Gemeinsamer Bundesausschuss

Alectinib (new therapeutic indication: non-small cell lung cancer, ALK+, high risk of recurrence, adjuvant treatment)

Resolution of: 16 January 2025 Valid until: unlimited
Entry into force on: 16 January 2025
Federal Gazette, BAnz AT 03 02 2025 B4

New therapeutic indication (according to the marketing authorisation of 6 June 2024):

Alecensa as monotherapy is indicated as adjuvant treatment following complete tumour resection for adult patients with ALK-positive NSCLC at high risk of recurrence.

Therapeutic indication of the resolution (resolution of 16 January 2025):

See new therapeutic indication according to marketing authorisation.

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

a) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection who are eligible for adjuvant platinum-based chemotherapy

Appropriate comparator therapy:

Patient-individual postoperative (adjuvant) systemic chemotherapy with selection of

- cisplatin in combination with vinorelbine

  and

- cisplatin in combination with pemetrexed

taking into account the general condition.

Extent and probability of the additional benefit of alectinib compared to a patient-individual therapy:

Hint for a major additional benefit.

b) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection after prior adjuvant platinum-based chemotherapy or who are ineligible for this

Appropriate comparator therapy:

– Monitoring wait-and-see approach

Extent and probability of the additional benefit of alectinib compared to the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[1]

a) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection who are eligible for adjuvant platinum-based chemotherapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↑	Advantages in the endpoints of recurrence rates and disease-free survival.
Health-related quality of life	↔	No relevant differences for the benefit assessment overall. Advantage in the mental component summary score of the SF-36 only at week 12.
Side effects	↑	Advantages in the endpoints of SAEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuations due to AEs. Advantages and disadvantages in the specific AEs, in detail.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n. a.: not assessable		

ALINA study

- Comparison: Alectinib **vs** platinum-based chemotherapy (cisplatin in combination with vinorelbine or cisplatin in combination with gemcitabine or cisplatin in combination with pemetrexed. In case of unacceptable toxicity, carboplatin could be used instead of cisplatin).
- Study design: open-label, randomised, multicentre
- data cut-off from 26.06.2023

[1] Data from the dossier assessment of the IQWiG (A24-73) and from the addendum (A24-115), unless otherwise indicated.

Mortality

Endpoint	Alectinib		Platinum-based chemotherapy		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Mortality					
Overall survival	130	n.r. 2 (1.5)	127	n.r. 4 (3.1)	0.46 [0.08; 2.52] 0.360[b]

Morbidity

Recurrences					
Recurrence rate[c] (principal investigator)	130	- 15 (11.5)	127	- 50 (39.4)	RR: 0.29 [0.17; 0.49] < 0.001[d] AD: - 27.9%
Death	130	- 0 (0)	127	- 1 (0.8)	-
Local recurrence	130	- 8 (6.2)	127	- 20 (15.7)	-
Regional recurrence	130	- 5 (3.8)	127	- 12 (9.4)	-
Distant recurrence	130	- 5 (3.8)	127	- 27 (21.3)	-
New primary NSCLC	130	- 1 (0.8)	127	- 0 (0)	-
Disease-free survival[e] (principal investigator)	130	n.r. 15 (11.5)	127	41.3 [28.5; n.c.] 50 (39.4)	0.24 [0.13; 0.43] < 0.001[b]
Recurrence rate (BICR; presented additionally)	130	- 16 (12.3)	127	- 39 (30.7)	RR: 0.40 [0.24; 0.67] < 0.001[d]
Disease-free survival[e] (BICR; presented additionally)	130	n.r. 16 (12.3)	127	n.r. [37.4; n.c.] 39 (30.7)	0.30 [0.17; 0.54] < 0.001[b]

Endpoint	Alectinib			Platinum-based chemotherapy			Intervention vs control
	N[f]	Values at the start of the study MV (SD)	Change at week 12 MV[g] (SE)	N	Values at the start of the study MV (SD)	Change at week 12 MV[g] (SE)	MD [95% CI][g]
Health status							
EQ-5D VAS[h]							
	126	81.1 (16.4)	- 0.5 (1.1)	119	76.1 (15.2)	- 1.5 (1.2)	1.01 [- 1.81; 3.83]

Health-related quality of life

Endpoint	Alectinib		Platinum-based chemotherapy		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value Absolute difference (AD)[a]
SF-36v2 - deterioration at week 12[i]					
Physical Component Summary (PCS) score	109	7 (6.4)	91	5 (5.5)	1.37 [0.45; 4.17] 0.576
Mental Component Summary (MCS) score	109	8 (7.3)	91	22 (24.2)	0.30 [0.14; 0.65] 0.002[d] AD: - 16.9%
Physical functioning	117	27 (23.1)	96	20 (20.8)	1.14 [0.69; 1.91]
Physical role functioning	117	19 (16.2)	96	26 (27.1)	0.59 [0.35; 1.00]
Physical pain	116	14 (12.1)	96	18 (18.8)	0.65 [0.34; 1.24]
General health perception	110	20 (18.2)	91	28 (30.8)	0.62 [0.38; 1.03]
Vitality	116	17 (14.7)	96	25 (26.0)	0.58 [0.33; 1.01]
Social functioning	117	15 (12.8)	96	22 (22.9)	0.55 [0.30; 1.00]

Emotional role functioning	117	22 (18.8)	96	38 (39.6)	0.46 [0.29; 0.72]
Psychological well-being	116	11 (9.5)	96	16 (16.7)	0.57 [0.28; 1.16]

Side effects

Endpoint	**Alectinib**		**Platinum-based chemotherapy**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value Absolute difference (AD)[a]
Total adverse events (presented additionally)					
	128	n.d. 126 (98.4)	120	n.d. 112 (93.3)	–
Serious adverse events (SAE)					
	128	n.d. 17 (13.3)	120	n.d. 10 (8.3)	0.32 [0.10; 1.04] 0.048[j]
Severe adverse events (CTCAE grade ≥ 3)					
	128	n.d. 38 (29.7)	120	n.d. 37 (30.8)	0.50 [0.29; 0.85] 0.009[j]
Therapy discontinuation due to adverse events					
	128	n.d. 7 (5.5)	120	n.d. 15 (12.5)	0.24 [0.08; 0.71] 0.005[j]
Specific adverse events					
Myalgia (PT, severe AE[k])	128	n.d. 1 (0.8)	120	n.d. 0 (0)	n.c. [0.00; n.c.] 0.333[j]
ILD / pneumonitis[l] (SMQ, SAE)	128	n.d. 1 (0.8)	120	n.d. 0 (0)	n.c. [0.00; n.c.] 0.333[j]
Hepatotoxicity[m] (SMQ, severe AE[k])	128	n.d. 6 (4.7)	120	n.d. 0 (0)	n.c. [0.00; n.c.] 0.029[j]
Gastrointestinal disorders (SOC, AE)	128	n.d. 87 (68.0)	120	n.d. 95 (79.2)	0.42 [0.31; 0.58] < 0.001[j]
Discomfort	128	n.d.	120	n.d.	0.27

(PT, AE)		6 (4.7)		16 (13.3)	[0.10; 0.74] 0.007[j]
Loss of appetite (PT, AE)	128	n.d. 7 (5.5)	120	n.d. 35 (29.2)	0.16 [0.07; 0.36] < 0.001[j]
Haematopoietic cytopenias[n] (SMQ, severe AE[k])	128	n.d. 1 (0.8)	120	n.d. 25 (20.8)	0.03 [0.00; 0.25] < 0.001[j]
Elevated creatine phosphokinase level in the blood (PT, severe AE[k])	128	n.d. 8 (6.3)	120	n.d. 1 (0.8)	6.77 [0.83; 55.13] 0.038[j]

[a] Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
[b] HR and CI from Cox regression model, stratified by disease stage (IB vs II vs IIIA) and descent (Asian vs non-Asian); p value from log-rank test
[c] Percentage of patients, individual components are shown in the rows below. According to information provided by the pharmaceutical company, the first qualifying event is shown in each case. However, the sum of the events of the individual components is greater than the number of events that are included in the recurrence rate.
[d] Logistic regression model, stratified by disease stage (IB vs II vs IIIA) and descent (Asian vs non-Asian)
[e] The fixed treatment duration and the associated discontinuation of observation in the comparator arm means that the hazard ratio only reflects approximately the first 4 months post randomisation.
[f] Number of patients who were taken into account in the effect estimation; the values at the start of the study can be based on other patient numbers.
[g] MMRM adjusted for disease stage (IB vs II vs IIIA) and descent (Asian vs non-Asian)
[h] Higher (increasing) values mean better symptomatology; positive effects (intervention minus comparison) mean an advantage for the intervention (scale range: 0 to 100).
[i] A decrease in PCS by ≥ 9.4 points or MCS by ≥ 9.6 points compared to the start of study is considered clinically relevant deterioration (scale range: 7.3 to 70.1 for PCS and 5.8 to 69.9 for MCS; determined using the 2009 normative sample [Maruish ME. User's manual for the SF-36v2 Health Survey. Lincoln: Quality Metric; 2011.]). The pharmaceutical company uses rounded response criteria for the subscales in Module 4 A. The response criteria of the two subscales physical role functioning and psychological well-being deviate slightly from 15% of the scale range.
[j] HR and CI from unstratified Cox regression model, p value from log-rank test
[k] Operationalised as CTCAE grade ≥ 3
[l] Operationalised via the SMQ interstitial lung disease (narrow)
[m] Operationalised via the SMQ drug-induced liver diseases - comprehensive search (narrow)
[n] Operationalised via the SMQ haematopoietic cytopenias (wide)

Abbreviations used:
AD: Absolute difference; BICR: Blinded Independent Central Review; CTCAE: Common Terminology Criteria for Adverse Events; ILD: interstitial lung disease; n.d.: no data available; CI: confidence interval; MCS: mental component summary score; MD: mean difference; MMRM: mixed model with repeated measures; MV: mean value; N: number of patients evaluated; n: number of patients with (at least one) event; n.c.: not calculable; n.r.: not reached; PCS: physical component summary score; PT: preferred term; RR: relative risk; SD: standard deviation; SE: standard error; SF-36v2: Short Form-36 Health Survey Version 2; SMQ: standardised MedDRA query; SOC: system organ class; VAS: visual analogue scale; vs: versus

b) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection after prior adjuvant platinum-based chemotherapy or who are ineligible for this

No data available.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n. a.: not assessable		

2. Number of patients or demarcation of patient groups eligible for treatment

a) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection who are eligible for adjuvant platinum-based chemotherapy

and

b) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection after prior adjuvant platinum-based chemotherapy or who are ineligible for this

Approx. 230 – 452 patients

3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Alecensa (active ingredient: alectinib) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 18 December 2024):

https://www.ema.europa.eu/en/documents/product-information/alecensa-epar-product-information_en.pdf

Treatment with alectinib should only be initiated and monitored by specialists in internal medicine, haematology and oncology who are experienced in the treatment of patients with non-small cell lung carcinoma, as well as specialists in internal medicine and pulmonology or specialists in pulmonary medicine and other doctors from specialist groups participating in the Oncology Agreement.

4. Treatment costs

Annual treatment costs:

a) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection who are eligible for adjuvant platinum-based chemotherapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Alectinib	€ 73,480.50
Appropriate comparator therapy:	
Patient-individual postoperative (adjuvant) systemic chemotherapy with selection of	
o cisplatin in combination with vinorelbine	
Cisplatin	€ 2,274.18
Vinorelbine	€ 5,008.76 - € 6,247.29
Total:	€ 7,282.94 - € 8,521.47
Additionally required SHI services:	€ 271.70 - € 341.48
o Cisplatin in combination with pemetrexed	
Cisplatin	€ 2,009.18
Pemetrexed	€ 18,617.48
Total:	€ 20,626.66

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 December 2024

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Appropriate comparator therapy:					
Cisplatin in combination with vinorelbine					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Vinorelbine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	2	34.8	€ 3,480
Cisplatin in combination with pemetrexed					
Cisplatin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Pemetrexed	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740

b) <u>Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection after prior adjuvant platinum-based chemotherapy or who are ineligible for this</u>

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Alectinib	€ 73,480.50
Appropriate comparator therapy:	
Monitoring wait-and-see approach	Not calculable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 December 2024

Costs for additionally required SHI services: not applicable

5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

a) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection who are eligible for adjuvant platinum-based chemotherapy

- No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

b) Adults with ALK-positive NSCLC at high risk of recurrence for adjuvant treatment following complete tumour resection after prior adjuvant platinum-based chemotherapy or who are ineligible for this

- No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.