# Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

**und**

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

**und**

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

# Vorgang: 2022-B-311 Atezolizumab

Stand: Juli 2024

| I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA | |
|---|---|
| **Atezolizumab**<br>**[NSCLC, Erstlinie, Platin-ungeeignet]** | |
| **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"<br><br>Ausgeschlossen wurden Arzneimittel zur Therapie eines NSCLC mit ALK-Translokation, EGFR-, BRAF-, 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:**<br>− Atezolizumab (Beschlüsse vom 02.04.2020 und 19.11.2021)<br>− Cemiplimab (Beschluss vom 20.01.2022)<br>− Ipilimumab (Beschluss vom 03.06.2021)<br>− Nivolumab (Beschluss vom 03.06.2021)<br>− Pembrolizumab (Beschlüsse vom 19.09.2019 und 03.08.2017) |
| Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören. | Siehe systematische Literaturrecherche |

# II. Zugelassene Arzneimittel im Anwendungsgebiet

| Wirkstoff ATC-Code Handelsname | Anwendungsgebiet (Text aus Fachinformation) |
|---|---|
| **Zu bewertendes Arzneimittel:** | |
| Atezolizumab L01FF05 Tecentriq | <u>Anwendungsgebiet laut Positive Opinion:</u><br>Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with advanced NSCLC who are ineligible for platinum-based therapy. |
| **Zytostatika:** | |
| Docetaxel L01CD02 generisch | Nicht-kleinzelliges Bronchialkarzinom:<br>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:<br>− Palliative Therapie des fortgeschrittenen, nicht-kleinzelligen Bronchialkarzinoms bei Patienten mit gutem Allgemeinzustand (Karnofsky-Index > 80 %), […] |
| Gemcitabin L01BC05 generisch | Eine Gemcitabin-Monotherapie kann bei älteren Patienten oder solchen mit einem Performance Status 2 in Betracht gezogen werden. |
| Ifosfamid L01AA06 Holoxan | Nicht-kleinzellige Bronchialkarzinome:<br>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 […]. |
| Vindesin L01CA03 | Kombinationschemotherapie:<br>Lokal fortgeschrittenes oder metastasiertes nicht-kleinzelliges Bronchialkarzinom (Stadium IIIB, IV). |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| Eldesine | |
| Vinorelbin L01CA04 generisch | Behandlung des nicht kleinzelligen Bronchialkarzinoms (Stadium 3 oder 4). |
| **Antikörper:** | |
| Atezolizumab L01XC32 Tecentriq | 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. |
| 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. |
| 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. […] |

Quellen: AMIce-Datenbank, Fachinformationen

**Abteilung Fachberatung Medizin**

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

# Vorgang: 2022-B-311 (Atezolizumab)

| | |
|---|---|
| Auftrag von: | Abt. AM |
| Bearbeitet von: | Abt. FB Med |
| Datum: | 5. Januar 2023 |

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# Abkürzungsverzeichnis

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

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

# 1 Indikation

Tecentriq als Monotherapie ist angezeigt zur Erstlinienbehandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC, die als Platin-ungeeignet angesehen werden und deren Erkrankung keine EGFR-Mutation oder ALK-Translokation haben.

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

# 2 Systematische Recherche

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

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

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

# 3 Ergebnisse

## 3.1 Cochrane Reviews

**Ferrara R et al., 2021 [7].**

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

### Fragestellung

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

### Methodik

Population:

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

Intervention/Komparator

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

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

Endpunkte:

- OS, PFS, ORR, HRQoL, AEs

Recherche/Suchzeitraum:

- from inception to 31st December 2020

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

### Ergebnisse

Anzahl eingeschlossener Studien:

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

Qualität der Studien:

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

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

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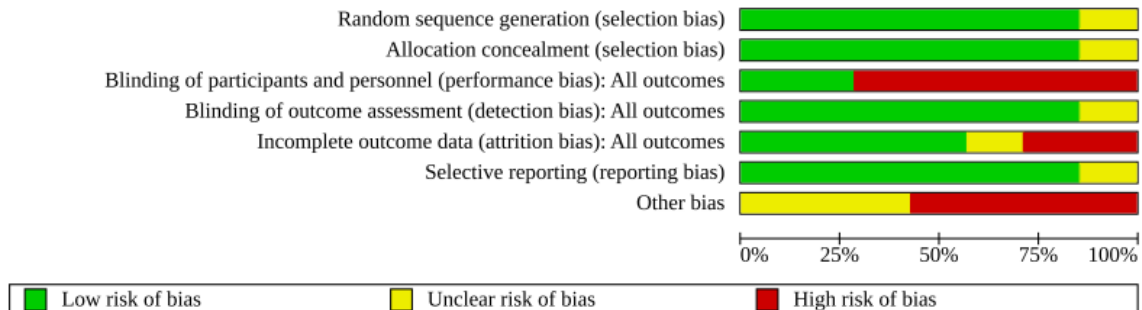
Studienergebnisse:

- Note: The majority of the included trials reported their outcomes by PD-L1 expressions, with PD-L1 ≥ 50 being considered the most clinically useful cut-off level for decision makers. Also, iIn order to avoid overlaps between various PDL-1 expressions we prioritised the review outcomes according to PD-L1 ≥ 50.

- Single-agent ICI: In the PD-L1 expression ≥ 50% group single-agent ICI probably improved OS compared to platinum-based chemotherapy (hazard ratio (HR) 0.68, 95% confidence interval (CI) 0.60 to 0.76, 6 RCTs, 2111 participants, moderate-certainty evidence). In this group, single-agent ICI also may improve PFS (HR: 0.68, 95% CI 0.52 to 0.88, 5 RCTs, 1886 participants, low-certainty evidence) and ORR (risk ratio (RR):1.40, 95% CI 1.12 to 1.75, 4 RCTs, 1672 participants, low-certainty evidence). HRQoL data were available for only one study including only people with PDL1 expression ≥ 50%, which suggested that single-agent ICI may improve HRQoL at 15 weeks compared to platinum-based chemotherapy (RR: 1.51, 95% CI 1.08 to 2.10, 1 RCT, 297 participants, low-certainty evidence). In the included studies, treatment-related AEs were not reported according to PD-L1 expression levels. Grade 3-4 AEs may be less frequent with single-agent ICI compared to platinum-based chemotherapy (RR: 0.41, 95% CI 0.33 to 0.50, I2 = 62%, 5 RCTs, 3346 participants, lowcertainty evidence).

- Double-agent ICI: Double-ICI treatment probably prolonged OS compared to platinum-based chemotherapy in people with PD-L1 expression ≥50% (HR: 0.72, 95% CI 0.59 to 0.89 2 RCTs, 612 participants, moderate-certainty evidence). Trials did not report data on HRQoL, PFS and ORR according to PD-L1 groups. Treatment related AEs were not reported according to PD-L1 expression levels. The frequency of grade 3-4 AEs may not differ between double-ICI treatment and platinum-based chemotherapy (RR: 0.78, 95% CI 0.55 to 1.09, I2 = 81%, 2 RCTs, 1869 participants, low-certainty evidence).

**Anmerkung/Fazit der Autoren**

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

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

**Vasconcellos VF et al., 2020 [25].**

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

### Fragestellung

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

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

### Methodik

Population:

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

Intervention/Komparator:

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

Endpunkte:

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

Recherche/Suchzeitraum:

- Bis Januar 2019
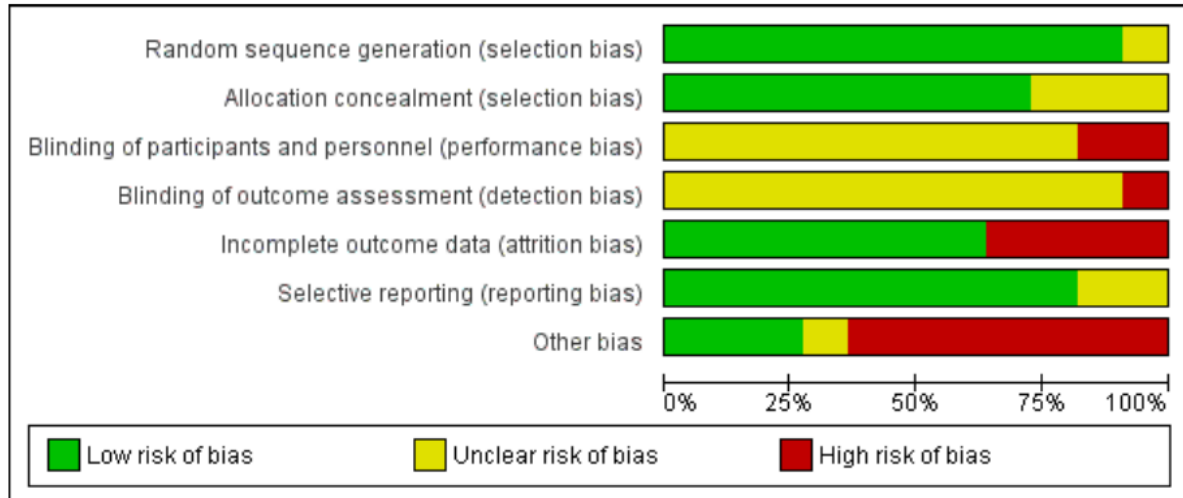
Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

### Ergebnisse

Anzahl eingeschlossener Studien:

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

<u>Qualität der Studien:</u>



<u>Studienergebnisse:</u>

- 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 [11].**

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 [20]

  Freemantle, N. et al., 2022 [8]

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

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

**Fragestellung**

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

**Methodik**

Population:

- patients with previously untreated advanced NSCLC

Intervention/Komparator:

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

Endpunkte:

- OS, PFS, ORR, TRAEs

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Cochrane approach

**Ergebnisse**

Anzahl eingeschlossener Studien:

- eight randomized clinical trials including a total of 4466 patients

Charakteristika der Population:

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

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

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

Qualität der Studien:

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

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

Studienergebnisse:

- The addition of a PD-(L)1 inhibitor to CT improved progression-free survival, overall survival, and objective response rate compared with CT alone.

- The risk of grade greater than or equal to 3 treatment-related adverse events was slightly higher with the addition of a PD-(L)1 inhibitor to CT as compared with CT alone.

- A subgroup analysis according to the targeted receptor (PD-1 versus PD-L1) revealed that the addition of a PD-1 inhibitor to CT led to better objective response rate (p ¼ 0.0001), progression-free survival (p = 0.006), and overall survival (p = 0.002) compared with that of a PD-L1 inhibitor.

- The risk of grade greater than or equal to 3 treatment-related adverse events was significantly increased with the addition of a PD-L1 inhibitor to CT, but not with the addition of a PD-1 inhibitor.

- A direct comparison using the meta-regression analysis confirmed the statistical significance of all previous findings.

**Fazit der Autoren**

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

*Kommentar zum Review:*

   Siehe auch:

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

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**Wang DD et al., 2021 [28].**

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

**Fragestellung**

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

**Methodik**

Population:

- patients with advanced non-small cell lung cancer

Intervention:

- PD-1/PD-L1 inhibitors

Komparator:

- Chemotherapy

Endpunkte:

- OS and/or PFS

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Cochrane Collaboration's Risk of Bias tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 19 RCTs, including 12,753 patients

Charakteristika der Population:

**Table I.** Details of all included trials.

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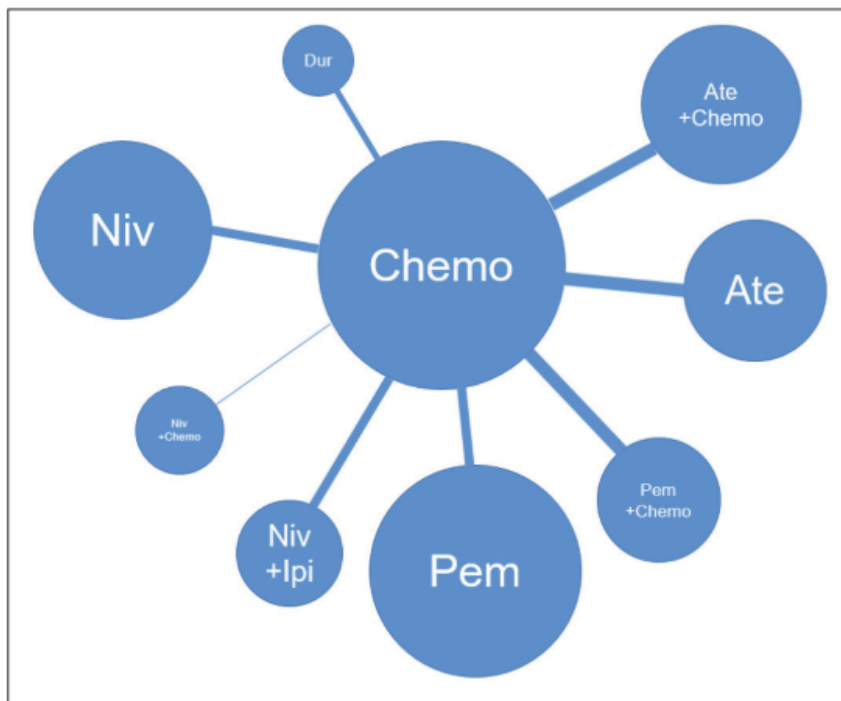
Studienergebnisse:



**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 [18]
- Jiang, M. et al., 2022 [13]
- Wang, L. et al., 2022 [28]
- Peng TR und Wu TW, 2019 [23]

### Yang Y et al., 2021 [30].

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

### Fragestellung

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

### Methodik

Population:

- advanced patients with NSCLC patients

Intervention/Komparator:

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

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 8 phase III RCTs with 4253 patients

Charakteristika der Population:

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

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

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

Qualität der Studien:

- All of the studies were of high quality.
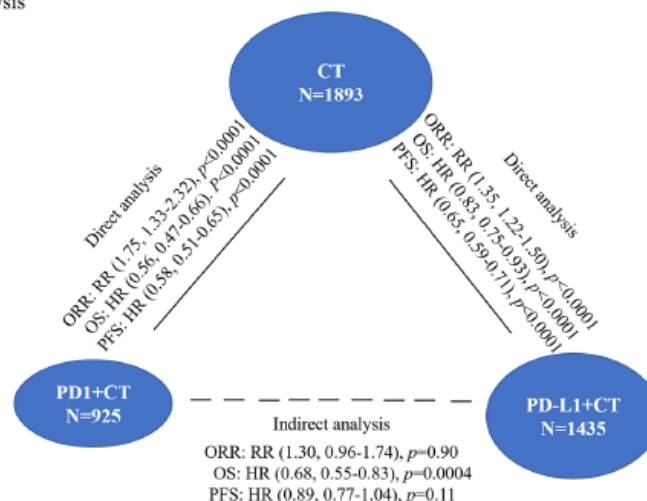
Studienergebnisse:



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

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

### Anmerkung/Fazit der Autoren

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

*Kommentare zum Review*
- Siehe auch: Li, L. et al., 2020 [17]

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### Dafni U et al., 2019 [2].

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

### Fragestellung

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

### Methodik

Population:
- untreated/chemotherapy-naive advanced/metastatic NSCLC patients

Intervention/Komparator:
- ICI(s), whether alone, in combination, or with chemotherapy

Endpunkte:
- PFS, OS, Toxicity

Recherche/Suchzeitraum:
- Until April-2019

Qualitätsbewertung der Studien:
- 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:
  o 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)
  o 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).
  o Based on the NMA estimates, the combination of chemotherapy with either pembrolizumab or atezolizumab exhibit significantly higher benefit than all other treatments evaluated, with the pembrolizumabcombination better than the atezolizumab-combination (HR=0.82 [0.70-0.97]). The combinations of ipilimumab with either nivolumab or chemotherapy are better than the ICI-monotherapies examined.

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

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

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

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

**Anmerkung/Fazit der Autoren**

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

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

*Kommentare zum Review*

Siehe auch:

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

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**Zhou Y et al., 2019 [32].**

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

### Fragestellung

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

### Methodik

Population:

- advanced NSCLC

Intervention/Komparator:

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

Endpunkte:

- OS, PFS, ORR

Recherche/Suchzeitraum:

- before November 1, 2018

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool

### Ergebnisse

Anzahl eingeschlossener Studien:

- five trials involving 1289 patients

## Charakteristika der Population:

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

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

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

## Qualität der Studien:

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

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

## Studienergebnisse:

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

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

**Anmerkung/Fazit der Autoren**

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


*Kommentare zum Review*
- Siehe auch: Kim R et al. 2019 [14]

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**Liu J et al., 2020 [19].**

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

**Fragestellung**

to compare these approved first-line treatments for advanced NSCLC
- Yang
-  or squamous NSCLC was categorized for subgroup analysis

**Methodik**

Population:
- advanced non-small cell lung carcinoma patients

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

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

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

Qualitätsbewertung der Studien:

- Cochrane Collaboration's risk of bias tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- Ten trials, involving 6,124 patients

Charakteristika der Population:

**Table 1.** Study characteristics.

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

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

Qualität der Studien:

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

| Trial | Sequence Generation | Allocation Concealment | Blinding | Incomplete Outcome Data | Selective Reporting | Other Source of bias |
|---|---|---|---|---|---|---|
| KEYNOTE-021 [6,16] | Adequate | Adequate (Central Allocation) | Adequate (Independent Radiologic Review) | Adequate | Adequate (PFS、OS was not reported) | |
| KEYNOTE-024 [8,17] | Inadequate | Inadequate (Central Allocation) | Adequate (Independent Radiologic Review) | Adequate | Adequate | |
| KEYNOTE-042 [9] | Adequate | Adequate (Central Allocation) | Adequate (Independent Radiologic Review) | Adequate | Adequate | |
| KEYNOTE-042 in China [20] | Inadequate | 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:
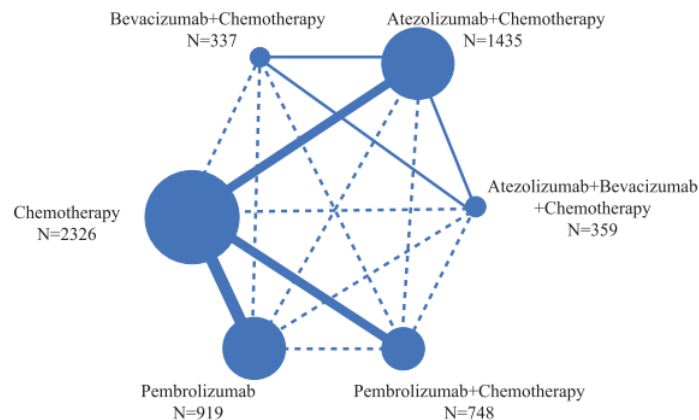


**Figure 2.** Network structure for all the included trials. Each circular node represents a treatment type. The circle size is proportional to the total number of patients. The width of lines is proportional to the number of studies performing head-to-head comparisons in the same study, and the dotted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

  o 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).

  o 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

  o For PD-L1-intermediate patients, the PFS-NMA was based on four trials and OS-NMA on five trials.

  o 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.

  o 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 (HR 0.70, 95% CI 0.53–0.92) and PC (HR 0.56, 95% CI 0.39–0.80) were significantly more effective than chemotherapy in terms of PFS and PC appears significantly superior to both chemotherapy alone (HR 0.57, 95% CI 0.36–0.90) and AC in terms of overall survival. For PD-L1-negative patients, PC appears significantly superior to chemotherapy alone in terms of ORR (OR 1.50, 95% CI 1.20–2.10), PFS (HR 0.68, 95% CI 0.47–0.98) and OS (HR 0.61, 95% CI 0.38–0.98). There was no identifiable difference among the other regimens included.

- NMA for safety analysis
  - Patients with low grade and grade 3–5 AEs perhaps benefit more from PC and Pembrolizumab alone compared to BC (OR 0.95, 95% CI 0.91–0.99 for PC, OR 0.69, 95% CI 0.64–0.74 for Pembrolizumab alone for grade 1–5 AEs; OR 0.73, 95% CI 0.61–0.88 for PC, OR 0.33, 95% CI 0.26–0.42 for Pembrolizumab alone for grade 3–5 AEs). ABC and AC appear significantly less safe than PC with an OR 1.60 (95% CI 1.30–1.90 for grade 3–5 AEs for ABC) and an OR 1.20 (95% CI 1.10–1.30 for grade 3–5 AEs for AC). Pembrolizumab alone appears to be the safest intervention among the regimens analyzed.

**Anmerkung/Fazit der Autoren**

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

*Kommentare zum Review*

Siehe auch:

- Cao, R. et al., 2019 [1]
- Herbst, R. et al., 2021 [12]

## 3.3 Leitlinien

**Leitlinienprogramm Onkologie, 2022 [16].**

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

Siehe auch: Leitlinienprogramm Onkologie, 2022 [15].

### 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
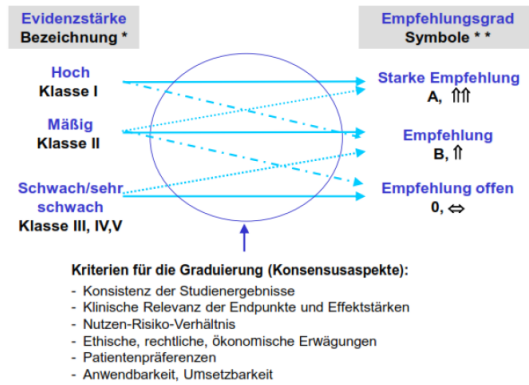
Abbildung 1: : Schema zur Darstellung der Kriteriengestützen Entscheidungsprozesse bei der Wahl des Empfehlungsgrades.
*: blau = Evidenzstärke nach GRADE bzgl. des gesamten ‚body of evidence', schwarz = Evidenzklassifikation bzgl. Einzelstudien, z.B. nach Oxford;
**: Empfehlungsgraduierung im Programm 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<br><br>**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<br><br>**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<br><br>**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:<br><br>• eine Monotherapie mit Atezolizumab (≥ 50% der Tumorzellen oder 10% der tumorinfiltrierenden Lymphozyten), Cemiplimab (≥ 50% der Tumorzellen) oder Pembrolizumab (≥ 50% der Tumorzellen) oder<br>• Pembrolizumab mit Chemotherapie oder Nivolumab und Ipilimumab mit Chemotherapie<br><br>als Erstlinientherapie angeboten werden. | |
| Level of Evidence<br><br>**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<br>**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<br>**1 b** | [944], [801], [950] | |
| | Starker Konsens | |

| 8.73 | Evidenzbasierte Empfehlung | modifiziert 2022 |
|---|---|---|
| Empfehlungsgrad<br>**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<br>**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<br><br>• 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**<br>**A** | Bei Patienten mit ECOG 2 ohne wesentliche Komorbiditäten sollen platinbasierte Kombinationen, z. B. Carboplatin/Paclitaxel angeboten werden. | |
| **Level of Evidence**<br>**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 | |

| 8.78 | Evidenzbasierte Empfehlung | modifiziert 2022 |
|---|---|---|
| Empfehlungsgrad<br>**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:<br><br>• Cisplatin/Carboplatin + Pemetrexed + Pembrolizumab, alle 3 Wochen über 4 Zyklen, gefolgt von einer Erhaltungstherapie mit Pemetrexed und Pembrolizumab<br>• Carboplatin + Paclitaxel + Bevacizumab + Atezolizumab, alle 3 Wochen über 4-6 Zyklen, gefolgt von einer Erhaltungstherapie mit Bevacizumab und Atezolizumab<br>• Carboplatin + nab-Paclitaxel + Atezolizumab alle 3 Wochen über 4 Zyklen, gefolgt von einer Erhaltungstherapie mit Atezolizumab<br>• platinbasierte Chemotherapie + Nivolumab + Ipilimumab über 2 Zyklen, gefolgt von einer Erhaltungstherapie mit Nivolumab +Ipilimumab über 2 Jahre. | |
| Level of Evidence<br>**1a** | [653], [984], [944], [802], [985], [946], [986], [987], [988], [989], [990], [947], [948] | |
| | Starker Konsens | |

| 8.79 | Evidenzbasierte Empfehlung | neu 2022 |
|---|---|---|
| Empfehlungsgrad<br>**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<br><br>• Atezolizumab (≥ 50% der Tumorzellen oder 10% der tumorinfiltrierenden Lymphozyten),<br>• Cemiplimab (≥ 50% der Tumorzellen) oder<br>• Pembrolizumab (≥ 50% der Tumorzellen)<br><br>als Erstlinientherapie angeboten werden, sofern nicht patienten- oder tumorbezogene Gründe für eine Kombinationsbehandlung sprechen. | |
| Level of Evidence<br>**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** | <u>Patienten mit besonderen Risikofaktoren für eine ICI basierte Therapie</u> 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.<br><br>Folgende Schemata werden empfohlen:<br><br>• Cisplatin/Carboplatin+Pemetrexed über 4 Zyklen, gefolgt von einer Erhaltungstherapie mit Pemetrexed,<br>• Carboplatin+Paclitaxel+Bevacizumab über 4-6 Zyklen, gefolgt von einer Erhaltungstherapie mit Bevacizumab bei geeigneten Patienten,<br>• Carboplatin + nab-Paclitaxel,<br>• Cisplatin/Carboplatin + Paclitaxel,<br>• Cisplatin/Carboplatin + Vinorelbine,<br>• Cisplatin/Carboplatin + Docetaxel,<br>• 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<br><br>• Atezolizumab (≥ 50% der Tumorzellen oder 10% der tumorinfiltrierenden Lymphozyten),<br>• Cemiplimab (≥ 50% der Tumorzellen) oder<br>• Pembrolizumab (≥ 50% der Tumorzellen)<br><br>als Erstlinientherapie angeboten werden. |
|---|---|

| | Starker Konsens |
|---|---|

**Daly ME et al., 2022 [3].**

*American Society of Clinical Oncology (ASCO)*

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

### Zielsetzung/Fragestellung

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

### Methodik

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)

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**National Institute for Health and Care Excellence (NICE), 2019 [21].**

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.

<u>LoE</u>

- trifft nicht zu (sieh sonstige methodische Hinweise)

<u>GoR</u>

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

<u>Sonstige methodische Hinweise (Bei Einschränkung der o. g. Kriterien)</u>

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.

<u>Updates-Kennzeichnung:</u>

- 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**

<u>EGFR-TK mutation</u>

- 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:
  - o 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:
  - o 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:
  - o 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:
  - o 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%:
  - o 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%:
  - o 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)



Systemic anti-cancer therapy: management options for people with non-squamous (adenocarcinoma, large cell undifferentiated) carcinoma and non-small-cell carcinoma (non-otherwise specified)
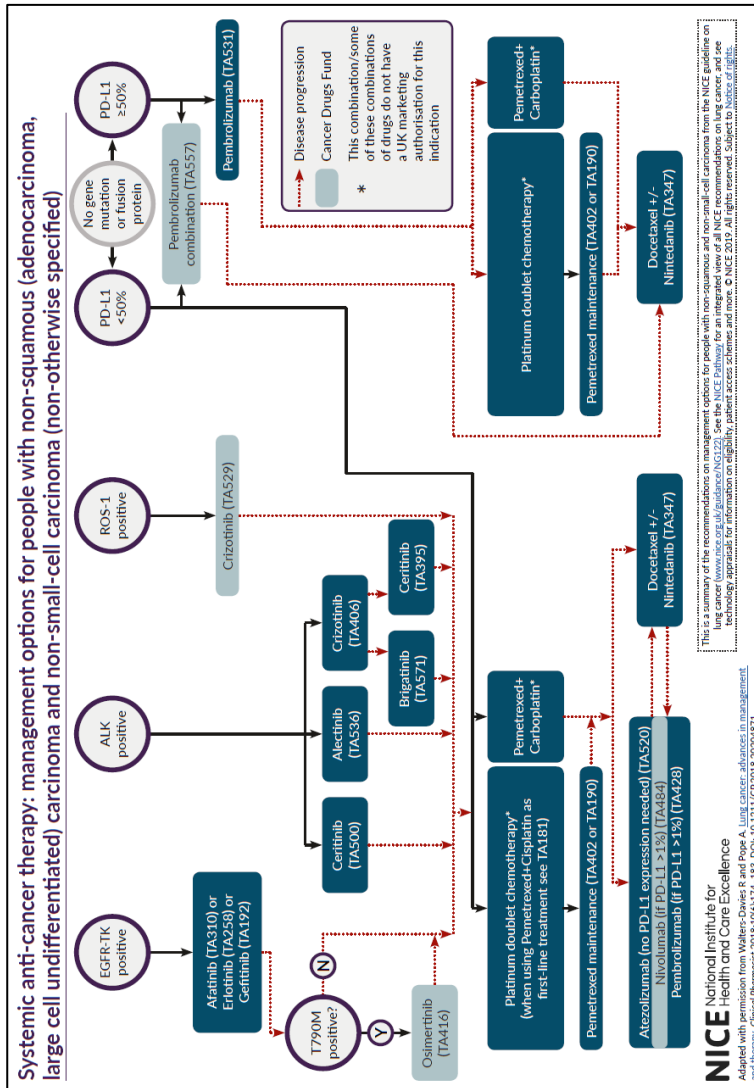
## Squamous non-small-cell lung cancer, stages IIIB and IV

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



**Systemic anti-cancer therapy:**
**management options for people with squamous non-small-cell carcinoma**

This is a summary of the recommendations on management options for people with squamous cell carcinoma from the NICE guideline on lung cancer (www.nice.org.uk/guidance/NG122). See the NICE Pathway for an integrated view of all NICE recommendations on lung cancer, and see technology appraisals for full details.
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NICE National Institute for Health and Care Excellence

Adapted with permission from Walters-Davies R and Pope A. Lung cancer: advances in management and therapy. *Clinical Pharmacist* 2018;10(6):174–183. DOI: 10.1211/CP.2018.20204871

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**Singh N et al., 2023 [24]**

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 [10]

- 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).
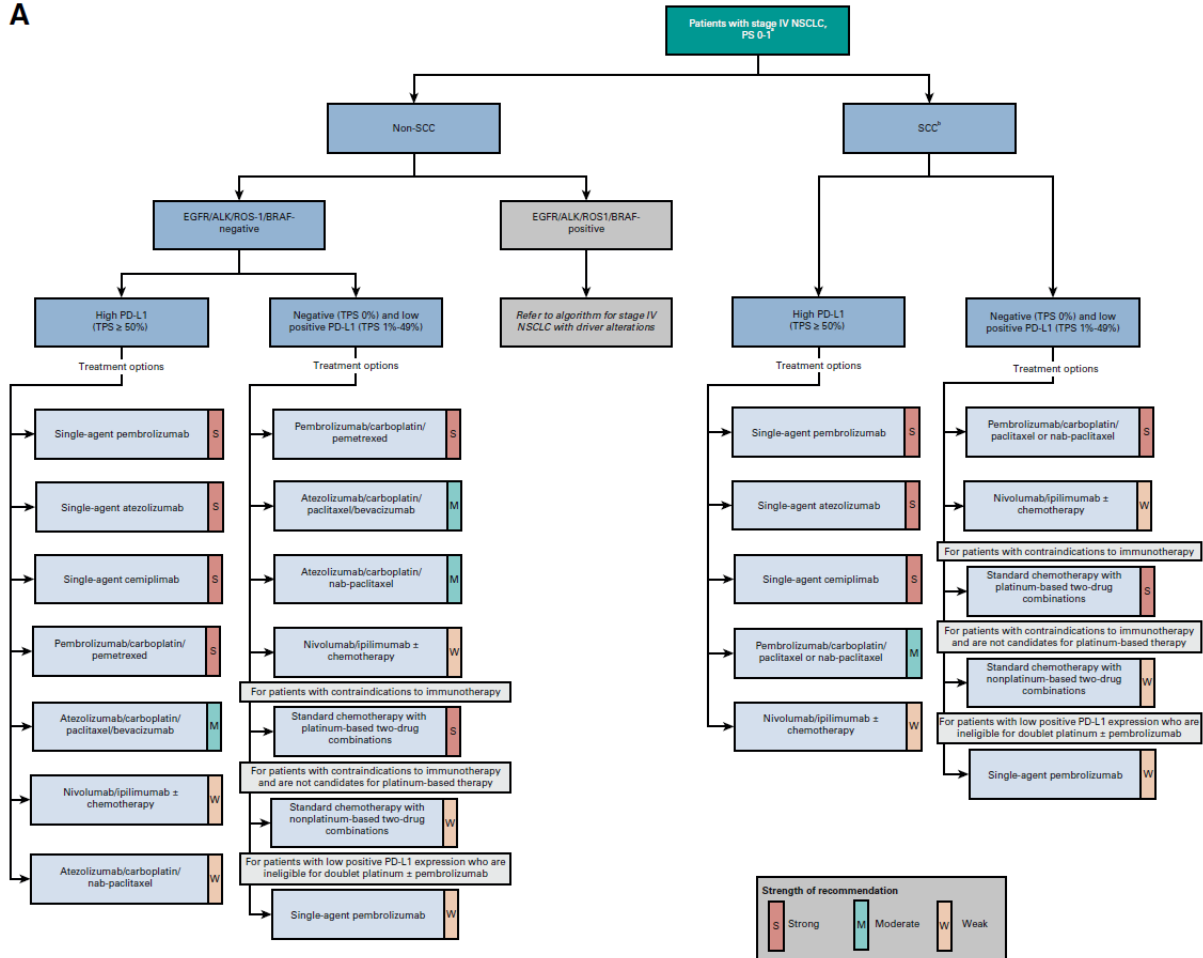
***Recommendation 3.5.*** In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), SCC, and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy (Type: Evidence based; Evidence quality: Moderate; 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).

**A**

Patients with stage IV NSCLC, PS 0-1[a]

- Non-SCC
  - EGFR/ALK/ROS-1/BRAF-negative
    - High PD-L1 (TPS ≥ 50%)
      - Treatment options
        - Single-agent pembrolizumab [S]
        - Single-agent atezolizumab [S]
        - Single-agent cemiplimab [S]
        - Pembrolizumab/carboplatin/pemetrexed [S]
        - Atezolizumab/carboplatin/paclitaxel/bevacizumab [M]
        - Nivolumab/ipilimumab ± chemotherapy [W]
        - Atezolizumab/carboplatin/nab-paclitaxel [W]
    - Negative (TPS 0%) and low positive PD-L1 (TPS 1%-49%)
      - Treatment options
        - Pembrolizumab/carboplatin/pemetrexed [S]
        - Atezolizumab/carboplatin/paclitaxel/bevacizumab [M]
        - Atezolizumab/carboplatin/nab-paclitaxel [M]
        - Nivolumab/ipilimumab ± chemotherapy [W]
        - For patients with contraindications to immunotherapy
          - Standard chemotherapy with platinum-based two-drug combinations [S]
        - For patients with contraindications to immunotherapy and are not candidates for platinum-based therapy
          - Standard chemotherapy with nonplatinum-based two-drug combinations [W]
        - For patients with low positive PD-L1 expression who are ineligible for doublet platinum ± pembrolizumab
          - Single-agent pembrolizumab [W]
  - EGFR/ALK/ROS1/BRAF-positive
    - Refer to algorithm for stage IV NSCLC with driver alterations
- SCC[b]
  - High PD-L1 (TPS ≥ 50%)
    - Treatment options
      - Single-agent pembrolizumab [S]
      - Single-agent atezolizumab [S]
      - Single-agent cemiplimab [S]
      - Pembrolizumab/carboplatin/paclitaxel or nab-paclitaxel [M]
      - Nivolumab/ipilimumab ± chemotherapy [W]
  - Negative (TPS 0%) and low positive PD-L1 (TPS 1%-49%)
    - Treatment options
      - Pembrolizumab/carboplatin/paclitaxel or nab-paclitaxel [S]
      - Nivolumab/ipilimumab ± chemotherapy [W]
      - For patients with contraindications to immunotherapy
        - Standard chemotherapy with platinum-based two-drug combinations [S]
      - For patients with contraindications to immunotherapy and are not candidates for platinum-based therapy
        - Standard chemotherapy with nonplatinum-based two-drug combinations [W]
      - For patients with low positive PD-L1 expression who are ineligible for doublet platinum ± pembrolizumab
        - Single-agent pembrolizumab [W]

Strength of recommendation: [S] Strong [M] Moderate [W] Weak

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**Passiglia F et al., 2020 [22].**

*Italian Association of Medical Oncologyg (AIOM)*

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

### Leitlinienorganisation/Fragestellung

Evidence-based guideline for the management of lung tumors.

### Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

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

LoE/GoR

- GRADE

The global quality of evidence was defined as follow:

- o High (high grade of confidence in the study results): high probability that the estimated effect is similar to the true effect.
- o 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.
- o 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
- o 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):

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

## Recommendations

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

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

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

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

# 4 Detaillierte Darstellung der Recherchestrategie

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

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

**Systematic Reviews in PubMed am 17.11.2022**

verwendete Suchfilter ohne Änderung:

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

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

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

**Leitlinien in PubMed am 17.11.2022**

verwendete Suchfilter ohne Änderung:

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

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

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

**Iterative Handsuche nach grauer Literatur, abgeschlossen am 17.11.2022**

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

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

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

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

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

**2022-B-311**

**Kontaktdaten**

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

Indikation gemäß Beratungsantrag

Erstlinienbehandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC, die als Platin-ungeeignet angesehen werden und deren Erkrankung keine EGFR-Mutation oder ALK-Translokation haben

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

Zusammenfassung

Die Gruppe der Patientinnen und Patienten (Pat.), die als Platin-ungeeignet angesehen werden, ist heterogen. Relevante Faktoren sind

- schlechter Allgemeinzustand, definiert durch ECOG PS $\geq$2 aufgrund

    - der Grundkrankheit

    - von Komorbidität

- Kontraindikationen sowohl gegen Cis- als auch gegen Carboplatin.

Daraus ergibt sich für Pat. mit lokal fortgeschrittenem oder metastasiertem NSCLC, die als Platin-ungeeignet angesehen werden und deren Erkrankung keine EGFR-Mutation oder ALK-Translokation haben, die Empfehlung zur Therapie nach ärztlicher Maßgabe unter Berücksichtigung von:

- molekular zielgerichtete Therapie

- Immuncheckpoint-Inhibitoren

- Mono-Chemotherapie

- Best Supportive Care

Stand des Wissens

**Kontaktdaten**

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

Indikation gemäß Beratungsantrag

Erstlinienbehandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC, die als Platin-ungeeignet angesehen werden und deren Erkrankung keine EGFR-Mutation oder ALK-Translokation haben

**Nicht für Platin geeignet**

Die Gruppe von Pat., die nicht für eine Platin-haltige Chemotherapie geeignet sind, ist sehr heterogen [1-3]. Sie umfasst vor allem ältere Pat. im Alter >70 Jahre und/oder Pat. in reduziertem Allgemeinzustand (AZ). Letzterer kann durch einen ECOG PS >2 beschrieben werden. Wenn der reduzierte Allgemeinzustand vor allem durch das fortgeschrittene, metastasierte Lungenkarzinom bedingt ist, kann eine intensitätsreduzierte Therapie begonnen mit dem Ziel begonnen werden, die Intensivität bei gutem Ansprechen und Verbesserung des AZ zu steigern. Wir orientieren uns in der Stellungnahme an den Pat., bei denen eine Persistenz des reduzierten AZ aufgrund von Alter und/oder Komorbidität zu erwarten ist.

Spezifische Kontraindikationen gegen eine Platin-haltige Therapie sind vor allem

- Cisplatin: schwere Myelosuppression, Neuropathie, vorbestehende Niereninsuffizienz (Kreatinin-Clearance <60 ml/min), Beeinträchtigung des Gehörs

- Carboplatin: schwere Myelosuppression, schwere Nierenfunktionsstörung (Kreatinin-Clearance ≤ 30 ml/min), Neuropathie.

Die Entscheidung über das Bestehen einer relativen oder absoluten Kontraindikation wird individuell getroffen und ist Gegenstand der gemeinsamen Nutzen-Risiko-Abschätzung im Rahmen der partizipativen Entscheidungsfindung.

**Therapieoptionen**

- Molekular stratifizierte Therapie (außer EGFR-Mutationen und ALK-Positivität): Hier werden Arzneimittel eingesetzt, deren Wirksamkeit und Sicherheit in der Erst- oder Zweitlinientherapie nachgewiesen ist:

    - *BRAF V600E*-Mutation: Dabrafenib + Trametinib [4]

    - *HER2*-Amplifikationen und -Mutationen [5]

    - *KRAS G12C* Mutation: Sotorasib [6, 7]

    - *c-METex14* Mutation: Capmatinib oder Tepotini

**Kontaktdaten**

*Fachgesellschaften:*
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Pneumologisch-Onkologische Arbeitsgemeinschaft der Deutschen Krebsgesellschaft (POA)

Indikation gemäß Beratungsantrag

Erstlinienbehandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC, die als Platin-ungeeignet angesehen werden und deren Erkrankung keine EGFR-Mutation oder ALK-Translokation haben

- *NTRK*-Translokationen: Entrectinib oder Larotrectinib [10, 11]

- *RET*-Translokationen: Pralsetinib oder Selpercatinib [12, 13]

- *ROS1*-Translokationen: Crizotinib oder Entrectinib [14, 15, 16]


- Immuncheckpoint-Inhibitoren

  - Expression des Immunmarkers PD-L1 auf ≥50% der Tumorzellen und/oder Expression des Immunmarkers PD-L1 auf ≥10% der Immunzellen anteilig an der Gesamttumorfläche: Atezolizumab [17]

  - Expression des Immunmarkers PD-L1 auf ≥50% der Tumorzellen: Cemiplimab [18] oder Pembrolizumab [19]

  - unabhängig von der Expression des Immunmarkers PD-L1 (off label): Atezolizumab [20], Pembrolizumab [21]

- Monochemotherapie

  - Gemcitabin [22, 23]

  - Vinorelbin [22]

  - ggf. Docetaxel [24, 25], Pemetrexed (Nicht-Plattenepithelkarzinom) [26]

- Best Supportive Care

  Die supportive Behandlung erfolgt Symptom-orientiert.


**Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der** *„Erstlinienbehandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC, die als Platin-ungeeignet angesehen werden und deren Erkrankung keine EGFR-Mutation oder ALK-Translokation haben"* **die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

**Kontaktdaten**

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

Indikation gemäß Beratungsantrag

Erstlinienbehandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC, die als Platin-ungeeignet angesehen werden und deren Erkrankung keine EGFR-Mutation oder ALK-Translokation haben

Die unterschiedlichen Behandlungsentscheidungen sind oben dargestellt.

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