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: 2024-B-059-z Tislelizumab

Stand: März 2024

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

Tislelizumab
[nicht-plattenepitheliales 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“ Nicht berücksichtigt wurden Arzneimittel mit expliziter Zulassung für die Behandlung des NSCLC mit plattenepithelialer Histologie. Ausgeschlossen wurden Arzneimittel zur Therapie eines NSCLC mit ALK-Translokation, EGFR-, BRAF, KRAS G12C, METex14, 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:** – Cemiplimab (Beschlüsse vom 20.01.2022 und 19.10.2023) – Tremelimumab (Beschluss vom 05.10.2023 – Durvalumab (Beschluss vom 05.10.2023) – Atezolizumab (Beschlüsse vom 02.04.2020 und 19.11.2021) – Ipilimumab (Beschluss vom 03.06.2021) – Nivolumab (Beschluss vom 03.06.2021) – Pembrolizumab (Beschlüsse vom 19.09.2019 und 03.08.2017) **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	

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

Tislelizumab
[nicht-plattenepitheliales NSCLC, Erstlinie]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet**
Zu bewertendes Arzneimittel:	
Tislelizumab L01FF09 Tizveni	Anwendungsgebiet: Tevimbra in Kombination mit Pemetrexed und platinhaltiger Chemotherapie wird angewendet zur Erstlinienbehandlung des nicht-plattenepithelialen NSCLC mit PD-L1-Expression auf ≥ 50 % der Tumorzellen ohne EGFR- oder ALK-positive Mutationen bei erwachsenen Patienten, die: • ein lokal fortgeschrittenes NSCLC haben und nicht für eine chirurgische Resektion oder eine platinbasierte Radiochemotherapie in Frage kommen
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	Nicht-kleinzelliges Bronchialkarzinom:

II. Zugelassene Arzneimittel im Anwendungsgebiet	
generisch	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 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 […].
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).

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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. 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. LIBTAYO ist indiziert in Kombination mit platinbasierter Chemotherapie für die Erstlinienbehandlung von erwachsenen Patienten mit NSCLC, das PD-L1 (in ≥ 1 % 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
Durvalumab L01FF03	IMFINZI in Kombination mit Tremelimumab und einer platinbasierten Chemotherapie ist angezeigt bei Erwachsenen zur Erstlinienbehandlung des metastasierten NSCLC ohne sensibilisierende EGFR-Mutationen oder ALK-positive Mutationen.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Imfinzi	
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. […]
Tremelimumab L01FX20 Imjudo	Tremelimumab AstraZeneca in Kombination mit Durvalumab und einer platinbasierten Chemotherapie ist angezeigt bei Erwachsenen zur Erstlinienbehandlung des metastasierten nicht-kleinzelligen Lungenkarzinoms (non-small cell lung cancer, NSCLC) ohne sensibilisierende EGFR-Mutationen oder ALK-positive Mutationen.

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-328 (Tislelizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	24. Januar 2023

Inhaltsverzeichnis

Abkürzungsverzeichnis

ABC	atezolizumab/bevacizumab/chemotherapy
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

Erstlinienbehandlung von erwachsenen Personen mit nicht-plattenepithelialem nicht-kleinzelligem Lungenkarzinom (NSCLC), deren Tumore keine positive Mutation des epidermalen Wachstumsfaktorrezeptors (EGFR) oder der anaplastischen Lymphomkinase (ALK) aufweisen, mit

- lokal fortgeschrittener Erkrankung, die nicht für eine chirurgische Resektion oder platinbasierte Radiochemotherapie infrage kommen, oder mit
- metastasierter Erkrankung

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 50 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Ferrara R et al., 2021 [13].

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:

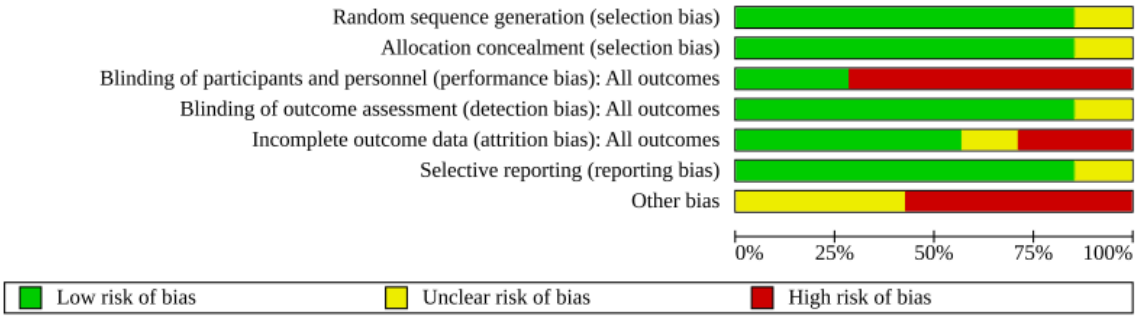
- 15 trials (seven completed and eight ongoing trials)
- Data for 5893 participants from seven trials comparing first-line single- (six trials) or double- (two trials) agent ICI with platinum-based chemotherapy, one trial comparing both firstline single- and double-agent ICsI with platinum-based chemotherapy.

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 [39].

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:

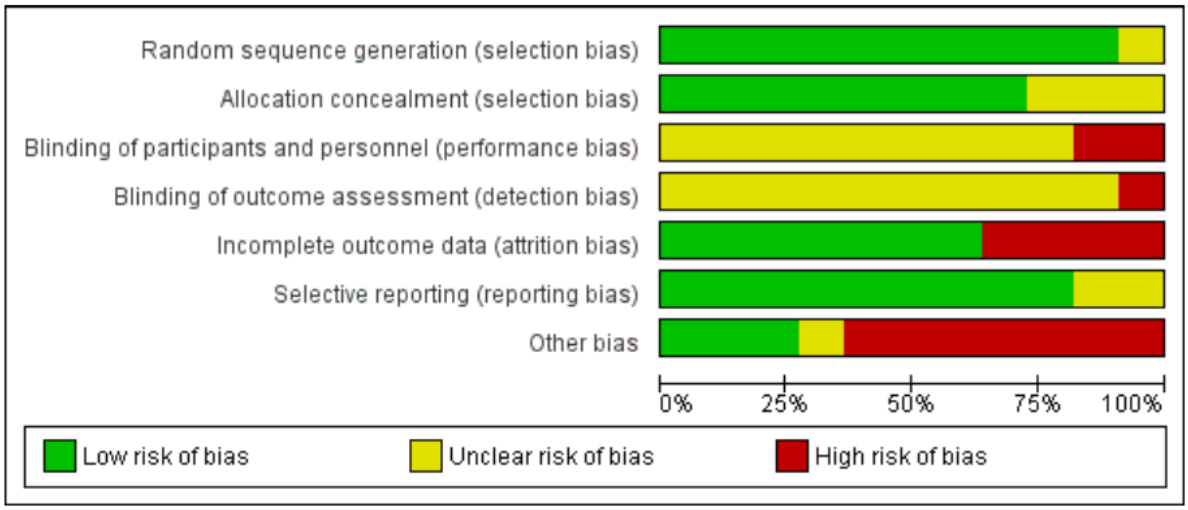
- Cochrane approach / GRADE

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 [19].

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:

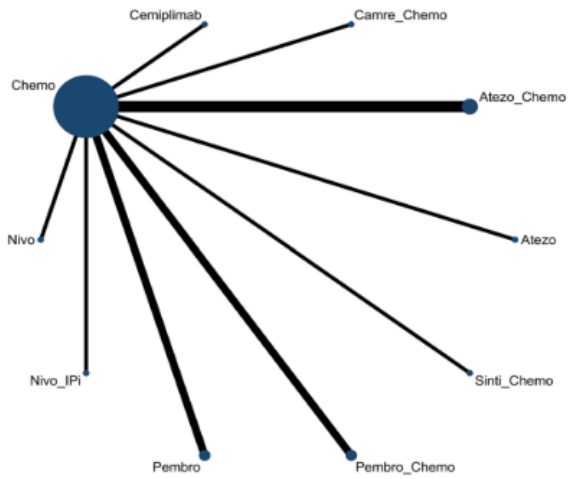


Fig. 2 Network plot of multiple therapies in the first-line treatment of advanced NSCLC with PD-L1 ≥ 50%

- 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 [30]
  Freemantle, N. et al., 2022 [14]

Chai Y et al., 2022 [4].

Combined Immunotherapy with Chemotherapy versus Bevacizumab with Chemotherapy in First-Line Treatment of Driver-Gene-Negative Non-Squamous Non-Small Cell Lung Cancer: An Updated Systematic Review and Network Meta-Analysis

Fragestellung

network meta-analysis was conducted to summarize randomized control trials and updated results to evaluate the efficacy and safety profiles of existing first-line therapies for advanced non-squamous non-small cell lung cancer (NSCLC) patients without known driver gene mutations.

Methodik

Population:

- patients with previously untreated advanced NSCLC

Intervention/Komparator:

- anti-angiogenic combined therapy to other treatment or an immunotherapy combined therapy to other treatment

Endpunkte:

- OS, PFS, ORR, TRAEs

Recherche/Suchzeitraum:

Cochrane Library, PubMed, Embase,Web of Science,Wanfang Data, and the China Knowledge Resource Integrated Database from January 2000 to December 2021.

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- Nineteen trials involving 8176 patients with driver-gene-negative advanced non-squamous NSCLC were included

Charakteristika der Population:

	NCT Identifier Number	Published Year	First Author	Phase	Arm	Non-Squamous Patients with Survival Data
ECOG4599	NCT00021060	2006	Sandler A, et al.	III	BCP	417
					CP	433
AVAiL	NCT00806923	2010	Reck M, et al.	III	BCG	351
					CG	347
JO19907	CTI-060338	2012	Niho S, et al.	II	BCP	117
					CP	58
PRONOUNCE	NCT00948675	2015	Zinner RG, et al.	III	BCP	182
					Pem + Cb	179
BEYOND	NCT01364012	2015	Zhou C, et al.	III	BCP	138
					CP	138
ERACLE	NCT01303926	2015	Galetta D, et al.	III	Cisplatin/Pemetrexed	60
					BCP	58
KEYNOTE-021G	NCT02039674	2016	Langer C, et al.	II	Pembrolizumab + Pem + Cb	60
					Pem + Cb	63
IMpower130	NCT02367781	2019	West H, et al.	III	Atezolizumab + Nab-paclitaxel + carboplatin	451
					Nab-paclitaxel+ carboplatin	228
KEYNOTE-189	NCT02578680	2020	Gadgeel S, et al.	III	Pembrolizumab + Pemetrexed + Platinum	410
					Pemetrexed + Platinum	206
CheckMate 227 4year part1A [i]	NCT02477826	2020	Hellmann MD, et al.	III	Nivolumab + Ipilimumab	278
					Chemotherapy	279
CheckMate 227 4year part1B [ii]	NCT02477826	2020	Hellmann MD, et al.	III	Nivolumab + Ipilimumab	134
					Chemotherapy	140
CheckMate 227 4year part2 [iii]	NCT02477826	2020	Hellmann MD, et al.	III	Nivolumab + chemotherapy	270
					Chemotherapy	273
IMpower132	NCT02657434	2021	Nishio M, et al.	III	APP	292
					PP	286
IMpower150 4 year update	NCT02366143	2021	Socinski MA, et al.	III	ABCP	350
					ACP	359
					BCP	338

	NCT Identifier Number	Published Year	First Author	Phase	Arm	Non-Squamous Patients with Survival Data
CheckMate 9LA 2-year update	NCT03215706	2021	Reck M, et al.	III	Nivolumab + ipilimumab + platinum-doublet Chemotherapy	248
					Chemotherapy	247
CameL	NCT03134872	2021	Zhou, et al.	III	Camrelizumab + Pem + Cb	205
					Pem + Cb	207
RATIONALE 304	NCT03663205	2021	Lu S, et al.	III	Tislelizumab + chemotherapy	222
					Chemotherapy	110
ORIENT 11	NCT03607539	2021	Yang Y, et al.	III	Sintilimab + pemetrexed + platinum	266
					Pemetrexed + platinum	131
GEMSTONE-302	NCT03789604	2021	Zhou C, et al.	III	Sugemalimab + platinum-based chemotherapy	191
					Platinum-based chemotherapy	96

Studienergebnisse - OS and PFS

- Sixteen trials included a total of 7802 individual patients, where 2181 received IC, 1601 patients received BC, 350 patients received BIC, 248 patients received DIC, 278 patients received DI, and 3144 patients received CT, provided OS data. Nineteen trials included a total of 8535 individual patients, where 2806 received IC, 1601 patients received BC, 350 patients received BIC, 248 patients received DIC, 278 patients received DI, and 3481 patients received CT, provided PFS data.
- IC had significantly prolonged OS (HR, 0.80; 95% CI: 0.67–0.95) and PFS (HR, 0.68; 95% CI: 0.53–0.86) compared with BC. BIC had significantly longer PFS (HR, 0.62; 95% CI:

0.41–0.95) but not OS (HR, 0.78; 95% CI: 0.58–1.04) compared with BC. BIC (HR, 0.70; 95% CI: 0.52–0.95/HR, 0.53; 95% CI: 0.34–0.86) and IC (HR, 0.73; 95% CI: 0.63–0.83/HR, 0.59; 95% CI: 0.51–0.68) had both longer OS and PFS than CT. DIC had significantly longer OS (HR, 0.69; 95% CI: 0.49–0.98) but not PFS (01.28, 0.95–1.76) compared with CT. BC and DI were statistically equivalent to CT for OS and PFS (Figure 3A).

Fazit der Autoren

- In conclusion, this NMA suggested that IC is a better efficient first-line therapy for patients with driver-gene-negative non-squamous advanced NSCLC, with prolonged PFS and OS and comparatively lower risk of 3 TRAEs in comparison to BC.

Chen J et al., 2022 [6].

Frontline anti-PD-1/PD-L1 versus bevacizumab in advanced non-small-cell lung cancer: a network meta-analysis

Fragestellung

To review the efficacy and safety of regimens containing anti-PD-1/PD-L1 and bevacizumab for patients with advanced nonsquamous, non-small-cell lung cancer.

Methodik

Population:

- patients with advanced nonsquamous, non-small-cell lung cancer

Intervention und Komparator:

- regimens containing anti-PD-1/PD-L1 and bevacizumab

Endpunkte:

- OS, PFS, ORR

Recherche/Suchzeitraum:

- Pubmed, Embase and Cochrane Library were searched to retrieve eligible RCTs up to 10 November 2021

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 16 studies

Charakteristika der Population:

Table 1. Baseline characters of included studies in first-line therapy (n = 16).

Study	Trial name	Year	Patients (n)	Liver metastases	Intervention	Comparison	Primary outcome
Reck *et al.*	AVAiL	2010	656	–	Bevacizumab + cisplatin + gemcitabine	Cisplatin + gemcitabine	OS, PFS
Zhou *et al.*	Beyond	2015	276	–	Bevacizumab + carboplatin + paclitaxel	Carboplatin + paclitaxel	OS, PFS
Zhou *et al.*	CameL	2020	412	–	Camerilizumab + carboplatin + pemetrexed	Carboplatin + pemetrexed	OS, PFS
Sandler *et al.*	ECOG4599	2006	850	163	Bevacizumab + carboplatin + paclitaxel	Carboplatin + paclitaxel	OS, PFS
Galetta *et al.*	ERACLE	2015	118	–	Bevacizumab + carboplatin + paclitaxel	Cisplatin + pemetrexed	OS, PFS
West *et al.*	IMpower130	2019	723	100	Atezolizumab + carboplatin + nab-paclitaxel	Carboplatin + nab-paclitaxel	OS, PFS
Barlesi *et al.*	IMpower132	2018	571	73	Atezolizumab + carboplatin/cisplatin + pemetrexed	Carboplatin/cisplatin + pemetrexed	OS, PFS
Socinski *et al.*	IMpower150	2021	1047	109	Atezolizumab + bevacizumab + carboplatin + paclitaxel/Atezolizumab + carboplatin + paclitaxel	Bevacizumab + carboplatin + paclitaxel	OS, PFS
Nishio *et al.*	JO19907	2012	180	–	Bevacizumab + carboplatin + paclitaxel	Carboplatin + paclitaxel	OS, PFS
Corey *et al.*	KeyNote 021	2019	123	–	Pembrolizumab + carboplatin + pemetrexed	Carboplatin + pemetrexed	OS, PFS
Gadgeel *et al.*	KeyNote 189	2020	616	115	Pembrolizumab + platinum-based drug + pemetrexed	Platinum-based drug + pemetrexed	OS, PFS
Yang *et al.*	ORIENT-11	2021	397	–	Sintilimab + cisplatin/carboplatin + pemetrexed	Cisplatin/carboplatin + pemetrexed	OS, PFS
Ralph *et al.*	PRONOUNCE	2015	361	–	Bevacizumab + carboplatin + paclitaxel	Carboplatin + paclitaxel	OS, PFS
Sugawara *et al.*	TASUKI-52	2021	548	39	Nivolumab + bevacizumab + carboplatin + paclitaxel	Bevacizumab + carboplatin + paclitaxel	OS, PFS
Lu *et al.*	RATIONALE 304	2021	334	37	Tislelizumab + carboplatin + pemetrexed	Carboplatin + pemetrexed	PFS
Paz-Ares *et al.*	CheckMate 227	2019	543	–	Nivolumab + cisplatin/carboplatin + pemetrexed	Cisplatin/carboplatin + pemetrexed	OS, PFS

NSCLC: Non-small-cell lung cancer; OS; Overall survival; PFS: Progression free survival.

Qualität der Studien:

- All included trials were of good quality, among which eight open-label studies were deemed to have a high risk of performance and selection bias due to lack of blinding. One trial only reported PFS, leading to an unclear risk of attrition bias.

Studienergebnisse:

- For indirect comparisons, six treatment regimens were evaluated in the overall population (Figure 2). Compared with CT, all combination treatments performed significantly better in terms of PFS. PD1 + Bev + CT (HR = 0.56, 95% CI: 0.34–0.95) was notably better than Bev + CT in prolonging PFS. PDL1 + Bev + CT (HR = 0.69, 95% CI: 0.48–1.00), PD1 + CT (HR = 0.69, 95% CI: 0.57–0.83), PDL1 + CT (HR = 0.81, 95% CI: 0.66–0.99) did significantly decrease the risk of death compared with traditional platinum-doublet alone. PD1 + CT (HR = 0.76, 95% CI: 0.60–0.96) were shown to be superior to Bev + CT in prolonging OS
- Among patients with PD-L1 negative (PD-L1 <1%) expression, PD1 + Bev + CT (HR = 0.34, 95% CI: 0.11–0.99), PD1 + CT (HR = 0.64, 95% CI: 0.44–0.90) and PDL1 + CT (HR = 0.60, 95% CI: 0.34–0.96), with effects comparable between the three, were superior to the platinum-based chemotherapeutic regimen for PFS. PD1 + CT showed significant OS (HR = 0.53, 95% CI: 0.31–0.91) benefit versus conventional chemotherapy. However, the advantage of anti-PD-1/anti-PD-L1 combination therapy was of no significance compared with bevacizumab combination therapy for PD-L1 negative patients in terms of PFS and OS
- For the PD-L1 intermediate (1% ≤PD-L1 <50%) population, there existed a trend that a PD-1 inhibitor plus chemotherapy conferred PFS benefit compared with platinum-doublet chemotherapy (HR = 0.64, 95% CI: 0.43–1.03), although statistical significance

was not reached. Moreover, PD-1/PD-L1 showed no superiority to bevacizumab in PFS and OS in this scenario

- Combination therapies, except for Bev + CT and PD1 + Bev + CT, were associated with significant PFS benefit compared with doublet-platinum therapy for the PD-L1 high (PD-L1 ≥50%) population. Moreover, PDL1 + Bev + CT (HR = 0.34, 95% CI: 0.18–0.65) and PD1 + CT (HR = 0.39, 95% CI: 0.16–0.95) were better at prolonging PFS compared with Bev + CT. However, the PFS benefit found in the PD-L1 high population failed to extend to OS benefit

Anmerkung/Fazit der Autoren

Taken together, compared with bevacizumab combination therapy, anti-PD-1 plus platinum-doublet chemotherapy is highly recommended for patients harboring high PD-L1 expression in frontline therapy. However, evidence for preferred chemoimmunotherapy in patients with PD-L1 <50% was insufficient. Direct head-to-head clinical trials are warranted to confirm these findings.

Fukuda N et al., 2022 [15].

Best regimens for treating chemo-naïve incurable squamous non-small cell lung cancer with a programmed death-ligand 1 tumor proportion score of 1%-49%: A network meta-analysis

Fragestellung

Non-small cell lung cancer (NSCLC) is the leading cause of cancerrelated mortality worldwide. It is advisable to select the appropriate treatment based on characteristics of the cancer such as pathology, mutations, and programmed deathligand 1 (PD-L1) levels. In this study, by remarking squamous NSCLC with low PDL1 expression without mutations, we investigated the efficacy and safety of regimens that included molecularly targeted drugs such as immune checkpoint inhibitors (ICIs) through a network meta-analysis.

Methodik

Population:

- treating chemo-naïve incurable squamous non-small cell lung cancer with a programmed death-ligand 1 tumor proportion score of 1%-49%

Intervention und Komparator:

- Appropriate treatments included platinum doublet chemotherapy, ICIs, and molecularly targeted therapies. Clinical studies on platinum plus an angiogenesis inhibitor have also been conducted. ICI can be administered alone or in combination with platinum-based treatments.

Endpunkte:

- OS, PFS, AE

Recherche/Suchzeitraum:

- To identify eligible articles, the MEDLINE, Web of Science Core Collection, Embase, and Cochrane Central Register of Controlled Trials databases were searched systematically on October 15, 2020

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Finally, 48 appropriate studies were identified

Qualität der Studien:

- bias evaluation indicated that all studies had at least one domain with a high risk of bias

Studienergebnisse:

- The hazard ratios of OS (HRos) were evaluated in 19 studies with 6785 total patients (Table 1). In the main model, the HRos ranged from 0.57 to 1.32 with a median of 0.94. There was no inconsistency between the Q statistics and the test for heterogeneity at any level (whole network level I2 = 0%; total p = 0.394; within designs, p = 0.394) (Figures 2 and S1). The targeted treatments were clustered in the same node. The platinum regimen + Pemb yielded the best OS benefit compared to chemotherapy (HR = 0.57, 95% CI = 0.36–0.90, p = 0.016), followed by the platinum regimen + nivolumab (Niv) + ipilimumab (Ipi) (HR = 0.61, 95% CI = 0.44–0.84, p = 0.003), and the platinum regimen + necitumumab (Nctm) (HR = 0.82, 95% CI = 0.73–0.92, p < 0.001) (Figure 3(a)). Atezolizumab (Atz) was not statistically different from the platinum regimen (HR = 1.08, 95% CI = 0.81–1.44, p = 0.60). The additional analysis including only studies in which PD-L1 was explicitly mentioned was conducted. The results did not conflict with the main analysis (Figure S2). In the separate model, HRos of the platinum regimen + Ptx + Pemb (HR = 0.57, 95% CI = 0.36–0.90, p = 0.016) ranked first. The effect of this regimen was significantly different between the separate models (Figure S3).

Anmerkung/Fazit der Autoren

In summary, we performed a systematic review and network meta-analysis of patients with squamous NSCLC with a PD-L1 TPS of 1%–49%. For the 16 391 patients diagnosed with NSCLC and part of 48 RCTs, the platinum regimen + Pemb and the platinum regimen + Niv + Ipi were considered appropriate first-line agents for treating squamous NSCLC with low PD-L1.

Zhou Y et al., 2021 [50].

The Safety and Effectiveness of Bevacizumab in the Treatment of Nonsquamous Non-Small-Cell Lung Cancer: A Meta-Analysis of Randomized Controlled Trials

Fragestellung

Bevacizumab was currently available for nonsquamous non-small-cell lung cancer (NSqNSCLC) patients and has been studied in several randomized controlled trials (RCTs) for treatment of these patients. This meta-analysis summarizes the most up-to-date evidences regarding the effects and adverse reactions of bevacizumab in the treatment of NSqNSCLC patients

Methodik

Population:

- NSqNSCLC patients

Intervention und Komparator:

- bevacizumab plus standard chemotherapy regimen and the control group using standard chemotherapy regimen alone

Endpunkte:

- OS, PFS

Recherche/Suchzeitraum:

- The last search was performed on December 8, 2020

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

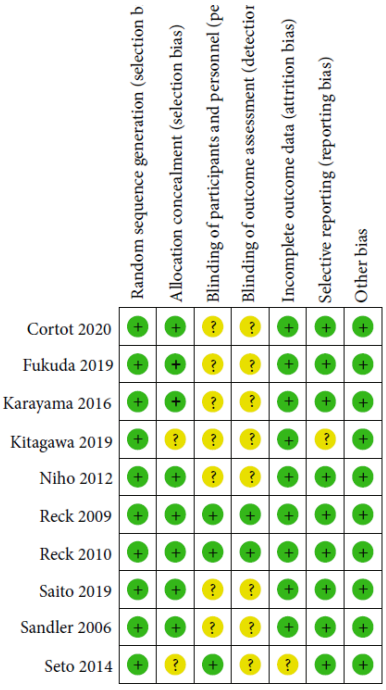
Anzahl eingeschlossener Studien:

- 10 RCTs

Charakteristika der Population:

Studies	Year	Intervention		Number (case/ control)	Type of study
		Experimental group	Control group		
Cortot et al.	2020	Bevacizumab+paclitaxel	Docetaxel	111/55	RCT
Kitagawa et al.	2019	Bevacizumab+gefitinib	Gefitinib	6/10	RCT
Fukuda et al.	2019	Bevacizumab+pemetrexed	Pemetrexed	20/20	RCT
Saito et al.	2019	Bevacizumab+erlotinib	Erlotinib	114/114	RCT
Karayama et al.	2016	Bevacizumab+pemetrexed	Pemetrexed	55/55	RCT
Seto et al.	2014	Bevacizumab+erlotinib	Erlotinib	77/77	RCT
Niho et al.	2012	Bevacizumab+carboplatin+paclitaxel	Carboplatin+paclitaxel	121/59	RCT
Reck et al.	2010	Bevacizumab 7.5 mg/kg+cisplatin +gemcitabine	Placebo+cisplatin +gemcitabine	345/347	RCT
Reck et al.	2009	Bevacizumab 15 mg/kg+cisplatin +gemcitabine	Placebo+cisplatin +gemcitabine	351/347	RCT
Sandler et al.	2006	Bevacizumab+paclitaxel+carboplatin	Paclitaxel+carboplatin	417/433	RCT

Qualität der Studien:



Studienergebnisse:

- Efficacy Profile. Compared to the bevacizumab-free group, the bevacizumab-containing group was associated with significantly superior ORR (RR 1.63, 95% CI 1.24 to 2.14, P < 0:001; Figure 3), OS (HR 0.90, 95% CI 0.82 to 0.99, z = 21:45, P < 0:001; Figure 4), and longer PFS (HR 0.68, 95% CI 0.62 to 0.74, z = 22:50, P < 0:001; Figure 5).

Anmerkung/Fazit der Autoren

Our meta-analysis showed that treatment containing bevacizumab was an option for patients with NSqNSCLC and patients with acceptable efficacy. Bevacizumab was superior to those without it in terms of ORR, OS, and PFS in patients with NSqNSCLC and no significant TRAE3-5 was observed.

Di Federico A et al., 2021 [10].

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 [9]
- García-González, J. et al., 2020 [16]
- Yi, K. et al., 2020 [47]

Wang DD et al., 2021 [42].

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:

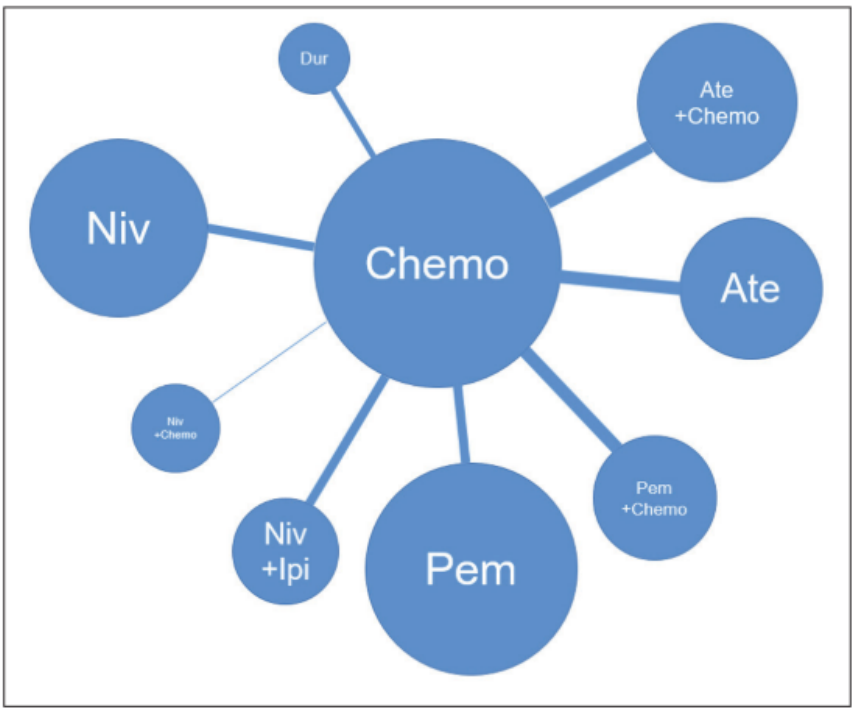


Figure 1. Network of eligible comparisons. The size of the nodes is proportional to the number of patients randomized to receive the treatment. The width of the lines is proportional to the number of trials comparing the connected treatments. Abbreviations: Pem, pembrolizumab; Ate, atezolizumab; Dur, 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 [28]
- Landre T et al., 2020 [24]
- Jiang, M. et al., 2022 [21]
- Wang, L. et al., 2022 [42]
- Peng TR und Wu TW, 2019 [33]

Wankhede D et al., 2022 [44].

PD-1/PD-L1 inhibitors in treatment-naïve, advanced non-small cell lung cancer patients with < 1% PD-L1 expression: a meta-analysis of randomized controlled trials

Fragestellung

PD-1/PD-L1 inhibitors prolong survival in treatment-naïve, locally advanced, and metastatic non-small cell lung cancer (NSCLC) with positive PD-L1 expression (> 1%/ > 50%). Recent evidence has suggested that tumors with < 1% PD-L1 expression may also be predictive of PD-1/PD-L1 inhibiting agents.

Methodik

Population:

- treatment-naïve, advanced non-small cell lung cancer patients with < 1% PD-L1 expression

Intervention und Komparator:

- PD-1/PD-L1 inhibitors (chemotherapy–immunotherapy combinations) to histology-selected chemotherapy in advanced NSCLC (locally advanced or metastatic)

Endpunkte:

- OS, PFS, ORR

Recherche/Suchzeitraum:

- PubMed, Embase, and Cochrane databases (up to May 1, 2022)

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 12 trials

Charakteristika der Population:

Author	Study	Study type	Histology	Treatment regimen	No. of patients (ITT)		Outcome	PD-L1 characteristics		
					Total	PD-L1 < 1% (*n*, %)		Sample type	Membrane-stained cell	Assay
Zhou et al. (2021a)	CameL	Phase III	Non-squamous NSCLC	Arm 1: camrelizumab + chemotherapy	205	49 (23.9)	PFS, OS,	Archival tumor tissue (< 6 months) or fresh samples	Tumor cell	22C3 pharmDx
				Arm 2: chemotherapy	207	69 (33.3)				
Ren, (2022)	CameL-Sq	Phase III	Squamous NSCLC	Arm 1: camrelizumab + chemotherapy	193	91 (47)	PFS, OS,	Archival tumor tissue or tissue obtained at screening	Tumor cell	E1L3N AmoxyDx
				Arm 2: chemotherapy	196	97 (49)				
West, (2019)	IMpower130	Phase III	Non-squamous NSCLC	Arm 1: atezolizumab + chemotherapy	483	253 (52.4)	PFS, OS,	Archival tumor tissue or tissue obtained at screening	Tumor cell/ tumor-infiltrating immune cell	VENTANA PD-L1 (SP142)
				Arm 2: chemotherapy	240	129 (53.8)				
Jotte, (2020)*	IMpower 131	Phase III	Squamous NSCLC	Arm 1: atezolizumab + chemotherapy (A + CnP)	343	160 (46.6)	PFS, OS, ORR	Archival tumor tissue or tissue obtained at screening	Tumor cell/ tumor-infiltrating immune cell	VENTANA PD-L1 (SP142)
				Arm 2: chemotherapy (CnP)	340	171 (50.3)				
Nishio (2020)	Impower 132	Phase III	Non-squamous NSCLC	Arm 1: atezolizumab + chemotherapy	292	88 (50)	FS, OS, ORR	Archival tumor tissue or tissue obtained at screening	Tumor cell/ tumor-infiltrating immune cell	VENTANA PD-L1 (SP142)
				Arm 2: chemotherapy	286	75 (44.6)				
Awad et al. (2021)	KEYNOTE-021	Phase II	Non-squamous NSCLC	Arm 1: pembrolizumab + chemotherapy	60	21 (35)	OS, PFS, ORR, DOR	Archival tumor tissue or tissue obtained from a biopsy at screening	Tumor cell	22C3 pharmDx
				Arm 2: chemotherapy	63	23 (36.5)				
Rodríguez-Abreu, (2021)	KEYNOTE-189	Phase III	Non-squamous NSCLC	Arm 1: pembrolizumab + chemotherapy	410	127 (30.9)	OS, PFS, ORR, DOR, Safety	newly obtained core or excisional biopsy or archival tissue	Tumor cell	22C3 pharmDx
				Arm 2: placebo + chemotherapy	206	63 (30.5)				
Paz-Ares, (2018)	KEYNOTE-407	Phase III	Squamous NSCLC	Arm 1: pembrolizumab + chemotherapy	278	95 (34.1)	OS, PFS, ORR, DOR, Safety	Archival tumor tissue or tissue obtained from a biopsy at screening	Tumor cell	22C3 pharmDx
				Arm 2: placebo + chemotherapy	281	99 (35.2)				
Yang, (2021)	ORIENT-11	Phase III	Non-squamous NSCLC	Arm 1: sintilimab + chemotherapy	266	85 (32)	OS, PFS	Archival tumor tissue or tissue obtained from a biopsy at screening	Tumor cell	22C3 pharmDx
				Arm 2: chemotherapy	131	44 (33.6)				
Zhou C, (2021)	ORIENT-12	Phase III	Squamous NSCLC	Arm 1: sintilimab + chemotherapy	179	59 (33)	OS, PFS	Archival tumor tissue or tissue obtained from a biopsy at screening	Tumor cell	22C3 pharmDx
				Arm 2: chemotherapy	178	63 (35.4)				
Lu S, (2021)	RATIONALE 304	Phase III	Non-squamous NSCLC	Arm 1: tislelizumab + chemotherapy	222	96 (43)	PFS, OS, ORR	Archival tumor tissue or tissue obtained at screening	Tumor cell	Ventana PD-L1 (SP263)
				Arm 2: chemotherapy	110	48 (43.2)				
Wang, (2021)$	RATIONALE 307	Phase III	Squamous NSCLC	Arm 1: tislelizumab + chemotherapy (T + CP)	120	48 (40)	PFS, OR, ORR	Archival tumor tissue or tissue obtained at screening	Tumor cell	Ventana PD-L1 (SP263)
				Arm 2: chemotherapy (CP)	121	49 (40.5)				

ITT intention to treat, *PFS* progression-free survival, *OS* overall survival, *ORR* objective response rate, *DOR* duration of response

*Three treatment arms (atezolizumab + carboplatin + paclitaxel (A + CP), atezolizumab + carboplatin + nab-paclitaxel (A + CnP) and carboplatin + nab-paclitaxel (CnP)

$Three treatment arms (tislelizumab + paclitaxel + carboplatin (T + CP), tislelizumab + nab-paclitaxel + carboplatin (T + CnP) and paclitaxel and carboplatin (CP)

Studienergebnisse:

- All included studies reported outcomes for PFS treatment effects, and nine studies reported data for the OS. Tumors with negative PD-L1 expression were associated with reduced risk of death [HR, 0.71; 95% CI, 0.63–0.80, p < 0.00001, Fig. 2] and progression [HR, 0.65; 95% CI, 0.58–0.72, p < 0.00001, Fig. 3] when treated with PC compared to

chemotherapy alone. Non-significant heterogeneity was evident among studies for both treatment effects. Results remained consistent for both OS and PFS outcomes following leave-one-out validation and performing analyses using both fixed- and random-effect models

Anmerkung/Fazit der Autoren

Tumors harboring < 1% PD-L1 expression are likely to derive significant OS and PFS benefits and clinical responses from PD-1/PD-L1 inhibitor therapy in advanced NSCLC. Our results were consistent irrespective of the histological subtypes and PD-L1 IHC assays. Robustness of results was evident with congruous OS and PFS outcomes following sensitivity analyses. PD-1/PD-L1 inhibitor–chemotherapy regimen may be advised as first-line therapy in both non-squamous and squamous NSCLC with negative PD-L1 expression.

Kommentare zum Review

Siehe auch:

Ding K et al., 2022 [11]: In summary, our meta-analysis demonstrated that advanced NSCLC patients with negative PD-L1 expression could have maximal benefits from the single-agent ICI plus chemotherapy or the doublet ICIs than chemotherapy in terms of OS and PFS. Meanwhile, the statistically significant benefit of the single-agent ICI versus chemotherapy and the single-agent ICI plus radiotherapy versus ICI was only observed in OS and PFS, respectively.

Yang Y et al., 2021 [46].

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

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:

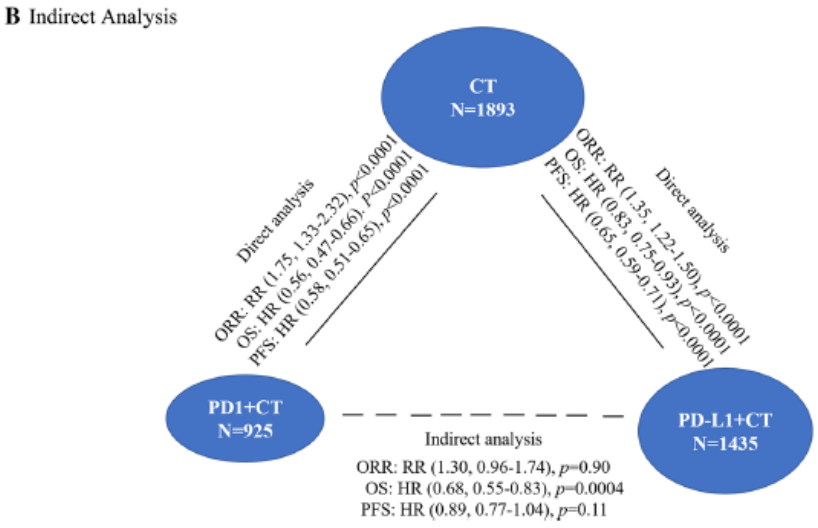


Fig. 3 Forest plots of progression-free survival (PFS) comparing PD-1+CT or PD-L1+CT versus chemotherapy alone and indirect comparison between PD-1+CT versus PD-L1+CT. In B, solid lines represented the existence of direct comparisons between treatment regimens, and dashed line represented the indirect 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 [27]
- Landre T et al., 2020 [24]

Dafni U et al., 2019 [7].

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 pembrolizumab combination 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 [40]
- Wang, D. et al., 2021 [41]
- Wang, Y. et al., 2022 [43]
- Abdelazeem, B et al., 2022 [1]:
- Petrelli F et al., 2021 [34]: In this systematic review and meta-analysis including nine trials and 5982 untreated NSCLC patients, ICI–CT combinations significantly improved responses and survival as compared with platinum-based CT. However, a higher rate of developing severe toxicities was reported for ICI–CT. The magnitude of benefit was low or absent in NSCLC patients with squamous histology, PD-L1 expression less than 50%, liver metastases, female sex and never-smoking history.
- Zhang X et al., 2022 [49]: Through the IA of first-line treatment regimens, a POS of 16.20 m can be determined as the LS standard. Further considering 1ySR and 2ySR, atezolizumab combined with bevacizumab and chemotherapy or pembrolizumab plus chemotherapy are likely to bring the longest LS in the overall population, while single ICI may be adequate for patients with a high PD-L1 expression. ICIs with bevacizumab and chemotherapy may be the best combination for LS for its further advantage over time.
- Chai Y et al., 2022 [5]
- Sheng L et al., 2021 [35]: A combination of ICIs with chemotherapy, rather than double ICIs, is the best first-line treatment for advanced wild-type NSCLC, with synergy that leads to better long-term survival.
- Shi Y et al., 2021 [36]: This meta-analysis confirmed the treatment effects of ICIs combined with chemotherapy for non-squamous NSCLC. The pembrolizumab combination group had a greater RMST benefit compared with the atezolizumab combination group. Furthermore, our study also demonstrated a PFS advantage for non-squamous NSCLC using ICIs combined with chemotherapy irrespective of programmed death-ligand 1 (PD-L1) expression level, smoking status, liver metastasis status, sex, age and ECOG score. Due to the significant increase in AEs (> grade 3), more attention should be paid to the additional use of atezolizumab.
- Siciliano M et al., 2022 [37]: The main findings of this NMA are as follows: (i) direct comparisons show that ICI-based regimens rank better in terms of efficacy in the unselected and stratified population compared to CT except for OS in patients with LM. This confirms a key role of ICI in frontline NSCLC treatment; (ii) considering together the efficacy and safety ranking profile, pembrolizumab/CT and cemiplimab rank first in the overall population with a better safety profile when compared with combinatory approaches burdened by more TRAEs; (iii) different ICI treatments rank differently in specific NSCLC cohorts of interest, emphasizing the lack of the optimal onetreatment-fits-all strategy. Atezolizumab/bevacizumab/CT ranks better in PFS in most cases but with a worse safety profile. In particular, nivolumab/ipilimumab ± CT ranks better for OS in the PD-L1-negative, SQ and BM population, while cemiplimab ranks better in PD-L1 >50%. In SQ, a combination strategy is better than ICI alone except for cemiplimab which shows a better ranking profile compared to NSQ.
- Xu Q et al., 2021 [45]: In the first-line therapy for advanced wild-type NSCLC, both SICI-based and DICI-based treatments could bring significant overall advantages vs. CT, with

comparable outcomes for mOS and ≥3AEs. DICI-based treatments were more effective than SICI-based treatments in squamous and PD-L1 <1% subgroups, while DICI in combination with CT could be the best first-line choice for most populations. We need more research to further evaluate the efficacy and safety of DICI-based treatments. At the same time, SICI-based therapies have established their position in the current first-line treatment. In addition, NMA and ranking possibilities of specific regimens could provide strong evidence for clinical selection of individualized treatment regimens to maximize survival benefits for related patients.

- Zhai J et al., 2022 [48]: This study elucidates that ICI-chemotherapy is superior to Bev-chemotherapy for improved OS in first-line treatment of advanced NS-NSCLC.

Zhou Y et al., 2019 [51].

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 [23]
- Guo WW et al., 2022 [17]

Liu J et al., 2020 [29].

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

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:

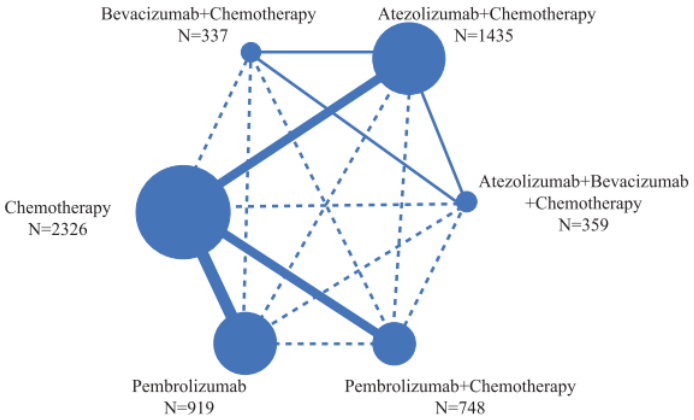


Figure 2. Network structure for all the included trials. Each circular node represents a treatment type. The circle size is proportional to the total number of patients. The width of lines is proportional to the number of studies performing head-to-head comparisons in the same study, and the dotted line 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 [3]
- Herbst, R. et al., 2021 [20]

Jiang P et al., 2022 [22]

First-line chemotherapy plus immune checkpoint inhibitors or bevacizumab in advanced non-squamous non-small-cell lung cancer without EGFR mutations or ALK fusions

Fragestellung

To compare the efficacy and safety of first-line chemotherapy (chemo) plus immune checkpoint inhibitors {ICis) or bevacizumab {Bev) in advanced non-squamous non-small-cell lung cancer without EGFR mutations or ALK fusions

Methodik

Population:

- advanced NSCLC

Intervention/Komparator:

- chemotherapy (chemo) plus immune checkpoint inhibitors {ICis) or bevacizumab {Bev)

Endpunkte:

- OS, PFS, ORR

Recherche/Suchzeitraum:

- Published between January 2000 and November 2020

Qualitätsbewertung der Studien:

- Cochrane Collaboration’s tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 15 RCTs

Charakteristika der Population:

Table 1. Baseline characteristics of studies included in the network meta-analysis.

Study	Experiment	Control	Sample size (N/n)	Median age (years)	Male (%)	Stage IV (%)
KEYNOTE 189	Pembro + AP	Chemo	410/206	63.5/63.0	62/53	100/100
KEYNOTE 021G	Pembro + AP	Chemo	60/63	62.5/63.2	37/41	98/95
IMpower132	Atezo + AP	Chemo	292/286	63.0/64.0	67/66	100/100
AVAIL	GP + BEV	Chemo	351/347	59.0/59.0	62/64	77/77
ERACLE	Chemo	TP + Bev	60/58	60.0/62.0	70/78	95/93
BEYOND	TP + Bev	Chemo	138/138	57.0/56.0	54/56	91/91
ECOG 4599	TP + Bev	Chemo	417/433	NG	50/58	74/78
JO 19907	TP + Bev	Chemo	121/59	61.0/66.0	64/64	69/71
IMpower130	Atezo + TP	Chemo	451/228	NG	59/59	100/100
CLEAR	AP + Bev	TP + Bev	131/66	66.0/67.0	74/71	73/76
PointBreak	AP + Bev	TP + Bev	472/467	64.9/64.6	53/53	90/90
CameL	Camre + AP	Chemo	205/207	59.0/61.0	71/72	85/80
CheckMate 227	Nivo + AP	Chemo	270/273	63.0/63.0	64/63	NG
PRONOUNCE	Chemo	TP + Bev	182/179	65.8/65.4	58/58	99/100
IMpower150	Atezo + TP	TP + Bev	402/400	63.0/63.0	60/60	NG

Studienergebnisse:

- Overall, Chemo + ICi appears to be superior to Chemo + Bev, both in OS (HR: 0, 92; 95% CI: 0.88-0,96) and in PFS (HR: 0.93; 95% CI; 0.90-0,97) in the whole population. Ranking results were in accordance with the pooled estimates. Chemo + ICI was most likely to rank first to provide PFS and OS benefit compared to Chemo + Bev and Chemo.

Anmerkung/Fazit der Autoren

In general Chemo + ICi is superior to Chemo + Bev in the first line treatment of ns-NSCLC without mutations. Pembro + Chemo is worth recommending first.

3.3 Leitlinien

Leitlinienprogramm Onkologie, 2022 [25].

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

Siehe auch: Leitlinienprogramm Onkologie, 2022 [26].

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:

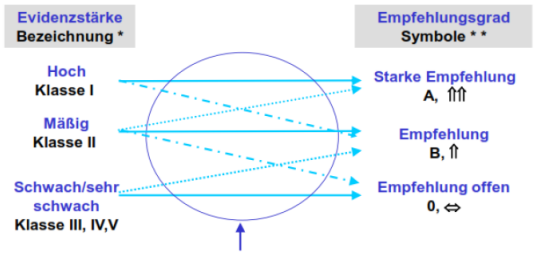
- Aktualisierung für den Zeitraum 2016-2022

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

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 [8].

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

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:

- 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 [31].

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.

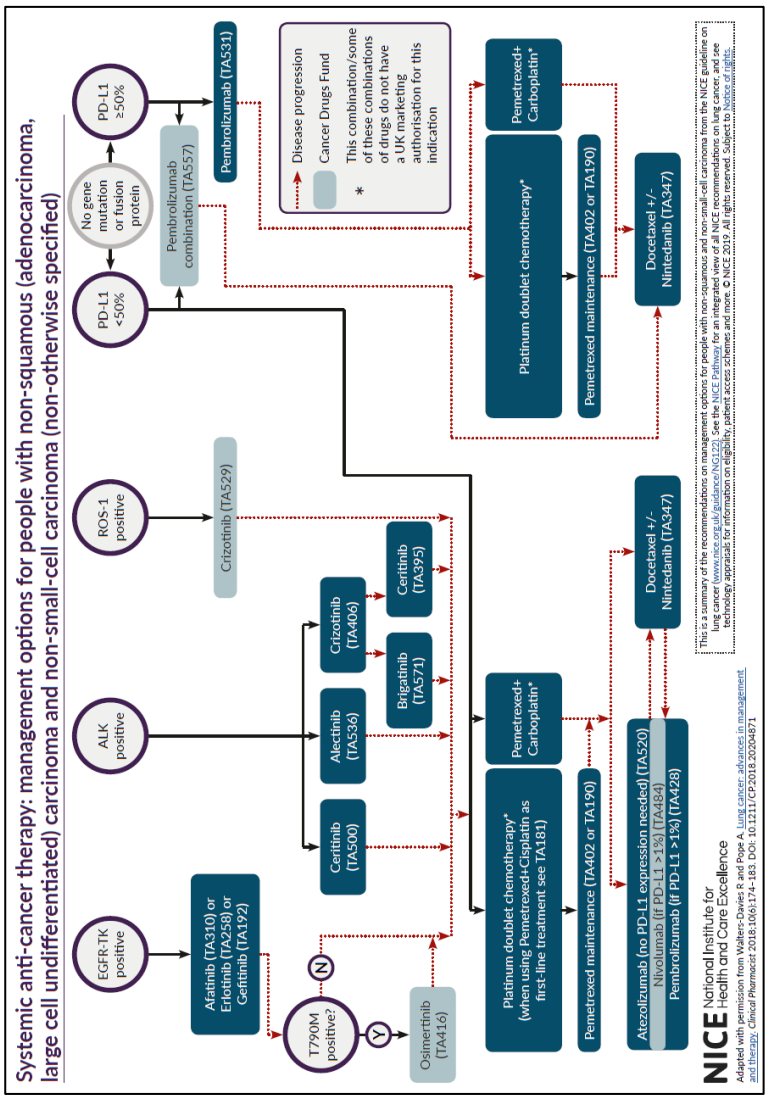
Squamous non-small-cell lung cancer

- 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%

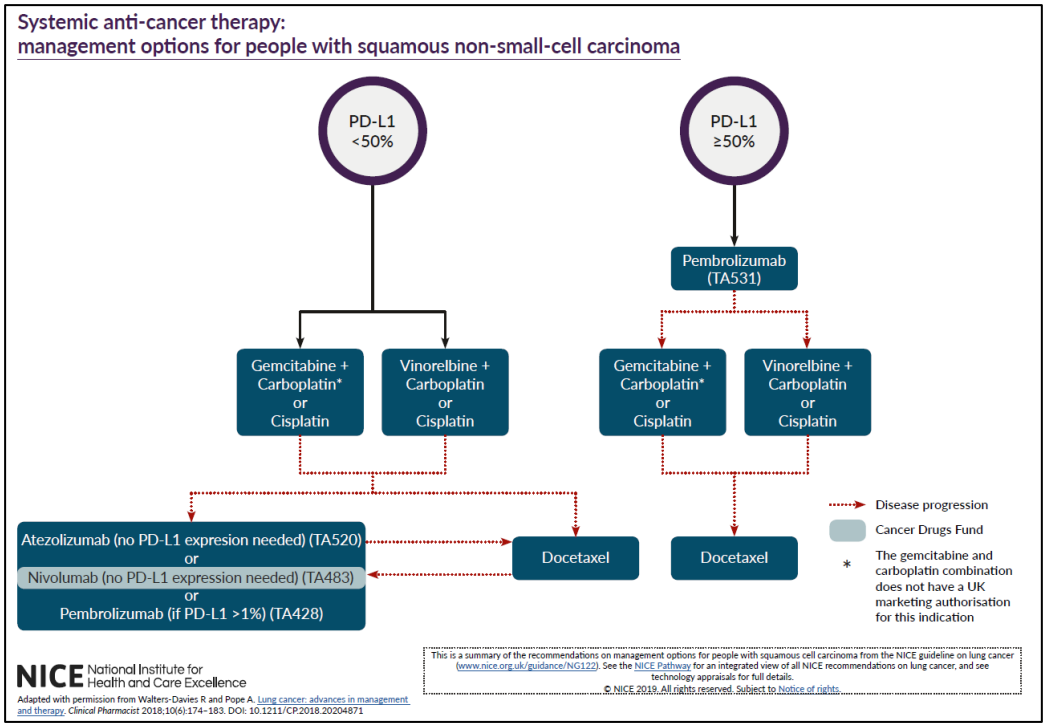
- 1.4.51 For guidance on treatment for squamous NSCLC in people whose tumours express PD-L1 below 50%:
  - for initial treatment, offer gemcitabine or vinorelbine and cisplatin or carboplatin.

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)



Singh N et al., 2023 [38].

Therapy for Stage IV Non–Small-Cell Lung Cancer Without Driver Alterations: ASCO Living Guideline

Zielsetzung/Fragestellung

To provide evidence-based recommendations updating the 2020 ASCO and Ontario Health (Cancer Care Ontario) guideline on systemic therapy for patients with stage IV non–small-cell lung cancer without driver alterations.

Methodik

Grundlage der Leitlinie

Update der Version von Hanna N. et al. 2020 [18]

- 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:

evidence identified through online searches of PubMed June 2018 through December 2021

LoE/GoR

GRADE

Empfehlungen

Recommendations

Recommendation 1.5 (note numbering change: 2020 1.5 will become 2022 1.8). In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%; Table 1), nonsquamous cell carcinoma (non-SCC), and performance status (PS) 0-1, clinicians may offer single-agent atezolizumab (Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Strong).

Recommendation 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).

Recommendation 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).

Recommendation 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).

Recommendation 3.3 (note numbering change: 2020 3.3 will become 2022 3.6). In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), squamous cell carcinoma (SCC), and PS 0-1, clinicians may offer single-agent atezolizumab (Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Strong).

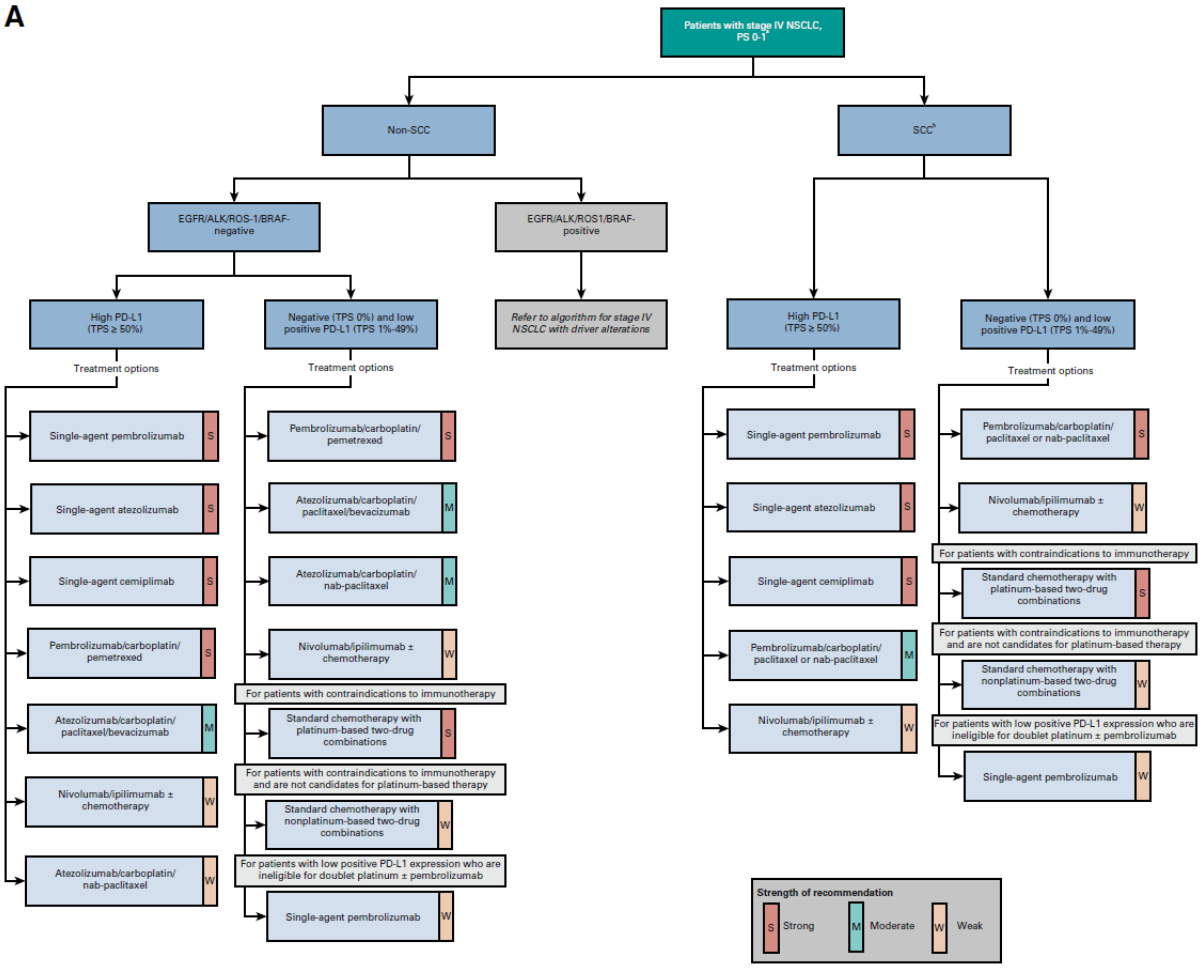
Recommendation 3.4. In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), SCC, and PS 0-1, clinicians may offer single-agent cemiplimab (Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Strong).

Recommendation 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).

Recommendation 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).

Recommendation 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).

Recommendation 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).



Passiglia F et al., 2020 [32].

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

<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:

- Medline (PubMed), Embase-databases and Cochrane-Library, up to September 2019.
- Update von Facchinetti F et al., 2019 [12].

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

2022-B-328

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)

Sachverständige:

Indikation gemäß Beratungsantrag

Erstlinienbehandlung von erwachsenen Patienten mit **nicht-plattenepithelialem** nicht-kleinzelligem Lungenkarzinom (NSCLC), deren Tumore keine positive Mutation des epidermalen Wachstumsfaktorrezeptors (EGFR) oder der anaplastischen Lymphomkinase (ALK) aufweisen, mit

- lokal fortgeschrittener Erkrankung, die nicht für eine chirurgische Resektion oder platinbasierte Radiochemotherapie infrage kommen, oder mit
- metastasierter Erkrankung

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

Zusammenfassung

Standard in der Erstlinientherapie von Patientinnen und Patienten (Pat.) mit nicht-plattenepithelialem, nicht-kleinzelligem Lungenkarzinom (non-small cell lung cancer, NSCLC), deren Tumoren keine positive Mutation des EGFR oder der ALK aufweisen und entweder lokal fortgeschritten (keine Indikation zur Resektion oder zur platinbasierten Radiochemotherapie) oder metastasiert sind, ist

- Kombination eines PD-1- oder PD-L1-Immuncheckpoint-Inhibitors mit platinhaltiger Chemotherapie, die Art der empfohlenen Chemotherapie ist abhängig von der Histologie
- Monotherapie mit einem Immuncheckpoint-Inhibitor
- platinhaltige Chemotherapie bei Kontraindikationen gegen eine Immuntherapie
- zielgerichtete Therapie bei Nachweis definierter, genetischer Aberrationen, insbesondere bei Kontraindikationen gegen Immun-, Immunchemotherapie oder Chemotherapie.

Fragestellung

Die Fragestellungen in den Verfahren 2022-B-328, 2022-B-329 und 2022-B-330 sind inhaltlich eng verwandt. Entsprechend unterscheiden sich unsere drei gutachterlichen Expertisen nur in den Aspekten des unterschiedlichen Einsatzes bestimmter Arzneimittel in Abhängigkeit von der Histologie.

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Stand des Wissens

Mehr als 50% der Pat. mit nicht-kleinzelligem Lungenkarzinom werden im Stadium IV diagnostiziert. Bei der Mehrzahl der Pat. ist der Therapieanspruch nicht kurativ [1, 2]. Ausnahme sind Pat. im neu definierten, sog. oligometastatischen Stadium M1b, z. B. mit solitären Nebennieren-, ZNS-, Lungen- oder Knochenmetastasen, bei denen ein potenziell kurativer Therapieansatz in Frage kommt.

In der aktuellen S3 Leitlinie werden die Empfehlungen folgendermaßen zusammengefasst [1]:

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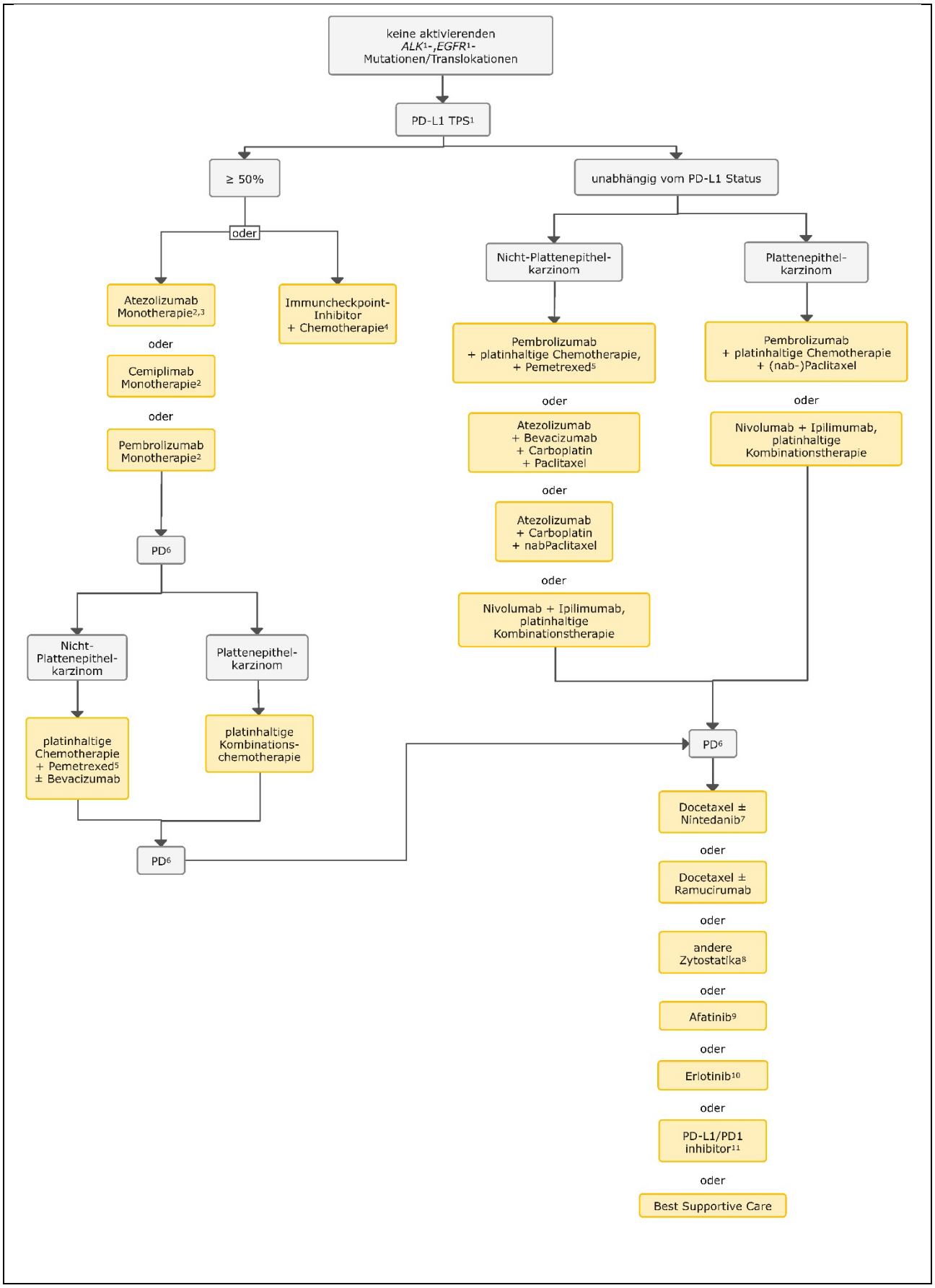
8.78	Evidenzbasierte Empfehlung	modifiziert 2022
Empfehlungsgrad **A**	Bei NSCLC-Patienten mit nicht-plattenepithelialer Histologie im UICC Stadium IV sowie ECOG 0-1, welche keine therapierbaren Mutationen und keine Kontraindikation gegenüber Checkpoint-Inhibitoren aufweisen, soll, unabhängig vom PD-L1 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	

In ONKOPEDIA wird der Algorithmus graphisch dargestellt [2]:


keine aktivierenden ALK[1]-,EGFR[1]-Mutationen/Translokationen
PD-L1 TPS[1]
≥ 50%
unabhängig vom PD-L1 Status
oder
Atezolizumab Monotherapie[2,3]
Immuncheckpoint-Inhibitor + Chemotherapie[4]
oder
Cemiplimab Monotherapie[2]
oder
Pembrolizumab Monotherapie[2]
PD[6]
Nicht-Plattenepithel-karzinom
Plattenepithel-karzinom
platinhaltige Chemotherapie + Pemetrexed[5] ± Bevacizumab
platinhaltige Kombinations-chemotherapie
PD[6]
Nicht-Plattenepithel-karzinom
Plattenepithel-karzinom
Pembrolizumab + platinhaltige Chemotherapie, + Pemetrexed[5]
oder
Atezolizumab + Bevacizumab + Carboplatin + Paclitaxel
oder
Atezolizumab + Carboplatin + nabPaclitaxel
oder
Nivolumab + Ipilimumab, platinhaltige Kombinationstherapie
Pembrolizumab + platinhaltige Chemotherapie + (nab-)Paclitaxel
oder
Nivolumab + Ipilimumab, platinhaltige Kombinationstherapie
PD[6]
Docetaxel ± Nintedanib[7]
oder
Docetaxel ± Ramucirumab
oder
andere Zytostatika[8]
oder
Afatinib[9]
oder
Erlotinib[10]
oder
PD-L1/PD1 inhibitor[11]
oder
Best Supportive Care

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Legende: [1]PD-L1 TPS - Expression von PD-L1 auf Tumorzellen, quantifiziert nach dem Tumor Proportion Score (TPS); [2] wenn für Immuntherapie geeignet und keine relevanten Kontraindikationen bestehen; siehe auch die aktuell gültigen Zulassungsinformationen; [3]alternativ IC≥10%; [4]aus einem Anti-PD1-/PD-L1-Antikörper und Chemotherapie, differenziert nach der Histologie; [5] TTF1 Negativität ist ein negativer Prädiktor für die Wirksamkeit von Pemetrexed; [6] PD – progrediente Erkrankung; [7] Nintedanib nur bei Adenokarzinom; [8] Zytostatikum der 3. Generation: Gemcitabin, Pemetrexed, Vinorelbin; Pemetrexed nur bei Nicht-Plattenepithelkarzinom; [9] Afatinib nur bei Plattenepithelkarzinom; [10] PD-1-/PD-L1-Inhibitor: Atezolizumab (unabhängig von PD-L1-Expression), Nivolumab (unabhängig von PD-L1-Expression), Pembrolizumab (nur bei TPS ≥1%); der Nachweis der Wirksamkeit ist nicht geführt bei Pat., die in der Erstlinientherapie mit einem Immuncheckpoint-Inhibitor vorbehandelt sind;

Die Evidenz für diese Empfehlungen kann folgendermaßen zusammengefasst werden:

- Expression des Immunmarkers PD-L1 auf >50% der Tumorzellen
    - Die Monotherapie mit dem Anti-PD1-Antikörper Pembrolizumab führte gegenüber Platin-haltiger Chemotherapie zur Verlängerung der Gesamtüberlebenszeit (Hazard Ratio 0,62; 26,3 vs 13,4 Monate), zur Verlängerung des progressionsfreien Überlebens (HR 0,50; Median 4,3 Monate) und zu einer Senkung der Rate schwerer Nebenwirkungen [3]. Die Daten werden bestätigt durch die Ergebnisse der KEYNOTE-042-Studie. Daten eines direkten Vergleichs von Pembrolizumab Monotherapie gegenüber Pembrolizumab + Kombinationschemotherapie liegen bisher nicht vor.
    - Die Monotherapie mit dem Anti-PD-L1-Antikörper Atezolizumab führte bei Pat. mit PD-L1 auf ≥50% der Tumorzellen oder einer Rate PD-L1-positiver Tumor-infiltrierender Immunzellen (IC) von ≥10% gegenüber Platin-haltiger Chemotherapie zur Verlängerung der Gesamtüberlebenszeit (HR 0,59; 20,2 vs 13,1 Monate), zur Verlängerung des progressionsfreien Überlebens (HR 0,63; Median 3,1 Monate) und in der Gesamtstudie zu einer Senkung der Rate schwerer Nebenwirkungen (52,5 vs 30,1%) [4].
    - Die Monotherapie mit dem Anti-PD-L1-Antikörper Cemiplimab führte bei Pat. mit einer PD-L1-Expression ≥50% gegenüber Platin-haltiger Chemotherapie zur Verlängerung der Gesamtüberlebenszeit (HR 0,57; Median nicht erreicht vs 14 Monate), zur Verlängerung des progressionsfreien Überlebens (HR 0,63; Median plus 2,5 Monate) und in der Gesamtstudie zu einer Senkung der Rate schwerer Nebenwirkungen (28 vs 39%) [5].
    - Die Kombination eines Immuncheckpoint-Inhibitors mit Platin-haltiger Chemotherapie ist eine mögliche Alternative insbesondere bei Pat. mit Remissionsdruck durch belastende

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Symptomatik, hohe Tumorlast bzw. rasches Tumorwachstum. In einer Metaanalyse der FDA zeigten sich keine signifikanten Unterschiede bei der Gesamtüberlebenszeit zwischen Monotherapie und Kombinationstherapie, allerdings einen leichten numerischen Vorteil zugunsten der Immunchemotherapie sowie einen signifikanten Vorteil bei der progressionsfreien Überlebenszeit. Bei Pat. ≥75 Jahre deutete sich ein Vorteil zugunsten der Immunmonotherapie an [6].

- unabhängig von der PD-L1-Expression auf Tumorzellen oder Tumor-infiltrierenden Immunzellen
    - Bei Nicht-Plattenepithelkarzinomen führte die Kombination von Pembrolizumab mit Chemotherapie (Platin/Pemetrexed) gegenüber Chemotherapie zur Verlängerung der Gesamtüberlebenszeit (HR 0,56; Median 11,3 Monate) und zur Verlängerung des progressionsfreien Überlebens (HR 0,48; Median 3,9 Monate) [7]. Der relative Gewinn durch Pembrolizumab steigt mit dem Grad der PD-L1-Expression, ist aber auch in der Gruppe der PD-L1-negativen Pat. signifikant in Bezug auf die Gesamtüberlebenszeit (HR 0,52). In der Subgruppe der TTF1 negativen Pat. sollte der Einsatz anderer Zytostatika anstelle von Pemetrexed berücksichtigt werden [8].
    - Bei Nicht-Plattenepithelkarzinomen führte die Kombination von Atezolizumab mit Carboplatin / Paclitaxel / Bevacizumab (BCP) gegenüber BCP zur Verlängerung der Gesamtüberlebenszeit (HR 0,78; Median 5,5 Monate) und des progressionsfreien Überlebens (HR 0,62; Median 1,5 Monate) [9]. Unklar ist die Notwendigkeit von Bevacizumab in dieser Kombination. Diese Kombination ist die einzige zugelassene Kombinationstherapie mit Immuncheckpoint-Inhibitoren für Pat. mit *EGFR* und *ALK* Alterationen. Diese Kombination sollte in dieser Indikation allerdings nur eingesetzt werden, wenn die Möglichkeiten der zielgerichteten Therapie ausgeschöpft sind. Eine Gruppe von Pat., die von der Atezolizumab-BCP Therapie gegenüber BCP möglicherweise besonders profitieren können, sind Pat. mit Lebermetastasen.
    - Bei Nicht-Plattenepithelkarzinomen führte auch die Kombination von Atezolizumab mit Carboplatin / nabPaclitaxel gegenüber Carboplatin / nabPaclitaxel zur Verlängerung der Gesamtüberlebenszeit (HR 0,79; Median 4,7 Monate) und des progressionsfreien Überlebens (HR 0,64; Median 1,5 Monate) [10].

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    - Bei Nicht-Plattenepithelkarzinomen unabhängig von der PD-L1-Expression führte die Kombination von Nivolumab / Ipilimumab in Kombination mit einer Chemotherapie für 2 Zyklen und Fortsetzung der Immunkombinationstherapie gegenüber einer konventionellen Chemotherapie mit 4 Zyklen zur signifikanten Verlängerung des Gesamtüberlebens (HR 0,66; Median 15,6 vs 10,9 Monate) [11], zur Zulassung siehe die aktuell gültigen Zulassungsinformationen. Die Nebenwirkungen der Immunkombinationstherapie sind höher als bei einer Immunmonotherapie oder der Kombination von Immun- mit Chemotherapie und betreffen vor allem hepatische, kutane und endokrine Toxizitäten. In der Studie profitierten insbesondere Pat. mit niedriger PD-L1-Expression und plattenepithelialer Histologie. Ein direkter Vergleich der doppelten Immuncheckpointinhibitor (I/O-I/O)-Chemotherapie gegenüber einer einfachen Immuncheckpointinhibitor (I/O)-Chemotherapie liegt nicht vor.

- Chemotherapie: Bei Entscheidung für eine ausschließliche Chemotherapie ist die Kombinationschemotherapie mit zwei Zytostatika wirksamer als die Monotherapie in Bezug auf die Remissionsrate, die progressionsfreie und die Gesamtüberlebenszeit. Kombinationen sind mit einer höheren Therapie-assoziierten Toxizität belastet. Die meisten Erfahrungen liegen mit Platin-haltigen Kombinationen vor. Frühere Untersuchungen haben gezeigt, dass mit Cisplatin signifikant höhere Remissionsraten als mit Carboplatin erreicht werden, allerdings zeigen sich diese Unterschiede nicht in Kombinationen mit Drittgenerationsmedikamenten. In Bezug auf die Gesamtüberlebenszeit sind die beiden Platinderivate äquieffektiv [12, 13]. Die Wahl orientiert sich vor allem an der individuell zu erwartenden Toxizität. Nicht-Platin-haltige Kombinationen haben niedrigere Remissionsraten als Platin-haltige Kombinationen.
- Bei Pat. mit Nicht-Plattenepithelkarzinom führte die Kombination von Bevacizumab mit Carboplatin/Paclitaxel, Cisplatin/Gemcitabin oder einer anderen Platin-haltigen Zweierkombination im Vergleich mit der alleinigen Chemotherapie zu einer Steigerung der Remissionsrate und zu einer Verlängerung des progressionsfreien Überlebens, allerdings auch zu einer Steigerung der Nebenwirkungsrate. Die Kombination Paclitaxel/Carboplatin/Bevacizumab führte auch zu einer Verlängerung der Gesamtüberlebenszeit.
- Molekular stratifizierte Therapie (außer *EGFR*-Mutationen und *ALK*-Positivität): Hier werden Arzneimittel eingesetzt, deren Wirksamkeit und Sicherheit in der Erst- oder Zweitlinientherapie

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nachgewiesen ist. Sie sind insbesondere eine Option bei Kontraindikationen gegen eine Immun- und/oder Chemotherapie:

- *BRAF V600E*-Mutation: Dabrafenib + Trametinib [14]
- *HER2*-Amplifikationen und -Mutationen [15]
- *KRAS G12C* Mutation: Sotorasib [16, 17]
- *c-METex14* Mutation: Capmatinib oder Tepotinib [18, 19]
- *NTRK*-Translokationen: Entrectinib oder Larotrectinib [20, 21]
- *RET*-Translokationen: Pralsetinib oder Selpercatinib [22, 23]
- *ROS1*-Translokationen: Crizotinib oder Entrectinib [24, 25, 26]

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der „*Erstlinienbehandlung von erwachsenen Patienten mit nicht-plattenepithelialem NSCLC, deren Tumore keine positive Mutation des EGFR oder der ALK aufweisen, mit lokal fortgeschrittener Erkrankung, die nicht für eine chirurgische Resektion oder platinbasierte Radiochemotherapie infrage kommen, oder mit metastasierter Erkrankung*“**, 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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Sachverständige:

Indikation gemäß Beratungsantrag

Erstlinienbehandlung von erwachsenen Patienten mit **nicht-plattenepithelialem** nicht-kleinzelligem Lungenkarzinom (NSCLC), deren Tumore keine positive Mutation des epidermalen Wachstumsfaktorrezeptors (EGFR) oder der anaplastischen Lymphomkinase (ALK) aufweisen, mit

- lokal fortgeschrittener Erkrankung, die nicht für eine chirurgische Resektion oder platinbasierte Radiochemotherapie infrage kommen, oder mit
- metastasierter Erkrankung

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