1.17]	0.458
North America/Australia	54 / 400 (13.5)	69 / 364 (19.0)	0.71	[0.51; 0.99]	0.042
Asia	3 / 102 (2.9)	8 / 101 (7.9)	0.37	[0.10; 1.36]	0.135
Latin America	9 / 75 (12.0)	10 / 73 (13.7)	0.88	[0.38; 2.03]	0.758
Age group 1 at randomization					
Interaction test	p = 0.394				
<45	11 / 60 (18.3)	13 / 52 (25.0)	0.73	[0.36; 1.49]	0.393
45 to 54	35 / 300 (11.7)	59 / 322 (18.3)	0.64	[0.43; 0.94]	0.022
55 to 64	81 / 651 (12.4)	90 / 642 (14.0)	0.89	[0.67; 1.17]	0.403
≥65	38 / 398 (9.5)	33 / 346 (9.5)	1.00	[0.64; 1.56]	0.996
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.474				
<Median	80 / 633 (12.6)	104 / 632 (16.5)	0.77	[0.59; 1.01]	0.055
≥Median	85 / 776 (11.0)	91 / 730 (12.5)	0.88	[0.67; 1.16]	0.362
Race					
Interaction test	p = 0.423				
Asian	8 / 128 (6.3)	14 / 127 (11.0)	0.57	[0.25; 1.30]	0.182
Non-Asian	141 / 1203 (11.7)	168 / 1167 (14.4)	0.81	[0.66; 1.00]	0.054
BMI at screening					
Interaction test	p = 0.262				
≥25	115 / 935 (12.3)	131 / 935 (14.0)	0.88	[0.70; 1.11]	0.274
<25	47 / 460 (10.2)	61 / 410 (14.9)	0.69	[0.48; 0.98]	0.039
AJCC Anatomic Stage Group					
Interaction test	p = 0.981				
Group I/II	71 / 585 (12.1)	87 / 589 (14.8)	0.82	[0.61; 1.10]	0.187
Group III	94 / 823 (11.4)	108 / 772 (14.0)	0.82	[0.63; 1.06]	0.124

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.222				
IA/IB/IIA	40 / 310 (12.9)	42 / 311 (13.5)	0.96	[0.64; 1.43]	0.825
IIB	31 / 275 (11.3)	45 / 278 (16.2)	0.70	[0.45; 1.07]	0.096
IIIA	53 / 482 (11.0)	75 / 450 (16.7)	0.66	[0.48; 0.92]	0.013
IIIB	15 / 100 (15.0)	13 / 82 (15.9)	0.95	[0.48; 1.87]	0.874
IIIC	26 / 241 (10.8)	20 / 240 (8.3)	1.29	[0.74; 2.25]	0.362
Tumor category					
Interaction test	p = 0.715				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	149 / 1287 (11.6)	181 / 1258 (14.4)	0.80	[0.66; 0.99]	0.035
>T3	15 / 113 (13.3)	14 / 97 (14.4)	0.92	[0.47; 1.81]	0.808
Nodal status					
Interaction test	p = 0.461				
N0	19 / 190 (10.0)	20 / 200 (10.0)	1.00	[0.55; 1.81]	1.000
N1-N3	146 / 1216 (12.0)	175 / 1160 (15.1)	0.80	[0.65; 0.98]	0.029
Histological grade at time of surgery					
Interaction test	p = 0.905				
Grade 1	13 / 102 (12.7)	18 / 106 (17.0)	0.75	[0.39; 1.45]	0.394
Grade 2	98 / 842 (11.6)	107 / 768 (13.9)	0.84	[0.65; 1.08]	0.169
Grade 3	41 / 373 (11.0)	57 / 397 (14.4)	0.77	[0.53; 1.11]	0.163
Histological subtype					
Interaction test	p = 0.642				
Ductal	122 / 1025 (11.9)	145 / 1010 (14.4)	0.83	[0.66; 1.04]	0.102
Lobular	34 / 291 (11.7)	38 / 276 (13.8)	0.85	[0.55; 1.31]	0.457
Other	8 / 92 (8.7)	12 / 76 (15.8)	0.55	[0.24; 1.28]	0.165
Ki67 status from surgical specimen					
Interaction test	p = 0.364				
Ki67≤20	67 / 660 (10.2)	92 / 629 (14.6)	0.69	[0.52; 0.93]	0.015
Ki67>20	51 / 489 (10.4)	63 / 516 (12.2)	0.85	[0.60; 1.21]	0.375
Type of NSAI					
Interaction test	p = 0.374				
Letrozole	107 / 907 (11.8)	121 / 895 (13.5)	0.87	[0.68; 1.11]	0.272
Anastrozole	58 / 502 (11.6)	74 / 467 (15.8)	0.73	[0.53; 1.00]	0.053
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.474				
Yes	139 / 1194 (11.6)	168 / 1146 (14.7)	0.79	[0.64; 0.98]	0.031
No	26 / 215 (12.1)	27 / 216 (12.5)	0.97	[0.58; 1.60]	0.898
Prior adjuvant chemotherapy					
Interaction test	p = 0.972				
Yes	83 / 694 (12.0)	98 / 673 (14.6)	0.82	[0.63; 1.08]	0.157
No	82 / 715 (11.5)	97 / 689 (14.1)	0.81	[0.62; 1.07]	0.144

Treatment Groups			Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.724				
Yes	59 / 528 (11.2)	72 / 503 (14.3)	0.78	[0.57; 1.08]	0.131
No	106 / 881 (12.0)	123 / 859 (14.3)	0.84	[0.66; 1.07]	0.159
Prior endocrine therapy					
Interaction test	p = 0.082				
Yes	118 / 957 (12.3)	126 / 940 (13.4)	0.92	[0.73; 1.16]	0.485
No	47 / 452 (10.4)	69 / 422 (16.4)	0.64	[0.45; 0.90]	0.010
Prior mastectomy					
Interaction test	p = 0.510				
Yes	85 / 857 (9.9)	110 / 847 (13.0)	0.76	[0.58; 1.00]	0.048
No	80 / 552 (14.5)	85 / 515 (16.5)	0.88	[0.66; 1.16]	0.364
Prior radiotherapy					
Interaction test	p = 0.871				
Yes	149 / 1253 (11.9)	174 / 1203 (14.5)	0.82	[0.67; 1.01]	0.060
No	16 / 156 (10.3)	21 / 159 (13.2)	0.78	[0.42; 1.43]	0.418
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.85 SOC eye disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Eye disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.075				
NA/WE/O	133 / 899 (14.8)	66 / 856 (7.7)	1.92	[1.45; 2.54]	<.001
ROW	49 / 510 (9.6)	39 / 506 (7.7)	1.25	[0.83; 1.86]	0.283
Geographical region					
Interaction test	p = 0.998				
Europe	93 / 832 (11.2)	54 / 824 (6.6)	1.71	[1.24; 2.35]	0.001
North America/Australia	72 / 400 (18.0)	41 / 364 (11.3)	1.60	[1.12; 2.28]	0.010
Asia	8 / 102 (7.8)	5 / 101 (5.0)	1.58	[0.54; 4.68]	0.405
Latin America	9 / 75 (12.0)	5 / 73 (6.8)	1.75	[0.62; 4.98]	0.293
Age group 1 at randomization					
Interaction test	p = 0.190				
<45	11 / 60 (18.3)	1 / 52 (1.9)	9.53	[1.27; 71.37]	0.028
45 to 54	34 / 300 (11.3)	18 / 322 (5.6)	2.03	[1.17; 3.51]	0.012
55 to 64	81 / 651 (12.4)	49 / 642 (7.6)	1.63	[1.16; 2.28]	0.005
≥65	56 / 398 (14.1)	37 / 346 (10.7)	1.32	[0.89; 1.94]	0.167
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.480				
<Median	73 / 633 (11.5)	39 / 632 (6.2)	1.87	[1.29; 2.71]	0.001
≥Median	109 / 776 (14.0)	66 / 730 (9.0)	1.55	[1.16; 2.07]	0.003
Race					
Interaction test	p = 0.667				
Asian	14 / 128 (10.9)	10 / 127 (7.9)	1.39	[0.64; 3.01]	0.405
Non-Asian	155 / 1203 (12.9)	91 / 1167 (7.8)	1.65	[1.29; 2.11]	<.001
BMI at screening					
Interaction test	p = 0.494				
≥25	121 / 935 (12.9)	76 / 935 (8.1)	1.59	[1.21; 2.09]	<.001
<25	58 / 460 (12.6)	27 / 410 (6.6)	1.91	[1.24; 2.96]	0.004
AJCC Anatomic Stage Group					
Interaction test	p = 0.897				
Group I/II	72 / 585 (12.3)	44 / 589 (7.5)	1.65	[1.15; 2.35]	0.006
Group III	110 / 823 (13.4)	61 / 772 (7.9)	1.69	[1.26; 2.28]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.350				
IA/IB/IIA	39 / 310 (12.6)	20 / 311 (6.4)	1.96	[1.17; 3.28]	0.011
IIB	33 / 275 (12.0)	24 / 278 (8.6)	1.39	[0.84; 2.29]	0.196
IIIA	56 / 482 (11.6)	33 / 450 (7.3)	1.58	[1.05; 2.39]	0.028
IIIB	15 / 100 (15.0)	12 / 82 (14.6)	1.03	[0.51; 2.07]	0.945
IIIC	39 / 241 (16.2)	16 / 240 (6.7)	2.43	[1.40; 4.22]	0.002
Tumor category					
Interaction test	p = 0.475				
T0	1 / 5 (20.0)	0 / 5 (0.0)	3.00	[0.15; 59.89]	0.472
T1-T3	163 / 1287 (12.7)	93 / 1258 (7.4)	1.71	[1.34; 2.18]	<.001
>T3	18 / 113 (15.9)	12 / 97 (12.4)	1.29	[0.65; 2.54]	0.465
Nodal status					
Interaction test	p = 0.298				
N0	24 / 190 (12.6)	20 / 200 (10.0)	1.26	[0.72; 2.21]	0.413
N1-N3	157 / 1216 (12.9)	85 / 1160 (7.3)	1.76	[1.37; 2.27]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.457				
Grade 1	13 / 102 (12.7)	8 / 106 (7.5)	1.69	[0.73; 3.90]	0.220
Grade 2	100 / 842 (11.9)	61 / 768 (7.9)	1.50	[1.10; 2.02]	0.009
Grade 3	58 / 373 (15.5)	30 / 397 (7.6)	2.06	[1.36; 3.12]	<.001
Histological subtype					
Interaction test	p = 0.872				
Ductal	133 / 1025 (13.0)	81 / 1010 (8.0)	1.62	[1.24; 2.10]	<.001
Lobular	36 / 291 (12.4)	18 / 276 (6.5)	1.90	[1.10; 3.26]	0.020
Other	13 / 92 (14.1)	6 / 76 (7.9)	1.79	[0.71; 4.48]	0.214
Ki67 status from surgical specimen					
Interaction test	p = 0.128				
Ki67≤20	75 / 660 (11.4)	55 / 629 (8.7)	1.30	[0.93; 1.81]	0.120
Ki67>20	58 / 489 (11.9)	31 / 516 (6.0)	1.97	[1.30; 3.00]	0.001
Type of NSAI					
Interaction test	p = 0.991				
Letrozole	109 / 907 (12.0)	64 / 895 (7.2)	1.68	[1.25; 2.26]	<.001
Anastrozole	73 / 502 (14.5)	41 / 467 (8.8)	1.66	[1.15; 2.38]	0.006
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.173				
Yes	156 / 1194 (13.1)	83 / 1146 (7.2)	1.80	[1.40; 2.32]	<.001
No	26 / 215 (12.1)	22 / 216 (10.2)	1.19	[0.70; 2.03]	0.530
Prior adjuvant chemotherapy					
Interaction test	p = 0.623				
Yes	93 / 694 (13.4)	57 / 673 (8.5)	1.58	[1.16; 2.16]	0.004
No	89 / 715 (12.4)	48 / 689 (7.0)	1.79	[1.28; 2.50]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.046				
Yes	70 / 528 (13.3)	28 / 503 (5.6)	2.38	[1.56; 3.63]	<.001
No	112 / 881 (12.7)	77 / 859 (9.0)	1.42	[1.08; 1.87]	0.013
Prior endocrine therapy					
Interaction test	p = 0.725				
Yes	118 / 957 (12.3)	67 / 940 (7.1)	1.73	[1.30; 2.30]	<.001
No	64 / 452 (14.2)	38 / 422 (9.0)	1.57	[1.08; 2.30]	0.019
Prior mastectomy					
Interaction test	p = 0.962				
Yes	114 / 857 (13.3)	67 / 847 (7.9)	1.68	[1.26; 2.24]	<.001
No	68 / 552 (12.3)	38 / 515 (7.4)	1.67	[1.14; 2.44]	0.008
Prior radiotherapy					
Interaction test	p = 0.214				
Yes	160 / 1253 (12.8)	86 / 1203 (7.1)	1.79	[1.39; 2.29]	<.001
No	22 / 156 (14.1)	19 / 159 (11.9)	1.18	[0.67; 2.09]	0.571
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.86 PT dry eye: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Dry eye					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.456				
NA/WE/O	44 / 899 (4.9)	20 / 856 (2.3)	2.09	[1.25; 3.52]	0.005
ROW	5 / 510 (1.0)	1 / 506 (0.2)	4.96	[0.58; 42.31]	0.143
Geographical region					
Interaction test	p = 0.512				
Europe	19 / 832 (2.3)	6 / 824 (0.7)	3.14	[1.26; 7.81]	0.014
North America/Australia	25 / 400 (6.3)	14 / 364 (3.8)	1.63	[0.86; 3.08]	0.136
Asia	3 / 102 (2.9)	1 / 101 (1.0)	2.97	[0.31; 28.08]	0.342
Latin America	2 / 75 (2.7)	0 / 73 (0.0)	4.87	[0.24; 99.70]	0.304
Age group 1 at randomization					
Interaction test	p = 0.341				
<45	3 / 60 (5.0)	1 / 52 (1.9)	2.60	[0.28; 24.24]	0.402
45 to 54	11 / 300 (3.7)	2 / 322 (0.6)	5.90	[1.32; 26.41]	0.020
55 to 64	21 / 651 (3.2)	14 / 642 (2.2)	1.48	[0.76; 2.88]	0.250
≥65	14 / 398 (3.5)	4 / 346 (1.2)	3.04	[1.01; 9.16]	0.048
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.338				
<Median	24 / 633 (3.8)	8 / 632 (1.3)	3.00	[1.36; 6.62]	0.007
≥Median	25 / 776 (3.2)	13 / 730 (1.8)	1.81	[0.93; 3.51]	0.079
Race					
Interaction test	p = 0.916				
Asian	6 / 128 (4.7)	3 / 127 (2.4)	1.98	[0.51; 7.76]	0.325
Non-Asian	38 / 1203 (3.2)	17 / 1167 (1.5)	2.17	[1.23; 3.82]	0.007
BMI at screening					
Interaction test	p = 0.063				
≥25	26 / 935 (2.8)	16 / 935 (1.7)	1.63	[0.88; 3.01]	0.122
<25	23 / 460 (5.0)	4 / 410 (1.0)	5.13	[1.79; 14.70]	0.002
AJCC Anatomic Stage Group					
Interaction test	p = 0.245				
Group I/II	22 / 585 (3.8)	13 / 589 (2.2)	1.70	[0.87; 3.35]	0.122
Group III	27 / 823 (3.3)	8 / 772 (1.0)	3.17	[1.45; 6.93]	0.004

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.581				
IA/IB/IIA	12 / 310 (3.9)	7 / 311 (2.3)	1.72	[0.69; 4.31]	0.247
IIB	10 / 275 (3.6)	6 / 278 (2.2)	1.68	[0.62; 4.57]	0.306
IIIA	14 / 482 (2.9)	6 / 450 (1.3)	2.18	[0.84; 5.62]	0.107
IIIB	2 / 100 (2.0)	0 / 82 (0.0)	4.11	[0.20; 84.40]	0.359
IIIC	11 / 241 (4.6)	2 / 240 (0.8)	5.48	[1.23; 24.45]	0.026
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	46 / 1287 (3.6)	21 / 1258 (1.7)	2.14	[1.29; 3.57]	0.003
>T3	3 / 113 (2.7)	0 / 97 (0.0)	6.02	[0.31; >99.99]	0.233
Nodal status					
Interaction test	p = 0.244				
N0	4 / 190 (2.1)	4 / 200 (2.0)	1.05	[0.27; 4.15]	0.942
N1-N3	45 / 1216 (3.7)	17 / 1160 (1.5)	2.53	[1.45; 4.39]	0.001
Histological grade at time of surgery					
Interaction test	p = 0.713				
Grade 1	6 / 102 (5.9)	0 / 106 (0.0)	13.50	[0.77; >99.99]	0.075
Grade 2	23 / 842 (2.7)	12 / 768 (1.6)	1.75	[0.88; 3.49]	0.113
Grade 3	16 / 373 (4.3)	8 / 397 (2.0)	2.13	[0.92; 4.92]	0.077
Histological subtype					
Interaction test	p = 0.751				
Ductal	37 / 1025 (3.6)	16 / 1010 (1.6)	2.28	[1.28; 4.07]	0.005
Lobular	7 / 291 (2.4)	4 / 276 (1.4)	1.66	[0.49; 5.61]	0.415
Other	5 / 92 (5.4)	1 / 76 (1.3)	4.13	[0.49; 34.60]	0.191
Ki67 status from surgical specimen					
Interaction test	p = 0.049				
Ki67≤20	25 / 660 (3.8)	7 / 629 (1.1)	3.40	[1.48; 7.81]	0.004
Ki67>20	7 / 489 (1.4)	8 / 516 (1.6)	0.92	[0.34; 2.53]	0.877
Type of NSAI					
Interaction test	p = 0.446				
Letrozole	32 / 907 (3.5)	12 / 895 (1.3)	2.63	[1.36; 5.08]	0.004
Anastrozole	17 / 502 (3.4)	9 / 467 (1.9)	1.76	[0.79; 3.90]	0.166
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.253				
Yes	43 / 1194 (3.6)	16 / 1146 (1.4)	2.58	[1.46; 4.55]	0.001
No	6 / 215 (2.8)	5 / 216 (2.3)	1.21	[0.37; 3.89]	0.754
Prior adjuvant chemotherapy					
Interaction test	p = 0.410				
Yes	25 / 694 (3.6)	13 / 673 (1.9)	1.86	[0.96; 3.61]	0.065
No	24 / 715 (3.4)	8 / 689 (1.2)	2.89	[1.31; 6.39]	0.009

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.121				
Yes	19 / 528 (3.6)	4 / 503 (0.8)	4.53	[1.55; 13.21]	0.006
No	30 / 881 (3.4)	17 / 859 (2.0)	1.72	[0.96; 3.10]	0.070
Prior endocrine therapy					
Interaction test	p = 0.973				
Yes	37 / 957 (3.9)	16 / 940 (1.7)	2.27	[1.27; 4.05]	0.006
No	12 / 452 (2.7)	5 / 422 (1.2)	2.24	[0.80; 6.31]	0.126
Prior mastectomy					
Interaction test	p = 0.880				
Yes	26 / 857 (3.0)	11 / 847 (1.3)	2.34	[1.16; 4.70]	0.017
No	23 / 552 (4.2)	10 / 515 (1.9)	2.15	[1.03; 4.46]	0.041
Prior radiotherapy					
Interaction test	p = 0.207				
Yes	48 / 1253 (3.8)	19 / 1203 (1.6)	2.43	[1.43; 4.10]	<.001
No	1 / 156 (0.6)	2 / 159 (1.3)	0.51	[0.05; 5.56]	0.580
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.87 PT lacrimation increased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Lacrimation increased					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.470				
NA/WE/O	30 / 899 (3.3)	6 / 856 (0.7)	4.76	[1.99; 11.38]	<.001
ROW	18 / 510 (3.5)	6 / 506 (1.2)	2.98	[1.19; 7.44]	0.020
Geographical region					
Interaction test	p = 0.596				
Europe	30 / 832 (3.6)	9 / 824 (1.1)	3.30	[1.58; 6.91]	0.002
North America/Australia	16 / 400 (4.0)	3 / 364 (0.8)	4.85	[1.43; 16.52]	0.011
Asia	0 / 102 (0.0)	0 / 101 (0.0)	N.E.	N.E.	N.E.
Latin America	2 / 75 (2.7)	0 / 73 (0.0)	4.87	[0.24; 99.70]	0.304
Age group 1 at randomization					
Interaction test	p = 0.606				
<45	1 / 60 (1.7)	0 / 52 (0.0)	2.61	[0.11; 62.64]	0.555
45 to 54	5 / 300 (1.7)	1 / 322 (0.3)	5.37	[0.63; 45.67]	0.124
55 to 64	28 / 651 (4.3)	6 / 642 (0.9)	4.60	[1.92; 11.04]	<.001
≥65	14 / 398 (3.5)	5 / 346 (1.4)	2.43	[0.89; 6.69]	0.085
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.629				
<Median	15 / 633 (2.4)	3 / 632 (0.5)	4.99	[1.45; 17.16]	0.011
≥Median	33 / 776 (4.3)	9 / 730 (1.2)	3.45	[1.66; 7.16]	<.001
Race					
Interaction test	p = 0.332				
Asian	1 / 128 (0.8)	1 / 127 (0.8)	0.99	[0.06; 15.69]	0.996
Non-Asian	45 / 1203 (3.7)	11 / 1167 (0.9)	3.97	[2.06; 7.63]	<.001
BMI at screening					
Interaction test	p = 0.715				
≥25	32 / 935 (3.4)	8 / 935 (0.9)	4.00	[1.85; 8.63]	<.001
<25	14 / 460 (3.0)	4 / 410 (1.0)	3.12	[1.04; 9.40]	0.043
AJCC Anatomic Stage Group					
Interaction test	p = 0.066				
Group I/II	22 / 585 (3.8)	2 / 589 (0.3)	11.08	[2.62; 46.89]	0.001
Group III	26 / 823 (3.2)	10 / 772 (1.3)	2.44	[1.18; 5.02]	0.016

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.112				
IA/IB/IIA	10 / 310 (3.2)	1 / 311 (0.3)	10.03	[1.29; 77.90]	0.027
IIB	12 / 275 (4.4)	1 / 278 (0.4)	12.13	[1.59; 92.66]	0.016
IIIA	8 / 482 (1.7)	6 / 450 (1.3)	1.24	[0.44; 3.56]	0.683
IIIB	4 / 100 (4.0)	0 / 82 (0.0)	7.40	[0.40; >99.99]	0.177
IIIC	14 / 241 (5.8)	4 / 240 (1.7)	3.49	[1.16; 10.44]	0.026
Tumor category					
Interaction test	N.E.				
T0	1 / 5 (20.0)	0 / 5 (0.0)	3.00	[0.15; 59.89]	0.472
T1-T3	42 / 1287 (3.3)	12 / 1258 (1.0)	3.42	[1.81; 6.47]	<.001
>T3	5 / 113 (4.4)	0 / 97 (0.0)	9.46	[0.53; >99.99]	0.127
Nodal status					
Interaction test	N.E.				
N0	8 / 190 (4.2)	0 / 200 (0.0)	17.89	[1.04; >99.99]	0.047
N1-N3	40 / 1216 (3.3)	12 / 1160 (1.0)	3.18	[1.68; 6.03]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.726				
Grade 1	3 / 102 (2.9)	1 / 106 (0.9)	3.12	[0.33; 29.48]	0.321
Grade 2	24 / 842 (2.9)	8 / 768 (1.0)	2.74	[1.24; 6.05]	0.013
Grade 3	14 / 373 (3.8)	3 / 397 (0.8)	4.97	[1.44; 17.15]	0.011
Histological subtype					
Interaction test	p = 0.947				
Ductal	33 / 1025 (3.2)	9 / 1010 (0.9)	3.61	[1.74; 7.51]	<.001
Lobular	10 / 291 (3.4)	2 / 276 (0.7)	4.74	[1.05; 21.45]	0.043
Other	5 / 92 (5.4)	1 / 76 (1.3)	4.13	[0.49; 34.60]	0.191
Ki67 status from surgical specimen					
Interaction test	p = 0.140				
Ki67≤20	22 / 660 (3.3)	7 / 629 (1.1)	3.00	[1.29; 6.96]	0.011
Ki67>20	20 / 489 (4.1)	2 / 516 (0.4)	10.55	[2.48; 44.91]	0.001
Type of NSAI					
Interaction test	p = 0.757				
Letrozole	18 / 907 (2.0)	4 / 895 (0.4)	4.44	[1.51; 13.07]	0.007
Anastrozole	30 / 502 (6.0)	8 / 467 (1.7)	3.49	[1.62; 7.53]	0.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.896				
Yes	41 / 1194 (3.4)	10 / 1146 (0.9)	3.94	[1.98; 7.82]	<.001
No	7 / 215 (3.3)	2 / 216 (0.9)	3.52	[0.74; 16.73]	0.114
Prior adjuvant chemotherapy					
Interaction test	p = 0.205				
Yes	22 / 694 (3.2)	8 / 673 (1.2)	2.67	[1.20; 5.95]	0.017
No	26 / 715 (3.6)	4 / 689 (0.6)	6.26	[2.20; 17.85]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.104				
Yes	21 / 528 (4.0)	2 / 503 (0.4)	10.00	[2.36; 42.44]	0.002
No	27 / 881 (3.1)	10 / 859 (1.2)	2.63	[1.28; 5.41]	0.008
Prior endocrine therapy					
Interaction test	p = 0.140				
Yes	24 / 957 (2.5)	9 / 940 (1.0)	2.62	[1.22; 5.61]	0.013
No	24 / 452 (5.3)	3 / 422 (0.7)	7.47	[2.27; 24.62]	<.001
Prior mastectomy					
Interaction test	p = 0.078				
Yes	36 / 857 (4.2)	6 / 847 (0.7)	5.93	[2.51; 14.00]	<.001
No	12 / 552 (2.2)	6 / 515 (1.2)	1.87	[0.71; 4.94]	0.209
Prior radiotherapy					
Interaction test	N.E.				
Yes	38 / 1253 (3.0)	12 / 1203 (1.0)	3.04	[1.60; 5.79]	<.001
No	10 / 156 (6.4)	0 / 159 (0.0)	21.40	[1.26; >99.99]	0.034
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.88 PT palpitations: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Palpitations					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.204				
NA/WE/O	43 / 899 (4.8)	16 / 856 (1.9)	2.56	[1.45; 4.51]	0.001
ROW	4 / 510 (0.8)	4 / 506 (0.8)	0.99	[0.25; 3.95]	0.991
Geographical region					
Interaction test	p = 0.159				
Europe	11 / 832 (1.3)	9 / 824 (1.1)	1.21	[0.50; 2.91]	0.669
North America/Australia	32 / 400 (8.0)	9 / 364 (2.5)	3.24	[1.57; 6.69]	0.002
Asia	2 / 102 (2.0)	0 / 101 (0.0)	4.95	[0.24; >99.99]	0.300
Latin America	2 / 75 (2.7)	2 / 73 (2.7)	0.97	[0.14; 6.73]	0.978
Age group 1 at randomization					
Interaction test	p = 0.926				
<45	4 / 60 (6.7)	1 / 52 (1.9)	3.47	[0.40; 30.05]	0.259
45 to 54	13 / 300 (4.3)	5 / 322 (1.6)	2.79	[1.01; 7.73]	0.048
55 to 64	20 / 651 (3.1)	10 / 642 (1.6)	1.97	[0.93; 4.18]	0.076
≥65	10 / 398 (2.5)	4 / 346 (1.2)	2.17	[0.69; 6.87]	0.186
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.772				
<Median	28 / 633 (4.4)	13 / 632 (2.1)	2.15	[1.12; 4.11]	0.021
≥Median	19 / 776 (2.4)	7 / 730 (1.0)	2.55	[1.08; 6.04]	0.033
Race					
Interaction test	p = 0.771				
Asian	4 / 128 (3.1)	2 / 127 (1.6)	1.98	[0.37; 10.64]	0.424
Non-Asian	40 / 1203 (3.3)	15 / 1167 (1.3)	2.59	[1.44; 4.66]	0.002
BMI at screening					
Interaction test	p = 0.027				
≥25	20 / 935 (2.1)	15 / 935 (1.6)	1.33	[0.69; 2.59]	0.395
<25	27 / 460 (5.9)	5 / 410 (1.2)	4.81	[1.87; 12.38]	0.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.827				
Group I/II	19 / 585 (3.2)	9 / 589 (1.5)	2.13	[0.97; 4.66]	0.060
Group III	28 / 823 (3.4)	11 / 772 (1.4)	2.39	[1.20; 4.76]	0.013

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.651				
IA/IB/IIA	11 / 310 (3.5)	6 / 311 (1.9)	1.84	[0.69; 4.91]	0.224
IIB	8 / 275 (2.9)	3 / 278 (1.1)	2.70	[0.72; 10.05]	0.140
IIIA	17 / 482 (3.5)	9 / 450 (2.0)	1.76	[0.79; 3.92]	0.163
IIIB	1 / 100 (1.0)	0 / 82 (0.0)	2.47	[0.10; 59.72]	0.579
IIIC	10 / 241 (4.1)	2 / 240 (0.8)	4.98	[1.10; 22.49]	0.037
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	45 / 1287 (3.5)	20 / 1258 (1.6)	2.20	[1.31; 3.70]	0.003
>T3	2 / 113 (1.8)	0 / 97 (0.0)	4.30	[0.21; 88.46]	0.345
Nodal status					
Interaction test	p = 0.137				
N0	3 / 190 (1.6)	4 / 200 (2.0)	0.79	[0.18; 3.48]	0.755
N1-N3	44 / 1216 (3.6)	16 / 1160 (1.4)	2.62	[1.49; 4.62]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.760				
Grade 1	2 / 102 (2.0)	1 / 106 (0.9)	2.08	[0.19; 22.57]	0.548
Grade 2	26 / 842 (3.1)	12 / 768 (1.6)	1.98	[1.00; 3.89]	0.049
Grade 3	17 / 373 (4.6)	6 / 397 (1.5)	3.02	[1.20; 7.57]	0.019
Histological subtype					
Interaction test	p = 0.476				
Ductal	33 / 1025 (3.2)	12 / 1010 (1.2)	2.71	[1.41; 5.22]	0.003
Lobular	8 / 291 (2.7)	6 / 276 (2.2)	1.26	[0.44; 3.60]	0.660
Other	6 / 92 (6.5)	2 / 76 (2.6)	2.48	[0.51; 11.93]	0.258
Ki67 status from surgical specimen					
Interaction test	p = 0.430				
Ki67≤20	19 / 660 (2.9)	8 / 629 (1.3)	2.26	[1.00; 5.13]	0.051
Ki67>20	9 / 489 (1.8)	7 / 516 (1.4)	1.36	[0.51; 3.61]	0.542
Type of NSAI					
Interaction test	p = 0.826				
Letrozole	22 / 907 (2.4)	9 / 895 (1.0)	2.41	[1.12; 5.21]	0.025
Anastrozole	25 / 502 (5.0)	11 / 467 (2.4)	2.11	[1.05; 4.25]	0.035
Prior neo/adjuvant chemotherapy					
Interaction test	N.E.				
Yes	41 / 1194 (3.4)	20 / 1146 (1.7)	1.97	[1.16; 3.34]	0.012
No	6 / 215 (2.8)	0 / 216 (0.0)	13.06	[0.74; >99.99]	0.079
Prior adjuvant chemotherapy					
Interaction test	p = 0.995				
Yes	28 / 694 (4.0)	12 / 673 (1.8)	2.26	[1.16; 4.41]	0.017
No	19 / 715 (2.7)	8 / 689 (1.2)	2.29	[1.01; 5.19]	0.048

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.293				
Yes	13 / 528 (2.5)	8 / 503 (1.6)	1.55	[0.65; 3.70]	0.326
No	34 / 881 (3.9)	12 / 859 (1.4)	2.76	[1.44; 5.30]	0.002
Prior endocrine therapy					
Interaction test	p = 0.095				
Yes	37 / 957 (3.9)	12 / 940 (1.3)	3.03	[1.59; 5.77]	<.001
No	10 / 452 (2.2)	8 / 422 (1.9)	1.17	[0.47; 2.93]	0.742
Prior mastectomy					
Interaction test	p = 0.406				
Yes	28 / 857 (3.3)	10 / 847 (1.2)	2.77	[1.35; 5.66]	0.005
No	19 / 552 (3.4)	10 / 515 (1.9)	1.77	[0.83; 3.78]	0.138
Prior radiotherapy					
Interaction test	p = 0.437				
Yes	42 / 1253 (3.4)	19 / 1203 (1.6)	2.12	[1.24; 3.63]	0.006
No	5 / 156 (3.2)	1 / 159 (0.6)	5.10	[0.60; 43.13]	0.135
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.89 SOC ear and labyrinth disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Ear and labyrinth disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.957				
NA/WE/O	67 / 899 (7.5)	36 / 856 (4.2)	1.77	[1.19; 2.63]	0.004
ROW	30 / 510 (5.9)	17 / 506 (3.4)	1.75	[0.98; 3.13]	0.059
Geographical region					
Interaction test	p = 0.976				
Europe	61 / 832 (7.3)	34 / 824 (4.1)	1.78	[1.18; 2.67]	0.006
North America/Australia	28 / 400 (7.0)	15 / 364 (4.1)	1.70	[0.92; 3.13]	0.089
Asia	3 / 102 (2.9)	2 / 101 (2.0)	1.49	[0.25; 8.70]	0.661
Latin America	5 / 75 (6.7)	2 / 73 (2.7)	2.43	[0.49; 12.15]	0.278
Age group 1 at randomization					
Interaction test	p = 0.637				
<45	4 / 60 (6.7)	2 / 52 (3.8)	1.73	[0.33; 9.08]	0.515
45 to 54	16 / 300 (5.3)	7 / 322 (2.2)	2.45	[1.02; 5.88]	0.044
55 to 64	38 / 651 (5.8)	27 / 642 (4.2)	1.39	[0.86; 2.25]	0.182
≥65	39 / 398 (9.8)	17 / 346 (4.9)	1.99	[1.15; 3.46]	0.014
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.669				
<Median	34 / 633 (5.4)	21 / 632 (3.3)	1.62	[0.95; 2.75]	0.077
≥Median	63 / 776 (8.1)	32 / 730 (4.4)	1.85	[1.23; 2.80]	0.003
Race					
Interaction test	p = 0.691				
Asian	5 / 128 (3.9)	2 / 127 (1.6)	2.48	[0.49; 12.55]	0.272
Non-Asian	88 / 1203 (7.3)	49 / 1167 (4.2)	1.74	[1.24; 2.45]	0.001
BMI at screening					
Interaction test	p = 0.685				
≥25	66 / 935 (7.1)	39 / 935 (4.2)	1.69	[1.15; 2.49]	0.007
<25	31 / 460 (6.7)	14 / 410 (3.4)	1.97	[1.06; 3.66]	0.031
AJCC Anatomic Stage Group					
Interaction test	p = 0.689				
Group I/II	40 / 585 (6.8)	21 / 589 (3.6)	1.92	[1.15; 3.21]	0.013
Group III	57 / 823 (6.9)	32 / 772 (4.1)	1.67	[1.10; 2.55]	0.017

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.819				
IA/IB/IIA	17 / 310 (5.5)	12 / 311 (3.9)	1.42	[0.69; 2.93]	0.340
IIB	23 / 275 (8.4)	9 / 278 (3.2)	2.58	[1.22; 5.48]	0.013
IIIA	34 / 482 (7.1)	18 / 450 (4.0)	1.76	[1.01; 3.08]	0.046
IIIB	7 / 100 (7.0)	4 / 82 (4.9)	1.44	[0.44; 4.73]	0.553
IIIC	16 / 241 (6.6)	10 / 240 (4.2)	1.59	[0.74; 3.44]	0.235
Tumor category					
Interaction test	p = 0.777				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	90 / 1287 (7.0)	49 / 1258 (3.9)	1.80	[1.28; 2.52]	<.001
>T3	7 / 113 (6.2)	4 / 97 (4.1)	1.50	[0.45; 4.98]	0.506
Nodal status					
Interaction test	p = 0.429				
N0	18 / 190 (9.5)	8 / 200 (4.0)	2.37	[1.05; 5.32]	0.037
N1-N3	79 / 1216 (6.5)	45 / 1160 (3.9)	1.67	[1.17; 2.39]	0.005
Histological grade at time of surgery					
Interaction test	p = 0.873				
Grade 1	6 / 102 (5.9)	3 / 106 (2.8)	2.08	[0.53; 8.09]	0.291
Grade 2	62 / 842 (7.4)	34 / 768 (4.4)	1.66	[1.11; 2.50]	0.014
Grade 3	28 / 373 (7.5)	15 / 397 (3.8)	1.99	[1.08; 3.66]	0.028
Histological subtype					
Interaction test	p = 0.052				
Ductal	75 / 1025 (7.3)	32 / 1010 (3.2)	2.31	[1.54; 3.46]	<.001
Lobular	17 / 291 (5.8)	16 / 276 (5.8)	1.01	[0.52; 1.95]	0.982
Other	5 / 92 (5.4)	5 / 76 (6.6)	0.83	[0.25; 2.75]	0.755
Ki67 status from surgical specimen					
Interaction test	p = 0.361				
Ki67≤20	42 / 660 (6.4)	27 / 629 (4.3)	1.48	[0.93; 2.37]	0.101
Ki67>20	32 / 489 (6.5)	16 / 516 (3.1)	2.11	[1.17; 3.80]	0.013
Type of NSAI					
Interaction test	p = 0.752				
Letrozole	64 / 907 (7.1)	37 / 895 (4.1)	1.71	[1.15; 2.53]	0.008
Anastrozole	33 / 502 (6.6)	16 / 467 (3.4)	1.92	[1.07; 3.44]	0.029
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.316				
Yes	73 / 1194 (6.1)	43 / 1146 (3.8)	1.63	[1.13; 2.35]	0.009
No	24 / 215 (11.2)	10 / 216 (4.6)	2.41	[1.18; 4.92]	0.016
Prior adjuvant chemotherapy					
Interaction test	p = 0.855				
Yes	46 / 694 (6.6)	26 / 673 (3.9)	1.72	[1.07; 2.74]	0.024
No	51 / 715 (7.1)	27 / 689 (3.9)	1.82	[1.16; 2.87]	0.010

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.452				
Yes	28 / 528 (5.3)	18 / 503 (3.6)	1.48	[0.83; 2.65]	0.183
No	69 / 881 (7.8)	35 / 859 (4.1)	1.92	[1.29; 2.86]	0.001
Prior endocrine therapy					
Interaction test	p = 0.167				
Yes	63 / 957 (6.6)	29 / 940 (3.1)	2.13	[1.39; 3.28]	<.001
No	34 / 452 (7.5)	24 / 422 (5.7)	1.32	[0.80; 2.19]	0.278
Prior mastectomy					
Interaction test	p = 0.119				
Yes	69 / 857 (8.1)	32 / 847 (3.8)	2.13	[1.42; 3.21]	<.001
No	28 / 552 (5.1)	21 / 515 (4.1)	1.24	[0.72; 2.16]	0.439
Prior radiotherapy					
Interaction test	p = 0.284				
Yes	75 / 1253 (6.0)	44 / 1203 (3.7)	1.64	[1.14; 2.35]	0.008
No	22 / 156 (14.1)	9 / 159 (5.7)	2.49	[1.18; 5.24]	0.016
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.2.90 PT vertigo: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Vertigo					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.427				
NA/WE/O	42 / 899 (4.7)	19 / 856 (2.2)	2.10	[1.23; 3.59]	0.006
ROW	8 / 510 (1.6)	6 / 506 (1.2)	1.32	[0.46; 3.79]	0.602
Geographical region					
Interaction test	p = 0.703				
Europe	31 / 832 (3.7)	17 / 824 (2.1)	1.81	[1.01; 3.24]	0.047
North America/Australia	17 / 400 (4.3)	7 / 364 (1.9)	2.21	[0.93; 5.27]	0.074
Asia	2 / 102 (2.0)	0 / 101 (0.0)	4.95	[0.24; >99.99]	0.300
Latin America	0 / 75 (0.0)	1 / 73 (1.4)	0.32	[0.01; 7.84]	0.489
Age group 1 at randomization					
Interaction test	p = 0.415				
<45	0 / 60 (0.0)	2 / 52 (3.8)	0.17	[<0.01; 3.54]	0.255
45 to 54	8 / 300 (2.7)	2 / 322 (0.6)	4.29	[0.92; 20.06]	0.064
55 to 64	20 / 651 (3.1)	13 / 642 (2.0)	1.52	[0.76; 3.02]	0.236
≥65	22 / 398 (5.5)	8 / 346 (2.3)	2.39	[1.08; 5.30]	0.032
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.440				
<Median	15 / 633 (2.4)	10 / 632 (1.6)	1.50	[0.68; 3.31]	0.318
≥Median	35 / 776 (4.5)	15 / 730 (2.1)	2.20	[1.21; 3.99]	0.010
Race					
Interaction test	N.E.				
Asian	4 / 128 (3.1)	0 / 127 (0.0)	8.93	[0.49; >99.99]	0.141
Non-Asian	44 / 1203 (3.7)	23 / 1167 (2.0)	1.86	[1.13; 3.05]	0.015
BMI at screening					
Interaction test	p = 0.266				
≥25	35 / 935 (3.7)	21 / 935 (2.2)	1.67	[0.98; 2.84]	0.060
<25	15 / 460 (3.3)	4 / 410 (1.0)	3.34	[1.12; 9.99]	0.031
AJCC Anatomic Stage Group					
Interaction test	p = 0.417				
Group I/II	22 / 585 (3.8)	9 / 589 (1.5)	2.46	[1.14; 5.30]	0.021
Group III	28 / 823 (3.4)	16 / 772 (2.1)	1.64	[0.90; 3.01]	0.109

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.218				
IA/IB/IIA	8 / 310 (2.6)	7 / 311 (2.3)	1.15	[0.42; 3.12]	0.789
IIB	14 / 275 (5.1)	2 / 278 (0.7)	7.08	[1.62; 30.84]	0.009
IIIA	16 / 482 (3.3)	6 / 450 (1.3)	2.49	[0.98; 6.31]	0.054
IIIB	3 / 100 (3.0)	2 / 82 (2.4)	1.23	[0.21; 7.19]	0.818
IIIC	9 / 241 (3.7)	8 / 240 (3.3)	1.12	[0.44; 2.86]	0.812
Tumor category					
Interaction test	p = 0.638				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	47 / 1287 (3.7)	23 / 1258 (1.8)	2.00	[1.22; 3.27]	0.006
>T3	3 / 113 (2.7)	2 / 97 (2.1)	1.29	[0.22; 7.55]	0.779
Nodal status					
Interaction test	p = 0.706				
N0	7 / 190 (3.7)	3 / 200 (1.5)	2.46	[0.64; 9.36]	0.188
N1-N3	43 / 1216 (3.5)	22 / 1160 (1.9)	1.86	[1.12; 3.10]	0.016
Histological grade at time of surgery					
Interaction test	p = 0.794				
Grade 1	4 / 102 (3.9)	3 / 106 (2.8)	1.39	[0.32; 6.04]	0.664
Grade 2	32 / 842 (3.8)	13 / 768 (1.7)	2.25	[1.19; 4.25]	0.013
Grade 3	13 / 373 (3.5)	8 / 397 (2.0)	1.73	[0.73; 4.13]	0.217
Histological subtype					
Interaction test	p = 0.047				
Ductal	39 / 1025 (3.8)	13 / 1010 (1.3)	2.96	[1.59; 5.50]	<.001
Lobular	8 / 291 (2.7)	8 / 276 (2.9)	0.95	[0.36; 2.49]	0.914
Other	3 / 92 (3.3)	4 / 76 (5.3)	0.62	[0.14; 2.68]	0.522
Ki67 status from surgical specimen					
Interaction test	p = 0.628				
Ki67≤20	21 / 660 (3.2)	11 / 629 (1.7)	1.82	[0.88; 3.74]	0.104
Ki67>20	16 / 489 (3.3)	7 / 516 (1.4)	2.41	[1.00; 5.81]	0.050
Type of NSAI					
Interaction test	p = 0.269				
Letrozole	31 / 907 (3.4)	19 / 895 (2.1)	1.61	[0.92; 2.83]	0.098
Anastrozole	19 / 502 (3.8)	6 / 467 (1.3)	2.95	[1.19; 7.31]	0.020
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.195				
Yes	38 / 1194 (3.2)	22 / 1146 (1.9)	1.66	[0.99; 2.79]	0.056
No	12 / 215 (5.6)	3 / 216 (1.4)	4.02	[1.15; 14.04]	0.029
Prior adjuvant chemotherapy					
Interaction test	p = 0.858				
Yes	25 / 694 (3.6)	12 / 673 (1.8)	2.02	[1.02; 3.99]	0.043
No	25 / 715 (3.5)	13 / 689 (1.9)	1.85	[0.96; 3.59]	0.068

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.194				
Yes	13 / 528 (2.5)	10 / 503 (2.0)	1.24	[0.55; 2.80]	0.607
No	37 / 881 (4.2)	15 / 859 (1.7)	2.41	[1.33; 4.35]	0.004
Prior endocrine therapy					
Interaction test	p = 0.045				
Yes	37 / 957 (3.9)	13 / 940 (1.4)	2.80	[1.50; 5.23]	0.001
No	13 / 452 (2.9)	12 / 422 (2.8)	1.01	[0.47; 2.19]	0.977
Prior mastectomy					
Interaction test	p = 0.957				
Yes	31 / 857 (3.6)	16 / 847 (1.9)	1.91	[1.06; 3.47]	0.033
No	19 / 552 (3.4)	9 / 515 (1.7)	1.97	[0.90; 4.31]	0.090
Prior radiotherapy					
Interaction test	p = 0.353				
Yes	45 / 1253 (3.6)	24 / 1203 (2.0)	1.80	[1.10; 2.94]	0.018
No	5 / 156 (3.2)	1 / 159 (0.6)	5.10	[0.60; 43.13]	0.135
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.2.91 SOC hepatobiliary disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Hepatobiliary disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.531				
NA/WE/O	40 / 899 (4.4)	20 / 856 (2.3)	1.90	[1.12; 3.23]	0.017
ROW	36 / 510 (7.1)	24 / 506 (4.7)	1.49	[0.90; 2.46]	0.120
Geographical region					
Interaction test	p = 0.979				
Europe	58 / 832 (7.0)	33 / 824 (4.0)	1.74	[1.15; 2.64]	0.009
North America/Australia	12 / 400 (3.0)	7 / 364 (1.9)	1.56	[0.62; 3.92]	0.344
Asia	4 / 102 (3.9)	3 / 101 (3.0)	1.32	[0.30; 5.75]	0.711
Latin America	2 / 75 (2.7)	1 / 73 (1.4)	1.95	[0.18; 21.01]	0.583
Age group 1 at randomization					
Interaction test	p = 0.649				
<45	0 / 60 (0.0)	0 / 52 (0.0)	N.E.	N.E.	N.E.
45 to 54	18 / 300 (6.0)	15 / 322 (4.7)	1.29	[0.66; 2.51]	0.457
55 to 64	37 / 651 (5.7)	19 / 642 (3.0)	1.92	[1.12; 3.30]	0.018
≥65	21 / 398 (5.3)	10 / 346 (2.9)	1.83	[0.87; 3.82]	0.110
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.256				
<Median	29 / 633 (4.6)	22 / 632 (3.5)	1.32	[0.76; 2.27]	0.322
≥Median	47 / 776 (6.1)	22 / 730 (3.0)	2.01	[1.22; 3.30]	0.006
Race					
Interaction test	p = 0.682				
Asian	4 / 128 (3.1)	3 / 127 (2.4)	1.32	[0.30; 5.79]	0.710
Non-Asian	67 / 1203 (5.6)	36 / 1167 (3.1)	1.81	[1.21; 2.69]	0.004
BMI at screening					
Interaction test	p = 0.906				
≥25	61 / 935 (6.5)	35 / 935 (3.7)	1.74	[1.16; 2.61]	0.007
<25	15 / 460 (3.3)	8 / 410 (2.0)	1.67	[0.72; 3.90]	0.235
AJCC Anatomic Stage Group					
Interaction test	p = 0.981				
Group I/II	30 / 585 (5.1)	18 / 589 (3.1)	1.68	[0.95; 2.98]	0.077
Group III	46 / 823 (5.6)	26 / 772 (3.4)	1.66	[1.04; 2.66]	0.035

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.271				
IA/IB/IIA	17 / 310 (5.5)	9 / 311 (2.9)	1.89	[0.86; 4.19]	0.114
IIB	13 / 275 (4.7)	9 / 278 (3.2)	1.46	[0.63; 3.36]	0.373
IIIA	23 / 482 (4.8)	20 / 450 (4.4)	1.07	[0.60; 1.93]	0.812
IIIB	9 / 100 (9.0)	2 / 82 (2.4)	3.69	[0.82; 16.61]	0.089
IIIC	14 / 241 (5.8)	4 / 240 (1.7)	3.49	[1.16; 10.44]	0.026
Tumor category					
Interaction test	p = 0.363				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	66 / 1287 (5.1)	41 / 1258 (3.3)	1.57	[1.07; 2.31]	0.020
>T3	10 / 113 (8.8)	3 / 97 (3.1)	2.86	[0.81; 10.10]	0.102
Nodal status					
Interaction test	p = 0.918				
N0	10 / 190 (5.3)	6 / 200 (3.0)	1.75	[0.65; 4.73]	0.267
N1-N3	66 / 1216 (5.4)	38 / 1160 (3.3)	1.66	[1.12; 2.45]	0.011
Histological grade at time of surgery					
Interaction test	p = 0.971				
Grade 1	7 / 102 (6.9)	4 / 106 (3.8)	1.82	[0.55; 6.03]	0.328
Grade 2	48 / 842 (5.7)	25 / 768 (3.3)	1.75	[1.09; 2.81]	0.020
Grade 3	18 / 373 (4.8)	12 / 397 (3.0)	1.60	[0.78; 3.27]	0.201
Histological subtype					
Interaction test	p = 0.826				
Ductal	51 / 1025 (5.0)	28 / 1010 (2.8)	1.79	[1.14; 2.82]	0.011
Lobular	19 / 291 (6.5)	12 / 276 (4.3)	1.50	[0.74; 3.04]	0.257
Other	6 / 92 (6.5)	4 / 76 (5.3)	1.24	[0.36; 4.23]	0.732
Ki67 status from surgical specimen					
Interaction test	p = 0.178				
Ki67≤20	33 / 660 (5.0)	24 / 629 (3.8)	1.31	[0.78; 2.19]	0.303
Ki67>20	32 / 489 (6.5)	15 / 516 (2.9)	2.25	[1.23; 4.10]	0.008
Type of NSAI					
Interaction test	p = 0.427				
Letrozole	49 / 907 (5.4)	32 / 895 (3.6)	1.51	[0.98; 2.34]	0.063
Anastrozole	27 / 502 (5.4)	12 / 467 (2.6)	2.09	[1.07; 4.08]	0.030
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.704				
Yes	60 / 1194 (5.0)	33 / 1146 (2.9)	1.75	[1.15; 2.65]	0.009
No	16 / 215 (7.4)	11 / 216 (5.1)	1.46	[0.69; 3.08]	0.318
Prior adjuvant chemotherapy					
Interaction test	p = 0.342				
Yes	36 / 694 (5.2)	17 / 673 (2.5)	2.05	[1.16; 3.62]	0.013
No	40 / 715 (5.6)	27 / 689 (3.9)	1.43	[0.89; 2.30]	0.143

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.611				
Yes	28 / 528 (5.3)	18 / 503 (3.6)	1.48	[0.83; 2.65]	0.183
No	48 / 881 (5.4)	26 / 859 (3.0)	1.80	[1.13; 2.87]	0.014
Prior endocrine therapy					
Interaction test	p = 0.226				
Yes	49 / 957 (5.1)	24 / 940 (2.6)	2.01	[1.24; 3.24]	0.004
No	27 / 452 (6.0)	20 / 422 (4.7)	1.26	[0.72; 2.21]	0.420
Prior mastectomy					
Interaction test	p = 0.847				
Yes	46 / 857 (5.4)	28 / 847 (3.3)	1.62	[1.02; 2.57]	0.039
No	30 / 552 (5.4)	16 / 515 (3.1)	1.75	[0.97; 3.17]	0.065
Prior radiotherapy					
Interaction test	p = 0.074				
Yes	66 / 1253 (5.3)	32 / 1203 (2.7)	1.98	[1.31; 3.00]	0.001
No	10 / 156 (6.4)	12 / 159 (7.5)	0.85	[0.38; 1.91]	0.693
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

5-3.3 Subgroup analysis for grade ≥ 3 adverse events by SOC and PT

Table 5-3.3.1 SOC blood and lymphatic system disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Blood and lymphatic system disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.473				
NA/WE/O	255 / 899 (28.4)	7 / 856 (0.8)	34.69	[16.47; 73.07]	<.001
ROW	141 / 510 (27.6)	6 / 506 (1.2)	23.32	[10.40; 52.29]	<.001
Geographical region					
Interaction test	p = 0.217				
Europe	263 / 832 (31.6)	12 / 824 (1.5)	21.71	[12.27; 38.40]	<.001
North America/Australia	96 / 400 (24.0)	1 / 364 (0.3)	87.36	[12.24; >99.99]	<.001
Asia	11 / 102 (10.8)	0 / 101 (0.0)	22.78	[1.36; >99.99]	0.030
Latin America	26 / 75 (34.7)	0 / 73 (0.0)	51.61	[3.20; >99.99]	0.005
Age group 1 at randomization					
Interaction test	p = 0.488				
<45	18 / 60 (30.0)	1 / 52 (1.9)	15.60	[2.16; >99.99]	0.007
45 to 54	83 / 300 (27.7)	1 / 322 (0.3)	89.09	[12.48; >99.99]	<.001
55 to 64	187 / 651 (28.7)	6 / 642 (0.9)	30.74	[13.73; 68.78]	<.001
≥ 65	108 / 398 (27.1)	5 / 346 (1.4)	18.78	[7.75; 45.50]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.338				
<Median	172 / 633 (27.2)	4 / 632 (0.6)	42.93	[16.03; >99.99]	<.001
\geq Median	224 / 776 (28.9)	9 / 730 (1.2)	23.41	[12.12; 45.24]	<.001
Race					
Interaction test	N.E.				
Asian	25 / 128 (19.5)	0 / 127 (0.0)	50.60	[3.11; >99.99]	0.006
Non-Asian	329 / 1203 (27.3)	12 / 1167 (1.0)	26.60	[15.04; 47.05]	<.001
BMI at screening					
Interaction test	p = 0.048				
≥ 25	221 / 935 (23.6)	11 / 935 (1.2)	20.09	[11.04; 36.56]	<.001
<25	172 / 460 (37.4)	2 / 410 (0.5)	76.65	[19.14; >99.99]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.509				
Group I/II	155 / 585 (26.5)	4 / 589 (0.7)	39.01	[14.56; >99.99]	<.001
Group III	241 / 823 (29.3)	9 / 772 (1.2)	25.12	[13.01; 48.51]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.721				
IA/IB/IIA	80 / 310 (25.8)	1 / 311 (0.3)	80.26	[11.24; >99.99]	<.001
IIB	75 / 275 (27.3)	3 / 278 (1.1)	25.27	[8.07; 79.17]	<.001
IIIA	142 / 482 (29.5)	6 / 450 (1.3)	22.10	[9.86; 49.51]	<.001
IIIB	28 / 100 (28.0)	0 / 82 (0.0)	46.84	[2.90; >99.99]	0.007
IIIC	71 / 241 (29.5)	3 / 240 (1.3)	23.57	[7.53; 73.79]	<.001
Tumor category					
Interaction test	N.E.				
T0	2 / 5 (40.0)	0 / 5 (0.0)	5.00	[0.30; 83.69]	0.263
T1-T3	360 / 1287 (28.0)	12 / 1258 (1.0)	29.32	[16.59; 51.85]	<.001
>T3	32 / 113 (28.3)	0 / 97 (0.0)	55.88	[3.47; >99.99]	0.005
Nodal status					
Interaction test	p = 0.679				
N0	44 / 190 (23.2)	1 / 200 (0.5)	46.32	[6.45; >99.99]	<.001
N1-N3	350 / 1216 (28.8)	12 / 1160 (1.0)	27.82	[15.74; 49.19]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.363				
Grade 1	31 / 102 (30.4)	0 / 106 (0.0)	65.45	[4.06; >99.99]	0.003
Grade 2	228 / 842 (27.1)	8 / 768 (1.0)	26.00	[12.93; 52.25]	<.001
Grade 3	101 / 373 (27.1)	2 / 397 (0.5)	53.75	[13.36; >99.99]	<.001
Histological subtype					
Interaction test	p = 0.762				
Ductal	271 / 1025 (26.4)	10 / 1010 (1.0)	26.70	[14.29; 49.89]	<.001
Lobular	93 / 291 (32.0)	2 / 276 (0.7)	44.10	[10.97; >99.99]	<.001
Other	32 / 92 (34.8)	1 / 76 (1.3)	26.43	[3.70; >99.99]	0.001
Ki67 status from surgical specimen					
Interaction test	p = 0.864				
Ki67≤20	195 / 660 (29.5)	7 / 629 (1.1)	26.55	[12.59; 55.98]	<.001
Ki67>20	139 / 489 (28.4)	6 / 516 (1.2)	24.45	[10.90; 54.83]	<.001
Type of NSAI					
Interaction test	p = 0.299				
Letrozole	271 / 907 (29.9)	11 / 895 (1.2)	24.31	[13.40; 44.11]	<.001
Anastrozole	125 / 502 (24.9)	2 / 467 (0.4)	58.14	[14.46; >99.99]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.244				
Yes	347 / 1194 (29.1)	10 / 1146 (0.9)	33.31	[17.86; 62.12]	<.001
No	49 / 215 (22.8)	3 / 216 (1.4)	16.41	[5.19; 51.84]	<.001
Prior adjuvant chemotherapy					
Interaction test	p = 0.052				
Yes	203 / 694 (29.3)	3 / 673 (0.4)	65.62	[21.09; >99.99]	<.001
No	193 / 715 (27.0)	10 / 689 (1.5)	18.60	[9.94; 34.81]	<.001

Treatment Groups			Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.220				
Yes	148 / 528 (28.0)	7 / 503 (1.4)	20.14	[9.53; 42.56]	<.001
No	248 / 881 (28.1)	6 / 859 (0.7)	40.30	[18.03; 90.08]	<.001
Prior endocrine therapy					
Interaction test	p = 0.200				
Yes	294 / 957 (30.7)	8 / 940 (0.9)	36.10	[17.99; 72.44]	<.001
No	102 / 452 (22.6)	5 / 422 (1.2)	19.05	[7.84; 46.28]	<.001
Prior mastectomy					
Interaction test	p = 0.941				
Yes	236 / 857 (27.5)	8 / 847 (0.9)	29.16	[14.50; 58.61]	<.001
No	160 / 552 (29.0)	5 / 515 (1.0)	29.86	[12.36; 72.12]	<.001
Prior radiotherapy					
Interaction test	p = 0.410				
Yes	361 / 1253 (28.8)	11 / 1203 (0.9)	31.51	[17.39; 57.11]	<.001
No	35 / 156 (22.4)	2 / 159 (1.3)	17.84	[4.36; 72.89]	<.001
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.3.2 PT neutropenia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Neutropenia					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.608				
NA/WE/O	238 / 899 (26.5)	2 / 856 (0.2)	>99.99	[28.26; >99.99]	<.001
ROW	136 / 510 (26.7)	2 / 506 (0.4)	67.47	[16.79; >99.99]	<.001
Geographical region					
Interaction test	N.E.				
Europe	250 / 832 (30.0)	4 / 824 (0.5)	61.90	[23.16; >99.99]	<.001
North America/Australia	89 / 400 (22.3)	0 / 364 (0.0)	>99.99	[10.15; >99.99]	<.001
Asia	10 / 102 (9.8)	0 / 101 (0.0)	20.80	[1.23; >99.99]	0.035
Latin America	25 / 75 (33.3)	0 / 73 (0.0)	49.66	[3.08; >99.99]	0.006
Age group 1 at randomization					
Interaction test	p = 0.303				
<45	16 / 60 (26.7)	1 / 52 (1.9)	13.87	[1.90; >99.99]	0.009
45 to 54	80 / 300 (26.7)	0 / 322 (0.0)	>99.99	[10.76; >99.99]	<.001
55 to 64	176 / 651 (27.0)	2 / 642 (0.3)	86.78	[21.63; >99.99]	<.001
≥65	102 / 398 (25.6)	1 / 346 (0.3)	88.67	[12.44; >99.99]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.828				
<Median	163 / 633 (25.8)	2 / 632 (0.3)	81.37	[20.27; >99.99]	<.001
≥Median	211 / 776 (27.2)	2 / 730 (0.3)	99.25	[24.75; >99.99]	<.001
Race					
Interaction test	N.E.				
Asian	24 / 128 (18.8)	0 / 127 (0.0)	48.62	[2.99; >99.99]	0.006
Non-Asian	310 / 1203 (25.8)	4 / 1167 (0.3)	75.18	[28.13; >99.99]	<.001
BMI at screening					
Interaction test	p = 0.453				
≥25	212 / 935 (22.7)	3 / 935 (0.3)	70.67	[22.69; >99.99]	<.001
<25	160 / 460 (34.8)	1 / 410 (0.2)	>99.99	[20.06; >99.99]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.563				
Group I/II	145 / 585 (24.8)	1 / 589 (0.2)	>99.99	[20.49; >99.99]	<.001
Group III	229 / 823 (27.8)	3 / 772 (0.4)	71.60	[23.02; >99.99]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.993				
IA/IB/IIA	74 / 310 (23.9)	0 / 311 (0.0)	>99.99	[9.30; >99.99]	<.001
IIB	71 / 275 (25.8)	1 / 278 (0.4)	71.77	[10.04; >99.99]	<.001
IIIA	133 / 482 (27.6)	2 / 450 (0.4)	62.09	[15.46; >99.99]	<.001
IIIB	27 / 100 (27.0)	0 / 82 (0.0)	45.20	[2.80; >99.99]	0.007
IIIC	69 / 241 (28.6)	1 / 240 (0.4)	68.71	[9.62; >99.99]	<.001
Tumor category					
Interaction test	N.E.				
T0	2 / 5 (40.0)	0 / 5 (0.0)	5.00	[0.30; 83.69]	0.263
T1-T3	339 / 1287 (26.3)	4 / 1258 (0.3)	82.84	[31.01; >99.99]	<.001
>T3	31 / 113 (27.4)	0 / 97 (0.0)	54.16	[3.36; >99.99]	0.005
Nodal status					
Interaction test	N.E.				
N0	42 / 190 (22.1)	0 / 200 (0.0)	89.45	[5.54; >99.99]	0.002
N1-N3	330 / 1216 (27.1)	4 / 1160 (0.3)	78.70	[29.46; >99.99]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.973				
Grade 1	31 / 102 (30.4)	0 / 106 (0.0)	65.45	[4.06; >99.99]	0.003
Grade 2	213 / 842 (25.3)	2 / 768 (0.3)	97.14	[24.22; >99.99]	<.001
Grade 3	95 / 373 (25.5)	1 / 397 (0.3)	>99.99	[14.17; >99.99]	<.001
Histological subtype					
Interaction test	p = 0.937				
Ductal	254 / 1025 (24.8)	3 / 1010 (0.3)	83.43	[26.82; >99.99]	<.001
Lobular	89 / 291 (30.6)	1 / 276 (0.4)	84.41	[11.84; >99.99]	<.001
Other	31 / 92 (33.7)	0 / 76 (0.0)	52.16	[3.24; >99.99]	0.005
Ki67 status from surgical specimen					
Interaction test	p = 0.836				
Ki67≤20	181 / 660 (27.4)	2 / 629 (0.3)	86.25	[21.50; >99.99]	<.001
Ki67>20	133 / 489 (27.2)	2 / 516 (0.4)	70.17	[17.46; >99.99]	<.001
Type of NSAI					
Interaction test	p = 0.851				
Letrozole	255 / 907 (28.1)	3 / 895 (0.3)	83.88	[26.97; >99.99]	<.001
Anastrozole	119 / 502 (23.7)	1 / 467 (0.2)	>99.99	[15.53; >99.99]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.441				
Yes	328 / 1194 (27.5)	3 / 1146 (0.3)	>99.99	[33.77; >99.99]	<.001
No	46 / 215 (21.4)	1 / 216 (0.5)	46.21	[6.43; >99.99]	<.001
Prior adjuvant chemotherapy					
Interaction test	N.E.				
Yes	198 / 694 (28.5)	0 / 673 (0.0)	>99.99	[24.05; >99.99]	<.001
No	176 / 715 (24.6)	4 / 689 (0.6)	42.40	[15.83; >99.99]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.136				
Yes	134 / 528 (25.4)	3 / 503 (0.6)	42.55	[13.64; >99.99]	<.001
No	240 / 881 (27.2)	1 / 859 (0.1)	>99.99	[32.90; >99.99]	<.001
Prior endocrine therapy					
Interaction test	p = 0.227				
Yes	278 / 957 (29.0)	2 / 940 (0.2)	>99.99	[34.08; >99.99]	<.001
No	96 / 452 (21.2)	2 / 422 (0.5)	44.81	[11.12; >99.99]	<.001
Prior mastectomy					
Interaction test	p = 0.591				
Yes	226 / 857 (26.4)	3 / 847 (0.4)	74.45	[23.93; >99.99]	<.001
No	148 / 552 (26.8)	1 / 515 (0.2)	>99.99	[19.39; >99.99]	<.001
Prior radiotherapy					
Interaction test	p = 0.300				
Yes	340 / 1253 (27.1)	3 / 1203 (0.2)	>99.99	[35.02; >99.99]	<.001
No	34 / 156 (21.8)	1 / 159 (0.6)	34.65	[4.80; >99.99]	<.001
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.3.3 PT leukopenia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Leukopenia					
	n / N (%)	n / N (%)			
Region					
Interaction test	N.E.				
NA/WE/O	30 / 899 (3.3)	0 / 856 (0.0)	58.09	[3.56; >99.99]	0.004
ROW	26 / 510 (5.1)	1 / 506 (0.2)	25.80	[3.51; >99.99]	0.001
Geographical region					
Interaction test	N.E.				
Europe	45 / 832 (5.4)	1 / 824 (0.1)	44.57	[6.16; >99.99]	<.001
North America/Australia	5 / 400 (1.3)	0 / 364 (0.0)	10.01	[0.56; >99.99]	0.118
Asia	0 / 102 (0.0)	0 / 101 (0.0)	N.E.	N.E.	N.E.
Latin America	6 / 75 (8.0)	0 / 73 (0.0)	12.66	[0.73; >99.99]	0.082
Age group 1 at randomization					
Interaction test	N.E.				
<45	2 / 60 (3.3)	0 / 52 (0.0)	4.34	[0.21; 88.48]	0.339
45 to 54	12 / 300 (4.0)	1 / 322 (0.3)	12.88	[1.68; 98.45]	0.014
55 to 64	28 / 651 (4.3)	0 / 642 (0.0)	56.21	[3.44; >99.99]	0.005
≥65	14 / 398 (3.5)	0 / 346 (0.0)	25.22	[1.51; >99.99]	0.025
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	N.E.				
<Median	25 / 633 (3.9)	1 / 632 (0.2)	24.96	[3.39; >99.99]	0.002
≥Median	31 / 776 (4.0)	0 / 730 (0.0)	59.27	[3.63; >99.99]	0.004
Race					
Interaction test	N.E.				
Asian	1 / 128 (0.8)	0 / 127 (0.0)	2.98	[0.12; 72.39]	0.503
Non-Asian	46 / 1203 (3.8)	1 / 1167 (0.1)	44.62	[6.16; >99.99]	<.001
BMI at screening					
Interaction test	N.E.				
≥25	34 / 935 (3.6)	1 / 935 (0.1)	34.00	[4.66; >99.99]	<.001
<25	22 / 460 (4.8)	0 / 410 (0.0)	40.12	[2.44; >99.99]	0.010
AJCC Anatomic Stage Group					
Interaction test	N.E.				
Group I/II	20 / 585 (3.4)	0 / 589 (0.0)	41.28	[2.50; >99.99]	0.009
Group III	36 / 823 (4.4)	1 / 772 (0.1)	33.77	[4.64; >99.99]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	N.E.				
IA/IB/IIA	13 / 310 (4.2)	0 / 311 (0.0)	27.09	[1.62; >99.99]	0.022
IIB	7 / 275 (2.5)	0 / 278 (0.0)	15.16	[0.87; >99.99]	0.062
IIIA	23 / 482 (4.8)	1 / 450 (0.2)	21.47	[2.91; >99.99]	0.003
IIIB	7 / 100 (7.0)	0 / 82 (0.0)	12.33	[0.71; >99.99]	0.084
IIIC	6 / 241 (2.5)	0 / 240 (0.0)	12.95	[0.73; >99.99]	0.080
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	49 / 1287 (3.8)	1 / 1258 (0.1)	47.90	[6.62; >99.99]	<.001
>T3	7 / 113 (6.2)	0 / 97 (0.0)	12.89	[0.75; >99.99]	0.079
Nodal status					
Interaction test	N.E.				
N0	7 / 190 (3.7)	0 / 200 (0.0)	15.79	[0.91; >99.99]	0.058
N1-N3	47 / 1216 (3.9)	1 / 1160 (0.1)	44.84	[6.20; >99.99]	<.001
Histological grade at time of surgery					
Interaction test	N.E.				
Grade 1	3 / 102 (2.9)	0 / 106 (0.0)	7.27	[0.38; >99.99]	0.188
Grade 2	32 / 842 (3.8)	1 / 768 (0.1)	29.19	[4.00; >99.99]	<.001
Grade 3	17 / 373 (4.6)	0 / 397 (0.0)	37.25	[2.25; >99.99]	0.012
Histological subtype					
Interaction test	N.E.				
Ductal	37 / 1025 (3.6)	1 / 1010 (0.1)	36.46	[5.01; >99.99]	<.001
Lobular	14 / 291 (4.8)	0 / 276 (0.0)	27.51	[1.65; >99.99]	0.021
Other	5 / 92 (5.4)	0 / 76 (0.0)	9.11	[0.51; >99.99]	0.133
Ki67 status from surgical specimen					
Interaction test	N.E.				
Ki67≤20	34 / 660 (5.2)	0 / 629 (0.0)	65.76	[4.04; >99.99]	0.003
Ki67>20	16 / 489 (3.3)	1 / 516 (0.2)	16.88	[2.25; >99.99]	0.006
Type of NSAI					
Interaction test	N.E.				
Letrozole	39 / 907 (4.3)	1 / 895 (0.1)	38.48	[5.30; >99.99]	<.001
Anastrozole	17 / 502 (3.4)	0 / 467 (0.0)	32.56	[1.96; >99.99]	0.015
Prior neo/adjuvant chemotherapy					
Interaction test	N.E.				
Yes	49 / 1194 (4.1)	1 / 1146 (0.1)	47.03	[6.51; >99.99]	<.001
No	7 / 215 (3.3)	0 / 216 (0.0)	15.07	[0.87; >99.99]	0.063
Prior adjuvant chemotherapy					
Interaction test	N.E.				
Yes	27 / 694 (3.9)	0 / 673 (0.0)	53.34	[3.26; >99.99]	0.005
No	29 / 715 (4.1)	1 / 689 (0.1)	27.95	[3.82; >99.99]	0.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	N.E.				
Yes	23 / 528 (4.4)	1 / 503 (0.2)	21.91	[2.97; >99.99]	0.002
No	33 / 881 (3.7)	0 / 859 (0.0)	65.33	[4.01; >99.99]	0.003
Prior endocrine therapy					
Interaction test	N.E.				
Yes	38 / 957 (4.0)	0 / 940 (0.0)	75.63	[4.65; >99.99]	0.002
No	18 / 452 (4.0)	1 / 422 (0.2)	16.81	[2.25; >99.99]	0.006
Prior mastectomy					
Interaction test	N.E.				
Yes	26 / 857 (3.0)	1 / 847 (0.1)	25.70	[3.49; >99.99]	0.001
No	30 / 552 (5.4)	0 / 515 (0.0)	56.92	[3.49; >99.99]	0.005
Prior radiotherapy					
Interaction test	N.E.				
Yes	54 / 1253 (4.3)	1 / 1203 (0.1)	51.85	[7.18; >99.99]	<.001
No	2 / 156 (1.3)	0 / 159 (0.0)	5.10	[0.25; >99.99]	0.292
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.3.4 SOC investigations: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Investigations					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.274				
NA/WE/O	233 / 899 (25.9)	25 / 856 (2.9)	8.87	[5.94; 13.26]	<.001
ROW	138 / 510 (27.1)	22 / 506 (4.3)	6.22	[4.04; 9.59]	<.001
Geographical region					
Interaction test	p = 0.010				
Europe	177 / 832 (21.3)	32 / 824 (3.9)	5.48	[3.81; 7.88]	<.001
North America/Australia	118 / 400 (29.5)	9 / 364 (2.5)	11.93	[6.15; 23.15]	<.001
Asia	61 / 102 (59.8)	4 / 101 (4.0)	15.10	[5.70; 39.97]	<.001
Latin America	15 / 75 (20.0)	2 / 73 (2.7)	7.30	[1.73; 30.80]	0.007
Age group 1 at randomization					
Interaction test	p = 0.988				
<45	18 / 60 (30.0)	2 / 52 (3.8)	7.80	[1.90; 32.04]	0.004
45 to 54	82 / 300 (27.3)	12 / 322 (3.7)	7.33	[4.09; 13.17]	<.001
55 to 64	178 / 651 (27.3)	22 / 642 (3.4)	7.98	[5.19; 12.26]	<.001
≥65	93 / 398 (23.4)	11 / 346 (3.2)	7.35	[4.00; 13.50]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.861				
<Median	170 / 633 (26.9)	23 / 632 (3.6)	7.38	[4.84; 11.25]	<.001
≥Median	201 / 776 (25.9)	24 / 730 (3.3)	7.88	[5.22; 11.88]	<.001
Race					
Interaction test	p = 0.015				
Asian	69 / 128 (53.9)	4 / 127 (3.1)	17.12	[6.44; 45.50]	<.001
Non-Asian	292 / 1203 (24.3)	40 / 1167 (3.4)	7.08	[5.14; 9.76]	<.001
BMI at screening					
Interaction test	p = 0.786				
≥25	243 / 935 (26.0)	33 / 935 (3.5)	7.36	[5.18; 10.47]	<.001
<25	125 / 460 (27.2)	14 / 410 (3.4)	7.96	[4.66; 13.60]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.753				
Group I/II	145 / 585 (24.8)	20 / 589 (3.4)	7.30	[4.64; 11.49]	<.001
Group III	225 / 823 (27.3)	27 / 772 (3.5)	7.82	[5.31; 11.51]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.861				
IA/IB/IIA	80 / 310 (25.8)	12 / 311 (3.9)	6.69	[3.72; 12.02]	<.001
IIB	65 / 275 (23.6)	8 / 278 (2.9)	8.21	[4.02; 16.79]	<.001
IIIA	138 / 482 (28.6)	19 / 450 (4.2)	6.78	[4.27; 10.76]	<.001
IIIB	19 / 100 (19.0)	2 / 82 (2.4)	7.79	[1.87; 32.47]	0.005
IIIC	68 / 241 (28.2)	6 / 240 (2.5)	11.29	[4.99; 25.51]	<.001
Tumor category					
Interaction test	p = 0.903				
T0	2 / 5 (40.0)	0 / 5 (0.0)	5.00	[0.30; 83.69]	0.263
T1-T3	345 / 1287 (26.8)	45 / 1258 (3.6)	7.49	[5.55; 10.12]	<.001
>T3	21 / 113 (18.6)	2 / 97 (2.1)	9.01	[2.17; 37.47]	0.002
Nodal status					
Interaction test	p = 0.310				
N0	48 / 190 (25.3)	4 / 200 (2.0)	12.63	[4.64; 34.35]	<.001
N1-N3	323 / 1216 (26.6)	43 / 1160 (3.7)	7.17	[5.27; 9.75]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.391				
Grade 1	22 / 102 (21.6)	5 / 106 (4.7)	4.57	[1.80; 11.61]	0.001
Grade 2	225 / 842 (26.7)	26 / 768 (3.4)	7.89	[5.32; 11.71]	<.001
Grade 3	106 / 373 (28.4)	12 / 397 (3.0)	9.40	[5.26; 16.79]	<.001
Histological subtype					
Interaction test	p = 0.301				
Ductal	293 / 1025 (28.6)	35 / 1010 (3.5)	8.25	[5.87; 11.58]	<.001
Lobular	54 / 291 (18.6)	10 / 276 (3.6)	5.12	[2.66; 9.85]	<.001
Other	23 / 92 (25.0)	2 / 76 (2.6)	9.50	[2.31; 39.01]	0.002
Ki67 status from surgical specimen					
Interaction test	p = 0.721				
Ki67≤20	168 / 660 (25.5)	22 / 629 (3.5)	7.28	[4.73; 11.20]	<.001
Ki67>20	123 / 489 (25.2)	20 / 516 (3.9)	6.49	[4.11; 10.24]	<.001
Type of NSAI					
Interaction test	p = 0.437				
Letrozole	229 / 907 (25.2)	32 / 895 (3.6)	7.06	[4.94; 10.10]	<.001
Anastrozole	142 / 502 (28.3)	15 / 467 (3.2)	8.81	[5.25; 14.77]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.021				
Yes	319 / 1194 (26.7)	34 / 1146 (3.0)	9.01	[6.38; 12.70]	<.001
No	52 / 215 (24.2)	13 / 216 (6.0)	4.02	[2.26; 7.16]	<.001
Prior adjuvant chemotherapy					
Interaction test	p = 0.301				
Yes	180 / 694 (25.9)	19 / 673 (2.8)	9.19	[5.80; 14.56]	<.001
No	191 / 715 (26.7)	28 / 689 (4.1)	6.57	[4.48; 9.64]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.348				
Yes	151 / 528 (28.6)	16 / 503 (3.2)	8.99	[5.45; 14.83]	<.001
No	220 / 881 (25.0)	31 / 859 (3.6)	6.92	[4.81; 9.96]	<.001
Prior endocrine therapy					
Interaction test	p = 0.097				
Yes	259 / 957 (27.1)	28 / 940 (3.0)	9.09	[6.22; 13.28]	<.001
No	112 / 452 (24.8)	19 / 422 (4.5)	5.50	[3.45; 8.79]	<.001
Prior mastectomy					
Interaction test	p = 0.099				
Yes	218 / 857 (25.4)	22 / 847 (2.6)	9.79	[6.38; 15.03]	<.001
No	153 / 552 (27.7)	25 / 515 (4.9)	5.71	[3.81; 8.56]	<.001
Prior radiotherapy					
Interaction test	p = 0.940				
Yes	326 / 1253 (26.0)	41 / 1203 (3.4)	7.63	[5.57; 10.46]	<.001
No	45 / 156 (28.8)	6 / 159 (3.8)	7.64	[3.36; 17.40]	<.001
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.3.5 PT neutrophil count decreased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Neutrophil count decreased					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.183				
NA/WE/O	145 / 899 (16.1)	1 / 856 (0.1)	>99.99	[19.36; >99.99]	<.001
ROW	57 / 510 (11.2)	2 / 506 (0.4)	28.28	[6.94; >99.99]	<.001
Geographical region					
Interaction test	p = 0.969				
Europe	78 / 832 (9.4)	1 / 824 (0.1)	77.25	[10.77; >99.99]	<.001
North America/Australia	69 / 400 (17.3)	1 / 364 (0.3)	62.79	[8.77; >99.99]	<.001
Asia	53 / 102 (52.0)	1 / 101 (1.0)	52.48	[7.40; >99.99]	<.001
Latin America	2 / 75 (2.7)	0 / 73 (0.0)	4.87	[0.24; 99.70]	0.304
Age group 1 at randomization					
Interaction test	p = 0.394				
<45	16 / 60 (26.7)	0 / 52 (0.0)	28.67	[1.76; >99.99]	0.018
45 to 54	53 / 300 (17.7)	2 / 322 (0.6)	28.44	[6.99; >99.99]	<.001
55 to 64	87 / 651 (13.4)	1 / 642 (0.2)	85.80	[11.99; >99.99]	<.001
≥65	46 / 398 (11.6)	0 / 346 (0.0)	80.88	[5.00; >99.99]	0.002
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	N.E.				
<Median	107 / 633 (16.9)	3 / 632 (0.5)	35.61	[11.37; >99.99]	<.001
≥Median	95 / 776 (12.2)	0 / 730 (0.0)	>99.99	[11.18; >99.99]	<.001
Race					
Interaction test	p = 0.769				
Asian	59 / 128 (46.1)	1 / 127 (0.8)	58.54	[8.24; >99.99]	<.001
Non-Asian	137 / 1203 (11.4)	2 / 1167 (0.2)	66.45	[16.49; >99.99]	<.001
BMI at screening					
Interaction test	p = 0.445				
≥25	111 / 935 (11.9)	1 / 935 (0.1)	>99.99	[15.53; >99.99]	<.001
<25	89 / 460 (19.3)	2 / 410 (0.5)	39.66	[9.83; >99.99]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.893				
Group I/II	73 / 585 (12.5)	1 / 589 (0.2)	73.50	[10.25; >99.99]	<.001
Group III	128 / 823 (15.6)	2 / 772 (0.3)	60.03	[14.90; >99.99]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.878				
IA/IB/IIA	38 / 310 (12.3)	1 / 311 (0.3)	38.12	[5.27; >99.99]	<.001
IIB	35 / 275 (12.7)	0 / 278 (0.0)	71.77	[4.42; >99.99]	0.003
IIIA	78 / 482 (16.2)	1 / 450 (0.2)	72.82	[10.17; >99.99]	<.001
IIIB	8 / 100 (8.0)	0 / 82 (0.0)	13.97	[0.82; >99.99]	0.069
IIIC	42 / 241 (17.4)	1 / 240 (0.4)	41.83	[5.80; >99.99]	<.001
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	190 / 1287 (14.8)	3 / 1258 (0.2)	61.91	[19.84; >99.99]	<.001
>T3	10 / 113 (8.8)	0 / 97 (0.0)	18.05	[1.07; >99.99]	0.045
Nodal status					
Interaction test	p = 0.260				
N0	21 / 190 (11.1)	1 / 200 (0.5)	22.11	[3.00; >99.99]	0.002
N1-N3	181 / 1216 (14.9)	2 / 1160 (0.2)	86.33	[21.48; >99.99]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.265				
Grade 1	13 / 102 (12.7)	1 / 106 (0.9)	13.51	[1.80; >99.99]	0.011
Grade 2	119 / 842 (14.1)	2 / 768 (0.3)	54.27	[13.46; >99.99]	<.001
Grade 3	60 / 373 (16.1)	0 / 397 (0.0)	>99.99	[7.99; >99.99]	<.001
Histological subtype					
Interaction test	N.E.				
Ductal	164 / 1025 (16.0)	3 / 1010 (0.3)	53.87	[17.25; >99.99]	<.001
Lobular	26 / 291 (8.9)	0 / 276 (0.0)	50.28	[3.08; >99.99]	0.006
Other	11 / 92 (12.0)	0 / 76 (0.0)	19.04	[1.14; >99.99]	0.040
Ki67 status from surgical specimen					
Interaction test	p = 0.455				
Ki67≤20	93 / 660 (14.1)	1 / 629 (0.2)	88.63	[12.39; >99.99]	<.001
Ki67>20	67 / 489 (13.7)	2 / 516 (0.4)	35.35	[8.71; >99.99]	<.001
Type of NSAI					
Interaction test	p = 0.924				
Letrozole	127 / 907 (14.0)	2 / 895 (0.2)	62.66	[15.55; >99.99]	<.001
Anastrozole	75 / 502 (14.9)	1 / 467 (0.2)	69.77	[9.74; >99.99]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	N.E.				
Yes	190 / 1194 (15.9)	3 / 1146 (0.3)	60.79	[19.49; >99.99]	<.001
No	12 / 215 (5.6)	0 / 216 (0.0)	25.12	[1.50; >99.99]	0.025
Prior adjuvant chemotherapy					
Interaction test	p = 0.687				
Yes	109 / 694 (15.7)	2 / 673 (0.3)	52.85	[13.10; >99.99]	<.001
No	93 / 715 (13.0)	1 / 689 (0.1)	89.62	[12.53; >99.99]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.450				
Yes	88 / 528 (16.7)	2 / 503 (0.4)	41.92	[10.38; >99.99]	<.001
No	114 / 881 (12.9)	1 / 859 (0.1)	>99.99	[15.56; >99.99]	<.001
Prior endocrine therapy					
Interaction test	N.E.				
Yes	153 / 957 (16.0)	3 / 940 (0.3)	50.09	[16.04; >99.99]	<.001
No	49 / 452 (10.8)	0 / 422 (0.0)	92.44	[5.72; >99.99]	0.001
Prior mastectomy					
Interaction test	p = 0.427				
Yes	114 / 857 (13.3)	1 / 847 (0.1)	>99.99	[15.77; >99.99]	<.001
No	88 / 552 (15.9)	2 / 515 (0.4)	41.05	[10.16; >99.99]	<.001
Prior radiotherapy					
Interaction test	N.E.				
Yes	189 / 1253 (15.1)	3 / 1203 (0.2)	60.49	[19.39; >99.99]	<.001
No	13 / 156 (8.3)	0 / 159 (0.0)	27.52	[1.65; >99.99]	0.021
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.3.6 PT alanine aminotransferase increased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Alanine aminotransferase increased					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.945				
NA/WE/O	73 / 899 (8.1)	3 / 856 (0.4)	23.17	[7.33; 73.23]	<.001
ROW	49 / 510 (9.6)	2 / 506 (0.4)	24.31	[5.94; 99.42]	<.001
Geographical region					
Interaction test	p = 0.599				
Europe	73 / 832 (8.8)	4 / 824 (0.5)	18.07	[6.64; 49.22]	<.001
North America/Australia	36 / 400 (9.0)	1 / 364 (0.3)	32.76	[4.51; >99.99]	<.001
Asia	4 / 102 (3.9)	0 / 101 (0.0)	8.91	[0.49; >99.99]	0.141
Latin America	9 / 75 (12.0)	0 / 73 (0.0)	18.50	[1.10; >99.99]	0.043
Age group 1 at randomization					
Interaction test	N.E.				
<45	1 / 60 (1.7)	0 / 52 (0.0)	2.61	[0.11; 62.64]	0.555
45 to 54	22 / 300 (7.3)	0 / 322 (0.0)	48.29	[2.94; >99.99]	0.007
55 to 64	63 / 651 (9.7)	5 / 642 (0.8)	12.43	[5.03; 30.69]	<.001
≥65	36 / 398 (9.0)	0 / 346 (0.0)	63.49	[3.91; >99.99]	0.004
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.327				
<Median	45 / 633 (7.1)	3 / 632 (0.5)	14.98	[4.68; 47.94]	<.001
≥Median	77 / 776 (9.9)	2 / 730 (0.3)	36.22	[8.93; >99.99]	<.001
Race					
Interaction test	N.E.				
Asian	5 / 128 (3.9)	0 / 127 (0.0)	10.91	[0.61; >99.99]	0.104
Non-Asian	113 / 1203 (9.4)	5 / 1167 (0.4)	21.92	[8.98; 53.50]	<.001
BMI at screening					
Interaction test	p = 0.218				
≥25	97 / 935 (10.4)	3 / 935 (0.3)	32.33	[10.29; >99.99]	<.001
<25	24 / 460 (5.2)	2 / 410 (0.5)	10.70	[2.54; 44.98]	0.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.770				
Group I/II	54 / 585 (9.2)	2 / 589 (0.3)	27.18	[6.66; >99.99]	<.001
Group III	67 / 823 (8.1)	3 / 772 (0.4)	20.95	[6.62; 66.33]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.928				
IA/IB/IIA	29 / 310 (9.4)	2 / 311 (0.6)	14.55	[3.50; 60.44]	<.001
IIB	25 / 275 (9.1)	0 / 278 (0.0)	51.55	[3.15; >99.99]	0.006
IIIA	46 / 482 (9.5)	2 / 450 (0.4)	21.47	[5.24; 87.94]	<.001
IIIB	4 / 100 (4.0)	0 / 82 (0.0)	7.40	[0.40; >99.99]	0.177
IIIC	17 / 241 (7.1)	1 / 240 (0.4)	16.93	[2.27; >99.99]	0.006
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	116 / 1287 (9.0)	5 / 1258 (0.4)	22.68	[9.30; 55.32]	<.001
>T3	4 / 113 (3.5)	0 / 97 (0.0)	7.74	[0.42; >99.99]	0.168
Nodal status					
Interaction test	p = 0.916				
N0	20 / 190 (10.5)	1 / 200 (0.5)	21.05	[2.85; >99.99]	0.003
N1-N3	102 / 1216 (8.4)	4 / 1160 (0.3)	24.33	[8.99; 65.84]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.525				
Grade 1	8 / 102 (7.8)	0 / 106 (0.0)	17.66	[1.03; >99.99]	0.047
Grade 2	77 / 842 (9.1)	4 / 768 (0.5)	17.56	[6.46; 47.74]	<.001
Grade 3	34 / 373 (9.1)	1 / 397 (0.3)	36.19	[4.98; >99.99]	<.001
Histological subtype					
Interaction test	N.E.				
Ductal	95 / 1025 (9.3)	5 / 1010 (0.5)	18.72	[7.65; 45.82]	<.001
Lobular	17 / 291 (5.8)	0 / 276 (0.0)	33.20	[2.01; >99.99]	0.014
Other	10 / 92 (10.9)	0 / 76 (0.0)	17.39	[1.04; >99.99]	0.047
Ki67 status from surgical specimen					
Interaction test	p = 0.112				
Ki67≤20	58 / 660 (8.8)	1 / 629 (0.2)	55.28	[7.68; >99.99]	<.001
Ki67>20	35 / 489 (7.2)	4 / 516 (0.8)	9.23	[3.31; 25.79]	<.001
Type of NSAI					
Interaction test	p = 0.939				
Letrozole	74 / 907 (8.2)	3 / 895 (0.3)	24.34	[7.70; 76.92]	<.001
Anastrozole	48 / 502 (9.6)	2 / 467 (0.4)	22.33	[5.46; 91.34]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.739				
Yes	92 / 1194 (7.7)	4 / 1146 (0.3)	22.08	[8.14; 59.87]	<.001
No	30 / 215 (14.0)	1 / 216 (0.5)	30.14	[4.15; >99.99]	<.001
Prior adjuvant chemotherapy					
Interaction test	p = 0.463				
Yes	53 / 694 (7.6)	3 / 673 (0.4)	17.13	[5.38; 54.56]	<.001
No	69 / 715 (9.7)	2 / 689 (0.3)	33.25	[8.18; >99.99]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.533				
Yes	42 / 528 (8.0)	1 / 503 (0.2)	40.01	[5.53; >99.99]	<.001
No	80 / 881 (9.1)	4 / 859 (0.5)	19.50	[7.18; 53.00]	<.001
Prior endocrine therapy					
Interaction test	p = 0.960				
Yes	74 / 957 (7.7)	3 / 940 (0.3)	24.23	[7.67; 76.58]	<.001
No	48 / 452 (10.6)	2 / 422 (0.5)	22.41	[5.48; 91.62]	<.001
Prior mastectomy					
Interaction test	p = 0.914				
Yes	69 / 857 (8.1)	3 / 847 (0.4)	22.73	[7.18; 71.94]	<.001
No	53 / 552 (9.6)	2 / 515 (0.4)	24.72	[6.06; >99.99]	<.001
Prior radiotherapy					
Interaction test	N.E.				
Yes	99 / 1253 (7.9)	5 / 1203 (0.4)	19.01	[7.77; 46.52]	<.001
No	23 / 156 (14.7)	0 / 159 (0.0)	47.90	[2.93; >99.99]	0.007
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.3.7 PT aspartate aminotransferase increased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Aspartate aminotransferase increased					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.359				
NA/WE/O	36 / 899 (4.0)	4 / 856 (0.5)	8.57	[3.06; 23.97]	<.001
ROW	38 / 510 (7.5)	2 / 506 (0.4)	18.85	[4.57; 77.72]	<.001
Geographical region					
Interaction test	N.E.				
Europe	45 / 832 (5.4)	6 / 824 (0.7)	7.43	[3.19; 17.32]	<.001
North America/Australia	19 / 400 (4.8)	0 / 364 (0.0)	35.50	[2.15; >99.99]	0.013
Asia	3 / 102 (2.9)	0 / 101 (0.0)	6.93	[0.36; >99.99]	0.198
Latin America	7 / 75 (9.3)	0 / 73 (0.0)	14.61	[0.85; >99.99]	0.065
Age group 1 at randomization					
Interaction test	p = 0.903				
<45	1 / 60 (1.7)	0 / 52 (0.0)	2.61	[0.11; 62.64]	0.555
45 to 54	13 / 300 (4.3)	1 / 322 (0.3)	13.95	[1.84; >99.99]	0.011
55 to 64	41 / 651 (6.3)	4 / 642 (0.6)	10.11	[3.64; 28.06]	<.001
≥65	19 / 398 (4.8)	1 / 346 (0.3)	16.52	[2.22; >99.99]	0.006
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.045				
<Median	25 / 633 (3.9)	5 / 632 (0.8)	4.99	[1.92; 12.96]	<.001
≥Median	49 / 776 (6.3)	1 / 730 (0.1)	46.10	[6.38; >99.99]	<.001
Race					
Interaction test	N.E.				
Asian	3 / 128 (2.3)	0 / 127 (0.0)	6.95	[0.36; >99.99]	0.198
Non-Asian	67 / 1203 (5.6)	6 / 1167 (0.5)	10.83	[4.72; 24.88]	<.001
BMI at screening					
Interaction test	p = 0.484				
≥25	56 / 935 (6.0)	4 / 935 (0.4)	14.00	[5.10; 38.45]	<.001
<25	17 / 460 (3.7)	2 / 410 (0.5)	7.58	[1.76; 32.59]	0.007
AJCC Anatomic Stage Group					
Interaction test	p = 0.626				
Group I/II	31 / 585 (5.3)	2 / 589 (0.3)	15.61	[3.75; 64.91]	<.001
Group III	43 / 823 (5.2)	4 / 772 (0.5)	10.08	[3.64; 27.96]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.617				
IA/IB/IIA	19 / 310 (6.1)	2 / 311 (0.6)	9.53	[2.24; 40.57]	0.002
IIB	12 / 275 (4.4)	0 / 278 (0.0)	25.27	[1.50; >99.99]	0.025
IIIA	26 / 482 (5.4)	4 / 450 (0.9)	6.07	[2.13; 17.25]	<.001
IIIB	5 / 100 (5.0)	0 / 82 (0.0)	9.04	[0.51; >99.99]	0.134
IIIC	12 / 241 (5.0)	0 / 240 (0.0)	24.90	[1.48; >99.99]	0.026
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	69 / 1287 (5.4)	6 / 1258 (0.5)	11.24	[4.90; 25.79]	<.001
>T3	5 / 113 (4.4)	0 / 97 (0.0)	9.46	[0.53; >99.99]	0.127
Nodal status					
Interaction test	p = 0.874				
N0	13 / 190 (6.8)	1 / 200 (0.5)	13.68	[1.81; >99.99]	0.011
N1-N3	61 / 1216 (5.0)	5 / 1160 (0.4)	11.64	[4.69; 28.86]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.549				
Grade 1	6 / 102 (5.9)	1 / 106 (0.9)	6.24	[0.76; 50.89]	0.088
Grade 2	49 / 842 (5.8)	2 / 768 (0.3)	22.35	[5.45; 91.58]	<.001
Grade 3	18 / 373 (4.8)	2 / 397 (0.5)	9.58	[2.24; 41.00]	0.002
Histological subtype					
Interaction test	p = 0.080				
Ductal	53 / 1025 (5.2)	3 / 1010 (0.3)	17.41	[5.46; 55.53]	<.001
Lobular	12 / 291 (4.1)	3 / 276 (1.1)	3.79	[1.08; 13.30]	0.037
Other	9 / 92 (9.8)	0 / 76 (0.0)	15.73	[0.93; >99.99]	0.056
Ki67 status from surgical specimen					
Interaction test	p = 0.341				
Ki67≤20	41 / 660 (6.2)	5 / 629 (0.8)	7.81	[3.11; 19.65]	<.001
Ki67>20	22 / 489 (4.5)	1 / 516 (0.2)	23.21	[3.14; >99.99]	0.002
Type of NSAI					
Interaction test	p = 0.712				
Letrozole	42 / 907 (4.6)	3 / 895 (0.3)	13.81	[4.30; 44.41]	<.001
Anastrozole	32 / 502 (6.4)	3 / 467 (0.6)	9.92	[3.06; 32.19]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.334				
Yes	53 / 1194 (4.4)	3 / 1146 (0.3)	16.96	[5.31; 54.11]	<.001
No	21 / 215 (9.8)	3 / 216 (1.4)	7.03	[2.13; 23.23]	0.001
Prior adjuvant chemotherapy					
Interaction test	p = 0.643				
Yes	32 / 694 (4.6)	2 / 673 (0.3)	15.52	[3.73; 64.49]	<.001
No	42 / 715 (5.9)	4 / 689 (0.6)	10.12	[3.65; 28.07]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.569				
Yes	21 / 528 (4.0)	1 / 503 (0.2)	20.01	[2.70; >99.99]	0.003
No	53 / 881 (6.0)	5 / 859 (0.6)	10.34	[4.15; 25.73]	<.001
Prior endocrine therapy					
Interaction test	N.E.				
Yes	42 / 957 (4.4)	6 / 940 (0.6)	6.88	[2.94; 16.10]	<.001
No	32 / 452 (7.1)	0 / 422 (0.0)	60.70	[3.73; >99.99]	0.004
Prior mastectomy					
Interaction test	N.E.				
Yes	45 / 857 (5.3)	0 / 847 (0.0)	89.94	[5.55; >99.99]	0.002
No	29 / 552 (5.3)	6 / 515 (1.2)	4.51	[1.89; 10.77]	<.001
Prior radiotherapy					
Interaction test	N.E.				
Yes	58 / 1253 (4.6)	6 / 1203 (0.5)	9.28	[4.02; 21.43]	<.001
No	16 / 156 (10.3)	0 / 159 (0.0)	33.63	[2.04; >99.99]	0.014
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.3.8 PT white blood cell count decreased: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
White blood cell count decreased					
	n / N (%)	n / N (%)			
Region					
Interaction test	N.E.				
NA/WE/O	25 / 899 (2.8)	3 / 856 (0.4)	7.93	[2.40; 26.18]	<.001
ROW	14 / 510 (2.7)	0 / 506 (0.0)	28.77	[1.72; >99.99]	0.019
Geographical region					
Interaction test	p = 0.930				
Europe	9 / 832 (1.1)	1 / 824 (0.1)	8.91	[1.13; 70.20]	0.038
North America/Australia	17 / 400 (4.3)	2 / 364 (0.5)	7.74	[1.80; 33.25]	0.006
Asia	11 / 102 (10.8)	0 / 101 (0.0)	22.78	[1.36; >99.99]	0.030
Latin America	2 / 75 (2.7)	0 / 73 (0.0)	4.87	[0.24; 99.70]	0.304
Age group 1 at randomization					
Interaction test	p = 0.654				
<45	6 / 60 (10.0)	1 / 52 (1.9)	5.20	[0.65; 41.80]	0.121
45 to 54	7 / 300 (2.3)	0 / 322 (0.0)	16.10	[0.92; >99.99]	0.057
55 to 64	19 / 651 (2.9)	1 / 642 (0.2)	18.74	[2.52; >99.99]	0.004
≥65	7 / 398 (1.8)	1 / 346 (0.3)	6.09	[0.75; 49.22]	0.090
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.419				
<Median	22 / 633 (3.5)	1 / 632 (0.2)	21.97	[2.97; >99.99]	0.002
≥Median	17 / 776 (2.2)	2 / 730 (0.3)	8.00	[1.85; 34.49]	0.005
Race					
Interaction test	N.E.				
Asian	14 / 128 (10.9)	0 / 127 (0.0)	28.78	[1.73; >99.99]	0.019
Non-Asian	24 / 1203 (2.0)	3 / 1167 (0.3)	7.76	[2.34; 25.70]	<.001
BMI at screening					
Interaction test	p = 0.562				
≥25	19 / 935 (2.0)	1 / 935 (0.1)	19.00	[2.55; >99.99]	0.004
<25	20 / 460 (4.3)	2 / 410 (0.5)	8.91	[2.10; 37.90]	0.003
AJCC Anatomic Stage Group					
Interaction test	p = 0.961				
Group I/II	13 / 585 (2.2)	1 / 589 (0.2)	13.09	[1.72; 99.73]	0.013
Group III	26 / 823 (3.2)	2 / 772 (0.3)	12.19	[2.90; 51.21]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.960				
IA/IB/IIA	7 / 310 (2.3)	1 / 311 (0.3)	7.02	[0.87; 56.74]	0.067
IIB	6 / 275 (2.2)	0 / 278 (0.0)	13.14	[0.74; >99.99]	0.079
IIIA	14 / 482 (2.9)	2 / 450 (0.4)	6.54	[1.49; 28.59]	0.013
IIIB	2 / 100 (2.0)	0 / 82 (0.0)	4.11	[0.20; 84.40]	0.359
IIIC	10 / 241 (4.1)	0 / 240 (0.0)	20.91	[1.23; >99.99]	0.035
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	35 / 1287 (2.7)	3 / 1258 (0.2)	11.40	[3.52; 36.98]	<.001
>T3	3 / 113 (2.7)	0 / 97 (0.0)	6.02	[0.31; >99.99]	0.233
Nodal status					
Interaction test	N.E.				
N0	7 / 190 (3.7)	0 / 200 (0.0)	15.79	[0.91; >99.99]	0.058
N1-N3	32 / 1216 (2.6)	3 / 1160 (0.3)	10.18	[3.12; 33.14]	<.001
Histological grade at time of surgery					
Interaction test	N.E.				
Grade 1	2 / 102 (2.0)	0 / 106 (0.0)	5.19	[0.25; >99.99]	0.286
Grade 2	25 / 842 (3.0)	3 / 768 (0.4)	7.60	[2.30; 25.07]	<.001
Grade 3	9 / 373 (2.4)	0 / 397 (0.0)	20.22	[1.18; >99.99]	0.038
Histological subtype					
Interaction test	p = 0.604				
Ductal	30 / 1025 (2.9)	2 / 1010 (0.2)	14.78	[3.54; 61.68]	<.001
Lobular	8 / 291 (2.7)	1 / 276 (0.4)	7.59	[0.96; 60.27]	0.055
Other	1 / 92 (1.1)	0 / 76 (0.0)	2.48	[0.10; 60.11]	0.576
Ki67 status from surgical specimen					
Interaction test	p = 0.189				
Ki67≤20	21 / 660 (3.2)	1 / 629 (0.2)	20.01	[2.70; >99.99]	0.003
Ki67>20	7 / 489 (1.4)	2 / 516 (0.4)	3.69	[0.77; 17.69]	0.102
Type of NSAI					
Interaction test	p = 0.469				
Letrozole	17 / 907 (1.9)	2 / 895 (0.2)	8.39	[1.94; 36.20]	0.004
Anastrozole	22 / 502 (4.4)	1 / 467 (0.2)	20.47	[2.77; >99.99]	0.003
Prior neo/adjuvant chemotherapy					
Interaction test	N.E.				
Yes	36 / 1194 (3.0)	3 / 1146 (0.3)	11.52	[3.56; 37.30]	<.001
No	3 / 215 (1.4)	0 / 216 (0.0)	7.03	[0.37; >99.99]	0.196
Prior adjuvant chemotherapy					
Interaction test	p = 0.617				
Yes	20 / 694 (2.9)	2 / 673 (0.3)	9.70	[2.28; 41.33]	0.002
No	19 / 715 (2.7)	1 / 689 (0.1)	18.31	[2.46; >99.99]	0.005

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.806				
Yes	16 / 528 (3.0)	1 / 503 (0.2)	15.24	[2.03; >99.99]	0.008
No	23 / 881 (2.6)	2 / 859 (0.2)	11.21	[2.65; 47.41]	0.001
Prior endocrine therapy					
Interaction test	p = 0.299				
Yes	25 / 957 (2.6)	1 / 940 (0.1)	24.56	[3.33; >99.99]	0.002
No	14 / 452 (3.1)	2 / 422 (0.5)	6.54	[1.49; 28.58]	0.013
Prior mastectomy					
Interaction test	p = 0.380				
Yes	23 / 857 (2.7)	1 / 847 (0.1)	22.73	[3.08; >99.99]	0.002
No	16 / 552 (2.9)	2 / 515 (0.4)	7.46	[1.72; 32.30]	0.007
Prior radiotherapy					
Interaction test	N.E.				
Yes	36 / 1253 (2.9)	3 / 1203 (0.2)	11.52	[3.56; 37.31]	<.001
No	3 / 156 (1.9)	0 / 159 (0.0)	7.13	[0.37; >99.99]	0.192
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.3.9 SOC infections and infestations: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Infections and infestations					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.501				
NA/WE/O	64 / 899 (7.1)	39 / 856 (4.6)	1.56	[1.06; 2.30]	0.024
ROW	25 / 510 (4.9)	12 / 506 (2.4)	2.07	[1.05; 4.07]	0.036
Geographical region					
Interaction test	p = 0.614				
Europe	43 / 832 (5.2)	29 / 824 (3.5)	1.47	[0.93; 2.33]	0.102
North America/Australia	35 / 400 (8.8)	19 / 364 (5.2)	1.68	[0.98; 2.88]	0.061
Asia	6 / 102 (5.9)	2 / 101 (2.0)	2.97	[0.61; 14.37]	0.176
Latin America	5 / 75 (6.7)	1 / 73 (1.4)	4.87	[0.58; 40.65]	0.144
Age group 1 at randomization					
Interaction test	p = 0.104				
<45	5 / 60 (8.3)	5 / 52 (9.6)	0.87	[0.27; 2.83]	0.813
45 to 54	20 / 300 (6.7)	5 / 322 (1.6)	4.29	[1.63; 11.29]	0.003
55 to 64	40 / 651 (6.1)	23 / 642 (3.6)	1.72	[1.04; 2.83]	0.035
≥65	24 / 398 (6.0)	18 / 346 (5.2)	1.16	[0.64; 2.10]	0.626
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.664				
<Median	37 / 633 (5.8)	20 / 632 (3.2)	1.85	[1.08; 3.15]	0.024
≥Median	52 / 776 (6.7)	31 / 730 (4.2)	1.58	[1.02; 2.43]	0.039
Race					
Interaction test	p = 0.731				
Asian	7 / 128 (5.5)	3 / 127 (2.4)	2.32	[0.61; 8.75]	0.216
Non-Asian	80 / 1203 (6.7)	43 / 1167 (3.7)	1.80	[1.26; 2.59]	0.001
BMI at screening					
Interaction test	p = 0.968				
≥25	65 / 935 (7.0)	39 / 935 (4.2)	1.67	[1.13; 2.45]	0.010
<25	23 / 460 (5.0)	12 / 410 (2.9)	1.71	[0.86; 3.39]	0.126
AJCC Anatomic Stage Group					
Interaction test	p = 0.835				
Group I/II	37 / 585 (6.3)	23 / 589 (3.9)	1.62	[0.97; 2.69]	0.063
Group III	52 / 823 (6.3)	28 / 772 (3.6)	1.74	[1.11; 2.73]	0.015

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.697				
IA/IB/IIA	18 / 310 (5.8)	11 / 311 (3.5)	1.64	[0.79; 3.42]	0.185
IIB	19 / 275 (6.9)	12 / 278 (4.3)	1.60	[0.79; 3.23]	0.190
IIIA	31 / 482 (6.4)	21 / 450 (4.7)	1.38	[0.80; 2.36]	0.243
IIIB	6 / 100 (6.0)	1 / 82 (1.2)	4.92	[0.60; 40.05]	0.136
IIIC	15 / 241 (6.2)	6 / 240 (2.5)	2.49	[0.98; 6.31]	0.054
Tumor category					
Interaction test	p = 0.127				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	80 / 1287 (6.2)	50 / 1258 (4.0)	1.56	[1.11; 2.21]	0.011
>T3	9 / 113 (8.0)	1 / 97 (1.0)	7.73	[1.00; 59.90]	0.050
Nodal status					
Interaction test	p = 0.025				
N0	15 / 190 (7.9)	2 / 200 (1.0)	7.89	[1.83; 34.06]	0.006
N1-N3	74 / 1216 (6.1)	49 / 1160 (4.2)	1.44	[1.01; 2.05]	0.042
Histological grade at time of surgery					
Interaction test	p = 0.177				
Grade 1	7 / 102 (6.9)	6 / 106 (5.7)	1.21	[0.42; 3.49]	0.721
Grade 2	52 / 842 (6.2)	35 / 768 (4.6)	1.36	[0.89; 2.06]	0.153
Grade 3	27 / 373 (7.2)	10 / 397 (2.5)	2.87	[1.41; 5.85]	0.004
Histological subtype					
Interaction test	p = 0.536				
Ductal	70 / 1025 (6.8)	38 / 1010 (3.8)	1.82	[1.23; 2.67]	0.002
Lobular	15 / 291 (5.2)	9 / 276 (3.3)	1.58	[0.70; 3.55]	0.268
Other	4 / 92 (4.3)	4 / 76 (5.3)	0.83	[0.21; 3.19]	0.782
Ki67 status from surgical specimen					
Interaction test	p = 0.055				
Ki67≤20	35 / 660 (5.3)	28 / 629 (4.5)	1.19	[0.73; 1.93]	0.479
Ki67>20	32 / 489 (6.5)	13 / 516 (2.5)	2.60	[1.38; 4.89]	0.003
Type of NSAI					
Interaction test	p = 0.033				
Letrozole	42 / 907 (4.6)	34 / 895 (3.8)	1.22	[0.78; 1.90]	0.381
Anastrozole	47 / 502 (9.4)	17 / 467 (3.6)	2.57	[1.50; 4.41]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.961				
Yes	72 / 1194 (6.0)	41 / 1146 (3.6)	1.69	[1.16; 2.45]	0.006
No	17 / 215 (7.9)	10 / 216 (4.6)	1.71	[0.80; 3.64]	0.166
Prior adjuvant chemotherapy					
Interaction test	p = 0.810				
Yes	47 / 694 (6.8)	26 / 673 (3.9)	1.75	[1.10; 2.80]	0.019
No	42 / 715 (5.9)	25 / 689 (3.6)	1.62	[1.00; 2.63]	0.051

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.860				
Yes	28 / 528 (5.3)	15 / 503 (3.0)	1.78	[0.96; 3.29]	0.067
No	61 / 881 (6.9)	36 / 859 (4.2)	1.65	[1.11; 2.47]	0.014
Prior endocrine therapy					
Interaction test	p = 0.734				
Yes	63 / 957 (6.6)	38 / 940 (4.0)	1.63	[1.10; 2.41]	0.015
No	26 / 452 (5.8)	13 / 422 (3.1)	1.87	[0.97; 3.59]	0.061
Prior mastectomy					
Interaction test	p = 0.073				
Yes	64 / 857 (7.5)	30 / 847 (3.5)	2.11	[1.38; 3.22]	<.001
No	25 / 552 (4.5)	21 / 515 (4.1)	1.11	[0.63; 1.96]	0.717
Prior radiotherapy					
Interaction test	p = 0.838				
Yes	80 / 1253 (6.4)	45 / 1203 (3.7)	1.71	[1.19; 2.44]	0.003
No	9 / 156 (5.8)	6 / 159 (3.8)	1.53	[0.56; 4.19]	0.410
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.3.10 SOC nervous system disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Nervous system disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.550				
NA/WE/O	33 / 899 (3.7)	12 / 856 (1.4)	2.62	[1.36; 5.04]	0.004
ROW	7 / 510 (1.4)	4 / 506 (0.8)	1.74	[0.51; 5.89]	0.376
Geographical region					
Interaction test	p = 0.911				
Europe	28 / 832 (3.4)	12 / 824 (1.5)	2.31	[1.18; 4.51]	0.014
North America/Australia	11 / 400 (2.8)	4 / 364 (1.1)	2.50	[0.80; 7.79]	0.113
Asia	0 / 102 (0.0)	0 / 101 (0.0)	N.E.	N.E.	N.E.
Latin America	1 / 75 (1.3)	0 / 73 (0.0)	2.92	[0.12; 70.56]	0.509
Age group 1 at randomization					
Interaction test	p = 0.123				
<45	0 / 60 (0.0)	0 / 52 (0.0)	N.E.	N.E.	N.E.
45 to 54	7 / 300 (2.3)	3 / 322 (0.9)	2.50	[0.65; 9.60]	0.180
55 to 64	18 / 651 (2.8)	3 / 642 (0.5)	5.92	[1.75; 19.99]	0.004
≥65	15 / 398 (3.8)	10 / 346 (2.9)	1.30	[0.59; 2.86]	0.509
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.483				
<Median	16 / 633 (2.5)	5 / 632 (0.8)	3.19	[1.18; 8.67]	0.023
≥Median	24 / 776 (3.1)	11 / 730 (1.5)	2.05	[1.01; 4.16]	0.046
Race					
Interaction test	N.E.				
Asian	1 / 128 (0.8)	0 / 127 (0.0)	2.98	[0.12; 72.39]	0.503
Non-Asian	34 / 1203 (2.8)	16 / 1167 (1.4)	2.06	[1.14; 3.71]	0.016
BMI at screening					
Interaction test	p = 0.581				
≥25	26 / 935 (2.8)	12 / 935 (1.3)	2.17	[1.10; 4.27]	0.025
<25	14 / 460 (3.0)	4 / 410 (1.0)	3.12	[1.04; 9.40]	0.043
AJCC Anatomic Stage Group					
Interaction test	p = 0.563				
Group I/II	11 / 585 (1.9)	6 / 589 (1.0)	1.85	[0.69; 4.96]	0.224
Group III	28 / 823 (3.4)	10 / 772 (1.3)	2.63	[1.28; 5.37]	0.008

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.653				
IA/IB/IIA	4 / 310 (1.3)	2 / 311 (0.6)	2.01	[0.37; 10.87]	0.419
IIB	7 / 275 (2.5)	4 / 278 (1.4)	1.77	[0.52; 5.97]	0.358
IIIA	18 / 482 (3.7)	8 / 450 (1.8)	2.10	[0.92; 4.78]	0.077
IIIB	1 / 100 (1.0)	1 / 82 (1.2)	0.82	[0.05; 12.91]	0.888
IIIC	9 / 241 (3.7)	1 / 240 (0.4)	8.96	[1.14; 70.20]	0.037
Tumor category					
Interaction test	p = 0.458				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	38 / 1287 (3.0)	15 / 1258 (1.2)	2.48	[1.37; 4.48]	0.003
>T3	1 / 113 (0.9)	1 / 97 (1.0)	0.86	[0.05; 13.54]	0.914
Nodal status					
Interaction test	p = 0.914				
N0	5 / 190 (2.6)	2 / 200 (1.0)	2.63	[0.52; 13.40]	0.244
N1-N3	35 / 1216 (2.9)	14 / 1160 (1.2)	2.38	[1.29; 4.41]	0.006
Histological grade at time of surgery					
Interaction test	p = 0.239				
Grade 1	3 / 102 (2.9)	4 / 106 (3.8)	0.78	[0.18; 3.40]	0.740
Grade 2	24 / 842 (2.9)	8 / 768 (1.0)	2.74	[1.24; 6.05]	0.013
Grade 3	11 / 373 (2.9)	3 / 397 (0.8)	3.90	[1.10; 13.88]	0.035
Histological subtype					
Interaction test	p = 0.702				
Ductal	33 / 1025 (3.2)	11 / 1010 (1.1)	2.96	[1.50; 5.82]	0.002
Lobular	7 / 291 (2.4)	3 / 276 (1.1)	2.21	[0.58; 8.47]	0.246
Other	0 / 92 (0.0)	2 / 76 (2.6)	0.17	[<0.01; 3.40]	0.243
Ki67 status from surgical specimen					
Interaction test	p = 0.088				
Ki67≤20	16 / 660 (2.4)	11 / 629 (1.7)	1.39	[0.65; 2.96]	0.400
Ki67>20	14 / 489 (2.9)	3 / 516 (0.6)	4.92	[1.42; 17.03]	0.012
Type of NSAI					
Interaction test	p = 0.402				
Letrozole	29 / 907 (3.2)	10 / 895 (1.1)	2.86	[1.40; 5.84]	0.004
Anastrozole	11 / 502 (2.2)	6 / 467 (1.3)	1.71	[0.64; 4.57]	0.289
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.068				
Yes	36 / 1194 (3.0)	11 / 1146 (1.0)	3.14	[1.61; 6.14]	<.001
No	4 / 215 (1.9)	5 / 216 (2.3)	0.80	[0.22; 2.95]	0.742
Prior adjuvant chemotherapy					
Interaction test	p = 0.125				
Yes	24 / 694 (3.5)	6 / 673 (0.9)	3.88	[1.60; 9.43]	0.003
No	16 / 715 (2.2)	10 / 689 (1.5)	1.54	[0.70; 3.37]	0.279

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.891				
Yes	12 / 528 (2.3)	5 / 503 (1.0)	2.29	[0.81; 6.44]	0.118
No	28 / 881 (3.2)	11 / 859 (1.3)	2.48	[1.24; 4.95]	0.010
Prior endocrine therapy					
Interaction test	p = 0.912				
Yes	29 / 957 (3.0)	12 / 940 (1.3)	2.37	[1.22; 4.62]	0.011
No	11 / 452 (2.4)	4 / 422 (0.9)	2.57	[0.82; 8.00]	0.104
Prior mastectomy					
Interaction test	p = 0.121				
Yes	26 / 857 (3.0)	7 / 847 (0.8)	3.67	[1.60; 8.41]	0.002
No	14 / 552 (2.5)	9 / 515 (1.7)	1.45	[0.63; 3.32]	0.378
Prior radiotherapy					
Interaction test	p = 0.623				
Yes	36 / 1253 (2.9)	15 / 1203 (1.2)	2.30	[1.27; 4.19]	0.006
No	4 / 156 (2.6)	1 / 159 (0.6)	4.08	[0.46; 36.07]	0.206
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.3.11 SOC general disorders and administration site conditions: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
General disorders and administration site conditions					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.660				
NA/WE/O	27 / 899 (3.0)	11 / 856 (1.3)	2.34	[1.17; 4.68]	0.017
ROW	7 / 510 (1.4)	2 / 506 (0.4)	3.47	[0.72; 16.64]	0.119
Geographical region					
Interaction test	p = 0.461				
Europe	18 / 832 (2.2)	5 / 824 (0.6)	3.57	[1.33; 9.56]	0.012
North America/Australia	13 / 400 (3.3)	7 / 364 (1.9)	1.69	[0.68; 4.19]	0.257
Asia	2 / 102 (2.0)	0 / 101 (0.0)	4.95	[0.24; >99.99]	0.300
Latin America	1 / 75 (1.3)	1 / 73 (1.4)	0.97	[0.06; 15.27]	0.985
Age group 1 at randomization					
Interaction test	p = 0.352				
<45	3 / 60 (5.0)	0 / 52 (0.0)	6.08	[0.32; >99.99]	0.229
45 to 54	9 / 300 (3.0)	2 / 322 (0.6)	4.83	[1.05; 22.17]	0.043
55 to 64	14 / 651 (2.2)	9 / 642 (1.4)	1.53	[0.67; 3.52]	0.312
≥65	8 / 398 (2.0)	2 / 346 (0.6)	3.48	[0.74; 16.27]	0.113
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.972				
<Median	15 / 633 (2.4)	6 / 632 (0.9)	2.50	[0.97; 6.39]	0.057
≥Median	19 / 776 (2.4)	7 / 730 (1.0)	2.55	[1.08; 6.04]	0.033
Race					
Interaction test	N.E.				
Asian	2 / 128 (1.6)	0 / 127 (0.0)	4.96	[0.24; >99.99]	0.300
Non-Asian	31 / 1203 (2.6)	12 / 1167 (1.0)	2.51	[1.29; 4.86]	0.006
BMI at screening					
Interaction test	p = 0.896				
≥25	22 / 935 (2.4)	9 / 935 (1.0)	2.44	[1.13; 5.28]	0.023
<25	12 / 460 (2.6)	4 / 410 (1.0)	2.67	[0.87; 8.23]	0.086
AJCC Anatomic Stage Group					
Interaction test	p = 0.905				
Group I/II	17 / 585 (2.9)	7 / 589 (1.2)	2.45	[1.02; 5.85]	0.045
Group III	17 / 823 (2.1)	6 / 772 (0.8)	2.66	[1.05; 6.71]	0.038

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.858				
IA/IB/IIA	9 / 310 (2.9)	4 / 311 (1.3)	2.26	[0.70; 7.25]	0.172
IIB	8 / 275 (2.9)	3 / 278 (1.1)	2.70	[0.72; 10.05]	0.140
IIIA	8 / 482 (1.7)	4 / 450 (0.9)	1.87	[0.57; 6.16]	0.305
IIIB	2 / 100 (2.0)	1 / 82 (1.2)	1.64	[0.15; 17.77]	0.684
IIIC	7 / 241 (2.9)	1 / 240 (0.4)	6.97	[0.86; 56.23]	0.068
Tumor category					
Interaction test	p = 0.739				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	32 / 1287 (2.5)	12 / 1258 (1.0)	2.61	[1.35; 5.04]	0.004
>T3	2 / 113 (1.8)	1 / 97 (1.0)	1.72	[0.16; 18.64]	0.657
Nodal status					
Interaction test	p = 0.762				
N0	6 / 190 (3.2)	2 / 200 (1.0)	3.16	[0.65; 15.45]	0.156
N1-N3	28 / 1216 (2.3)	11 / 1160 (0.9)	2.43	[1.21; 4.85]	0.012
Histological grade at time of surgery					
Interaction test	p = 0.626				
Grade 1	4 / 102 (3.9)	0 / 106 (0.0)	9.35	[0.51; >99.99]	0.132
Grade 2	21 / 842 (2.5)	8 / 768 (1.0)	2.39	[1.07; 5.37]	0.034
Grade 3	8 / 373 (2.1)	5 / 397 (1.3)	1.70	[0.56; 5.16]	0.347
Histological subtype					
Interaction test	p = 0.407				
Ductal	27 / 1025 (2.6)	12 / 1010 (1.2)	2.22	[1.13; 4.35]	0.021
Lobular	6 / 291 (2.1)	1 / 276 (0.4)	5.69	[0.69; 46.97]	0.106
Other	1 / 92 (1.1)	0 / 76 (0.0)	2.48	[0.10; 60.11]	0.576
Ki67 status from surgical specimen					
Interaction test	p = 0.435				
Ki67≤20	11 / 660 (1.7)	6 / 629 (1.0)	1.75	[0.65; 4.70]	0.269
Ki67>20	12 / 489 (2.5)	4 / 516 (0.8)	3.17	[1.03; 9.75]	0.045
Type of NSAI					
Interaction test	p = 0.982				
Letrozole	18 / 907 (2.0)	7 / 895 (0.8)	2.54	[1.07; 6.05]	0.036
Anastrozole	16 / 502 (3.2)	6 / 467 (1.3)	2.48	[0.98; 6.29]	0.055
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.041				
Yes	32 / 1194 (2.7)	9 / 1146 (0.8)	3.41	[1.64; 7.12]	0.001
No	2 / 215 (0.9)	4 / 216 (1.9)	0.50	[0.09; 2.71]	0.424
Prior adjuvant chemotherapy					
Interaction test	p = 0.269				
Yes	24 / 694 (3.5)	7 / 673 (1.0)	3.32	[1.44; 7.66]	0.005
No	10 / 715 (1.4)	6 / 689 (0.9)	1.61	[0.59; 4.40]	0.356

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.842				
Yes	9 / 528 (1.7)	3 / 503 (0.6)	2.86	[0.78; 10.50]	0.114
No	25 / 881 (2.8)	10 / 859 (1.2)	2.44	[1.18; 5.04]	0.016
Prior endocrine therapy					
Interaction test	p = 0.554				
Yes	20 / 957 (2.1)	9 / 940 (1.0)	2.18	[1.00; 4.77]	0.050
No	14 / 452 (3.1)	4 / 422 (0.9)	3.27	[1.08; 9.85]	0.035
Prior mastectomy					
Interaction test	p = 0.491				
Yes	24 / 857 (2.8)	8 / 847 (0.9)	2.96	[1.34; 6.56]	0.007
No	10 / 552 (1.8)	5 / 515 (1.0)	1.87	[0.64; 5.42]	0.252
Prior radiotherapy					
Interaction test	p = 0.649				
Yes	30 / 1253 (2.4)	12 / 1203 (1.0)	2.40	[1.23; 4.67]	0.010
No	4 / 156 (2.6)	1 / 159 (0.6)	4.08	[0.46; 36.07]	0.206
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.3.12 PT fatigue: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Fatigue					
	n / N (%)	n / N (%)			
Region					
Interaction test	N.E.				
NA/WE/O	12 / 899 (1.3)	3 / 856 (0.4)	3.81	[1.08; 13.45]	0.038
ROW	3 / 510 (0.6)	0 / 506 (0.0)	6.95	[0.36; >99.99]	0.199
Geographical region					
Interaction test	N.E.				
Europe	5 / 832 (0.6)	0 / 824 (0.0)	10.89	[0.60; >99.99]	0.106
North America/Australia	9 / 400 (2.3)	3 / 364 (0.8)	2.73	[0.74; 10.01]	0.130
Asia	1 / 102 (1.0)	0 / 101 (0.0)	2.97	[0.12; 72.08]	0.503
Latin America	0 / 75 (0.0)	0 / 73 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.435				
<Median	6 / 633 (0.9)	2 / 632 (0.3)	3.00	[0.61; 14.78]	0.178
≥Median	9 / 776 (1.2)	1 / 730 (0.1)	8.47	[1.08; 66.66]	0.042
Race					
Interaction test	N.E.				
Asian	1 / 128 (0.8)	0 / 127 (0.0)	2.98	[0.12; 72.39]	0.503
Non-Asian	14 / 1203 (1.2)	3 / 1167 (0.3)	4.53	[1.30; 15.71]	0.017
BMI at screening					
Interaction test	p = 0.735				
≥25	8 / 935 (0.9)	2 / 935 (0.2)	4.00	[0.85; 18.79]	0.079
<25	7 / 460 (1.5)	1 / 410 (0.2)	6.24	[0.77; 50.50]	0.086
AJCC Anatomic Stage Group					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Anatomic stages					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	15 / 1287 (1.2)	3 / 1258 (0.2)	4.89	[1.42; 16.84]	0.012
>T3	0 / 113 (0.0)	0 / 97 (0.0)	N.E.	N.E.	N.E.
Nodal status					
Interaction test	p = 0.670				
N0	3 / 190 (1.6)	1 / 200 (0.5)	3.16	[0.33; 30.09]	0.317
N1-N3	12 / 1216 (1.0)	2 / 1160 (0.2)	5.72	[1.28; 25.52]	0.022
Histological grade at time of surgery					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Histological subtype					
Interaction test	N.E.				
Ductal	11 / 1025 (1.1)	3 / 1010 (0.3)	3.61	[1.01; 12.91]	0.048
Lobular	3 / 291 (1.0)	0 / 276 (0.0)	6.64	[0.34; >99.99]	0.210
Other	1 / 92 (1.1)	0 / 76 (0.0)	2.48	[0.10; 60.11]	0.576
Ki67 status from surgical specimen					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Type of NSAI					
Interaction test	p = 0.645				
Letrozole	7 / 907 (0.8)	1 / 895 (0.1)	6.91	[0.85; 56.03]	0.070
Anastrozole	8 / 502 (1.6)	2 / 467 (0.4)	3.72	[0.79; 17.43]	0.095
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.235				
Yes	14 / 1194 (1.2)	2 / 1146 (0.2)	6.72	[1.53; 29.50]	0.012
No	1 / 215 (0.5)	1 / 216 (0.5)	1.00	[0.06; 15.96]	0.997
Prior adjuvant chemotherapy					
Interaction test	p = 0.205				
Yes	11 / 694 (1.6)	1 / 673 (0.1)	10.67	[1.38; 82.40]	0.023
No	4 / 715 (0.6)	2 / 689 (0.3)	1.93	[0.35; 10.49]	0.448
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.602				
Yes	3 / 528 (0.6)	1 / 503 (0.2)	2.86	[0.30; 27.38]	0.362
No	12 / 881 (1.4)	2 / 859 (0.2)	5.85	[1.31; 26.06]	0.020

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior endocrine therapy					
Interaction test	p = 0.857				
Yes	9 / 957 (0.9)	2 / 940 (0.2)	4.42	[0.96; 20.40]	0.057
No	6 / 452 (1.3)	1 / 422 (0.2)	5.60	[0.68; 46.34]	0.110
Prior mastectomy					
Interaction test	p = 0.193				
Yes	11 / 857 (1.3)	1 / 847 (0.1)	10.87	[1.41; 84.02]	0.022
No	4 / 552 (0.7)	2 / 515 (0.4)	1.87	[0.34; 10.14]	0.470
Prior radiotherapy					
Interaction test	N.E.				
Yes	13 / 1253 (1.0)	3 / 1203 (0.2)	4.16	[1.19; 14.56]	0.026
No	2 / 156 (1.3)	0 / 159 (0.0)	5.10	[0.25; >99.99]	0.292
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.3.13 SOC hepatobiliary disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Hepatobiliary disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	N.E.				
NA/WE/O	15 / 899 (1.7)	2 / 856 (0.2)	7.14	[1.64; 31.13]	0.009
ROW	8 / 510 (1.6)	0 / 506 (0.0)	16.87	[0.98; >99.99]	0.052
Geographical region					
Interaction test	N.E.				
Europe	14 / 832 (1.7)	2 / 824 (0.2)	6.93	[1.58; 30.41]	0.010
North America/Australia	7 / 400 (1.8)	0 / 364 (0.0)	13.65	[0.78; >99.99]	0.073
Asia	1 / 102 (1.0)	0 / 101 (0.0)	2.97	[0.12; 72.08]	0.503
Latin America	1 / 75 (1.3)	0 / 73 (0.0)	2.92	[0.12; 70.56]	0.509
Age group 1 at randomization					
Interaction test	N.E.				
<45	0 / 60 (0.0)	0 / 52 (0.0)	N.E.	N.E.	N.E.
45 to 54	6 / 300 (2.0)	2 / 322 (0.6)	3.22	[0.65; 15.83]	0.150
55 to 64	10 / 651 (1.5)	0 / 642 (0.0)	20.71	[1.22; >99.99]	0.036
≥65	7 / 398 (1.8)	0 / 346 (0.0)	13.05	[0.75; >99.99]	0.078
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	N.E.				
<Median	8 / 633 (1.3)	2 / 632 (0.3)	3.99	[0.85; 18.73]	0.079
≥Median	15 / 776 (1.9)	0 / 730 (0.0)	29.16	[1.75; >99.99]	0.019
Race					
Interaction test	N.E.				
Asian	1 / 128 (0.8)	0 / 127 (0.0)	2.98	[0.12; 72.39]	0.503
Non-Asian	20 / 1203 (1.7)	1 / 1167 (0.1)	19.40	[2.61; >99.99]	0.004
BMI at screening					
Interaction test	N.E.				
≥25	20 / 935 (2.1)	2 / 935 (0.2)	10.00	[2.34; 42.66]	0.002
<25	3 / 460 (0.7)	0 / 410 (0.0)	6.24	[0.32; >99.99]	0.225
AJCC Anatomic Stage Group					
Interaction test	N.E.				
Group I/II	10 / 585 (1.7)	0 / 589 (0.0)	21.14	[1.24; >99.99]	0.035
Group III	13 / 823 (1.6)	2 / 772 (0.3)	6.10	[1.38; 26.93]	0.017
Anatomic stages					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	21 / 1287 (1.6)	2 / 1258 (0.2)	10.26	[2.41; 43.68]	0.002
>T3	2 / 113 (1.8)	0 / 97 (0.0)	4.30	[0.21; 88.46]	0.345
Nodal status					
Interaction test	N.E.				
N0	2 / 190 (1.1)	0 / 200 (0.0)	5.26	[0.25; >99.99]	0.283
N1-N3	21 / 1216 (1.7)	2 / 1160 (0.2)	10.02	[2.35; 42.62]	0.002
Histological grade at time of surgery					
Interaction test	N.E.				
Grade 1	3 / 102 (2.9)	0 / 106 (0.0)	7.27	[0.38; >99.99]	0.188
Grade 2	14 / 842 (1.7)	0 / 768 (0.0)	26.45	[1.58; >99.99]	0.023
Grade 3	5 / 373 (1.3)	1 / 397 (0.3)	5.32	[0.62; 45.34]	0.126
Histological subtype					
Interaction test	p = 0.497				
Ductal	16 / 1025 (1.6)	1 / 1010 (0.1)	15.77	[2.09; >99.99]	0.007
Lobular	6 / 291 (2.1)	1 / 276 (0.4)	5.69	[0.69; 46.97]	0.106
Other	1 / 92 (1.1)	0 / 76 (0.0)	2.48	[0.10; 60.11]	0.576
Ki67 status from surgical specimen					
Interaction test	N.E.				
Ki67≤20	9 / 660 (1.4)	2 / 629 (0.3)	4.29	[0.93; 19.77]	0.062
Ki67>20	8 / 489 (1.6)	0 / 516 (0.0)	17.94	[1.04; >99.99]	0.047
Type of NSAI					
Interaction test	N.E.				
Letrozole	15 / 907 (1.7)	2 / 895 (0.2)	7.40	[1.70; 32.27]	0.008
Anastrozole	8 / 502 (1.6)	0 / 467 (0.0)	15.82	[0.92; >99.99]	0.058
Prior neo/adjuvant chemotherapy					
Interaction test	N.E.				
Yes	18 / 1194 (1.5)	2 / 1146 (0.2)	8.64	[2.01; 37.14]	0.004
No	5 / 215 (2.3)	0 / 216 (0.0)	11.05	[0.61; >99.99]	0.103
Prior adjuvant chemotherapy					
Interaction test	N.E.				
Yes	12 / 694 (1.7)	0 / 673 (0.0)	24.24	[1.44; >99.99]	0.027
No	11 / 715 (1.5)	2 / 689 (0.3)	5.30	[1.18; 23.82]	0.030
Prior neoadjuvant chemotherapy					
Interaction test	N.E.				
Yes	6 / 528 (1.1)	2 / 503 (0.4)	2.86	[0.58; 14.09]	0.197
No	17 / 881 (1.9)	0 / 859 (0.0)	34.13	[2.06; >99.99]	0.014

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior endocrine therapy					
Interaction test	N.E.				
Yes	14 / 957 (1.5)	2 / 940 (0.2)	6.88	[1.57; 30.17]	0.011
No	9 / 452 (2.0)	0 / 422 (0.0)	17.74	[1.04; >99.99]	0.047
Prior mastectomy					
Interaction test	N.E.				
Yes	12 / 857 (1.4)	2 / 847 (0.2)	5.93	[1.33; 26.42]	0.020
No	11 / 552 (2.0)	0 / 515 (0.0)	21.46	[1.27; >99.99]	0.034
Prior radiotherapy					
Interaction test	N.E.				
Yes	20 / 1253 (1.6)	2 / 1203 (0.2)	9.60	[2.25; 40.99]	0.002
No	3 / 156 (1.9)	0 / 159 (0.0)	7.13	[0.37; >99.99]	0.192
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

5-3.4 Subgroup analysis for serious adverse events by SOC and PT

Table 5-3.4.1 SOC infections and infestations: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Infections and infestations					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.226				
NA/WE/O	51 / 899 (5.7)	33 / 856 (3.9)	1.47	[0.96; 2.26]	0.077
ROW	31 / 510 (6.1)	13 / 506 (2.6)	2.37	[1.25; 4.47]	0.008
Geographical region					
Interaction test	p = 0.850				
Europe	48 / 832 (5.8)	27 / 824 (3.3)	1.76	[1.11; 2.79]	0.016
North America/Australia	26 / 400 (6.5)	16 / 364 (4.4)	1.48	[0.81; 2.71]	0.206
Asia	4 / 102 (3.9)	2 / 101 (2.0)	1.98	[0.37; 10.57]	0.424
Latin America	4 / 75 (5.3)	1 / 73 (1.4)	3.89	[0.45; 34.01]	0.219
Age group 1 at randomization					
Interaction test	p = 0.506				
<45	6 / 60 (10.0)	5 / 52 (9.6)	1.04	[0.34; 3.21]	0.946
45 to 54	14 / 300 (4.7)	5 / 322 (1.6)	3.01	[1.10; 8.24]	0.033
55 to 64	35 / 651 (5.4)	19 / 642 (3.0)	1.82	[1.05; 3.14]	0.033
≥65	27 / 398 (6.8)	17 / 346 (4.9)	1.38	[0.77; 2.49]	0.283
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.896				
<Median	32 / 633 (5.1)	18 / 632 (2.8)	1.77	[1.01; 3.13]	0.047
≥Median	50 / 776 (6.4)	28 / 730 (3.8)	1.68	[1.07; 2.64]	0.024
Race					
Interaction test	p = 0.914				
Asian	5 / 128 (3.9)	3 / 127 (2.4)	1.65	[0.40; 6.77]	0.484
Non-Asian	75 / 1203 (6.2)	41 / 1167 (3.5)	1.77	[1.22; 2.57]	0.003
BMI at screening					
Interaction test	p = 0.816				
≥25	62 / 935 (6.6)	37 / 935 (4.0)	1.68	[1.13; 2.49]	0.011
<25	19 / 460 (4.1)	9 / 410 (2.2)	1.88	[0.86; 4.11]	0.113
AJCC Anatomic Stage Group					
Interaction test	p = 0.700				
Group I/II	37 / 585 (6.3)	20 / 589 (3.4)	1.86	[1.09; 3.17]	0.022
Group III	45 / 823 (5.5)	26 / 772 (3.4)	1.62	[1.01; 2.60]	0.045

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.168				
IA/IB/IIA	16 / 310 (5.2)	9 / 311 (2.9)	1.78	[0.80; 3.97]	0.157
IIB	21 / 275 (7.6)	11 / 278 (4.0)	1.93	[0.95; 3.93]	0.070
IIIA	23 / 482 (4.8)	21 / 450 (4.7)	1.02	[0.57; 1.82]	0.940
IIIB	7 / 100 (7.0)	1 / 82 (1.2)	5.74	[0.72; 45.71]	0.099
IIIC	15 / 241 (6.2)	4 / 240 (1.7)	3.73	[1.26; 11.09]	0.018
Tumor category					
Interaction test	p = 0.101				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	72 / 1287 (5.6)	45 / 1258 (3.6)	1.56	[1.09; 2.25]	0.016
>T3	10 / 113 (8.8)	1 / 97 (1.0)	8.58	[1.12; 65.86]	0.039
Nodal status					
Interaction test	p = 0.049				
N0	13 / 190 (6.8)	2 / 200 (1.0)	6.84	[1.56; 29.92]	0.011
N1-N3	69 / 1216 (5.7)	44 / 1160 (3.8)	1.50	[1.03; 2.16]	0.033
Histological grade at time of surgery					
Interaction test	p = 0.259				
Grade 1	7 / 102 (6.9)	7 / 106 (6.6)	1.04	[0.38; 2.86]	0.941
Grade 2	48 / 842 (5.7)	30 / 768 (3.9)	1.46	[0.93; 2.28]	0.096
Grade 3	23 / 373 (6.2)	9 / 397 (2.3)	2.72	[1.28; 5.80]	0.010
Histological subtype					
Interaction test	p = 0.357				
Ductal	64 / 1025 (6.2)	35 / 1010 (3.5)	1.80	[1.20; 2.70]	0.004
Lobular	15 / 291 (5.2)	7 / 276 (2.5)	2.03	[0.84; 4.91]	0.115
Other	3 / 92 (3.3)	4 / 76 (5.3)	0.62	[0.14; 2.68]	0.522
Ki67 status from surgical specimen					
Interaction test	p = 0.158				
Ki67≤20	33 / 660 (5.0)	24 / 629 (3.8)	1.31	[0.78; 2.19]	0.303
Ki67>20	31 / 489 (6.3)	14 / 516 (2.7)	2.34	[1.26; 4.34]	0.007
Type of NSAI					
Interaction test	p = 0.099				
Letrozole	44 / 907 (4.9)	32 / 895 (3.6)	1.36	[0.87; 2.12]	0.180
Anastrozole	38 / 502 (7.6)	14 / 467 (3.0)	2.53	[1.39; 4.60]	0.002
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.452				
Yes	64 / 1194 (5.4)	38 / 1146 (3.3)	1.62	[1.09; 2.40]	0.017
No	18 / 215 (8.4)	8 / 216 (3.7)	2.26	[1.00; 5.09]	0.049
Prior adjuvant chemotherapy					
Interaction test	p = 0.283				
Yes	40 / 694 (5.8)	27 / 673 (4.0)	1.44	[0.89; 2.31]	0.136
No	42 / 715 (5.9)	19 / 689 (2.8)	2.13	[1.25; 3.63]	0.005

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.385				
Yes	26 / 528 (4.9)	11 / 503 (2.2)	2.25	[1.12; 4.51]	0.022
No	56 / 881 (6.4)	35 / 859 (4.1)	1.56	[1.03; 2.35]	0.034
Prior endocrine therapy					
Interaction test	p = 0.868				
Yes	55 / 957 (5.7)	32 / 940 (3.4)	1.69	[1.10; 2.59]	0.016
No	27 / 452 (6.0)	14 / 422 (3.3)	1.80	[0.96; 3.39]	0.068
Prior mastectomy					
Interaction test	p = 0.042				
Yes	61 / 857 (7.1)	27 / 847 (3.2)	2.23	[1.43; 3.48]	<.001
No	21 / 552 (3.8)	19 / 515 (3.7)	1.03	[0.56; 1.90]	0.921
Prior radiotherapy					
Interaction test	p = 0.448				
Yes	68 / 1253 (5.4)	40 / 1203 (3.3)	1.63	[1.11; 2.39]	0.012
No	14 / 156 (9.0)	6 / 159 (3.8)	2.38	[0.94; 6.03]	0.068
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.4.2 SOC respiratory, thoracic and mediastinal disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Respiratory, thoracic and mediastinal disorders					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.607				
NA/WE/O	24 / 899 (2.7)	10 / 856 (1.2)	2.29	[1.10; 4.75]	0.027
ROW	10 / 510 (2.0)	6 / 506 (1.2)	1.65	[0.61; 4.52]	0.326
Geographical region					
Interaction test	p = 0.092				
Europe	13 / 832 (1.6)	12 / 824 (1.5)	1.07	[0.49; 2.34]	0.859
North America/Australia	16 / 400 (4.0)	3 / 364 (0.8)	4.85	[1.43; 16.52]	0.011
Asia	1 / 102 (1.0)	0 / 101 (0.0)	2.97	[0.12; 72.08]	0.503
Latin America	4 / 75 (5.3)	1 / 73 (1.4)	3.89	[0.45; 34.01]	0.219
Age group 1 at randomization					
Interaction test	p = 0.096				
<45	2 / 60 (3.3)	1 / 52 (1.9)	1.73	[0.16; 18.57]	0.649
45 to 54	6 / 300 (2.0)	3 / 322 (0.9)	2.15	[0.54; 8.51]	0.277
55 to 64	7 / 651 (1.1)	9 / 642 (1.4)	0.77	[0.29; 2.05]	0.596
≥65	19 / 398 (4.8)	3 / 346 (0.9)	5.51	[1.64; 18.45]	0.006
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.783				
<Median	11 / 633 (1.7)	6 / 632 (0.9)	1.83	[0.68; 4.92]	0.231
≥Median	23 / 776 (3.0)	10 / 730 (1.4)	2.16	[1.04; 4.51]	0.040
Race					
Interaction test	N.E.				
Asian	1 / 128 (0.8)	0 / 127 (0.0)	2.98	[0.12; 72.39]	0.503
Non-Asian	33 / 1203 (2.7)	14 / 1167 (1.2)	2.29	[1.23; 4.25]	0.009
BMI at screening					
Interaction test	p = 0.387				
≥25	28 / 935 (3.0)	14 / 935 (1.5)	2.00	[1.06; 3.77]	0.032
<25	6 / 460 (1.3)	1 / 410 (0.2)	5.35	[0.65; 44.23]	0.120
AJCC Anatomic Stage Group					
Interaction test	p = 0.205				
Group I/II	12 / 585 (2.1)	3 / 589 (0.5)	4.03	[1.14; 14.20]	0.030
Group III	22 / 823 (2.7)	13 / 772 (1.7)	1.59	[0.81; 3.13]	0.182

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.231				
IA/IB/IIA	5 / 310 (1.6)	2 / 311 (0.6)	2.51	[0.49; 12.83]	0.270
IIB	7 / 275 (2.5)	1 / 278 (0.4)	7.08	[0.88; 57.13]	0.066
IIIA	7 / 482 (1.5)	8 / 450 (1.8)	0.82	[0.30; 2.23]	0.694
IIIB	6 / 100 (6.0)	3 / 82 (3.7)	1.64	[0.42; 6.36]	0.474
IIIC	9 / 241 (3.7)	2 / 240 (0.8)	4.48	[0.98; 20.52]	0.053
Tumor category					
Interaction test	p = 0.809				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	28 / 1287 (2.2)	13 / 1258 (1.0)	2.11	[1.10; 4.05]	0.025
>T3	6 / 113 (5.3)	3 / 97 (3.1)	1.72	[0.44; 6.68]	0.436
Nodal status					
Interaction test	N.E.				
N0	6 / 190 (3.2)	0 / 200 (0.0)	13.68	[0.78; >99.99]	0.074
N1-N3	28 / 1216 (2.3)	16 / 1160 (1.4)	1.67	[0.91; 3.07]	0.099
Histological grade at time of surgery					
Interaction test	p = 0.112				
Grade 1	1 / 102 (1.0)	4 / 106 (3.8)	0.26	[0.03; 2.29]	0.224
Grade 2	19 / 842 (2.3)	6 / 768 (0.8)	2.89	[1.16; 7.19]	0.023
Grade 3	14 / 373 (3.8)	5 / 397 (1.3)	2.98	[1.08; 8.19]	0.034
Histological subtype					
Interaction test	p = 0.938				
Ductal	29 / 1025 (2.8)	13 / 1010 (1.3)	2.20	[1.15; 4.20]	0.017
Lobular	5 / 291 (1.7)	2 / 276 (0.7)	2.37	[0.46; 12.12]	0.300
Other	0 / 92 (0.0)	1 / 76 (1.3)	0.28	[0.01; 6.68]	0.428
Ki67 status from surgical specimen					
Interaction test	p = 0.538				
Ki67≤20	15 / 660 (2.3)	6 / 629 (1.0)	2.38	[0.93; 6.10]	0.070
Ki67>20	12 / 489 (2.5)	8 / 516 (1.6)	1.58	[0.65; 3.84]	0.310
Type of NSAI					
Interaction test	p = 0.497				
Letrozole	20 / 907 (2.2)	8 / 895 (0.9)	2.47	[1.09; 5.57]	0.030
Anastrozole	14 / 502 (2.8)	8 / 467 (1.7)	1.63	[0.69; 3.85]	0.266
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.977				
Yes	30 / 1194 (2.5)	14 / 1146 (1.2)	2.06	[1.10; 3.86]	0.025
No	4 / 215 (1.9)	2 / 216 (0.9)	2.01	[0.37; 10.86]	0.417
Prior adjuvant chemotherapy					
Interaction test	p = 0.837				
Yes	18 / 694 (2.6)	9 / 673 (1.3)	1.94	[0.88; 4.29]	0.102
No	16 / 715 (2.2)	7 / 689 (1.0)	2.20	[0.91; 5.32]	0.079

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.807				
Yes	12 / 528 (2.3)	5 / 503 (1.0)	2.29	[0.81; 6.44]	0.118
No	22 / 881 (2.5)	11 / 859 (1.3)	1.95	[0.95; 4.00]	0.068
Prior endocrine therapy					
Interaction test	p = 0.974				
Yes	25 / 957 (2.6)	12 / 940 (1.3)	2.05	[1.03; 4.05]	0.040
No	9 / 452 (2.0)	4 / 422 (0.9)	2.10	[0.65; 6.77]	0.214
Prior mastectomy					
Interaction test	p = 0.819				
Yes	24 / 857 (2.8)	11 / 847 (1.3)	2.16	[1.06; 4.37]	0.033
No	10 / 552 (1.8)	5 / 515 (1.0)	1.87	[0.64; 5.42]	0.252
Prior radiotherapy					
Interaction test	p = 0.993				
Yes	32 / 1253 (2.6)	15 / 1203 (1.2)	2.05	[1.11; 3.76]	0.021
No	2 / 156 (1.3)	1 / 159 (0.6)	2.04	[0.19; 22.25]	0.559
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.4.3 SOC general disorders and administration site conditions: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
General disorders and administration site conditions					
	n / N (%)	n / N (%)			
Region					
Interaction test	N.E.				
NA/WE/O	12 / 899 (1.3)	5 / 856 (0.6)	2.29	[0.81; 6.46]	0.119
ROW	3 / 510 (0.6)	0 / 506 (0.0)	6.95	[0.36; >99.99]	0.199
Geographical region					
Interaction test	p = 0.699				
Europe	9 / 832 (1.1)	4 / 824 (0.5)	2.23	[0.69; 7.21]	0.181
North America/Australia	4 / 400 (1.0)	1 / 364 (0.3)	3.64	[0.41; 32.42]	0.247
Asia	2 / 102 (2.0)	0 / 101 (0.0)	4.95	[0.24; >99.99]	0.300
Latin America	0 / 75 (0.0)	0 / 73 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.104				
<Median	5 / 633 (0.8)	4 / 632 (0.6)	1.25	[0.34; 4.63]	0.740
≥Median	10 / 776 (1.3)	1 / 730 (0.1)	9.41	[1.21; 73.30]	0.032
Race					
Interaction test	N.E.				
Asian	2 / 128 (1.6)	0 / 127 (0.0)	4.96	[0.24; >99.99]	0.300
Non-Asian	12 / 1203 (1.0)	4 / 1167 (0.3)	2.91	[0.94; 9.00]	0.064
BMI at screening					
Interaction test	p = 0.251				
≥25	7 / 935 (0.7)	4 / 935 (0.4)	1.75	[0.51; 5.96]	0.371
<25	8 / 460 (1.7)	1 / 410 (0.2)	7.13	[0.90; 56.77]	0.063
AJCC Anatomic Stage Group					
Interaction test	p = 0.947				
Group I/II	6 / 585 (1.0)	2 / 589 (0.3)	3.02	[0.61; 14.90]	0.175
Group III	9 / 823 (1.1)	3 / 772 (0.4)	2.81	[0.76; 10.36]	0.120
Anatomic stages					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Tumor category					
Interaction test	p = 0.927				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	12 / 1287 (0.9)	4 / 1258 (0.3)	2.93	[0.95; 9.07]	0.062
>T3	3 / 113 (2.7)	1 / 97 (1.0)	2.58	[0.27; 24.36]	0.409
Nodal status					
Interaction test	p = 0.121				
N0	1 / 190 (0.5)	2 / 200 (1.0)	0.53	[0.05; 5.76]	0.599
N1-N3	14 / 1216 (1.2)	3 / 1160 (0.3)	4.45	[1.28; 15.45]	0.019
Histological grade at time of surgery					
Interaction test	p = 0.503				
Grade 1	0 / 102 (0.0)	0 / 106 (0.0)	N.E.	N.E.	N.E.
Grade 2	7 / 842 (0.8)	3 / 768 (0.4)	2.13	[0.55; 8.20]	0.272
Grade 3	8 / 373 (2.1)	2 / 397 (0.5)	4.26	[0.91; 19.92]	0.066
Histological subtype					
Interaction test	N.E.				
Ductal	12 / 1025 (1.2)	5 / 1010 (0.5)	2.36	[0.84; 6.69]	0.105
Lobular	3 / 291 (1.0)	0 / 276 (0.0)	6.64	[0.34; >99.99]	0.210
Other	0 / 92 (0.0)	0 / 76 (0.0)	N.E.	N.E.	N.E.
Ki67 status from surgical specimen					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Type of NSAI					
Interaction test	p = 0.611				
Letrozole	10 / 907 (1.1)	4 / 895 (0.4)	2.47	[0.78; 7.84]	0.126
Anastrozole	5 / 502 (1.0)	1 / 467 (0.2)	4.65	[0.55; 39.67]	0.160
Prior neo/adjuvant chemotherapy					
Interaction test	N.E.				
Yes	14 / 1194 (1.2)	5 / 1146 (0.4)	2.69	[0.97; 7.44]	0.057
No	1 / 215 (0.5)	0 / 216 (0.0)	3.01	[0.12; 73.57]	0.499
Prior adjuvant chemotherapy					
Interaction test	p = 0.611				
Yes	7 / 694 (1.0)	3 / 673 (0.4)	2.26	[0.59; 8.71]	0.235
No	8 / 715 (1.1)	2 / 689 (0.3)	3.85	[0.82; 18.09]	0.087
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.619				
Yes	8 / 528 (1.5)	2 / 503 (0.4)	3.81	[0.81; 17.86]	0.090
No	7 / 881 (0.8)	3 / 859 (0.3)	2.28	[0.59; 8.77]	0.232

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior endocrine therapy					
Interaction test	N.E.				
Yes	11 / 957 (1.1)	5 / 940 (0.5)	2.16	[0.75; 6.20]	0.152
No	4 / 452 (0.9)	0 / 422 (0.0)	8.40	[0.45; >99.99]	0.153
Prior mastectomy					
Interaction test	p = 0.804				
Yes	11 / 857 (1.3)	4 / 847 (0.5)	2.72	[0.87; 8.50]	0.086
No	4 / 552 (0.7)	1 / 515 (0.2)	3.73	[0.42; 33.28]	0.238
Prior radiotherapy					
Interaction test	N.E.				
Yes	15 / 1253 (1.2)	4 / 1203 (0.3)	3.60	[1.20; 10.82]	0.022
No	0 / 156 (0.0)	1 / 159 (0.6)	0.34	[0.01; 8.28]	0.507
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.4.4 SOC hepatobiliary disorders: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Hepatobiliary disorders					
	n / N (%)	n / N (%)			
Region The subgroup analysis is not presented as all subgroups have less than 10 events.					
Geographical region The subgroup analysis is not presented as all subgroups have less than 10 events.					
Age group 1 at randomization The subgroup analysis is not presented as all subgroups have less than 10 events.					
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	N.E.				
<Median	4 / 633 (0.6)	1 / 632 (0.2)	3.99	[0.45; 35.63]	0.215
≥Median	11 / 776 (1.4)	0 / 730 (0.0)	21.64	[1.28; >99.99]	0.033
Race					
Interaction test	N.E.				
Asian	2 / 128 (1.6)	0 / 127 (0.0)	4.96	[0.24; >99.99]	0.300
Non-Asian	12 / 1203 (1.0)	1 / 1167 (0.1)	11.64	[1.52; 89.38]	0.018
BMI at screening					
Interaction test	N.E.				
≥25	13 / 935 (1.4)	1 / 935 (0.1)	13.00	[1.70; 99.17]	0.013
<25	2 / 460 (0.4)	0 / 410 (0.0)	4.46	[0.21; 92.58]	0.334
AJCC Anatomic Stage Group The subgroup analysis is not presented as all subgroups have less than 10 events.					
Anatomic stages The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Tumor category					
Interaction test	N.E.				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	14 / 1287 (1.1)	1 / 1258 (0.1)	13.68	[1.80; >99.99]	0.011
>T3	1 / 113 (0.9)	0 / 97 (0.0)	2.58	[0.11; 62.59]	0.560
Nodal status					
Interaction test	N.E.				
N0	2 / 190 (1.1)	0 / 200 (0.0)	5.26	[0.25; >99.99]	0.283
N1-N3	13 / 1216 (1.1)	1 / 1160 (0.1)	12.40	[1.62; 94.65]	0.015
Histological grade at time of surgery					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Histological subtype					
Interaction test	N.E.				
Ductal	12 / 1025 (1.2)	0 / 1010 (0.0)	24.63	[1.46; >99.99]	0.026
Lobular	2 / 291 (0.7)	1 / 276 (0.4)	1.90	[0.17; 20.80]	0.600
Other	1 / 92 (1.1)	0 / 76 (0.0)	2.48	[0.10; 60.11]	0.576
Ki67 status from surgical specimen					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Type of NSAI					
Interaction test	N.E.				
Letrozole	11 / 907 (1.2)	1 / 895 (0.1)	10.85	[1.40; 83.90]	0.022
Anastrozole	4 / 502 (0.8)	0 / 467 (0.0)	8.37	[0.45; >99.99]	0.154
Prior neo/adjuvant chemotherapy					
Interaction test	N.E.				
Yes	11 / 1194 (0.9)	1 / 1146 (0.1)	10.56	[1.37; 81.64]	0.024
No	4 / 215 (1.9)	0 / 216 (0.0)	9.04	[0.49; >99.99]	0.139
Prior adjuvant chemotherapy					
Interaction test	N.E.				
Yes	6 / 694 (0.9)	0 / 673 (0.0)	12.61	[0.71; >99.99]	0.084
No	9 / 715 (1.3)	1 / 689 (0.1)	8.67	[1.10; 68.27]	0.040
Prior neoadjuvant chemotherapy					
Interaction test	N.E.				
Yes	5 / 528 (0.9)	1 / 503 (0.2)	4.76	[0.56; 40.63]	0.154
No	10 / 881 (1.1)	0 / 859 (0.0)	20.48	[1.20; >99.99]	0.037

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior endocrine therapy					
Interaction test	N.E.				
Yes	9 / 957 (0.9)	1 / 940 (0.1)	8.84	[1.12; 69.64]	0.039
No	6 / 452 (1.3)	0 / 422 (0.0)	12.14	[0.69; >99.99]	0.089
Prior mastectomy					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior radiotherapy					
Interaction test	N.E.				
Yes	12 / 1253 (1.0)	1 / 1203 (0.1)	11.52	[1.50; 88.47]	0.019
No	3 / 156 (1.9)	0 / 159 (0.0)	7.13	[0.37; >99.99]	0.192
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

5-3.5 Subgroup analysis for adverse events of special interest

Table 5-3.5.1 Hepatobiliary toxicity: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Hepatobiliary toxicity					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.131				
NA/WE/O	220 / 899 (24.5)	67 / 856 (7.8)	3.13	[2.42; 4.04]	<.001
ROW	183 / 510 (35.9)	85 / 506 (16.8)	2.14	[1.70; 2.68]	<.001
Geographical region					
Interaction test	p = 0.375				
Europe	256 / 832 (30.8)	111 / 824 (13.5)	2.28	[1.87; 2.79]	<.001
North America/Australia	102 / 400 (25.5)	26 / 364 (7.1)	3.57	[2.38; 5.36]	<.001
Asia	27 / 102 (26.5)	10 / 101 (9.9)	2.67	[1.37; 5.23]	0.004
Latin America	18 / 75 (24.0)	5 / 73 (6.8)	3.50	[1.37; 8.94]	0.009
Age group 1 at randomization					
Interaction test	p = 0.040				
<45	12 / 60 (20.0)	3 / 52 (5.8)	3.47	[1.03; 11.62]	0.044
45 to 54	69 / 300 (23.0)	41 / 322 (12.7)	1.81	[1.27; 2.57]	0.001
55 to 64	204 / 651 (31.3)	62 / 642 (9.7)	3.24	[2.50; 4.22]	<.001
≥65	118 / 398 (29.6)	46 / 346 (13.3)	2.23	[1.64; 3.04]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.102				
<Median	162 / 633 (25.6)	73 / 632 (11.6)	2.22	[1.72; 2.85]	<.001
≥Median	241 / 776 (31.1)	79 / 730 (10.8)	2.87	[2.27; 3.62]	<.001
Race					
Interaction test	p = 0.958				
Asian	30 / 128 (23.4)	11 / 127 (8.7)	2.71	[1.42; 5.16]	0.003
Non-Asian	356 / 1203 (29.6)	132 / 1167 (11.3)	2.62	[2.18; 3.14]	<.001
BMI at screening					
Interaction test	p = 0.038				
≥25	311 / 935 (33.3)	111 / 935 (11.9)	2.80	[2.30; 3.41]	<.001
<25	88 / 460 (19.1)	39 / 410 (9.5)	2.01	[1.41; 2.86]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.276				
Group I/II	173 / 585 (29.6)	61 / 589 (10.4)	2.86	[2.18; 3.73]	<.001
Group III	229 / 823 (27.8)	91 / 772 (11.8)	2.36	[1.89; 2.95]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.514				
IA/IB/IIA	89 / 310 (28.7)	32 / 311 (10.3)	2.79	[1.92; 4.05]	<.001
IIB	84 / 275 (30.5)	29 / 278 (10.4)	2.93	[1.99; 4.32]	<.001
IIIA	130 / 482 (27.0)	56 / 450 (12.4)	2.17	[1.63; 2.88]	<.001
IIIB	33 / 100 (33.0)	14 / 82 (17.1)	1.93	[1.11; 3.36]	0.019
IIIC	66 / 241 (27.4)	21 / 240 (8.8)	3.13	[1.98; 4.94]	<.001
Tumor category					
Interaction test	p = 0.357				
T0	0 / 5 (0.0)	1 / 5 (20.0)	0.33	[0.02; 6.65]	0.472
T1-T3	367 / 1287 (28.5)	136 / 1258 (10.8)	2.64	[2.20; 3.16]	<.001
>T3	34 / 113 (30.1)	15 / 97 (15.5)	1.95	[1.13; 3.35]	0.016
Nodal status					
Interaction test	p = 0.748				
N0	57 / 190 (30.0)	22 / 200 (11.0)	2.73	[1.74; 4.28]	<.001
N1-N3	346 / 1216 (28.5)	130 / 1160 (11.2)	2.54	[2.11; 3.05]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.685				
Grade 1	26 / 102 (25.5)	13 / 106 (12.3)	2.08	[1.13; 3.82]	0.018
Grade 2	245 / 842 (29.1)	82 / 768 (10.7)	2.73	[2.16; 3.43]	<.001
Grade 3	112 / 373 (30.0)	44 / 397 (11.1)	2.71	[1.97; 3.73]	<.001
Histological subtype					
Interaction test	p = 0.055				
Ductal	288 / 1025 (28.1)	125 / 1010 (12.4)	2.27	[1.88; 2.75]	<.001
Lobular	81 / 291 (27.8)	19 / 276 (6.9)	4.04	[2.52; 6.48]	<.001
Other	34 / 92 (37.0)	8 / 76 (10.5)	3.51	[1.73; 7.12]	<.001
Ki67 status from surgical specimen					
Interaction test	p = 0.836				
Ki67≤20	177 / 660 (26.8)	71 / 629 (11.3)	2.38	[1.85; 3.06]	<.001
Ki67>20	150 / 489 (30.7)	66 / 516 (12.8)	2.40	[1.85; 3.12]	<.001
Type of NSAI					
Interaction test	p = 0.434				
Letrozole	266 / 907 (29.3)	108 / 895 (12.1)	2.43	[1.98; 2.98]	<.001
Anastrozole	137 / 502 (27.3)	44 / 467 (9.4)	2.90	[2.11; 3.97]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.957				
Yes	321 / 1194 (26.9)	117 / 1146 (10.2)	2.63	[2.17; 3.20]	<.001
No	82 / 215 (38.1)	35 / 216 (16.2)	2.35	[1.66; 3.33]	<.001
Prior adjuvant chemotherapy					
Interaction test	p = 0.399				
Yes	175 / 694 (25.2)	70 / 673 (10.4)	2.42	[1.88; 3.13]	<.001
No	228 / 715 (31.9)	82 / 689 (11.9)	2.68	[2.13; 3.37]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.309				
Yes	157 / 528 (29.7)	52 / 503 (10.3)	2.88	[2.15; 3.84]	<.001
No	246 / 881 (27.9)	100 / 859 (11.6)	2.40	[1.94; 2.97]	<.001
Prior endocrine therapy					
Interaction test	p = 0.159				
Yes	252 / 957 (26.3)	85 / 940 (9.0)	2.91	[2.32; 3.66]	<.001
No	151 / 452 (33.4)	67 / 422 (15.9)	2.10	[1.63; 2.72]	<.001
Prior mastectomy					
Interaction test	p = 0.671				
Yes	253 / 857 (29.5)	101 / 847 (11.9)	2.48	[2.01; 3.05]	<.001
No	150 / 552 (27.2)	51 / 515 (9.9)	2.74	[2.04; 3.68]	<.001
Prior radiotherapy					
Interaction test	p = 0.267				
Yes	335 / 1253 (26.7)	115 / 1203 (9.6)	2.80	[2.30; 3.40]	<.001
No	68 / 156 (43.6)	37 / 159 (23.3)	1.87	[1.34; 2.62]	<.001
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.5.2 ILD Pneumonitis: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
ILD Pneumonitis					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.164				
NA/WE/O	12 / 899 (1.3)	4 / 856 (0.5)	2.86	[0.92; 8.82]	0.068
ROW	13 / 510 (2.5)	12 / 506 (2.4)	1.07	[0.50; 2.33]	0.855
Geographical region					
Interaction test	p = 0.359				
Europe	15 / 832 (1.8)	15 / 824 (1.8)	0.99	[0.49; 2.01]	0.979
North America/Australia	7 / 400 (1.8)	0 / 364 (0.0)	13.65	[0.78; >99.99]	0.073
Asia	3 / 102 (2.9)	1 / 101 (1.0)	2.97	[0.31; 28.08]	0.342
Latin America	0 / 75 (0.0)	0 / 73 (0.0)	N.E.	N.E.	N.E.
Age group 1 at randomization					
Interaction test	p = 0.850				
<45	1 / 60 (1.7)	0 / 52 (0.0)	2.61	[0.11; 62.64]	0.555
45 to 54	4 / 300 (1.3)	3 / 322 (0.9)	1.43	[0.32; 6.34]	0.637
55 to 64	13 / 651 (2.0)	10 / 642 (1.6)	1.28	[0.57; 2.90]	0.551
≥65	7 / 398 (1.8)	3 / 346 (0.9)	2.03	[0.53; 7.78]	0.303
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.682				
<Median	9 / 633 (1.4)	7 / 632 (1.1)	1.28	[0.48; 3.43]	0.618
≥Median	16 / 776 (2.1)	9 / 730 (1.2)	1.67	[0.74; 3.76]	0.214
Race					
Interaction test	p = 0.536				
Asian	3 / 128 (2.3)	1 / 127 (0.8)	2.98	[0.31; 28.24]	0.342
Non-Asian	22 / 1203 (1.8)	15 / 1167 (1.3)	1.42	[0.74; 2.73]	0.289
BMI at screening					
Interaction test	p = 0.411				
≥25	18 / 935 (1.9)	14 / 935 (1.5)	1.29	[0.64; 2.57]	0.477
<25	6 / 460 (1.3)	2 / 410 (0.5)	2.67	[0.54; 13.17]	0.227
AJCC Anatomic Stage Group					
Interaction test	p = 0.789				
Group I/II	10 / 585 (1.7)	6 / 589 (1.0)	1.68	[0.61; 4.59]	0.313
Group III	15 / 823 (1.8)	10 / 772 (1.3)	1.41	[0.64; 3.11]	0.399

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.654				
IA/IB/IIA	4 / 310 (1.3)	3 / 311 (1.0)	1.34	[0.30; 5.93]	0.702
IIB	6 / 275 (2.2)	3 / 278 (1.1)	2.02	[0.51; 8.00]	0.316
IIIA	10 / 482 (2.1)	6 / 450 (1.3)	1.56	[0.57; 4.25]	0.388
IIIB	4 / 100 (4.0)	1 / 82 (1.2)	3.28	[0.37; 28.78]	0.284
IIIC	1 / 241 (0.4)	3 / 240 (1.3)	0.33	[0.03; 3.17]	0.338
Tumor category					
Interaction test	p = 0.424				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	21 / 1287 (1.6)	15 / 1258 (1.2)	1.37	[0.71; 2.64]	0.350
>T3	4 / 113 (3.5)	1 / 97 (1.0)	3.43	[0.39; 30.21]	0.266
Nodal status					
Interaction test	p = 0.463				
N0	5 / 190 (2.6)	2 / 200 (1.0)	2.63	[0.52; 13.40]	0.244
N1-N3	20 / 1216 (1.6)	14 / 1160 (1.2)	1.36	[0.69; 2.69]	0.371
Histological grade at time of surgery					
Interaction test	p = 0.581				
Grade 1	0 / 102 (0.0)	4 / 106 (3.8)	0.12	[<0.01; 2.12]	0.146
Grade 2	11 / 842 (1.3)	7 / 768 (0.9)	1.43	[0.56; 3.68]	0.454
Grade 3	10 / 373 (2.7)	5 / 397 (1.3)	2.13	[0.73; 6.17]	0.164
Histological subtype					
Interaction test	p = 0.450				
Ductal	20 / 1025 (2.0)	12 / 1010 (1.2)	1.64	[0.81; 3.34]	0.171
Lobular	3 / 291 (1.0)	1 / 276 (0.4)	2.85	[0.30; 27.19]	0.364
Other	2 / 92 (2.2)	3 / 76 (3.9)	0.55	[0.09; 3.21]	0.507
Ki67 status from surgical specimen					
Interaction test	p = 0.602				
Ki67≤20	11 / 660 (1.7)	7 / 629 (1.1)	1.50	[0.58; 3.84]	0.400
Ki67>20	9 / 489 (1.8)	9 / 516 (1.7)	1.06	[0.42; 2.64]	0.908
Type of NSAI					
Interaction test	p = 0.431				
Letrozole	21 / 907 (2.3)	12 / 895 (1.3)	1.73	[0.85; 3.49]	0.128
Anastrozole	4 / 502 (0.8)	4 / 467 (0.9)	0.93	[0.23; 3.70]	0.918
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.072				
Yes	22 / 1194 (1.8)	10 / 1146 (0.9)	2.11	[1.00; 4.44]	0.049
No	3 / 215 (1.4)	6 / 216 (2.8)	0.50	[0.13; 1.98]	0.326
Prior adjuvant chemotherapy					
Interaction test	p = 0.981				
Yes	11 / 694 (1.6)	7 / 673 (1.0)	1.52	[0.59; 3.91]	0.381
No	14 / 715 (2.0)	9 / 689 (1.3)	1.50	[0.65; 3.44]	0.340

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.025				
Yes	14 / 528 (2.7)	3 / 503 (0.6)	4.45	[1.29; 15.38]	0.018
No	11 / 881 (1.2)	13 / 859 (1.5)	0.83	[0.37; 1.83]	0.636
Prior endocrine therapy					
Interaction test	p = 0.219				
Yes	17 / 957 (1.8)	8 / 940 (0.9)	2.09	[0.91; 4.81]	0.084
No	8 / 452 (1.8)	8 / 422 (1.9)	0.93	[0.35; 2.47]	0.890
Prior mastectomy					
Interaction test	p = 0.629				
Yes	15 / 857 (1.8)	11 / 847 (1.3)	1.35	[0.62; 2.92]	0.449
No	10 / 552 (1.8)	5 / 515 (1.0)	1.87	[0.64; 5.42]	0.252
Prior radiotherapy					
Interaction test	p = 0.406				
Yes	19 / 1253 (1.5)	10 / 1203 (0.8)	1.82	[0.85; 3.91]	0.122
No	6 / 156 (3.8)	6 / 159 (3.8)	1.02	[0.34; 3.09]	0.973
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.5.3 Infections: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Infections					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.854				
NA/WE/O	505 / 899 (56.2)	352 / 856 (41.1)	1.37	[1.24; 1.51]	<.001
ROW	193 / 510 (37.8)	129 / 506 (25.5)	1.48	[1.23; 1.79]	<.001
Geographical region					
Interaction test	p = 0.454				
Europe	387 / 832 (46.5)	276 / 824 (33.5)	1.39	[1.23; 1.57]	<.001
North America/Australia	231 / 400 (57.8)	159 / 364 (43.7)	1.32	[1.15; 1.53]	<.001
Asia	42 / 102 (41.2)	28 / 101 (27.7)	1.49	[1.00; 2.20]	0.047
Latin America	38 / 75 (50.7)	18 / 73 (24.7)	2.05	[1.30; 3.25]	0.002
Age group 1 at randomization					
Interaction test	p = 0.009				
<45	37 / 60 (61.7)	20 / 52 (38.5)	1.60	[1.08; 2.39]	0.020
45 to 54	172 / 300 (57.3)	105 / 322 (32.6)	1.76	[1.46; 2.12]	<.001
55 to 64	300 / 651 (46.1)	239 / 642 (37.2)	1.24	[1.09; 1.41]	0.001
≥65	189 / 398 (47.5)	117 / 346 (33.8)	1.40	[1.17; 1.68]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.013				
<Median	346 / 633 (54.7)	222 / 632 (35.1)	1.56	[1.37; 1.77]	<.001
≥Median	352 / 776 (45.4)	259 / 730 (35.5)	1.28	[1.13; 1.45]	<.001
Race					
Interaction test	p = 0.627				
Asian	57 / 128 (44.5)	42 / 127 (33.1)	1.35	[0.98; 1.84]	0.063
Non-Asian	604 / 1203 (50.2)	411 / 1167 (35.2)	1.43	[1.30; 1.57]	<.001
BMI at screening					
Interaction test	p = 0.542				
≥25	472 / 935 (50.5)	331 / 935 (35.4)	1.43	[1.28; 1.59]	<.001
<25	219 / 460 (47.6)	144 / 410 (35.1)	1.36	[1.15; 1.60]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.012				
Group I/II	264 / 585 (45.1)	215 / 589 (36.5)	1.24	[1.08; 1.42]	0.003
Group III	434 / 823 (52.7)	266 / 772 (34.5)	1.53	[1.36; 1.72]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.037				
IA/IB/IIA	137 / 310 (44.2)	110 / 311 (35.4)	1.25	[1.03; 1.52]	0.026
IIB	127 / 275 (46.2)	105 / 278 (37.8)	1.22	[1.00; 1.49]	0.046
IIIA	253 / 482 (52.5)	171 / 450 (38.0)	1.38	[1.19; 1.60]	<.001
IIIB	50 / 100 (50.0)	21 / 82 (25.6)	1.95	[1.29; 2.96]	0.002
IIIC	131 / 241 (54.4)	74 / 240 (30.8)	1.76	[1.41; 2.20]	<.001
Tumor category					
Interaction test	p = 0.136				
T0	2 / 5 (40.0)	1 / 5 (20.0)	2.00	[0.26; 15.62]	0.509
T1-T3	637 / 1287 (49.5)	455 / 1258 (36.2)	1.37	[1.25; 1.50]	<.001
>T3	58 / 113 (51.3)	24 / 97 (24.7)	2.07	[1.40; 3.07]	<.001
Nodal status					
Interaction test	p = 0.936				
N0	85 / 190 (44.7)	63 / 200 (31.5)	1.42	[1.10; 1.84]	0.008
N1-N3	611 / 1216 (50.2)	418 / 1160 (36.0)	1.39	[1.27; 1.53]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.458				
Grade 1	50 / 102 (49.0)	44 / 106 (41.5)	1.18	[0.87; 1.59]	0.278
Grade 2	416 / 842 (49.4)	267 / 768 (34.8)	1.42	[1.26; 1.60]	<.001
Grade 3	197 / 373 (52.8)	142 / 397 (35.8)	1.48	[1.25; 1.74]	<.001
Histological subtype					
Interaction test	p = 0.913				
Ductal	501 / 1025 (48.9)	347 / 1010 (34.4)	1.42	[1.28; 1.58]	<.001
Lobular	154 / 291 (52.9)	107 / 276 (38.8)	1.37	[1.14; 1.64]	<.001
Other	43 / 92 (46.7)	27 / 76 (35.5)	1.32	[0.91; 1.91]	0.150
Ki67 status from surgical specimen					
Interaction test	p = 0.202				
Ki67≤20	322 / 660 (48.8)	232 / 629 (36.9)	1.32	[1.16; 1.50]	<.001
Ki67>20	227 / 489 (46.4)	154 / 516 (29.8)	1.56	[1.32; 1.83]	<.001
Type of NSAI					
Interaction test	p = 0.332				
Letrozole	433 / 907 (47.7)	313 / 895 (35.0)	1.37	[1.22; 1.53]	<.001
Anastrozole	265 / 502 (52.8)	168 / 467 (36.0)	1.47	[1.27; 1.70]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.026				
Yes	608 / 1194 (50.9)	400 / 1146 (34.9)	1.46	[1.32; 1.61]	<.001
No	90 / 215 (41.9)	81 / 216 (37.5)	1.12	[0.88; 1.41]	0.356
Prior adjuvant chemotherapy					
Interaction test	p = 0.592				
Yes	364 / 694 (52.4)	262 / 673 (38.9)	1.35	[1.20; 1.52]	<.001
No	334 / 715 (46.7)	219 / 689 (31.8)	1.47	[1.28; 1.68]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.018				
Yes	259 / 528 (49.1)	148 / 503 (29.4)	1.67	[1.42; 1.96]	<.001
No	439 / 881 (49.8)	333 / 859 (38.8)	1.29	[1.15; 1.43]	<.001
Prior endocrine therapy					
Interaction test	p = 0.934				
Yes	488 / 957 (51.0)	343 / 940 (36.5)	1.40	[1.26; 1.55]	<.001
No	210 / 452 (46.5)	138 / 422 (32.7)	1.42	[1.20; 1.68]	<.001
Prior mastectomy					
Interaction test	p = 0.522				
Yes	433 / 857 (50.5)	299 / 847 (35.3)	1.43	[1.28; 1.60]	<.001
No	265 / 552 (48.0)	182 / 515 (35.3)	1.36	[1.17; 1.57]	<.001
Prior radiotherapy					
Interaction test	p = 0.233				
Yes	631 / 1253 (50.4)	425 / 1203 (35.3)	1.43	[1.30; 1.57]	<.001
No	67 / 156 (42.9)	56 / 159 (35.2)	1.22	[0.92; 1.61]	0.162
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.5.4 Myelosuppression - Anaemia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Myelosuppression - Anaemia					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.811				
NA/WE/O	70 / 899 (7.8)	23 / 856 (2.7)	2.90	[1.83; 4.60]	<.001
ROW	67 / 510 (13.1)	22 / 506 (4.3)	3.02	[1.90; 4.81]	<.001
Geographical region					
Interaction test	p = 0.872				
Europe	87 / 832 (10.5)	30 / 824 (3.6)	2.87	[1.92; 4.30]	<.001
North America/Australia	33 / 400 (8.3)	10 / 364 (2.7)	3.00	[1.50; 6.01]	0.002
Asia	7 / 102 (6.9)	1 / 101 (1.0)	6.93	[0.87; 55.32]	0.068
Latin America	10 / 75 (13.3)	4 / 73 (5.5)	2.43	[0.80; 7.41]	0.118
Age group 1 at randomization					
Interaction test	p = 0.978				
<45	7 / 60 (11.7)	2 / 52 (3.8)	3.03	[0.66; 13.97]	0.154
45 to 54	16 / 300 (5.3)	5 / 322 (1.6)	3.43	[1.27; 9.26]	0.015
55 to 64	49 / 651 (7.5)	18 / 642 (2.8)	2.68	[1.58; 4.56]	<.001
≥65	65 / 398 (16.3)	20 / 346 (5.8)	2.83	[1.75; 4.57]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.874				
<Median	35 / 633 (5.5)	11 / 632 (1.7)	3.18	[1.63; 6.20]	<.001
≥Median	102 / 776 (13.1)	34 / 730 (4.7)	2.82	[1.94; 4.11]	<.001
Race					
Interaction test	p = 0.338				
Asian	8 / 128 (6.3)	1 / 127 (0.8)	7.94	[1.01; 62.55]	0.049
Non-Asian	123 / 1203 (10.2)	43 / 1167 (3.7)	2.77	[1.98; 3.89]	<.001
BMI at screening					
Interaction test	p = 0.757				
≥25	95 / 935 (10.2)	32 / 935 (3.4)	2.97	[2.01; 4.39]	<.001
<25	39 / 460 (8.5)	13 / 410 (3.2)	2.67	[1.45; 4.94]	0.002
AJCC Anatomic Stage Group					
Interaction test	p = 0.308				
Group I/II	50 / 585 (8.5)	21 / 589 (3.6)	2.40	[1.46; 3.94]	<.001
Group III	86 / 823 (10.4)	24 / 772 (3.1)	3.36	[2.16; 5.23]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.352				
IA/IB/IIA	28 / 310 (9.0)	7 / 311 (2.3)	4.01	[1.78; 9.05]	<.001
IIB	22 / 275 (8.0)	14 / 278 (5.0)	1.59	[0.83; 3.04]	0.162
IIIA	44 / 482 (9.1)	11 / 450 (2.4)	3.73	[1.95; 7.14]	<.001
IIIB	20 / 100 (20.0)	6 / 82 (7.3)	2.73	[1.15; 6.49]	0.023
IIIC	22 / 241 (9.1)	7 / 240 (2.9)	3.13	[1.36; 7.19]	0.007
Tumor category					
Interaction test	p = 0.857				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	115 / 1287 (8.9)	38 / 1258 (3.0)	2.96	[2.07; 4.23]	<.001
>T3	21 / 113 (18.6)	6 / 97 (6.2)	3.00	[1.26; 7.14]	0.013
Nodal status					
Interaction test	p = 0.742				
N0	19 / 190 (10.0)	6 / 200 (3.0)	3.33	[1.36; 8.17]	0.008
N1-N3	116 / 1216 (9.5)	39 / 1160 (3.4)	2.84	[1.99; 4.04]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.945				
Grade 1	9 / 102 (8.8)	3 / 106 (2.8)	3.12	[0.87; 11.19]	0.081
Grade 2	83 / 842 (9.9)	24 / 768 (3.1)	3.15	[2.02; 4.92]	<.001
Grade 3	39 / 373 (10.5)	15 / 397 (3.8)	2.77	[1.55; 4.93]	<.001
Histological subtype					
Interaction test	p = 0.804				
Ductal	102 / 1025 (10.0)	36 / 1010 (3.6)	2.79	[1.93; 4.04]	<.001
Lobular	28 / 291 (9.6)	7 / 276 (2.5)	3.79	[1.68; 8.54]	0.001
Other	7 / 92 (7.6)	2 / 76 (2.6)	2.89	[0.62; 13.51]	0.177
Ki67 status from surgical specimen					
Interaction test	p = 0.875				
Ki67≤20	68 / 660 (10.3)	22 / 629 (3.5)	2.95	[1.84; 4.70]	<.001
Ki67>20	53 / 489 (10.8)	18 / 516 (3.5)	3.11	[1.85; 5.23]	<.001
Type of NSAI					
Interaction test	p = 0.575				
Letrozole	98 / 907 (10.8)	31 / 895 (3.5)	3.12	[2.11; 4.62]	<.001
Anastrozole	39 / 502 (7.8)	14 / 467 (3.0)	2.59	[1.43; 4.71]	0.002
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.108				
Yes	107 / 1194 (9.0)	29 / 1146 (2.5)	3.54	[2.37; 5.29]	<.001
No	30 / 215 (14.0)	16 / 216 (7.4)	1.88	[1.06; 3.35]	0.031
Prior adjuvant chemotherapy					
Interaction test	p = 0.680				
Yes	57 / 694 (8.2)	17 / 673 (2.5)	3.25	[1.91; 5.53]	<.001
No	80 / 715 (11.2)	28 / 689 (4.1)	2.75	[1.81; 4.18]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.255				
Yes	53 / 528 (10.0)	13 / 503 (2.6)	3.88	[2.14; 7.04]	<.001
No	84 / 881 (9.5)	32 / 859 (3.7)	2.56	[1.72; 3.80]	<.001
Prior endocrine therapy					
Interaction test	p = 0.693				
Yes	80 / 957 (8.4)	25 / 940 (2.7)	3.14	[2.02; 4.88]	<.001
No	57 / 452 (12.6)	20 / 422 (4.7)	2.66	[1.63; 4.35]	<.001
Prior mastectomy					
Interaction test	p = 0.557				
Yes	95 / 857 (11.1)	34 / 847 (4.0)	2.76	[1.89; 4.04]	<.001
No	42 / 552 (7.6)	11 / 515 (2.1)	3.56	[1.85; 6.84]	<.001
Prior radiotherapy					
Interaction test	p = 0.724				
Yes	105 / 1253 (8.4)	32 / 1203 (2.7)	3.15	[2.14; 4.64]	<.001
No	32 / 156 (20.5)	13 / 159 (8.2)	2.51	[1.37; 4.60]	0.003
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.5.5 Myelosuppression - Leukopenia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Myelosuppression - Leukopenia					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.277				
NA/WE/O	171 / 899 (19.0)	24 / 856 (2.8)	6.78	[4.47; 10.29]	<.001
ROW	171 / 510 (33.5)	21 / 506 (4.2)	8.08	[5.22; 12.50]	<.001
Geographical region					
Interaction test	p = 0.023				
Europe	215 / 832 (25.8)	23 / 824 (2.8)	9.26	[6.09; 14.08]	<.001
North America/Australia	71 / 400 (17.8)	17 / 364 (4.7)	3.80	[2.28; 6.33]	<.001
Asia	35 / 102 (34.3)	3 / 101 (3.0)	11.55	[3.67; 36.36]	<.001
Latin America	21 / 75 (28.0)	2 / 73 (2.7)	10.22	[2.48; 42.03]	0.001
Age group 1 at randomization					
Interaction test	p = 0.859				
<45	21 / 60 (35.0)	2 / 52 (3.8)	9.10	[2.24; 36.98]	0.002
45 to 54	66 / 300 (22.0)	9 / 322 (2.8)	7.87	[3.99; 15.51]	<.001
55 to 64	152 / 651 (23.3)	19 / 642 (3.0)	7.89	[4.96; 12.55]	<.001
≥65	103 / 398 (25.9)	15 / 346 (4.3)	5.97	[3.54; 10.06]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.831				
<Median	141 / 633 (22.3)	18 / 632 (2.8)	7.82	[4.85; 12.61]	<.001
≥Median	201 / 776 (25.9)	27 / 730 (3.7)	7.00	[4.75; 10.33]	<.001
Race					
Interaction test	p = 0.705				
Asian	39 / 128 (30.5)	5 / 127 (3.9)	7.74	[3.15; 19.00]	<.001
Non-Asian	274 / 1203 (22.8)	38 / 1167 (3.3)	6.99	[5.03; 9.73]	<.001
BMI at screening					
Interaction test	p = 0.277				
≥25	224 / 935 (24.0)	27 / 935 (2.9)	8.30	[5.62; 12.24]	<.001
<25	116 / 460 (25.2)	18 / 410 (4.4)	5.74	[3.56; 9.27]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.206				
Group I/II	123 / 585 (21.0)	12 / 589 (2.0)	10.32	[5.77; 18.46]	<.001
Group III	218 / 823 (26.5)	33 / 772 (4.3)	6.20	[4.36; 8.82]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.522				
IA/IB/IIA	73 / 310 (23.5)	5 / 311 (1.6)	14.65	[6.00; 35.75]	<.001
IIB	50 / 275 (18.2)	7 / 278 (2.5)	7.22	[3.33; 15.65]	<.001
IIIA	123 / 482 (25.5)	20 / 450 (4.4)	5.74	[3.64; 9.05]	<.001
IIIB	35 / 100 (35.0)	4 / 82 (4.9)	7.18	[2.66; 19.36]	<.001
IIIC	60 / 241 (24.9)	9 / 240 (3.8)	6.64	[3.37; 13.07]	<.001
Tumor category					
Interaction test	p = 0.998				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	302 / 1287 (23.5)	40 / 1258 (3.2)	7.38	[5.36; 10.17]	<.001
>T3	38 / 113 (33.6)	5 / 97 (5.2)	6.52	[2.67; 15.92]	<.001
Nodal status					
Interaction test	p = 0.323				
N0	45 / 190 (23.7)	4 / 200 (2.0)	11.84	[4.34; 32.29]	<.001
N1-N3	295 / 1216 (24.3)	41 / 1160 (3.5)	6.86	[5.00; 9.42]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.538				
Grade 1	25 / 102 (24.5)	2 / 106 (1.9)	12.99	[3.16; 53.44]	<.001
Grade 2	206 / 842 (24.5)	29 / 768 (3.8)	6.48	[4.45; 9.44]	<.001
Grade 3	95 / 373 (25.5)	12 / 397 (3.0)	8.43	[4.70; 15.10]	<.001
Histological subtype					
Interaction test	p = 0.762				
Ductal	255 / 1025 (24.9)	34 / 1010 (3.4)	7.39	[5.22; 10.46]	<.001
Lobular	69 / 291 (23.7)	10 / 276 (3.6)	6.54	[3.44; 12.44]	<.001
Other	18 / 92 (19.6)	1 / 76 (1.3)	14.87	[2.03; >99.99]	0.008
Ki67 status from surgical specimen					
Interaction test	p = 0.122				
Ki67≤20	176 / 660 (26.7)	17 / 629 (2.7)	9.87	[6.07; 16.04]	<.001
Ki67>20	108 / 489 (22.1)	19 / 516 (3.7)	6.00	[3.74; 9.61]	<.001
Type of NSAI					
Interaction test	p = 0.683				
Letrozole	225 / 907 (24.8)	29 / 895 (3.2)	7.66	[5.26; 11.15]	<.001
Anastrozole	117 / 502 (23.3)	16 / 467 (3.4)	6.80	[4.10; 11.29]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.997				
Yes	285 / 1194 (23.9)	37 / 1146 (3.2)	7.39	[5.30; 10.31]	<.001
No	57 / 215 (26.5)	8 / 216 (3.7)	7.16	[3.50; 14.64]	<.001
Prior adjuvant chemotherapy					
Interaction test	p = 0.643				
Yes	159 / 694 (22.9)	19 / 673 (2.8)	8.12	[5.10; 12.90]	<.001
No	183 / 715 (25.6)	26 / 689 (3.8)	6.78	[4.56; 10.09]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.624				
Yes	138 / 528 (26.1)	20 / 503 (4.0)	6.57	[4.18; 10.34]	<.001
No	204 / 881 (23.2)	25 / 859 (2.9)	7.96	[5.31; 11.92]	<.001
Prior endocrine therapy					
Interaction test	p = 0.983				
Yes	208 / 957 (21.7)	27 / 940 (2.9)	7.57	[5.12; 11.18]	<.001
No	134 / 452 (29.6)	18 / 422 (4.3)	6.95	[4.33; 11.16]	<.001
Prior mastectomy					
Interaction test	p = 0.740				
Yes	209 / 857 (24.4)	27 / 847 (3.2)	7.65	[5.18; 11.29]	<.001
No	133 / 552 (24.1)	18 / 515 (3.5)	6.89	[4.28; 11.11]	<.001
Prior radiotherapy					
Interaction test	p = 0.679				
Yes	300 / 1253 (23.9)	40 / 1203 (3.3)	7.20	[5.23; 9.92]	<.001
No	42 / 156 (26.9)	5 / 159 (3.1)	8.56	[3.48; 21.07]	<.001
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.5.6 Myelosuppression - Neutropenia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		RR	Comparison	
	Ribociclib + ET (N = 1409)	ET (N = 1362)		[95% CI]	p-value
Myelosuppression - Neutropenia					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.247				
NA/WE/O	512 / 899 (57.0)	20 / 856 (2.3)	24.38	[15.75; 37.73]	<.001
ROW	333 / 510 (65.3)	24 / 506 (4.7)	13.77	[9.27; 20.45]	<.001
Geographical region					
Interaction test	p = 0.475				
Europe	509 / 832 (61.2)	27 / 824 (3.3)	18.67	[12.83; 27.16]	<.001
North America/Australia	219 / 400 (54.8)	12 / 364 (3.3)	16.61	[9.45; 29.18]	<.001
Asia	78 / 102 (76.5)	3 / 101 (3.0)	25.75	[8.40; 78.89]	<.001
Latin America	39 / 75 (52.0)	2 / 73 (2.7)	18.98	[4.76; 75.74]	<.001
Age group 1 at randomization					
Interaction test	p = 0.652				
<45	43 / 60 (71.7)	5 / 52 (9.6)	7.45	[3.19; 17.41]	<.001
45 to 54	181 / 300 (60.3)	10 / 322 (3.1)	19.43	[10.48; 36.00]	<.001
55 to 64	386 / 651 (59.3)	20 / 642 (3.1)	19.03	[12.31; 29.44]	<.001
≥65	235 / 398 (59.0)	9 / 346 (2.6)	22.70	[11.85; 43.48]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.072				
<Median	382 / 633 (60.3)	27 / 632 (4.3)	14.13	[9.71; 20.54]	<.001
≥Median	463 / 776 (59.7)	17 / 730 (2.3)	25.62	[15.96; 41.13]	<.001
Race					
Interaction test	p = 0.203				
Asian	98 / 128 (76.6)	5 / 127 (3.9)	19.45	[8.19; 46.16]	<.001
Non-Asian	694 / 1203 (57.7)	38 / 1167 (3.3)	17.72	[12.91; 24.31]	<.001
BMI at screening					
Interaction test	p = 0.315				
≥25	515 / 935 (55.1)	20 / 935 (2.1)	25.75	[16.63; 39.88]	<.001
<25	324 / 460 (70.4)	23 / 410 (5.6)	12.56	[8.40; 18.76]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.609				
Group I/II	332 / 585 (56.8)	15 / 589 (2.5)	22.28	[13.45; 36.91]	<.001
Group III	512 / 823 (62.2)	29 / 772 (3.8)	16.56	[11.54; 23.76]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.766				
IA/IB/IIA	181 / 310 (58.4)	9 / 311 (2.9)	20.18	[10.53; 38.67]	<.001
IIB	151 / 275 (54.9)	6 / 278 (2.2)	25.44	[11.45; 56.55]	<.001
IIIA	299 / 482 (62.0)	19 / 450 (4.2)	14.69	[9.41; 22.94]	<.001
IIIB	61 / 100 (61.0)	1 / 82 (1.2)	50.02	[7.09; >99.99]	<.001
IIIC	152 / 241 (63.1)	9 / 240 (3.8)	16.82	[8.80; 32.16]	<.001
Tumor category					
Interaction test	p = 0.715				
T0	5 / 5 (100.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	767 / 1287 (59.6)	40 / 1258 (3.2)	18.74	[13.77; 25.51]	<.001
>T3	69 / 113 (61.1)	4 / 97 (4.1)	14.81	[5.61; 39.09]	<.001
Nodal status					
Interaction test	p = 0.476				
N0	105 / 190 (55.3)	7 / 200 (3.5)	15.79	[7.54; 33.06]	<.001
N1-N3	738 / 1216 (60.7)	37 / 1160 (3.2)	19.03	[13.81; 26.21]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.560				
Grade 1	65 / 102 (63.7)	3 / 106 (2.8)	22.52	[7.31; 69.36]	<.001
Grade 2	493 / 842 (58.6)	27 / 768 (3.5)	16.65	[11.45; 24.23]	<.001
Grade 3	221 / 373 (59.2)	10 / 397 (2.5)	23.52	[12.68; 43.63]	<.001
Histological subtype					
Interaction test	p = 0.381				
Ductal	616 / 1025 (60.1)	32 / 1010 (3.2)	18.97	[13.44; 26.77]	<.001
Lobular	169 / 291 (58.1)	11 / 276 (4.0)	14.57	[8.10; 26.21]	<.001
Other	59 / 92 (64.1)	1 / 76 (1.3)	48.74	[6.91; >99.99]	<.001
Ki67 status from surgical specimen					
Interaction test	p = 0.999				
Ki67≤20	408 / 660 (61.8)	22 / 629 (3.5)	17.67	[11.67; 26.76]	<.001
Ki67>20	302 / 489 (61.8)	18 / 516 (3.5)	17.70	[11.19; 28.02]	<.001
Type of NSAI					
Interaction test	p = 0.811				
Letrozole	551 / 907 (60.7)	29 / 895 (3.2)	18.75	[13.06; 26.92]	<.001
Anastrozole	294 / 502 (58.6)	15 / 467 (3.2)	18.23	[11.02; 30.16]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.266				
Yes	738 / 1194 (61.8)	37 / 1146 (3.2)	19.14	[13.90; 26.37]	<.001
No	107 / 215 (49.8)	7 / 216 (3.2)	15.36	[7.32; 32.22]	<.001
Prior adjuvant chemotherapy					
Interaction test	p = 0.134				
Yes	420 / 694 (60.5)	17 / 673 (2.5)	23.96	[14.93; 38.45]	<.001
No	425 / 715 (59.4)	27 / 689 (3.9)	15.17	[10.43; 22.06]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.121				
Yes	335 / 528 (63.4)	24 / 503 (4.8)	13.30	[8.95; 19.75]	<.001
No	510 / 881 (57.9)	20 / 859 (2.3)	24.86	[16.06; 38.48]	<.001
Prior endocrine therapy					
Interaction test	p = 0.726				
Yes	580 / 957 (60.6)	30 / 940 (3.2)	18.99	[13.30; 27.10]	<.001
No	265 / 452 (58.6)	14 / 422 (3.3)	17.67	[10.50; 29.75]	<.001
Prior mastectomy					
Interaction test	p = 0.942				
Yes	513 / 857 (59.9)	27 / 847 (3.2)	18.78	[12.90; 27.33]	<.001
No	332 / 552 (60.1)	17 / 515 (3.3)	18.22	[11.36; 29.22]	<.001
Prior radiotherapy					
Interaction test	p = 0.638				
Yes	762 / 1253 (60.8)	41 / 1203 (3.4)	17.84	[13.16; 24.19]	<.001
No	83 / 156 (53.2)	3 / 159 (1.9)	28.20	[9.10; 87.34]	<.001
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					

Table 5-3.5.7 Myelosuppression - Other: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Myelosuppression - Other					
	n / N (%)	n / N (%)			
Region					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Geographical region					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Age group 1 at randomization					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Race					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
BMI at screening					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
AJCC Anatomic Stage Group					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Anatomic stages					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Tumor category The subgroup analysis is not presented as all subgroups have less than 10 events.					
Nodal status The subgroup analysis is not presented as all subgroups have less than 10 events.					
Histological grade at time of surgery The subgroup analysis is not presented as all subgroups have less than 10 events.					
Histological subtype The subgroup analysis is not presented as all subgroups have less than 10 events.					
Ki67 status from surgical specimen The subgroup analysis is not presented as all subgroups have less than 10 events.					
Type of NSAI The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior neo/adjuvant chemotherapy The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior adjuvant chemotherapy The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior neoadjuvant chemotherapy The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior endocrine therapy The subgroup analysis is not presented as all subgroups have less than 10 events.					

Treatment Groups		Comparison		
Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior mastectomy The subgroup analysis is not presented as all subgroups have less than 10 events.				
Prior radiotherapy The subgroup analysis is not presented as all subgroups have less than 10 events.				
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.				

Table 5-3.5.8 Myelosuppression - Thrombocytopenia: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Myelosuppression - Thrombocytopenia					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.193				
NA/WE/O	53 / 899 (5.9)	10 / 856 (1.2)	5.05	[2.58; 9.85]	<.001
ROW	53 / 510 (10.4)	19 / 506 (3.8)	2.77	[1.66; 4.61]	<.001
Geographical region					
Interaction test	p = 0.513				
Europe	63 / 832 (7.6)	22 / 824 (2.7)	2.84	[1.76; 4.56]	<.001
North America/Australia	27 / 400 (6.8)	5 / 364 (1.4)	4.91	[1.91; 12.63]	<.001
Asia	10 / 102 (9.8)	2 / 101 (2.0)	4.95	[1.11; 22.03]	0.036
Latin America	6 / 75 (8.0)	0 / 73 (0.0)	12.66	[0.73; >99.99]	0.082
Age group 1 at randomization					
Interaction test	p = 0.539				
<45	5 / 60 (8.3)	1 / 52 (1.9)	4.33	[0.52; 35.91]	0.174
45 to 54	11 / 300 (3.7)	6 / 322 (1.9)	1.97	[0.74; 5.25]	0.177
55 to 64	47 / 651 (7.2)	14 / 642 (2.2)	3.31	[1.84; 5.95]	<.001
≥65	43 / 398 (10.8)	8 / 346 (2.3)	4.67	[2.23; 9.80]	<.001
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.399				
<Median	31 / 633 (4.9)	11 / 632 (1.7)	2.81	[1.43; 5.55]	0.003
≥Median	75 / 776 (9.7)	18 / 730 (2.5)	3.92	[2.37; 6.49]	<.001
Race					
Interaction test	p = 0.445				
Asian	15 / 128 (11.7)	3 / 127 (2.4)	4.96	[1.47; 16.72]	0.010
Non-Asian	83 / 1203 (6.9)	26 / 1167 (2.2)	3.10	[2.01; 4.78]	<.001
BMI at screening					
Interaction test	p = 0.323				
≥25	59 / 935 (6.3)	20 / 935 (2.1)	2.95	[1.79; 4.86]	<.001
<25	45 / 460 (9.8)	9 / 410 (2.2)	4.46	[2.21; 9.00]	<.001
AJCC Anatomic Stage Group					
Interaction test	p = 0.872				
Group I/II	40 / 585 (6.8)	11 / 589 (1.9)	3.66	[1.90; 7.07]	<.001
Group III	65 / 823 (7.9)	18 / 772 (2.3)	3.39	[2.03; 5.66]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.706				
IA/IB/IIA	17 / 310 (5.5)	6 / 311 (1.9)	2.84	[1.14; 7.11]	0.026
IIB	23 / 275 (8.4)	5 / 278 (1.8)	4.65	[1.79; 12.06]	0.002
IIIA	33 / 482 (6.8)	12 / 450 (2.7)	2.57	[1.34; 4.91]	0.004
IIIB	14 / 100 (14.0)	2 / 82 (2.4)	5.74	[1.34; 24.53]	0.018
IIIC	18 / 241 (7.5)	4 / 240 (1.7)	4.48	[1.54; 13.05]	0.006
Tumor category					
Interaction test	p = 0.752				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	90 / 1287 (7.0)	26 / 1258 (2.1)	3.38	[2.20; 5.20]	<.001
>T3	14 / 113 (12.4)	3 / 97 (3.1)	4.01	[1.19; 13.53]	0.025
Nodal status					
Interaction test	p = 0.299				
N0	10 / 190 (5.3)	5 / 200 (2.5)	2.11	[0.73; 6.05]	0.167
N1-N3	96 / 1216 (7.9)	24 / 1160 (2.1)	3.82	[2.46; 5.92]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.156				
Grade 1	8 / 102 (7.8)	3 / 106 (2.8)	2.77	[0.76; 10.16]	0.124
Grade 2	66 / 842 (7.8)	22 / 768 (2.9)	2.74	[1.71; 4.39]	<.001
Grade 3	27 / 373 (7.2)	3 / 397 (0.8)	9.58	[2.93; 31.31]	<.001
Histological subtype					
Interaction test	p = 0.535				
Ductal	85 / 1025 (8.3)	21 / 1010 (2.1)	3.99	[2.49; 6.38]	<.001
Lobular	16 / 291 (5.5)	6 / 276 (2.2)	2.53	[1.00; 6.37]	0.049
Other	5 / 92 (5.4)	2 / 76 (2.6)	2.07	[0.41; 10.35]	0.378
Ki67 status from surgical specimen					
Interaction test	p = 0.540				
Ki67≤20	49 / 660 (7.4)	13 / 629 (2.1)	3.59	[1.97; 6.56]	<.001
Ki67>20	39 / 489 (8.0)	15 / 516 (2.9)	2.74	[1.53; 4.91]	<.001
Type of NSAI					
Interaction test	p = 0.775				
Letrozole	76 / 907 (8.4)	22 / 895 (2.5)	3.41	[2.14; 5.43]	<.001
Anastrozole	30 / 502 (6.0)	7 / 467 (1.5)	3.99	[1.77; 8.99]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.004				
Yes	92 / 1194 (7.7)	18 / 1146 (1.6)	4.91	[2.98; 8.08]	<.001
No	14 / 215 (6.5)	11 / 216 (5.1)	1.28	[0.59; 2.75]	0.530
Prior adjuvant chemotherapy					
Interaction test	p = 0.715				
Yes	37 / 694 (5.3)	11 / 673 (1.6)	3.26	[1.68; 6.34]	<.001
No	69 / 715 (9.7)	18 / 689 (2.6)	3.69	[2.22; 6.14]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.013				
Yes	57 / 528 (10.8)	8 / 503 (1.6)	6.79	[3.27; 14.08]	<.001
No	49 / 881 (5.6)	21 / 859 (2.4)	2.28	[1.38; 3.76]	0.001
Prior endocrine therapy					
Interaction test	p = 0.096				
Yes	65 / 957 (6.8)	13 / 940 (1.4)	4.91	[2.73; 8.85]	<.001
No	41 / 452 (9.1)	16 / 422 (3.8)	2.39	[1.36; 4.20]	0.002
Prior mastectomy					
Interaction test	p = 0.188				
Yes	65 / 857 (7.6)	22 / 847 (2.6)	2.92	[1.82; 4.69]	<.001
No	41 / 552 (7.4)	7 / 515 (1.4)	5.46	[2.47; 12.07]	<.001
Prior radiotherapy					
Interaction test	p = 0.093				
Yes	87 / 1253 (6.9)	19 / 1203 (1.6)	4.40	[2.69; 7.18]	<.001
No	19 / 156 (12.2)	10 / 159 (6.3)	1.94	[0.93; 4.03]	0.077
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.5.9 QT interval prolongation: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
QT interval prolongation					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.035				
NA/WE/O	33 / 899 (3.7)	13 / 856 (1.5)	2.42	[1.28; 4.56]	0.006
ROW	35 / 510 (6.9)	4 / 506 (0.8)	8.68	[3.11; 24.25]	<.001
Geographical region					
Interaction test	p = 0.562				
Europe	40 / 832 (4.8)	11 / 824 (1.3)	3.60	[1.86; 6.97]	<.001
North America/Australia	17 / 400 (4.3)	6 / 364 (1.6)	2.58	[1.03; 6.47]	0.044
Asia	5 / 102 (4.9)	0 / 101 (0.0)	10.89	[0.61; >99.99]	0.104
Latin America	6 / 75 (8.0)	0 / 73 (0.0)	12.66	[0.73; >99.99]	0.082
Age group 1 at randomization					
Interaction test	p = 0.381				
<45	4 / 60 (6.7)	0 / 52 (0.0)	7.82	[0.43; >99.99]	0.164
45 to 54	11 / 300 (3.7)	1 / 322 (0.3)	11.81	[1.53; 90.90]	0.018
55 to 64	27 / 651 (4.1)	10 / 642 (1.6)	2.66	[1.30; 5.46]	0.007
≥65	26 / 398 (6.5)	6 / 346 (1.7)	3.77	[1.57; 9.05]	0.003
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.802				
<Median	25 / 633 (3.9)	7 / 632 (1.1)	3.57	[1.55; 8.18]	0.003
≥Median	43 / 776 (5.5)	10 / 730 (1.4)	4.05	[2.05; 7.99]	<.001
Race					
Interaction test	N.E.				
Asian	8 / 128 (6.3)	0 / 127 (0.0)	16.87	[0.98; >99.99]	0.051
Non-Asian	57 / 1203 (4.7)	16 / 1167 (1.4)	3.46	[2.00; 5.98]	<.001
BMI at screening					
Interaction test	p = 0.458				
≥25	41 / 935 (4.4)	9 / 935 (1.0)	4.56	[2.23; 9.32]	<.001
<25	27 / 460 (5.9)	8 / 410 (2.0)	3.01	[1.38; 6.55]	0.006
AJCC Anatomic Stage Group					
Interaction test	p = 0.066				
Group I/II	32 / 585 (5.5)	4 / 589 (0.7)	8.05	[2.87; 22.63]	<.001
Group III	36 / 823 (4.4)	13 / 772 (1.7)	2.60	[1.39; 4.86]	0.003

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.194				
IA/IB/IIA	13 / 310 (4.2)	2 / 311 (0.6)	6.52	[1.48; 28.66]	0.013
IIB	19 / 275 (6.9)	2 / 278 (0.7)	9.60	[2.26; 40.84]	0.002
IIIA	25 / 482 (5.2)	10 / 450 (2.2)	2.33	[1.13; 4.80]	0.021
IIIB	6 / 100 (6.0)	0 / 82 (0.0)	10.68	[0.61; >99.99]	0.105
IIIC	5 / 241 (2.1)	3 / 240 (1.3)	1.66	[0.40; 6.87]	0.484
Tumor category					
Interaction test	N.E.				
T0	1 / 5 (20.0)	0 / 5 (0.0)	3.00	[0.15; 59.89]	0.472
T1-T3	61 / 1287 (4.7)	17 / 1258 (1.4)	3.51	[2.06; 5.97]	<.001
>T3	6 / 113 (5.3)	0 / 97 (0.0)	11.18	[0.64; >99.99]	0.099
Nodal status					
Interaction test	p = 0.363				
N0	9 / 190 (4.7)	1 / 200 (0.5)	9.47	[1.21; 74.06]	0.032
N1-N3	59 / 1216 (4.9)	16 / 1160 (1.4)	3.52	[2.04; 6.08]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.790				
Grade 1	6 / 102 (5.9)	3 / 106 (2.8)	2.08	[0.53; 8.09]	0.291
Grade 2	38 / 842 (4.5)	10 / 768 (1.3)	3.47	[1.74; 6.91]	<.001
Grade 3	14 / 373 (3.8)	4 / 397 (1.0)	3.73	[1.24; 11.22]	0.019
Histological subtype					
Interaction test	p = 0.072				
Ductal	53 / 1025 (5.2)	9 / 1010 (0.9)	5.80	[2.88; 11.70]	<.001
Lobular	11 / 291 (3.8)	5 / 276 (1.8)	2.09	[0.73; 5.93]	0.167
Other	4 / 92 (4.3)	3 / 76 (3.9)	1.10	[0.25; 4.77]	0.897
Ki67 status from surgical specimen					
Interaction test	p = 0.039				
Ki67≤20	29 / 660 (4.4)	10 / 629 (1.6)	2.76	[1.36; 5.62]	0.005
Ki67>20	28 / 489 (5.7)	2 / 516 (0.4)	14.77	[3.54; 61.68]	<.001
Type of NSAI					
Interaction test	p = 0.823				
Letrozole	45 / 907 (5.0)	11 / 895 (1.2)	4.04	[2.10; 7.75]	<.001
Anastrozole	23 / 502 (4.6)	6 / 467 (1.3)	3.57	[1.47; 8.68]	0.005
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.070				
Yes	63 / 1194 (5.3)	13 / 1146 (1.1)	4.65	[2.57; 8.40]	<.001
No	5 / 215 (2.3)	4 / 216 (1.9)	1.26	[0.34; 4.61]	0.732
Prior adjuvant chemotherapy					
Interaction test	p = 0.240				
Yes	33 / 694 (4.8)	11 / 673 (1.6)	2.91	[1.48; 5.71]	0.002
No	35 / 715 (4.9)	6 / 689 (0.9)	5.62	[2.38; 13.28]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.029				
Yes	33 / 528 (6.3)	3 / 503 (0.6)	10.48	[3.23; 33.95]	<.001
No	35 / 881 (4.0)	14 / 859 (1.6)	2.44	[1.32; 4.50]	0.004
Prior endocrine therapy					
Interaction test	p = 0.058				
Yes	42 / 957 (4.4)	15 / 940 (1.6)	2.75	[1.54; 4.93]	<.001
No	26 / 452 (5.8)	2 / 422 (0.5)	12.14	[2.90; 50.82]	<.001
Prior mastectomy					
Interaction test	p = 0.805				
Yes	49 / 857 (5.7)	12 / 847 (1.4)	4.04	[2.16; 7.53]	<.001
No	19 / 552 (3.4)	5 / 515 (1.0)	3.55	[1.33; 9.43]	0.011
Prior radiotherapy					
Interaction test	p = 0.807				
Yes	59 / 1253 (4.7)	15 / 1203 (1.2)	3.78	[2.15; 6.62]	<.001
No	9 / 156 (5.8)	2 / 159 (1.3)	4.59	[1.01; 20.89]	0.049
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.5.10 Renal toxicity: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Renal toxicity					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.323				
NA/WE/O	62 / 899 (6.9)	22 / 856 (2.6)	2.68	[1.66; 4.32]	<.001
ROW	57 / 510 (11.2)	30 / 506 (5.9)	1.89	[1.23; 2.88]	0.003
Geographical region					
Interaction test	p = 0.197				
Europe	80 / 832 (9.6)	44 / 824 (5.3)	1.80	[1.26; 2.57]	0.001
North America/Australia	29 / 400 (7.3)	6 / 364 (1.6)	4.40	[1.85; 10.47]	<.001
Asia	3 / 102 (2.9)	1 / 101 (1.0)	2.97	[0.31; 28.08]	0.342
Latin America	7 / 75 (9.3)	1 / 73 (1.4)	6.81	[0.86; 54.01]	0.069
Age group 1 at randomization					
Interaction test	p = 0.545				
<45	3 / 60 (5.0)	0 / 52 (0.0)	6.08	[0.32; >99.99]	0.229
45 to 54	14 / 300 (4.7)	10 / 322 (3.1)	1.50	[0.68; 3.33]	0.316
55 to 64	51 / 651 (7.8)	20 / 642 (3.1)	2.51	[1.52; 4.17]	<.001
≥65	51 / 398 (12.8)	22 / 346 (6.4)	2.02	[1.25; 3.25]	0.004
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.919				
<Median	35 / 633 (5.5)	16 / 632 (2.5)	2.18	[1.22; 3.91]	0.008
≥Median	84 / 776 (10.8)	36 / 730 (4.9)	2.20	[1.51; 3.20]	<.001
Race					
Interaction test	p = 0.624				
Asian	4 / 128 (3.1)	1 / 127 (0.8)	3.97	[0.45; 35.02]	0.215
Non-Asian	107 / 1203 (8.9)	47 / 1167 (4.0)	2.21	[1.58; 3.08]	<.001
BMI at screening					
Interaction test	p = 0.437				
≥25	95 / 935 (10.2)	40 / 935 (4.3)	2.38	[1.66; 3.40]	<.001
<25	22 / 460 (4.8)	11 / 410 (2.7)	1.78	[0.88; 3.63]	0.111
AJCC Anatomic Stage Group					
Interaction test	p = 0.396				
Group I/II	54 / 585 (9.2)	21 / 589 (3.6)	2.59	[1.58; 4.23]	<.001
Group III	65 / 823 (7.9)	31 / 772 (4.0)	1.97	[1.30; 2.98]	0.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.483				
IA/IB/IIA	33 / 310 (10.6)	12 / 311 (3.9)	2.76	[1.45; 5.24]	0.002
IIB	21 / 275 (7.6)	9 / 278 (3.2)	2.36	[1.10; 5.06]	0.027
IIIA	35 / 482 (7.3)	12 / 450 (2.7)	2.72	[1.43; 5.18]	0.002
IIIB	16 / 100 (16.0)	11 / 82 (13.4)	1.19	[0.59; 2.43]	0.627
IIIC	14 / 241 (5.8)	8 / 240 (3.3)	1.74	[0.74; 4.08]	0.200
Tumor category					
Interaction test	p = 0.053				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	102 / 1287 (7.9)	39 / 1258 (3.1)	2.56	[1.78; 3.67]	<.001
>T3	17 / 113 (15.0)	13 / 97 (13.4)	1.12	[0.57; 2.19]	0.735
Nodal status					
Interaction test	p = 0.174				
N0	21 / 190 (11.1)	15 / 200 (7.5)	1.47	[0.78; 2.77]	0.229
N1-N3	98 / 1216 (8.1)	37 / 1160 (3.2)	2.53	[1.75; 3.66]	<.001
Histological grade at time of surgery					
Interaction test	p = 0.929				
Grade 1	10 / 102 (9.8)	4 / 106 (3.8)	2.60	[0.84; 8.02]	0.097
Grade 2	79 / 842 (9.4)	34 / 768 (4.4)	2.12	[1.44; 3.13]	<.001
Grade 3	25 / 373 (6.7)	13 / 397 (3.3)	2.05	[1.06; 3.94]	0.032
Histological subtype					
Interaction test	p = 0.957				
Ductal	89 / 1025 (8.7)	39 / 1010 (3.9)	2.25	[1.56; 3.24]	<.001
Lobular	21 / 291 (7.2)	9 / 276 (3.3)	2.21	[1.03; 4.75]	0.041
Other	9 / 92 (9.8)	4 / 76 (5.3)	1.86	[0.60; 5.80]	0.286
Ki67 status from surgical specimen					
Interaction test	p = 0.801				
Ki67≤20	64 / 660 (9.7)	26 / 629 (4.1)	2.35	[1.51; 3.65]	<.001
Ki67>20	41 / 489 (8.4)	20 / 516 (3.9)	2.16	[1.29; 3.64]	0.004
Type of NSAI					
Interaction test	p = 0.139				
Letrozole	79 / 907 (8.7)	41 / 895 (4.6)	1.90	[1.32; 2.74]	<.001
Anastrozole	40 / 502 (8.0)	11 / 467 (2.4)	3.38	[1.76; 6.51]	<.001
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.717				
Yes	84 / 1194 (7.0)	37 / 1146 (3.2)	2.18	[1.49; 3.18]	<.001
No	35 / 215 (16.3)	15 / 216 (6.9)	2.34	[1.32; 4.16]	0.004
Prior adjuvant chemotherapy					
Interaction test	p = 0.951				
Yes	50 / 694 (7.2)	22 / 673 (3.3)	2.20	[1.35; 3.60]	0.002
No	69 / 715 (9.7)	30 / 689 (4.4)	2.22	[1.46; 3.36]	<.001

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.846				
Yes	37 / 528 (7.0)	15 / 503 (3.0)	2.35	[1.31; 4.23]	0.004
No	82 / 881 (9.3)	37 / 859 (4.3)	2.16	[1.48; 3.15]	<.001
Prior endocrine therapy					
Interaction test	p = 0.190				
Yes	67 / 957 (7.0)	24 / 940 (2.6)	2.74	[1.74; 4.33]	<.001
No	52 / 452 (11.5)	28 / 422 (6.6)	1.73	[1.12; 2.69]	0.014
Prior mastectomy					
Interaction test	p = 0.158				
Yes	77 / 857 (9.0)	40 / 847 (4.7)	1.90	[1.31; 2.75]	<.001
No	42 / 552 (7.6)	12 / 515 (2.3)	3.27	[1.74; 6.13]	<.001
Prior radiotherapy					
Interaction test	p = 0.622				
Yes	86 / 1253 (6.9)	34 / 1203 (2.8)	2.43	[1.65; 3.58]	<.001
No	33 / 156 (21.2)	18 / 159 (11.3)	1.87	[1.10; 3.18]	0.021
N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.					

Table 5-3.5.11 Reproductive toxicity: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Reproductive toxicity					
	n / N (%)	n / N (%)			
Region					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Geographical region					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Age group 1 at randomization					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Race					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
BMI at screening					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
AJCC Anatomic Stage Group					
The subgroup analysis is not presented as all subgroups have less than 10 events.					
Anatomic stages					
The subgroup analysis is not presented as all subgroups have less than 10 events.					

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Tumor category The subgroup analysis is not presented as all subgroups have less than 10 events.					
Nodal status The subgroup analysis is not presented as all subgroups have less than 10 events.					
Histological grade at time of surgery The subgroup analysis is not presented as all subgroups have less than 10 events.					
Histological subtype The subgroup analysis is not presented as all subgroups have less than 10 events.					
Ki67 status from surgical specimen The subgroup analysis is not presented as all subgroups have less than 10 events.					
Type of NSAI The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior neo/adjuvant chemotherapy The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior adjuvant chemotherapy The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior neoadjuvant chemotherapy The subgroup analysis is not presented as all subgroups have less than 10 events.					
Prior endocrine therapy The subgroup analysis is not presented as all subgroups have less than 10 events.					

Treatment Groups		Comparison		
Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior mastectomy The subgroup analysis is not presented as all subgroups have less than 10 events.				
Prior radiotherapy The subgroup analysis is not presented as all subgroups have less than 10 events.				
N: Number of patients n: Number of patients with event CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$ Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.				

Table 5-3.5.12 Second Primary Malignancies: binary analysis - subgroup analysis (Safety Set)

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Second Primary Malignancies					
	n / N (%)	n / N (%)			
Region					
Interaction test	p = 0.862				
NA/WE/O	21 / 899 (2.3)	24 / 856 (2.8)	0.83	[0.47; 1.49]	0.536
ROW	11 / 510 (2.2)	12 / 506 (2.4)	0.91	[0.41; 2.04]	0.818
Geographical region					
Interaction test	p = 0.371				
Europe	19 / 832 (2.3)	17 / 824 (2.1)	1.11	[0.58; 2.11]	0.758
North America/Australia	10 / 400 (2.5)	13 / 364 (3.6)	0.70	[0.31; 1.58]	0.389
Asia	1 / 102 (1.0)	5 / 101 (5.0)	0.20	[0.02; 1.67]	0.136
Latin America	2 / 75 (2.7)	1 / 73 (1.4)	1.95	[0.18; 21.01]	0.583
Age group 1 at randomization					
Interaction test	p = 0.039				
<45	2 / 60 (3.3)	0 / 52 (0.0)	4.34	[0.21; 88.48]	0.339
45 to 54	7 / 300 (2.3)	3 / 322 (0.9)	2.50	[0.65; 9.60]	0.180
55 to 64	16 / 651 (2.5)	16 / 642 (2.5)	0.99	[0.50; 1.96]	0.968
≥65	7 / 398 (1.8)	17 / 346 (4.9)	0.36	[0.15; 0.85]	0.020
Age group 2 at randomization (median for subpopulation post-menopausal female patients)					
Interaction test	p = 0.025				
<Median	15 / 633 (2.4)	8 / 632 (1.3)	1.87	[0.80; 4.38]	0.149
≥Median	17 / 776 (2.2)	28 / 730 (3.8)	0.57	[0.32; 1.03]	0.065
Race					
Interaction test	p = 0.321				
Asian	2 / 128 (1.6)	5 / 127 (3.9)	0.40	[0.08; 2.01]	0.264
Non-Asian	28 / 1203 (2.3)	29 / 1167 (2.5)	0.94	[0.56; 1.56]	0.802
BMI at screening					
Interaction test	p = 0.568				
≥25	22 / 935 (2.4)	27 / 935 (2.9)	0.81	[0.47; 1.42]	0.470
<25	10 / 460 (2.2)	8 / 410 (2.0)	1.11	[0.44; 2.80]	0.818
AJCC Anatomic Stage Group					
Interaction test	p = 0.668				
Group I/II	10 / 585 (1.7)	14 / 589 (2.4)	0.72	[0.32; 1.61]	0.421
Group III	21 / 823 (2.6)	22 / 772 (2.8)	0.90	[0.50; 1.61]	0.714

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Anatomic stages					
Interaction test	p = 0.960				
IA/IB/IIA	6 / 310 (1.9)	7 / 311 (2.3)	0.86	[0.29; 2.53]	0.784
IIB	4 / 275 (1.5)	7 / 278 (2.5)	0.58	[0.17; 1.95]	0.377
IIIA	13 / 482 (2.7)	15 / 450 (3.3)	0.81	[0.39; 1.68]	0.570
IIIB	3 / 100 (3.0)	2 / 82 (2.4)	1.23	[0.21; 7.19]	0.818
IIIC	5 / 241 (2.1)	5 / 240 (2.1)	1.00	[0.29; 3.40]	0.995
Tumor category					
Interaction test	p = 0.616				
T0	0 / 5 (0.0)	0 / 5 (0.0)	N.E.	N.E.	N.E.
T1-T3	28 / 1287 (2.2)	34 / 1258 (2.7)	0.80	[0.49; 1.32]	0.389
>T3	3 / 113 (2.7)	2 / 97 (2.1)	1.29	[0.22; 7.55]	0.779
Nodal status					
Interaction test	p = 0.727				
N0	5 / 190 (2.6)	5 / 200 (2.5)	1.05	[0.31; 3.58]	0.935
N1-N3	27 / 1216 (2.2)	31 / 1160 (2.7)	0.83	[0.50; 1.38]	0.476
Histological grade at time of surgery					
Interaction test	p = 0.592				
Grade 1	2 / 102 (2.0)	6 / 106 (5.7)	0.35	[0.07; 1.68]	0.188
Grade 2	20 / 842 (2.4)	22 / 768 (2.9)	0.83	[0.46; 1.51]	0.539
Grade 3	5 / 373 (1.3)	7 / 397 (1.8)	0.76	[0.24; 2.37]	0.637
Histological subtype					
Interaction test	p = 0.792				
Ductal	25 / 1025 (2.4)	28 / 1010 (2.8)	0.88	[0.52; 1.50]	0.637
Lobular	5 / 291 (1.7)	7 / 276 (2.5)	0.68	[0.22; 2.11]	0.502
Other	2 / 92 (2.2)	1 / 76 (1.3)	1.65	[0.15; 17.87]	0.679
Ki67 status from surgical specimen					
Interaction test	p = 0.469				
Ki67≤20	19 / 660 (2.9)	23 / 629 (3.7)	0.79	[0.43; 1.43]	0.433
Ki67>20	9 / 489 (1.8)	8 / 516 (1.6)	1.19	[0.46; 3.05]	0.722
Type of NSAI					
Interaction test	p = 0.685				
Letrozole	25 / 907 (2.8)	27 / 895 (3.0)	0.91	[0.53; 1.56]	0.741
Anastrozole	7 / 502 (1.4)	9 / 467 (1.9)	0.72	[0.27; 1.93]	0.517
Prior neo/adjuvant chemotherapy					
Interaction test	p = 0.374				
Yes	27 / 1194 (2.3)	27 / 1146 (2.4)	0.96	[0.57; 1.63]	0.879
No	5 / 215 (2.3)	9 / 216 (4.2)	0.56	[0.19; 1.64]	0.288
Prior adjuvant chemotherapy					
Interaction test	p = 0.075				
Yes	10 / 694 (1.4)	19 / 673 (2.8)	0.51	[0.24; 1.09]	0.082
No	22 / 715 (3.1)	17 / 689 (2.5)	1.25	[0.67; 2.33]	0.488

	Treatment Groups		Comparison		
	Ribociclib + ET (N = 1409)	ET (N = 1362)	RR	[95% CI]	p-value
Prior neoadjuvant chemotherapy					
Interaction test	p = 0.020				
Yes	17 / 528 (3.2)	9 / 503 (1.8)	1.80	[0.81; 4.00]	0.149
No	15 / 881 (1.7)	27 / 859 (3.1)	0.54	[0.29; 1.01]	0.054
Prior endocrine therapy					
Interaction test	p = 0.299				
Yes	22 / 957 (2.3)	29 / 940 (3.1)	0.75	[0.43; 1.29]	0.292
No	10 / 452 (2.2)	7 / 422 (1.7)	1.33	[0.51; 3.47]	0.555
Prior mastectomy					
Interaction test	p = 0.090				
Yes	22 / 857 (2.6)	18 / 847 (2.1)	1.21	[0.65; 2.24]	0.548
No	10 / 552 (1.8)	18 / 515 (3.5)	0.52	[0.24; 1.11]	0.092
Prior radiotherapy					
Interaction test	p = 0.163				
Yes	27 / 1253 (2.2)	34 / 1203 (2.8)	0.76	[0.46; 1.26]	0.287
No	5 / 156 (3.2)	2 / 159 (1.3)	2.55	[0.50; 12.94]	0.259
<p>N: Number of patients n: Number of patients with event N.E.: Not estimable CI: Confidence interval RR: Relative risk ET: Endocrine therapy (Anastrozole/Letrozole) </p> <p>Analysis method for interaction test: p-value from logistic regression model. $\text{logit}(\text{proportion}) = \text{treatment} + \text{subgroup factor} + \text{treatment} * \text{subgroup factor}$</p> <p>Analysis method for within subgroup analysis: RR and RD with Wald 95% CI and p-value were calculated directly. In case of zero events in only one treatment arm, one patient with 0.5 events was added to each treatment arm. ET was the reference group for treatment group comparison.</p>					