Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2022-B-312 Encorafenib (NSCLC, Erstlinie)

und

2023-B-198 Encorafenib (NSCLC, Zweitlinie)

Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

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Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

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Vorgang: 2022-B-312 Encorafenib (NSCLC, Erstlinie)

Stand: Februar 2023

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Encorafenib in Kombination mit Binimetinib
[NSCLC, Erstlinie]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“ Ausgeschlossen wurden Arzneimittel zur Therapie eines NSCLC mit ALK-Translokation, EGFR-, ROS1 oder RET-Mutationen.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	**Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:** – Atezolizumab (Beschlüsse vom 02.04.2020 und 19.11.2021) – Cemiplimab (Beschluss vom 20.01.2022) – Dabrafenib (Beschluss vom 19.10.2017) – Ipilimumab (Beschluss vom 03.06.2021) – Nivolumab (Beschluss vom 03.06.2021) – Pembrolizumab (Beschlüsse vom 03.08.2017 und 19.09.2019) – Trametinib (Beschluss vom 19.10.2017) **Richtlinien:** Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie - Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (Off-Label-Use): Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Encorafenib L01EC03 Braftovi Binimetinib L01EE0 Mektovi	<u>Geplantes Anwendungsgebiet laut Beratungsanforderung:</u> Encorafenib ist angezeigt in Kombination mit Binimetinib zur Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligem Lungenkarzinom (non-small cell lungcancer, NSCLC) mit einer BRAF-V600E-Mutation (Erstlinientherapie).
Zytostatika:	
Cisplatin L01XA01 generisch	Cisplatin wird angewendet zur Behandlung des fortgeschrittenen oder metastasierten nichtkleinzelligen Bronchialkarzinoms. Cisplatin kann als Mono- oder Kombinationstherapie angewendet werden.
Docetaxel L01CD02 generisch	Nicht-kleinzelliges Bronchialkarzinom: Docetaxel ist in Kombination mit Cisplatin zur Behandlung von Patienten mit nicht resezierbarem, lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Bronchialkarzinom ohne vorausgegangene Chemotherapie angezeigt.
Etoposid L01CB01 Riboposid	Kombinationstherapie folgender Malignome: – Palliative Therapie des fortgeschrittenen, nicht-kleinzelligen Bronchialkarzinoms bei Patienten mit gutem Allgemeinzustand (Karnofsky-Index > 80 %), […]
Gemcitabin L01BC05 generisch	Gemcitabin ist in Kombination mit Cisplatin als Erstlinientherapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nichtkleinzelligen Bronchialkarzinom (NSCLC) angezeigt. Eine Gemcitabin-Monotherapie kann bei älteren Patienten oder solchen mit einem Performance Status 2 in Betracht gezogen werden.
Ifosfamid	Nicht-kleinzellige Bronchialkarzinome:

II. Zugelassene Arzneimittel im Anwendungsgebiet	
L01AA06 Holoxan	Zur Einzel- oder Kombinationschemotherapie von Patienten mit inoperablen oder metastasierten Tumoren.
Mitomycin L01DC03 generisch	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Bei intravenöser Gabe ist es in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei folgenden metastasierenden Tumoren wirksam: […] nicht-kleinzelliges Bronchialkarzinom […].
Nab-Paclitaxel L01CD01 Abraxane	Abraxane ist in Kombination mit Carboplatin indiziert für die Erstlinienbehandlung des nicht-kleinzelligen Bronchialkarzinoms bei erwachsenen Patienten, bei denen keine potentiell kurative Operation und/oder Strahlentherapie möglich ist.
Paclitaxel L01CD01 generisch	Fortgeschrittenes nicht-kleinzelliges Bronchialkarzinom (NSCLC): Paclitaxel ist, in Kombination mit Cisplatin, zur Behandlung des nicht-kleinzelligen Bronchialkarzinoms bei Patienten angezeigt, für die potentiell kurative chirurgische Maßnahmen und/oder eine Strahlentherapie nicht in Frage kommen.
Pemetrexed L01BA04 generisch	Pemetrexed ist in Kombination mit Cisplatin angezeigt zur first-line Therapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie.
Vindesin L01CA03 Eldesine	Kombinationschemotherapie: Lokal fortgeschrittenes oder metastasiertes nicht-kleinzelliges Bronchialkarzinom (Stadium IIIB, IV).
Vinorelbin L01CA04 generisch	Behandlung des nicht kleinzelligen Bronchialkarzinoms (Stadium 3 oder 4).
Antikörper:	
Atezolizumab L01XC32 Tecentriq	Tecentriq wird angewendet in Kombination mit Bevacizumab, Paclitaxel und Carboplatin bei erwachsenen Patienten zur Erstlinienbehandlung des metastasierten nichtkleinzelligen Lungenkarzinoms (NSCLC) mit nicht-plattenepithelialer Histologie. Tecentriq wird angewendet in Kombination mit nab-Paclitaxel und Carboplatin zur Erstlinienbehandlung des metastasierten NSCLC mit nicht-plattenepithelialer Histologie bei erwachsenen Patienten, die keine EGFR-Mutationen und kein ALK-positives NSCLC haben.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	Tecentriq als Monotherapie wird angewendet bei erwachsenen Patienten zur Erstlinienbehandlung des metastasierten NSCLC, deren Tumoren eine PD-L1-Expression ≥ 50 % der Tumorzellen (tumour cells, TC) oder ≥ 10 % bei tumorinfiltrierenden Immunzellen (immune cells, IC) aufweisen und die keine EGFR-Mutationen oder ein ALK-positives NSCLC haben.
Bevacizumab L01XC07 Avastin	Bevacizumab wird zusätzlich zu einer platinhaltigen Chemotherapie zur First-Line-Behandlung von erwachsenen Patienten mit inoperablem fortgeschrittenem, metastasiertem oder rezidivierendem nicht-kleinzelligem Bronchialkarzinom, außer bei vorwiegender Plattenepithel-Histologie, angewendet.
Cemiplimab L01XC33 Libtayo	LIBTAYO ist indiziert als Monotherapie für die Erstlinienbehandlung von erwachsenen Patienten mit nicht-kleinzelligem Lungenkarzinom (non-small cell lung cancer, NSCLC), das PD-L1 (in ≥ 50 % der Tumorzellen) exprimiert und keine EGFR-, ALK- oder ROS1-Aberrationen aufweist. Die Behandlung ist bestimmt für: · Patienten mit lokal fortgeschrittenem NSCLC, die keine Kandidaten für eine definitive Radiochemotherapie sind, oder · Patienten mit metastasiertem NSCLC.
Ipilimumab L01XC11 Yervoy	YERVOY ist in Kombination mit Nivolumab und 2 Zyklen platinbasierter Chemotherapie für die Erstlinientherapie des metastasierten nicht-kleinzelligen Lungenkarzinoms (NSCLC) bei Erwachsenen, deren Tumoren keine sensitivierende EGFR-Mutation oder ALK-Translokation aufweisen, indiziert.
Nivolumab L01XC17 Opdivo	OPDIVO ist in Kombination mit Ipilimumab und 2 Zyklen platinbasierter Chemotherapie für die Erstlinientherapie des metastasierten nicht-kleinzelligen Lungenkarzinoms (NSCLC) bei Erwachsenen, deren Tumoren keine sensitivierende EGFR-Mutation oder ALK-Translokation aufweisen, indiziert.
Pembrolizumab L01XC18 Keytruda	KEYTRUDA ist als Monotherapie zur Erstlinienbehandlung des metastasierenden nicht-kleinzelligen Lungenkarzinoms (NSCLC) mit PD-L1 exprimierenden Tumoren (Tumor Proportion Score [TPS] ≥ 50 %) ohne EGFR oder ALK-positive Tumormutationen bei Erwachsenen angezeigt. KEYTRUDA ist in Kombination mit Pemetrexed und Platin-Chemotherapie zur Erstlinienbehandlung des metastasierenden nicht-plattenepithelialen NSCLC ohne EGFR- oder ALK-positive Tumormutationen bei Erwachsenen angezeigt. KEYTRUDA ist in Kombination mit Carboplatin und entweder Paclitaxel oder nab-Paclitaxel zur Erstlinienbehandlung des metastasierenden plattenepithelialen NSCLC bei Erwachsenen angezeigt.
Proteinkinase-Inhibitoren:	
Dabrafenib	<u>Nicht-kleinzelliges Lungenkarzinom (NSCLC)</u>

II. Zugelassene Arzneimittel im Anwendungsgebiet	
L01EC02 Tafinlar	Dabrafenib in Kombination mit Trametinib ist angezeigt zur Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligen Lungenkarzinom mit einer BRAF-V600-Mutation.
Trametinib L01EE01 Mekenist	<u>Nicht-kleinzelliges Lungenkarzinom (NSCLC)</u> Trametinib in Kombination mit Dabrafenib ist angezeigt zur Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligen Lungenkarzinom mit einer BRAF-V600-Mutation.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2022-B-312 (Encorafenib_Binimetinib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	6. Januar 2023

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Adverse event
AFA	Afatinib
ALK	Anaplastic Lymphoma Kinase
ALT	Alanin-Aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartat-Aminotransferase
ATEZO	Atezolizumab
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
Bev	Bevacizumab
BSC	Best supportive care
CIS	Cisplatin
CNS	Zentrales Nervensystem/central nervous system
CTX	Cytotoxic Chemotherapy
DAHTA	DAHTA Datenbank
DCR	Disease Control Rate
DOC	Docetaxel
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organisation for QLQ Research and Treatment of Cancer Quality of Life Questionnaire
EPHPP	Effective Public Health Practice Project Tool
ERL	Erlotinib
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
Gem	Gemcitabin
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
ICI	Immune-Checkpoint Inhibitor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
k.A.	Keine Angaben
KI	Konfidenzintervall
KRAS	Kirsten rat sarcoma oncogene Mutation
LoE	Level of Evidence

M+	mutation positive (EGFR)
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NINTE	Nintedanib
NIVO	Nivolumab
NSCLC	non-small cell lung cancer
NSQ	Non-Squamous
OR	Odds Ratio
ORR	Objective response rate
OS	Overall Survival
PAX	Paclitaxel
PC	paclitaxel and carboplatin
PD-1	anti-programmed cell death receptor 1
PD-L1	antiprogrammed cell death ligand
PEM	Pemetrexed
PEMBRO	Pembrolizumab
PFS	Progression Free Survival
Pt+B	Platinum plus Bevacizumab
QoL	Quality of Life
RCT	Randomized Controlled Trial
RR	Relatives Risiko
SQ	Squamous
SIGN	Scottish Intercollegiate Guidelines Network
TA	Targeted Agent
TKI	Tyrosinkinsaseinhibitor
TPS	Tumor Proportion Score
TRAE	Treatment related adverse event
TRIP	Turn Research into Practice Database
TTP	Time to Progression
VEGFR	Vascular endothelial growth factor receptor
VTE	Venous Thromboembolism
WHO	World Health Organization
WMD	Weighted mean difference.
WT	Wild Type

1 Indikation

Encorafenib ist angezeigt in Kombination mit Binimetinib zur Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligem Lungenkarzinom (non-small cell lung cancer, NSCLC) mit einer BRAF-V600EMutation (Erstlinientherapie).

Hinweis zur Synopse: „Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt“.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *nicht-kleinzelliges Lungenkarzinom* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.startpage.com*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Die Erstrecherche wurde am 03.06.2021 durchgeführt, die folgenden am 13.06.2022 und 17.11.2022. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter ist am Ende der Synopse detailliert dargestellt. Die Recherchen ergaben insgesamt 3547 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 32 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Ferrara R et al., 2021 [7].

Single or combined immune checkpoint inhibitors compared to first-line platinum-based chemotherapy with or without bevacizumab for people with advanced non-small cell lung cancer.

Fragestellung

To determine the effectiveness and safety of first-line immune checkpoint inhibitors, as monotherapy or in combination compared to platinum-based chemotherapy with or without bevacizumab for people with advanced non-small cell lung cancer (NSCLC), according to the level of PD-L1 expression.

Methodik

Population:

- participants with metastatic NSCLC or locally advanced NSCLC not susceptible to curative treatment. People should have not received any first-line systemic treatment.

Intervention/Komparator

- Single-agent immune checkpoint inhibitors (ICIs) versus standard first-line therapy (doublet chemotherapy ± bevacizumab).
- Doublet immune checkpoint inhibitors (ICIs) versus standard first-line therapy (doublet chemotherapy ± bevacizumab).

A doublet chemotherapy regimen includes any platinum-based doublet along with a third-generation agent (i.e. gemcitabine, vinorelbine, taxanes, pemetrexed).

Endpunkte:

- OS, PFS, ORR, HRQoL, AEs

Recherche/Suchzeitraum:

- from inception to 31st December 2020

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

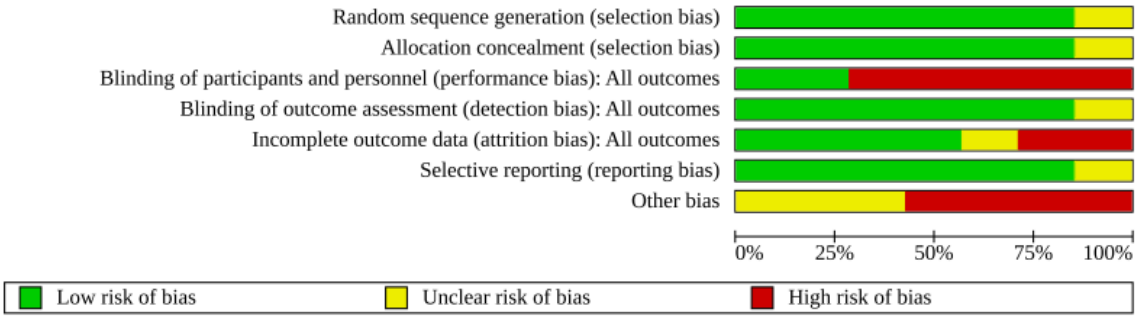
- 15 trials (seven completed and eight ongoing trials)
- Data for 5893 participants from seven trials comparing first-line single- (six trials) or double- (two trials) agent ICI with platinum-based chemotherapy, one trial comparing both firstline single- and double-agent ICsI with platinum-based chemotherapy.

Qualität der Studien:

- All trials were at low risk of selection and detection bias, some were classified at high risk of performance, attrition or other source of bias. The overall certainty of evidence

according to GRADE ranged from moderate-to-low because of risk of bias, inconsistency, or imprecision.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Studienergebnisse:

- Note: The majority of the included trials reported their outcomes by PD-L1 expressions, with PD-L1 ≥ 50 being considered the most clinically useful cut-off level for decision makers. Also, iIn order to avoid overlaps between various PDL-1 expressions we prioritised the review outcomes according to PD-L1 ≥ 50.
- Single-agent ICI: In the PD-L1 expression ≥ 50% group single-agent ICI probably improved OS compared to platinum-based chemotherapy (hazard ratio (HR) 0.68, 95% confidence interval (CI) 0.60 to 0.76, 6 RCTs, 2111 participants, moderate-certainty evidence). In this group, single-agent ICI also may improve PFS (HR: 0.68, 95% CI 0.52 to 0.88, 5 RCTs, 1886 participants, low-certainty evidence) and ORR (risk ratio (RR):1.40, 95% CI 1.12 to 1.75, 4 RCTs, 1672 participants, low-certainty evidence). HRQoL data were available for only one study including only people with PDL1 expression ≥ 50%, which suggested that single-agent ICI may improve HRQoL at 15 weeks compared to platinum-based chemotherapy (RR: 1.51, 95% CI 1.08 to 2.10, 1 RCT, 297 participants, low-certainty evidence). In the included studies, treatment-related AEs were not reported according to PD-L1 expression levels. Grade 3-4 AEs may be less frequent with single-agent ICI compared to platinum-based chemotherapy (RR: 0.41, 95% CI 0.33 to 0.50, I2 = 62%, 5 RCTs, 3346 participants, lowcertainty evidence).
- Double-agent ICI: Double-ICI treatment probably prolonged OS compared to platinum-based chemotherapy in people with PD-L1 expression ≥50% (HR: 0.72, 95% CI 0.59 to 0.89 2 RCTs, 612 participants, moderate-certainty evidence). Trials did not report data on HRQoL, PFS and ORR according to PD-L1 groups. Treatment related AEs were not reported according to PD-L1 expression levels. The frequency of grade 3-4 AEs may not differ between double-ICI treatment and platinum-based chemotherapy (RR: 0.78, 95% CI 0.55 to 1.09, I2 = 81%, 2 RCTs, 1869 participants, low-certainty evidence).

Anmerkung/Fazit der Autoren

The evidence in this review suggests that single-agent ICI in people with NSCLC and PD-L1 ≥50% probably leads to a higher overall survival rate and may lead to a higher progression-free survival and overall response rate when compared to platinum-based chemotherapy and may also lead to a lower rate of adverse events and higher HRQoL. Combined ICI in people with NSCLC and PD-L1 ≥50% also probably leads to a higher overall survival rate when compared to platinum-based chemotherapy, but its effect on progression-free survival, overall response rate and HRQoL is unknown due to a lack of data. The rate of adverse events may not differ between groups.

This review used to be a living review. It is transitioned out of living mode because current research is exploring ICI in association with chemotherapy or other immunotherapeutic drugs versus ICI as single agent rather than platinum based chemotherapy.

Vasconcellos VF et al., 2020 [25].

Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer.

Fragestellung

To assess the effectiveness and safety of carboplatin-based chemotherapy compared with cisplatin-based chemotherapy, both in combination with a third-generation drug, in people with advanced NSCLC.

To compare the QoL of people with advanced NSCLC receiving chemotherapy with cisplatin and carboplatin combined with a third-generation drug.

Methodik

Population:

- People with pathologically confirmed NSCLC, with metastatic disease, or pleural or pericardial effusion (stage IIIB or IV)

Intervention/Komparator:

- Cisplatin plus gemcitabine versus carboplatin plus gemcitabine
- Cisplatin plus docetaxel versus carboplatin plus docetaxel
- Cisplatin plus paclitaxel versus carboplatin plus paclitaxel
- Cisplatin plus vinorelbine versus carboplatin plus vinorelbine
- Cisplatin plus irinotecan versus carboplatin plus irinotecan

Endpunkte:

- Overall survival, Health-related quality of life (HRQoL), One-year survival rate, Objective response rate, Drug toxicities

Recherche/Suchzeitraum:

- Bis Januar 2019

Qualitätsbewertung der Studien:

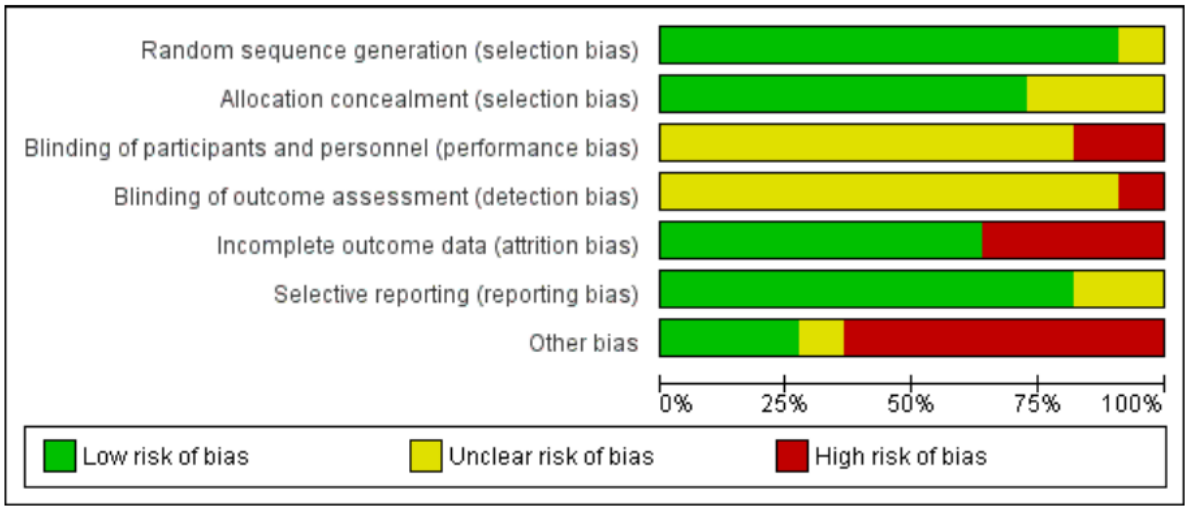
- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- one additional RCT, for a total of 11 included RCTs (5088 participants, 4046 for metaanalysis)

Qualität der Studien:



Studienergebnisse:

- No difference in overall survival (hazard ratio (HR) 0.99, 95% confidence interval (CI) 0.82 to 1.20; 10 RCTs; 2515 participants; high-quality evidence); one-year survival rate (risk ratio (RR) 0.98, 95% CI 0.89 to 1.08; I2 = 17%; 4004 participants; all 11 RCTs; high-quality evidence); or response rate (RR 0.89, 95% CI 0.79 to 1.00; I2 = 12%; all 11 RCTs; 4020 participants; high-quality evidence).
- A subgroup analysis comparing carboplatin with different doses of cisplatin found an overall survival benefit in favour of carboplatin-based regimens when compared to cisplatin at lower doses (40 to 80 mg/m2) (HR 1.15, 95% CI 1.03 to 1.28; 6 RCTs; 2508 participants), although there was no overall survival benefit when carboplatin-based chemotherapy was compared to cisplatin at higher doses (80 to 100 mg/ m2) (HR 0.93, 95% CI 0.83 to 1.04; I2 = 0%; 4 RCTs; 1823 participants).
- Carboplatin caused more thrombocytopenia (RR 2.46, 95% CI 1.49 to 4.04; I2 = 68%; 10 RCTs; 3670 participants) and was associated with more neurotoxicity (RR 1.42, 95% CI 0.91 to 2.23; I2 = 0%, 5 RCTs; 1489 participants), although we believe this last finding is probably related to a confounding factor (higher dose of paclitaxel in the carboplatincontaining treatment arm of a large study included in the analysis).
- There was no statistically significant difference in renal toxicity (RR 0.52, 95% CI 0.19 to 1.45; I2 = 3%; 3 RCTs; 1272 participants); alopecia (RR 1.11, 95% CI 0.73 to 1.68; I2 = 0%; 2 RCTs; 300 participants); anaemia (RR 1.37, 95% CI 0.79 to 2.38; I2 = 77%; 10 RCTs; 3857 participants); and neutropenia (RR 1.18, 95% CI 0.85 to 1.63; I2 = 94%; 10 RCTs; 3857 participants) between cisplatin-based chemotherapy and carboplatin-based chemotherapy regimens.
- Two RCTs performed a healthrelated quality of life analysis; however, as they used different methods of measurement we were unable to perform a meta-analysis. One RCT reported comparative health-related quality of life data between cisplatin and carboplatin-containing arms but found no significant differences in global indices of quality of life, including global health status or functional scales.

Anmerkung/Fazit der Autoren

Advanced NSCL patients treated with carboplatin or cisplatin doublet with third-generation chemotherapy drugs showed equivalent overall survival, one-year survival, and response rate. Regarding adverse events, carboplatin caused more thrombocytopenia, and cisplatin

caused more nausea/vomiting. Therefore, in this palliative therapeutic intent, the choice of the platin compound should take into account the expected toxicity profile, patient's comorbidities and preferences.

Kommentare zum Review

- Gemischte Population; keine Subgruppenanalysen zu Therapielinie oder Stadium

3.2 Systematische Reviews

He M et al., 2021 [10].

First-line treatment options for advanced non-small cell lung cancer patients with PD-L1 ≥ 50%: a systematic review and network meta-analysis.

Fragestellung

to evaluate the efficacy and toxicity of first-line single-agent ICIs versus ICI combinations for advanced NSCLC patients with PD-L1 ≥ 50%.

Methodik

Population:

- patients with advanced NSCLC

Intervention/Komparator

- first-line ICIs or chemo-ICIs in the treatment

Endpunkte:

- overall survival (OS), progression free survival (PFS), objective response rate (ORR) and treatment related adverse events (TRAEs) of grades 3–5

Recherche/Suchzeitraum:

- PubMed, Embase, Cochrane Library and the Clinicaltrials.gov were systematically searched to extract eligible literature until December 2020

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- Fourteen studies with 3448 patients

Qualität der Studien:

- The studies were considered adequate for performing random sequence generation and allocation concealment as well as having a low risk of detection and reporting bias. Most studies were open-label trials, and two studies had incomplete outcome data.

Studienergebnisse:

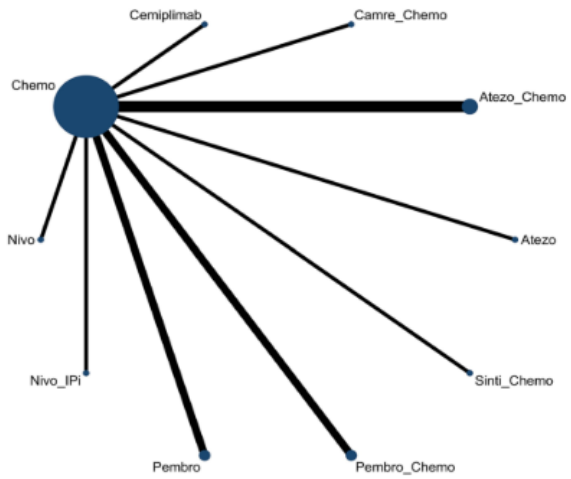


Fig. 2 Network plot of multiple therapies in the first-line treatment of advanced NSCLC with PD-L1 ≥ 50%

- Chemotherapy plus ICIs significantly improved PFS and ORR compared to chemotherapy, and sinti-chemo (HR: 0.31, 95% CI: 0.20–0.49) and pembro-chemo (OR: 4.2, 95% CI: 2.6–6.7) ranked first.
- In terms of OS, cemiplimab provided the best benefit versus chemotherapy (HR: 0.57, 95% CI: 0.43–0.77), followed by atezolizumab and pembro-chemo.
- In the subgroup analysis of histological type, pembro-chemo and sinti-chemo showed the best benefit of PFS in squamous and nonsquamous NSCLC, respectively, while there was no significant difference between ICI combinations with single-agent ICIs in OS.
- Addition of chemotherapy to ICIs elevated toxicity compared to chemotherapy.

Fazit der Autoren

In the current NMA, it was found that the addition of chemotherapy to ICIs might improve PFS and ORR in advanced NSCLC patients with PD-L1 ≥ 50%. However, there was no OS benefit for chemo-ICIs compared to single-agent ICIs or dual-agent ICIs. In terms of PFS and ORR, pembro-chemo, sinti-chemo and atezo-chemo might be superior choices, while in terms of OS, cemiplimab, atezolizumab and pembro-chemo might be superior choices. However, further studies of head-to-head comparisons are required.

Kommentare zum Review

- Siehe auch:
  Majem, M. et al., 2021 [19]
  Freemantle, N. et al., 2022 [8]

Di Federico A et al., 2021 [5].

Programmed Cell Death Protein-1 Inhibitors Versus Programmed Death-Ligand 1 Inhibitors in Addition to Chemotherapy for the First-Line Treatment of Advanced NSCLC: A Systematic Review and Meta-Analysis.

Fragestellung

to evaluate and compare the efficacy and safety of PD-(L)1 inhibitors in combination with first-line CT for advanced NSCLC.

Methodik

Population:

- patients with previously untreated advanced NSCLC

Intervention/Komparator:

- treatment with the combination of either a PD-1 or PD-L1 inhibitor and first-line CT-based treatment

Endpunkte:

- OS, PFS, ORR, TRAEs

Recherche/Suchzeitraum:

- before February 1, 2021 through the online databases MEDLINE (PubMed), EMBASE, and Cochrane Database of Systematic Reviews and Central Register of Controlled Trials

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- eight randomized clinical trials including a total of 4466 patients

Charakteristika der Population:

Table 2. Main Characteristics of the Randomized Clinical Trials Selected for the Meta-Analysis

Trial	Phase	Histology	No. of Intervention/ Control	Arms of Treatment	Primary Outcome	TRAEs Reported
KEYNOTE 021[6,7]	II	Nonsquamous	60/63	Pembrolizumab + carboplatin + pemetrexed vs. carboplatin + pemetrexed	ORR	Yes
KEYNOTE 189[10,11]	III	Nonsquamous	410/206	Pembrolizumab + cisplatin or carboplatin + pemetrexed vs. cisplatin or carboplatin + pemetrexed	PFS, OS	No
KEYNOTE 407[8,9]	III	Squamous	278/281	Pembrolizumab + carboplatin + nab-paclitaxel or paclitaxel vs. carboplatin + nab-paclitaxel or paclitaxel	PFS, OS	Yes
ORIENT-11[12]	III	Nonsquamous	266/131	Sintilimab + pemetrexed + cisplatin or carboplatin vs. pemetrexed + cisplatin or carboplatin	PFS, OS	No
IMpower130[15]	III	Nonsquamous	483/240	Atezolizumab + carboplatin + nab-paclitaxel vs. carboplatin + nab-paclitaxel	PFS, OS	Yes
IMpower131[13]	III	Squamous	343/340	Atezolizumab + carboplatin + nab-paclitaxel vs. carboplatin + nab-paclitaxel	PFS, OS	Yes
IMpower132[16]	III	Nonsquamous	292/286	Atezolizumab + cisplatin or carboplatin + pemetrexed vs. cisplatin or carboplatin + pemetrexed	PFS, OS	Yes
IMpower150[14]	III	Nonsquamous	400/400	Atezolizumab + bevacizumab + carboplatin + paclitaxel vs. bevacizumab + carboplatin + paclitaxel	PFS, OS	Yes

ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TRAE, treatment-related adverse event.

Qualität der Studien:

Table 1. Summary of Authors' Judgment on the Risk of Bias for Each Selected Randomized Controlled Clinical Trial According to the Cochrane Collaboration for Assessing Risk of Bias

Category	KEYNOTE021	KEYNOTE189	KEYNOTE407	IMpower130	IMpower131	IMpower132	IMpower150	ORIENT-11
Random sequence generation	Low	Low	Low	Low	Low	Low	Low	Low
Allocation concealment	Low	Low	Low	Low	Low	Low	Low	Low
Selective reporting	Low	Low	Low	Low	Low	Low	Low	Low
Blinding participants and personnel	High	Low	Low	High	High	High	High	High
Blinding outcome assessment	Low	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Incomplete outcome data	Low	Low	Low	Low	Low	Low	Low	Low
Other	Unclear	Unclear	Short follow-up duration	Unclear	Unclear	Low	Low	Unclear

Studienergebnisse:

- The addition of a PD-(L)1 inhibitor to CT improved progression-free survival, overall survival, and objective response rate compared with CT alone.
- The risk of grade greater than or equal to 3 treatment-related adverse events was slightly higher with the addition of a PD-(L)1 inhibitor to CT as compared with CT alone.
- A subgroup analysis according to the targeted receptor (PD-1 versus PD-L1) revealed that the addition of a PD-1 inhibitor to CT led to better objective response rate (p ¼ 0.0001), progression-free survival (p = 0.006), and overall survival (p = 0.002) compared with that of a PD-L1 inhibitor.
- The risk of grade greater than or equal to 3 treatment-related adverse events was significantly increased with the addition of a PD-L1 inhibitor to CT, but not with the addition of a PD-1 inhibitor.
- A direct comparison using the meta-regression analysis confirmed the statistical significance of all previous findings.

Fazit der Autoren

In conclusion, our meta-analysis revealed that the addition of a PD-1 inhibitor to CT seems to be more effective and safer than that of a PD-L1 inhibitor. These findings need validation in prospective trials of direct comparison among different ICIs in combination with platinum-based CT.

Kommentar zum Review:

Siehe auch:

- Di Federico, A. et al., 2021 [4]
- García-González, J. et al., 2020 [9]
- Yi, K. et al., 2020 [31]

Wang DD et al., 2021 [28].

Comparative efficacy and safety of PD-1/PD-L1 immunotherapies for non-small cell lung cancer: a network meta-analysis.

Fragestellung

to conduct a network meta-analysis to compare the safety and efficacy of these immune checkpoint inhibitors (ICIs).

Methodik

Population:

- patients with advanced non-small cell lung cancer

Intervention:

- PD-1/PD-L1 inhibitors

Komparator:

- Chemotherapy

Endpunkte:

- OS and/or PFS

Recherche/Suchzeitraum:

- PubMed and Embase databases for English-language articles published up to December 20, 2020

Qualitätsbewertung der Studien:

- Cochrane Collaboration's Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 19 RCTs, including 12,753 patients

Charakteristika der Population:

Table I. Details of all included trials.

Study	Study characteristics					D-L1 expression			Patient characteristics			
	Treatment details	Sample size	Line of treatment	Histology types	Median follow-up (months)	≥50% (n)	1%-49% (n)	<1% (n)	% Male	% of current or former smokers	% of non-squamous	Median age
KEYNOTE -010	Pem Chemo	690 343	Second or late	Mixed	42.6	290 152	400 191	0 0	62% 61%	82% 78%	70% 70%	63 62
KEYNOTE -024	Pem Chemo	154 151	First-line	Mixed	25.2	154 151	0 0	0 0	59.7% 62.9%	96.8% 87.4%	81.2% 82.1%	64.5 66
KEYNOTE -033	Pem Chemo	213 212	Second or later	Mixed	18.8	114 98	112 98	0 0	73.7% 77.4%	N/A N/A	N/A N/A	60.6† 61.0†
KEYNOTE -042	Pem Chemo	637 637	First-line	Mixed	14	299 300	338 337	0 0	71% 71%	78% 78%	62% 61%	63 63
KEYNOTE -189	Pem+Chemo Chemo	410 206	First-line	Non-SCC	23.1	132 70	128 58	127 63	62.0% 52.9%	88.3% 87.9%	100% 100%	65 63.5
KEYNOTE -407	Pem+Chemo Chemo	278 281	First-line	SCC	14.3	73 73	103 104	95 99	79.1% 83.6%	92.1% 93.2%	0% 0%	65 65
CheckMate 017	Niv Chemo	135 137	Second or later	SCC	36.6 (minimum)	17 12	NA NA	54 52	82% 71%	90% 94%	0% 0%	63 63
CheckMate 026	Niv Chemo	271 270	First-line	Mixed	13.5	88 126	NA NA	0 0	89% 88%	88% 87%	76% 76%	63 65
CheckMate 057	Niv Chemo	292 290	Second or later	Non-SCC	36.6 (minimum)	66 46	NA NA	108 101	53% 58%	79% 78%	100%	61 64
CheckMate 078	Niv Chemo	338 166	Second or late	Mixed	25.9 (minimum)	NA NA	NA NA	138 67	78% 81%	70% 71%	61% 60%	60 60
CheckMate 227 (Part 1)	Niv+Ipi Niv Niv+Chemo Chemo	583 396 177 583	First-line	Mixed	29.3 (minimum)	205 214 0 192	191 182 1 205	187 0 176 186	67.4% 68.7% 73.4% 66.0%	85.2% 86.4% 83.1% 85.6%	71.9% 70.5% 75.7% 72.2%	64 64 64 64
CheckMate 277 (Part 2)	Niv+Chemo Chemo	377 378	First-line	Mixed	19.5 (minimum)	NA NA	NA NA	NA NA	NA NA	NA NA	NA NA	NA NA
OAK	Ate Chemo	425 425	Second or later	Mixed	26 (minimum)	72 65	173 161	180 199	61% 61%	80% 83%	74% 74%	63 64
IMpower110	Ate Chemo	277 277	First-line	Mixed	13.4	107 98	170 179	0 0	70.8% 69.7%	86.6% 87.4%	69.3% 69.7%	64 65
IMpower130	Ate+Chemo Chemo	451 228	First-line	Non-SCC	18.5 19.2	88 42	128 65	235 121	59% 59%	89% 92%	100% 100%	64 65
IMpower131	Ate+Chemo Chemo	343 340	First-line	SCC	26.8 24.8	48 44	134 126	161 170	80% 80%	77.20% 77.20%	0% 0%	65 63
IMpower132	Ate+Chemo Chemo	292 286	First-line	Non-SCC	28.4	25 20	63 72	88 75	66.4% 66.4%	87% 90%	100% 100%	64 63
MYSTIC	Dur Chemo	374 372	First-Line	Mixed	30.2	118 107	161 182	95 83	68.4% 67.2%	84.8% 86.0%	71.4% 71.5%	65 64
ARCTIC (Study B)	Dur Chemo	117 118	Third-line or later	Mixed	9.1	0 0	N/A N/A	52 58	62.4% 68.6%	76.1% 81.4%	75.2% 76.3%	63 65

Abbreviations: NA: not available; Ate: atezolizumab; Pem: pembrolizumab; Ipi: ipilimumab; Niv: nivolumab; Dur: durvalumab; Chemo: chemotherapy; SCC: Squamous Cell Carcinoma.
Notes: † Mean age

Qualität der Studien:

- Overall, 18 trials were considered to have low risk of bias for the overall survival outcome. One trial (CM 227 Part 2) was considered to have an unclear risk of bias as three domains were assessed as having an unclear risk.
- In the selection bias domain, 18 trials were considered low risk, and one (CM 227 Part 2) was considered unclear risk. In the reporting bias domain, 18 trials were considered low risk, and one (CM 227 Part 2) was considered unclear risk. In the performance bias domain, all trials were considered to be low risk for the overall survival outcome as this is unlikely to be affected by the lack of blinding in the open trial design. Only two trials (KN-189 and KN-407) had a low risk of bias for PFS, as these were the only double-blind trials.
- In the detection bias domain, all trials were considered low risk for the overall survival outcome as this is unlikely to be affected by lack of blinding. Ten trials (KN-010, KN-024, KN-033, KN-042, KN-189, KN-407, CM 017, CM 026, CM 227 Part 1, MYSTIC) were also considered low risk for the PFS outcome, as they used blinded independent central reviewers for radiographic assessment of progression.
- All trials were considered low risk for attrition bias. Most trials allowed crossover, and this was considered to be a source of other potential bias.

Studienergebnisse:

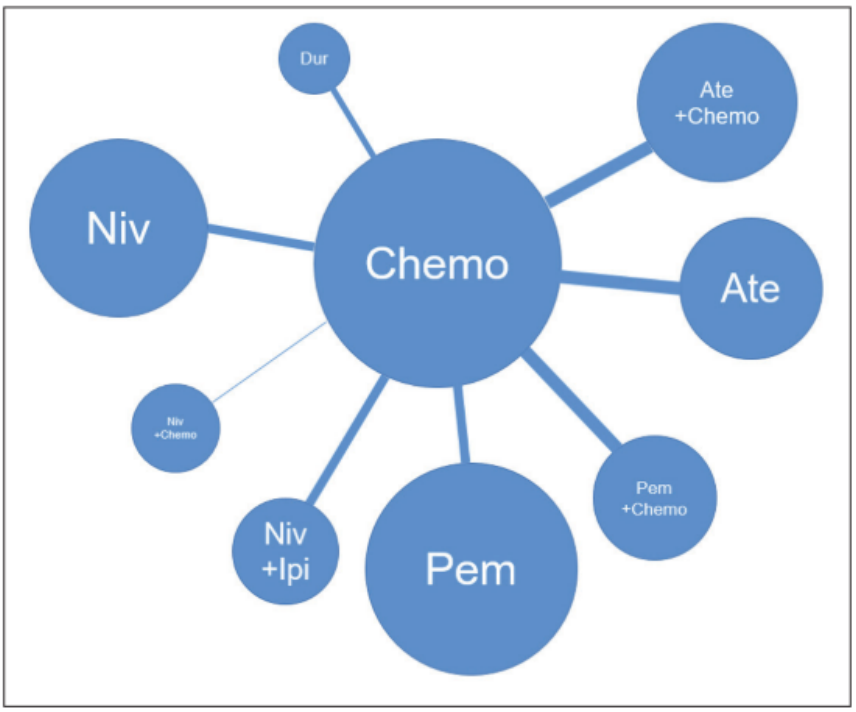


Figure 1. Network of eligible comparisons. The size of the nodes is proportional to the number of patients randomized to receive the treatment. The width of the lines is proportional to the number of trials comparing the connected treatments. Abbreviations: Pem, pembrolizumab; Ate, atezolizumab; Dur, durvalumab; Ipi, ipilimumab; Niv, nivolumab; Chemo, chemotherapy.

- In the analysis of all-comers, the pembrolizumab/chemotherapy combination ranked best for overall survival (OS) and progression-free survival (PFS).
- Durvalumab was the only ICI treatment that showed no benefit over chemotherapy.
- In the first-line setting only, in terms of OS, atezolizumab, pembrolizumab/chemotherapy, and nivolumab/ipilimumab ranked as the best treatments for patients with PD-L1 expression levels of ≥50%, 1-49%, and <1%, respectively.

- Nivolumab, atezolizumab, pembrolizumab, and durvalumab all had lower odds of grade 3 or greater treatment-related adverse events (TRAEs) compared to chemotherapy.
- With the addition of chemotherapy to any ICI regimen, the odds of TRAEs increased in a considerable and statistically significant way.

Anmerkung/Fazit der Autoren

While the pembrolizumab/chemotherapy combination was the most effective therapy in the overall cohort of all-comers, treatment preferences varied by treatment-line setting, tumor characteristics, and outcome of interest. In the first-line setting, the most effective treatments for patients with PD-L1 expressions of ≥50%, 1-49%, and <1% were atezolizumab, pembrolizumab/chemotherapy, and nivolumab/ipilimumab, respectively.

Kommentare zum Review

Siehe auch:

- Liang, J.et al., 2020 [17]
- Jiang, M. et al., 2022 [12]
- Wang, L. et al., 2022 [28]
- Peng TR und Wu TW, 2019 [23]

Yang Y et al., 2021 [30].

The optimal immune checkpoint inhibitors combined with chemotherapy for advanced non-small-cell lung cancer: a systematic review and meta-analysis.

Fragestellung

Metaanalysis that compared the efficacy and safety of PD-1 inhibitor + CT with PD-L1 inhibitor + CT.

Methodik

Population:

- advanced patients with NSCLC patients

Intervention/Komparator:

- PD-1 + CT vs PD-L1 + CT

Endpunkte:

- progression-free survival (PFS), overall survival (OS), objective response rate (ORR) and treatmentrelated adverse events (TRAEs)

Recherche/Suchzeitraum:

- PubMed, Embase, Web of Science, Cochrane Library, and major international scientific meetings were searched from inception dates to March 2020

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 phase III RCTs with 4253 patients

Charakteristika der Population:

Table 1 Characteristics of patients comparing PD-1/PD-L1 inhibitors plus chemotherapy or PD-1/PD-L1 inhibitors alone with chemotherapy in 8 randomized controlled trials included in the meta-analysis

Study	Author	Year	Trial phase	Study group (regime and no. of Pts.)		Control group (regime and no. of Pts.)		Inclusion criteria
CheckMate 227	Hellmann	2018	III	NIV plus PBC	177	PBC alone	160	Stage IV or recurrent NSCLC without targetable genetic aberration, with a high tumor mutational burden (≥ 10 mutations per megabase)
KEYNOTE-021	Langer	2016	III	PEM plus PBC	60	PBC alone	63	Stage IIIB or IV, non-squamous NSCLC without targetable genetic aberration
KEYNOTE-189	Gandhi	2018	III	PEM plus PBC	410	PBC alone	206	Stage IV non-squamous NSCLC without targetable genetic aberration
KEYNOTE-407	Paz-Ares	2018	III	PEM plus PBC	278	PBC alone	281	Stage IV, squamous NSCLC
Impower 130	West	2019	III	ATE plus PBC	447	PBC alone	226	Stage IV, non-squamous NSCLC without targetable genetic aberration
Impower 131	Jotte	2018	III	ATE plus PBC	343	PBC alone	340	Stage IV, squamous NSCLC
Impower 132	Papadimitra-kopoulou	2018	III	ATE plus PBC	292	PBC alone	286	Stage IV non-squamous NSCLC without targetable genetic aberration
Impower 150	Socinski	2018	III	ATE plus PBC	353	PBC alone	331	Stage IIIB or IV, non-squamous NSCLC without targetable genetic aberration

NIV nivolumab, *PBC* platinum-based chemotherapy, *PEM* pembrolizumab, *ATE* atezolizumab

Qualität der Studien:

- All of the studies were of high quality.

Studienergebnisse:

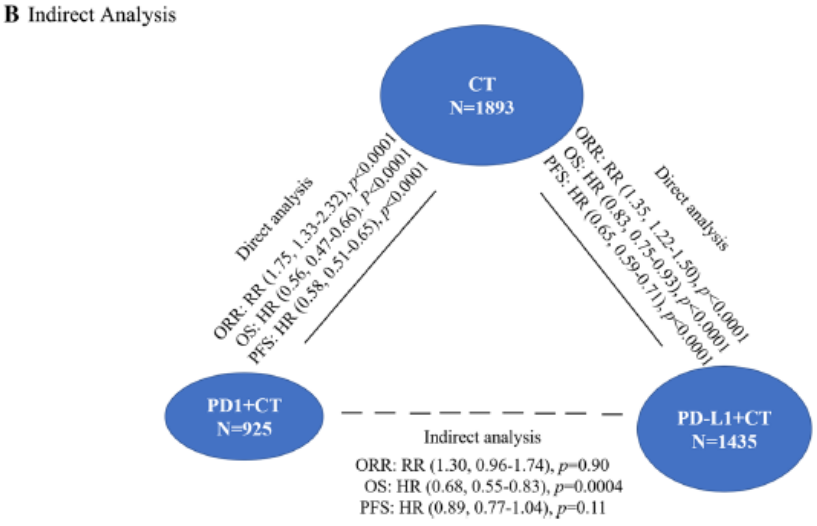


Fig. 3 Forest plots of progression-free survival (PFS) comparing PD-1+CT or PD-L1+CT versus chemotherapy alone and indirect comparison between PD-1+CT versus PD-L1+CT. In B, solid lines represented the existence of direct comparisons between treatment regimens, and dashed line represented the indirect comparison between PD-1+CT versus PD-L1+CT. The size of the circle corresponds to the enrolled patient number. *PD-1* anti-PD-1 immune checkpoint inhibitor, *PD-L1* anti-PD-L1 immune checkpoint inhibitor, *CT* chemotherapy, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival

- PD-1 + CT led to notably longer OS most in low/negative expression of PD-L1 for NSCLC patients compared with PD-L1 + CT.
- In terms of Grade 3–5 TRAEs, the results showed that PD-1 + CT and PD-L1 + CT exclusively increased the risk of adverse incidence than CT alone, especially for PD-L1 + CT ($p < 0.00001$).
- For subgroups including female, young patients, patients with nonsmoker, and EGFR/ALK wild-type, PD-1 + CT was associated with prolonged OS ($p < 0.05$).
- For no liver metastasis of NSCLC patients, obviously OS advantage for patients treated with PD-1 + CT compared to PD-L1 + CT was found.

Anmerkung/Fazit der Autoren

This exploratory analysis from our meta-analysis demonstrated ICIs + CT provides a survival advantage over CT alone in a large proportion of metastatic NSCLC patients, and it is worth noting that in terms of tumor response, OS and PFS, the superiority of combined PD-1 + CT over PD-L1 + CT as a first-line treatment strategy for advanced NSCLC patients according to indirect analysis.

Kommentare zum Review

- Siehe auch: Li, L. et al., 2020 [16]

Dafni U et al., 2019 [2].

Immune checkpoint inhibitors, alone or in combination with chemotherapy, as first-line treatment for advanced non-small cell lung cancer. A systematic review and network meta-analysis.

Fragestellung

to summarize and compare in a systematic way, through a Network Meta-Analysis (NMA), all the available to date published information on the efficacy of ICI(s), whether alone, in combination, or with chemotherapy, as first-line treatment for advanced/metastatic NSCLC patients, with wild-type ALK and EGFR.

Methodik

<u>Population:</u>

- untreated/chemotherapy-naive advanced/metastatic NSCLC patients

<u>Intervention/Komparator:</u>

- ICI(s), whether alone, in combination, or with chemotherapy

<u>Endpunkte:</u>

- PFS, OS, Toxicity

<u>Recherche/Suchzeitraum:</u>

- Until April-2019

<u>Qualitätsbewertung der Studien:</u>

- Cochrane’s risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- a total of seven distinct published articles and eight presentations were identified as eligible to be included in our analysis. These 15 articles/presentations correspond to 12 clinical trials, further confirmed as eligible (SP).
- Total 9,236 NSCLC patients

Charakteristika der Population:

- In 11 studies, the control arm was chemotherapy-alone (3 placebocontrolled) with only one study adding bevacizumab in both the experimental and control arm (IM150). ICI-monotherapy was tested in four studies (pembrolizumab: two, nivolumab:one, durvalumab: one), and in combination with chemotherapy in eight (pembrolizumab: two; nivolumab:one; ipilimumab:one; atezolimumab:four, one with/without bevacizumab). Finally, dual ICI-combination was tested in two trials (nivolumab/ipilimumab; durvalumab/tremelimumab)
- Nine studies use an all-comers design, entering NSCLC patients irrelevant of PD-L1 status. Only three studies use an enrichment design, two by including only PD-L1-positive patients (KN042,CM026) and one only PD-L1-high patients (KN024).
- Only squamous patients were included in three trials while only non-squamous in four. Five included NSCLC patients of both histologies, with histology as stratification factor. For nonsquamous histology, ALK/EGFR status was confirmed for all studies except one that simply used the known mutation status (CM026). Patients with confirmed or known ALK/EGFR mutation were excluded from the NMA.

Qualität der Studien:

- Based on Cochrane's tool for randomized trials, all studies were considered of low risk of bias

Studienergebnisse:

- PFS-NMA for overall study cohort:
  - The primary NMA includes nine of the ten studies with available PFS information either in all-comers or PD-L1-positive patients, evaluating six ICI-including treatments. For the one study not included, PFS is currently available only for a treatment combination not connected in the network (IM150)
  - In the overall NMA, the active study treatment is directly compared to the corresponding control arm of chemotherapy-alone. The combination of chemotherapy with pembrolizumab (HRpooled=0.53, 95%CI [0.47-0.61]) or atezolizumab (HRpooled=0.65 [0.59-0.72]) and of nivolumab/ipilimumab (HR=0.83 [0.72-0.96]) show a significant benefit in PFS over chemotherapy-alone. No such significant benefit is found for ipilimumab/chemotherapy or for the ICI-monotherapies examined (pembrolizumab, nivolumab). Of note, negative final results are used for ipilimumab/ chemotherapy and nivolumab, while interim ones for pembrolizumab-monotherapy ((KN042: study ongoing for PFS).
  - Based on the NMA estimates, the combination of chemotherapy with either pembrolizumab or atezolizumab exhibit significantly higher benefit than all other treatments evaluated, with the pembrolizumabcombination better than the atezolizumab-combination (HR=0.82 [0.70-0.97]). The combinations of ipilimumab with either nivolumab or chemotherapy are better than the ICI-monotherapies examined.

- PFS-NMA by histological subtype:
  - PFS results were reported separately for 2,120 squamous patients and 2,285 non-squamous from seven trials. For both subtypes, the combinations of either pembrolizumab or atezolizumab with chemotherapy are significantly better than chemotherapy-alone and not significantly different between them. The combination ipilimumab/chemotherapy, evaluated only in squamous patients, is no better than chemotherapy or nivolumab-monotherapy. Nivolumab shows an effect not significantly different than chemotherapy for the squamous patients, while significantly worse than chemotherapy for the non-squamous patients (pinteraction=0.074).
- PFS-NMA by PD-L1 category:
  - PD-L1≥50% Cohort: The PFS-NMA for PD-L1-high patients is based on eight trials evaluating four experimental treatments (N=1,742). The ICI/chemotherapy combinations of atezolizumab or pembrolizumab, are significantly better than chemotherapy-alone as well as the ICI-monotherapies examined, and no different between them. Pembrolizumab is also significantly better than chemotherapy and nivolumab.
  - PD-L1 < 1% Cohort: The PFS-NMA for PD-L1-negative patients is based on six trials evaluating four experimental treatments, all combinations of ICIs (with chemotherapy:3; dual-ICIs:1) (N=1,784), with no ICI-alone used for PD-L1-negative patients. The combination of nivolumab/chemotherapy is evaluated only for this cohort. Any tested combination of ICI/chemotherapy is significantly better than chemotherapy-alone (HRs: 0.69-0.74), with no treatment combination significantly better than another (HRs: 0.88-1.04). The dual-ICI combination (nivolumab/ipilimumab) is marginally non-significantly better than chemotherapy (p=0.058).
  - Intermediate PD-L1 (1≤PD-L1≤49%) Cohort: For the subgroup of PD-L1-intermediate patients, results are more limited (five studies, 972 patients). The only treatments evaluated are the combination of chemotherapy with either pembrolizumab or atezolizumab versus chemotherapy-alone. Both of the combinations are significantly better than chemotherapy-alone (HRpooled=0.55 [0.44-0.70]; HRpooled=0.68 [0.57-0.81]) while not different between them.
- OS-NMA for full study cohort
  - In the overall NMA model for OS, with data from 10 studies, initially nine experimental treatments are compared to the chemotherapy-alone control arm, including an indirect comparison of the bevacizumab combinations. The combinations of chemotherapy with without bevacizumab) (NMA estimate: HR=0.75 [0.59-0.94]; HRpooled=0.85 [0.75-0.95], respectively) as well as the pembrolizumab-monotherapy (HR=0.81 [0.71-0.93]) show a significant OS benefit over chemotherapy-alone.
  - Based on the NMA estimates, the combination of pembrolizumab/chemotherapy is estimated to be consistently better than all other treatments evaluated (HRs: 0.51-0.72), while other promising treatments are ABC and pembrolizumab-monotherapy, followed by atezolizumab/ chemotherapy, all no different between them. Pembrolizumab-monotherapy and ABC are also better than the durvalumab/tremelimumab combination, with ABC also better than bevacizumab/chemotherapy. Excluding the non-significant interim analysis results on atezolizumab/chemotherapy combination, similar evidence for the OS benefit is provided (results not shown).
- OS-NMA by histological subtype

- OS results by histology were similar to the overall cohort regarding the combination of pembrolizumab/chemotherapy being the better treatment choice for both histological types, with also ABC and atezolizumab/chemotherapy in non-squamous. ABC is evaluated only in non-squamous, ipilimumab/chemotherapy only in squamous, while pembrolizumab-monotherapy (among others) could not be evaluated here.

- OS-NMA by PD-L1 category
  - PD-L1 < 1% Cohort: The NMA OS analysis for PD-L1-negative patients is based on five trials evaluating four experimental treatments (N=1325). Available immature OS information, from the non-significant interim analysis of IM131 is used for atezolizumab/chemotherapy along with the final OS data from IM130. Both combinations of pembrolizumab and atezolizumab with chemotherapy display a significant benefit over chemotherapy-alone (HRpooled=0.60 [0.45-0.80] and HRpooled=0.83 [0.69-1.00], respectively). Based on NMA estimates, durvalumab-monotherapy is worse than all combination treatments (pembrolizumab/chemotherapy, atezolizumab/chemotherapy, durvalumab/ not significantly different than the combination treatments of either atezolizumab/chemotherapy or durvalumab/tremelimumab.
  - Intermediate PD-L1 (1≤PD-L1≤49%) Cohort: Results for PD-L1-intermediate patients, are available only for five studies and three experimental treatments on 1,511 patients. The combination of pembrolizumab/chemotherapy is estimated to be significantly better than chemotherapy and the other two treatments. It should be noted, that once more for the atezolizumab/chemotherapy combination, OS data is based on two trials with one providing only non-significant interim results (IM131).

- Toxicity results
  - In the ICI/chemotherapy combinations, no significant difference in incidence of any grade≥3 AE is detected between pembrolizumab/chemotherapy and chemotherapy-alone while a significant increase is observed with atezolizumab/chemotherapy (both any-cause and treatment-related AEs) and ipilimumab/chemotherapy (treatment-related AEs). For the ABC combination no significant increase is detected versus bevacizumab/chemotherapy.
  - In the two ICI-combinations, a non-significant decrease in treatment-related severe AEs is detected for nivolumab/ipilimumab, while for durvalumab/tremelimumab this decrease is significant compared to chemotherapy-alone. Similarly, all ICImonotherapies of either pembrolizumab, nivolumab, or durvalumab exhibit significantly lower incidence of treatment-related severe AEs compared to chemotherapy.

Anmerkung/Fazit der Autoren

A very strong message comes from this systematic review and NMA of ICI treatments as first-line, demonstrating the evidence-based definition of new standards of care for advanced NSCLC. First, chemotherapy is clearly inferior of any ICI and chemotherapy combination. Second, in ICI treatment combinations a backbone of chemotherapy is preferred than another ICI. The addition of chemotherapy to ICIs has enhanced the treatment efficacy as first-line treatment for advanced NSCLC patients. The NMA, subject to the limitations described, consistently suggests as preferred treatments, the combination of pembrolizumab/ chemotherapy and of atezolizumab/chemotherapy without or with bevacizumab (ABC: only OS available in non-squamous patients in the overall cohort). Pembrolizumab-monotherapy benefit in high-PDL1 is also confirmed,

inferior to pembrolizumab/chemotherapy for PFS but not different for OS in this specific subgroup of patients.

Kommentare zum Review

Siehe auch:

- Wagner, G. et al. 2020 [26]
- Wang, D. et al., 2021 [27]
- Wang, Y. et al., 2022 [29]

Zhou Y et al., 2019 [32].

First-line treatment for patients with advanced non-small cell lung carcinoma and high PD-L1 expression: pembrolizumab or pembrolizumab plus chemotherapy.

Fragestellung

We evaluated the efficacy of pembrolizumab (pem) plus chemotherapy (chemo) versus pembrolizumab alone for the first-line treatment of patients with advanced NSCLC and a PD-L1 TPS of ≥50% using indirect comparison meta-analysis.

Methodik

Population:

- advanced NSCLC

Intervention/Komparator:

- pembrolizumab plus chemotherapy or pembrolizumab alone with chemotherapy for first-line treatment

Endpunkte:

- OS, PFS, ORR

Recherche/Suchzeitraum:

- before November 1, 2018

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool

Ergebnisse

Anzahl eingeschlossener Studien:

- five trials involving 1289 patients

Charakteristika der Population:

Table 1 Characteristics of Patients Comparing Pembrolizumab plus Chemotherapy or Pembrolizumab alone with Chemotherapy in Included Trials

Source	Histology	Therapeutic regimen	Chemotherapy Drug	No. of patients		NO. of response		PFS[a](m)	HR for PFS	OS[a](m)	HR for OS	Median Follow-up time (m)
				Pem/Pem + Chemo	Chemo	Pem/Pem + Chemo	Chemo					
KEYNOTE-021 2016, 2018	nonsquamous	Pem + Chemo vs. Chemo	AC 1) carboplatin (5 mg/ml/min Q3W) 2) pemetrexed (500 mg/m^2 Q3W)	20	17	16	6	NR	NR	NR	NR	23.9
KEYNOTE-189 2018	nonsquamous	Pem + Chemo vs. Chemo	AP or AC 1) cisplatin (75 mg/m^2 Q3W) or carboplatin (6 mg/ml/min Q3W) 2) pemetrexed (500 mg/m^2 Q3W)	132	70	81	16	NR	0.36 (0.25–0.52)	NR	0.42 (0.26–0.68)	10.5
KEYNOTE-407 2018	squamous	Pem + Chemo vs. Chemo	PC 1) carboplatin (6 mg/ml/min Q3W) 2) paclitaxel(200 mg/m^2 Q3W) or nab-paclitaxel (100 mg/m^2 Q1W)	73	73	44	24	8.0 vs. 4.2	0.37 (0.24–0.58)	NR	0.64 (0.37–1.10)	7.8
KEYNOTE-024 2016, 2017	squamous and nonsquamous	Pem vs. Chemo	AP or AC or PC or GP or GC 1) cisplatin (75 mg/m^2 Q3W) or carboplatin (5-6 mg/ml/min Q3W) 2) pemetrexed (500 mg/m^2 Q3W) or paclitaxel (200 mg/m^2 Q3W) or Gemicitabine (1250 mg/m2 d1,8 of Q3W)	154	151	70	45	10.3 vs. 6.0	0.50 (0.37–0.68)	30.0 vs. 14.2	0.63 (0.47–0.86)	25.2
KEYNOTE-042 2018	squamous and nonsquamous	Pem vs. Chemo	AC or PC 1) carboplatin (5-6 mg/ml/min Q3W) 2) pemetrexed (500 mg/m^2 Q3W) or paclitaxel (200 mg/m^2 Q3W)	299	300	118	96	7.1 vs. 6.4	0.81 (0.67–0.99)	20.0 vs. 12.2	0.69 (0.56–0.85)	12.8

[a]Data presented as "Pem/Pem + Chemo vs. Chemo"
Abbreviation: *Pem* Pembrolizumab, *Chemo* Chemotherapy, *NR* Not Reported, *HR* Hazard Ratio, *PFS* Progression-free Survival, *OS* Overall survival;

Qualität der Studien:

Supplemental Table 1. Quality assessment: risk of bias by Cochrane Collaboration's tool

Trial	Sequence generation	Allocation Concealment	Bliding	Incomplete outcome data	Selective reporting	Other source of bias
KEYNOTE-021 2016, 2018	Adequate	Adequate (Central allocation)	Adequate (Independent Radiologic review)	Adequate	Inadequate (PFS、OS was not reported)	
KEYNOTE-189 2018	Adequate	Adequate (Central allocation)	Adequate (Independent Radiologic review)	Adequate	Adequate	
KEYNOTE-407 2018	Adequate	Adequate (Central allocation)	Adequate (Independent Radiologic review)	Adequate	Adequate	
KEYNOTE-024 2016, 2017	Adequate	Adequate (Central allocation)	Adequate (Independent Radiologic review)	Adequate	Adequate	
KEYNOTE-042 2018	Adequate	Adequate (Central allocation)	Adequate (Independent Radiologic review)	Adequate	Adequate	Data from the abstract and the presentation slides

Studienergebnisse:

- Direct metaanalysis:
  - Significant difference of ORR was observed in favor of pembrolizumab plus chemotherapy versus chemotherapy (RRpem + chemo/chemo 2.16, 95% CI 1.66–2.82; P < 0.001; heterogeneity, P = 0.441). And for pembrolizumab vs chemotherapy, the pooled RRpem/chemo was 1.33 (95% CI 1.11–1.58; P = 0.002).
  - For PFS, pembrolizumab plus chemotherapy significantly reduced the risk of disease progression compared with chemotherapy (HRpem + chemo/chemo, 0.36; 95% CI 0.27–0.48; z = 7.03, P < 0.001).
  - While pembrolizumab monotherapy failed to demonstrate significant improvement in PFS (HRpem/chemo, 0.65; 95% CI 0.40–1.04; z = 1.82, P = 0.069)
  - In terms of OS, both pembrolizumab plus chemotherapy (HRpem+ chemo/chemo, 0.51; 95% CI 0.35–0.72; z = 3.71, P < 0.001) and pembrolizumab monotherapy (HRpem/chemo, 0.67; 95% CI 0.56–0.80; z = 4.57, P < 0.001) significantly decreased the risk of death compared with chemotherapy.

- Indirect meta-analysis
- The results indicated that patients treated with pembrolizumab plus chemotherapy had better clinical outcomes including ORR (RRpem + chemo/pem 1.62, 95% CI 1.18–2.23; P = 0.003) and PFS (HRpem + chemo/pem 0.55, 95% CI 0.32–0.97; P = 0.037) than those treated with pembrolizumab alone. However, there was only a trend towards improved OS with the three-drug combination therapy.

Anmerkung/Fazit der Autoren

In conclusion, the addition of chemotherapy to pembrolizumab as first-line treatment further improves the outcomes of patients with advanced NSCLC and a PD-L1 TPS of at least 50%. With proved survival benefit, manageable toxicities and avoidance of PD-L1-based patient selection, clinicians could prefer pembrolizumab plus chemotherapy in patients without contraindications, especially for those with high tumor burden.

Kommentare zum Review

- Siehe auch: Kim R et al. 2019 [13]

Liu J et al., 2020 [18].

Identifying optimal first-line interventions for advanced non-small cell lung carcinoma according to PD-L1 expression: a systematic review and network meta-analysis.

Fragestellung

to compare these approved first-line treatments for advanced NSCLC

- Yang
- or squamous NSCLC was categorized for subgroup analysis

Methodik

Population:

- advanced non-small cell lung carcinoma patients

Intervention/Komparator:

- Pembrolizumab alone, or PC (pembrolizumab plus chemotherapy) or AC (atezolizumab plus chemotherapy), or ABC (atezolizumab plus bevacizumab plus chemotherapy), or BC (bevacizumab plus chemotherapy), with chemotherapy alone, as first-line treatments for advanced NSCLC

Endpunkte:

- objective response rate (ORR), progression-free survival (PFS) or overall survival (OS)

Recherche/Suchzeitraum:

- Pubmed, Embase, the Cochrane Library and Medline, as well as abstracts from major conference proceedings of the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (EMSO), the American Association for Cancer Research (AACR), and the World Conference on Lung Cancer (WCLC) were searched from inception until September 10, 2019

Qualitätsbewertung der Studien:

- Cochrane Collaboration's risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Ten trials, involving 6,124 patients

Charakteristika der Population:

Table 1. Study characteristics.

Source	Histology	PD-L1 Expression	Treatment Regimen	Median ages (years)	mPFS (months)	mOS (months)	Median Follow-up Time (months)
KEYNOTE-021[9,19]	Non-squamous	All	PC	62.50	13.00	NR	23.90
			Chemo	63.20	8.90	NR	23.90
KEYNOTE-024[11,20]	Squamous and Non-squamous	≥50%	Pembro	64.50	10.30	30.00	25.20
			Chemo	66.00	6.00	14.20	25.20
KEYNOTE-042[12]	Squamous and Non-squamous	≥1%	Pembro	63.00	7.10	20.00	12.80
			Chemo	63.00	6.40	12.20	12.80
KEYNOTE-042 in China[23]	Squamous and Non-squamous	≥1%	Pembro	NR	NR	20.00	11.30
			Chemo	NR	NR	13.70	11.30
KEYNOTE-189[10]	Non-squamous	All	PC	65.00	8.80	NR	10.50
			Placebo+Chemo	63.50	4.90	11.30	10.50
KEYNOTE-407[13]	Squamous	All	PC	65.00	6.40	15.90	7.80
			Placebo+Chemo	65.00	4.80	11.30	7.80
IMpower-130[14]	Non-squamous	All	AC	64.00	7.00	18.60	18.50
			Chemo	65.00	5.50	13.90	18.80
IMpower-131[17,21]	Squamous	All	AC	65.00	6.30	14.20	25.50
			Chemo	65.00	5.60	13.50	25.50
IMpower-132[18]	Non-squamous	All	AC	64.00	7.60	18.10	14.80
			Chemo	63.00	5.20	13.60	14.80
IMpower-150[16,22]	Non-squamous	All	ABC	63.00	8.40	19.80	13.50
			AC	63.00	6.90	19.50	19.60
			BC	63.00	6.80	14.90	19.70

Abbreviation: Pembro: pembrolizumab; Chemo: chemotherapy; Placebo+Chemo: placebo plus chemotherapy; PC: pembrolizumab plus chemotherapy; AC: atezolizumab plus chemotherapy; ABC: atezolizumab plus bevacizumab plus chemotherapy; BC: bevacizumab plus chemotherapy. NR: not reported; PFS: progression-free survival; OS: overall survival.

Qualität der Studien:

Table S1: Quality assessment: risk of bias according to Cochrane Collaboration's tool

Trial	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting	Other Source of bias
KEYNOTE-021 [6,16]	Adequate	Adequate (Central Allocation)	Adequate (Independent Radiologic Review)	Adequate	Adequate (PFS、OS was not reported)	
KEYNOTE-024 [8,17]	Inadequate	Inadequate (Central Allocation)	Adequate (Independent Radiologic Review)	Adequate	Adequate	
KEYNOTE-042 [9]	Adequate	Adequate (Central Allocation)	Adequate (Independent Radiologic Review)	Adequate	Adequate	
KEYNOTE-042 in China [20]	Indequate	Inadequate (Central Allocation)	Inadequate (Independent Radiologic Review)	Inadequate	Inadequate (ORR、PFS was not reported)	Data from the abstract and the presentation slides
KEYNOTE-189 [7]	Adequate	Adequate (Central Allocation)	Adequate (Independent Radiologic Review)	Adequate	Adequate	
KEYNOTE-407 [10]	Adequate	Adequate (Central Allocation)	Adequate (Independent Radiologic Review)	Adequate	Adequate	
IMpower-130 [11]	Adequate	Adequate (Central Allocation)	Adequate (Independent Radiologic Review)	Adequate	Adequate	
IMpower-131 [14,18]	Inadequate	Inadequate (Central Allocation)	Inadequate (Independent Radiologic Review)	Inadequate	Inadequate	Data from the abstract and the presentation slides
IMpower-132 [15]	Inadequate	Inadequate (Central Allocation)	Inadequate (Independent Radiologic Review)	Inadequate	Inadequate	Data from the abstract and the presentation slides
IMpower-150 [13,19]	Adequate	Adequate (Central Allocation)	Adequate (Independent Radiologic Review)	Adequate	Adequate	

Studienergebnisse:

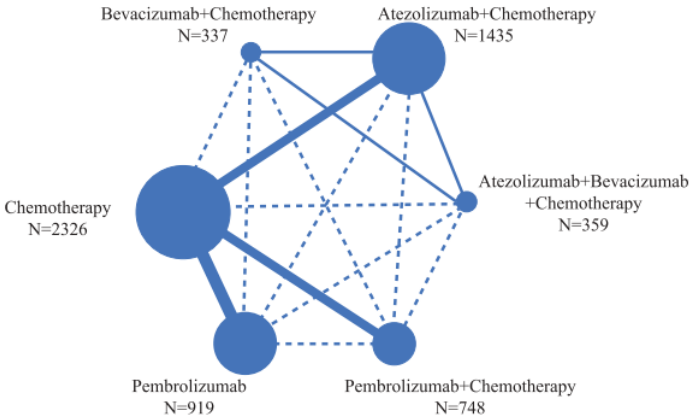


Figure 2. Network structure for all the included trials. Each circular node represents a treatment type. The circle size is proportional to the total number of patients. The width of lines is proportional to the number of studies performing head-to-head comparisons in the same study, and the dotted line is the indirect comparison which was shown in this NWM.

- NMA for non-squamous NSCLC

  PD-L1 ≥ 50% cohort For PD-L1-high patients, the PFS-NMA and the OS-NMA were based on six separate trials. ORR-NMA was not possible, between ABC and PC or Pembrolizumab alone, because connections could not be established due to the lack of AC data.

  - For PFS, ABC appears superior to PC; however,; these intervention strategies were both significantly more effective than Pembrolizumab alone (HR 0.37, 95% CI 0.19–0.75 for ABC; HR 0.51, 95% CI 0.31–0.76 for PC), BC (HR 0.33, 95% CI 0.22–0.51 for ABC; HR 0.45, 95% CI 0.24–0.86 for PC) and chemotherapy alone (HR 0.27, 95% CI 0.13–0.52 for ABC; HR 0.36, 95% CI 0.25–0.52 for PC). AC was significantly superior to BC (HR 0.63, 95% CI 0.43–0.92) and chemotherapy alone (HR 0.50, 95% CI 0.35–0.71). Pembrolizumab alone was marginally superior to BC (HR 0.89, 95% CI 0.51–1.50), but was substantially more effective than chemotherapy alone (HR 0.71, 95% CI 0.60–0.83).
  - For OS, PC performed significantly better than BC (HR 0.38, 95% CI 0.16–0.87) and chemotherapy alone (HR 0.42, 95% CI 0.26–0.68). Pembrolizumab alone performed significantly better than chemotherapy alone (HR 0.67, 95% CI 0.57–0.78). Although there were no statistically significant difference between treatment groups, except for those previously mentioned.

  Intermediate PD-L1 (1%≤PD-L1 < 50%) cohort

  - For PD-L1-intermediate patients, the PFS-NMA was based on four trials and OS-NMA on five trials.
  - ORR-NMA was not analyzed for PD-L1-high patients analysis due to the missing AC connection. It was also not possible to analyze Pembrolizumab alone in this cohort due to the lack of PFS data.
  - For PFS, ABC appears superior to PC, AC, and was significantly more effective than BC (HR 0.55, 95% CI 0.42–0.73) and chemotherapy alone (HR 0.48, 95% CI 0.31–0.76). AC (HR 0.69, 95% CI 0.54–0.89) and PC (HR 0.55, 95% CI 0.37–0.81) were significantly more effective than chemotherapy, although there was only a marginal improvement compared to BC (HR 0.79, 95% CI 0.61–1.00 for AC; HR 0.63, 95% CI 0.37–1.10 for PC). There were no significant differences among ABC, AC, and PC in terms of progression-free survival.

- For OS, PC appears superior to chemotherapy alone (HR 0.55, 95% CI 0.34–0.89). Although there was no significant difference when comparing ABC, AC, PC, pembrolizumab alone, BC, and chemotherapy.

PD-L1 < 1% cohort

- For PD-L1-low patients, the PFS-NMA was based on four trials and OS-NMA on three. ORR-NMA was not analyzed due to the missing AC connection, for the same reason as for the PD-L1-high expression analysis. Pembrolizumab alone was also not analyzed due to the lack of data.
- For PFS, ABC appears to provide a significant improvement compared with AC (HR 0.68, 95% CI 0.50–0.93), PC (HR 0.56, 95% CI 0.34–0.93), BC (HR 0.75, 95% CI 0.60–0.94) and chemotherapy alone (HR 0.42, 95% CI 0.29–0.61). AC (HR 0.62, 95% CI 0.50–0.75) performed significantly better than chemotherapy and appears superior to PC. Although PC appears inferior to BC while being superior to chemotherapy alone. BC was significantly more effective than chemotherapy alone (HR 0.56, 95% CI 0.42–0.75).
- PC appears superior to chemotherapy in terms of OS (HR 0.59, 95% CI 0.38–0.92). However, there was no significant difference among other interventions in terms of overall survival.

- NMA for squamous non-small cell lung cancer
  - For PD-L1-high patients with squamous NSCLC, the ORR NMA, PFS-NMA, and OS-NMA were both based on separate five trials.
  - For ORR: PC (OR 1.80, 95% CI 1.30–2.70) and Pembrolizumab alone (OR 1.30, 95% CI 1.10–1.60) performed significantly better than chemotherapy alone. PC and AC also appear superior to Pembrolizumab alone.
  - For PFS: PC was significantly more effective than Pembrolizumab alone (HR 0.53, 95% CI 0.33–0.84) and chemotherapy alone (HR 0.37, 95% CI 0.24–0.58). Pembrolizumab appears to provide a significant benefit compared to chemotherapy alone (HR 0.71, 95% CI 0.60–0.84). AC on the other hand appears inferior to PC, yet superior to Pembrolizumab alone.
  - For OS: PC appears superior to Pembrolizumab alone. Both AC (HR 0.56, 95% CI 0.32–0.99) and Pembrolizumab alone (HR 0.67, 95% CI 0.57–0.80) performed significantly more effectively than chemotherapy alone.
  - For patients with intermediate PD-L1 expression, AC (HR0.70, 95% CI 0.53–0.92) and PC (HR 0.56, 95% CI 0.39–0.80) were significantly more effective than chemotherapy in terms of PFS and PC appears significantly superior to both chemotherapy alone (HR 0.57, 95% CI 0.36–0.90) and AC in terms of overall survival. For PD-L1-negative patients, PC appears significantly superior to chemotherapy alone in terms of ORR (OR 1.50, 95% CI 1.20–2.10), PFS (HR 0.68, 95% CI 0.47–0.98) and OS (HR 0.61, 95% CI 0.38–0.98). There was no identifiable difference among the other regimens included.
- NMA for safety analysis
  - Patients with low grade and grade 3–5 AEs perhaps benefit more from PC and Pembrolizumab alone compared to BC (OR 0.95, 95% CI 0.91–0.99 for PC, OR 0.69, 95% CI 0.64–0.74 for Pembrolizumab alone for grade 1–5 AEs; OR 0.73, 95% CI 0.61–0.88 for PC, OR 0.33, 95% CI 0.26–0.42 for Pembrolizumab alone for grade 3–5 AEs). ABC and AC appear significantly less safe than PC with an OR 1.60 (95% CI 1.30–1.90 for grade 3–5 AEs for ABC) and an OR 1.20 (95% CI 1.10–1.30 for grade 3–5 AEs for AC). Pembrolizumab alone appears to be the safest intervention among the regimens analyzed.

Anmerkung/Fazit der Autoren

Evidence from this study suggests combined immunotherapies are superior to Pembrolizumab alone for PD-L1 ≥ 1% but especially for PD-L1 ≥ 50%. For advanced non-squamous NSCLC, BC can also be recommended as an initial first-line treatment for PDL1 ≥ 1%. Combined immunotherapies can still be recommended for PD-L1-negative patients with advanced NSCLC, but ABC can be recommended specifically for those with non-squamous NSCLC. This study suggests PD-L1 expression may shed light on individual response differences although there are other potential predictive biomarkers which could be factored into identify and target specific populations who respond best to specific combinations. This new collaborative, biomarker-driven phase in research, necessitates bridging traditional boundaries between basic medical and clinical research, where interdisciplinary research teams record and report more sophisticated data. This additional knowledge will help to align specific combinations to specific patient groups, although of course, further research is required.

Kommentare zum Review

Siehe auch:

- Cao, R. et al., 2019 [1]
- Herbst, R. et al., 2021 [11]

3.3 Leitlinien

Leitlinienprogramm Onkologie, 2022 [15].

Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms (AWMF-Registernr. 020-007)

Siehe auch: Leitlinienprogramm Onkologie, 2022 [14].

Fragestellung

Die Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V., die Deutsche Krebsgesellschaft e. V. und die Stiftung Deutsche Krebshilfe haben sich mit dem Leitlinienprogramm Onkologie (OL) das Ziel gesetzt, gemeinsam die Entwicklung und Fortschreibung und den Einsatz wissenschaftlich begründeter und praktikabler Leitlinien in der Onkologie zu fördern und zu unterstützen.

Methodik

Grundlage der Leitlinie

Update: gezielte Aktualisierung der Version von 2018

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert. Diese Version der S3-Leitlinie ist bis zur nächsten Aktualisierung gültig maximal jedoch 5 Jahre (2027).

Recherche/Suchzeitraum:

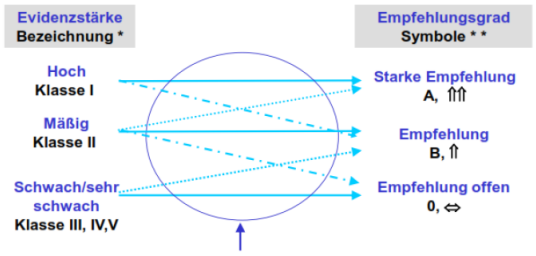
- Aktualisierung für den Zeitraum 2016-2022

LoE

- entsprechend der Vorgaben des Oxford Centre for Evidence-Based Medicine

GoR

- Stärke der aktualisierten Empfehlung (gekennzeichnet mit „2018“) unterschieden in A/B/0, die sich auch in der Formulierung der Empfehlungen widerspiegeln



Kriterien für die Graduierung (Konsensusaspekte):

- Konsistenz der Studienergebnisse
- Klinische Relevanz der Endpunkte und Effektstärken
- Nutzen-Risiko-Verhältnis
- Ethische, rechtliche, ökonomische Erwägungen
- Patientenpräferenzen
- Anwendbarkeit, Umsetzbarkeit

Abbildung 1: : Schema zur Darstellung der Kriteriengestützen Entscheidungsprozesse bei der Wahl des Empfehlungsgrades.

*: blau = Evidenzstärke nach GRADE bzgl. des gesamten ‚body of evidence', schwarz = Evidenzklassifikation bzgl. Einzelstudien, z.B. nach Oxford;

**: Empfehlungsgraduierung im Programm für Nationale Versorgungsleitlinien. Die Empfehlungen werden nach Möglichkeit analog formuliert: Starke Empfehlung: „soll"; (abgeschwächte) Empfehlung: „sollte"; Negativ-Empfehlungen werden entweder rein sprachlich ausgedrückt („nicht" / „kann verzichtet werden") bei gleichen Symbolen oder sprachlich mit zusätzlich nach unten gerichteten Pfeilen; Offene Empfehlungen drücken eine Handlungsoption in Unsicherheit aus („kann erwogen werden" / „kann verzichtet werden").

Quelle: modifiziert AWMF-Regelwerk [1]

Empfehlungen

Systemtherapie bei Patienten mit BRAF-V600-Mutation

8.126	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **B**	NSCLC IV- Patienten mit nachgewiesener BRAF-V600-Mutation sollte eine Kombination aus Dabrafenib und Trametinib angeboten werden. Nicht-V600 Mutations+ NSCLC Patienten sollten in einem Thorax-Onkologischen Tumorboard besprochen werden.	
Level of Evidence **2b**	[1171], [1172], [1173]	
	Starker Konsens	

Literatur:

Planchard D, Smit E, Groen H, Mazieres J, Besse B, Helland Å, et al. Dabrafenib plus trametinib in patients with previously untreated BRAF. Lancet Oncol. 2017;18(10):1307-1316.

Gautschi O, Milia J, Cabarrou B, Bluthgen M, Besse B, Smit E, et al. Targeted Therapy for Patients with BRAF-Mutant Lung Cancer: Results from the European EURAF Cohort. J Thorac Oncol. 2015;10(10):1451-7.

Hyman D, Puzanov I, Subbiah V, Faris J, Chau I, Blay J, et al. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. N Engl J Med. 2015;373(8):726-36

8.55	Konsensbasierte Empfehlung	modifiziert 2022
EK	Patienten im Stadium IIIA4 / IIIB und IIIC sollen in der Regel– wenn Allgemeinzustand und Tumorausdehnung dies zulassen – eine Kombination aus Strahlentherapie und Chemotherapie erhalten.Die Chemotherapie soll bei definitiver Radiochemotherapie simultan und nur bei medizinischer Kontraindikation allein sequentiell durchgeführt werden.	
	Starker Konsens	

8.64	Evidenzbasierte Empfehlung	neu 2022
Empfehlungsgrad **0**	Patienten im Stadium III, die nach Entscheidung im Thorax-Onkologischen Tumorboard, nicht für eine Operation oder Radio-Chemotherapie geeignet sind und eine PD-L1 Expression ≥ 50 % aufweisen, kann eine Therapie mit dem PD-1-Antikörper Cemiplimab angeboten werden	
Level of Evidence **2**	[938]	
	Konsens	

8.6.2.1 Patienten mit Plattenepithelkarzinom mit PD-L1-Expression von ≥ 50 % und ECOG 0-1

8.71	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **A**	Bei Patienten im Stadium IV mit Plattenepithelkarzinom, welche keine therapierbaren Mutationen (z. B. EGFR, EML4-ALK, ROS1) aufweisen, und welche in Gewebeproben eine PD-L1-Expression von ≥ 50 % der Tumorzellen oder >10% auf Immunzellen aufweisen, soll: • eine Monotherapie mit Atezolizumab (≥ 50% der Tumorzellen oder 10% der tumorinfiltrierenden Lymphozyten), Cemiplimab (≥ 50% der Tumorzellen) oder Pembrolizumab (≥ 50% der Tumorzellen) oder • Pembrolizumab mit Chemotherapie oder Nivolumab und Ipilimumab mit Chemotherapie als Erstlinientherapie angeboten werden.	
Level of Evidence **1b**	[944], [945], [946], [947], [948]	
	Starker Konsens	

8.6.2.2 Patienten mit Plattenepithelkarzinom mit einer PD-L1-Expression von < 50 % und ECOG 0-1

8.72	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **A**	Bei Patienten im Stadium IV mit Plattenepithelkarzinom und PD-L1 Expression < 50% sowie einem guten Allgemeinzustand (ECOG 0-1) soll eine Chemo-Immuntherapie angeboten werden, z.B. eine platinbasierte Kombinationschemotherapie mit Taxan kombiniert mit Pembrolizumab oder eine Therapie mit platinbasierter Chemotherapie und Nivolumab/Ipilimumab.	
Level of Evidence **1b**	[944], [801], [950]	
	Starker Konsens	

8.73	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **A**	Bei Patienten im Stadium IV mit Plattenepithelkarzinom in gutem Allgemeinzustand (ECOG 0-1) und Kontraindikationen gegen eine Immuntherapie soll eine platinbasierte Kombinationschemotherapie angeboten werden.	
Level of Evidence **1**	[951], [791], [952], [953], [954], [955], [956], [957], [958], [959]	
	Starker Konsens	

8.6.2.3 Patienten mit Plattenepithelkarzinom mit einer PD-L1-Expression von ≥ 50 % und ECOG 2

8.74	Konsensbasierte Empfehlung	neu 2022
EK	Bei Patienten im Stadium IV mit Plattenepithelkarzinom und ECOG 2, welche in Gewebeproben eine PD-L1-Expression von ≥ 50 % der Tumorzellen oder >10% auf Immunzellen aufweisen, sollte eine Monotherapie mit • Atezolizumab (≥ 50% der Tumorzellen oder 10% der tumorinfiltrierenden Lymphozyten), Cemiplimab (≥ 50% der Tumorzellen) oder Pembrolizumab (≥ 50% der Tumorzellen)	
	Starker Konsens	

8.75	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **A**	Bei Patienten mit ECOG 2 ohne wesentliche Komorbiditäten sollen platinbasierte Kombinationen, z. B. Carboplatin/Paclitaxel angeboten werden.	
Level of Evidence **1a**	[962]	
	Starker Konsens	

8.76	Konsensbasierte Empfehlung	geprüft 2022
EK	Bei Patienten mit ECOG 2 mit Komorbiditäten, bei denen die Komorbiditäten eine platinhaltige Kombinationstherapie nicht erlauben, kann eine Monotherapie angeboten werden.	
	Starker Konsens	

8.77	Konsensbasierte Empfehlung	modifiziert 2022
EK	Patienten mit Stadium IV NSCLC ECOG 2 können Immuntherapie bzw. Chemotherapie zusätzlich zu „Best Supportive Care“ angeboten werden.	
	Starker Konsens	

8.6.3 Systemtherapie (Erstlinie) bei Patienten mit Nicht-Plattenepithelkarzinom ohne therapierbare genetische Alterationen

8.78	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **A**	Bei NSCLC-Patienten mit nicht-plattenepithelialer Histologie im UICC Stadium IV sowie ECOG 0-1, welche keine therapierbaren Mutationen und keine Kontraindikation gegenüber Checkpoint-Inhibitoren aufweisen, soll, unabhängig vom PD-L1 Status, in der Erstlinientherapie eine Immuntherapie angeboten werden. In der Regel erfolgt diese als Chemo-Immuntherapie: • Cisplatin/Carboplatin + Pemetrexed + Pembrolizumab, alle 3 Wochen über 4 Zyklen, gefolgt von einer Erhaltungstherapie mit Pemetrexed und Pembrolizumab • Carboplatin + Paclitaxel + Bevacizumab + Atezolizumab, alle 3 Wochen über 4-6 Zyklen, gefolgt von einer Erhaltungstherapie mit Bevacizumab und Atezolizumab • Carboplatin + nab-Paclitaxel + Atezolizumab alle 3 Wochen über 4 Zyklen, gefolgt von einer Erhaltungstherapie mit Atezolizumab • platinbasierte Chemotherapie + Nivolumab + Ipilimumab über 2 Zyklen, gefolgt von einer Erhaltungstherapie mit Nivolumab +I pilimumab über 2 Jahre.	
Level of Evidence **1a**	[653], [984], [944], [802], [985], [946], [986], [987], [988], [989], [990], [947], [948]	
	Starker Konsens	

8.79	Evidenzbasierte Empfehlung	neu 2022
Empfehlungsgrad **A**	Bei Patienten im Stadium IV mit Nicht-Plattenepithelkarzinom, welche keine therapierbaren Mutationen (z. B. EGFR, EML4-ALK, ROS1) aufweisen, und welche in Gewebeproben eine PD-L1-Expression von ≥ 50 % der Tumorzellen oder >10% auf Immunzellen aufweisen, soll eine Monotherapie mit • Atezolizumab (≥ 50% der Tumorzellen oder 10% der tumorinfiltrierenden Lymphozyten), • Cemiplimab (≥ 50% der Tumorzellen) oder • Pembrolizumab (≥ 50% der Tumorzellen) als Erstlinientherapie angeboten werden, sofern nicht patienten- oder tumorbezogene Gründe für eine Kombinationsbehandlung sprechen.	
Level of Evidence **1**	[944], [945], [946]	
	Konsens	

8.80	Konsensbasierte Empfehlung	modifiziert 2022
EK	In aller Regel sollte nach 2 Zyklen (6 Wochen), spätestens aber nach 3 Zyklen (9 Wochen) eine radiologische Verlaufskontrolle erfolgen.	
	Starker Konsens	

8.81	Evidenzbasierte Empfehlung	neu 2022
Empfehlungsgrad A	Bei radiologischem Ansprechen oder Stabilisierung und entsprechender Verträglichkeit soll nach studienanaloger Zyklenzahl der platinhaltigen Chemo-/Immuntherapie eine Erhaltungstherapie erfolgen.	
Level of Evidence 1a	[653], [984], [944], [802], [985], [800], [946], [986], [988], [990], [991], [947], [948]	
	Starker Konsens	

8.82	Konsensbasierte Empfehlung	neu 2022
EK	Die Gesamtdauer der Chemo-ICI-Therapie bzw. der ICI-Monotherapie ist derzeit noch nicht hinreichend geklärt. Die Checkpointinhibitoren Pembrolizumab und Cemiplimab wurden in den zulassungsrelevanten Studien über zwei Jahre verabreicht. Eine Fortsetzung der Therapie über dieses Intervall hinaus kann bei weiter bestehender Tumorkontrolle und Verträglichkeit dem Patienten angeboten werden. Für Atezolizumab wurde in der Zulassungsstudie keine Begrenzung der Therapiedauer festgelegt.	
	Starker Konsens	

8.83	Konsensbasierte Empfehlung	neu 2022
EK	Patienten mit besonderen Risikofaktoren für eine ICI basierte Therapie Patienten mit Autoimmunerkrankungen und gutem Allgemeinzustand (ECOG 0-1) kann eine ICI (Kombinations-) Therapie angeboten werden, wenn die Autoimmunerkrankung nicht lebensbedrohlich und nicht aktiv ist. Ein engmaschiges Monitoring ist in solchen Fällen besonders notwendig. Patienten mit kontrollierter Hepatitis B oder C oder einer kontrollierten HIV-Erkrankung und gutem Allgemeinzustand (ECOG 0-1) kann eine ICI (Kombinations-) Therapie angeboten werden. Ein engmaschiges Monitoring ist in solchen Fällen besonders notwendig.	
	Konsens	

8.84	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **A**	Patienten mit einem NSCLC im UICC Stadium IV und mit nichtplattenepithelialer Histologie, die für eine Therapie mit Checkpoint-Inhibitoren nicht geeignet sind und einen guten Allgemeinzustand aufweisen (ECOG 0-1) sollen 4-6 Zyklen einer platinbasierten Kombinationschemotherapie erhalten. Folgende Schemata werden empfohlen: • Cisplatin/Carboplatin+Pemetrexed über 4 Zyklen, gefolgt von einer Erhaltungstherapie mit Pemetrexed, • Carboplatin+Paclitaxel+Bevacizumab über 4-6 Zyklen, gefolgt von einer Erhaltungstherapie mit Bevacizumab bei geeigneten Patienten, • Carboplatin + nab-Paclitaxel, • Cisplatin/Carboplatin + Paclitaxel, • Cisplatin/Carboplatin + Vinorelbine, • Cisplatin/Carboplatin + Docetaxel, • Cisplatin/Carboplatin + Gemcitabin.	
Level of Evidence **1b**	[599], [672], [673], [674], [675], [676], [992], [993], [994], [995], [996], [681], [684], [686], [997], [998], [942], [999], [1000], [1001], [1002], [964], [965], [966], [967], [968], [969], [970]	
	Starker Konsens	

8.85	Konsensbasierte Empfehlung	neu 2022
EK	Bei Patienten im Stadium IV mit Nicht-Plattenepithelkarzinom und ECOG 2, welche in Gewebeproben eine PD-L1-Expression von ≥ 50 % der Tumorzellen oder >10% auf Immunzellen aufweisen, sollte eine Monotherapie mit • Atezolizumab (≥ 50% der Tumorzellen oder 10% der tumorinfiltrierenden Lymphozyten), • Cemiplimab (≥ 50% der Tumorzellen) oder • Pembrolizumab (≥ 50% der Tumorzellen) als Erstlinientherapie angeboten werden.	
	Starker Konsens	

Daly ME et al., 2022 [3].

American Society of Clinical Oncology (ASCO)

Management of Stage III Non-Small-Cell Lung Cancer: ASCO Guideline.

Zielsetzung/Fragestellung

To provide evidence-based recommendations to practicing clinicians on management of patients with stage III non–small-cell lung cancer (NSCLC).

Methodik

<u>Grundlage der Leitlinie</u>

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;

- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- from 1990 through 2021

LoE/GoR:

- The quality of the evidence for each outcome was assessed using the Cochrane Risk of Bias tool and elements of the GRADE quality assessment and recommendations development process

Table 1. Definitions for Quality of Evidence Grades[7]

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

- Strength of recommendations: The Expert Panel provides a rating of the strength of each recommendation. This assessment reflects the extent to which a guideline panel is confident that desirable effects of an intervention outweigh undesirable effects, or vice versa, across the range of patients for whom the recommendation is intended. Recommendations may fall into two categories; strong and weak. Factors determining the strength of a recommendation include balance between benefits and harms, certainty of evidence, confidence in values & preferences, and resource use. Recommendations may be made for or against the use of an intervention.

Recommendations

Unresectable disease:

- Recommendation 5.1.: Patients with stage III NSCLC who are medically or surgically inoperable and with good performance status should be offered concurrent instead of sequential chemotherapy and radiation therapy (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).
- Recommendation 5.2.: Concurrent chemotherapy delivered with radiation therapy for definitive treatment of stage III NSCLC should include a platinum-based doublet, preferably cisplatin plus etoposide, carboplatin plus paclitaxel, cisplatin plus pemetrexed (non-squamous only), or cisplatin plus vinorelbine (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

  Qualifying Statement: Carboplatin may be substituted for cisplatin in patients with contraindications to or deemed ineligible for cisplatin.
- Recommendation 5.3.: Patients with stage III NSCLC who are not candidates for concurrent chemoradiation but are candidates for chemotherapy should be offered sequential chemotherapy and radiation therapy over radiation alone (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

- Recommendation 5.4.: Patients with stage III NSCLC receiving concurrent chemoradiation should be treated to 60 Gy (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).
- Recommendation 5.5.: Doses higher than 60 Gy and up to 70 Gy may be considered for selected patients, with careful attention to doses to heart, lungs, and esophagus (Type: Evidence based; benefit outweighs harm; Evidence quality: low; Strength of recommendation: strong).
- Recommendation 5.6.: Patients with stage III NSCLC receiving definitive radiation without chemotherapy in standard fractionation may be considered for radiation dose escalation and for modest hypofractionation from 2.15 to 4 Gy per fraction (Type: Evidence based; benefit outweighs harm; Evidence quality: low; Strength of recommendation: weak).
- Recommendation 5.7.: Patients with stage III NSCLC receiving concurrent chemoradiation without disease progression during the initial therapy should be offered consolidation durvalumab for up to 12 months (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

  Qualifying Statement: There is insufficient evidence to alter the recommendation for consolidation durvalumab following concurrent chemoradiation for molecularly defined subgroups (namely, patients with an oncogenic driver alteration or those with low or no expression of programmed death-ligand 1)

National Institute for Health and Care Excellence (NICE), 2019 [20].

Lung cancer: diagnosis and management

- This guideline replaces CG121.
- This guideline is the basis of QS17.

Leitlinienorganisation/Fragestellung

This guideline covers diagnosing and managing non-small-cell and small-cell lung cancer. It aims to improve outcomes for patients by ensuring that the most effective tests and treatments are used, and that people have access to suitable palliative care and follow-up.

Methodik

Grundlage der Leitlinie

Update (This guideline replaces CG121, and is the basis of QS17).

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- NICE initially produced guidance on the diagnosis and treatment of lung cancer in February 2005, which was substantially updated and replaced in 2011 and has since

been partially updated in March 2019. However pleural interventions were not included in either update, and so the recommendations below on pleural effusion date back to development of the original guideline in February 2005.

- The searches were conducted between October 2017 and April 2018 for 9 review questions (RQ).
- Searches were re-run in May 2018.

LoE

- trifft nicht zu (sieh sonstige methodische Hinweise)

GoR

- To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations.

Sonstige methodische Hinweise (Bei Einschränkung der o. g. Kriterien)

The guideline committee discussed the review questions and the need for clinical guidance in this area [note: systemic anti-cancer therapy] and agreed that instead of updating the chemotherapy for NSCLC recommendations (2005 recommendations 1.4.40 – 1.4.43) the guideline update should develop an algorithm outlining the treatment pathway for systemic anti-cancer therapy treatments. This algorithm would provide a clear overview and contextualisation of systemic anti-cancer therapy treatments.

In March 2019, we reviewed the evidence and made new recommendations on:

- intrathoracic lymph node assessment
- brain imaging for people with non-small-cell lung cancer
- radical radiotherapy (including stereotactic ablative radiotherapy [SABR]) for people with non-small-cell lung cancer
- chemoradiotherapy and surgery for people with stage IIIA-N2 non-small-cell lung cancer
- thoracic radiotherapy and prophylactic cranial irradiation for people with small-cell lung cancer

We checked this guideline in June 2019. We found no new evidence that affects the recommendations in this guideline.

Updates-Kennzeichnung:

- These recommendations are marked [2005, amended 2019] or [2011, amended 2019].
- Recommendations marked [2005] or [2011] last had an evidence review in 2005 or 2011. In some cases, minor changes have been made to the wording to bring the language and style up to date, without changing the meaning.

Empfehlungen

Non-Squamous non-small-cell lung cancer, stages IIIB and IV

EGFR-TK mutation

- 1.4.45 For guidance on treatment for stage IIIB and IV non-squamous NSCLC in people with the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation:
  - for initial treatment, see the NICE technology appraisal guidance on afatinib, erlotinib and gefitinib.

ALK gene rearrangement

- 1.4.46 For guidance on treatment for stage IIIB and IV non-squamous NSCLC in people with the anaplastic lymphoma kinase-positive gene rearrangement:
  - for first-line systemic treatment, see the NICE technology appraisal guidance on crizotinib, ceritinib and alectinib

PDL1≥50% and no gene mutation or fusion protein

- 1.4.47 For guidance on treatment for stage IIIB and IV non-squamous NSCLC in people whose tumours express PD-L1 at 50% or above and who have no gene mutation or fusion protein:
  - for initial treatment, see the NICE technology appraisal guidance on pembrolizumab and pembrolizumab combination

ROS1 positive

- 1.4.48 For guidance on treatment for stage IIIB and IV ROS1-positive non-squamous NSCLC:
  - for initial treatment, see the NICE technology appraisal guidance on crizotinib

No gene mutation or fusion protein and PD-L1<50%

- 1.4.49 For guidance on treatment for stage IIIB and IV non-squamous NSCLC in people who do not have a gene mutation, fusion protein or biomarker:
  - see the NICE technology appraisal guidance on pembrolizumab combination and pemetrexed with cisplatin or offer pemetrexed with carboplatin or other platinum doublet chemotherapy.

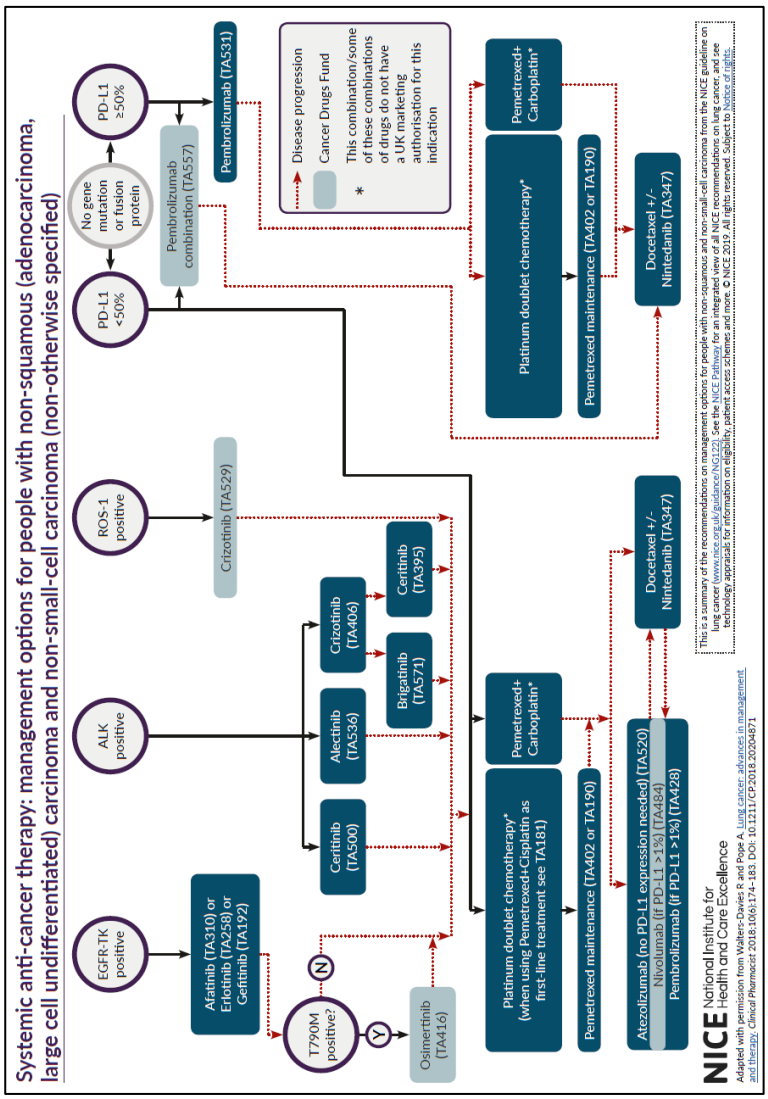
Squamous non-small-cell lung cancer

- PDL1≥50%: For guidance on treatment for squamous NSCLC in people whose tumours express PD-L1 at or above 50%:
  - for initial treatment, offer gemcitabine or vinorelbine and cisplatin or carboplatin

PDL1<50%

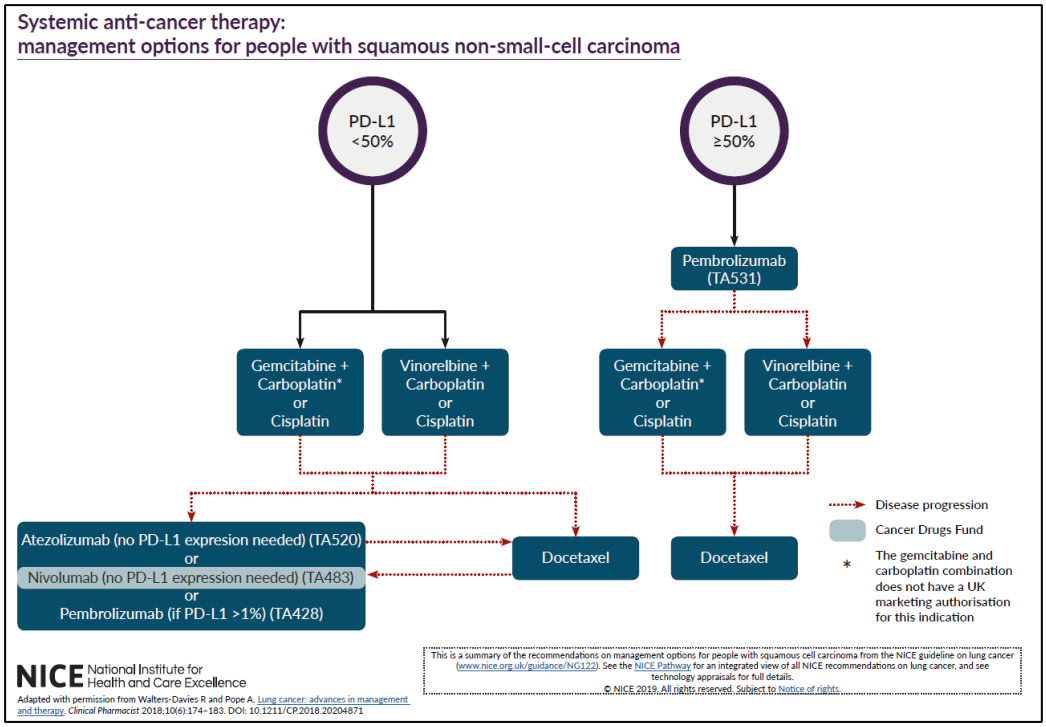
- 1.4.51 For guidance on treatment for squamous NSCLC in people whose tumours express PD-L1 below 50%:
  - for initial treatment, offer gemcitabine or vinorelbine and cisplatin or carboplatin.

Systemic anti-cancer therapy (SACT) for advanced non-small-cell lung cancer (non-squamous)



Squamous non-small-cell lung cancer, stages IIIB and IV

Systemic anti-cancer therapy (SACT) for advanced non-small-cell lung cancer (squamous)



Owen DH et al., 2023 [21].

Therapy for Stage IV Non–Small-Cell Lung Cancer With Driver Alterations: ASCO Living Guideline, Version 2022.2

Zielsetzung/Fragestellung

this version of the stage IV NSCLC with driver alterations living guideline reviews evidence and provides updated recommendations on human epidermal growth factor receptor 2 (HER2; ERBB2) and KRAS G12C mutations

Methodik

Grundlage der Leitlinie

Update der Version von Singh N. et al. 2022 [24] Repräsentatives Gremium;

- Interessenkonflikte untersucht, finanzielle Unabhängigkeit nicht erwähnt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale und informale Konsensusprozesse durchgeführt und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

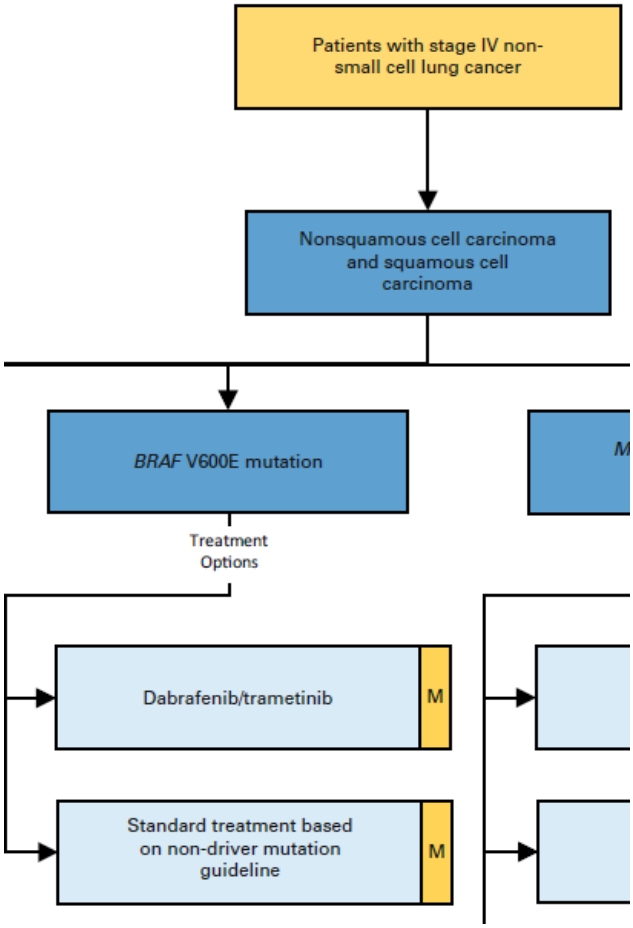
Recherche/Suchzeitraum:
August 2022

LoE/GoR
GRADE

Empfehlungen

What is the most effective first-line therapy for patients with stage IV NSCLC with a tumor *EGFR*-sensitizing mutation and PS 0-2?	1.1. For patients with a sensitizing (L858R/Exon19 deletion, with or without a concomitant T790M mutation) *EGFR* mutation with stage IV NSCLC and a performance status of 0-2 who have not had previous systemic therapy, clinicians should use osimertinib monotherapy	Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong
	Qualifying Statement: Although Recommendation 1.1 addresses many patients in the target population, the guideline manuscript presents additional options that may be reasonable, based on the evidence reviewed. This statement applies to all recommendations with the word should. In addition, use of osimertinib in patients previously treated with adjuvant or consolidation tyrosine kinase inhibitors is not part of this guideline	
	1.2. For patients with a sensitizing (L858R/Exon19deletion) *EGFR* mutation with stage IV NSCLC and a performance status of 0-2 who have not had previous systemic therapy and for whom osimertinib is not available, clinicians may use combination gefitinib with doublet chemotherapy (platinum/pemetrexed with maintenance pemetrexed)	Type: Evidence based; Evidence quality: High; Strength of recommendation: Moderate
	1.3. For patients with a sensitizing (L858R/Ex19del) *EGFR* mutation with stage IV NSCLC and a performance status of 0-2 previously untreated with systemic therapy and for whom osimertinib is not available, clinicians may use dacomitinib monotherapy	Type: Evidence based; Evidence quality: High; Strength of recommendation: Moderate
	1.4. For patients with a sensitizing (L858R/Ex19del) *EGFR* mutation with stage IV NSCLC and a performance status of 0-2 who have not had previous systemic therapy, and do not have access to osimertinib, clinicians may use monotherapy with afatinib or erlotinib/bevacizumab or erlotinib/ramucirumab	Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate
	1.5. For patients with a sensitizing (L858R/Ex19del) *EGFR* mutation with stage IV NSCLC and a performance status of 0-2 who have not had previous systemic therapy, and do not have access to other regimens, clinicians may use monotherapy with gefitinib, erlotinib, or icotinib	Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate
	1.6. For patients with a sensitizing (L858R/Ex19del) *EGFR* mutation with stage IV NSCLC and a performance status of 3, who have not had previous systemic therapy, monotherapy with an EGFR tyrosine kinase inhibitor may be given, with the choice dependent on access and toxicity profile of each agent	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Weak
	1.7. For patients with an activating *EGFR* mutation other than exon 20 insertion mutations, T790M, L858R or Ex19Del, (eg, G719X, L861Q, S768I), and a performance status of 0-2 who have not had previous systemic therapy, clinicians may offer afatinib monotherapy	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate
	or osimertinib	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Weak
	or standard treatment based on non-driver mutation guideline	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate
	1.8. For patients with any activating *EGFR* mutation, regardless of PD-L1 expression levels (including exon 20 insertion mutations), single-agent immunotherapy should not be used as first-line therapy	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate
	1.9. For patients with an exon 20 insertion mutation causing resistance to first- and second-generation EGFR tyrosine kinase inhibitors, clinicians may offer platinum doublet chemotherapy with or without bevacizumab	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate
	or standard treatment based on the non-driver mutation guideline	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate

Clinical Question	Recommendation	Type; Evidence Quality; Strength of Recommendation
What is the most effective second-line therapy for patients with stage IV NSCLC with a sensitizing *EGFR* mutation who received a first-line EGFR TKI and experienced disease progression?	2.1. For patients with a sensitizing (L858R/Ex19del) *EGFR* mutation with stage IV NSCLC and a performance status of 0-2 who have had previous EGFR targeted therapy (except osimertinib) and subsequently have an *EGFR* T790M resistance mutation, clinicians should recommend osimertinib	Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong
	2.2. For patients with any *EGFR* mutation who have progressed on EGFR TKIs with no T790M mutation OR whose disease has progressed on osimertinib, clinicians may treat based on the non-driver mutation guidelines	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate
What is the most effective third-line therapy for patients with tumor *EGFR*-sensitizing mutation positive status who have had prior platinum-based chemotherapy and EGFR TKI?	See second-line above	—
What is the most effective first-line therapy for patients with stage IV NSCLC with *ALK* gene rearrangement and PS 0-1 or possibly PS 2?	3.1. For patients with an *ALK* rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians should offer alectinib or brigatinib	Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong
	or lorlatinib	Type: Evidence based; Evidence quality: Low; Strength of recommendation: Weak
	3.2. For patients with an *ALK* rearrangement, a PS of 0-2, and previously untreated NSCLC, if alectinib, brigatinib, or lorlatinib are not available, clinicians should offer ceritinib or crizotinib	Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong
What is the most effective second-line therapy for patients with stage IV NSCLC with *ALK* rearrangement with progression after first-line crizotinib?	4.2. For patients with an *ALK* rearrangement, a performance status of 0-2, and have previously received crizotinib in the first-line setting, clinicians should offer alectinib, brigatinib, or ceritinib in the second-line setting	Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Strong
What is the most effective second- or third-line therapy for patients with stage IV NSCLC with *ALK* gene rearrangement and PS 0-2?	4.1. For patients with an *ALK* rearrangement, a performance status of 0-2, and have previously received alectinib or brigatinib, clinicians may offer lorlatinib	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate
	4.3. For patients with an *ALK* rearrangement, a performance status of 0-2 and have received prior crizotinib in the first-line setting and either alectinib, brigatinib, or ceritinib in the second-line setting, clinicians may offer lorlatinib	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate
	or clinicians may offer standard therapy following the non-driver mutation guideline in the third-line setting	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Weak
What is the most effective first-line therapy for patients with stage IV NSCLC with *ROS1* rearrangement?	5.1. For patients with *ROS1* rearrangement, a performance status of 0-2, previously untreated lung cancer, clinicians may offer crizotinib or entrectinib	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate
	5.2. For patients with *ROS1* rearrangement, a performance status of 0-2, previously untreated lung cancer, clinicians may offer standard therapy based on the non-driver mutation guideline	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate
	5.3. For patients with *ROS1* rearrangement, a performance status of 0-2, previously untreated lung cancer, clinicians may offer ceritinib or lorlatinib	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Weak
What is the most effective second-line therapy for patients with *ROS1* rearrangement?	6.1. For patients with *ROS1* rearrangement, a performance status of 0-2, previously treated with ROS1 targeted therapy, clinicians should offer standard therapy following the non-driver mutation guideline	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate
	6.2. For patients with *ROS1* rearrangement, a performance status of 0-2, previously treated with nontargeted therapy first-line, clinicians may offer crizotinib or entrectinib or ceritinib	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate
For patients with a *BRAF* V600E mutation, what is the optimal first-line therapy?	7.1. For patients with a *BRAF* V600E mutation, clinicians may offer dabrafenib/trametinib as first-line treatment	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate
	7.2. For patients with a *BRAF* V600E mutation, clinicians may offer standard first-line therapy following the non-driver alterations guideline	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate



(Ausschnitt aus Behandlungsalgorithmus, die komplette Abbildung findet sich im Anhang)

Passiglia F et al., 2020 [22].

Italian Association of Medical Oncologyg (AIOM)

Treatment of advanced non-small-cell lung cancer: The 2019 AIOM (Italian Association of Medical Oncology) clinical practice guidelines.

Leitlinienorganisation/Fragestellung

Evidence-based guideline for the management of lung tumors.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Medline (PubMed), Embase-databases and Cochrane-Library, up to September 2019.
- Update von Facchinetti F et al., 2019 [6]

LoE/GoR

- GRADE

The global quality of evidence was defined as follow:

- High (high grade of confidence in the study results): high probability that the estimated effect is similar to the true effect.
- Moderate (moderate grade of confidence in the study results): moderate probability that the estimated effect is similar to the true effect, but limited possibility that it is substantially different.
- Low (low grade of confidence in the study results): limited probability that the estimated effect is similar to the true effect, with high possibility that it is substantially different
- Very low (very low grade of confidence in the study results): very limited probability that the estimated effect is similar to the true effect, with very high possibility that it is substantially different.

Strength of recommendation The strength of clinical recommendations is graduated on four levels according to their clinical relevance, considering the benefit/risk outcomes ratio, the quality of evidence and other additional variables (equity, acceptability, feasibility, and patients' preference):

- Strong for: The intervention should be considered as the treatment of choice (benefits are higher than risks)
- Conditional for: The intervention may be considered as treatment of choice (not sure that benefits are higher than risks)
- Conditional against: The intervention should not be considered as treatment of choice, except for selected cases after discussion with the patient (not sure that benefits are higher than risks)

Recommendations

Table 1
Clinical Recommendations for the Treatment of oncogene-addicted advanced NSCLC.

Global quality of evidence GRADE	Clinical recommendation	Strength of recommendation
Low	For patients with metastatic NSCLC harboring *"classic"* (exon 19 deletions, L858R) *EGFR* mutations, first-line therapy with osimertinib should be considered as treatment of choice, compared to first-generation EGFR inhibitors (gefitinib, erlotinib).	Strong for
Very low	For patients with metastatic NSCLC harboring *"classic"* (exon 19 deletions, L858R) *EGFR* mutations, first-line therapy with an EGFR inhibitor (gefitinib, erlotinib, afatinib) should be considered as treatment of choice, compared to chemotherapy.	Strong for
Very low	For patients with metastatic NSCLC harboring *EGFR* mutations, who experienced radiological progression to first/second generation EGFR inhibitors (gefitinib, erlotinib or afatinib), and had *T790M* mutation (detected through liquid or tumor biopsy), osimertinib should be considered as treatment of choice (compared to chemotherapy).	Strong for
Moderate	For patients with metastatic NSCLC harboring *ALK* rearrangements, first-line therapy with alectinib should be considered as treatment of choice compared to crizotinib.	Strong for
Moderate	For patients with metastatic NSCLC harboring *ALK* rearrangements, first-line therapy with crizotinib or ceritinib should be considered as treatment of choice, compared to chemotherapy.	Strong for
Low	For patients with metastatic NSCLC harboring *ALK* rearrangements, who experienced radiological progression to crizotinib, second-line therapy with ceritinib or alectinib should be considered as treatment of choice, compared to chemotherapy.	Strong for
Very low	For patients with metastatic NSCLC harboring *ROS1* rearrangements, first-line therapy with crizotinib should be considered as treatment of choice.	Strong for

Table 2
Clinical Recommendations for the Treatment of non oncogene-addicted advanced NSCLC.

Global quality of evidence GRADE	Clinical recommendation	Strength of recommendation
Moderate	For patients with EGFR/ALK wild-type, advanced NSCLC and PD-L1 TPS ≥ 50 %, first-line therapy with Pembrolizumab should be considered as treatment of choice	Strong for
Low	For patients with advanced, non-squamous NSCLC who completed 4–6 cycles of first-line chemotherapy with platinum-pemetrexed and experienced partial response or stable disease, maintenance therapy with single agent pemetrexed until disease progression or unacceptable toxicities could be considered as a treatment option.	Conditional for

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 11 of 12, November 2022) am 17.11.2022

#	Suchfrage
1	[mh “Carcinoma, Non-Small-Cell Lung”]
2	[mh ^"Lung Neoplasms"]
3	{OR #1-#2}
4	((((non NEXT small) OR nonsmall) NEXT cell NEXT lung) OR pulmon*):ti,ab,kw
5	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesion* OR malignan*):ti,ab,kw
6	#4 AND #5
7	nsclc*:ti,ab,kw
8	{OR #3, #6-#7}
9	#8 with Cochrane Library publication date from Nov 2017 to present

Systematic Reviews in PubMed am 17.11.2022

verwendete Suchfilter ohne Änderung:

Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.

#	Suchfrage
1	Carcinoma, Non-Small-Cell Lung[majr]
2	((((non[tiab]) AND small[tiab]) OR nonsmall[tiab]) AND cell[tiab]) AND lung[tiab]
3	(((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]) OR malignan*[tiab]
4	#1 OR (#2 AND #3)
5	(#4) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of

#	Suchfrage
	care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
6	((#5) AND ("2017/11/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in PubMed am 17.11.2022

verwendete Suchfilter ohne Änderung:

Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	"Carcinoma, Non-Small-Cell Lung"[mh]
2	Lung Neoplasms/therapy/drug therapy
3	Medical Oncology/methods/standards
4	((((non[tiab]) AND small[tiab]) OR nonsmall[tiab]) AND cell[tiab]) AND lung[tiab]
5	(((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]) OR malignan*[tiab]
6	lung[ti] AND #5
7	(#4 AND #5) OR #6
8	#1 OR #2 OR #3 OR #7
9	(#8) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])

#	Suchfrage
10	(((#9) AND ("2017/11/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
11	(#10) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 17.11.2022

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- National Cancer Institute (NCI)

- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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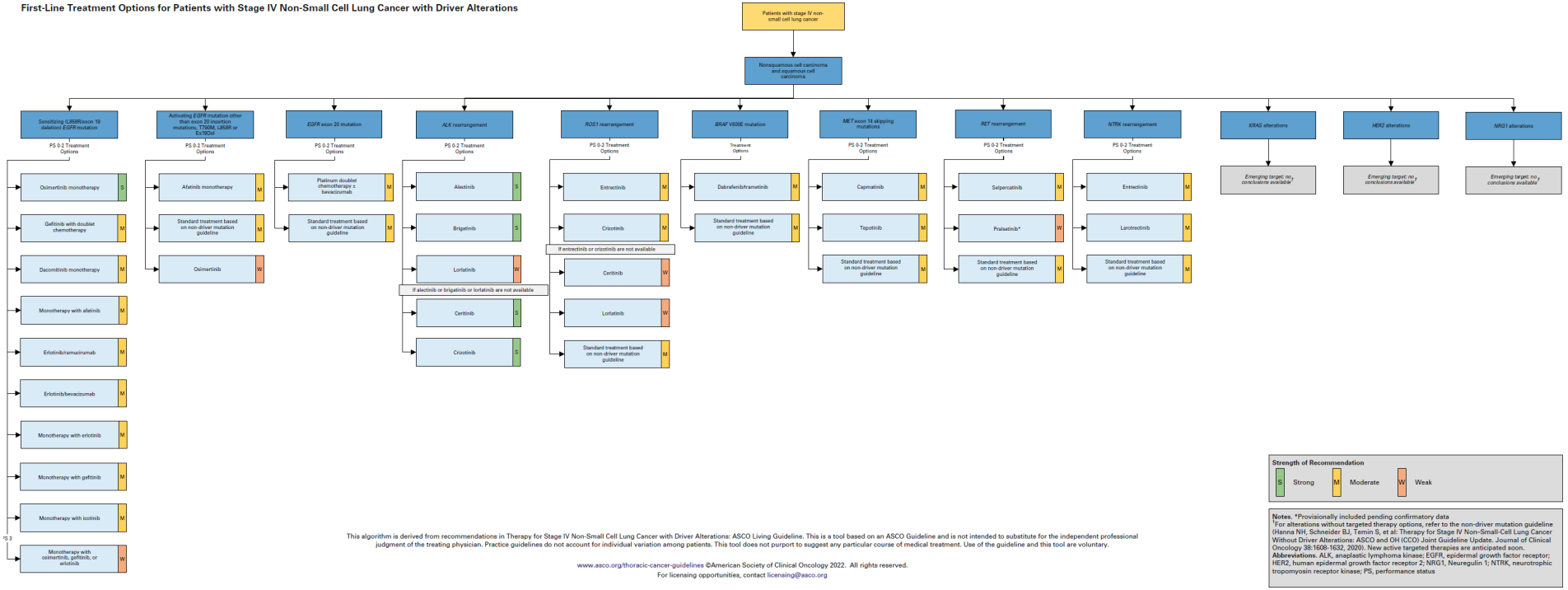
Anhang

Behandlungspfad der ASCO-LL für Patienten mit NSCLC, Stadium IV und Treibermutationen [21]



Stand: 23.01.2023

Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

2022-B-312

Kontaktdaten

Fachgesellschaften:
Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)
Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (DGP)
Arbeitsgemeinschaft Thorakale Onkologie in der Arbeitsgemeinschaft Internistische Onkologie der Deutschen Krebsgesellschaft (AIO)
Pneumologisch-Onkologische Arbeitsgemeinschaft der Deutschen Krebsgesellschaft (POA)

Indikation gemäß Beratungsantrag

Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligem Lungenkarzinom (non-small cell lungcancer, NSCLC) mit einer BRAF-V600E-Mutation (Erstlinientherapie)

Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Zusammenfassung

Bei der Behandlung von Patientinnen und Patienten (Pat.) mit fortgeschrittenem, nicht-kleinzelligem Lungenkarzinom (NSCLC) und Nachweis einer *BRAF*-V600E-Mutation bestehen zwei Therapieoptionen:

- Dabrafenib + Trametinib
- Immunchemotherapie, bzw. Immunmonotherapie bei PD-L1-Expression ≥50%

Da keine Daten randomisierter Studien zum Vergleich dieser zugelassenen Therapieoptionen vorliegen, wird die Entscheidung individuell getroffen.

Stand des Wissens

Das NSCLC ist eine biologisch heterogene Erkrankung [1, 2]. *BRAF*-Mutationen werden bei 1-2% aller Pat. mit nicht-kleinzelligem Lungenkarzinom nachgewiesen [3]. Sie können pathophysiologisch in drei Gruppen eingeteilt werden [4]:

- V600-Mutationen mit Bildung von Kinase-aktivierenden Monomeren
- Kinase-aktivierende Dimere
- Kinase-inaktivierende Heterodimere.

Auch das klinische Verhalten unterscheidet sich in den drei Gruppen.

Kontaktdaten

Fachgesellschaften:
Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)
Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (DGP)
Arbeitsgemeinschaft Thorakale Onkologie in der Arbeitsgemeinschaft Internistische Onkologie der Deutschen Krebsgesellschaft (AIO)
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Indikation gemäß Beratungsantrag

Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligem Lungenkarzinom (non-small cell lungcancer, NSCLC) mit einer BRAF-V600E-Mutation (Erstlinientherapie)

Die V600-Mutationen machen etwa die Hälfte der Aberrationen aus. Davon handelt es sich in der großen Mehrzahl um V600E-Mutationen, selten V600G oder andere Varianten [3, 4]. Histologisch liegen fast immer Adenokarzinome vor. *BRAF* V600-Mutationen führen zu einer Aktivierung des MAPK-Signalübertragungswegs.

Bei bisher unbehandelten Pat. führte der BRAF-Inhibitor Dabrafenib in einer einarmigen Phase-II-Studie in Kombination mit dem MEK-Inhibitor Trametinib zu einer Remissionsrate von 64% und einer medianen Gesamtüberlebenszeit von 24,6 Monaten [5, 6]. Bei mit Chemotherapie vorbehandelten Pat. lag die Remissionsrate bei 63%. Im indirekten Vergleich ist die Rate schwerer Nebenwirkungen niedriger als unter Chemotherapie. Daten randomisierter Studien liegen nicht vor. Die Wirksamkeit der BRAF-Inhibitoren wurde auch mit anderen Substanzen bestätigt [7].

Dabrafenib/Trametinib kann in der Erst- oder Zweitlinientherapie bei BRAFV600 Mutationen eingesetzt werden. Bei anderen Punktmutationen außerhalb der Position V600 ist die Situation komplex, da auch Kinase-inaktivierende Mutationen auftreten. Hier sollte ein molekulares Tumorboard konsultiert werden.

Direkte Vergleiche gegenüber Immunchemotherapie liegen nicht vor. Tumoren mit BRAF V600E können auf Immuntherapie ansprechen [8], weshalb die Chemo-Immuntherapie ebenfalls eine sinnvolle Option ist. Diese früheren Ergebnisse wurden kürzlich in einer retrospektiven Analyse aus China bestätigt [9]. In der aktuellen S3 Leitlinie werden die Empfehlungen folgendermaßen zusammengefasst [1]:

Kontaktdaten

Fachgesellschaften:
Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)
Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (DGP)
Arbeitsgemeinschaft Thorakale Onkologie in der Arbeitsgemeinschaft Internistische Onkologie der Deutschen Krebsgesellschaft (AIO)
Pneumologisch-Onkologische Arbeitsgemeinschaft der Deutschen Krebsgesellschaft (POA)

Indikation gemäß Beratungsantrag

Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligem Lungenkarzinom (non-small cell lungcancer, NSCLC) mit einer BRAF-V600E-Mutation (Erstlinientherapie)

8.126	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **B**	NSCLC IV- Patienten mit nachgewiesener BRAF-V600-Mutation sollte eine Kombination aus Dabrafenib und Trametinib angeboten werden. Nicht-V600 Mutations+ NSCLC Patienten sollten in einem Thorax-Onkologischen Tumorboard besprochen werden.	
Level of Evidence **2b**	[1171], [1172], [1173]	
	Starker Konsens	

In ONKOPEDIA wird die „oder“-Situation mit den Optionen des gezielten Einsatzes von BRAF- und MEK-Inhibitor in der Erst- oder Zweitlinientherapie dargestellt [2]:

Kontaktdaten

Fachgesellschaften:
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Arbeitsgemeinschaft Thorakale Onkologie in der Arbeitsgemeinschaft Internistische Onkologie der Deutschen Krebsgesellschaft (AIO)
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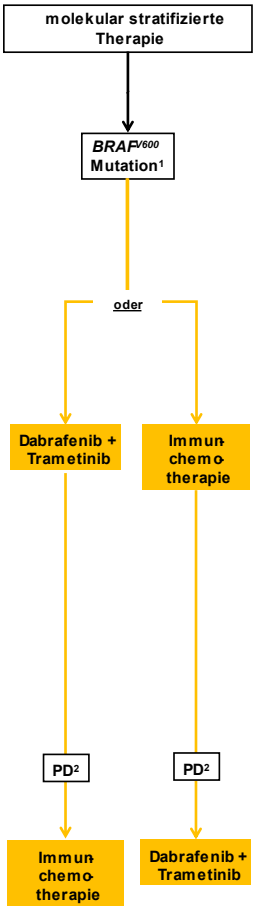
Indikation gemäß Beratungsantrag

Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligem Lungenkarzinom (non-small cell lungcancer, NSCLC) mit einer BRAF-V600E-Mutation (Erstlinientherapie)



Legende: [1]*BRAF V600* – in der Mehrzahl V600E, aber auch andere aktivierende V600 Mutationen; [2]CR – komplette Remission, PR – partielle Remission, SD – stabile Erkrankung, PD – progrediente Erkrankung;

Kontaktdaten

Fachgesellschaften:
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Indikation gemäß Beratungsantrag

Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligem Lungenkarzinom (non-small cell lungcancer, NSCLC) mit einer BRAF-V600E-Mutation (Erstlinientherapie)

Ergänzend muss hier angemerkt werden, dass auch bei Pat. mit BRAF-V600-Mutation eine PD-L1-Expression ≥50% vorliegen kann. Bei diesen Pat. steht differentialtherapeutisch eine Immunmonotherapie zur Verfügung.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von *„erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligem Lungenkarzinom (non-small cell lungcancer, NSCLC) mit einer BRAF-V600E-Mutation (Erstlinientherapie)“***, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

Ja, diese sind oben dargestellt.

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Kontaktdaten

Fachgesellschaften:
Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)
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Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2023-B-198 Encorafenib (NSCLC, Zweitlinie)

Stand: September 2023

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Encorafenib in Kombination mit Binimetinib
[NSCLC, Zweitlinie]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“ Ausgeschlossen wurden Arzneimittel zur Therapie eines NSCLC mit ALK-Translokation, EGFR-, ROS1-, KRAS-, MET- oder RET-Mutationen.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	**Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:** – Afatinib: Beschluss vom 05.11.2015 – Atezolizumab: Beschluss vom 16.03.2018 – Dabrafenib: Beschluss vom 19.10.2017 – Nintedanib: Beschluss vom 18.06.2015 – Nivolumab: Beschluss vom 20.10.2016 – Pembrolizumab: Beschluss vom 02.02.2017 – Trametinib: Beschluss vom 19.10.2017 – Ramucirumab: Beschluss vom 01.09.2016 **Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie – Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (Off-Label-Use):** Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligen Bronchialkarzinom (NSCLC) – Kombinationstherapie
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Encorafenib L01EC03 Braftovi Binimetinib L01EE0 Mektovi	<u>Geplantes Anwendungsgebiet laut Beratungsanforderung:</u> Encorafenib in Kombination mit Binimetinib ist angezeigt für die Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligem Lungenkrebs mit einer BRAF-V600-Mutation (Zweitlinientherapie).
Zytostatika:	
Carboplatin L01XA02 Generisch	Off-Label-Indikation für Carboplatin: Kombinationstherapie des fortgeschrittenen NSCLC (palliativ)
Cisplatin L01XA01 generisch	Cisplatin wird angewendet zur Behandlung des fortgeschrittenen oder metastasierten nichtkleinzelligen Bronchialkarzinoms. Cisplatin kann als Mono- oder Kombinationstherapie angewendet werden.
Docetaxel L01CD02 generisch	Nicht-kleinzelliges Bronchialkarzinom: Docetaxel ist in Kombination mit Cisplatin zur Behandlung von Patienten mit nicht resezierbarem, lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Bronchialkarzinom <u>ohne vorausgegangene Chemotherapie</u> angezeigt. Docetaxel ist zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Bronchialkarzinom <u>nach Versagen einer vorausgegangenen Chemotherapie</u> angezeigt.
Etoposid L01CB01	Kombinationstherapie folgender Malignome:

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Riboposid	− Palliative Therapie des fortgeschrittenen, nicht-kleinzelligen Bronchialkarzinoms bei Patienten mit gutem Allgemeinzustand (Karnofsky-Index > 80 %), […]
Ifosfamid L01AA06 Holoxan	Nicht-kleinzellige Bronchialkarzinome: Zur Einzel- oder Kombinationschemotherapie von Patienten mit inoperablen oder metastasierten Tumoren.
Mitomycin L01DC03 generisch	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Bei intravenöser Gabe ist es in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei folgenden metastasierenden Tumoren wirksam: […] nicht-kleinzelliges Bronchialkarzinom […].
Paclitaxel L01CD01 generisch	Fortgeschrittenes nicht-kleinzelliges Bronchialkarzinom (NSCLC): Paclitaxel ist, in Kombination mit Cisplatin, zur Behandlung des nicht-kleinzelligen Bronchialkarzinoms bei Patienten angezeigt, für die potentiell kurative chirurgische Maßnahmen und/oder eine Strahlentherapie nicht in Frage kommen.
Pemetrexed L01BA04 generisch	Pemetrexed in Monotherapie ist angezeigt für die Erhaltungstherapie bei lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie bei Patienten, deren Erkrankung nach einer platinbasierten Chemotherapie nicht unmittelbar fortgeschritten ist. Pemetrexed in Monotherapie ist angezeigt zur Behandlung in Zweitlinientherapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligem Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie.
Vindesin L01CA03 Eldesine	Kombinationschemotherapie: Lokal fortgeschrittenes oder metastasiertes nicht-kleinzelliges Bronchialkarzinom (Stadium IIIB, IV).
Vinorelbin L01CA04 generisch	Behandlung des nicht kleinzelligen Bronchialkarzinoms (Stadium 3 oder 4).
Antikörper:	

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Atezolizumab L01FF05 Tecentriq	Tecentriq als Monotherapie wird angewendet bei erwachsenen Patienten zur Behandlung des lokal fortgeschrittenen oder metastasierten NSCLC nach vorheriger Chemotherapie. Patienten mit EGFR-mutiertem oder ALK-positivem NSCLC sollten vor der Therapie mit Tecentriq zudem auch bereits entsprechende zielgerichtete Therapien erhalten haben (siehe Abschnitt 5.1).
Durvalumab L01FF03 Imfinzi	IMFINZI ist angezeigt als Monotherapie zur Behandlung des lokal fortgeschrittenen, inoperablen nicht-kleinzelligen Lungenkarzinoms (NSCLC) bei Erwachsenen, deren Tumoren PD-L1 in ≥ 1 % der Tumorzellen exprimieren und deren Krankheit nach einer platinbasierten Radiochemotherapie nicht fortgeschritten ist (siehe Abschnitt 5.1).
Nivolumab L01FF01 Opdivo	OPDIVO ist als Monotherapie zur Behandlung des lokal fortgeschrittenen oder metastasierten nicht-kleinzelligen Lungenkarzinoms nach vorheriger Chemotherapie bei Erwachsenen indiziert.
Pembrolizumab L01FF02 Keytruda	KEYTRUDA ist als Monotherapie zur Behandlung des lokal fortgeschrittenen oder metastasierenden nicht-kleinzelligen Lungenkarzinoms mit PD-L1-exprimierenden Tumoren (TPS ≥ 1 %) nach vorheriger Chemotherapie bei Erwachsenen angezeigt. Patienten mit EGFR- oder ALK-positiven Tumormutationen sollten vor der Therapie mit KEYTRUDA ebenfalls eine auf diese Mutationen zielgerichtete Therapie erhalten haben
Ramucirumab L01FG02 Cyramza	Nicht-kleinzelliges Lungenkarzinom […] Cyramza ist in Kombination mit Docetaxel indiziert zur Behandlung von erwachsenen Patienten mit einem lokal fortgeschrittenen oder metastasierten nicht-kleinzelligen Lungenkarzinom mit Tumorprogress nach platinhaltiger Chemotherapie.
Proteinkinase-Inhibitoren:	
Afatinib L01EB03 Giotrif	GIOTRIF als Monotherapie wird angewendet zur Behandlung von […] • erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC mit Plattenepithel-Histologie, das unter oder nach Platin-basierter Chemotherapie fortschreitet
Erlotinib L01EB02 generisch	Nicht-kleinzelliges Lungenkarzinom (NSCLC) […] Erlotinib ist auch zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC angezeigt, bei denen mindestens eine vorausgegangene Chemotherapie versagt hat. Bei Patienten mit Tumoren ohne aktivierende EGFR-Mutationen ist Erlotinib angezeigt, wenn andere Therapieoptionen als ungeeignet erachtet werden.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Nintedanib L01EX09 Vargatef	Vargatef wird angwendet in Kombination mit Docetaxel zur Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem, metastasiertem oder lokal rezidiviertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit Adenokarzinom-Histologie nach Erstlinienchemotherapie.
Dabrafenib L01EC02 Tafinlar	Nicht-kleinzelliges Lungenkarzinom (NSCLC) Dabrafenib in Kombination mit Trametinib ist angezeigt zur Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligen Lungenkarzinom mit einer BRAF-V600-Mutation.
Trametinib L01EE01 Mekenist	Nicht-kleinzelliges Lungenkarzinom (NSCLC) Trametinib in Kombination mit Dabrafenib ist angezeigt zur Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligen Lungenkarzinom mit einer BRAF-V600-Mutation.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2023-B-198 (Encorafenib Binimetinib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	13. September 2023

Inhaltsverzeichnis

Abkürzungsverzeichnis

ASCO	American Society of Clinical Oncology
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
EGFR	Epidermal growth factor receptor
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
ICI	Immun-Checkpoint-Inhibitor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
NSCLC	nicht-kleinzelliges Lungenkarzinom
OR	Odds Ratio
ORR	objective response rate
OS	overall survival
PD-L1	Programmed cell death ligand 1
PD-1	Programmed cell death-1
PFS	progression-free survival
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht- kleinzelligem Lungenkrebs mit einer BRAFV600-Mutation. (Zweitlinientherapie)

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Nicht-kleinzelliges Lungenkarzinom* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.startpage.com*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 14.06.2023 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 2468 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Anhand einer initialen Prüfung von Leitlinien wurden nur systematische Reviews ab Erscheinungsdatum 12.2020 (Datum der Recherche für relevante Empfehlungen der S3-Leitlinie [2,3]) gescreent. Nachträglich wurden die aktualisierten Leitlinien von ASCO und NICE, beide von Juli 2023, identifiziert und in die Synopse aufgenommen. Basierend darauf, wurden insgesamt 7 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

3.2 Systematische Reviews

Wu LG et al., 2021 [7].

The efficacy and safety of PD-1/PD-L1 inhibitors versus chemotherapy in patients with previously treated advanced non-small-cell lung cancer: A meta-analysis

Fragestellung

To assess the effectiveness and safety of programmed death-1 (PD-1)/PD ligand 1 (PD-L1) inhibitors versus chemotherapy as second-line or late-line treatment for patients with advanced non-small-cell lung cancer (NSCLC)

Methodik

Population:

- Patients with advanced NSCLC

Intervention:

- Experimental group treated with PD-1 or PD-L1 inhibitors alone (e.g., durvalumab, nivolumab, atezolizumab, pembrolizumab, or avelumab)

Komparator:

- Chemotherapie

Endpunkte:

- Primär: OS
- Sekundär: PFS, ORR

Recherche/Suchzeitraum:

- PubMed, EMBASE, Cochrane Library, März 2020

Qualitätsbewertung der Studien:

- Cochrane RoB

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs, N=4.122

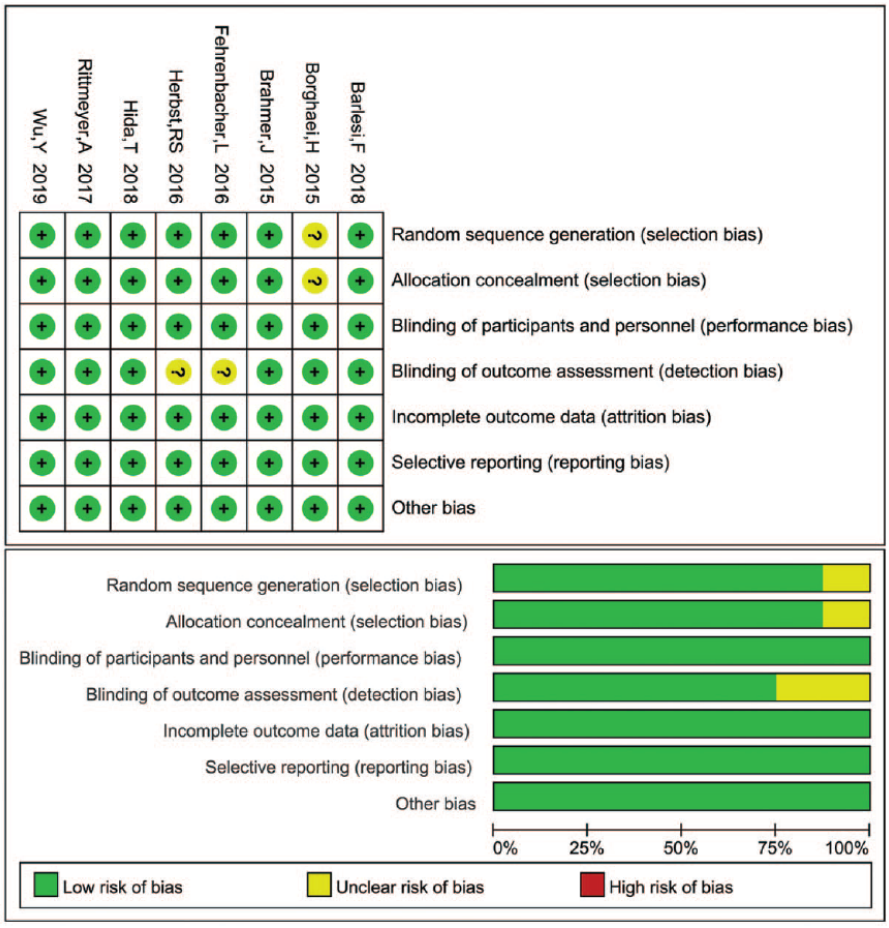
Charakteristika der Population/Studien:

Clinicopathological characteristics of the eligible studies.

Study	Year	Inclusion criteria for patient selection	Exclusion criteria for patient selection	Previous treatment	Treatment	No. of patients*
Rittmeyer et al[20]	2017	Stage IIIB or IV squamous cell or non-squamous cell NSCLC; measurable disease per Response Evaluation Criteria in Solid Tumors; ECOG PS of 0 or 1. Aged≥18.	Autoimmune disease; prior therapy with checkpoint-targeted agents; prior docetaxel therapy.	One to two previous cytotoxic chemotherapy regimens	Atezolizumab (1200 mg q3w) or docetaxel (75 mg/m^2 q3w)	850 (425/425)
Brahmer et al[16]	2015	Stage IIIB or IV squamous cell NSCLC; with treated stable brain metastases; ECOG PS of 0 or 1. Aged≥18.	Autoimmune disease; symptomatic interstitial lung disease; systemic immunosuppression; prior therapy with T-cell costimulation or checkpoint-targeted agents; prior docetaxel therapy.	One prior platinum containing regimen	Nivolumab (3 mg/kg q2w) or docetaxel (75 mg/m^2 q3w)	272 (135/137)
Borghaei et al[15]	2015	Stage IIIB or IV recurrent non-squamous NSCLC; after radiation therapy or surgical resection and had also had disease recurrence or progression; adequate hematologic, hepatic, and renal function; ECOG PS of 0 or 1. Aged≥18.	Autoimmune disease; symptomatic interstitial lung disease; systemic immunosuppression; prior treatment with immune-stimulatory antitumor agents; prior docetaxel therapy.	One prior platinum-based doublet chemotherapy regimen	Nivolumab (3 mg/kg q2w) or docetaxel (75 mg/m^2 q3w)	582 (292/290)
Barlesi et al[14]	2018	Stage IIIB or IV or recurrent NSCLC; disease progression after treatment with a platinum-containing doublet; adequate hematological, renal, and hepatic function; ECOG PS of 0 or 1. Aged≥18.	Brain metastases; non-squamous cell NSCLC harbouring an EGFR or ALK mutation; persisting toxicity after previous treatment, or other clinically significant diseases.	One prior platinum-based doublet chemotherapy regimen	Avelumab (10 mg/kg q2w) or docetaxel (75 mg/m^2 q3w)	529 (264/265)
Herbst et al[18]	2016	Stage IIIB or IV NSCLC with progression as per RECIST v1.1 after 2 or more cycles of platinum-doublet chemotherapy; PD-L1 TPS≥1%; aged≥18; ECOG PS of 0 or 1.	Autoimmune disease; brain metastases; carcinomatous meningitis; interstitial lung disease or history of pneumonitis; prior treatment with PD-1 checkpoint inhibitors or docetaxel.	Two or more prior cycles of platinum-doublet chemotherapy	Pembrolizumab (2 mg/kg q3w) or pembrolizumab (10 mg/kg q3w) or docetaxel (75 mg/m^2 q3w)	1034 (345/346/343)Δ
Hida et al[19]	2018	Squamous or non-squamous cell locally advanced or metastatic NSCLC; disease progression during or after a platinum-based regimen; measurable disease per RECIST v1.1; tumor sample available for evaluation of PD-L1 expression; had received ≤2 prior chemotherapy regimens; aged≥18; ECOG PS of 0 or 1.	Autoimmune disease; had received prior therapy with docetaxel, CD137 agonists, anticytotoxic T-lymphocyte-associated antigen 4, or anti-PD L1/PD-1 therapies.	One or two prior platinum-based chemotherapy	Atezolizumab (1200 mg) or docetaxel (75 mg/m^2 q3w)	64 (36/28)
Wu et al[21]	2019	Stage IIIB or IV or recurrent squamous or non-squamous cell NSCLC progressing during or after 1 previous platinum-based doublet chemotherapy regimen; measurable disease per RECIST v1.1; aged≥18; ECOG PS of 0 or 1.	Active autoimmune disease, symptomatic interstitial lung disease, systemic immunosuppression; with EGFR-mutation-positive tumors or known ALK receptor tyrosine kinase (ALK) translocation-positive tumors; prior treatment with an EGFR, anaplastic lymphoma kinase inhibitor, anti-tumor vaccine, immunostimulatory antitumor agent, immune checkpoint inhibitor, or docetaxel.	One or more prior platinum containing regimen	Nivolumab (3 mg/kg q2w) or docetaxel (75 mg/m^2 q3w)	504 (338/166)
Fehrenbacher et al[17]	2016	Advanced or metastatic NSCLC; measurable disease per RECIST v1.1; adequate hematological; end-organ function; provided tumor specimens for central PD-L1 testing on formalin-fixed paraffin-embedded sections before enrolment; aged≥18; ECOG PS of 0 or 1.	Active or untreated CNS metastases; history of pneumonitis, autoimmune or chronic viral diseases; previous treatment with docetaxel, CD137 agonists, anti-CTLA4, anti-PD L1, or anti-PD-1 therapeutic antibodies, or PD-1/PD-L1 pathway-targeting agents.	One or more prior platinum containing regimen	Atezolizumab (1200 mg) or docetaxel (75 mg/m^2 q3w)	287 (144/143)

* Expressed as total number of patients (number of patients in intervention arm/number of patients in control arm). ΔThe trial is divided into 3 groups (number of patients in intervention arm received pembrolizumab 2 mg/kg/number of patients in intervention arm received pembrolizumab 10 mg/kg/number of patients in control arm). CNS = central nervous system, ECOG = Eastern Cooperative Oncology Group, NSCLC = non-small-cell lung cancer, PS = performance status, RECIST = response evaluation criteria in solid tumors.

Qualität der Studien:



Studienergebnisse:

- OS:
  - PD-1 oder PD-L1-Inhibitoren vs. Chemotherapie: HR 0.71, 95%-CI 0.66–0.77, P<.001, I^2=4%
- PFS:
  - PD-1 oder PD-L1-Inhibitoren vs. Chemotherapie: HR 0.88, 95%CI 0.81–0.94, P=.0004, I^2=46%
- ORR:
  - PD-1 oder PD-L1-Inhibitoren vs. Chemotherapie: HR 2.03, 95%CI 1.66–2.49, P<.001, I^2=52%

Anmerkung/Fazit der Autoren

This meta-analysis aimed to conduct a comprehensive and strict search of clinical trials that met appropriate standards. It showed that PD-L1 inhibitors possess significant efficacy and safety as a second-line and later-line therapies for patients with advanced NSCLC.

Kommentare zum Review

Vergleichbarer SR:

3.3 Leitlinien

Owen DH, et al., 2023 [1,5].

Therapy for Stage IV Non-Small-Cell Lung Cancer With Driver Alterations: ASCO Living Guideline, Version 2023.2

Zielsetzung/Fragestellung

What systemic therapy treatment options should be offered to patients with stage IV non–small-cell lung cancer (NSCLC) with driver alterations*, depending on the subtype of the patient's cancer?

1. What is the most effective first-line therapy?
2. What is the most effective second-line therapy?
3. Is there a role for a third-line therapy or beyond?

•With driver alterations in epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS-1 fusions, BRAF V600e mutations, RET fusions, MET exon 14 skipping mutations, HER2 alterations, and NTRK fusions (with known marker status test results available to the clinician).

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;

- Formale und informelle Konsensusprozesse sind beschrieben, externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig, Verbindung zu der zugrundeliegenden Evidenz ist schwer nachvollziehbar (bedingt durch den Aktualisierungsprozess);
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Routine literature searches (up to February 6, 2023)

LoE / GoR

Term	Definitions
Quality of Evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Strength of Recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects. In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects. All or almost all informed people would make the recommended choice for or against an intervention.
Weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists. In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not.

Sonstige methodische Hinweise

- Empfehlungsgrad moderat ist nicht definiert
- Living Guideline mit regelmäßigen Updates. Da nur einzelne Empfehlungen aktualisiert werden und für unveränderte Empfehlung die Evidenzbasis nicht abgebildet wird, ist die den Empfehlungen zugrundeliegende Evidenz für unveränderte Empfehlungen nicht nachvollziehbar.

Empfehlungen

For patients with a *BRAF* V600E mutation, what is the optimal first-line therapy?	7.1. For patients with a *BRAF* V600E mutation, clinicians may offer dabrafenib/trametinib as first-line treatment	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate
	7.2. For patients with a *BRAF* V600E mutation, clinicians may offer standard first-line therapy following the nondriver alterations guideline	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate
What is appropriate second-line therapy and above for patients with a *BRAF* V600E mutation?	8.1. For patients with a *BRAF* V600E mutation who have had previous B-RAF/MEK targeted therapy, clinicians should offer standard first-line therapy following the nondriver alterations guideline	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate
	8.2. For patients with a *BRAF* V600E mutation who have had previous chemotherapy or chemotherapy/immunotherapy, clinicians may offer dabrafenib/trametinib	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate
	or dabrafenib alone	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Weak
	or vemurafenib	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Weak
	8.3. For patients with a *BRAF* V600E mutation who have had previous chemotherapy, immunotherapy, and BRAF targeted therapy, clinicians should offer treatment following the nondriver mutation guideline	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate
	8.4. For patients with *BRAF* mutations other than *BRAF* V600E mutations, clinicians should offer standard therapy following the nondriver mutation guidelines	Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate

Literature review and analysis aus [1].

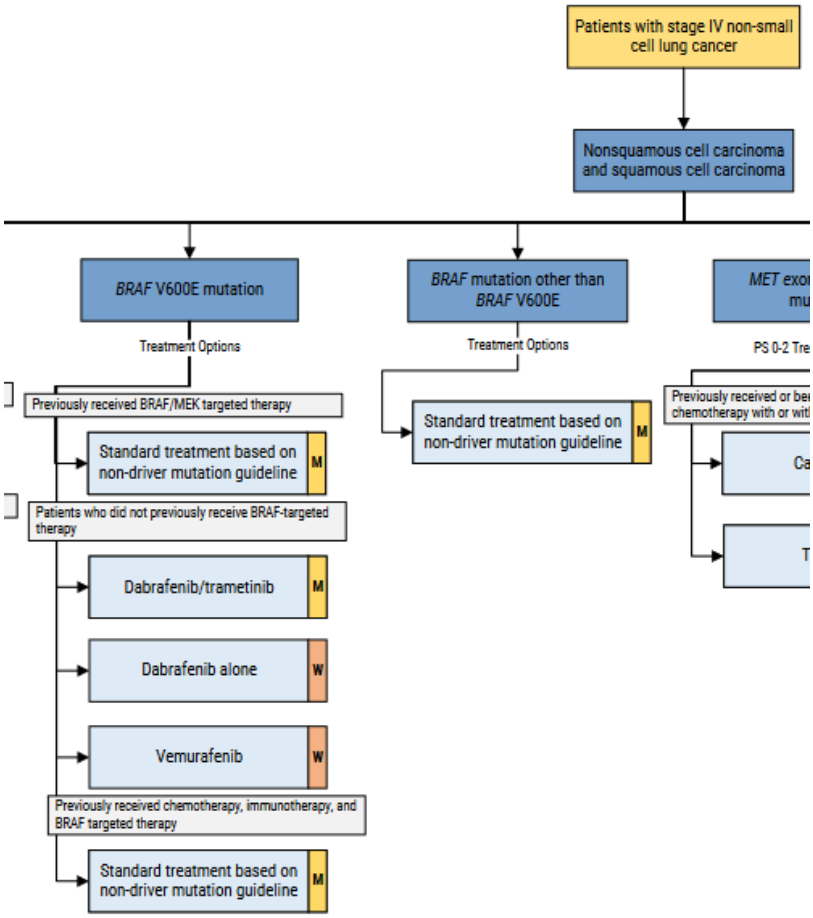
In the VE Basket trial of vemurafenib for patients with BRAF V600 mutation–positive NSCLC, the primary outcome, investigator-assessed RR, was 37%.50 The PFS was 6.5 months. Grade 3-4 AEs were 77%; those that were treatment-related were 40%.

Clinical interpretation aus [1].

According to My Cancer Genome, 4.75% of patients with NSCLC have BRAF alterations and BRAF V600 alterations, specifically in 1.24% of all NSCLC.[51,52] There are no RCTs comparing vemurafenib with standard-of care chemotherapy in first-line or with dabrafenib or dabrafenib/trametinib (latter recommended in 2017). Therefore, the 2017 recommendations including standard-of-care chemotherapy or dabrafenib/trametinib remain as options in the first-line for these patients. In addition to the 2017 recommendations for BRAF V600, clinicians may discuss vemurafenib as another option for second-line therapy compared with standard-of-care chemotherapy, although the occurrence of significant AEs is somewhat greater (note: in 2017, “If patients with BRAF mutations received immunotherapy in the second-line, clinicians may offer patients dabrafenib alone or in combination with trametinib in the third-line” [Type: informal consensus]).

Behandlungsalgorithmus

Second- and Third-Line Treatment Options for Patients with Stage IV Non-Small Cell Lung Cancer with Driver Alterations


Patients with stage IV non-small cell lung cancer
Nonsquamous cell carcinoma and squamous cell carcinoma
BRAF V600E mutation
BRAF mutation other than BRAF V600E
MET exo
mu
Treatment Options
Treatment Options
PS 0-2 Tre
Previously received BRAF/MEK targeted therapy
Standard treatment based on non-driver mutation guideline
M
Patients who did not previously receive BRAF-targeted therapy
Dabrafenib/trametinib
M
Dabrafenib alone
W
Vemurafenib
W
Previously received chemotherapy, immunotherapy, and BRAF targeted therapy
Standard treatment based on non-driver mutation guideline
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Standard treatment based on non-driver mutation guideline
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Previously received or be
chemotherapy with or wit
Ca
T

Empfehlung (without Driver Alterations) [6]

Clinical Question	Recommendation	Type; Evidence Quality; Strength of Recommendation
New recommendations		
What is the most effective first-line therapy for patients with non-SCC and PD-L1 TPS 0%-49%, without known *EGFR*, *ALK*, or *ROS-1* alterations, and PS 0-1?	2.8. For patients with non-SCC, PD-L1 TPS 0%-49%, and PS 0-1, clinicians may offer cemiplimab plus chemotherapy	Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Weak
	2.9. For patients with non-SCC, PD-L1 TPS 0%-49%, and PS 0-1, clinicians may offer durvalumab and tremelimumab plus platinum-based chemotherapy	Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Weak
What is the most effective first-line therapy for patients with SCC and PD-L1 TPS 0%-49%, without known *EGFR*, *ALK*, or *ROS-1* alterations, and PS 0-1?	4.6. For patients with SCC, PD-L1 TPS 0%-49%, and PS 0-1, clinicians may offer cemiplimab plus chemotherapy	Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Weak
	4.7. For patients with SCC, PD-L1 TPS 0%-49%, and PS 0-1, clinicians may offer durvalumab and tremelimumab plus platinum-based chemotherapy	Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Weak

Clinical Question	Unchanged Recommendations	Type; Evidence Quality; Strength of Recommendation
Which patients with stage IV NSCLC should be treated with chemotherapy?	For patients with PS of 0 or 1 receiving chemotherapy a combination of two cytotoxic drugs is recommended. Platinum combinations are recommended over nonplatinum therapy; however, nonplatinum therapy combinations are recommended for patients who have contraindications to platinum therapy. Chemotherapy may also be used to treat selected patients with PS of 2 who desire aggressive treatment after a thorough discussion of the risks and benefits of such treatment	
	Because there is no cure for patients with stage IV NSCLC, early concomitant palliative care assistance has improved the survival and well-being of patients and is therefore recommended	—
What is the most effective first-line therapy for patients with non-SCC and high PD-L1 (TPS ≥ 50%) status, and PS 0-1?	For patients with high PD-L1/PD-1 expression (TPS ≥ 50%), in the absence of contraindications to immune checkpoint inhibitor therapies, non-SCC PS 0-1	—
	1.1. Clinicians should offer single-agent pembrolizumab	Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong
	1.2. Clinicians may offer pembrolizumab/carboplatin/pemetrexed	Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong
	1.3. Clinicians may offer atezolizumab/carboplatin/nab-paclitaxel/bevacizumab in the absence of contraindications to bevacizumab	Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate
	1.4. For patients with high PD-L1 expression (TPS ≥ 50%), non-SCC, and PS 0-1, clinicians may offer atezolizumab/carboplatin/nab-paclitaxel	Type: Evidence based; Evidence quality: Low; Strength of recommendation: Weak
	1.5. In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), non-SCC, and PS 0-1, clinicians may offer single-agent atezolizumab	Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Strong
	1.6. In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), non-SCC, and PS 0-1, clinicians may offer single-agent cemiplimab	Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Strong
	1.7. In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), non-SCC, and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy	Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Weak

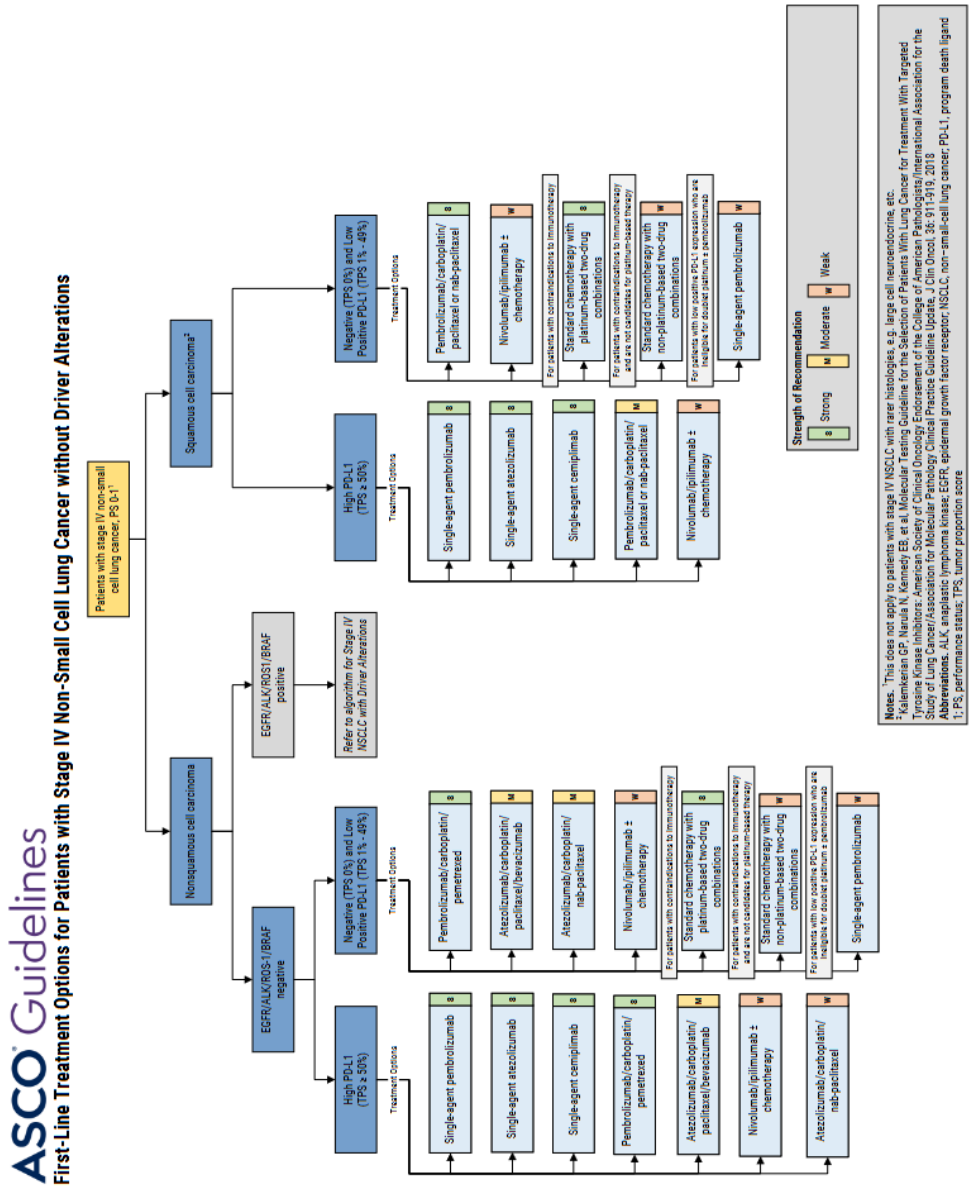
Clinical Question	Unchanged Recommendations	Type; Evidence Quality; Strength of Recommendation
What is the most effective first-line therapy for patients with stage IV NSCLC, non-SCC and no contraindications to bevacizumab?	7.1. For patients receiving carboplatin plus paclitaxel, the Update Committee recommends the addition of bevacizumab 15 mg/kg once every 3 weeks, except for patients with SCC histologic type, clinically significant hemoptysis, inadequate organ function, ECOG PS > 1, clinically significant cardiovascular disease, or medically uncontrolled hypertension. Bevacizumab may be continued, as tolerated, until disease progression (no change)	—
	7.2. Bevacizumab should not be added to pemetrexed plus carboplatin or given as maintenance with pemetrexed for patients who do not have contraindications to bevacizumab. Note that first line platinum chemotherapy alone without immunotherapy is not considered standard of care but may be considered in patients ineligible for immunotherapy	Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Weak
What is the most effective first-line therapy for patients with stage IV NSCLC with non-SCC, and negative or unknown PD-L1 status (TPS 0%-49%), and PS 0-1?	For patients with negative (<1% or unknown) and low positive (TPS 1%-49%) PD-L1 expression, non-SCC, PS 0-1, AND are eligible for chemotherapy and pembrolizumab	—
	2.1. Clinicians should offer pembrolizumab/carboplatin/pemetrexed	Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong
	2.2. Clinicians may offer atezolizumab/carboplatin/paclitaxel/bevacizumab in the absence of contraindications to bevacizumab	Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate
	2.3. Clinicians may offer atezolizumab/carboplatin/nab-paclitaxel	Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate
	2.4. (Patients who have the above characteristics) AND have contraindications to/declines immunotherapy, clinicians should offer standard chemotherapy with platinum-based two drug combinations as outlined in the 2015 update	Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong
	2.5. (Patients with above characteristics) AND have contraindications to/declines immunotherapy AND not deemed candidates for platinum-based therapy, clinicians should offer nonplatinum based two-drug therapy as outlined in the 2015 update	Type: Evidence based; Evidence quality: Low; Strength of recommendation: Weak
	2.6. For patients with low positive PD-L1 expression (TPS 1%-49%), non-SCC, PS 0-1, AND who are ineligible for or decline combination of doublet platinum ± pembrolizumab, clinicians may offer single-agent pembrolizumab	Type: Evidence based; Evidence quality: Low; Strength of recommendation: Weak
	2.7. In addition to 2020 options, for patients with negative (0%) and low positive PD-L1 expression (TPS 1%-49%), non-SCC, and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy	Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Weak
What is the most effective first-line therapy for patients with stage IV NSCLC with PS 2, non-SCC?	In the context of shared decision making, combination therapy, single-agent therapy, or palliative therapy alone may be used for patients in this population with PS of 2	Chemotherapy — Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Weak
		Palliative Care — Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Strong

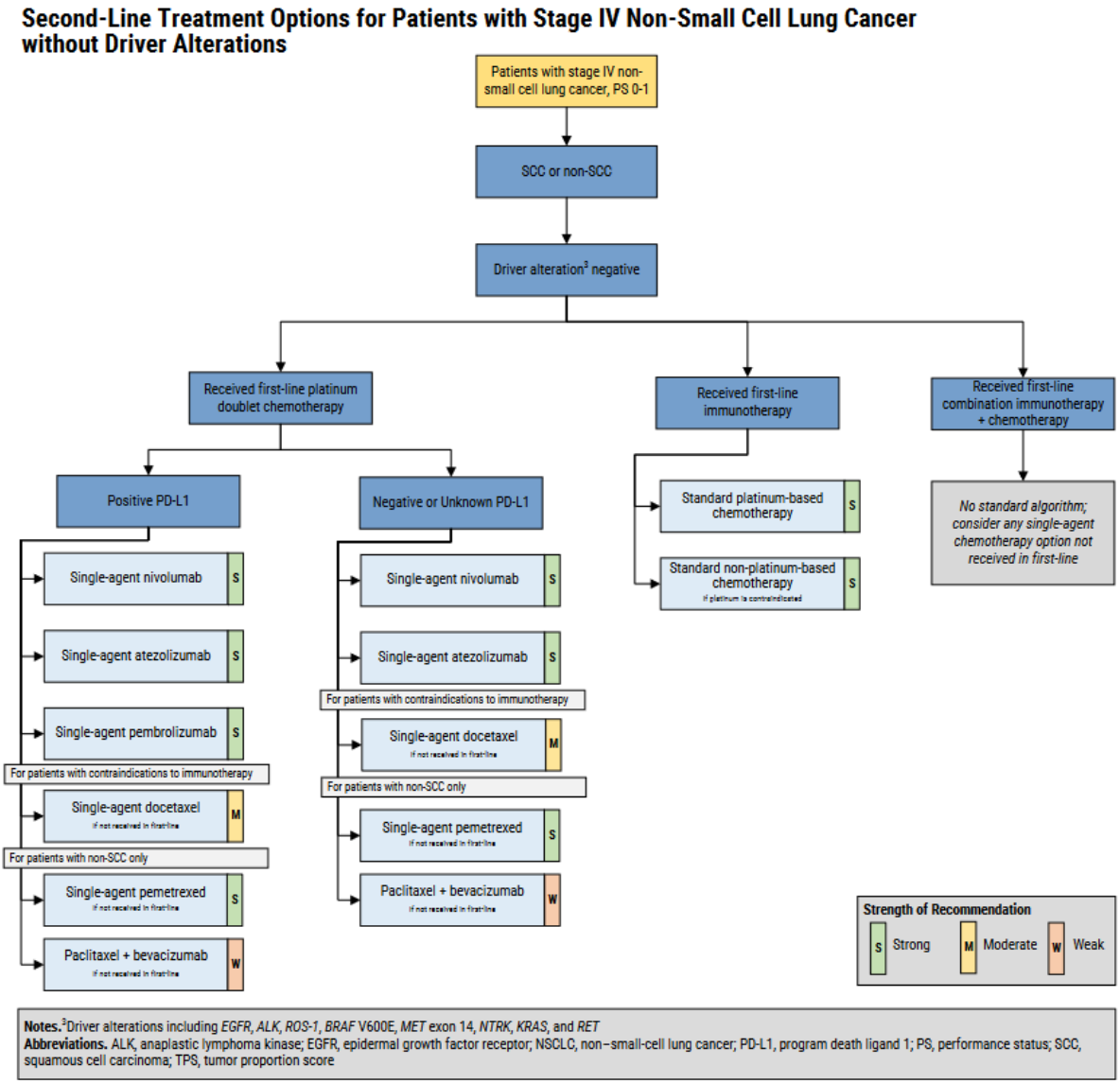
Clinical Question	Unchanged Recommendations	Type; Evidence Quality; Strength of Recommendation
What is the most effective first-line therapy for patients with stage IV NSCLC with SCC, and high PD-L1 status (TPS ≥ 50%), and PS 0-1?	For patients with high PD-L1 expression (TPS ≥ 50%) SCC, PS 0-1, in the absence of contraindications to immune checkpoint inhibitor therapy	—
	3.1. Clinicians should offer single-agent pembrolizumab	Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong
	3.2. Clinicians may offer pembrolizumab/carboplatin/(paclitaxel or nab-paclitaxel)	Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Moderate
	3.3. In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), SCC, and PS 0-1, clinicians may offer single-agent atezolizumab	Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Strong
	3.4. In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), SCC, and PS 0-1, clinicians may offer single-agent cemiplimab	Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Strong
	3.5. In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), SCC, and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy	Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Weak
What is the most effective first-line therapy for patients with stage IV NSCLC with SCC, and negative or unknown PD-L1 status (TPS 0%-49%), and PS 0-1?	For patients with negative (TPS 0%, < 1%, or unknown) and/or low positive (TPS 1%-49%) PD-L1 expression and SCC, in the absence of contraindications to immune checkpoint inhibitor therapies	—
	4.1. Clinicians should offer pembrolizumab/carboplatin/(paclitaxel or nab-paclitaxel)	Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Strong
	4.2. (For patients who have the above characteristics) AND with contraindications to immunotherapy, clinicians should offer standard chemotherapy with platinum-based two-drug combinations as outlined in the 2015 update	Type: Evidence based; Evidence quality: High; Strength of recommendation: Strong
	4.3. (For patients who have the above characteristics) AND with contraindications to immunotherapy AND not deemed candidates for platinum-based therapy, clinicians should offer standard chemotherapy with non-platinum-based two drug combinations as outlined in the 2015 update	Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Weak
	4.4. Patients with low positive PD-L1 (TPS 1%-49%) AND who are ineligible for or decline combination of doublet platinum/pembrolizumab AND have contraindications to doublet-chemotherapy, clinicians may offer single-agent pembrolizumab, in the absence of contraindications to immune checkpoint therapies	Type: Evidence based; Evidence quality: Low; Strength of recommendation: Weak
	4.5. In addition to 2020 recommendations 4.1-4.4, for patients with negative (TPS 0%) and low positive (TPS 1%-49%) PD-L1 expression, SCC, and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy	Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Weak
What is the most effective first-line therapy for patients with stage IV NSCLC, SCC, and PS 2?	In the context of shared decision making, combination chemotherapy, single-agent therapy, or palliative therapy alone may be used for patients with the characteristics described in Clinical Question A3a	Chemotherapy—Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Weak
		Palliative Care—Type: Evidence based; Evidence quality: Intermediate; Strength of recommendation: Strong

Clinical Question	Unchanged Recommendations	Type; Evidence Quality; Strength of Recommendation
What is the most effective therapy for patients with non-SCC who have received one prior chemotherapy regimen?	5.1. For patients with non-SCC who received an immune checkpoint inhibitor and chemotherapy as first-line therapy, clinicians may offer paclitaxel plus bevacizumab in the second-line setting	Type: Evidence based; Evidence quality: Low; Strength of recommendation: Weak
	The evidence does not support the selection of a specific second-line chemotherapy drug or combination based on age alone. This recommendation has not changed. Age alone is not a contraindication to chemotherapy for NSCLC	—
What is the most effective third-line therapy for patients with stage IV NSCLC and PS 0-1?	6.1. For the majority of patients with non-SCC, who received chemotherapy with or without bevacizumab and immune checkpoint inhibitor therapy (in either sequence), clinicians should offer the options of single-agent pemetrexed or docetaxel or paclitaxel plus bevacizumab in the third-line setting	Type: Evidence based; Evidence quality: Low; Strength of recommendation: Weak
Is there a role for cytotoxic therapy for patients who have received three prior regimens and good PS?	Data are not sufficient to make a recommendation for or against using cytotoxic drugs as fourth-line therapy; patients should consider experimental treatment, clinical trials, and continued best supportive (palliative) care	—

Abbreviations: ECOG, Eastern Cooperative Oncology Group; non-SCC, non-squamous cell carcinoma; NSCLC, non–small-cell lung cancer; PS, performance status; SCC, squamous cell carcinoma; TPS, tumor proportion score.

Behandlungsalgorithmen (without Driver Alterations)





Referenzen
51. My Cancer Genome: BRAF: https://www.mycancergenome.org/content/gene/braf
52. Nguyen-Ngoc T, Bouchaab H, Adjei AA, et al: BRAF alterations as therapeutic targets in non-small-cell lung cancer. J Thorac Oncol 10:1396-1403, 2015

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft (DKG), Deutsche Krebshilfe (DKH), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)), 2022 [2,3].

Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms, Langversion 2.0

Zielsetzung/Fragestellung

Ziele der vorliegenden S3-Leitlinie sind:

•Unterstützung von Ärzten, betroffenen Patienten und Bürgern mit einem erhöhten Risiko für ein Lungenkarzinom bei medizinischen Entscheidungen durch evidenzbasierte und formal konsentierte Empfehlungen

•Schaffung einer Grundlage für inhaltlich gezielte ärztliche Aus-, Fort- und Weiterbildungsmaßnahmen

•flächendeckende Umsetzung einer multidisziplinären, qualitätsgesicherten und sektorübergreifenden Versorgung des Lungenkarzinoms

•Optimierung der Diagnosekette und der stadiengerechten Therapie sowohl bei der Ersterkrankung als auch beim Rezidiv bzw. bei einer Metastasierung

Durch die Umsetzung dieser Ziele soll mittel- und langfristig die Mortalität der Patienten mit Lungenkarzinomen gesenkt und die Lebensqualität erhöht werden.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Für das Stadium III erfolgte eine Systematische Suche im Zeitraum September bis November 2020 in zwei elektronischen Datenbanken (Medline (Ovid), CENTRAL) nach geeigneten randomisierten kontrollierten Studien (RCTs), systematischen Übersichten und Metaanalysen
- Für Stadium IV erfolgte eine systematische Suche am 1.12.2020 in Pubmed, Cochrane; weiterhin wurde für Stadium IV nach Nutzenbewertungen des G-BA gesucht

LoE

- Oxford Centre for Evidence-based Medicine in der Version von 2009

GoR

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll
B	Empfehlung	sollte
C	Empfehlung offen	kann

8.6.Stadium IV (ohne Indikation zur Lokaltherapie)

8.6.9 Systemtherapie bei Patienten mit BRAF-V600-Mutation

8.126	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **B**	NSCLC IV- Patienten mit nachgewiesener BRAF-V600-Mutation sollte eine Kombination aus Dabrafenib und Trametinib angeboten werden. Nicht-V600 Mutations+ NSCLC Patienten sollten in einem Thorax-Onkologischen Tumorboard besprochen werden.	
Level of Evidence **2b**	[1171], [1172], [1173]	
	Starker Konsens	

Hintergrund

Bei ungefähr 2 bis 4 % der NSCLC-Patienten liegt eine Mutation der BRAF-Kinase vor. In wiederum 1 bis 2 % dieser Patienten lässt sich eine BRAF-V600-Mutation nachweisen. Damit geht eine Aktivierung des entsprechenden Signalweges daher, welches wiederum Voraussetzung ist, dass eine antitumoröse Behandlung mit einem BRAF- und einem MEK-Inhibitor erfolgsversprechend ist.

BRAF und MEK sind Bestandteile der RAS-RAF-MEK-ERK-Signalkette, welche zu dem MAP-Kinase-Signalweg gehört. Dabrafenib hemmt selektiv die BRAF-Kinase, während Trametinib die im Signalweg nachgeschalteten Mitogen-aktivierten Kinasen 1 und 2 (MEK1 und MEK2) inhibiert.

Bislang war die Kombination aus Dabrafenib und Trametinib bei Patienten mit nicht resezierbarem oder metastasiertem Melanom mit einer BRAF-V600-Mutation zugelassen. Im April 2017 hat die Europäische Kommission die Kombination aus Dabrafenib und Trametinib für Patienten mit fortgeschrittenem NSCLC mit einer BRAF-V600-Mutation zugelassen.

In einer retrospektiven europäischen Kohortenstudie von n=35 Patienten mit fortgeschrittenem BRAF-positivem NSCLC (83 % V600E, 17 % andere Mutationen) zeigte sich bei Behandlung mit verschiedenen BRAF-Inhibitoren (Vemurafenib 29x, Dabrafenib 9x, Sorafenib 1x), die in der Erstlinie (14 %) oder im Rezidiv (86 %) eingesetzt wurden, eine Ansprechrate (ORR) von 53 % (95% CI: 35-70) und eine Krankheitskontrollrate (DCR) von 85 % (95% CI: 69-95 %). Im Falle von BRAF-V600E betrug das PFS 9.3 Monate, und das mediane Gesamtüberleben (OS) 25,3 Monate [1172]

In einer prospektiven Phase-II-Basket-Studie wurden 20 Patienten (davon 95 % vorbehandelt) mit fortgeschrittenem BRAF-V600 positivem NSCLC (90 % V600E) mit dem BRAF Inhibitor Vemurafenib behandelt. Die Ansprechrate war 42 % (95 % CI: 20-67), das mediane PFS 7.3 Monate (95% CI: 3,5-10,8 Mo) [1173].

Daten der Zulassungsstudie

In der für die Zulassungs maßgeblichen Studie wurden die Daten von insgesamt 135 Patienten mit fortgeschrittenem Lungenkarzinom und einer BRAF-V600-Mutation ausgewertet. Die Studie beinhaltete zwei Studienarme: in dem einem Arm erhielten n=78 Patienten Dabrafenib, in dem anderen Arm erhielten n=57 Patienten eine Kombination aus Dabrafenib und Trametinib.

In der Monotherapiestudie mit Dabrafenib betrug die Ansprechrate 33 % (95% CI: 23-45 %) bei n=26 von 78 vorbehandelten mit BRAF V600E positivem rezidiviertem NSCLC [1174] Das PFS betrug 5,5 Mo (95 %CI: 3,4 – 7,3 Mo), die mediane Überlebenszeit (OS) betrug 12,7 Mo (95% CI: 7,3 – 16,9 Mo). Schwerwiegend unerwünschte Wirkungen (UAW) traten bei 42 % der Patienten auf. An Grad >3 UAW sind zu nennen: kutanes Plattenepithelkarzinom (12 %), Asthenie (5 %) und Basalzellkarzinom (5 %).

Für den Vergleich zu einer zytostatischen Zweitlinienchemotherapie bei BRAF-mutiertem NSCLC-Patienten steht eine historische Kohorten zur Verfügung: bei 59 Patienten zeigte sich eine Ansprechrate von 9 % und ein medianes PFS von 3,1 Mo (95% CI 1,4- 6,1 Mo) [1175].

In dem anderen Studienarm wurde die Kombination aus dem BRAF-Inhibitor Dabrafenib (150 mg zweimal täglich) und dem MEK-Inhibitor Trametinib (2 mg einmal täglich) bei vorbehandelten BRAF-V600E positiven NSCLC Patienten eingesetzt. Die Ansprechrate (=primärer Endpunkt) betrug 63,2 % (95 % CI: 49,3-75,6 %; 36/57 Patienten). Das PFS betrug 9,7 Monate (95 % CI: 6,9-19,6 Mo). Eine Angabe zum Gesamtüberleben war noch nicht möglich, wobei nach 6 Monaten 82 % der Patienten lebten [1176].Schwerwiegend UAW wurden bei 57 % der Patienten beobachtet. An Grad >3 UAW traten auf: Neutropenie (9 %), Hyponatriämie (7 %), Anämie (5 %). Plattenepithelkarzinome der Haut traten bei 2 Patienten (4 %) auf. Ein Patient starb an einer intrakraniellen Blutung.

Diese Studien verdeutlichen, dass

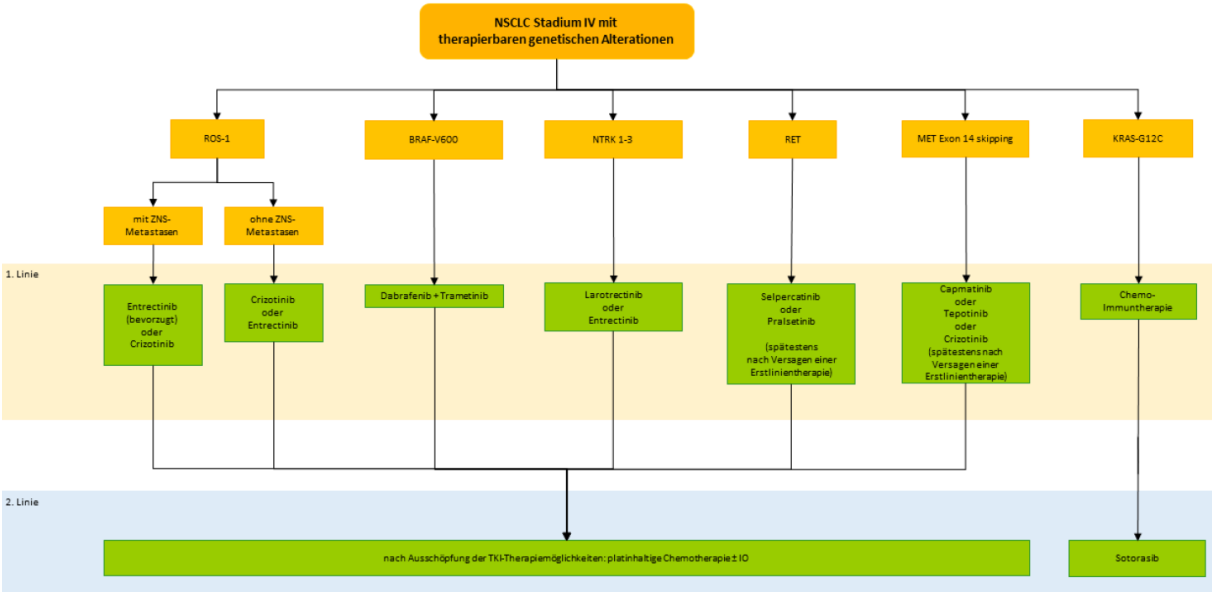
• die zielgerichtete Systemtherapie bei BRAF-Mutation an Wirksamkeit der zytostatischen Chemotherapie deutlich überlegen sein könnte (direkter Vergleich fehlt)

• die duale MAPK-Pathway Blockade (MAPK=Mitogen-Activated Protein Kinase) mit Dabrafenib und Trametinib bezogen auf Ansprechraten undprogressionfreies Überleben wirksamer ist als die Monotherapie mit Dabrafenib
• die Verträglichkeit einer Kombinationstherapie deutlich besser ist als die einer Monotherapie mit Dabrafenib
• die Kombination Dabrafenib und Trametinib aufgrund ihrer Wirksamkeit eine wichtige Therapieoption bei BRAF-V600E-positivem NSCLC darstellt.

Die Ergebnisse zur Wirksamkeit von Dabrafenib/Trametinib in der Erstlinientherapie des BRAF-V600E-positiven NSCLC wurden 2017 publiziert [1171]. Bei 36 therapienaiven Patienten war die (investigator-assessed) ORR mit 64% (95% CI 46-79), darunter 6% Komplettremissionen, nahezu identisch mit der Effektivität in der Zulassungsstudie bei vorbehandelten Patienten.

Entsprechend der Zulassung kann die Kombination aus Dabrafenib und Trametinib linienunabhängig eingesetzt werden, d.h. die Kombination kann sowohl im Rahmen einer Erstlinien- oder z.B. Zweitliniensystemtherapie zur Anwendung kommen.

Flowchart NSCLC IV mit therapierbaren Treibermutationen - ROS, BRAF, NTRK, RET, MET, KRAS



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8.55	Konsensbasierte Empfehlung	modifiziert 2022
EK	Patienten im Stadium IIIA4 / IIIB und IIIC sollen in der Regel– wenn Allgemeinzustand und Tumorausdehnung dies zulassen – eine Kombination aus Strahlentherapie und Chemotherapie erhalten.Die Chemotherapie soll bei definitiver Radiochemotherapie simultan und nur bei medizinischer Kontraindikation allein sequentiell durchgeführt werden.	
	Starker Konsens	

8.64	Evidenzbasierte Empfehlung	neu 2022
Empfehlungsgrad 0	Patienten im Stadium III, die nach Entscheidung im Thorax-Onkologischen Tumorboard, nicht für eine Operation oder Radio-Chemotherapie geeignet sind und eine PD-L1 Expression ≥ 50 % aufweisen, kann eine Therapie mit dem PD-1-Antikörper Cemiplimab angeboten werden	
Level of Evidence 2	[938]	
	Konsens	

8.6.2.1 Patienten mit Plattenepithelkarzinom mit PD-L1-Expression von ≥ 50 % und ECOG 0-1

8.71	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad A	Bei Patienten im Stadium IV mit Plattenepithelkarzinom, welche keine therapierbaren Mutationen (z. B. EGFR, EML4-ALK, ROS1) aufweisen, und welche in Gewebeproben eine PD-L1-Expression von ≥ 50 % der Tumorzellen oder >10% auf Immunzellen aufweisen, soll: • eine Monotherapie mit Atezolizumab (≥ 50% der Tumorzellen oder 10% der tumorinfiltrierenden Lymphozyten), Cemiplimab (≥ 50% der Tumorzellen) oder Pembrolizumab (≥ 50% der Tumorzellen) oder • Pembrolizumab mit Chemotherapie oder Nivolumab und Ipilimumab mit Chemotherapie als Erstlinientherapie angeboten werden.	
Level of Evidence 1b	[944], [945], [946], [947], [948]	
	Starker Konsens	

8.6.2.2 Patienten mit Plattenepithelkarzinom mit einer PD-L1-Expression von < 50 % und ECOG 0-1

8.72	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **A**	Bei Patienten im Stadium IV mit Plattenepithelkarzinom und PD-L1 Expression < 50% sowie einem guten Allgemeinzustand (ECOG 0-1) soll eine Chemo-Immuntherapie angeboten werden, z.B. eine platinbasierte Kombinationschemotherapie mit Taxan kombiniert mit Pembrolizumab oder eine Therapie mit platinbasierter Chemotherapie und Nivolumab/Ipilimumab.	
Level of Evidence **1b**	[944], [801], [950]	
	Starker Konsens	

8.73	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **A**	Bei Patienten im Stadium IV mit Plattenepithelkarzinom in gutem Allgemeinzustand (ECOG 0-1) und Kontraindikationen gegen eine Immuntherapie soll eine platinbasierte Kombinationschemotherapie angeboten werden.	
Level of Evidence **1**	[951], [791], [952], [953], [954], [955], [956], [957], [958], [959]	
	Starker Konsens	

8.6.2.3 Patienten mit Plattenepithelkarzinom mit einer PD-L1-Expression von ≥ 50 % und ECOG 2

8.74	Konsensbasierte Empfehlung	neu 2022
EK	Bei Patienten im Stadium IV mit Plattenepithelkarzinom und ECOG 2, welche in Gewebeproben eine PD-L1-Expression von ≥ 50 % der Tumorzellen oder >10% auf Immunzellen aufweisen, sollte eine Monotherapie mit • Atezolizumab (≥ 50% der Tumorzellen oder 10% der tumorinfiltrierenden Lymphozyten), Cemiplimab (≥ 50% der Tumorzellen) oder Pembrolizumab (≥ 50% der Tumorzellen)	
	Starker Konsens	

8.75	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **A**	Bei Patienten mit ECOG 2 ohne wesentliche Komorbiditäten sollen platinbasierte Kombinationen, z. B. Carboplatin/Paclitaxel angeboten werden.	
Level of Evidence **1a**	[962]	
	Starker Konsens	

8.76	Konsensbasierte Empfehlung	geprüft 2022
EK	Bei Patienten mit ECOG 2 mit Komorbiditäten, bei denen die Komorbiditäten eine platinhaltige Kombinationstherapie nicht erlauben, kann eine Monotherapie angeboten werden.	
	Starker Konsens	

8.77	Konsensbasierte Empfehlung	modifiziert 2022
EK	Patienten mit Stadium IV NSCLC ECOG 2 können Immuntherapie bzw. Chemotherapie zusätzlich zu „Best Supportive Care“ angeboten werden.	
	Starker Konsens	

8.6.3 Systemtherapie (Erstlinie) bei Patienten mit Nicht-Plattenepithelkarzinom ohne therapierbare genetische Alterationen

8.78	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **A**	Bei NSCLC-Patienten mit nicht-plattenepithelialer Histologie im UICC Stadium IV sowie ECOG 0-1, welche keine therapierbaren Mutationen und keine Kontraindikation gegenüber Checkpoint-Inhibitoren aufweisen, soll, unabhängig vom PD-L1 Status, in der Erstlinientherapie eine Immuntherapie angeboten werden. In der Regel erfolgt diese als Chemo-Immuntherapie: • Cisplatin/Carboplatin + Pemetrexed + Pembrolizumab, alle 3 Wochen über 4 Zyklen, gefolgt von einer Erhaltungstherapie mit Pemetrexed und Pembrolizumab • Carboplatin + Paclitaxel + Bevacizumab + Atezolizumab, alle 3 Wochen über 4-6 Zyklen, gefolgt von einer Erhaltungstherapie mit Bevacizumab und Atezolizumab • Carboplatin + nab-Paclitaxel + Atezolizumab alle 3 Wochen über 4 Zyklen, gefolgt von einer Erhaltungstherapie mit Atezolizumab • platinbasierte Chemotherapie + Nivolumab + Ipilimumab über 2 Zyklen, gefolgt von einer Erhaltungstherapie mit Nivolumab +I pilimumab über 2 Jahre.	
Level of Evidence **1a**	[653], [984], [944], [802], [985], [946], [986], [987], [988], [989], [990], [947], [948]	
	Starker Konsens	

8.79	Evidenzbasierte Empfehlung	neu 2022
Empfehlungsgrad **A**	Bei Patienten im Stadium IV mit Nicht-Plattenepithelkarzinom, welche keine therapierbaren Mutationen (z. B. EGFR, EML4-ALK, ROS1) aufweisen, und welche in Gewebeproben eine PD-L1-Expression von ≥ 50 % der Tumorzellen oder >10% auf Immunzellen aufweisen, soll eine Monotherapie mit • Atezolizumab (≥ 50% der Tumorzellen oder 10% der tumorinfiltrierenden Lymphozyten), • Cemiplimab (≥ 50% der Tumorzellen) oder • Pembrolizumab (≥ 50% der Tumorzellen) als Erstlinientherapie angeboten werden, sofern nicht patienten- oder tumorbezogene Gründe für eine Kombinationsbehandlung sprechen.	
Level of Evidence **1**	[944], [945], [946]	
	Konsens	

8.80	Konsensbasierte Empfehlung	modifiziert 2022
EK	In aller Regel sollte nach 2 Zyklen (6 Wochen), spätestens aber nach 3 Zyklen (9 Wochen) eine radiologische Verlaufskontrolle erfolgen.	
	Starker Konsens	

8.81	Evidenzbasierte Empfehlung	neu 2022
Empfehlungsgrad A	Bei radiologischem Ansprechen oder Stabilisierung und entsprechender Verträglichkeit soll nach studienanaloger Zyklenzahl der platinhaltigen Chemo-/Immuntherapie eine Erhaltungstherapie erfolgen.	
Level of Evidence 1a	[653], [984], [944], [802], [985], [800], [946], [986], [988], [990], [991], [947], [948]	
	Starker Konsens	

8.82	Konsensbasierte Empfehlung	neu 2022
EK	Die Gesamtdauer der Chemo-ICI-Therapie bzw. der ICI-Monotherapie ist derzeit noch nicht hinreichend geklärt. Die Checkpointinhibitoren Pembrolizumab und Cemiplimab wurden in den zulassungsrelevanten Studien über zwei Jahre verabreicht. Eine Fortsetzung der Therapie über dieses Intervall hinaus kann bei weiter bestehender Tumorkontrolle und Verträglichkeit dem Patienten angeboten werden. Für Atezolizumab wurde in der Zulassungsstudie keine Begrenzung der Therapiedauer festgelegt.	
	Starker Konsens	

8.83	Konsensbasierte Empfehlung	neu 2022
EK	Patienten mit besonderen Risikofaktoren für eine ICI basierte Therapie Patienten mit Autoimmunerkrankungen und gutem Allgemeinzustand (ECOG 0-1) kann eine ICI (Kombinations-) Therapie angeboten werden, wenn die Autoimmunerkrankung nicht lebensbedrohlich und nicht aktiv ist. Ein engmaschiges Monitoring ist in solchen Fällen besonders notwendig. Patienten mit kontrollierter Hepatitis B oder C oder einer kontrollierten HIV-Erkrankung und gutem Allgemeinzustand (ECOG 0-1) kann eine ICI (Kombinations-) Therapie angeboten werden. Ein engmaschiges Monitoring ist in solchen Fällen besonders notwendig.	
	Konsens	

8.84	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **A**	Patienten mit einem NSCLC im UICC Stadium IV und mit nichtplattenepithelialer Histologie, die für eine Therapie mit Checkpoint-Inhibitoren nicht geeignet sind und einen guten Allgemeinzustand aufweisen (ECOG 0-1) sollen 4-6 Zyklen einer platinbasierten Kombinationschemotherapie erhalten. Folgende Schemata werden empfohlen: • Cisplatin/Carboplatin+Pemetrexed über 4 Zyklen, gefolgt von einer Erhaltungstherapie mit Pemetrexed, • Carboplatin+Paclitaxel+Bevacizumab über 4-6 Zyklen, gefolgt von einer Erhaltungstherapie mit Bevacizumab bei geeigneten Patienten, • Carboplatin + nab-Paclitaxel, • Cisplatin/Carboplatin + Paclitaxel, • Cisplatin/Carboplatin + Vinorelbine, • Cisplatin/Carboplatin + Docetaxel, • Cisplatin/Carboplatin + Gemcitabin.	
Level of Evidence **1b**	[599], [672], [673], [674], [675], [676], [992], [993], [994], [995], [996], [681], [684], [686], [997], [998], [942], [999], [1000], [1001], [1002], [964], [965], [966], [967], [968], [969], [970]	
	Starker Konsens	

8.85	Konsensbasierte Empfehlung	neu 2022
EK	Bei Patienten im Stadium IV mit Nicht-Plattenepithelkarzinom und ECOG 2, welche in Gewebeproben eine PD-L1-Expression von ≥ 50 % der Tumorzellen oder >10% auf Immunzellen aufweisen, sollte eine Monotherapie mit • Atezolizumab (≥ 50% der Tumorzellen oder 10% der tumorinfiltrierenden Lymphozyten), • Cemiplimab (≥ 50% der Tumorzellen) oder • Pembrolizumab (≥ 50% der Tumorzellen) als Erstlinientherapie angeboten werden.	
	Starker Konsens	

National Institute for Health and Care Excellence (NICE), 2019 [4].

Lung cancer: diagnosis and management

Zielsetzung/Fragestellung

This guideline covers diagnosing and managing non-small-cell and small-cell lung cancer. It aims to improve outcomes for patients by ensuring that the most effective tests and treatments are used, and that people have access to suitable palliative care and follow-up.

Methodik

Grundlage der Leitlinie

Update (This guideline replaces CG121, and is the basis of QS17).

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;

- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig. Die Verbindung zu der zugrundeliegenden Evidenz ist nur durch die Verlinkung mit den jeweiligen Technology Appraisals dargestellt;
- Aktualisierung der letzten Jahre über Integration von NICE Technology Appraisals

Recherche/Suchzeitraum:

- NICE initially produced guidance on the diagnosis and treatment of lung cancer in February 2005, which was substantially updated and replaced in 2011 and has since been partially updated in March 2019. However pleural interventions were not included in either update, and so the recommendations below on pleural effusion date back to development of the original guideline in February 2005.
- The searches were conducted between October 2017 and April 2018 for 9 review questions (RQ).
- Searches were re-run in May 2018.

In March 2019, we reviewed the evidence and made new recommendations on:

- intrathoracic lymph node assessment
- brain imaging for people with non-small-cell lung cancer
- radical radiotherapy (including stereotactic ablative radiotherapy [SABR]) for people with non-small-cell lung cancer
- chemoradiotherapy and surgery for people with stage IIIA-N2 non-small-cell lung cancer
- thoracic radiotherapy and prophylactic cranial irradiation for people with small-cell lung cancer

We checked this guideline in June 2019. We found no new evidence that affects the recommendations in this guideline.

September 2022:

We have produced treatment pathways bringing together NICE recommended treatment options from this guideline and relevant technology appraisal guidance on advanced non-small-cell lung cancer (squamous and non-squamous). The treatment pathways cover the recommended treatment options at each decision point.

July 2023 (Last updated: 26 July 2023):

In July 2023, we added to and updated the systemic anti-cancer therapy treatment pathways for advanced non-small-cell lung cancer.

LoE

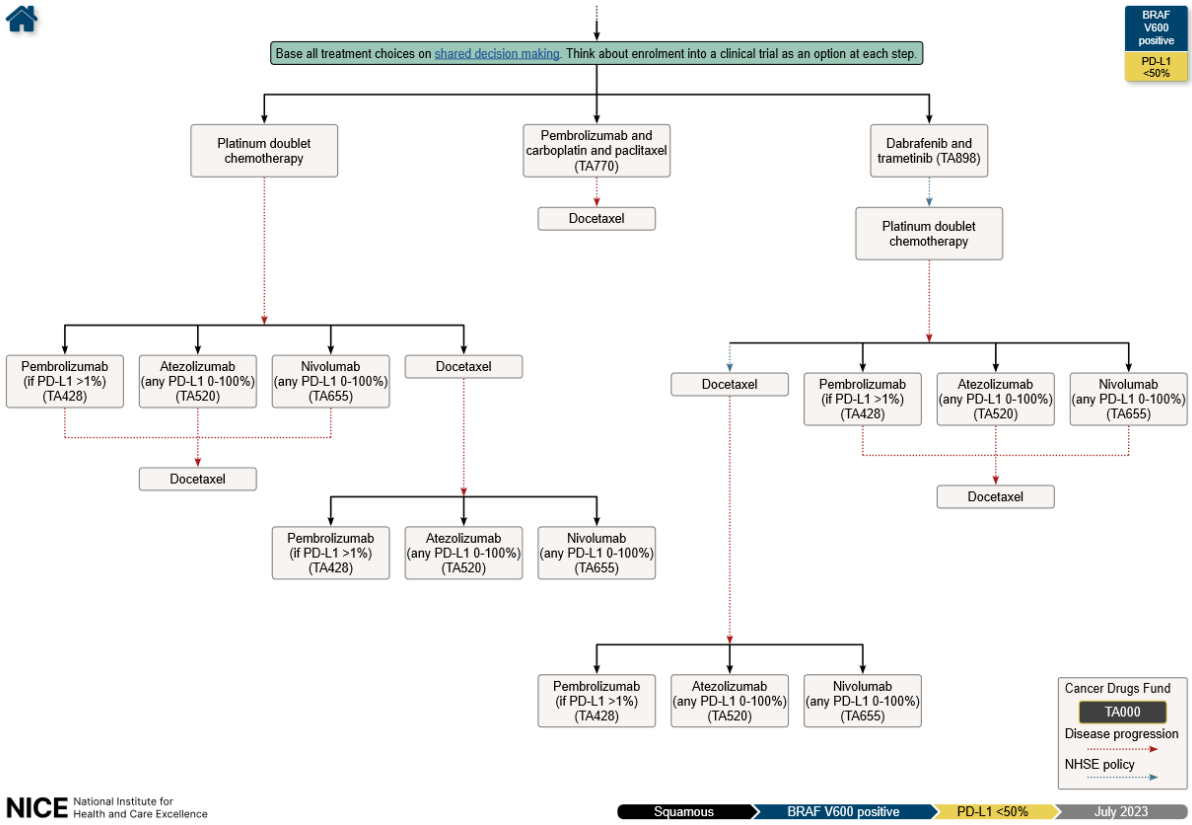
- trifft nicht zu

GoR

- To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations.

Empfehlungen

Squamous non-small cell lung cancer, BRAF V600 positive, PD L1 below 50%



Initial recommended treatment options are:

- platinum doublet chemotherapy or
- the NICE technology appraisal guidance on pembrolizumab with carboplatin and paclitaxel or
- the NICE technology appraisal guidance on dabrafenib and trametinib.

For people who have disease progression after initial treatment with platinum doublet chemotherapy, recommended treatment options are:

- the NICE technology appraisal guidance on pembrolizumab (if PD-L1 above 1%) or
- the NICE technology appraisal guidance on atezolizumab (any PD-L1 0% to 100%) or
- the NICE technology appraisal guidance on nivolumab (any PD-L1 0% to 100%) or
- docetaxel.

For people who have had initial treatment with platinum doublet chemotherapy and who have disease progression after treatment in line with the NICE technology appraisal guidance on pembrolizumab, atezolizumab or nivolumab, the only recommended treatment option is docetaxel.

For people who have had initial treatment with platinum doublet chemotherapy and who have disease progression after treatment with docetaxel, recommended treatment options are:

- the NICE technology appraisal guidance on pembrolizumab (if PD-L1 above 1%) or
- the NICE technology appraisal guidance on atezolizumab (any PD-L1 0% to 100%) or
- the NICE technology appraisal guidance on nivolumab (any PD-L1 0% to 100%).

- For people who have disease progression after initial treatment in line with the NICE technology appraisal guidance on pembrolizumab with carboplatin and paclitaxel, the only recommended treatment option is docetaxel.

For people who have disease progression after initial treatment in line with the NICE technology appraisal guidance on dabrafenib and trametinib, the only recommended treatment option is platinum doublet chemotherapy (NHS England policy).

For people who have had initial treatment in line with the NICE technology appraisal guidance on dabrafenib and trametinib and who have disease progression after treatment with platinum doublet chemotherapy, recommended treatment options are:

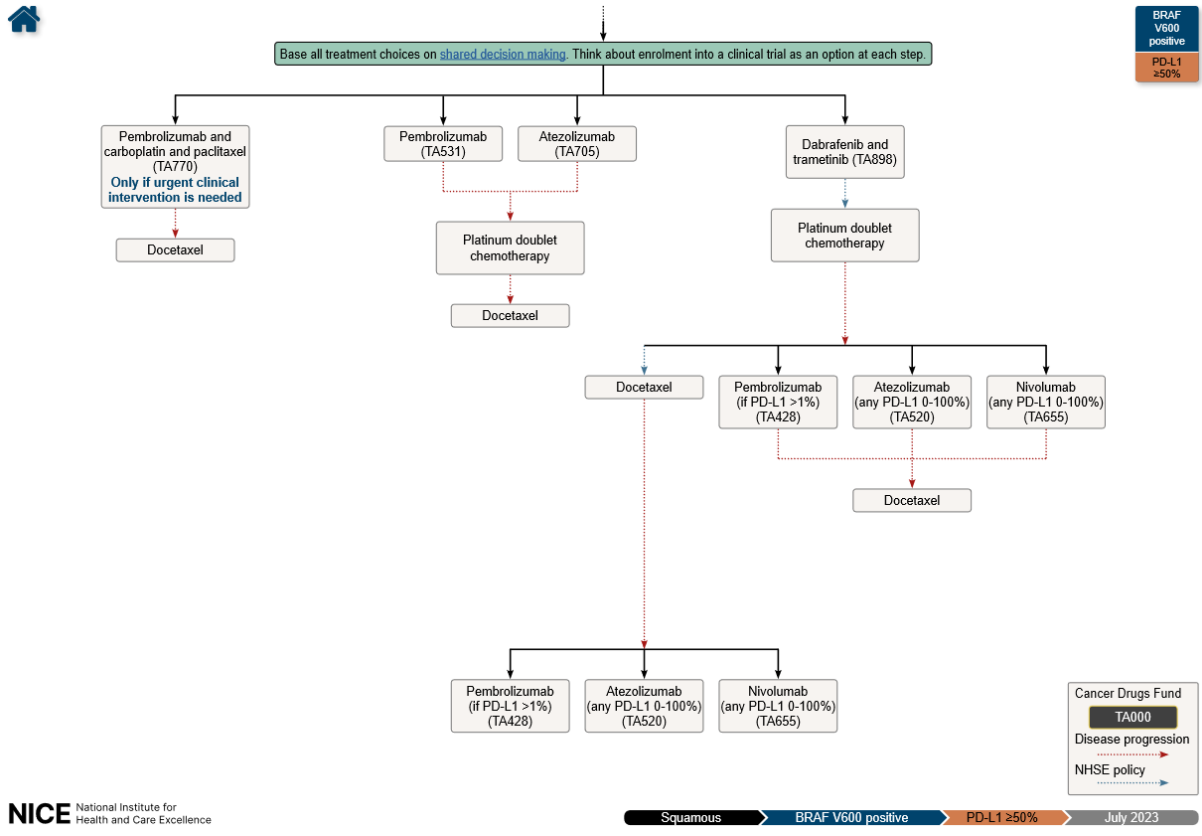
- docetaxel (NHS England policy) or
- the NICE technology appraisal guidance on pembrolizumab (if PD-L1 above 1%) or
- the NICE technology appraisal guidance on atezolizumab (any PD-L1 0% to 100%) or
- the NICE technology appraisal guidance on nivolumab (any PD-L1 0% to 100%).

For people who have had treatment with platinum doublet chemotherapy and who have disease progression after follow-up treatment with docetaxel, recommended treatment options are:

- the NICE technology appraisal guidance on pembrolizumab (if PD-L1 above 1%) or
- the NICE technology appraisal guidance on atezolizumab (any PD-L1 0% to 100%) or
- the NICE technology appraisal guidance on nivolumab (any PD-L1 0% to 100%).

For people who have had treatment with platinum doublet chemotherapy and who have disease progression after follow-up treatment in line with the NICE technology appraisal guidance on pembrolizumab, atezolizumab or nivolumab, the only recommended treatment option is docetaxel.

<u>Squamous non-small cell lung cancer, BRAF V600 positive, PD L1 50% or higher</u>



Initial recommended treatment options are:

- the NICE technology appraisal guidance on pembrolizumab with carboplatin and paclitaxel (only if urgent clinical intervention is needed) or
- the NICE technology appraisal guidance on pembrolizumab or
- the NICE technology appraisal guidance on atezolizumab or
- the NICE technology appraisal guidance on dabrafenib and trametinib.

For people who have disease progression after initial treatment in line with the NICE technology appraisal guidance on pembrolizumab with carboplatin and paclitaxel, the only recommended treatment option is docetaxel.

For people who have disease progression after initial treatment in line with the NICE technology appraisal guidance on pembrolizumab or atezolizumab, the only recommended treatment option is platinum doublet chemotherapy.

For people who have had initial treatment in line with the NICE technology appraisal guidance on pembrolizumab or atezolizumab and who have disease progression after treatment with platinum doublet chemotherapy, the only recommended treatment option is docetaxel.

For people who have disease progression after initial treatment in line with the NICE technology appraisal guidance on dabrafenib and trametinib, the only recommended treatment option is platinum doublet chemotherapy (NHS England policy).

For people who have had initial treatment in line with the NICE technology appraisal guidance on dabrafenib and trametinib and who have disease progression after treatment with platinum doublet chemotherapy, recommended treatment options are:

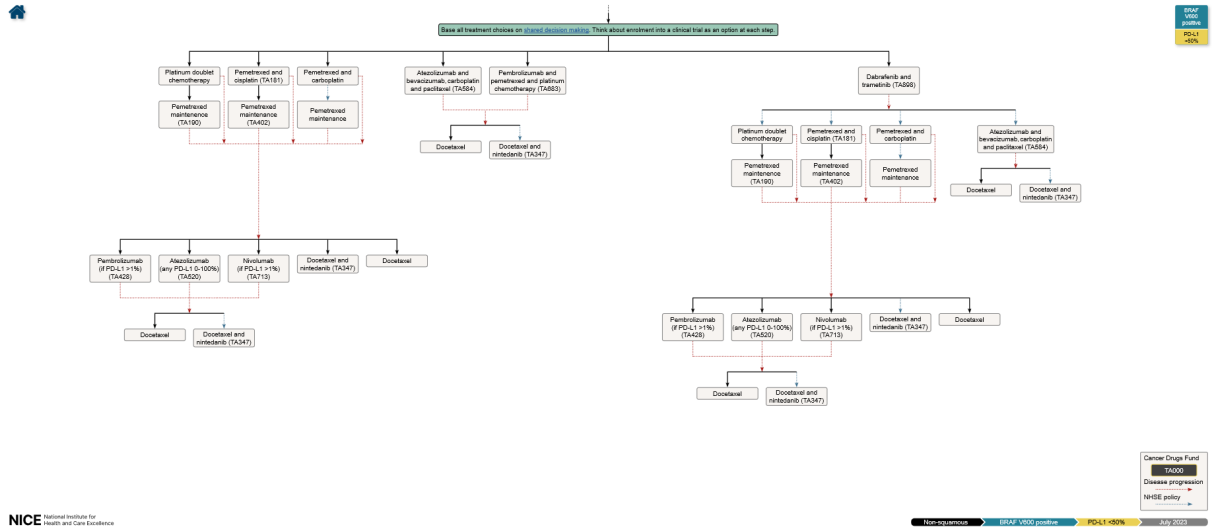
- docetaxel (NHS England policy) or
- the NICE technology appraisal guidance on pembrolizumab (if PD-L1 above 1%) or
- the NICE technology appraisal guidance on atezolizumab (any PD-L1 0% to 100%) or
- the NICE technology appraisal guidance on nivolumab (any PD-L1 0% to 100%).

For people who have had treatment with platinum doublet chemotherapy and who have disease progression after follow-up treatment with docetaxel, recommended treatment options are:

- the NICE technology appraisal guidance on pembrolizumab (if PD-L1 above 1%) or
- the NICE technology appraisal guidance on atezolizumab (any PD-L1 0% to 100%) or
- the NICE technology appraisal guidance on nivolumab (any PD-L1 0% to 100%).

For people who have had treatment with platinum doublet chemotherapy and who have disease progression after follow-up treatment in line with the NICE technology appraisal guidance on pembrolizumab, atezolizumab or nivolumab, the only recommended treatment option is docetaxel.

Non-squamous non-small cell lung cancer, BRAF V600 positive, PD L1 below 50%



Initial recommended treatment options are:

- platinum doublet chemotherapy or
- the NICE technology appraisal guidance on pemetrexed and cisplatin or
- pemetrexed and carboplatin or
- the NICE technology appraisal guidance on atezolizumab and bevacizumab, carboplatin and paclitaxel or
- the NICE technology appraisal guidance on pembrolizumab and pemetrexed and platinum chemotherapy or
- the NICE technology appraisal guidance on dabrafenib and trametinib.

For maintenance treatment for people who have had initial treatment with platinum doublet chemotherapy, the only recommended treatment option is the NICE technology appraisal guidance on pemetrexed maintenance.

For maintenance treatment for people who have had initial treatment in line with the NICE technology appraisal guidance on pemetrexed and cisplatin, the only recommended treatment option is the NICE technology appraisal guidance on pemetrexed maintenance.

Pemetrexed maintenance is a recommended maintenance treatment option for people who have had initial treatment with pemetrexed and carboplatin (NHS England policy).

For people who have disease progression after initial treatment with platinum doublet chemotherapy, the NICE technology appraisal guidance on pemetrexed and cisplatin, pemetrexed and carboplatin, or who have had pemetrexed maintenance, recommended treatment options are:

- the NICE technology appraisal guidance on pembrolizumab (if PD L1 above 1%) or
- the NICE technology appraisal guidance on atezolizumab (any PD-L1 0% to 100%) or
- the NICE technology appraisal guidance on nivolumab (if PD-L1 above 1%) or
- the NICE technology appraisal guidance on docetaxel and nintedanib or
- docetaxel.

For people who have disease progression after follow-up treatment in line with the NICE technology appraisal guidance on pembrolizumab, atezolizumab or nivolumab, recommended treatment options are:

- docetaxel or

- the NICE technology appraisal guidance on docetaxel and nintedanib (NHS England policy).

For people who have disease progression after initial treatment in line with the NICE technology appraisal guidance on atezolizumab and bevacizumab, carboplatin and paclitaxel or pembrolizumab and pemetrexed and platinum chemotherapy, recommended treatment options are:

- docetaxel or
- the NICE technology appraisal guidance on docetaxel and nintedanib (NHS England policy).

For people who have disease progression after initial treatment in line with the NICE technology appraisal guidance on dabrafenib and trametinib, recommended treatment options (NHS England policy) are:

- platinum doublet chemotherapy or
- the NICE technology appraisal guidance on pemetrexed and cisplatin or
- pemetrexed and carboplatin or
- the NICE technology appraisal guidance on atezolizumab and bevacizumab, carboplatin and paclitaxel.

For maintenance treatment for people who have had treatment with platinum doublet chemotherapy, the only recommended treatment option is the NICE technology appraisal guidance on pemetrexed maintenance.

For maintenance treatment for people who have had treatment in line with the NICE technology appraisal guidance on pemetrexed and cisplatin, the only recommended treatment option is the NICE technology appraisal guidance on pemetrexed maintenance.

Pemetrexed maintenance is a recommended maintenance treatment option for people who have had treatment with pemetrexed and carboplatin (NHS England policy).

For people who have had initial treatment in line with the NICE technology appraisal guidance on dabrafenib and trametinib and who have disease progression after treatment with platinum doublet chemotherapy, the NICE technology appraisal guidance on pemetrexed and cisplatin, pemetrexed and carboplatin, or who have had pemetrexed maintenance, recommended treatment options are:

- the NICE technology appraisal guidance on pembrolizumab (if PD L1 above 1%) or
- the NICE technology appraisal guidance on atezolizumab (any PD-L1 0% to 100%) or
- the NICE technology appraisal guidance on nivolumab (if PD-L1 above 1%) or
- the NICE technology appraisal guidance on docetaxel and nintedanib (NHS England policy) or
- docetaxel.

For people who have disease progression after follow-up treatment in line with the NICE technology appraisal guidance on pembrolizumab, atezolizumab or nivolumab, recommended treatment options are:

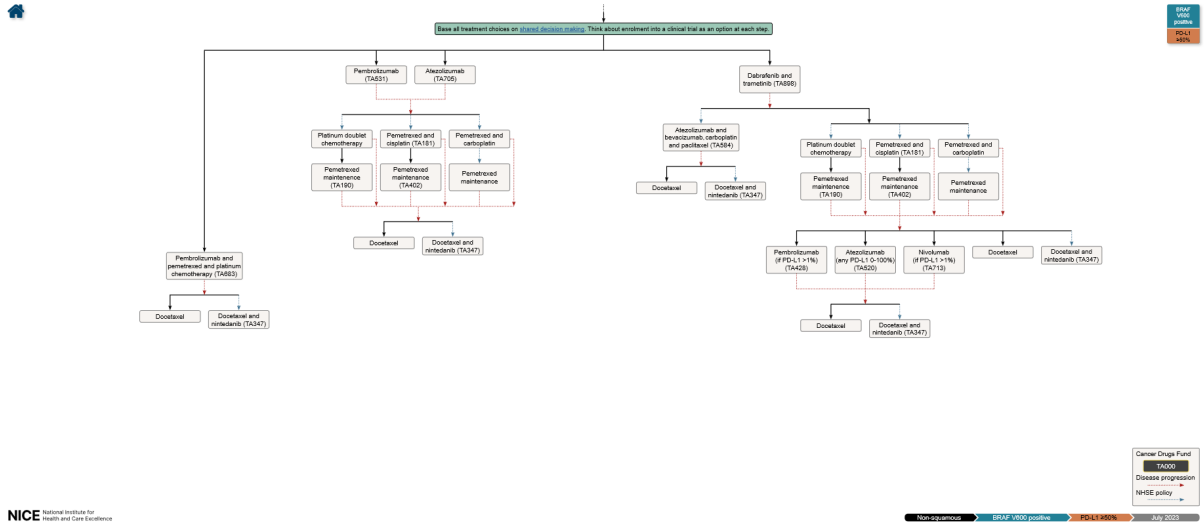
- docetaxel or
- the NICE technology appraisal guidance on docetaxel and nintedanib (NHS England policy).

For people who have had initial treatment in line with the NICE technology appraisal guidance on dabrafenib and trametinib and who have disease progression after treatment in line with the NICE technology appraisal guidance on atezolizumab and bevacizumab, carboplatin and paclitaxel, recommended treatment options are:

- docetaxel or

- the NICE technology appraisal guidance on docetaxel and nintedanib (NHS England policy).

Non-squamous non-small cell lung cancer, BRAF V600 positive, PD L1 50% or higher



Initial recommended treatment options are:

- the NICE technology appraisal guidance on pembrolizumab and pemetrexed and platinum chemotherapy or
- the NICE technology appraisal guidance on pembrolizumab or
- the NICE technology appraisal guidance on atezolizumab or
- the NICE technology appraisal guidance on dabrafenib and trametinib.

For people who have disease progression after initial treatment in line with the NICE technology appraisal guidance on pembrolizumab and pemetrexed and platinum chemotherapy, recommended treatment options are:

- docetaxel or
- the NICE technology appraisal guidance on docetaxel and nintedanib (NHS England policy).

For people who have disease progression after initial treatment in line with the NICE technology appraisal guidance on pembrolizumab or atezolizumab, recommended treatment options (NHS England policy) are:

- platinum doublet chemotherapy or
- the NICE technology appraisal guidance on pemetrexed and cisplatin or
- pemetrexed and carboplatin.

For maintenance treatment for people who have had treatment with platinum doublet chemotherapy, the only recommended treatment option is the NICE technology appraisal guidance on pemetrexed maintenance.

For maintenance treatment for people who have had treatment in line with the NICE technology appraisal guidance on pemetrexed and cisplatin, the only recommended treatment option is the NICE technology appraisal guidance on pemetrexed maintenance.

Pemetrexed maintenance is a recommended maintenance treatment option for people who have had treatment with pemetrexed and carboplatin (NHS England policy).

For people who have had initial treatment in line with the NICE technology appraisal guidance on pembrolizumab or atezolizumab and who have disease progression after treatment with platinum doublet chemotherapy, the NICE technology appraisal guidance

on pemetrexed and cisplatin, pemetrexed and carboplatin, or who have had pemetrexed maintenance, recommended treatment options are:

- docetaxel or
- the NICE technology appraisal guidance on docetaxel and nintedanib (NHS England policy).

For people who have disease progression after initial treatment in line with the NICE technology appraisal guidance on dabrafenib and trametinib, recommended treatment options (NHS England policy) are:

- the NICE technology appraisal guidance on atezolizumab and bevacizumab, carboplatin and paclitaxel or
- platinum doublet chemotherapy or
- the NICE technology appraisal guidance on pemetrexed and cisplatin or
- pemetrexed and carboplatin.

For people who have had initial treatment in line with the NICE technology appraisal guidance on dabrafenib and trametinib and who have disease progression after treatment in line with the NICE technology appraisal guidance on atezolizumab and bevacizumab, carboplatin and paclitaxel, recommended treatment options are:

- docetaxel or
- the NICE technology appraisal guidance on docetaxel and nintedanib (NHS England policy).

For maintenance treatment for people who have had treatment with platinum doublet chemotherapy, the only recommended treatment option is the NICE technology appraisal guidance on pemetrexed maintenance.

For maintenance treatment for people who have had treatment in line with the NICE technology appraisal guidance on pemetrexed and cisplatin, the only recommended treatment option is the NICE technology appraisal guidance on pemetrexed maintenance.

Pemetrexed maintenance is a recommended maintenance treatment option for people who have had treatment with pemetrexed and carboplatin (NHS England policy).

For people who have had initial treatment in line with the NICE technology appraisal guidance on dabrafenib and trametinib and who have disease progression after treatment with platinum doublet chemotherapy, the NICE technology appraisal guidance on pemetrexed and cisplatin, pemetrexed and carboplatin, or who have had pemetrexed maintenance, recommended treatment options are:

- the NICE technology appraisal guidance on pembrolizumab (if PD L1 above 1%) or
- the NICE technology appraisal guidance on atezolizumab (any PD-L1 0% to 100%) or
- the NICE technology appraisal guidance on nivolumab (if PD-L1 above 1%) or
- docetaxel or
- the NICE technology appraisal guidance on docetaxel and nintedanib (NHS England policy).

For people who have disease progression after follow-up treatment in line with the NICE technology appraisal guidance on pembrolizumab, atezolizumab, or nivolumab, recommended treatment options are:

- docetaxel or
- the NICE technology appraisal guidance on docetaxel and nintedanib (NHS England policy).

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 06 of 12, June 2023) am 13.06.2023

#	Suchfrage
1	[mh "Carcinoma, Non-Small-Cell Lung"] OR [mh ^"Lung Neoplasms"]
2	(((non NEXT small) OR nonsmall) NEXT cell NEXT lung):ti,ab,kw
3	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesion* OR malignan*):ti,ab,kw
4	#2 AND #3
5	nsclc*:ti,ab,kw
6	#1 OR #4 OR #5
7	#6 with Cochrane Library publication date from Jun 2018 to present

Systematic Reviews in PubMed am 13.06.2023

verwendete Suchfilter ohne Änderung:

Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	**"Carcinoma, Non-Small-Cell Lung"[majr]**
2	"nonsmall cell lung"[tiab:~0] OR "non small cell lung"[tiab:~0]
3	#2 AND ((((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]) OR malignan*[tiab])
4	#1 OR (#3)
5	(#4) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR

#	Suchfrage
	apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
6	((#5) AND ("2018/06/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 13.06.2023

verwendete Suchfilter ohne Änderung:

Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	"Carcinoma, Non-Small-Cell Lung"[mh]
2	Lung Neoplasms/therapy
3	"nonsmall cell lung"[tiab:~0] OR "non small cell lung"[tiab:~0] OR Lung[ti]
4	(#3) AND ((((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]) OR malignan*[tiab])
5	#1 OR #2 OR #4
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
7	(((#6) AND ("2018/06/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 13.06.2023

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- *Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)*
- *Alberta Health Service (AHS)*
- *European Society for Medical Oncology (ESMO)*
- *National Comprehensive Cancer Network (NCCN)*
- *National Cancer Institute (NCI)*

- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2023-B-198

Verfasser	
Institution	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO) Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (DGP) Arbeitsgemeinschaft Thorakale Onkologie in der Arbeitsgemeinschaft Internistische Onkologie der Deutschen Krebsgesellschaft (AIO)
Sachverständige	
Datum	22. September 2023

Indikation
Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligem Lungenkrebs mit einer BRAFV600-Mutation (Zweitlinientherapie)
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Zusammenfassung

Bei der Behandlung von Patientinnen und Patienten (Pat.) mit fortgeschrittenem, nicht-kleinzelligem ngenkarzinom (NSCLC) und Nachweis einer BRAF-V600E-Mutation wird in der Zweitlinientherapie empfohlen:

- Dabrafenib + Trametinib für Pat., die in der Erstlinientherapie eine Chemo-Immuntherapie oder Immunmonotherapie erhalten haben
- Präferentiell Immunchemotherapie (bzw. Immunmonotherapie bei primär nicht chemotherapiefähigen Pat.), falls in der Erstlinientherapie ein BRAF+MEK-Inhibitor eingesetzt wurde.

Stand des Wissens

Das NSCLC ist eine biologisch heterogene Erkrankung [1, 2]. BRAF-Mutationen werden bei 1-2% aller Pat. mit nicht-kleinzelligem Lungenkarzinom nachgewiesen [3]. Bei etwa der Hälfte handelt es sich um V600-Mutationen, davon in der großen Mehrzahl V600E, selten V600G. Bei bisher unbehandelten Pat. führte der BRAF-Inhibitor Dabrafenib in einer einarmigen Phase-II-Studie in Kombination mit dem MEK-Inhibitor Trametinib zu einer Remissionsrate von 64% und einer medianen Gesamtüberlebenszeit von 24,6 Monaten [4]. Bei mit Chemotherapie vorbehandelten Pat.

lag die Remissionsrate bei 63%. Im indirekten Vergleich ist die Rate schwerer Nebenwirkungen niedriger als unter Chemotherapie. Daten randomisierter Studien liegen nicht vor. Dabrafenib/Trametinib kann in der Erst- oder Zweitlinientherapie bei BRAFV600 Mutationen eingesetzt werden [5]. Bei Pat. mit Vorbehandlung durch Dabrafenib/Trametinib wird in der Zweitlinientherapie eine Immunchemotherapie empfohlen. Bei Nachweis einer hohen PD-L1-Expression (≥50%) kann auch eine Immunmonotherapie (insbesondere bei nicht chemotherapiefähigen Patienten) mit einem der zugelassenen Immuncheckpoint-Inhibitoren durchgeführt werden. Bei anderen Punktmutationen außerhalb der Position V600 ist die Situation komplex, da auch Kinase-inaktivierende Mutationen auftreten. Hier sollte ein molekulares Tumorboard konsultiert werden [6, 7].
Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?
Ja, diese sind oben dargestellt.

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