Gemeinsamer Bundesausschuss

# Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

# und

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

# und

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

## Vorgang: 2020-B-134 Ipilimumab

Stand: Oktober 2020

| I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA | |
|---|---|
| **Ipilimumab<br>[zur Behandlung des metastasierten NSCLC, Erstlinienbehandlung]** | |
| **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“* |
| 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 (nicht-plattenepithelial, Kombination mit Bevacizumab, Paclitaxel und Carboplatin): Beschluss vom 02.04.2020<br>• Atezolizumab (nicht-plattenepithelial, Kombination mit nab-Paclitaxel und Carboplatin): Beschluss vom 02.04.2020<br>• Pembrolizumab (plattenepithelial): Beschluss vom 19.09.2019<br>• Pembrolizumab (nicht-plattenepithelial): Beschluss vom 19.09.2019<br>• Dabrafenib (mit BRAF-V600-Mutation): Beschluss vom 19.10.2017<br>• Trametinib (mit BRAF-V600-Mutation): Beschluss vom 19.10.2017<br>• Pembrolizumab: Beschluss vom 03.08.2017<br>• Crizotinib (ROS1-positives NSCLC): Beschluss vom 16.03.2017<br>• Necitumumab (plattenepitheliale Histologie): Beschluss vom 15.09.2016<br>**Richtlinien:**<br>Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie - Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (Off-Label-Use):<br>• Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie |

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|---|---|
| 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<br>ATC-Code<br>Handelsname** | **Anwendungsgebiet**<br>(Text aus Beratungsanforderung/Fachinformation) |
|---|---|
| Zu prüfendes Arzneimittel: | |
| Ipilimumab<br>L01XC11<br>Yervoy® | zu prüfendes Anwendungsgebiet:<br>Yervoy ist in Kombination mit Nivolumab und 2 Zyklen platinbasierter Chemotherapie für die Erstlinientherapie des metastasierten nicht-kleinzelligen Lungenkarzinoms (NSCLC) bei Erwachsenen, deren Tumoren keine sensitivierende EGFR-Mutation oder ALK-Translokation aufweisen, indiziert. |
| **Chemotherapien:** | |
| Carboplatin<br>L01XA02<br>generisch | Off-Label-Indikation für Carboplatin: Kombinationstherapie des fortgeschrittenen NSCLC (palliativ) |
| Cisplatin<br>L01XA01<br>generisch | Cisplatin wird angewendet zur Behandlung des fortgeschrittenen oder metastasierten nichtkleinzelligen Bronchialkarzinoms.<br>Cisplatin kann als Mono- oder Kombinationstherapie angewendet werden. |
| Docetaxel<br>L01CD02<br>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.<br>[…] |
| Etoposid<br>L01CB01<br>Riboposid® | Kombinationstherapie folgender Malignome:<br>• Palliative Therapie des fortgeschrittenen, nicht-kleinzelligen Bronchialkarzinoms bei Patienten mit gutem Allgemeinzustand (Karnofsky-Index > 80 %), […] |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| **Wirkstoff**<br>**ATC-Code**<br>**Handelsname** | **Anwendungsgebiet**<br>(Text aus Beratungsanforderung/Fachinformation) |
| Gemcitabin<br>L01BC05<br>generisch | Gemcitabin ist in Kombination mit Cisplatin als Erstlinientherapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nichtkleinzelligen Bronchialkarzinom (NSCLC) angezeigt. Eine Gemcitabin-Monotherapie kann bei älteren Patienten oder solchen mit einem Performance Status 2 in Betracht gezogen werden. |
| Ifosfamid<br>L01AA06<br>Holoxan® | Nicht-kleinzellige Bronchialkarzinome:<br>Zur Einzel- oder Kombinationschemotherapie von Patienten mit inoperablen oder metastasierten Tumoren. |
| Mitomycin<br>L01DC03<br>generisch | Mitomycin wird in der palliativen Tumortherapie eingesetzt. Bei intravenöser Gabe ist es in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei folgenden metastasierenden Tumoren wirksam: […] nicht-kleinzelliges Bronchialkarzinom […]. |
| Paclitaxel<br>L01CD01<br>generisch | Fortgeschrittenes nicht-kleinzelliges Bronchialkarzinom (NSCLC):<br>Paclitaxel ist, in Kombination mit Cisplatin, zur Behandlung des nicht-kleinzelligen Bronchialkarzinoms bei Patienten angezeigt, für die potentiell kurative chirurgische Maßnahmen und/oder eine Strahlentherapie nicht in Frage kommen. |
| Nab-Paclitaxel<br>L01CD01<br>Abraxane® | Abraxane ist in Kombination mit Carboplatin indiziert für die Erstlinienbehandlung des nicht-kleinzelligen Bronchialkarzinoms bei erwachsenen Patienten, bei denen keine potentiell kurative Operation und/oder Strahlentherapie möglich ist. |
| Pemetrexed<br>L01BA04<br>generisch | Pemetrexed ist in Kombination mit Cisplatin angezeigt zur first-line Therapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie.<br>Pemetrexed in Monotherapie ist angezeigt für die Erhaltungstherapie bei lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie bei Patienten, deren Erkrankung nach einer platinbasierten Chemotherapie nicht unmittelbar fortgeschritten ist.<br>[…] |
| Vindesin<br>L01CA03 | Kombinationschemotherapie:<br>Lokal fortgeschrittenes oder metastasiertes nicht-kleinzelliges Bronchialkarzinom (Stadium IIIB, IV). |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| **Wirkstoff<br>ATC-Code<br>Handelsname** | **Anwendungsgebiet**<br>(Text aus Beratungsanforderung/Fachinformation) |
| Eldesine® | |
| Vinorelbin<br>L01CA04<br>generisch | Behandlung des nicht kleinzelligen Bronchialkarzinoms (Stadium 3 oder 4). |
| **Proteinkinase-Inhibitoren:** | |
| Crizotinib<br>L01XE16<br>Xalkori® | XALKORI als Monotherapie wird angewendet bei:<br>• Erwachsenen zur Erstlinienbehandlung des Anaplastische-Lymphom-Kinase (ALK)-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, NSCLC)<br>• […]<br>• Erwachsenen zur Behandlung des ROS1-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, NSCLC) |
| Dabrafenib<br>L01XE23<br>Tafinlar® | Dabrafenib in Kombination mit Trametinib ist angezeigt zur Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligen Lungenkarzinom mit einer BRAF-V600-Mutation. |
| Trametinib<br>L01XE25<br>Mekinist® | Trametinib in Kombination mit Dabrafenib ist angezeigt zur Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligen Lungenkarzinom mit einer BRAF-V600-Mutation. |
| **Antikörper:** | |
| Atezolizumab<br>L01XC32<br>Tecentriq® | Tecentriq wird angewendet in Kombination mit Bevacizumab, Paclitaxel und Carboplatin bei erwachsenen Patienten zur Erstlinienbehandlung des metastasierten nichtkleinzelligen Lungenkarzinoms (NSCLC) mit nicht-plattenepithelialer Histologie. Bei Patienten mit EGFR-Mutationen oder ALK-positivem NSCLC ist Tecentriq in Kombination mit Bevacizumab, Paclitaxel und Carboplatin nur nach Versagen der entsprechenden zielgerichteten Therapien anzuwenden (siehe Abschnitt 5.1).<br>Tecentriq wird angewendet in Kombination mit nab-Paclitaxel und Carboplatin zur Erstlinienbehandlung des metastasierten NSCLC mit nicht-plattenepithelialer Histologie bei erwachsenen Patienten, die keine EGFR-Mutationen und kein ALK-positives NSCLC haben.<br>[…] |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| **Wirkstoff<br>ATC-Code<br>Handelsname** | **Anwendungsgebiet**<br>(Text aus Beratungsanforderung/Fachinformation) |
| Bevacizumab<br>L01XC07<br>Avastin® | Bevacizumab wird zusätzlich zu einer platinhaltigen Chemotherapie zur First-Line-Behandlung von erwachsenen Patienten mit inoperablem fortgeschrittenem, metastasiertem oder rezidivierendem nicht-kleinzelligem Bronchialkarzinom, außer bei vorwiegender Plattenepithel-Histologie, angewendet.<br>Bevacizumab wird in Kombination mit Erlotinib zur First-Line-Behandlung von erwachsenen Patienten mit inoperablem fortgeschrittenem, metastasiertem oder rezidivierendem nicht-kleinzelligem Nicht-Plattenepithel-Bronchialkarzinom mit Mutationen, die den epidermalen Wachstumsfaktorrezeptor Wachstumsfaktorrezeptor (EGFR) aktivieren, angewendet. |
| Necitumumab<br>L01XC22<br>Portrazza® | Portrazza ist in Kombination mit Gemcitabin- und Cisplatin-Chemotherapie indiziert zur Therapie von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem, den epidermalen Wachstumsfaktor-Rezeptor (EGFR) exprimierenden, plattenepithelialen, nicht-kleinzelligen Lungenkarzinom, wenn diese bislang keine Chemotherapie für dieses Stadium der Erkrankung erhalten haben. |
| Pembrolizumab<br>L01XC18<br>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.<br>[…]<br>KEYTRUDA ist in Kombination mit Pemetrexed und Platin-Chemotherapie zur Erstlinienbehandlung des metastasierenden nicht-plattenepithelialen NSCLC ohne EGFR- oder ALK-positive Tumormutationen bei Erwachsenen angezeigt.<br>KEYTRUDA ist in Kombination mit Carboplatin und entweder Paclitaxel oder nab-Paclitaxel zur Erstlinienbehandlung des metastasierenden plattenepithelialen NSCLC bei Erwachsenen angezeigt. |

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

## Abteilung Fachberatung Medizin

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

# Vorgang: 2020-B-134 (Ipilimumab)

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|---|---|
| Auftrag von: | Abt. AM |
| Bearbeitet von: | Abt. FB Med |
| Datum: | 18. Juni 2020 |

# Inhaltsverzeichnis

# Abkürzungsverzeichnis

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|---|---|
| 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

Indikation für die Synopse: Erstlinienbehandlung für Patienten mit metastasiertem NSCLC ohne EGFR- oder ALK-positive Tumormutationen.

# 2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *nicht-kleinzelliges Lungenkarzinom* durchgeführt. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, SIGN, TRIP, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien.

Die Erstrecherche wurde am 12.04.2019 durchgeführt, die Folgerecherchen am 12.10 2019 und 15.05.2020. Die Recherchestrategie der Erstrecherche wurde für die Folgerecherchen übernommen und der Suchzeitraum jeweils auf die letzten 5 Jahre eingeschränkt. Die letzte Suchstrategie ist am Ende der Synopse detailliert dargestellt.

Die Recherchen ergaben insgesamt 1755 Quellen, die in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Es wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen und nur die Quellen der letzten 5 Jahre berücksichtigt. 49 Quellen wurden in die synoptische Evidenz-Übersicht aufgenommen.

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# 3 Ergebnisse

## 3.1 G-BA-Beschlüsse/IQWiG-Berichte

**G-BA, 2020 [13].**

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Atezolizumab (neues Anwendungsgebiet: NSCLC, nicht-plattenepithelial, 1. Linie, Kombination mit nab-Paclitaxel und Carboplatin). Vom 2. April 2020.

**Anwendungsgebiet**

Tecentriq wird angewendet in Kombination mit nab-Paclitaxel und Carboplatin zur Erstlinienbehandlung des metastasierten NSCLC mit nicht-plattenepithelialer Histologie bei erwachsenen Patienten, die keine EGFR-Mutationen und kein ALK-positives NSCLC haben.

**Zweckmäßige Vergleichstherapie**

a) Erwachsene Patienten mit einem metastasierten nicht-kleinzelligen Lungenkarzinom mit nicht-plattenepithelialer Histologie und einem Tumor Proportion Score [TPS] von ≥ 50 % (PD-L1-Expression) und ohne EGFR- oder ALK-positive Tumormutationen; Erstlinientherapie

- Pembrolizumab als Monotherapie

b) Erwachsene Patienten mit einem metastasierten nicht-kleinzelligen Lungenkarzinom mit nicht-plattenepithelialer Histologie und einem Tumor Proportion Score [TPS] von < 50 % (PD-L1-Expression) und ohne EGFR- oder ALK-positive Tumormutationen; Erstlinientherapie

- Cisplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel oder Pemetrexed) oder
- Carboplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel oder Pemetrexed) vgl. Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie oder
- Carboplatin in Kombination mit nab-Paclitaxel oder
- Pembrolizumab in Kombination mit Pemetrexed und Platin-Chemotherapie

**Fazit / Ausmaß des Zusatznutzens**

a) Erwachsene Patienten mit einem metastasierten nicht-kleinzelligen Lungenkarzinom mit nicht-plattenepithelialer Histologie und einem Tumor Proportion Score [TPS] von ≥ 50 % (PD-L1-Expression) und ohne EGFR- oder ALK-positive Tumormutationen; Erstlinientherapie:

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Atezolizumab + Carboplatin + nab-Paclitaxel gegenüber zweckmäßiger Vergleichstherapie:

- Ein Zusatznutzen ist nicht belegt

b) Erwachsene Patienten mit einem metastasierten nicht-kleinzelligen Lungenkarzinom mit nicht-plattenepithelialer Histologie und einem Tumor Proportion Score [TPS] von < 50 % (PD-L1-Expression) und ohne EGFR- oder ALK-positive Tumormutationen; Erstlinientherapie:

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Atezolizumab + Carboplatin + nab-Paclitaxel gegenüber Carboplatin + nab-Paclitaxel:

- Ein Zusatznutzen ist nicht belegt.

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**G-BA, 2020 [12].**

Beschluss über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Atezolizumab (neues Anwendungsgebiet: NSCLC, nicht-plattenepithelial, 1. Linie, Kombination mit Bevacizumab, Paclitaxel und Carboplatin). Vom 02. April 2020.

**Anwendungsgebiet**

Tecentriq wird angewendet in Kombination mit Bevacizumab, Paclitaxel und Carboplatin bei erwachsenen Patienten zur Erstlinienbehandlung des metastasierten nicht-kleinzelligen Lungenkarzinoms (NSCLC) mit nicht-plattenepithelialer Histologie. Bei Patienten mit EGFRMutationen oder ALK-positivem NSCLC ist Tecentriq in Kombination mit Bevacizumab, Paclitaxel und Carboplatin nur nach Versagen der entsprechenden zielgerichteten Therapien anzuwenden.

**Zweckmäßige Vergleichstherapie**

a) Erwachsene mit einem metastasierten nicht-kleinzelligen Lungenkarzinom mit nichtplattenepithelialer Histologie und einem Tumor Proportion Score [TPS] von ≥ 50 % (PD-L1-Expression) und ohne EGFR-Mutationen oder ALK-Translokationen; Erstlinientherapie

- Pembrolizumab als Monotherapie

b) Erwachsene mit einem metastasierten nicht-kleinzelligen Lungenkarzinom mit nichtplattenepithelialer Histologie; und einem Tumor Proportion Score [TPS] von < 50 % (PD-L1-Expression); Erstlinientherapie; oder einem EGFR-mutierten oder ALKpositiven NSCLC unabhängig vom Tumor Proportion Score [TPS] nach Vorbehandlung mit einer entsprechenden zielgerichteten Therapie

- Cisplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel oder Pemetrexed) unter Beachtung des Zulassungsstatus

  oder

- Carboplatin in Kombination mit einem Drittgenerationszytostatikum (nur für Patienten mit erhöhtem Risiko für Cisplatin-induzierte Nebenwirkungen im Rahmen einer Kombinationstherapie; vgl. Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie)

  Oder

- Carboplatin in Kombination mit nab-Paclitaxel

  Oder

- Pembrolizumab in Kombination mit Pemetrexed und platinhaltiger Chemotherapie (nur für Patienten ohne EGFR- oder ALK-positive Tumormutationen)

**Fazit / Ausmaß des Zusatznutzens**

a) Erwachsene mit einem metastasierten nicht-kleinzelligen Lungenkarzinom mit nichtplattenepithelialer Histologie und einem Tumor Proportion Score [TPS] von ≥ 50 % (PD-L1-Expression) und ohne EGFR-Mutationen oder ALK-Translokationen; Erstlinientherapie

- Ein Zusatznutzen ist nicht belegt.

b) Erwachsene mit einem metastasierten nicht-kleinzelligen Lungenkarzinom mit nichtplattenepithelialer Histologie; und einem Tumor Proportion Score [TPS] von < 50 % (PD-L1-Expression); Erstlinientherapie; oder einem EGFR-mutierten oder ALKpositiven NSCLC unabhängig vom Tumor Proportion Score [TPS] nach Vorbehandlung mit einer entsprechenden zielgerichteten Therapie

- Ein Zusatznutzen ist nicht belegt.

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**G-BA, 2019 [20]**

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Pembrolizumab (neues Anwendungsgebiet: nicht-kleinzelliges Lungenkarzinom, nicht-plattenepithelial, Erstlinie, Kombination mit Pemetrxed und Platin-Chemotherapie) vom 19. September 2019.

**Anwendungsgebiet**

KEYTRUDA ist in Kombination mit Pemetrexed und Platin-Chemotherapie zur Erstlinienbehandlung des metastasierenden nicht-plattenepithelialen NSCLC ohne EGFR- oder ALK-positive Tumormutationen bei Erwachsenen angezeigt.

**Zweckmäßige Vergleichstherapie**

a) Erwachsene Patienten mit Erstlinienbehandlung des metastasierenden nicht-plattenepithelialen NSCLC ohne EGFR- oder ALK-positive Tumormutationen mit einer PD-L1-Expression von < 50 % (TPS1):

Zweckmäßige Vergleichstherapie:

− Cisplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel oder Pemetrexed)

oder

− Carboplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel oder Pemetrexed; vgl. Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie)

oder

− Carboplatin in Kombination mit nab-Paclitaxel

**Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Pembrolizumab in Kombination mit Pemetrexed und Platin-Chemotherapie gegenüber Pemetrexed plus Platin-Chemotherapie:**

Anhaltspunkt für einen nicht-quantifizierbaren Zusatznutzen

b) Erwachsene Patienten mit Erstlinienbehandlung des metastasierenden nicht-plattenepithelialen NSCLC ohne EGFR- oder ALK-positive Tumormutationen mit einer PD-L1-Expression von ≥ 50 % (TPS1):

- Zweckmäßige Vergleichstherapie: Pembrolizumab als Monotherapie

**Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Pembrolizumab in Kombination mit Pemetrexed und Platin-Chemotherapie gegenüber Pembrolizumab als Monotherapie:**

Anhaltspunkt für einen nicht-quantifizierbaren Zusatznutzen

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**G-BA, 2019 [19].**

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 19. September 2019 – Pembrolizumab (neues Anwendungsgebiet: nicht-kleinzelliges Lungenkarzinom (plattenepithelial), Erstlinie, Kombination mit Carboplatin und (nab-) Paclitaxel).

**Anwendungsgebiet**

KEYTRUDA ist in Kombination mit Carboplatin und entweder Paclitaxel oder nab-Paclitaxel zur Erstlinienbehandlung des metastasierenden plattenepithelialen NSCLC bei Erwachsenen angezeigt.

**Zweckmäßige Vergleichstherapie**

a) Erwachsene Patienten mit Erstlinienbehandlung des metastasierenden plattenepithelialen NSCLC und einer PD-L1-Expression von < 50 % (TPS1):

Zweckmäßige Vergleichstherapie:

− Cisplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel)

oder

− Carboplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel; vgl. Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie)

oder

− Carboplatin in Kombination mit nab-Paclitaxel

**Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Pembrolizumab in Kombination mit Carboplatin und (nab-) Paclitaxel gegenüber Carboplatin und (nab-) Paclitaxel:**

Anhaltspunkt für einen beträchtlichen Zusatznutzen.

b) Erwachsene Patienten mit Erstlinienbehandlung des metastasierenden plattenepithelialen NSCLC und einer PD-L1-Expression von ≥ 50 % (TPS1):

- Zweckmäßige Vergleichstherapie: Pembrolizumab als Monotherapie

**Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Pembrolizumab in Kombination mit Carboplatin und (nab-) Paclitaxel gegenüber Carboplatin und (nab-) Paclitaxel:**

Ein Zusatznutzen ist nicht belegt.

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**G-BA, 2019 [11].**

Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (sog. Off-Label-Use); letzte Änderung in Kraft getreten am 01.04.2020.

III. Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie

1. Hinweise zur Anwendung von Carboplatin gemäß § 30 Abs. 1 a) Nicht zugelassenes Anwendungsgebiet (Off-Label-Indikation): Fortgeschrittenes nicht-kleinzelliges Bronchialkarzinom (NSCLC) -Kombinationstherapie

b) Behandlungsziel: palliativ

c) Folgende Wirkstoffe sind zugelassen:

- Cisplatin
- Docetaxel
- Etoposid
- Gemcitabin
- Ifosfamid
- Mitomycin
- Paclitaxel
- Pemetrexed
- Vindesin
- Vinorelbin
- Afatinib
- Alectinib
- Erlotinib
- Gefitinib
- Osimertinib
- Ceritinib
- Crizotinib
- Nintedanib
- Atezolizumab
- Bevacizumab
- Necitumumab
- Nivolumab
- Ramucirumab
- Pembrolizumab

d) Spezielle Patientengruppe: Patientinnen und Patienten, die für eine platinbasierte Kombinationstherapie mit einem Drittgenerationszytostatikum wie Paclitaxel, Docetaxel oder Gemcitabin in Frage kommen. Die Auswahl der Platin-Komponente (Carboplatin oder Cisplatin) sollte sich im jeweiligen Fall am unterschiedlichen Toxizitätsprofil der beiden Substanzen und an den bestehenden Komorbiditäten orientieren.

e) Patienten, die nicht behandelt werden sollten:

− Monotherapie

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**G-BA, 2017 [16].**

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 16. März 2017 - Crizotinib (neues Anwendungsgebiet: nicht-kleinzelliges Lungenkarzinom, ROS1-positiv).

**Zugelassenes Anwendungsgebiet (laut Zulassung vom 25.08.2016):**

XALKORI wird angewendet bei Erwachsenen zur Behandlung des ROS1-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, NSCLC)

1) nicht vorbehandelte Patienten mit ROS1-positivem, fortgeschrittenem nicht kleinzelligem Lungenkarzinom (NSCLC)

**Zweckmäßige Vergleichstherapie**

- Patienten mit ECOG-Performance-Status 0, 1 oder 2:

  Cisplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel oder Pemetrexed) unter Beachtung des Zulassungsstatus

  *oder*

  Carboplatin in Kombination mit einem Drittgenerationszytostatikum (nur für Patienten mit erhöhtem Risiko für Cisplatin-induzierte Nebenwirkungen im Rahmen einer Kombinationstherapie; vgl. Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie)

- Patienten mit ECOG-Performance-Status 2:

  alternativ zur platinbasierten Kombinationsbehandlung: Monotherapie mit Gemcitabin oder Vinorelbin

**Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Cisplatin in Kombination mit Pemetrexed oder Carboplatin in Kombination mit Pemetrexed:**

- Ein Zusatznutzen ist nicht belegt.

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**G-BA, 2017 [17].**

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 19. Oktober 2017 - Dabrafenib (BRAF-V600 Mutation).

**Anwendungsgebiet**

„Dabrafenib (Tafinlar®) in Kombination mit Trametinib ist angezeigt zur Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligen Lungenkarzinom mit einer BRAF-V600-Mutation."

1) Patienten ohne Vorbehandlung:

**Zweckmäßige Vergleichstherapie:**

- Patienten mit ECOG-Performance-Status 0, 1 oder 2:

  Cisplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel oder Pemetrexed) unter Beachtung des Zulassungsstatus

  *oder*

  Carboplatin in Kombination mit einem Drittgenerationszytostatikum (nur für Patienten mit erhöhtem Risiko für Cisplatin-induzierte Nebenwirkungen im Rahmen einer Kombinationstherapie; vgl. Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie)

  *oder*

  Carboplatin in Kombination mit nab-Paclitaxel

- Patienten mit ECOG-Performance-Status 2:

  alternativ zur platinbasierten Kombinationsbehandlung: eine Monotherapie mit Gemcitabin oder Vinorelbin

**Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:**

- Ein Zusatznutzen ist nicht belegt.

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**G-BA, 2017 [14].**

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 3. August 2017 - Pembrolizumab.

**Anwendungsgebiet**

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.

**Zweckmäßige Vergleichstherapie**

- Patienten mit ECOG-Performance-Status 0, 1 oder 2:

  Cisplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel oder Pemetrexed) unter Beachtung des Zulassungsstatus

*oder*

  Carboplatin in Kombination mit einem Drittgenerationszytostatikum (nur für Patienten mit erhöhtem Risiko für Cisplatin-induzierte Nebenwirkungen im Rahmen einer Kombinationstherapie; vgl. Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie)

*oder*

Carboplatin in Kombination mit nab-Paclitaxel

- Patienten mit ECOG-Performance-Status 2:

  alternativ zur Platin-basierten Kombinationsbehandlung: eine Monotherapie mit Gemcitabin oder Vinorelbin

**Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie**

- Hinweis auf einen beträchtlichen Zusatznutzen.

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**G-BA, 2017 [18].**

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 19. Oktober 2017 – Trametinib.

**Anwendungsgebiet**

Trametinib (Mekinist®) in Kombination mit Dabrafenib ist angezeigt zur Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligen Lungenkarzinom mit einer BRAF-V600-Mutation.

1) Patienten ohne Vorbehandlung:

**Zweckmäßige Vergleichstherapie**

- Patienten mit ECOG-Performance-Status 0, 1 oder 2:
  - Cisplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel oder Pemetrexed) unter Beachtung des Zulassungsstatus

    oder
  - Carboplatin in Kombination mit einem Drittgenerationszytostatikum (nur für Patienten mit erhöhtem Risiko für Cisplatin-induzierte Nebenwirkungen im Rahmen einer Kombinationstherapie; vgl. Anlage VI zum Abschnitt K der Arz-neimittel-Richtlinie)

    oder
  - Carboplatin in Kombination mit nab-Paclitaxel
- Patienten mit ECOG-Performance-Status 2:
  - alternativ zur platinbasierten Kombinationsbehandlung: eine Monotherapie mit Gemcitabin oder Vinorelbin

**Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:**

- Ein Zusatznutzen ist nicht belegt.

**G-BA, 2016 [15].**

Beschluss über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Necitumumab vom 15.09.2016.

**Anwendungsgebiet**

Portrazza ist in Kombination mit Gemcitabin- und Cisplatin-Chemotherapie indiziert zur Therapie von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem, den epidermalen Wachstumsfaktor-Rezeptor (EGFR) exprimierenden, plattenepithelialen, nicht-kleinzelligen Lungenkarzinom, wenn diese bislang keine Chemotherapie für dieses Stadium der Erkrankung erhalten haben.

**Zweckmäßige Vergleichstherapie**

Cisplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel) unter Beachtung des Zulassungsstatus.

**Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Cisplatin in Kombination mit Gemcitabin**

- Ein Zusatznutzen ist nicht belegt.

## 3.2 Cochrane Reviews

**Vasconcellos VF et al., 2020 [44].**

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

**Fragestellung**

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

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

**Methodik**

Population:

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

Intervention/Komparator:

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

Endpunkte:

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

Recherche/Suchzeitraum:

- Bis Januar 2019

Qualitätsbewertung der Studien:

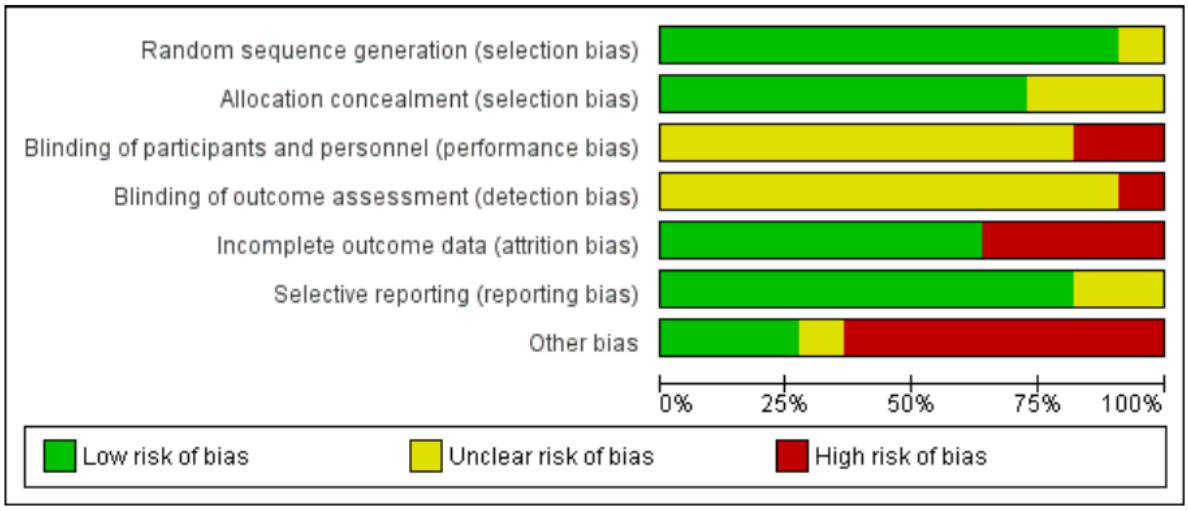
- Cochrane approach / GRADE

**Ergebnisse**

Anzahl eingeschlossener Studien:

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

Qualität der Studien:




Studienergebnisse:

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

**Anmerkung/Fazit der Autoren**

Advanced NSCL patients treated with carboplatin or cisplatin doublet with third-generation chemotherapy drugs showed equivalent overall survival, one-year survival, and response rate. Regarding adverse events, carboplatin caused more thrombocytopenia, and cisplatin caused more nausea/vomiting. Therefore, in this palliative therapeutic intent, the choice of the platin compound should take into account the expected toxicity profile, patient's comorbidities and preferences.

*Kommentare zum Review*

- Gemischte Population; keine Subgruppenanalysen zu Therapielinie oder Stadium

## 3.3 Systematische Reviews

**Liu J et al., 2020 [30]**

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

- non-squamous or squamous NSCLC was categorized for subgroup analysis

**Methodik**

Population:

- advanced non-small cell lung carcinoma patients

Intervention/Komparator:

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

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Cochrane Collaboration’s risk of bias tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- Ten trials, involving 6,124 patients

## Charakteristika der Population:

**Table 1.** Study characteristics.

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

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

## Qualität der Studien:

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

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

## Studienergebnisse:

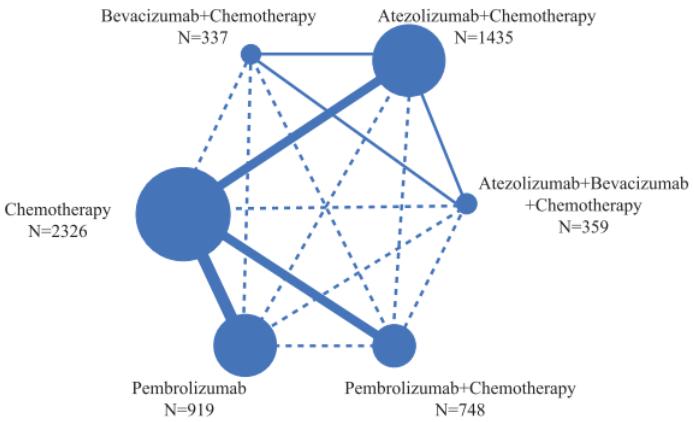



**Figure 2.** Network structure for all the included trials. Each circular node represents a treatment type. The circle size is proportional to the total number of patients. The width of lines is proportional to the number of studies performing head-to-head comparisons in the same study, and the dotted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

- NMA for non-squamous NSCLC

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

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

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

  - For PD-L1-intermediate patients, the PFS-NMA was based on four trials and OS-NMA on five trials.
  - ORR-NMA was not analyzed for PD-L1-high patients analysis due to the missing AC connection. It was also not possible to analyze Pembrolizumab alone in this cohort due to the lack of PFS data.
  - For PFS, ABC appears superior to PC, AC, and was significantly more effective than BC (HR 0.55, 95% CI 0.42–0.73) and chemotherapy alone (HR 0.48, 95% CI 0.31–0.76). AC (HR 0.69, 95% CI 0.54–0.89) and PC (HR 0.55, 95% CI 0.37–0.81) were significantly more effective than chemotherapy, although there was only a marginal improvement compared to BC (HR 0.79, 95% CI 0.61–1.00 for AC; HR 0.63, 95% CI 0.37–1.10 for PC). There were no significant differences among ABC, AC, and PC in terms of progression-free survival.
  - For OS, PC appears superior to chemotherapy alone (HR 0.55, 95% CI 0.34–0.89). Although there was no significant difference when comparing ABC, AC, PC, pembrolizumab alone, BC, and chemotherapy.

  PD-L1 < 1% cohort

  - For PD-L1-low patients, the PFS-NMA was based on four trials and OS-NMA on three. ORR-NMA was not analyzed due to the missing AC connection, for the same reason as for the PD-L1-high expression analysis. Pembrolizumab alone was also not analyzed due to the lack of data.
  - For PFS, ABC appears to provide a significant improvement compared with AC (HR 0.68, 95% CI 0.50–0.93), PC (HR 0.56, 95% CI 0.34–0.93), BC (HR 0.75, 95% CI 0.60–0.94) and chemotherapy alone (HR 0.42, 95% CI 0.29–0.61). AC (HR 0.62, 95% CI 0.50–0.75) performed significantly better than chemotherapy and appears superior to PC. Although PC appears inferior to BC while being superior to chemotherapy alone. BC was significantly more effective than chemotherapy alone (HR 0.56, 95% CI 0.42–0.75).

  - PC appears superior to chemotherapy in terms of OS (HR 0.59, 95% CI 0.38–0.92). However, there was no significant difference among other interventions in terms of overall survival.

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

**Anmerkung/Fazit der Autoren**

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

sophisticated data. This additional knowledge will help to align specific combinations to specific patient groups, although of course, further research is required.

*Kommentare zum Review*

- Siehe auch: Wang, C. et al., 2020 [45] & Chen, Y. et al., 2019 [7] & Tun, A. M. et al., 2019 [43] & Cao, R. et al., 2019 [3]

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**Chen RL et al., 2019 [5]**

The efficacy of PD-1/PD-L1 inhibitors in advanced squamous-cell lung cancer: a meta-analysis of 3112 patients.

**Fragestellung**

to conduct a meta-analysis of all eligible published studies to explore the efficacy of PD-1/PD-L1 inhibitors for advanced squamous-cell lung cancer patients.

**Methodik**

Population:

- patients with advanced squamous NSCLC

Intervention/Komparator:

- chemotherapy or immunotherapy (nivolumab, pembrolizumab, atezolizumab or avelumab) alone or in combination

Endpunkte:

- OS and/or PFS

Recherche/Suchzeitraum:

- Pubmed,Embase and the Cochrane library to identify all eligible trials regarding NSCLC, from the inception to each database until 1 May 2019

Qualitätsbewertung der Studien:

- Jadad scoring system

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 11 studies involving 3112 patients with advanced squamous-cell NSCLC
- 6 were conducted in first-line setting, whereas five were conducted with second or additional lines oftherapy.

Charakteristika der Population:

Table 1. Characteristics of the studies included in the meta-analysis.

| Clinical trials | Study | Phase | Line | Treatment groups | Patients | Median follow-up | Overall survival | Progression-free survival | Quality assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | HR (95% CI) | HR (95% CI) | |
| Checkmate 017 [19] | Brahmer *et al.* (2015) | 3 | >1 | Nivolumab vs docetaxel | 272 | 11.0 | 0.5 (0.44–0.79) | 0.62 (0.47–0.81) | 3 |
| Checkmate 026 [22] | Carbone *et al.* (2017) | 3 | 1 | Nivolumab vs ICC | 129 | 13.5 | 0.82 (0.54–1.24) | 0.83 (0.54–1.26) | 3 |
| Checkmate 078 [17] | Wu *et al.* (2018) | 3 | >1 | Nivolumab vs docetaxel | 200 | 10.4 | 0.61 (0.42–0.89) | 0.61 (0.42–0.87) | 3 |
| KEYNOTE 010 [18] | Herbst *et al.* (2016) | 2/3 | >1 | Pembrolizumab vs docetaxel | 222 | 13.1 | 0.74 (0.50–1.09) | 0.86 (0.62–1.20) | 3 |
| KEYNOTE 024 [26] | Reck *et al.* (2016) | 3 | 1 | Pembrolizumab vs ICC | 56 | 11.2 | NA | 0.35 (0.17–0.71) | 3 |
| KEYNOTE 042 [27] | Mok *et al.* (2019) | 3 | 1 | Pembrolizumab vs ICC | 492 | 12.8 | 0.75 (0.6–0.93) | NA | 3 |
| KEYNOTE 407 [20] | Paz-Ares *et al.* (2018) | 3 | >1 | Pembrolizumab + ICC vs placebo + ICC | 559 | 7.8 | 0.64 (0.49–0.85) | 0.56 (0.45–0.70) | 5 |
| OAK [16] | Rittmeyer *et al.* (2016) | 3 | >1 | Atezolizumab vs docetaxel | 222 | 21.0 | 0.73 (0.54–0.98) | NA | 3 |
| POPLAR [21] | Fehrenbacher *et al.* (2016) | 2 | >1 | Atezolizumab vs docetaxel | 97 | 14.8 | 0.80 (0.49–1.30) | NA | 3 |
| IMpower 131 [23] | Jotte *et al.* (2018) | 3 | 1 | Atezolizumab + CnP vs CnP | 683 | 17.1 | 0.96 (0.78–1.18) | 0.71 (0.60–0.85) | 3 |
| JAVELIN LUNG 200 [15] | Barlesi *et al.* (2018) | 3 | >1 | Avelumab vs docetaxel | 180 | 18.3 | 0.70 (0.48–1.01) | NA | 3 |

CnP: Paclitaxel plus carboplatin; ICC: Investigator's choice of chemotherapy; NA: Not available.

Qualität der Studien:

- Siehe Charakteristika der Population (Tabelle 1)

Studienergebnisse:

- PD-1/PD-L1 inhibitors demonstrated significant superiority to chemotherapy in overall survival (OS) (hazard ratio [HR]: 0.74; p < 0.001) and progression-free survival (PFS) (HR: 0.66; p < 0.001) for squamous NSCLC.
- The OS and PFS benefits of PD-1/PD-L1 inhibitors for squamous NSCLC were similar in subgroup analyses of line settings, PD-L1 expression and different study methodologies.
- No advantage in OS was found in advanced squamous NSCLC patients treated with atezolizumab (HR: 0.87; p = 0.087).

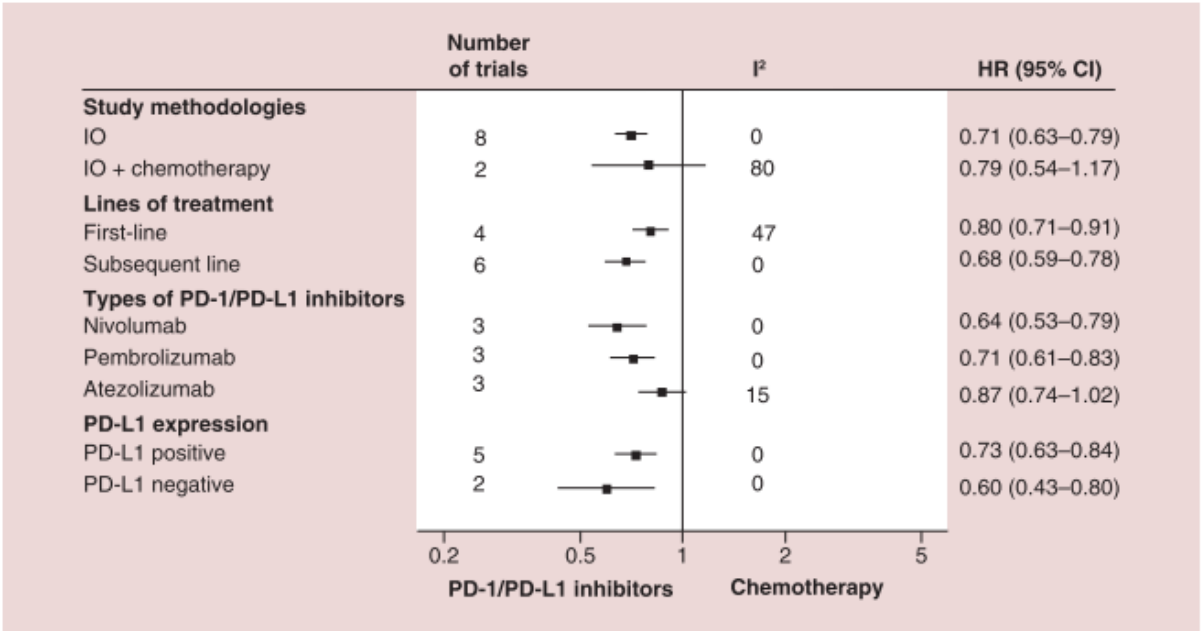


**Figure 4. Subgroup analyses on overall survival according to study methodologies, lines of treatment, types of PD-1/PD-L1 inhibitors and PD-L1 expression.**
HR: Hazard ratio; IO: Immunotherapy; IO+Chemotherapy: The combination of immunotherapy and chemotherapy; PD-1: Programmed death-1; PD-L1: Programmed death-ligand-1.

**Anmerkung/Fazit der Autoren**

In summary, treatment with PD-1/PD-L1 inhibitors resulted in significantly longer OS and PFS in advanced squamous NSCLC patients compared with chemotherapy. With improved PFS and OS, immunotherapy may be an optional treatment for squamous NSCLC patients.

*Kommentar zum Review:*

- Siehe auch: Li, S. et al., 2019 [29]

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**Hess LM et al., 2018 [24].**

First-line treatment of patients with advanced or metastatic squamous non-small cell lung cancer: systematic review and network meta-analyses.

**Fragestellung**

The objectives of this systematic review and meta-analysis were to compare the survival, toxicity, and quality of life of patients treated with necitumumab in combination with gemcitabine and cisplatin.

**Methodik**

Population:

- Advanced or metastatic squamous NSCLC, who had not received any prior chemotherapy treatment for the disease

Intervention/ Komparator:

- Nicht klar definiert; market authorization for use in NSCLC or that were recommended by clinical treatment guidelines

Endpunkte:

- OS, PFS, QOL, and toxicity outcome

Recherche/Suchzeitraum:

- search strategy was conducted on January 27, 2015 and was updated on August 21, 2016

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 35 Studien
- davon wurden 12 Studien in die Meta-Analyse aufgenommen

Charakteristika der Population:

- Only three of the studies were phase II trials (27,29,61)
- The majority of the trials included were not limited to squamous NSCLC

| Citation | Comparators | Planned maximum treatment duration | No. of squamous patients (% of study arm) |
|---|---|---|---|
| Included in meta-analysis | | | |
| Chen *et al.* (27) | Erlotinib 150 mg/day | 6 cycles, optional to PD | 19 (33.3%) |
| | Vinorelbine 60–80 mg/m$^2$ | 6 cycles, optional to PD | 13 (23.2%) |
| Hoang *et al.* (25) | Paclitaxel 135 mg/m$^2$ + cisplatin 75 mg/m$^2$ | Not reported | 60 (20.9%) |
| | Gemcitabine 1,000 mg/m$^2$ + cisplatin 75 mg/m$^2$ | Not reported | 50 (17.8%) |
| | Docetaxel 75 mg/m$^2$ + cisplatin 75 mg/m$^2$ | Not reported | 56 (19.6%) |
| | Paclitaxel 225 mg/m$^2$ + carboplatin AUC 6 | Not reported | 58 (20.3%) |
| Kubota *et al.* (28) | Docetaxel 60 mg/m$^2$ + gemcitabine 1,000 mg/m$^2$ + vinorelbine 25 mg/m$^2$ | 6 cycles | 46 (23%) |
| | Paclitaxel 225 mg/m$^2$ + carboplatin AUC 6 | 6 cycles | 30 (15%) |
| Lilenbaum *et al.* (29) | Erlotinib 150 mg/day | To PD | 11 (21.2%) |
| | Paclitaxel 200 mg/m$^2$ + carboplatin AUC 6 | 4 cycles | 8 (15.7%) |
| Morabito *et al.* (30) (CAPPA-2) | Gemcitabine 1,200 mg/m$^2$ | 4 cycles | 9 (32%) |
| | Gemcitabine 1,000 mg/m$^2$ + cisplatin 60 mg/m$^2$ | 4 cycles | 10 (36%) |
| Pirker *et al.* (31,32) | Cisplatin 80 mg/m$^2$ + vinorelbine 25 mg/m$^2$ | 6 cycles | 187 (33%) |
| Gatzemeier *et al.* (33) (FLEX) | Cisplatin 80 mg/m$^2$ + vinorelbine 25 mg/m$^2$ + cetuximab 250 mg/m$^2$ (starting dose 400 mg/m$^2$) | 6 cycles; cetuximab to PD | 190 (34%) |
| Socinski *et al.* (34) | Nab-paclitaxel 100 mg/m$^2$ + carboplatin AUC 6 | 6 cycles, optional to PD | 229 (44%) |
| | Paclitaxel 200 mg/m$^2$ + carboplatin AUC 6 | 6 cycles, optional to PD | 221 (42%) |
| Spigel *et al.* (35) | Paclitaxel 200 mg/m$^2$ + carboplatin AUC 6 day 1, every 21 days | 6 cycles | 57 (100%) |
| | Necitumumab 800 mg days 1,8 + paclitaxel 200 mg/m$^2$ day 1 + carboplatin AUC 6 day 1, every 21 days | Up to 6 cycles; necitumumab to PD | 110 (100%) |
| Tan *et al.* (36) (GLOB-3) | Docetaxel 75 mg/m$^2$ + cisplatin 75 mg/m$^2$ | 6 cycles | 64 (33.5%) |
| | Vinorelbine (IV 30 mg/m$^2$; oral 80 mg) + cisplatin 80 mg/m$^2$ | 6 cycles | 65 (34.2%) |
| Thatcher *et al.* (14) (SQUIRE) | Gemcitabine 1,250 mg/m$^2$ + cisplatin 75 mg/m$^2$ | Up to 6 cycles | 548 (100%) |
| | Necitumumab 800 mg/m$^2$ + gemcitabine 1,250 mg/m$^2$ + cisplatin 75 mg/m$^2$ | Up to 6 cycles; necitumumab to PD | 545 (100%) |
| Treat *et al.* (37) | Gemcitabine 1,000 mg/m$^2$ + carboplatin AUC 5.5 | 6 cycles | 67 (17.7%) |
| | Gemcitabine 1,000 mg/m$^2$ + paclitaxel 200 mg/m$^2$ | 6 cycles | 74 (19.6%) |
| | Paclitaxel 225 mg/m$^2$ + carboplatin AUC 6 | 6 cycles | 61 (16.1%) |
| Yoshioka *et al.* (38) (LETS Study) | Paclitaxel 200 mg/m$^2$ + carboplatin AUC 6 | 6 cycles | 59 (20.9%) |
| | S-1 40 mg/day, days 1–14 + carboplatin AUC 5 | 6 cycles | 55 (19.5%) |

Qualität der Studien:

- Only 3 clinical trials included in the systematic literature review were categorized as low quality

Studienergebnisse:

- **OS (8 Studien)**
  - All comparators, with the exception of carbo + S-1, were associated with a higher HR than neci + gem + cis. A very wide CrI for OS was observed in one study
  - When including carbo + S-1, the probability of neci + gem + cis being the highest ranked treatment option was 22.0%, whereas the probability for carbo + S-1 was 45.2%. Neci + carbo + tax had a 17.3% probability, gem + docetaxel + vinorelbine had a 9.8% probability, and all others had less than a 5% probability of being the highest ranked OS option.
  - When excluding the carbo + S-1 regimen because this agent is not available beyond Asia and may not be a relevant comparator worldwide, neci + gem + cis had a 35.4% probability

of being ranked first for OS, neci + carbo + tax had a 30.8% probability, gem + docetaxel + vinorelbine had a 18.5% probability, and nab-tax + carbo had a 10.8% probability.

- **PFS (9 Studien)**
  - Neci + gem + cis demonstrated longer PFS compared with all other comparators.
  - The probability of neci + gem + cis being the highest ranked for PFS in the HR analysis was 63.0%. Nab-tax + carbo had an 11.1% probability, carbo + S-1 had an 11.0% probability, and gem + docetaxel + vinorelbine had a 6.5% probability. All other comparators had less than a 5% probability of being the highest ranked
  - When excluding carbo + S-1, neci + gem + cis had a 70.8% probability of being the highest ranked option for PFS, nab-tax + carbo had a 12.7% probability, gem + docetaxel + vinorelbine had a 7.0% probability, and all other comparators had less than a 5% probability.
- **Adverse events and Quality of life**
  - No analyses

**Anmerkung/Fazit der Autoren**

Results of this clinical-trial based network meta-analysis suggest that carboplatin plus S-1 and necitumumab in combination with gemcitabine and cisplatin may have OS benefits versus other regimens and that necitumumab in combination with gemcitabine and cisplatin may also have PFS benefits versus other comparators. However, these results should be interpreted with caution due to the limited number of studies, few of which focused exclusively on squamous NSCLC, the inability to adjust for covariates, and the wide credible intervals. Data were not available to conduct a network meta-analysis of either toxicity or QOL.

*Kommentare zum Review*

- The consistency assumption could not be explored because of the lack of closed loops in the network that included neci + gem + cis.
- Mutationsstatus unklar

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**Chen JH et al., 2018 [4].**

Indirect comparison of efficacy and safety between immune checkpoint inhibitors and antiangiogenic therapy in advanced non–small-cell lung cancer.

**Fragestellung**

(…) indirect comparison to compare the safety and efficacy of immune checkpoint inhibitors, antiangiogenic therapy, and conventional chemotherapy.

**Methodik**

Population:

- patients with unresectable locally advanced or metastatic NSCLC either treatment-naive or first-line chemotherapy failure

Intervention/Komparator:

- anti-angiogenesis inhibitors, immunotherapy or chemotherapy as first-line therapy or subsequent therapy

Endpunkte:

- overall survival, progression free survival and all grade 3 to 5 adverse events

Recherche/Suchzeitraum:

- up to July 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 37 RCTs involving 16810 patients were included to conduct meta-analysis and indirect comparisons
- Eighteen trials were conducted as first line setting and nineteen trials were designed as subsequent therapy. Among the trials of first line setting, eighteen trials compared anti-angiogenetic agents or immune checkpoint inhibitors with doublet platinum-based treatment. In terms of the trials of subsequent therapy, seventeen trials compared anti-angiogenic agents or immune checkpoint inhibitors with docetaxel and two trials compared these newer treatments with pemetrexed.
- Nineteen anticancer agents were analyzed, including anti-angiogenetic agents (bevacizumab, aflibercept, ramucirumab, nintedanib, axitinib, sorafenib, vandetanib, and sunitinib), immune checkpoint inhibitors (ipilimumab, pembrolizumab, nivolumab and atezolizumab) and traditional chemotherapy (cisplatin, carboplatin, oxaliplatin, gemcitabine, paclitaxel, docetaxel and pemetrexed)

Qualität der Studien:

- The quality of the included RCTs were generally good with low risk of bias. The most common bias was the lack of blinding in about 38% of included trials with open-label designed. In the domain of other risk of bias, one trial by Wang Y. et al. was at high risk of bias due to single center design.

Studienergebnisse:

- Overall survival (OS):
  - The results of pairwise meta-analysis of direct comparisons of OS: In the first line setting, use of pembrolizumab significantly prolonged OS (HR: 0.60; 95%CI: 0.41–0.88; p = 0.010; heterogeneity: single trial). In the subsequent setting, the use of nivolumab (HR: 0.67; 95%CI: 0.55–0.82; p = 0.0001; heterogeneity: p = 0.24; $I_2$ = 27%), pembrolizumab (HR: 0.71; 95%CI: 0.58–0.87; p = 0.001; heterogeneity: single trial), atezolizumab (HR: 0.73; 95%CI: 0.63–0.84; p < 0.0001; heterogeneity: p = 1.00; $I_2$ = 0%) and ramucirumab plus docetaxel (HR: 0.86; 95%CI: 0.75–0.98; p = 0.02; heterogeneity: p = 1.00; $I_2$ = 0%) showed significant OS benefit versus standard chemotherapy.

- Indirect comparison of OS: For the first line setting, both use of pembrolizumab alone (HR: 0.6; 95%CI: 0.4–0.91) and the combination of bevacizumab and doublet platinum-base therapy (HR: 0.86; 95%CI: 0.75–0.99) showed significant survival benefit as compared to doublet platinum therapy. Overall, anti-PD1 monoclonal antibodies appears superior to anti-angiogenic therapies in terms of OS. The use of pembrolizumab alone was associated with statistically significant survival benefit as compared to the combination of axitinib and doublet platinum-based therapy (HR: 0.41; 95%CI: 0.22–0.78), the combination of sorafenib and doublet platinum-based therapy (HR: 0.57; 95%CI: 0.36–0.89), and the combination of vandetanib and doublet platinum-based therapy (HR: 0.52; 95%CI: 0.28–0.96); it was also superior to the combination of ramucirumab and doublet platinum-based therapy (HR: 0.58; 95%CI: 0.32–1.05) and the combination of bevacizumab and doublet platinum-based therapy, although these difference did not reach statistical significance. In addition, the use of pembrolizumab alone resulted in significant survival advantage when compared to nivolumab alone, regardless of PD-1/PD-L1 expression level (HR: 0.59; 95%CI: 0.36–0.97).

- PFS:
  - In the first line setting, statistically significant improvement of PFS were shown in the combination of bevacizumab and doublet platinum-based therapy (HR: 0.62; 95%CI: 0.47–0.82; p = 0.0009; heterogeneity: p = 0.0002; I2 = 84%), the combination of pembrolizumab and doublet platinum-based therapy (HR: 0.53; 95%CI: 0.31–0.91; p = 0.02; heterogeneity: single trial), and pembrolizumab alone (HR: 0.50; 95%CI: 0.37–0.68; p < 0.00001; heterogeneity: single trial) versus standard doublet platinum-based therapy. In the subsequent setting, statistically significant benefit of PFS were shown in the combination of ramucirumab and docetaxel (HR: 0.75; 95%CI: 0.67–0.84; p < 0.00001; heterogeneity: p = 0.65; I2 = 0%), the combination of nintedanib and docetaxel (HR: 0.79; 95%CI: 0.68–0.92; p = 0.002; heterogeneity: single trial), the combination of aflibercept and docetaxel (HR: 0.82; 95%CI:0.72–0.94; p = 0.004; heterogeneity: single trial), and the combination of vandetanib and docetaxel (HR: 0.78; 95%CI: 0.70–0.87; p < 0.00001; heterogeneity: p = 0.44; I2 = 0%) versus docetaxel.
  - Indirect comparison: In the first line setting, pembrolizumab alone (HR: 0.5; 95%CI: 0.32–0.79) and combination of bevacizumab and doublet platinum-based therapy (HR: 0.64; 95%CI: 0.52–0.78) showed significantly increased efficacy compared with doublet platinum-based therapy.

    → Overall, pembrolizumab showed increased efficacy compared with anti-angiogenic therapies, although statistical significance did not reach in some comparisons: pembrolizumab vs combination of bevacizumab and doublet platinum-based therapy, pembrolizumab vs combination of ramucirumab and doublet platinum-based therapy, pembrolizumab vs combination of sorafenib and doublet platinum-based therapy (HR: 0.54; 95%CI: 0.32–0.91), and pembrolizumab vs combination of vandetanib and doublet platinum-based therapy.

- Toxicity:

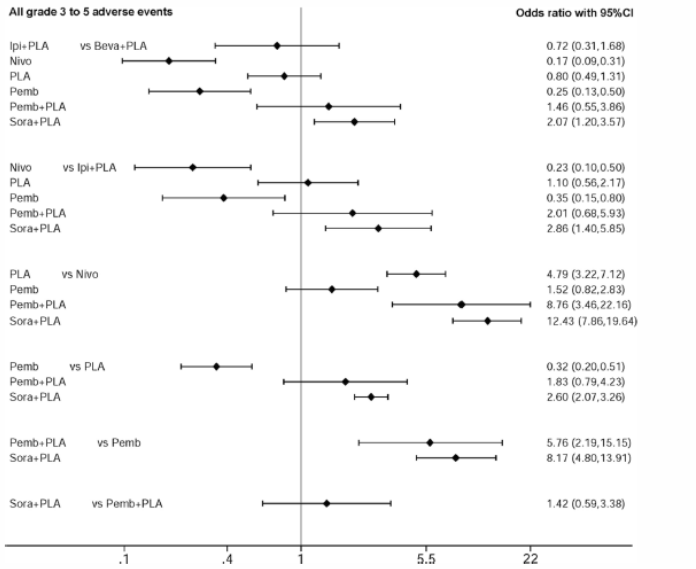


**Figure 2.** Forest plot of indirect comparison: all grade 3 to 5 adverse events in first line therapy. All individual regimens compared with reference treatment. Odds ratios (OR) and 95% confidence intervals were given. Beva: bevacizumab; Ipi: ipilimumab; Nivo: nivolumab; Pemb: pembrolizumab; Sora: sorafenib; PLA: doublet platinum-based treatment.

**Anmerkung/Fazit der Autoren**

In conclusion, based on current evidence, our results revealed that pembrolizumab and nivolumab may be preferable first-line and subsequent treatment options, respectively, for patients with advanced NSCLC without target gene mutations. These findings enhance our understanding of the efficacy and safety of immune checkpoint inhibitors and antiangiogenic therapy in advanced NSCLC.

*Kommentare zum Review*

- Gemischte Population: Keine seperaten Analysen/Ergebnisse zum Stadium oder Status (z.B. fortgeschritten vs. metastasierte Patienten) bzw. EGFR Status.

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**Han S et al., 2018 [21].**

The efficacy and safety of paclitaxel and carboplatin with versus without bevacizumab in patients with non-small-cell lung cancer: a systematic review and meta-analysis

**Fragestellung**

To investigate the efficacy and safety of Bevacizumab (Bev) used in combination with paclitaxel and carboplatin (PC), compared with PC alone in patients with advanced non-small-cell lung cancer (NSCLC).

**Methodik**

Population:

- patients with untreated locally advanced, recurrent or previously metastatic NSCLC

Intervention/Komparator:

- PC with or without Bev as a first-line therapy for patients with untreated locally advanced, recurrent or previously metastatic NSCLC

Endpunkte:

- PFS, OS, ORR, toxicity, treatment related mortality

Recherche/Suchzeitraum:

- up to May 2017

Qualitätsbewertung der Studien:

- Cochrane Collaboration tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- five RCTs (1486 patients) that compared PC with or without Bev (dose: 15 mg/kg) for locally advanced (stage IIIB), recurrent or metastatic (stage IV) NSCLC

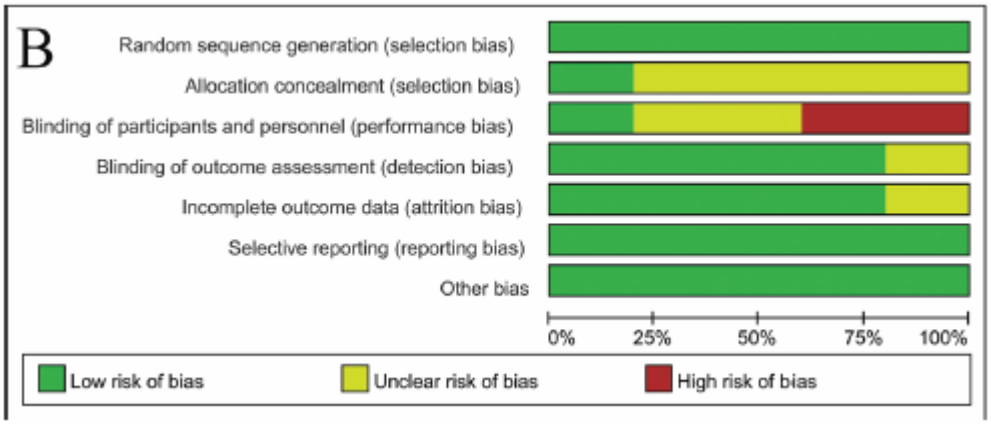
Charakteristika der Population:

**Table 1: Characteristics of RCTs included in the meta-analysis**

| study | year | region | trial phase | participants | intervention and comparisons | patients enrolled | Histology | primary endpoint |
|---|---|---|---|---|---|---|---|---|
| Johnson | 2004 | USA | II | 99 | C:CP<br>T:CP+BEV(7.5 mg/kg)<br>T:CP+BEV(15 mg/kg) | 32<br>32<br>35 | adenocarcinoma, large cell carcinoma, squamous cell carcinoma, other | time to disease progression and tumor response rate |
| Sandler | 2006 | USA | III | 878 | C:CP<br>T:CP+BEV(15 mg/kg) | 444<br>434 | adenocarcinoma, large cell carcinoma, bronchoalveolar carcinoma, other | overall survival |
| Soria | 2011 | Europe | II | 85 | C:CP<br>T:CP+BEV(15 mg/kg) | 41<br>44 | adenocarcinoma, bronchoalveolar carcinoma, large cell carcinoma, other | objective response rate |
| Niho | 2012 | Japan | II | 180 | C:CP<br>T:CP+BEV(15 mg/kg) | 59<br>121 | adenocarcinoma, large cell carcinoma, other | progression-free survival |
| Zhou | 2015 | China | III | 276 | C:CP<br>T:CP+BEV(15 mg/kg) | 138<br>138 | adenocarcinoma, large cell carcinoma, mixed cell carcinoma | progression-free survival |

Qualität der Studien:

- low risk of bias in most domains except for the allocation concealment and binding. Because the outcomes (such as PFS and OS) in cancer trials are objective and are not influenced by a lack of blinding, the risk of bias was considered acceptable.




Studienergebnisse:

- Progression-free survival
  - PFS was prolonged in patients treated who were with PC plus Bev, compared with PC, with an estimated HR of 0.57 (random effects: 95% CI = 0.46–0.71, $p < 0.01$; $I_2 = 56\%$, $p = 0.06$).
- Overall survival:
  - The five included trials all reported OS. The HR for the OS favored Bev combined with PC (fixed effect: HR = 0.81; 95% CI = 0.71–0.92; $p < 0.01$), without significant heterogeneity ($I_2 = 0\%$; $p = 0.48$) among the trials, and HR was calculated using a fixed effects model. There was also no significant heterogeneity ($I^2 = 15\%$, $P = 0.32$) with regarding the effect of Bev on the OS after excluding the study published by Johnson et al., which was the only study that included patients with squamous cell histology.
- Overall response rates:
  - The fixed-effects model evaluation ($\chi_2 = 4.67$; $p = 0.32$, $I^2 = 14\%$), including 1,486 patients, showed an increased response rate in the Bev plus PC versus the PC along group (RR = 2.06, 95% CI = 1.73–2.44).
- Toxicities and safety:
  - Bev showed a significant increase in treatment-related deaths in patients with NLCLC (fixed effect: RR = 2.96; 95% CI = 1.46–5.99; $p = 0.003$).
  - According to the haematological toxicities (grade 3/4), the group that received PC plus Bev had higher rates of neutropenia (fixed effect: RR = 1.29; 95% CI = 1.12– 1.49; $p = 0.0006$). The proportions of febrile anemia, febrile neutropenia and thrombocytopenia were similar.
  - The non-haematologic toxicities were also more frequent for patients receiving PC plus Bev. These toxicities included haemoptysis (fixed effect: RR = 4.87; 95%CI = 1.13–20.90; p = 0.03), hypertension (fixed effect: RR = 6.89; 95% CI = 3.21–14.79; p < 0.00001), proteinuria (fixed effect: RR = 12.58; 95% CI = 2.61–60.57; p = 0.002) and bleeding events (fixed effect: RR = 4.59; 95% CI = 1.78–11.80; p = 0.002). There was no difference in the proportion of patients with thrombocytopenia.

**Anmerkung/Fazit der Autoren**

Our meta-analysis demonstrated that Bev significantly prolonged the PFS, OS and RR when combined with PC as first-line therapy in patients with non-squamous advanced NSCLC. This

combination caused more adverse events and slightly increased the risk of treatment-related death. Thus, Bev plus PC can be considered a good option for reasonably selected target patients. Importantly, the patient's own value, complicated diseases and expected toxicity profile should be considered before making a treatment decision.

*Kommentare zum Review*

- Gemischte Population: Keine separaten Angaben zum Stadium oder Status (z.B. fortgeschritten vs. metastasierte Patienten bzw. EGFR Status.

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**Zhao S et al., 2018 [47].**

Bevacizumab in combination with different platinum-based doublets in the first-line treatment for advanced nonsquamous non-small-cell lung cancer: A network meta-analysis.

**Fragestellung**

to estimate the relative efficacy and tolerability of bevacizumab in combination with different platinumbased doublets in the first-line treatment for advanced nonsquamous non-small cell lung cancer (NS-NSCLC), attempting to identify the most and least preferable regimen to be used with bevacizumab for this population

**Methodik**

Population:

- advanced NS-NSCLC patients (first-line setting)

Intervention/Komparator

- least two of the following treatments:
  - platinumbased doublets with and without bevacizumab for untreated advanced NS-NSCLC were classified into six categories, taxane–platinum chemotherapy (Taxane–Pt), gemcitabine–platinum chemotherapy (Gem–Pt), pemetrexed–platinum chemotherapy (Pem–Pt), taxane–platinum plus bevacizumab (Taxane–Pt+B), gemcitabine–platinum plus bevacizumab (Gem–Pt+B) and pemetrexed–platinum plus bevacizumab (Pem–Pt+B)

Endpunkte:

- OS, PFS, SAE

Recherche/Suchzeitraum:

- PubMed, EMBASE, Cochrane Central Register of Controlled Trials databases and ClinicalTrials.gov until the end of June 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- Data of 8,548 patients from 18 randomized controlled trials (RCTs) receiving six treatments, including taxane–platinum (Taxane–Pt), gemcitabine–platinum (Gem–Pt), pemetrexed–platinum (Pem–Pt), taxane–platinum+bevacizumab (Taxane–Pt+B), gemcitabine–platinum+bevacizumab (Gem–Pt+B) and pemetrexed–platinum+bevacizumab (Pem–Pt+B), were incorporated into the analyses

Qualität der Studien:

- As for the risks of bias, one trial (Boutsikou et al.33) was rated with high overall risk of bias, as it had three rated with an unclear risk of bias. Among the remaining trials, eleven trials had two items and three trials had one item rated with unclear risk of bias.

Studienergebnisse:

- Direct and indirect evidence of overall survival (OS) and progression-free survival (PFS) were synthesized at the hazard ratio (HR) scale and evidence of objective response rate (ORR) and serious adverse events (SAE) were synthesized at the odds ratio (OR) scale.
- Taxane–Pt+B showed significant advantages in OS (HR=0.79, p < 0.001), PFS (HR=0.54, p < 0.001) and ORR (OR=2.7, p < 0.001) over Taxane–Pt with comparable tolerability (OR53.1, p=0.08).
- Gem–Pt+B showed no OS benefit compared to any other treatment.
- No significant differences were detected between Pem–Pt+B and Pem–Pt in four outcomes.
- In terms of the benefit-risk ratio, Pem–Pt and Taxane–Pt+B were ranked the first and second, respectively.

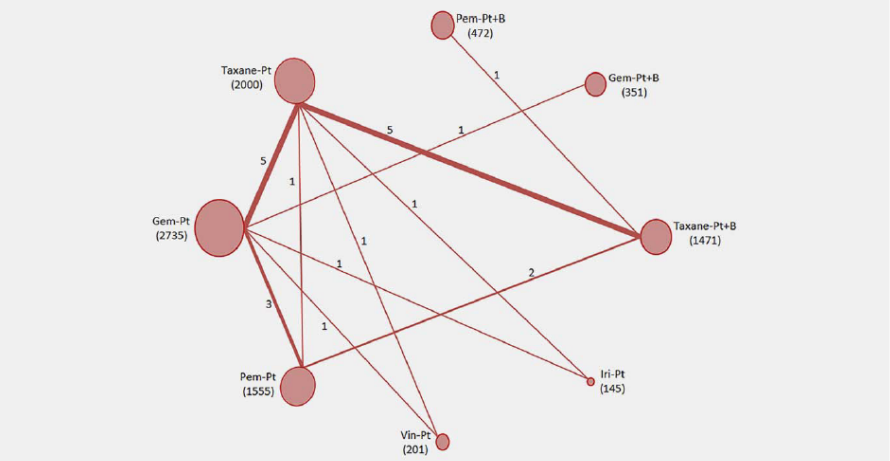


Figure 2. Network of all eligible trials assessing the six treatments in the first-line setting for advanced NS-NSCLC established for the Bayesian network meta-analysis. The size of the nodes is proportional to the number of patients (in parentheses) randomized to receive the treatment. The width of the lines is proportional to the number of trials (beside the line) comparing the connected treatments (nodes). Taxane–Pt + B, taxane–platinum plus bevacizumab; Gem–Pt + B, gemcitabine–platinum plus bevacizumab; Pem-Pt + B, pemetrexed–platinum plus bevacizumab; Taxane–Pt, taxane–platinum chemotherapy; Gem–Pt, gemcitabine–platinum chemotherapy; Pem–Pt, pemetrexed–platinum chemotherapy; Vin–Pt, vinorelbine–platinum chemotherapy; Iri–Pt, irinotecan–platinum chemotherapy. [Color figure can be viewed at

**Anmerkung/Fazit der Autoren**

In conclusion, in the first-line treatment for advanced NS-NSCLC, Taxane–Pt and Gem–Pt are the most and least preferable regimens to be used with bevacizumab, respectively. Adding bevacizumab to Pem–Pt remains unjustified because it fails to improve efficacy or tolerability.

In terms of the benefit-risk ratio, Pem–Pt and Taxane–Pt+B are the best and second-best treatment for this population.

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**Luo W et al., 2018 [33].**

Safety and tolerability of PD-1/PD-L1 inhibitors in the treatment of non-small cell lung cancer: a meta-analysis of randomized controlled trials

**Fragestellung**

We conducted a comprehensive meta-analysis to state the safety profile of PD-1/PD-L1 inhibitors in NSCLC, and identify the exact incidence and relative risk (RR) of both summary and detailed AEs.

**Methodik**

Population:

- patients with lung cancer

Intervention:

- PD-1/PD-L1 inhibitor

Komparator:

- Chemotherapy

Endpunkte:

- relevant symptoms (fatigue, anorexia, nausea, constipation diarrhea, and peripheral sensory neuropathy), hematologic AEs (neutropenia and anemia), and immune-related AEs (irAEs; rash, pruritus, colitis, hypothyroidism, hyperthyroidism, hypophysitis, alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevations, and pneumonitis)

Recherche/Suchzeitraum:

- PubMed, Embase, and the Cochrane library databases to May 1, 2018

Qualitätsbewertung der Studien:

- Cochrane Collaboration’s risk of bias tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 8 RCTs with 4413 patients

Charakteristika der Population:

**Table 1** Characteristics of studies included in the meta-analysis (PD-1/PD-L1 inhibitors vs. chemotherapy)

| Reference | Author, year | Phase | Masking | Histology | Treatment arms | Number of patients available for analysis | Age in years (median) | Follow-up duration (months) | CTCAE version |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Brahmer, 2015 | III | Open-label | Squamous NSCLC | Nivolumab | 131 | 62 | Minimum 11 | 4.0 |
| | | | | | Docetaxel | 129 | 64 | | |
| 2 | Borghaei, 2015 | III | Open-label | Non-squamous NSCLC | Nivolumab | 287 | 61 | Minimum 13.2 | 4.0 |
| | | | | | Docetaxel | 268 | 64 | | |
| 3 | Carbone, 2017 | III | Open-label | NSCLC | Nivolumab | 267 | 63 | Median 13.5 | 4.0 |
| | | | | | Platinum-based chemo-therapy | 263 | 65 | | |
| 4 | Fehren-bacher, 2016 | II | Open-label | NSCLC | Atezoli-zumab | 142 | 62 | Median; 14.8 for Atezoli-zumab; 15.7 for Docetaxel | 4.0 |
| | | | | | Docetaxel | 135 | 62 | | |
| 5 | Rittmeyer, 2017 | III | Open-label | NSCLC | Atezoli-zumab | 609 | 63 | median 21 | 4.0 |
| | | | | | Docetaxel | 578 | 64 | | |
| 6* | Herbst, 2016 (1) | II/III | Open-label | NSCLC | Pembroli-zumab 2 mg/kg | 339 | 63 | Median 13.1 | 4.0 |
| | | | | | Docetaxel | 309 | 62 | | |
| 7* | Herbst, 2016 (2) | II/III | Open-label | NSCLC | Pembroli-zumab 10 mg/kg | 343 | 63 | Median 13.1 | 4.0 |
| | | | | | Docetaxel | 309 | 62 | | |
| 8 | Reck, 2016 | III | Open-label | NSCLC | Pembroli-zumab | 154 | 64.5 | MEDIAN 11.2 | 4.0 |
| | | | | | Platinum-based chemo-therapy | 150 | 66 | | |

*Different cohorts with different dose of PD-1/PD-L1 inhibitors in the same trial

*PD-1* programmed death receptor-1, *PD-L1* programmed death ligand 1, *NSCLC* non-small cell lung cancer, *CTCAE* the Common Terminology Criteria for Adverse Events version

Qualität der Studien:

- Most of the included studies had a high risk of selection bias, performance bias, and detection bias due to their open-label design

Studienergebnisse:

**Table 2** Incidence and RR of summary toxic events

| Summary toxic events | Number of trials | Incidence (%, 95% CI) | | Effect estimate | | Heterogeneity | |
|---|---|---|---|---|---|---|---|
| | | PD-1/PD-L1 inhibitor | Control | RR (95% CI) | *P* | *P* | $I^2$ (%) |
| Any all-grade AEs | 8 | 66.20 (64.21; 68.14) | 86.08 (84.54; 87.52) | 0.77 (0.74; 0.80) | <0.0001 | 0.5215 | 0.0 |
| Any high-grade AEs | 8 | 14.26 (12.85; 15.77) | 43.53 (41.42; 45.66) | 0.32 (0.25; 0.41) | <0.0001 | 0.0001 | 76.2 |
| Treatment discontinuation | 8 | 5.94 (5.01; 6.99) | 13.92 (12.48; 15.46) | 0.44 (0.33; 0.59) | <0.0001 | 0.067 | 47.0 |
| Toxic deaths | 8 | 0.48 (0.24; 0.86) | 1.12 (0.71; 1.66) | 0.45 (0.23; 0.90) | 0.0229 | 0.9858 | 0.0 |

*AEs* adverse events, *RR* relative risk, *CI* confidence interval, *PD-1* programmed death receptor-1, *PD-L1* programmed death ligand 1

- Incidence and relative risk of toxic symptoms
  - Patients receiving PD-1/PD-L1 inhibitors had a significantly lower risk for five evaluated all-grade toxic symptoms when compared with chemotherapy: fatigue (18.75 vs. 30.83%; RR 0.61; 95% CI: 0.55–0.68; P < 0.0001), nausea (12.54 vs. 25.69%; RR 0.45; 95% CI: 0.31–0.65; P < 0.0001), constipation (6.34 vs. 8.08%; RR 0.49; 95% CI: 0.26–0.94; P = 0.031), diarrhea (10.61 vs. 19.85%; RR 0.51; 95% CI: 0.37–0.72; P < 0.0001), and peripheral sensory neuropathy (1.32 vs. 6.31%; RR 0.13; 95% CI: 0.05–0.34; P < 0.0001). The risk of four high-grade toxic symptoms was significantly lower from PD-1/PD-L1

inhibitors therapy than chemotherapy: fatigue (1.58 vs. 4.06%; RR 0.39; 95% CI: 0.27–0.57; P < 0.0001), anorexia (0.35 vs. 1.26%; RR 0.30; 95% CI: 0.14–0.64; P = 0.0018), diarrhea (0.75 vs. 1.77%; RR 0.44; 95% CI: 0.25–0.76; P = 0.0034), and peripheral sensory neuropathy (0.00 vs. 0.61%; RR 0.10; 95% CI: 0.02–0.53; P = 0.0068).

- Incidence and relative risk of hematologic toxicities
  - Patients receiving PD-1/PD-L1 inhibitors were at a significantly lower risk of all-grade neutropenia (0.70 vs. 18.68%; RR 0.03; 95% CI: 0.01–0.08; P < 0.0001), thrombocytopenia (0.09 vs. 2.57%; RR 0.04; 95% CI: 0.01–0.16; P < 0.0001), and anemia (5.59 vs. 23.26%; RR 0.19; 95% CI: 0.10–0.34; P < 0.0001) when compared with chemotherapy. A significantly lower risk of high-grade neutropenia (0.13 vs. 14.53%; RR 0.02; 95% CI: 0.01–0.04; P < 0.0001), thrombocytopenia (0.04 vs. 1.40%; RR 0.05; 95% CI: 0.01–0.25; P = 0.0003), and anemia (1.01 vs. 6.03%; RR 0.17; 95% CI: 0.07–0.42; P = 0.0001) was also observed in PD-1/PD-L1 inhibitors
- Incidence and relative risk of immune-related AEs
  - The most frequently reported all-grade irAEs from PD-1/ PD-L1 inhibitors therapy included rash (5.77%), hypothyroidism (4.89%), and pneumonitis (3.21%), while the most frequently observed high-grade irAE was pneumonitis (1.45%), ALT/AST elevations (0.57%) and colitis (0.40%). Compared to chemotherapy, PD-1/PD-L1 inhibitors therapy was associated to a significantly increased risk of seven all-grade irAEs: rash (5.77 vs. 2.76%; RR 2.07; 95% CI: 1.54–2.80; P < 0.0001), pruritus (2.16 vs. 0.51%; RR 4.15; 95% CI: 2.20–7.81; P < 0.0001), colitis (0.70 vs. 0.00%; RR 5.44; 95% CI: 1.42–20.80; P = 0.013), hypothyroidism (4.89 vs. 0.23%; RR 17.59; 95% CI: 7.74–39.98; P < 0.0001), hyperthyroidism (2.11 vs. 0.37%; RR 5.27; 95% CI: 2.56–10.86; P < 0.0001), ALT/AST elevations (1.85 vs. 0.89%; RR 2.15; 95% CI: 1.31–3.51; P = 0.002), and pneumonitis (3.21 vs. 0.65%; RR 3.83; 95% CI: 2.20–6.68; P < 0.0001). There was also a small, but significantly increased risk of high-grade pneumonitis from PD-1/PD-L1 inhibitors compared with chemotherapy (1.45 vs. 0.19%; RR 3.78; 95% CI: 1.43–10.03; P = 0.007)

**Anmerkung/Fazit der Autoren**

Our meta-analysis has demonstrated that PD-1/PD-L1 inhibitors are generally safer and better tolerated than chemotherapy for patients with NSCLC with regard to summary toxic events, detailed toxic symptoms and hematologic toxicities. However, PD-1/PD-L1 inhibitors can generate a unique spectrum of irAEs, and several of them can be severe and even life-threatening. Clinicians should be aware of the risk of these AEs, as they may have a potentially negative impact on the patients' quality of life and survival outcome.

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**Zhou Y et al., 2018 [48].**

Immune-checkpoint inhibitor plus chemotherapy versus conventional chemotherapy for first-line treatment in advanced non-small cell lung carcinoma: a systematic review and meta-analysis

Ähnliche Reviews zu dem Thema:

- **Shen K et al., 2018 [42].** Effectiveness and safety of PD-1/PD-L1 or CTLA4 inhibitors combined with chemotherapy as a first-line treatment for lung cancer: A meta-analysis

**Fragestellung**

We performed a meta-analysis of randomized trials that compared PD-1/PD-L1 inhibitor plus chemotherapy with chemotherapy in first line of treatment for advanced NSCLC.

**Methodik**

Population:

- patients with advanced NSCLC.

Intervention:

- PD-1/PD-L1 inhibitor plus chemotherapy (pembrolizumab, nivolumab, atezolizumab, durvalumab)

Komparator:

- chemotherapy

Endpunkte:

- progression-free survival (PFS), overall survival (OS), objective response rate (ORR), duration of response, and treatment-related adverse events (AEs)

Recherche/Suchzeitraum:

- Pubmed, Embase and the Cochrane Central Register of Controlled Trials to June 10, 2018

Qualitätsbewertung der Studien:

- Cochrane Collaboration's risk of bias tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 6 RCTs with 3144 patients

Charakteristika der Population:

**Table 1** Characteristics of Patients Comparing IO-Chemotherapy with Chemotherapy in Included Trials

| Source | PD-(L)1 Drug[b] | Histology | No. of patients[a] | | Median age (years)[a] | Male (%)[a] | Performance status[a] | | PD-L1 subgroups[a] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | ITT | As treated | | | ECOG 0 (%) | ECOG 1 (%) | <1% (%) | 1–49% (%) | ≥50% (%) |
| KEYNOTE-189 2018 [6] | Pembrolizumab | nonsquamous | 410 vs 206 | 405 vs 202 | 65 vs 64 | 62 vs 53 | 45 vs 39 | 54 vs 61 | 31 vs 31 | 31 vs 28 | 32 vs 34 |
| IMpower150 2018 [15] | Atezolizumab | nonsquamous | 400 vs 400 | 393 vs 394 | 63 vs 63 | 60 vs 60 | 39 vs 43 | 60 vs 57 | 47 vs 50 | 33 vs 31 | 20 vs 19 |
| KEYNOTE-021 2016 [5], 2018 [20] | Pembrolizumab | nonsquamous | 60 vs 63 | 59 vs 62 | 63 vs 63 | 37 vs 41 | 40 vs 46 | 58 vs 54 | 35 vs 37 | 32 vs 37 | 33 vs 27 |
| KEYNOTE-407 2018 | Pembrolizumab | squamous | 278 vs 281 | 278 vs 280 | 65 vs 65 | 79 vs 84 | 26 vs 32 | 74 vs 68 | 34 vs 35 | 37 vs 37 | 26 vs 26 |
| IMpower131 2018 [17] | Atezolizumab | squamous | 343 vs 340 | 334 vs 334 | 65 vs 65 | 81 vs 82 | 34 vs 32 | 66 vs 68 | 47 vs 50 | 38 vs 36 | 15 vs 14 |
| CheckMate 227 2018 [18] | Nivolumab | suqamous and nonsquamous | 177 vs 186 | 172 vs 185 | 64 vs 64 | 73 vs 67 | 33 vs 31 | 66 vs 68 | 100 vs 100 | 0 vs 0 | 0 vs 0 |

[a]Data presented as "IO-chemotherapy group vs chemotherapy group"
[b]Pembrolizumab (200 mg, Q3W), Atezolizumab (1200 mg, Q3W), Nivolumab (360 mg, Q3W)
*Abbreviation*: *IO* immuno-oncology, *ITT* intention-to-treat

Qualität der Studien:

- All the trials were well designed and reported. The main source of bias was that data in three trials (CheckMate 227, KEYNOTE-407, and Impower131) could only be retrieved from conference presentations. For one trial OS was not reported yet (selective reporting).

Studienergebnisse:

- PFS, OS, ORR

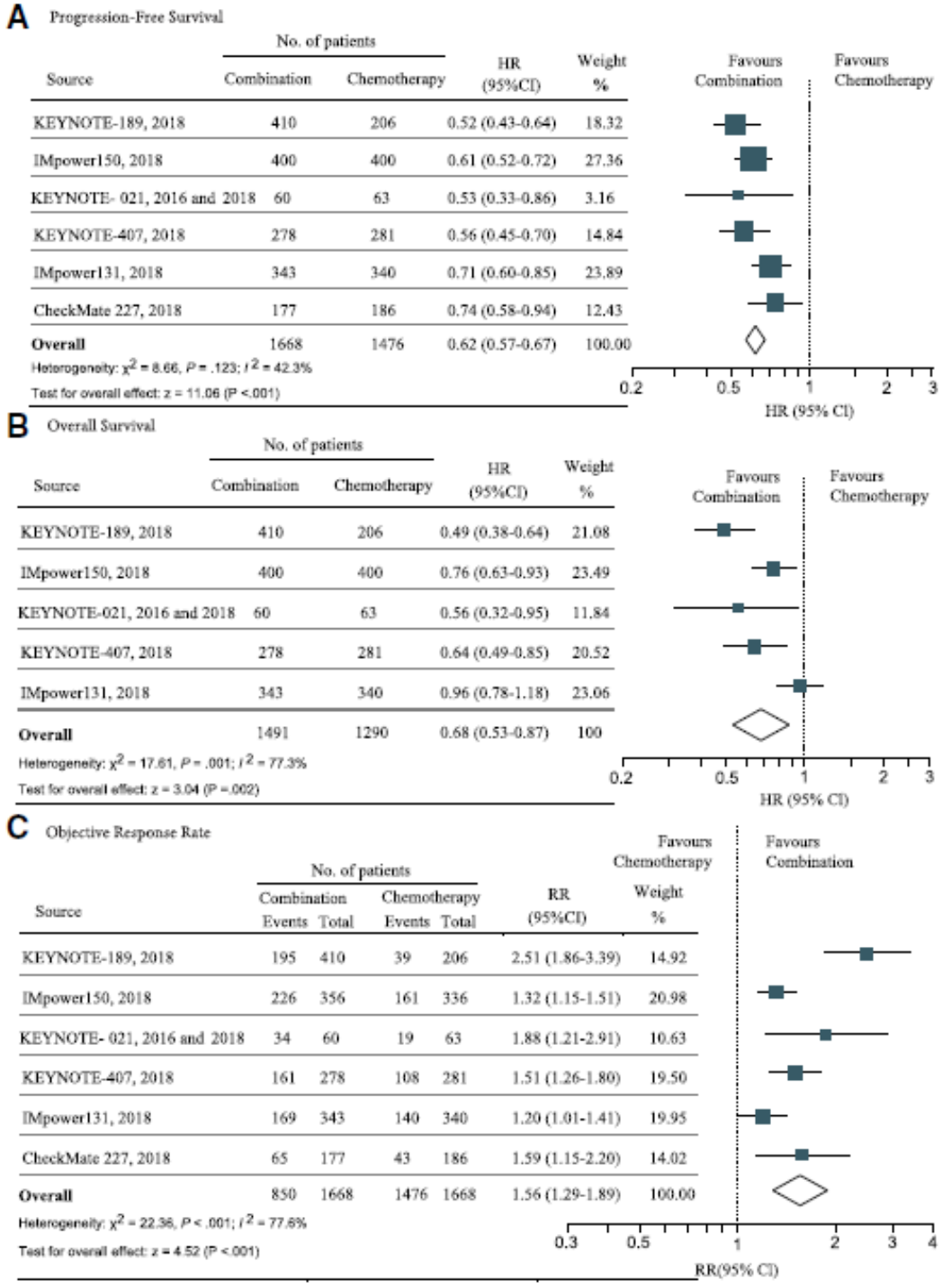


Fig. 1 Forest plot of hazard ratios and risk ratios comparing (a) progression-free survival, (b) overall survival, and (c) objective response rate in patients who received IO-Chemotherapy vs Chemotherapy alone. Squares represent study-specific effect

size (HR or RR). The area of square is inversely proportional to the standard error of the study (and therefore indirectly to the sample size) and larger area indicates greater weight in the calculation of the pooled effect size. The horizontal line crossing the square represents the 95% CI. The diamonds represent the estimated overall effect, based on the meta-analysis. HR, hazard ratio; RR, relative risk; CI, confidence interval

- Subgroup Analysis
  - PD-1/PD-L1 inhibitor plus chemotherapy led to statistically longer PFS across all tested subgroups of PD-L1 expression level, including those with a PD-L1 TPS of less than 1% (HR, 0.76; 95% CI, 0.67–0.86; P < .001; heterogeneity, P = .952), a score of 1 to 49% (HR, 0.60; 95% CI, 0.51–0.71; P < .001; heterogeneity, P = .635), and a score of at least 50% (HR, 0.38; 95% CI, 0.31–0.47; P < .001; heterogeneity, P = .928). The magnitude of PFS benefit was significantly different among subgroups of PD-L1 TPS (P < .001).
  - For patients in whom the PD-L1 TPS was less than 1%, the pooled HR for OS was 0.76 (95% CI, 0.64– 0.91; P = .002; heterogeneity, P = .378), compared with the HR of 0.78 (95% CI, 0.51–1.19; P = .244; heterogeneity, P = .050) in those with a score of 1 to 49% and 0.57 (95% CI, 0.44–0.73, P < .001; heterogeneity, P = .487) in those with a score of 50% or greater. The difference of OS benefit across PD-L1 subgroups obtained a near-significant trend (P = .057).
  - The response rate was the highest in patients with a PD-L1 TPS of at least 50% (RR, 1.95; 95% CI 1.34–2.82; P < .001; heterogeneity, P = .093). In the subgroup with a score between 1 and 49%, the pooled RR was 1.39 (95% CI 0.98–1.96; P = .062; heterogeneity, P = .079). In the subgroup with a score of less than 1%, the pooled RR was 1.54 (95% CI 1.16–2.05; P = .003; heterogeneity, P = .064). There was no significant interaction between treatment effect in terms of ORR and PD-L1 expression level (P = .232).
- Adverse Events

| AEs[a] | No. of trials | No. of patients (Events/Enrolled) Combination | Chemotherapy | $I^2$ (P) | RR (95%CI) | P |
|---|---|---|---|---|---|---|
| Any grade | 6 | 1577/1641 | 1351/1457 | 82.7% (<0.001) | 1.03 (0.99-1.06) | 0.132 |
| Grade 3-5 | 6 | 1045/1641 | 802/1457 | 59.6% (0.030) | 1.14 (1.04-1.26) | 0.007 |
| Led to discontinuation | 5 | 185/1307 | 126/1123 | 47.9% (0.104) | 1.29 (1.01-1.60) | 0.022 |
| Serious AEs | 3 | 184/786 | 117/790 | 56.7% (0.099) | 1.70 (1.17-2.49) | 0.006 |
| Led to death | 6 | 70/1641 | 50/1457 | 0.0% (0.948) | 1.14 (0.80-1.63) | 0.47 |
| **Immune mediated AEs[a]** | | | | | | |
| Any grade | 4 | 347/1076 | 126/878 | 23.2% (0.272) | 2.37 (1.98-2.84) | <0.001 |
| Grade 3-5 | 5 | 160/1469 | 37/1272 | 17.9% (0.301) | 3.71 (2.63-5.24) | <0.001 |
| Led to death | 5 | 5/1469 | 1/1272 | 0.0% (0.803) | 2.24 (0.42-11.8) | 0.343 |

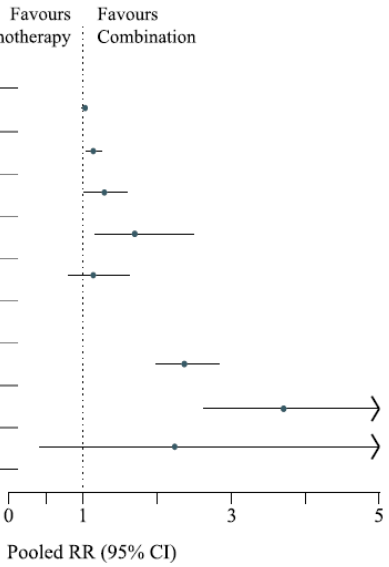


**Fig. 4** Forest plot of risk ratios comparing treatment-related adverse events in patients who received IO-Chemotherapy vs Chemotherapy alone. The horizontal line crossing the dot represents the 95%CI of the pooled risk ratio in each subgroup-analysis. No. of trials refers to the number of trials included in each subgroup-analysis. $I^2$ (P) shows the heterogeneity in each subgroup meta-analysis. [a]Data provided in KEYNOTE-189 and KEYNOTE-407 were all-cause adverse events, regardless of attribution to any treatment. CI, confidence interval; RR, risk ratio; AEs, adverse events; IO, Immuno-oncology

### Anmerkung/Fazit der Autoren

In conclusion, PD-1/PD-L1 inhibitor plus chemotherapy, compared with chemotherapy, significantly prolonged PFS and OS in first-line of treatment for advanced NSCLC, irrespective

of PD-L1 expression level. Future studies are needed to explore reliable predictors of treatment efficacy and to determine which chemotherapeutic modality will improve patient's survival in combination with PD-1/PD-L1 inhibitor. Finally, the trade-off between benefits and risk of side effects as well as treatment costs should be considered in clinical practice.

*Kommentare zum Review*

- Keine Ergebnisdarstellung für die einzelnen Arzneimittel.

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**Khan M et al., 2018 [25].**

Comparative analysis of immune checkpoint inhibitors and chemotherapy in the treatment of advanced non-small cell lung cancer A meta-analysis of randomized controlled trials.

Ähnliche Reviews zu dem Thema:

- **Peng TR & Wu TW, 2019 [41].** Efficacy of PD-1/PD-L1 inhibitors in patients with advanced non-small cell lung cancer: A meta-analysis of randomized clinical trials

**Fragestellung**

to gather and analyze the available evidence (Evidence level I; Randomized Controlled Trials) comparing efcacy and safety of anti-programmed cell death-1 (PD1)/programmed cell death ligand 1 (PD-L1) therapies and chemotherapy in the treatment of advanced NSCLC.

**Methodik**

Population:

- Advanced non-small cell lung cancer.

Intervention/Komparator:

- comparing the anti-PD1/PD-L1 therapies with chemotherapy

Endpunkte:

- OS, PFS, ORR, TRAEs

Recherche/Suchzeitraum:

- until December 2017

Qualitätsbewertung der Studien:

- Cochrane Collaboration Tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- seven RCTs (n=3867)

Qualität der Studien:

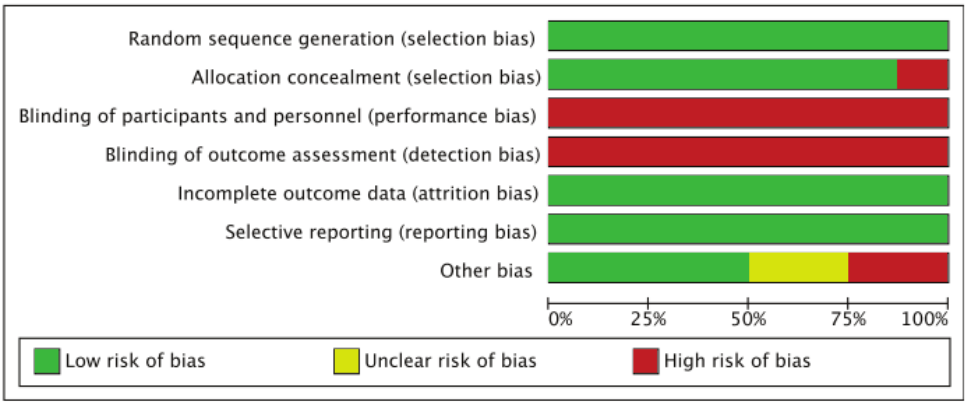


**Figure 2.** Risk of bias graph. +: low risk of bias; –: high risk of bias; ?: unclear risk of bias.

Studienergebnisse:

- Anti-PD1/PD-L1 therapies (nivolumab, pembrolizumab, atezolizumab) resulted in better OS (HR 0.72 [95% confidence interval [CI] 0.63, 0.82; P<.00001]), PFS (HR 0.84 [95% CI 0.72, 0.97; P<.02]), and ORR (odds ratio [OR] 1.52 [95% CI 1.08, 2.14; P<.02]) in comparison to chemotherapy in advanced NSCLC.
- Improved safety was observed with anti-PD1/PD-L1 therapies (OR 0.31 [95%CI 0.26, 0.38; P<.00001]).
- Subgroup analysis: While ECOG PS 1, squamous cell type, current/former smoker, EGFRwild type, KRAS mutant, and absent CNS metastases subgroups were associated with better overall survival. Male sex, ECOG PS 1, never smoker, KRAS wild type and absent CNS metastases subgroups were associated with better PFS. Histology types showed no association to PFS while EGFR mutant as well as wild type was associated with significant PFS.

**Anmerkung/Fazit der Autoren**

Anti-PD1/PD-L1 therapies represent better choice over chemotherapy in advance NSCLC. Immune response associated with PD1 pathway inhibition in NSCLC is more complex and could not be fully explained only by PD-L1 tumor expression and hence further investigations are warranted to identify more biomarkers. Proper selection of patients is recommended in order to derive full advantage of these agents. Further studies are needed to prove efficacy of these agents in first line treatment.

*Kommentare zum Review*

- Gemischte Population: Keine seperaten Angaben zum Stadium oder Status (z.B. fortgeschritten vs. metastasierte Patienten.

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**Chen S, Hu B und Li H, 2018 [6].**

A meta-analysis of nivolumab for the treatment of advanced non-small-cell lung cancer.

**Fragestellung**

The purpose of this meta-analysis was to systematically evaluate the efficacy and safety of nivolumab in patients with advanced NSCLC.

**Methodik**

Population:

- advanced NSCLC

Intervention:

- Nivolumab plus chemotherapy

Komparator:

- Chemotherapy

Endpunkte:

- OS, PFS, ORR, and SAE

Recherche/Suchzeitraum:

- PubMed, Embase, and Cochrane Library databases were searched up to June 2017

Qualitätsbewertung der Studien:

- Cochrane Handbook for Systematic Reviews of Interventions risk of bias tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 3 RCTs with 1,395 patients

Charakteristika der Population:

**Table 1** The primary characteristics of the eligible studies in more detail

| Study | Year | Trial name | Trial phase | Stage | Histology | PD-L1 tumor expression level | Study arm (N) | Comparative arm (N) |
|---|---|---|---|---|---|---|---|---|
| Brahmer et al[15] | 2015 | CheckMate 017 | 3 | IIIb/IV | Squamous | ≥1%, ≥5%, and ≥10% | Nivolumab 3 mg/kg every 2 weeks (n=135) | Docetaxel 75 mg/m$^2$ every 3 weeks (n=137) |
| Borghaei et al[14] | 2015 | CheckMate 057 | 3 | IIIb/IV | Nonsquamous | ≥1%, ≥5%, and ≥10% | Nivolumab 3 mg/kg every 2 weeks (n=292) | Docetaxel 75 mg/m$^2$ every 3 weeks (n=290) |
| Carbone et al[16] | 2017 | CheckMate 026 | 3 | IV or recurrent | Squamous and nonsquamous | ≥1% and ≥5% | Nivolumab 3 mg/kg every 2 weeks (n=271) | Investigator's choice of platinum-based doublet chemotherapy (n=270) |

Qualität der Studien:

- All included studies were based on moderate- to high-quality evidence.

Studienergebnisse:

- PFS: nivolumab did not lead to PFS benefit (odds ratio [OR]: 0.88, 95% CI: 0.64–1.20, P=0.41) compared with chemotherapy
- OS: The pooled data showed that nivolumab plus chemotherapy did not improve OS (OR: 0.77, 95% CI: 0.57–1.03, P=0.08) over chemotherapy (random effects model because of high heterogeneity)

- ORR: Pooling ORR data did not improve efficacy for nivolumab (OR: 1.40, 95% CI: 0.66–2.96, P=0.39).
- SAE: Results showed much worse (grade 3–5 adverse events) SAEs in the nivolumab group than in the chemotherapy group (OR: 0.13, 95% CI: 0.09–0.17, P<0.00001)
- Subgroup Analysis:
  - patients with tumor PD-L1 expression levels ≥5% demonstrated that nivolumab therapy did not prolong PFS (OR: 0.84, 95% CI: 0.70–1.00, P=0.05) or OS (OR: 0.63, 95% CI: 0.34–1.15, P=0.13)

**Anmerkung/Fazit der Autoren**

In conclusion, nivolumab monotherapy for patients with advanced NSCLC was generally well tolerated, with promising antitumor activity and a manageable safety profile. More RCTs with larger sample sizes are needed to detect relevant biomarkers that have sufficient sensitivity and specificity to predict patient populations that would most benefit from nivolumab, in particular those patients with pretreated and advanced NSCLC.

*Kommentare zum Review*

- Die Interpretation der SAEs grad 3-4 zum Nachteil von Nivolumab ist nicht nachvollziehbar, da der OR Schätzer auf geringere SAEs in den Nivolumab Behandlungsgruppen hinweist.

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**Xiao HQ et al., 2016 [46].**

Efficacy of pemetrexed plus platinum doublet chemotherapy as first-line treatment for advanced nonsquamous non-small-cell-lung cancer: a systematic review and meta-analysis.

**Fragestellung**

To assess the efficacy of pemetrexed plus platinum doublet chemotherapy as first-line treatment for advanced nonsquamous non-small-cell lung cancer (NSCLC) through a trial-level meta-analysis.

**Methodik**

Population:

- chemotherapy-naïve advanced nonsquamous NSCLC patients

Intervention:

- pemetrexed plus platinum doublet chemotherapy

Komparator:

- platinum plus other first-line chemotherapy

Endpunkte:

- ORR, PFS; OS

Recherche/Suchzeitraum:

- Systematische Literaturrecherche zwischen 1990 und 2015

Qualitätsbewertung der Studien:

- Jadad scale

**Ergebnisse**

Anzahl eingeschlossener Studien:

- A total of 2,551 patients with advanced nonsquamous NSCLC from 10 trials

Charakteristika der Population:

**Table 1** Baseline characteristics of ten trials included for meta-analysis

| Source | Country | Chemotherapy regimen | Patients enrolled | Median age (years) | Median OS (months) | Median PFS (months) | ORR (%) |
|---|---|---|---|---|---|---|---|
| Scagliotti et al[8] | Multicenter | Pemetrexed + cisplatin | 618 | NR | 11.8 | 5.3 | NR |
| | | Gemcitabine + cisplatin | 614 | NR | 10.4 | 4.7 | NR |
| Gronberg et al[10] | Multicenter | Pemetrexed + carboplatin | 162 | 64 | 7.8 | NR | NR |
| | | Gemcitabine + carboplatin | 167 | 66 | 7.5 | NR | NR |
| Rodrigues-Pereira et al[20] | Multicenter | Pemetrexed + carboplatin | 106 | 60.1 | 14.9 | 5.8 | 36 |
| | | Docetaxel + carboplatin | 105 | 58.9 | 14.7 | 6 | NR |
| Kim et al[14] | Japan | Pemetrexed + carboplatin | 49 | 63 | 24.3 | 7.9 | 51 |
| Kawano et al[15] | Japan | Pemetrexed + cisplatin | 50 | 60 | 22.2 | 4.3 | 44.00 |
| Zhang et al[21] | People's Republic of China | Pemetrexed + platinum | 105 | 54 | 16.69 | NR | NR |
| | | Gemcitabine + platinum | 100 | 55 | 16.66 | NR | NR |
| Belani et al[16] | USA | Pemetrexed + cisplatin | 57 | 59 | 15.9 | 7.1 | 26 |
| Kanazawa et al[17] | Japan | Pemetrexed + carboplatin | 41 | 63 | 16.2 | 4.7 | 37 |
| Yu et al[18] | People's Republic of China | Pemetrexed + platinum | 59 | 54.9 | 20.8 | 7 | 28 |
| Paz-Ares et al[19] | Multicenter | Pemetrexed + cisplatin | 318 | 60 | 11.5 | 5.6 | 32.08 |

Abbreviations: OS, overall survival; PFS, progression-free survival; ORR, objective response rate; NR, not reported.

Qualität der Studien:

- The quality of four RCTs was approximately assessed according to Jadad scale. Four of the included trials did not mention the blinding of allocation clearly in the randomization process and thus had Jadad scores of 3.

Studienergebnisse:

- All of the four RCTs reported OS data. The pooled results demonstrated that PPC significantly improved OS in comparison with other platinum-based doublet chemotherapy treatments (0.86, 95% CI: 0.77–0.97, *P*=0.01) using a fixed-effects model (*I*2=0%, *P*=0.65).

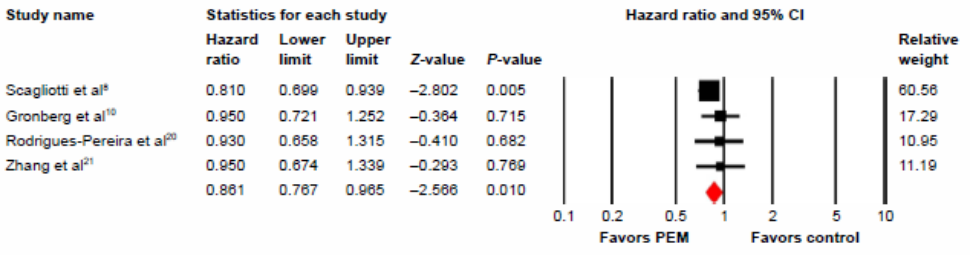


*Abbildung 1: Fixed-effects model of HR (95% CI) of OS associated with PEM plus platinum versus other platinum-based chemotherapy.*

- Two of four RCTs reported PFS data. The pooled hazard ratio for PFS demonstrated that PPC tends to improve PFS by giving HR 0.90(not significant), compared with other platinum-based doublet chemotherapy in advanced nonsquamous NSCLC patients. There was no significant heterogeneity between trials (*I*2=0%, *P*=0.95), and the pooled HR for PFS was performed by using fixed-effects model.

**Anmerkung/Fazit der Autoren**

In conclusion, pemetrexed plus platinum doublet regimen is an efficacious treatment for advanced nonsquamous NSCLC patients. Our findings support the use of pemetrexed plus platinum doublet regimens as first-line treatment in advanced nonsquamous NSCLC patients because of its potential survival benefits. Further investigation of this regimen as first-line treatment in nonsquamous NSCLC patients is still warranted.

*Kommentare zum Review*

- In den SR wurden auch Beobachtungsstudien eingeschlossen. Daher wurden ausschließlich die Ergebnisse der RCTs extrahiert.

*Kommentare zum Review*

- heterogeneity across included trials

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**Dafni U et al., 2019 [8].**

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:

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

Qualität der Studien:

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

Studienergebnisse:

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

combination (HR=0.82 [0.70-0.97]). The combinations of ipilimumab with either nivolumab or chemotherapy are better than the ICI-monotherapies examined.

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

- OS-NMA by histological subtype
  - OS results by histology were similar to the overall cohort regarding the combination of pembrolizumab/chemotherapy being the better treatment choice for both histological types, with also ABC and atezolizumab/chemotherapy in non-squamous. ABC is evaluated only in non-squamous, ipilimumab/chemotherapy only in squamous, while pembrolizumab-monotherapy (among others) could not be evaluated here.
- OS-NMA by PD-L1 category
  - PD-L1≥50% Cohort. : The OS-NMA for PD-L1-high patients is based on eight trials evaluating six experimental treatments with 1,113 patients, and 917 patients in the control arm of chemotherapy-alone. Pembrolizumab-alone and its combination with chemotherapy are significantly better treatments than chemotherapy-alone (HR=0.67 [0.56-0.80] and HR=0.49 [0.35-0.67], respectively). These treatments do not display a significantly different OS between them or compared to the combination of atezolizumab and chemotherapy, the third preferred treatment according to the overall OS NMA.
  - 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: Addeo A et al. 2019 [1] & Liu T et al. 2019 [31].

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**Zhou Y et al., 2019 [49].**

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<br>1) carboplatin (5 mg/ml/min Q3W)<br>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<br>1) cisplatin (75 mg/m^2 Q3W) or carboplatin (6 mg/ml/min Q3W)<br>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<br>1) carboplatin (6 mg/ml/min Q3W)<br>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<br>1) cisplatin (75 mg/m^2 Q3W) or carboplatin (5-6 mg/ml/min Q3W)<br>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<br>1) carboplatin (5-6 mg/ml/min Q3W)<br>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 [26] & Liu Y et al. 2019 [32].
- Unklar Anteil metastasierte Patienten

## 3.4 Leitlinien

**National Institute for Health and Care Excellence (NICE), 2019 [37].**

Lung cancer: diagnosis and management

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

**Leitlinienorganisation/Fragestellung**

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

**Methodik**

Grundlage der Leitlinie

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

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

Recherche/Suchzeitraum:

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

LoE

- trifft nicht zu (sieh sonstige methodische Hinweise)

GoR

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

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

The guideline committee discussed the review questions and the need for clinical guidance in this area [note: systemic anti-cancer therapy] and agreed that instead of updating the chemotherapy for NSCLC recommendations (2005 recommendations 1.4.40 – 1.4.43) the

guideline update should develop an algorithm outlining the treatment pathway for systemic anti-cancer therapy treatments. This algorithm would provide a clear overview and contextualisation of systemic anti-cancer therapy treatments.

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

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

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

Updates-Kennzeichnung:

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

**Empfehlungen**

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

PDL1≥50% and no gene mutation or fusion protein

- 1.4.47 For guidance on treatment for stage IIIB and IV non-squamous NSCLC in people whose tumours express PD-L1 at 50% or above and who have no gene mutation or fusion protein:
  - for initial treatment, see the NICE technology appraisal guidance on pembrolizumab [38] and pembrolizumab combination [39]

    (…)

ROS1 positive

- 1.4.48 For guidance on treatment for stage IIIB and IV ROS1-positive non-squamous NSCLC:
  - for initial treatment, see the NICE technology appraisal guidance on crizotinib. [36]

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

- 1.4.49 For guidance on treatment for stage IIIB and IV non-squamous NSCLC in people who do not have a gene mutation, fusion protein or biomarker:
  - see the NICE technology appraisal guidance on pembrolizumab combination [39] and pemetrexed with cisplatin or offer pemetrexed with carboplatin or other platinum doublet chemotherapy.

**Squamous non-small-cell lung cancer**

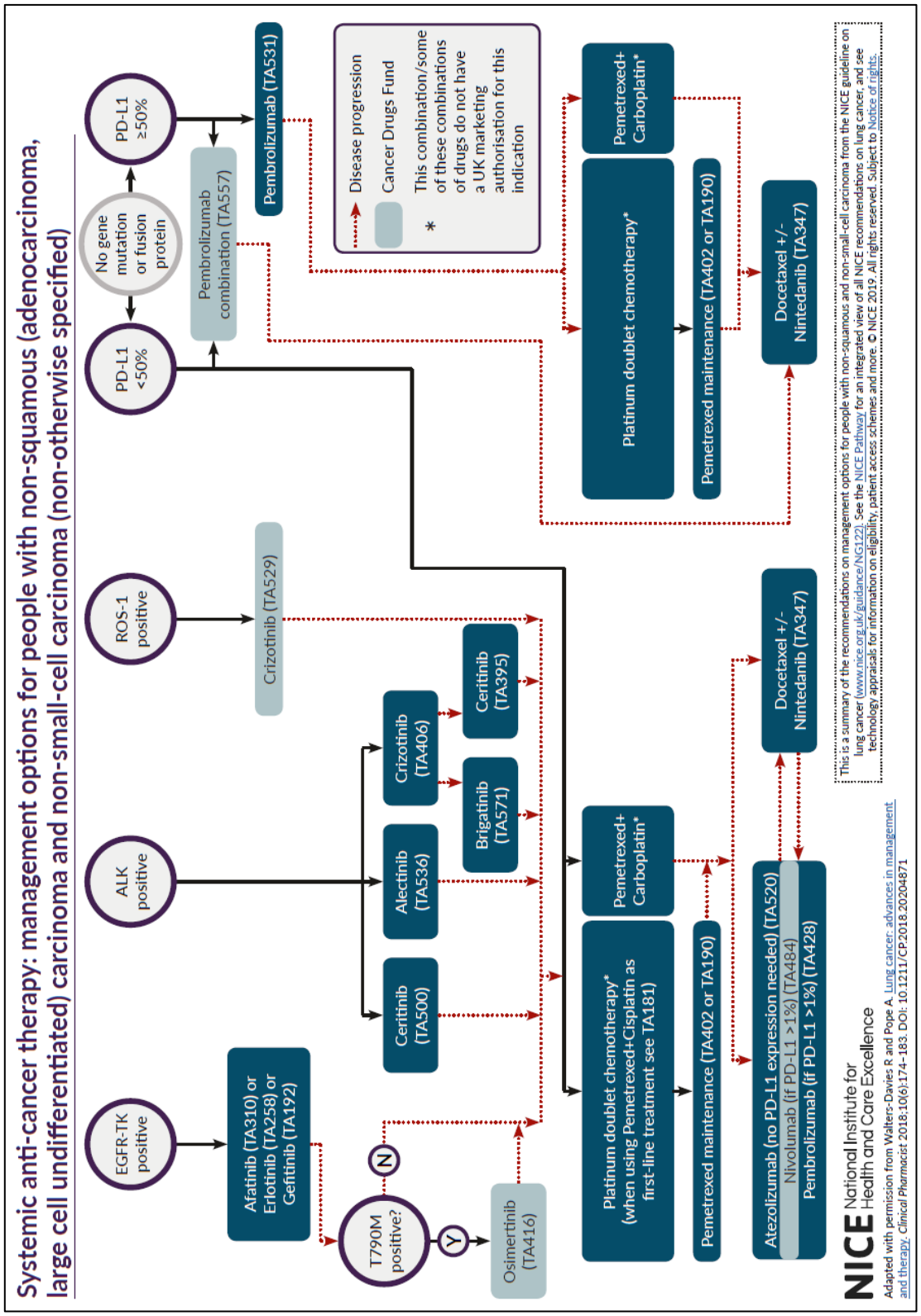
PDL1≥50%

- 1.4.50 For guidance on treatment for squamous NSCLC in people whose tumours express PD-L1 at or above 50%:
  - for initial treatment, see the NICE technology appraisal guidance on pembrolizumab [38]

PDL1<50%

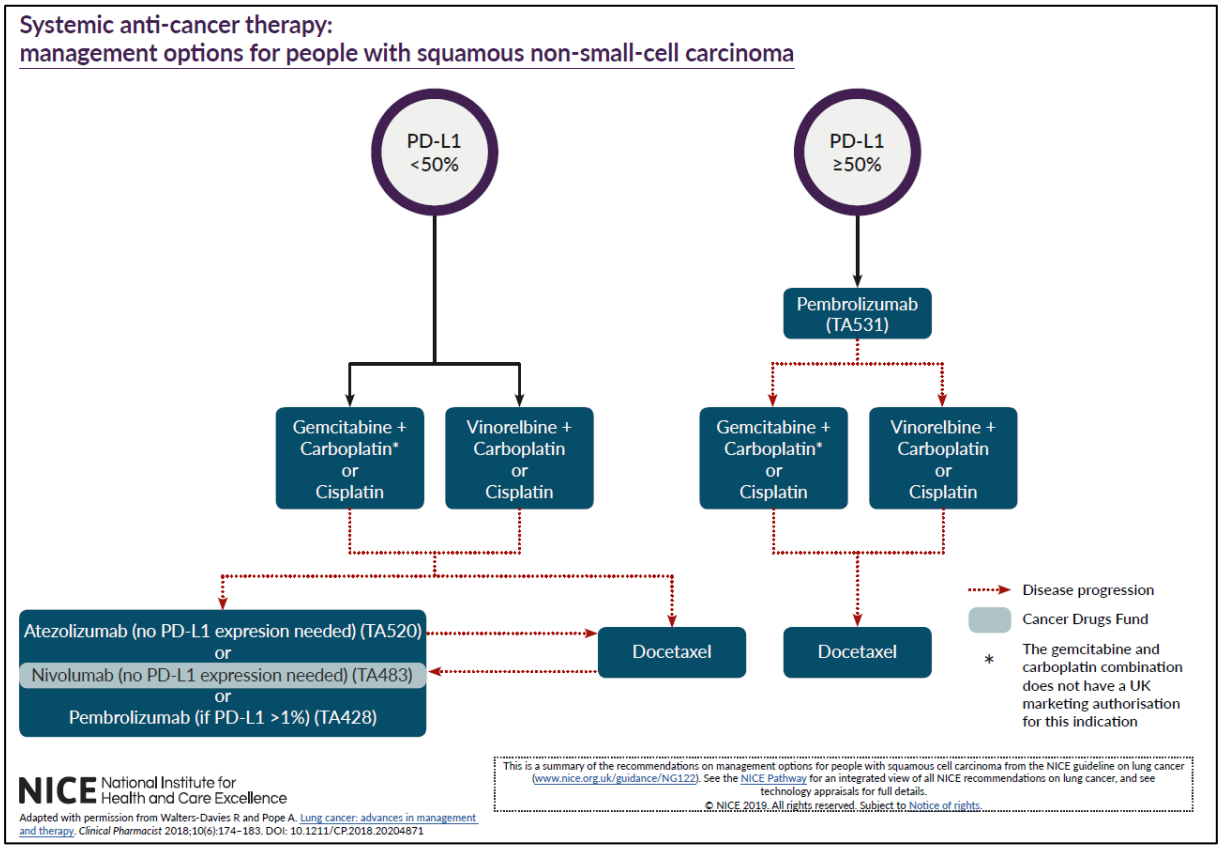
- 1.4.51 For guidance on treatment for squamous NSCLC in people whose tumours express PD-L1 below 50%:
  - for initial treatment, offer gemcitabine or vinorelbine and cisplatin or carboplatin.

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



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

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




**Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft (DKG), et al., 2018 [28].**

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

Siehe auch: Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft (DKG), et al., 2018 [27].

**Fragestellung**

Von der Steuergruppe wurden für die Aktualisierung der Leitlinie die folgenden Themen priorisiert:

- …
- Therapie des NSCLC im Stadium IV
- …

**Methodik**

Grundlage der Leitlinie

Update: gezielte Aktualisierung der Originalversion von 2010

- 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:

- 1. Aktualisierung für den Zeitraum 2013-2018

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

Sonstige methodische Hinweise (Zitat aus dem Leitlinienreport):

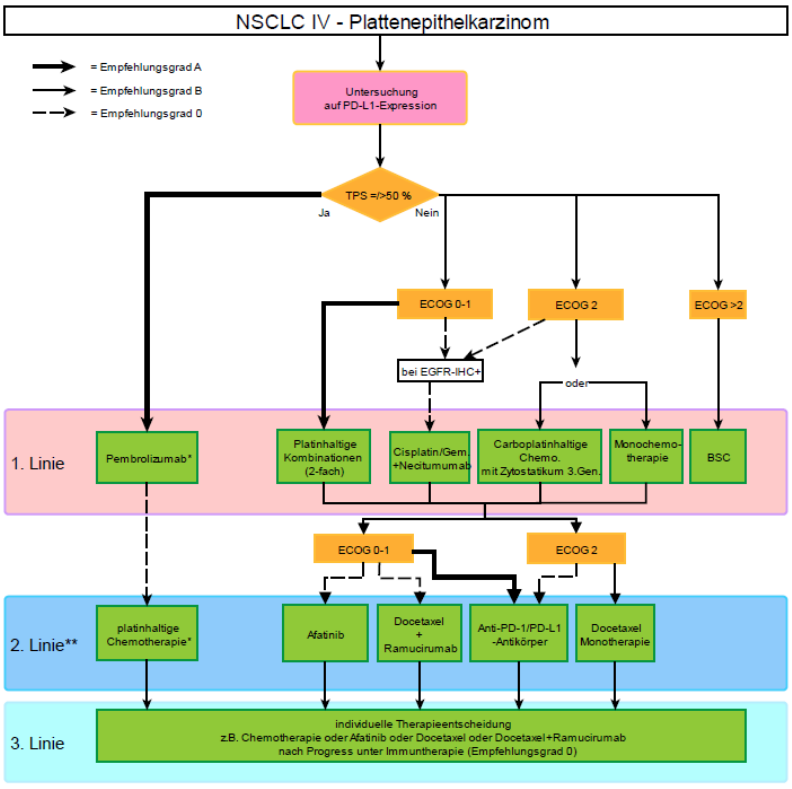
Unter dem Stichwort „Personalisierte Therapie“ oder „Stratifizierende Therapie“ hatten sich die Prinzipien insbesondere der Chemotherapie im metastasierten Stadium tiefgreifend geändert. Dieses galt in 2013 insbesondere für die Erstlinien-Chemotherapie bei Nachweis einer EGFR-Mutation sowie für die Zweitlinien-Chemotherapie bei Nachweis einer EML4-ALK-Translokation.

Ein weiterer Aspekt der Chemotherapie im metastasierten Stadium des NSCLC mit neuen wissenschaftlichen Erkenntnisse war die sog. Erhaltungschemotherapie: nach Abschluss der Erstlinienchemotherapie kann durch die sich sofort anschließende Therapie mit dem Tyrosinkinase-Inhibitor Erlotinib oder dem Zytostatikum Pemetrexed eine Verlängerung des Progressionfreien Überlebens (PSF) – allerdings nicht der Gesamtüberlebenszeit – erreicht werden.

Im Zuge des Aktualisierungsprozesses wurde weitere neue Arzneimittel für die Therapie des Lungenkarzinoms zugelassen. Dies machte weitere Diskussionen der Therapieempfehlungen notwendig.

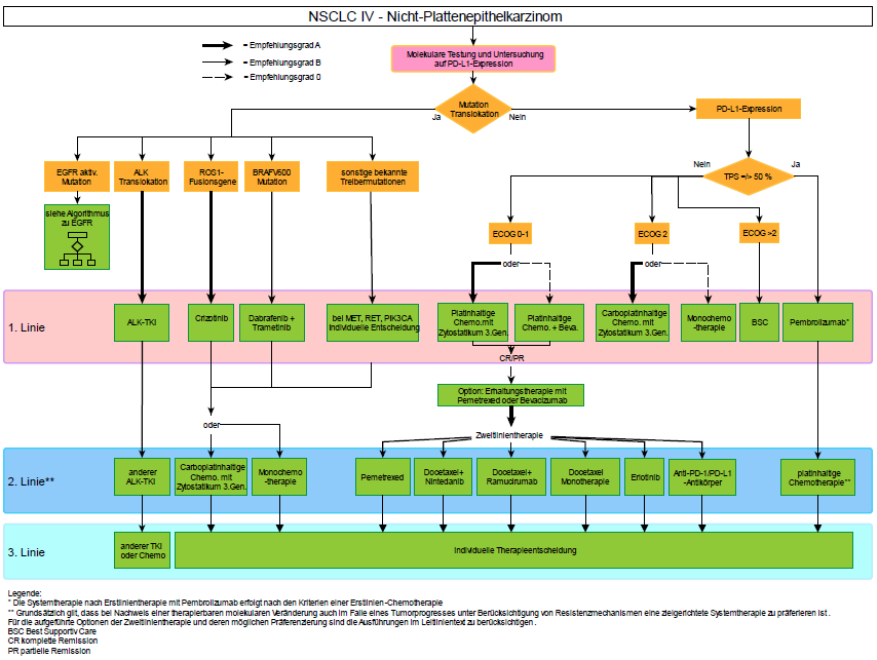
## Empfehlungen

Algorithmus zur Therapie des nicht-kleinzelligen Plattenepithelkarzinoms im Stadium IV/IIIB (ohne Indikation zur definitiven Radiatio)



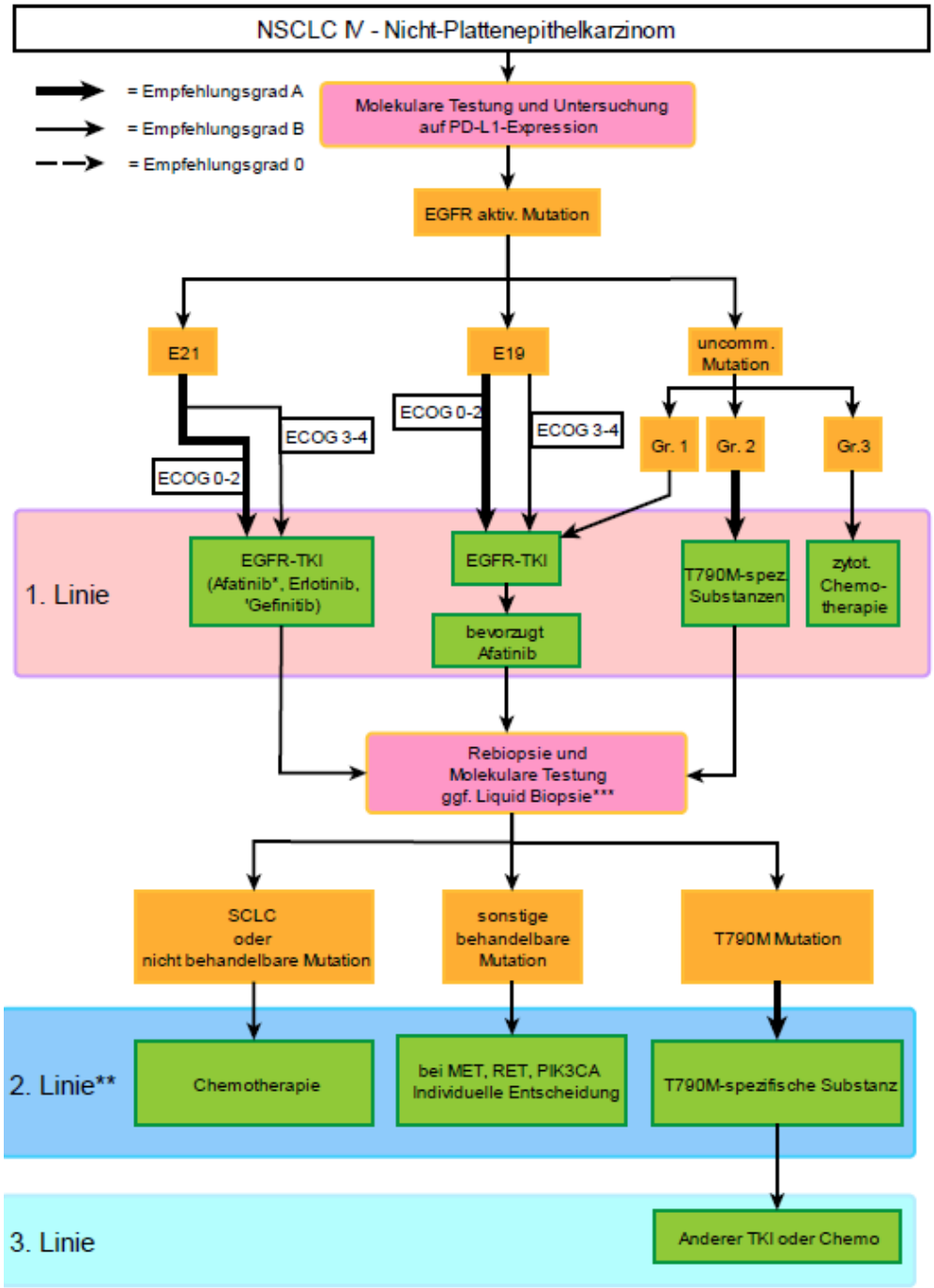

Legende:
* Die Systemtherapie nach Erstlinientherapie mit Pembrolizumab erfolgt nach den Kriterien einer Erstlinien -Chemotherapie
** Grundsätzlich gilt, dass bei Nachweis einer therapierbaren molekularen Veränderung auch im Falle eines Tumorprogresses unter Berücksichtigung von Resistenzmechanismen eine zielgerichtete Systemtherapie zu präferieren ist. Für die aufgeführte Optionen der Zweitlinientherapie und deren möglichen Präferenzierung sind die Ausführungen im Leitlinientext zu berücksichtigen.
BSC Best Supportiv Care

Algorithmus zur Therapie des nicht-kleinzelligen Nicht-Plattenepithelkarzinoms im Stadium IV/IIIB (ohne Indikation zur definitiven Radiatio)




Legende:
* Die Systemtherapie nach Erstlinientherapie mit Pembrolizumab erfolgt nach den Kriterien einer Erstlinien-Chemotherapie
** Grundsätzlich gilt, dass bei Nachweis einer therapierbaren molekularen Veränderung auch im Falle eines Tumorprogresses unter Berücksichtigung von Resistenzmechanismen eine zielgerichtete Systemtherapie zu präferieren ist.
Für die aufgeführte Optionen der Zweitlinientherapie und deren möglichen Präferenzierung sind die Ausführungen im Leitlinientext zu berücksichtigen.
BSC Best Supportiv Care
CR komplette Remission
PR partielle Remission

Abbildung 14: Algorithmus zur Therapie des nicht-kleinzelligen Nicht-Plattenepithelkarzinoms mit EGFR aktivierenden Mutationen im Stadium IV/IIIB (ohne Indikation zur definitiven Radiatio)




Legende:
* Afatinib zeigte in einer Phase-II-Studie eine signifikant erhöhte ORR gegenüber Gefitinib (Lux-7-Studie)
** Grundsätzlich gilt, dass bei Nachweis einer therapierbaren molekularen Veränderung auch im Falle eines Tumorprogresses unter Berücksichtigung von Resistenzmechanismen eine zielgerichtete Systemtherapie zu präferieren ist.Für die aufgeführte Optionen der Zweitlinientherapie und deren möglichen Präferenzierung sind die Ausführungen im Leitlinientext zu berücksichtigen
*** Bei nicht ausreichendem Gewebe für eine molekulare Diagnostik und wenn eine erneute Biopsie nicht mit vertretbarem Risiko durchgeführt werden kann.
Bei akquirierter EGFR-TKI-Resistenz und negativer Biopsie in Bezug auf T790M.
Bei akquirierter EGFR-TKI-Resistenz und wenn eine Gewebe-Rebiospie nicht zur Verfügung steht.

**Patienten mit PD-L1-Expression von ≥ 50 %**

| 8.6.2.1. | Patienten mit PD-L1-Expression von ≥50 % | |
|---|---|---|
| **8.66.** | **Evidenzbasierte Empfehlung** | **2018** |
| Empfehlungsgrad **B** | Bei Therapie-naiven Patienten im Stadium IV, welche keine therapierbaren Mutationen (z.B. EGFR, EML4-ALK, ROS1) aufweisen, und welche in Gewebeproben eine PD-L1-Expression von ≥50 % der Tumorzellen aufweisen, sollte Pembrolizumab (200 mg i.v. alle 3 Wochen) als Erstlinientherapie angeboten werden. | |
| Level of Evidence **1b** | Literatur : [773] | |
| | Konsensstärke: | |

| 8.6.2.2. | Patienten mit PD-L1-Expression von <50 % und ECOG 0-1 | |
|---|---|---|
| **8.67.** | **Evidenzbasierte Empfehlung** | **2018** |
| Empfehlungsgrad **A** | Bei Patienten im Stadium IV (neu: IV B) in gutem Allgemeinzustand (ECOG 0-1) soll eine platinbasierte Kombinationschemotherapie angeboten werden, vorzugsweise mit Cisplatin. | |
| Level of Evidence **1a** | Literatur: [774-783] | |
| | Konsensstärke: 100 % | |

| **8.68.** | **Evidenzbasierte Empfehlung** | **2018** |
|---|---|---|
| Empfehlungsgrad **A** | In der Erstlinienchemotherapie sollen 4-6 Zyklen gegeben werden. | |
| Level of Evidence **1a** | Literatur : [784][660][659] | |
| | Konsensstärke: 80% | |

| **8.69.** | **Evidenzbasierte Empfehlung** | **2018** |
|---|---|---|
| Empfehlungsgrad **0** | Als Alternative zu einer cisplatinhaltigen 2xKombination kann eine additive Gabe von Bevacizumab zu Carboplatin/Paclitaxel mit anschließender Erhaltungstherapie mit Bevacizumab bei geeigneten Patienten mit einem nicht-plattenepithelialen NSCLC unter Ausschluss von relevanten Komborbiditäten, die mit einer erhöhten Toxizität von Bevacizumab assoziiert sind, erwogen werden. | |
| Level of Evidence **1b** | Literatur : [770, 787-791] | |
| | Konsensstärke: 96 % | |

| 8.70. | Evidenzbasierte Empfehlung | 2018 |
|---|---|---|
| Empfehlungsgrad<br>0 | Bei Patienten mit Plattenepithelkarzinom und einer EGFR-Expression größer 1% in der immunhistochemischen Untersuchung (IHC) kann als Erstlinientherapie Cisplatin/Gemcitabin in Kombination mit Necitumumab angeboten werden.<br>Nach der Erstlinientherapie kann bei fehlendem Krankheitsprogress und bei guter Verträglichkeit der Therapie eine Erhaltungstherapie mit Necitumumab angeboten werden. | |
| Level of Evidence<br>1b | Literatur : [798-800] | |
| | Konsensstärke: 96 % | |

Patienten mit PD-L1-Expression von <50 % und ECOG 2

| 8.71. | Evidenzbasiertes Statement | 2018 |
|---|---|---|
| Level of Evidence<br>1a | Auch beim NSCLC ECOG 2 sind die Therapieziele der palliativen (nicht kurativen) Therapie (ohne therapierbare Mutationen/Translokationen) Symptomlinderung, Verbesserung oder Erhalt der Lebensqualität, Tumoransprechen und Überlebensverlängerung). Diese Therapieziele können mit einer palliativen Chemotherapie, zusätzlich zu best supportive care erreicht werden. | |
| | Quellen :[804, 805] | |
| | Konsensstärke: 100 % | |

| 8.72. | Evidenzbasierte Empfehlung | 2018 |
|---|---|---|
| Empfehlungsgrad<br>A | Bei Patienten mit ECOG 2 ohne wesentliche Komorbiditäten sollen platinbasierte Kombinationen, z.B. Carbo/Pacli oder Carbo/Pem angeboten werden. | |
| Level of Evidence<br>1a | Quellen : :[804] | |
| | Konsensstärke: 100 % | |

| 8.73. | Konsensbasierte Empfehlung | 2018 |
|---|---|---|
| EK | Bei Patienten mit ECOG 2 mit Komorbiditäten, bei denen die Komorbiditäten eine platinhaltige Kombinationstherapie nicht erlauben, kann eine Monotherapie angeboten werden. | |
| | Konsensstärke: 100 % | |

Systemtherapie bei Patienten mit ROS1-Fusionsgenen (ROS1 + NSCLC)

| 8.105. | Evidenzbasierte Empfehlung | 2018 |
|---|---|---|
| Empfehlungsgrad<br>A | Bei Patienten mit ROS1-Fusionsgenen (ROS1 + NSCLC) soll in der Erstlinientherapie Crizotinib angeboten werden. | |
| Level of Evidence<br>1b | Literatur: [880] | |
| | Konsensstärke: 100 % | |

Systemtherapie bei Patienten mit BRAF-V600-Mutation

| 8.107. | Evidenzbasierte Empfehlung | 2018 |
|---|---|---|
| Empfehlungsgrad<br>B | NSCLC IV- Patienten mit nachgewiesener BRAF-V600-Mutation sollte eine Kombination aus Dabrafenib und Trametinib angeboten werden. | |
| Level of Evidence<br>2b | Literatur: [880] | |
| | Konsensstärke: 100 % | |

Therapie bei sonstigen Treibermutationen beim NSCLC

Neben den aktivierenden EGFR-Mutationen, ALK- sowie ROS1-Fusionen und und BRAF V600-Mutationen gibt es weitere zielgerichtet behandelbare Treibermutationen beim NSCLC. Die Evidenz ist hier jedoch noch nicht ausreichend, um Empfehlungen für eine Erstlinienbehandlung auszusprechen. Für einen Teil dieser Treibermutationen zeigen Ergebnisse aus frühen klinischen Studien (Phase I und II) im Vergleich zur Rezidivche-motherapie bessere Ergebnisse für die Ansprechrate, das PFS und das Toxizitätsprofil.

| 8.108. | Konsensbasierte Empfehlung | 2018 |
|---|---|---|
| EK | Bei Patienten mit Wildtypkonfiguration für EGFR, ALK und ROS1 sowie BRAF V600 Mutationen sollte eine umfassende Genotypisierung auf bekannte Treibermutationen stattfinden, um bei dem Nachweis einer solchen eine zielgerichtete Therapie im Rahmen der Zulassung (z.B. für BRAF-V600 Mutationen), einer Studie oder im Off-Label-Use zu ermöglichen. Diese Analyse sollte insbesondere HER2-Mutationen, MET-Amplifikationen, MET-Exon-14-skipping-Mutationen und RET-Fusionen beinhalten. Vor dem Hintergrund der dynamischen Entwicklung in der molekularen Pathologie soll dadurch eine umfassende Analyse von potentiell therapierbaren Treibermutationen und ein auf dem Ergebnis der Mutationsanalyse basierendes Therapieangebot an den Patienten (inkl. Aufnahme in klinische Studien) ermöglicht werden. | |
| | Konsensstärke: 92 % | |

Hintergrund

**RET-Fusionen** finden sich in ca. 1% der Patienten mit Adenokarzinom der Lunge. Ansprechen auf RET-Inhibitoren wurde kasuistisch beschrieben (Vandetanib: [886]; Cabo-zantinib: [887]. Ergebnisse laufender prospektiver Studien in dieser Subgruppe mit RET-Inhibitoren stehen noch aus.

886. Gautschi, O., et al., A patient with lung adenocarcinoma and RET fusion treated with vandetanib. J Thorac Oncol, 2013. 8(5): p. e43-4.

887. Drilon, A., et al., Response to Cabozantinib in patients with RET fusion-positive lung adenocarcinomas. Cancer Discov, 2013. 3(6): p. 630-5.

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**Department of Health, 2017 [35].**

*National Cancer Control Programme Guideline Development Group (GDG), National Clinical Guideline No. 16*

Diagnosis, staging and treatment of patients with lung cancer.

**Leitlinienorganisation/Fragestellung**

(…) Clinical question 2.6.4: In patients with advanced/stage IV NSCLC what is the effectiveness of **first-line therapy** and is there any evidence that particular regimens or drugs are more effective or less toxic than others?

**Methodik**

Grundlage der Leitlinie

- Repräsentatives Gremium (ohne Patientenvertretung);
- Standardisierter Umgang mit Interessenkonflikten beschrieben aber nicht offengelegt und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Konsensusprozesse nicht erwähnt und externes Begutachtungsverfahren (Patientinnen und Patienten, Interessenvertretungen, internationale Fachleute) dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist indirekt über den Hintergrundtext dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- literature was updated prior to publication, made a complete review and rewrite of the medical oncology section in July 2016 necessary

LoE/GoR

- SIGN grading system 1999-2012
- B: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+.

**Empfehlungen**

**Clinical question 2.6.4: In patients with advanced/stage IV NSCLC what is the effectiveness of first-line chemotherapy and is there any evidence that particular regimens or drugs are more effective or less toxic than others?**

Effectiveness of first-line targeted therapy

| Recommendation 2.6.4.1 | Grade |
|---|---|
| **Effectiveness of first-line cytotoxic chemotherapy**<br>In patients with a good performance status (PS) (i.e. Eastern Cooperative Oncology Group [ECOG] level 0 or 1) and stage IV NSCLC, a platinum-based chemotherapy regimen is recommended based on the survival advantage and improvement in quality of life (QOL) over best supportive care (BSC). | A |

| Recommendation 2.6.4.2 | Grade |
|---|---|
| **Effectiveness of first-line cytotoxic chemotherapy**<br>In patients with stage IV NSCLC and a good performance status, two-drug combination chemotherapy is recommended. The addition of a third cytotoxic chemotherapeutic agent is **not** recommended because it provides no survival benefit and may be harmful. | A |

| Recommendation 2.6.4.3 | Grade |
|---|---|
| **Effectiveness of first-line cytotoxic chemotherapy**<br>In patients receiving palliative chemotherapy for stage IV NSCLC, it is recommended that the choice of chemotherapy is guided by histological type of NSCLC. | B |

| Recommendation 2.6.4.4 | Grade |
|---|---|
| **Effectiveness of first-line cytotoxic chemotherapy**<br>Bevacizumab plus platinum-based chemotherapy may be considered an option in carefully selected patients with advanced NSCLC. Risks and benefits should be discussed with patients before decision making. | B |

| Recommendation 2.6.4.5 | Grade |
|---|---|
| **Effectiveness of first-line targeted therapy**<br>First-line single agent EGFR tyrosine kinase inhibitors (TKI) should be offered to patients with sensitising EGFR mutation positive NSCLC. Adding combination chemotherapy to TKI confers no benefit and should **not** be used. | A |

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**Hanna N et al., 2020 [23]**

Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Update.

**Fragestellung**

to provide evidence-based recommendations updating the 2017 ASCO guideline on systemic therapy for patients with stage IV non–small-cell lung cancer (NSCLC) without driver alterations. A guideline update for patients with stage IV NSCLC with driver alterations will be published separately

**Methodik**

Grundlage der Leitlinie

Update der Version von Hanna N. et al. 2017 [22] & Masters GA, et al. 2015 [34]

- 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:

- systematic review of randomized controlled trials from December 2015 to 2019

LoE/SoE:

- GRADE

**Recommendations**

For patients with stage IV NSCLC without driver alterations, what are the most effective first-line therapies? The following recommendations apply to patients with non-SCC, in the absence of contraindications to immune checkpoint therapy (unless noted) and high PD-L1 TPS (≥ 50%).

- For patients with high PD-L1 expression (TPS≥ 50%), nonSCC, and PS 0 to 1, clinicians should offer single-agent pembrolizumab (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).
- For patients with high PD-L1 expression (TPS≥ 50%), nonSCC, and PS 0 to 1, clinicians may offer pembrolizumab/ carboplatin/pemetrexed (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).
- For patients with high PD-L1 expression (TPS≥50%), nonSCC, and PS 0 to 1, clinicians may offer atezolizumab/ carboplatin/paclitaxel/bevacizumab in the absence of contraindications to bevacizumab (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).
- For patients with high PD-L1 expression (TPS≥50%), nonSCC, and PS 0 to 1, clinicians may offer atezolizumab/ carboplatin/nab-paclitaxel (Type: evidence based; Evidence quality: low; Strength of recommendation: weak).
- There are insufficient data to recommend any other checkpoint inhibitors, or to recommend combination checkpoint inhibitors or any other combinations of immune checkpoint inhibitors with chemotherapy in the first-line setting (Type: evidence based, benefits outweigh harm; Evidence quality: high; Strength of recommendation: strong).
- For patients with negative (0%) and low positive PD-L1 expression (TPS 1% to 49%), non-SCC, and PS 0 to 1, and who are eligible for chemotherapy and pembrolizumab, clinicians should offer pembrolizumab/carboplatin/pemetrexed (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).
- For patients with negative (TPS 0%) and low positive (TPS 1% to 49%) PD-L1 expression, non-SCC, and PS 0 to 1, clinicians may offer atezolizumab/carboplatin/paclitaxel/ bevacizumab in the absence of contraindications to bevacizumab (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).
- For patients with negative (TPS 0%) and low positive (TPS 1% to 49%) PD-L1 expression, non-SCC, and PS 0 to 1, clinicians may offer atezolizumab/carboplatin/nab-paclitaxel (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).
- For patients with negative (TPS 0%) and low positive (TPS 1% to 49%) PD-L1 expression, non-SCC, and PS 0 to 1, and who have contraindications to or decline immunotherapy, clinicians should offer standard chemotherapy with platinumbased two-

drug combinations as outlined in the 2015 update (Type: evidence based; Evidence quality: high; Strength of recommendation: strong). NOTE. This corresponds to the first part of Recommendation A2.a.iii in 2017: “For patients with low PD-L1 expression (TPS , 50%), clinicians should offer standard chemotherapy with platinumbased two-drug combinations as outlined in the 2015 update (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong) or (see below)”.1(p6)

- For patients with negative (TPS 0%) and low positive (TPS 1% to 49%) PD-L1 expression, non-SCC, and PS 0 to 1, and who have contraindications to or decline immunotherapy and not deemed candidates for platinum-based therapy, clinicians should offer non–platinum-based two-drug therapy as outlined in the 2015 update (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: weak).
- For patients with low positive PD-L1 expression (TPS 1% to 49%), non-SCC, and PS 0 to 1, and who are ineligible for or decline combination of doublet platinum with or without pembrolizumab, clinicians may offer single-agent pembrolizumab (Type: evidence based; Evidence quality: low; Strength of recommendation: weak).
- For patients with high PD-L1 expression (TPS ≥ 50%), SCC, and PS 0 to 1, clinicians should offer single-agent pembrolizumab (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).
- For patients with high PD-L1 expression (TPS ≥ 50%), SCC, and PS 0 to 1, clinicians may offer pembrolizumab/ carboplatin/paclitaxel or nab-paclitaxel (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).
- There are insufficient data to recommend any other checkpoint inhibitors or to recommend combination checkpoint inhibitors or any other combinations of immune checkpoint inhibitors with chemotherapy in the first-line setting (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).
- For patients with negative (TPS 0%) and low positive (TPS 1% to 49%) PD-L1 expression, SCC, and PS 0 to 1, clinicians should offer pembrolizumab/carboplatin/paclitaxel or nab-paclitaxel (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).
- For patients with negative (TPS 0%) and low positive (TPS 1% to 49%) PD-L1 expression, SCC, and PS 0 to 1, and with contraindications to immunotherapy, clinicians should offer standard chemotherapy with platinum-based two-drug combinations as outlined in the 2015 update (Type: evidence based; Evidence quality: high; Strength of recommendation: strong). NOTE. Similar to first part of Recommendation A3.iii in 2017 “For patients with low (TPS , 50%) or unknown PD-L1 expression, clinicians should offer standard chemotherapy with platinum-based, two-drug combinations as outlined in the 2015 update (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).”1(p25)
- For patients with negative (TPS 0%) and low positive (TPS 1% to 49%) PD-L1 expression, SCC, and PS 0 to 1, and with contraindications to immunotherapy and not deemed candidates for platinum-based therapy, clinicians should offer standard chemotherapy with non–platinum-based two-drug combinations as outlined in the 2015 update (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: weak). NOTE. Similar to the second part of Recommendation A3.iii in 2017 “For patients with low (TPS , 50%) or unknown PD-L1 expression, clinicians should

offer standard chemotherapy with…non–platinumbased, two-drug therapy as outlined in the 2015 update for patents not deemed candidates for platinum-based therapy (Type: evidence-based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: weak).”1(p25)

- For patients with low positive PD-L1 expression (TPS 1% to 49%), SCC, and PS 0 to 1, and who are ineligible for or decline a combination of doublet platinum/pembrolizumab and have contraindications to doublet-chemotherapy, clinicians may offer single-agent pembrolizumab in the absence of contraindications to immune checkpoint therapies (Type: evidence based; Evidence quality: low; Strength of recommendation: weak).

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**Ellis PM et al., 2016 [9].**

*Cancer Care Ontario (CCO)*

Systemic treatment for patients with advanced non-small cell lung cancer.

**Fragestellung**

Clinical Question A5: What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with ALK gene rearrangement and PS 0 to 1 or possibly PS 2?

**Methodik**

Grundlage der Leitlinie

Update der Version von 2010 (Originalversion von 2009), “guideline based on content from the ASCO” (siehe oben)

- Gremium aus Onkologie, Radiologie, Chirurgie (ohne Patientenvertretung);
- Interessenkonflikte dargelegt und finanzielle Unabhängigkeit nicht erklärt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Ableitung der Empfehlung und Konsensusprozesse nicht beschrieben 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:

- 1996 Present (February 16, 2016)

LoE

- Cochrane Risk of Bias Tool (low, high, unclear …)

GoR

- nach ASCO (siehe oben) durch Fomulierung abgebildet

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

- für den Adaptationsprozess der ASCO-LL fehlt die systematische Suche und Auswahl von Quellleitlinien, eine Bewertung mit AGREE liegt vor: „The Working Group considered the guideline to be of high quality because the rigour of development domain, which assesses the methodological quality of the guideline, was well above 50%.”

**Empfehlungen**

Which patients with stage IIIB/IV NSCLC should be treated with chemotherapy?

| **Recommendation A1.a** |
|---|
| For patients with Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, a combination of two cytotoxic drugs is recommended. Platinum combinations are recommended over nonplatinum therapy; however, nonplatinum therapy combinations are recommended for patients who have contraindications to platinum therapy. Chemotherapy may also be used to treat selected patients with PS 2 who desire aggressive treatment after a thorough discussion of the risks and benefits of such treatment. |
| ***Implementation Considerations for Recommendation A1.a*** |
| Nonplatinum doublet chemotherapy is currently not funded in Ontario. |
| **Recommendation A1.b** |
| Because there is no cure for patients with stage IIIB/IV NSCLC, early concomitant palliative care assistance has improved the survival and well-being of patients and is therefore recommended. |
| ***Implementation Considerations for Recommendation A1.b*** |
| This will require additional resources from the Ontario government to implement early integration of palliative care. |

What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with non-squamous (NSCC), negative or unknown epidermal growth factor receptor (EGFR)- sensitizing mutation and ALK gene rearrangement status, and PS 0 to 1 or possibly PS 2?

| **Recommendation A2** |
|---|
| For patients who have the characteristics described in Clinical Question A2 and who have non-squamous histology, the following options are acceptable:<br>● Cisplatin-based combinations<br>● Cisplatin plus docetaxel<br>● Cisplatin plus paclitaxel<br>● Cisplatin plus pemetrexed<br>● Cisplatin plus vinorelbine<br>● *Cisplatin plus gemcitabine*<br>● Carboplatin-based combinations<br>● Carboplatin plus albumin-bound (nab) –paclitaxel<br>● Carboplatin plus paclitaxel<br>● Carboplatin plus pemetrexed<br>● Carboplatin plus docetaxel<br>● *Carboplatin plus gemcitabine*<br>● Nonplatinum doublets |
| ***Key Evidence from ASCO for Recommendation A2*** |
| This recommendation was supported by high-quality evidence for cisplatin-based and carboplatin-based combination therapies and intermediate-quality evidence for therapies with nonplatinum doublets from ASCO's reviews [1,5]. ASCO's systematic reviews found that two-drug combinations were superior to single-agent therapy for OS. Also, platinum-based two-drug combinations were slightly superior to nonplatinum combinations for OS, and cisplatin was slightly superior to carboplatin for survival. Individual patient decisions should reflect the balance among improved survival, increased toxicity, and patient preference. |
| ***Interpretation of Evidence for Recommendation A2*** |

| |
|---|
| The Working Group agreed with the interpretation of the evidence provided by ASCO, except the Working Group wanted to add the cisplatin plus gemcitabine and carboplatin and gemcitabine combinations as acceptable options. The evidence for platinum-based chemotherapy plus gemcitabine that was included in ASCO's review was conflicting [1]. Scagliotti et al. [6] found inferior efficacy with cisplatin plus gemcitabine compared with cisplatin plus pemetrexed for patients with NSCC, and Gronberg et al. [7] found no difference in efficacy according to histology for patients who received carboplatin plus gemcitabine compared with carboplatin plus pemetrexed. Based on the lack of consistency, the Working Group decided not to exclude platinum-based chemotherapies combined with gemcitabine as options. |
| ***Implementation Considerations for Recommendation A2*** |
| Nonplatinum doublets will be a funding gap for Ontario. |

What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with negative or unknown EGFR/ALK status, NSCC, and no contraindications to bevacizumab?

| **Recommendation A2.a.1** |
|---|
| For patients receiving carboplatin plus paclitaxel, the addition of bevacizumab 15 mg/kg once every three weeks is recommended, except for patients with squamous cell carcinoma (SCC) histologic type, clinically significant hemoptysis, a *known bleeding disorder,* inadequate organ function, Eastern Cooperative Oncology Group PS > 1, clinically significant cardiovascular disease, or medically uncontrolled hypertension. *Caution should be exercised in patients with brain metastases.* Bevacizumab may be continued, as tolerated, until disease progression.<br>*An alternative treatment strategy for patients who are eligible for carboplatin, paclitaxel, and bevacizumab would include cisplatin or carboplatin plus pemetrexed and maintenance pemetrexed.* |
| ***Key Evidence from ASCO for Recommendation A2.a.1*** |
| This recommendation was supported by intermediate quality evidence from one large phase III randomized controlled trial (RCT) from ASCO's systematic review, which reported a statistically significant increase in OS when bevacizumab was added to carboplatin plus paclitaxel in first-line therapy for patients meeting the above criteria [1,8]. These criteria were chosen to exclude patients with a potential increased risk of toxicity associated with the addition of bevacizumab. Subgroup analysis also suggested that the elderly population may be at increased risk for adverse events with no improvement in OS. The trial also excluded patients with hemorrhagic disorders as well as patients with central nervous system metastases due to risk of bleeding [8]. However, one retrospective study found that bevacizumab may be safe and effective in patients with brain metastases, especially in patients with small lesions that are less likely to hemorrhage [9]. However, the authors do suggest that bevacizumab should be used with caution in these patients.<br>A more recent trial published after the search cut-off date of the ASCO review, found that carboplatin plus paclitaxel and bevacizumab and maintenance bevacizuamb compared with carboplatin plus pemetrexed and maintenance pemetrexed had similar progression-free survival (PFS) and grade IV toxicity [10]. |
| ***Interpretation of Evidence for Recommendation A2.a.1*** |
| The Working Group agreed with the interpretation of the evidence, but wanted to add any known bleeding disorder as a contraindication since patients with hemorrhagic disorders were excluded. Furthermore, low-quality data from one study suggested that bevacizumab may be effective in patients with brain metastases; therefore, the Working Group recommended caution when prescribing bevacizumab to patients with brain metastases.<br>The Working Group also wanted to add another treatment strategy in response to the recently published trial by Zinner et al. (2015) [10]. |
| ***Implementation Considerations for Recommendation A2.a.1*** |

| |
|---|
| There is no funding for bevacizumab in Ontario. |
| **Recommendation A2.a.2** |
| There is insufficient evidence (for or against) to recommend pemetrexed in combination with bevacizumab plus carboplatin for patients who do not have contraindications to bevacizumab. |

What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with PS 2, NSCC, and negative or unknown EGFR-sensitizing mutation and ALK gene rearrangement status?

| |
|---|
| **Recommendation A2.b** |
| In the context of shared decision making, combination therapy, single-agent chemotherapy, or palliative therapy alone may be used for patients in this population with PS 2. |

Clinical Question A3

What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with SCC, negative or unknown EGFR-sensitizing mutation and ALK gene rearrangement status, and PS 0 to 1 or possibly PS 2?

| |
|---|
| **Recommendation A3** |
| Patients with the characteristics listed in Clinical Question A3 and with SCC histology should be offered the following options:<br>● Cisplatin-based combinations<br>● Cisplatin plus docetaxel<br>● Cisplatin plus gemcitabine<br>● Cisplatin plus paclitaxel<br>● Cisplatin plus vinorelbine<br>● Carboplatin-based combinations<br>● Carboplatin plus gemcitabine<br>● Carboplatin plus paclitaxel<br>● Carboplatin plus nab-paclitaxel<br>● Carboplatin plus docetaxel<br>● Nonplatinum doublets |

What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with negative or unknown EGFR/ALK status, SCC, and PS 2?

| |
|---|
| **Recommendation A3.a** |
| In the context of shared decision making, combination chemotherapy, single-agent chemotherapy, or palliative therapy alone may be used for patients with the characteristics described in Clinical Question A3.a. |

What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with ROS1 rearrangement, no ALK gene rearrangement, negative or unknown EGFR-sensitizing mutation status, and PS 0 to 1 or possibly PS 2?

| |
|---|
| **Recommendation A6** |
| If patients have stage IIIB/IV NSCLC with *ROS1* rearrangement, single-agent crizotinib is recommended, because it has shown some results indicating improved response rate and duration of response. |
| ***Implementation Considerations for Recommendation A6*** |
| There is no funding to test for *ROS1* and no funding for crizotinib for this indication in Ontario. |

**Australian Government Cancer Council Australia, 2017 [2].**

Clinical practice guidelines for the treatment of lung cancer

**Leitlinienorganisation/Fragestellung**

In a project commissioned by Cancer Australia (CA), CCA undertook to develop a sustainable web-based wiki platform with revised guidelines for the treatment of lung cancer as the first topic.

**Methodik**

Grundlage der Leitlinie

- The small Management Committee appointed in 2009 is responsible to oversee the guidelines revision project. The Management Committee is responsible for the overall management and strategic leadership of the guidelines review process.
- The Management Committee proposed lead authors for each included clinical question.
- The Management Committee agreed to use Cancer Council Australia's Cancer Guidelines Wiki Platform and approach to develop the guidelines. The Wiki Platform is web-based and supports all processes of guidelines development, such as the literature search, critical appraisal, data extraction, evidence assessment and summary processes, as well as content and recommendation development, online consultation, review and web publication.
- Steps in preparing clinical practice guidelines
  - Develop a structured clinical question in PICO format
  - Search for existing relevant guidelines and SR answering the clinical question
  - Perform systematic review process (systematic review protocol and systematic literature search strategy for each PICO question; Body evidence table of all included literature)
  - Summarise the relevant data
  - Assess the body of evidence and formulate recommendations
  - Write the content narrative
  - Funding: The revised Clinical practice guidelines for the prevention and diagnosis of lung cancer are developed by Cancer Council Australia. No external funding has been received.

Recherche/Suchzeitraum:

- Bis 2015

LoE

- NHMRC Evidence Hierarchy (Siehe Anhang Abbildung 3)

GoR

| Component of Recommendation | Recommendation Grade | | | |
|---|---|---|---|---|
| | A Excellent | B Good | C Satisfactory | D Poor |
| **Volume of evidence** 1** | one or more level I studies with a low risk of bias or several level II studies with a low risk of bias | one or two level II studies with a low risk of bias or a systematic review/several level III studies with a low risk of bias | one or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias | level IV studies, or level I to III studies/systematic reviews with a high risk of bias |
| **Consistency** 2** | all studies consistent | most studies consistent and inconsistency may be explained | some inconsistency reflecting genuine uncertainty around clinical question | evidence is inconsistent |
| **Clinical impact** | very large | substantial | moderate | slight or restricted |
| **Generalisability** | population/s studied in body of evidence are the same as the target population for the guideline | population/s studied in the body of evidence are similar to the target population for the guideline | population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population[3] | population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population |
| **Applicability** | directly applicable to Australian healthcare context | applicable to Australian healthcare context with few caveats | probably applicable to Australian healthcare context with some caveats | not applicable to Australian healthcare context |

**Table 3. Overall recommendation grades**

| Grade of recommendation | Description |
|---|---|
| A | Body of evidence can be trusted to guide practice |
| B | Body of evidence can be trusted to guide practice in most situations |
| C | Body of evidence provides some support for recommendation(s) but care should be taken in its application |
| D | Body of evidence is weak and recommendation must be applied with caution |

Sonstige methodische Hinweise

- Da diese Leitlinie die Empfehlungen erst im Jahr 2015 getroffen hat, wird die zugrundeliegende Literatur aufgeführt.

## Empfehlungen - Stage IV inoperable NSCLC

What is the optimal first-line chemotherapy regimen in patients with stage IV inoperable NSCLC?

| Evidence summary | Level | References |
|---|---|---|
| Platinum-based chemotherapy improves survival in stage IV NSCLC compared with best supportive care. Note that this evidence is based on clinical trials conducted in fit patients, with predominant performance status 0-1, no unstable co-morbidities, adequate organ function and without uncontrolled brain metastases.<br>Last reviewed September 2017 | I | [4], [5] |

| + Evidence-based recommendation? | Grade |
|---|---|
| Platinum-based chemotherapy can be used to extend survival in newly diagnosed patients with stage IV NSCLC.<br>Last reviewed September 2017 | A |

| ✓ Practice point? |
|---|
| The decision to undertake empirical platinum-based chemotherapy in a given patient should consider factors such as patient performance status (0,1 versus 2 or more) and co-morbidities, their disease extent and symptoms, proposed treatment toxicity and their individual preferences for benefit from specific treatment(s) and toxicities.<br>Last reviewed September 2017 |

The first piece of evidence to establish a standard of practice was the meta-analysis of randomised trials until 1992 evaluating chemotherapy for non-Small Cell Lung Cancer by the Non-small Cell Lung Cancer Collaborative Group. Data from eight trials (N = 778) evaluating best supportive care versus best supportive care and cisplatin based chemotherapy showed a clear survival benefit in favour of chemotherapy with a hazard ratio of 0.73 (P<0.0001), or 27% reduction in the risk of death. This is equivalent to an absolute improvement in survival of 10% at one year, improving survival from 15% to 25%.

It is important to note that empirical chemotherapy has only been formally evaluated in "fit" patients. Patient performance status (PS) has conventionally been used to standardise and quantify cancer patient's general well-being and activities of daily life. The simplest of such scores in widespread use is the ECOG/WHO/ZUBROD score.[3]

By Convention, "fit" patients have a low PS and in most chemotherapy trials, the predominant patient group included is that with PS 0 or 1, with a minority being PS 2 or greater (referred to as poor performance status and described separately in the section below). Furthermore, chemotherapy trials have usually only included patients with adequate organ function and excluded patients with medically unstable co-morbidities and uncontrolled brain metastases. The median age of patients on chemotherapy trials is also lower than the median of the Australian lung cancer population.

A large number of randomised controlled studies and subsequent meta-analyses have been reported addressing questions such as, which platinum agent is best (carboplatin versus cisplatin)?; which new agent paired with a platinum agent is best (often referred to as "third generation (3G)" regimens)"?; is monotherapy with new ("3G") agents as effective as platinum combination therapy?;are three chemotherapy agents ("triplet regimens") better than two ("doublet regimens")?; are non-platinum doublet chemotherapy regimens as effective as platinum doublet regimens?; what is the optimal duration of chemotherapy?; and is chemotherapy and a "biologic" or "targeted" therapy superior to chemotherapy alone?

Is carboplatin based chemotherapy as effective as cisplatin based chemotherapy for treatment of stage IV inoperable NSCLC?

Evidence summary and recommendations

| Evidence summary | Level | References |
|---|---|---|
| First-line chemotherapy involving cisplatin results in a slightly higher likelihood of tumour response than the same chemotherapy with carboplatin. Last reviewed September 2017 | I | [1], [2], [3] |
| There is no definite overall survival difference between cisplatin or carboplatin based first-line chemotherapy. Last reviewed September 2017 | I | [1], [2], [3] |
| Cisplatin-based chemotherapy is associated with more severe nausea and vomiting and nephrotoxicity; severe thrombocytopaenia is more frequent during carboplatin-based chemotherapy. Last reviewed September 2017 | I | [1], [2], [3] |

| + Evidence-based recommendation? | Grade |
|---|---|
| In patients with high tumour burden and symptoms from stage IV NSCLC cisplatin based chemotherapy may be used in preference to carboplatin for the purpose of inducing a response, however, this benefit may be offset by its greater risk of toxicity. Last reviewed September 2017 | B |

✓ Practice point?

The choice of cisplatin versus carboplatin in a given patient may consider the balance between perceived benefit (in tumour response) versus known toxicity, whilst considering patient preferences.
Last reviewed September 2017

Three meta-analyses have addressed the question of whether carboplatin based chemotherapy is as effective as cisplatin based,[1][2][3] which collectively confirm that cisplatin based regimens are associated with a slightly higher response rate than carboplatin regimens, with no definite survival difference.The first meta-analysis by Hotta et al, evaluated 2948 patients from eight randomised controlled trials (RCTs) from 1990-2004.[1]. Cisplatin-based chemotherapy produced a higher response rate (RR), but overall survival (OS) was not significantly different.[1] The second, by Ardizzoni et al, was an individual patient data meta-analysis of 2968 patients from nine RCTs from 1990 to 2004. This study found that objective RR was higher for patients treated with cisplatin than for patients treated with carboplatin (30% versus 24%, respectively; Odds ratio (OR) = 1.37; 95% CI = 1.16 to 1.61; P <.001).[2] There was no overall difference in mortality, however, as in the Jiang meta-analysis, a subset analysis of survival in five trials evaluating “new” agents (gemcitabine, docetaxel, paclitaxel and vinorelbine) found OS with carboplatin slightly inferior to cisplatin (hazard ratio (HR) = 1.12; 95% CI = 1.01 to 1.23).[2] Cisplatin-based chemotherapy was associated with more severe nausea and vomiting and nephrotoxicity; severe thrombocytopaenia was more frequent during carboplatin-based chemotherapy.[2] Jiang et al, evaluated published data from 6906 patients from 18 RCTs from 1990-2006.[3] This study confirmed the findings of Hotta and Arziddoni with regard to RR in favour of cisplatin, however it did not find any survival difference in eight studies evaluating the new agents above.[3]

A more recent Cochrane review of cisplatin versus carboplatin in combination with third-generation drugs found that no survival difference, slightly higher response rates to cisplatin in the overall analysis, but that trials using paclitaxel or gemcitabine had equivalent response rates for cisplatin or carboplatin. [4]

The question of whether to use cisplatin versus carboplatin is of lower significance today especially given the new information arguing in favour of selecting specific treatments for greater benefit by histology and the presence of activating gene mutations.

Which new agent or platinum combination regimen is best for treatment of stage IV inoperable NSCLC?

Evidence summary and recommendations

| Evidence summary | Level | References |
|---|---|---|
| 3G platinum-based chemotherapy (vinorelbine, paclitaxel, docetaxel or gemcitabine) is associated with higher response ratio than older 2G platinum-based chemotherapy.<br>Last reviewed September 2017 | I | [1], [2], [3] |
| No 3G platinum-based chemotherapy regimen (vinorelbine, paclitaxel, docetaxel or gemcitabine) has been shown to be superior to another.<br>Last reviewed September 2017 | I | [1], [2], [3] |
| In first-line empirical treatment of advanced NSCLC, chemotherapy with cisplatin and pemetrexed is superior to cisplatin/gemcitabine in patients with non-squamous cell carcinoma histology.<br>Last reviewed September 2017 | II | [5] |
| In first-line empirical treatment of advanced NSCLC, chemotherapy with cisplatin and pemetrexed is inferior to cisplatin/gemcitabine in patients with SCC histology.<br>Last reviewed September 2017 | II | [5] |

| + Evidence-based recommendation? | Grade |
|---|---|
| 3G platinum-based chemotherapy (with vinorelbine, paclitaxel, docetaxel or gemcitabine) is a standard of care as first-line chemotherapy in fit patients with stage IV NSCLC.<br>Last reviewed September 2017 | A |

| + Evidence-based recommendation? | Grade |
|---|---|
| In the first-line setting, chemotherapy with cisplatin and pemetrexed is recommended in preference to cisplatin and gemcitabine in patients with non-squamous cell carcinoma histology.<br>Last reviewed September 2017 | B |

| + Evidence-based recommendation? | Grade |
|---|---|
| In the first-line setting, chemotherapy with cisplatin and gemcitabine is recommended in preference to cisplatin and pemetrexed in patients with squamous cell carcinoma histology.<br>Last reviewed September 2017 | B |

| ✓ Practice point? |
|---|
| The choice of first-line platinum combination chemotherapy in a given patient may consider patient performance status and co-morbidities, the proposed treatment toxicity, treatment scheduling and individual patient preferences.<br>Last reviewed September 2017 |

Several meta-analyses and numerous RCTS have evaluated this question either as their primary endpoint or as part of secondary analyses. New agents making up so – called “third generation” regimens include gemcitabine, vinorelbine, docetaxel, paclitaxel and irinotecan.[1][2][3][4]

Baggstrom et al, meta-analysed results from twelve RCTs from 1994 – 2004 (n= 3995 patients) comparing response rate (RR) and overall survival (OS) with 3G combination regimens including platinum-based compounds with second generation (2G) platinum-based regimens.[1] The estimated absolute risk difference (RD) in RR in favour of 3G regimens was 12% (95% CI: 10 -15%), corresponding to a number need to treat (NNT) of eight for one patient to benefit.[1] Owing to a high degree of heterogeneity across the studies, analysis of OS could not be undertaken.

Grossi et al, evaluated the relative impact of different 3G drugs (vinorelbine, gemcitabine, paclitaxel, docetaxel) on the activity of first-line chemotherapy in advanced NSCLC by considering RR and progressive disease (PD), in 45 RCTs (N = 11,867 patients).[3] They found the odds of obtaining an objective response to treatment similar across the different regimens. Different rates of disease control were observed, with gemcitabine chemotherapy associated with a significant 14% lower risk for immediate progression, whereas patients receiving paclitaxel-based treatment appear to be at a higher risk for having PD as their best response.[3] However, OS was not assessed in this meta-analysis.

Gao et al, examined whether platinum plus gemcitabine or vinorelbine are equally effective in the treatment of advanced NSCLC.[2] This publication only meta-analysis evaluated nine RCTs involving 2186 patients, and found that no differences in RR or one-year OS.[2] Vinorelbine plus platinum regimens led to more frequent grade 3 or 4 neutropaenia, nephrotoxicity, constipationand phlebitiswhile gemcitabineplus platinum chemotherapy was associated with more grade 3 or 4 thrombocytopaenia.[2]

These meta-analyses collectively confirm better RR with 3G regimens compared with 2G but with differing toxicity profiles across the regimens and uncertainty or no difference in OS. A RCT of 1155 patients, evaluating four commonly used 3G platinum based regimens (vinorelbine, docetaxel, paclitaxel and gemcitabine) similarly failed to demonstrate superiority (in OS and RR) of one regimen over another although toxicity differences were observed.[4]

In the setting of first-line empirical chemotherapy, the study by Scagliotti et al compared the effectiveness of cisplatin and pemetrexed to cisplatin and gemcitabine in a RCT of 1,725 patients.[5] This study confirmed non-inferiority of cisplatin/pemetrexed compared with cisplatin/gemcitabine for the overall population, but also confirmed (in pre-planned analyses), superiority of cisplatin/pemetrexed for OS compared with cisplatin/gemcitabine in patients with non-SCC histology (HR 0.81, 95% CI 0.70 - 0.94), with median OS 12.6 versus 10.9 months for adenocarcinoma histology (n = 847, and 10.4 versus 6.7 months for large cell carcinoma (n = 153).[5] Conversely, in patients with SCC, there was a significant improvement in survival with cisplatin/gemcitabine versus cisplatin/pemetrexed (n = 473; median OS 10.8 versus 9.4 months, respectively, HR 1.23 (95% CI 1.00 – 1.51, p = 0.05)). For cisplatin/pemetrexed, rates of grade 3/4 neutropaenia, anaemia, and thrombocytopaenia (p = 0.001); febrile neutropaenia (p = 0.002); and alopecia (p = 0.001) were significantly lower, whereas grade 3 or 4 nausea (p = 0 .004) was more common.

Gronberg et al compared carboplatin/pemetrexed to carboplatin/gemcitabine in a RCT of 436 patients with the primary endpoint of health-related quality of life.[6] Compliance with completion of health-related QOL questionnaires was 87%. There were no significant differences for the primary health-related QOL endpoints, or in OS between the two treatment arms (pemetrexed/carboplatin, 7.3 months; gemcitabine/carboplatin, 7.0 months; P=0.63). Multivariate analyses and interaction tests did not reveal any significant associations between histology and survival. As in the Scagliotti study, rates of Grade ¾ haematologic toxicity were less with carboplatin/pemetrexed.[6]

## Is monotherapy with new third generation (3G) agents as effective as platinum combination therapy for treatment of stage IV inoperable NSCLC?

### Evidence summary and recommendations

| Evidence summary | Level | References |
|---|---|---|
| 3G platinum-based combination chemotherapy (vinorelbine, paclitaxel, docetaxel, irinotecan or gemcitabine) is superior to 3G agent monotherapy.<br>Last reviewed September 2017 | I | [1], [4] |
| 3G platinum-based monotherapy (vinorelbine, paclitaxel, docetaxel, or gemcitabine) improves survival compared with best supportive care.<br>Last reviewed September 2017 | I | [2] |

| + Evidence-based recommendation? | Grade |
|---|---|
| Patients fit for chemotherapy should be offered 3G platinum-based combination chemotherapy (vinorelbine, paclitaxel, docetaxel, irinotecan or gemcitabine) in preference to 3G agent monotherapy, as it is more effective.<br>Last reviewed September 2017 | A |

| + Evidence-based recommendation? | Grade |
|---|---|
| Patients unfit for combination chemotherapy could be considered for 3G monotherapy with vinorelbine, paclitaxel, docetaxel or gemcitabine.<br>Last reviewed September 2017 | A |

A meta-analysis by Hotta et al, examined the question of how treatment with single agent 3G agents (vinorelbine, paclitaxel, docetaxel, gemcitabine and irinotecan) compares with the same agent and a platinum agent.[1] This meta-analysis evaluated 2374 patients from eight RCTs between 1994 – 2003. A greater than two-fold higher overall response rate (RR) was seen with platinum combination than the new agent alone [odds ratio = 2.32; 95% CI 1.68–3.20]. Platinum-based doublet therapy was associated with a 13% prolongation of overall survival (OS) (HR = 0.87; 95% CI = 0.80–0.94,P <0.001).[1] Despite significant increases in the frequencies of various toxicities in patients receiving platinum-based doublets, no significant difference in treatment-related mortality was observed.[1]

Baggstrom et al in their meta-analsysis examined the effectiveness of 3G agents (vinorelbine, paclitaxel, docetaxel and gemcitabine) as first-line monotherapy compared with best supportive care in five RCTS of 1029 patients from 1996 – 2000.[2] One trial used 5-fluorouracil (5FU)/leucovorin as the control arm. RR for the 3G regimens ranged from 12-20%. One-year survival favored the 3G agents over best supportive care with a summary absolute risk difference of 7% (95% CI: 2 - 12%). They calculated that the NNT for one patient to realise a benefit in the probability of one-year survival was 14.

Delbaldo et al examined the effectiveness of two-drug platinum combination chemotherapy compared with single agent therapy.[3][4] This study evaluated 7175 patients from 29 RCTs but also included studies using older agents such as etoposide, vindesine and mitomycin C, as well as the modern 3G agents previously listed. Some of the studies included used a non-platinum combination in the comparator arm. Two-drug combination therapy was found to have a higher RR (OR, 0.42; 95% CI 0.37-0.47; p <.001). The absolute benefit was 13%, which corresponds to a two-fold increase in RR from 13% with a single-agent regimen to 26% with a doublet regimen.[4] The benefit was higher when the control arm was an older drug (OR, 0.35) than when it was a newer drug (OR, 0.52) (P=.001). Two-drug combination therapy was associated with a significant increase in one-year survival (OR, 0.80; 95% CI, 0.70-0.91; P<.001)[4] The absolute benefit was 5%, which corresponds to an increase in one-year survival from 30% with a single agent regimen to 35% with a doublet regimen. The benefit was higher when the control arm was an older drug than newer drug for both one-year survival rate (p=.03) and median survival (p=.007).[4]

## Are three chemotherapy agents better than two chemotherapy agents for treatment of stage IV inoperable NSCLC?

| Evidence summary | Level | References |
|---|---|---|
| Triplet chemotherapy regimens are associated with higher response rate, but no improvement in survival.<br>Last reviewed September 2017 | I | [1] |
| Triplet chemotherapy regimens are associated with greater grade 3 /4 toxicities.<br>Last reviewed September 2017 | I | [2] |

| + Evidence-based recommendation? | Grade |
|---|---|
| Triplet chemotherapy regimens are not recommended, as benefit in response rate does not outweigh extra toxicity.<br>Last reviewed September 2017 | A |

Delbaldo et al also examined the effectiveness of three-drug combination chemotherapy compared with two-drug combination chemotherapy.[1] This study evaluated 4814 patients from 28 RCTs.Adding a third drug to a doublet regimen was associated with a significantly increased response rate (RR) (OR, 0.66; 95%CI, 0.58-0.75; p <.001).[1] The absolute benefit was 8%, which corresponds to an increase in tumour RR from 23% (doublet regimen) to 31% (triplet regimen).[1] There was no difference in RR whether the doublet regimens contained older or newer (3G) drugs (p=0.33). Adding a third drug to a doublet regimen did not improve one-year survival (OR, 1.01;95% CI, 0.85-1.21; P=0.88) and there was no significant difference according to the type of control regimens used (older drugs versus newer (3G) drugs) for both one-year survival rate (p =.28) and median survival (p =.36).[1] However, grade ¾ toxicity was more common in triplet regimens than in doublet regimens with ORs ranging from 1.4 to 2.9,except for neurological, renal, auditory and gastrointestinal toxic effects.[1]

Are non-platinum doublet chemotherapy regimens as effective as platinum doublet regimens for treatment of stage IV inoperable NSCLC?

| Evidence summary | Level | References |
|---|---|---|
| Platinum-based doublet 3G chemotherapy is associated with a higher response rate and slightly higher one-year survival than non-platinum doublet chemotherapy.<br>Last reviewed September 2017 | I | [1], [2], [3] |
| Platinum-based doublet 3G chemotherapy is associated with greater risk of anaemia and thrombocytopaenia than non-platinum combination therapy.<br>Last reviewed September 2017 | I | [1], [2], [3] |
| Gemcitabine and paclitaxel improves response ratio without added toxicity, compared with gemcitabine or paclitexel and carboplatin combinations.<br>Last reviewed September 2017 | I | [3] |

| + Evidence-based recommendation? | Grade |
|---|---|
| Non-platinum 3G doublet chemotherapy is an effective alternative option for patients unsuitable for platinum-based therapy.<br>Last reviewed September 2017 | B |

D'Addario et alevaluated this question in a meta-analysis of 7633 patients from 37 RCTs between 1983 and 2002.[1] Platinum-based therapy was associated with a 62% increase in the odds ratio (OR) for response rate (RR) (OR, 1.62; 95% CI,1.46 =1.8; P <.0001). The one-year overall survival (OS) was increased by 5% with platinum-based regimens (34% versus 29%; OR, 1.21; 95% CI, 1.09 to 1.35; P =.0003).[1] However, no statistically significant increase in one-year survival was found when platinum therapies were compared to 3G –based combination regimens (OR, 1.11; 95% CI, 0.96 to 1.28; P = .17).[1] The toxicity of platinum-based regimens was significantly higher for hematologic toxicity,nephrotoxicity, and nausea and vomiting, but not for neurotoxicity, febrile neutropaenia rate,or toxic death rate.[1]

Rajeswaran et al also evaluated this question in a meta-analysis of 4920 patients from 17 RCTs.[2] Platinum based doublet regimens were associated with a slightly higher one-year survival (RR = 1.08, 95% CI 1.01—1.16, p = 0.03), a greater response rate (RR = 1.11, 95% CI 1.02—1.21, p = 0.02), but with a higher risk of anaemia, nausea, and neurotoxicity.[2] Cisplatin-based doublet regimens improved one-year survival (RR = 1.16, 95% CI 1.06-1.27, p = 0.001), complete response. (RR = 2.29, 95% CI 1.08-4.88, p = 0.03), and partial response (RR = 1.19, 95% CI 1.07-1.32, p = 0.002), but with an increased risk of anaemia, neutropaenia, neurotoxicity and nausea.[2] Conversely, carboplatin based doublet regimens did not increase one-year survival (RR = 0.95, 95% CI 0.85—1.07,p = 0.43). However, although carboplatin-based doublet regimens were associated with higher risk of anaemia and thrombocytopaenia, there was no increased nausea and/or vomiting.[2]

Li et al compared the activity, efficacy, and toxicity of gemcitabine plus paclitaxel versus carboplatin plus either gemcitabine or paclitaxel in 2186 patients with untreated advanced NSCLC from four RCTSs.[3] A significant difference in RR favouring gemcitabine plus paclitaxel over carboplatin-based doublets was observed [OR = 1.20; 95% CI 1.02–1.42; P = 0.03], whereas the trend toward an improved one-year OS was not significant (OR = 1.07; 95% CI = 0.91–1.26; P = 0.41).[3] An increased risk of grade 3/4 toxicities for patients receiving carboplatin-based chemotherapy was demonstrated.[3]

What is the optimal duration of first-line chemotherapy for treatment of stage IV inoperable NSCLC?

## Evidence summary and recommendations

| Evidence summary | Level | References |
|---|---|---|
| Extending the duration of first-line combination chemotherapy beyond four cycles of chemotherapy, in non-progressive patients, improves progression free survival but not overall survival, and at the expense of increased toxicity and potentially reduced quality of life.<br>Last reviewed September 2017 | I | [2], [1] |

| + Evidence-based recommendation? | Grade |
|---|---|
| First-line combination chemotherapy should in most cases be stopped at disease progression or after four cycles in patients with advanced NSCLC.<br>Last reviewed September 2017 | B |

### ✓ Practice point?

The duration of first-line chemotherapy in a given patient in practice may be based on the benefit being obtained in terms of tumour response, the desire to delay tumour progression and improve or maintain quality of life balanced against treatment toxicity. In practice maximum benefit from first-line chemotherapy has usually been obtained by four cycles of treatment.
Last reviewed September 2017

By convention, many clinical trials evaluating chemotherapy in stage IV NSCLC capped treatment to a maximum of six cycles, often being limited due to toxicity. Efficacy assessments usually occurred after the second or third chemotherapy cycle at six to eight weekly intervals. Although several small randomised controlled trials (RCTs) have been conducted addressing the question of duration of treatment, there is a great deal of heterogeneity in the design of these studies in terms of the treatment regimens used, the scheduling and duration of chemotherapy being explored. Two systematic reviews have attempted to address the optimal duration of chemotherapy [1][2].

The study by Soon et al was designed to determine the effects of extending chemotherapy beyond a standard number of cycles. It evaluated 3,027 patients from 13 RCTs comparing a defined number of cycles with continuation of the same chemotherapy until disease progression, a larger defined number of cycles of identical chemotherapy, RCTs comparing a defined number of cycles of identical initial chemotherapy followed by additional cycles of an alternative chemotherapy.[1]

The key findings were that extending chemotherapy appeared to significantly improve progression free survival (PFS; HR0.75; 95% CI: 0.69 -0.81; p < .00001) whereas the effect on overall survival (OS) was modest and less certain (HR, 0.92; 95% CI: 0.86 - 0.99; P < .03).[1] Subgroup analysis revealed that the effects on PFS were greater for trials extending chemotherapy with 3G regimens rather than older regimens (P < .003).[1] Extending chemotherapy was associated with more frequent adverse events in all trials where it was reported and impaired health related quality of life (QOL) in two of seven trials.[1]

The study by Lima et al was designed to determine the effects of continuing first-line chemotherapy. It evaluated 1559 patients from seven RCTs (included in the Soon meta-analysis) comparing different durations of first-line treatment of advanced NSCLC[2]. Treatment for more than four cycles was not associated with a decrease in mortality relative to shorter treatment (HR = 0.97; 95% CI = 0.84 - 1.11; P = 0.65)[2]. Patients receiving more chemotherapy had significant longer progression-free survival (HR = .75; 95% CI = 0.60 – 0.85; P < 0.0001) than the group with shorter duration of treatment, but there was no difference in response rate (RR) and longer treatment was associated with more severe leucopaenia, although non-haematological toxicities were not significantly increased[2].

The study by Lima et al more closely addressed the question of duration of first line chemotherapy, whereas the study by Soon et al, focused on whether more chemotherapy is better than a fixed amount. It, however, contains a more

heterogeneous mix of studies with a greater variety of regimens, including regimens not in use (involving alkylating agents). However, the overall study findings are not changed with the inclusion of these individual studies[1]. Both studies agree in the finding that PFS is prolonged with longer chemotherapy however, a consistent improvement in overall survival was not observed. Given the toxicity associated with standard first-line chemotherapy, it appears reasonable to stop after four cycles of treatment. Continuing the same first line treatment beyond this should be individually based and consider the evidence for continuation or switch maintenance therapy discussed in detail in the section below.

## Is chemotherapy with a biologic or targeted therapy superior to chemotherapy alone in unselected patients for treatment of stage IV inoperable NSCLC?

| Evidence summary | Level | References |
|---|---|---|
| In carefully selected^ patients with advanced NSCLC, high dose bevacizumab improves tumour response rate and progression free survival.<br>^Patients with the following criteria were excluded from the trials: SCC histologic type, brain metastases, clinically significant haemoptysis, tumours invading or abutting major blood vessels, inadequate organ function, ECOG PS of 1, therapeutic anticoagulation, clinically significant cardiovascular disease, or medically uncontrolled hypertension.<br>Last reviewed September 2017 | I | [4], [5] |
| In carefully selected** patients with advanced NSCLC, treatment with high dose bevacizumab is associated with an increase in treatment related deaths.<br>Last reviewed September 2017 | I | [4] |

| + Evidence-based recommendation? | Grade |
|---|---|
| High dose bevacizumab (15 mg/kg three-weekly) may be considered in addition to chemotherapy (carboplatin/paclitaxel or cisplatin/gemcitabine) in carefully selected** patients with non-squamous cell carcinoma.<br>Last reviewed December 2015 | B |

| Evidence summary | Level | References |
|---|---|---|
| The addition of the EGFR TKIs gefitinib or erlotinib to a standard chemotherapy regimen does not improve outcomes (OS, RR or time to progression (TTP)) compared with chemotherapy alone.<br>Last reviewed September 2017 | II | [8], [9], [11], [10] |

| + Evidence-based recommendation? | Grade |
|---|---|
| The first generation EGFR TKIs gefitinib or erlotinib should not be used in unselected patients in combination with standard chemotherapy.<br>Last reviewed September 2017 | A |

| Evidence summary | Level | References |
|---|---|---|
| In patients with advanced NSCLC (selected by the presence of EGFR-positive tumour as measured by immunohistochemistry), the addition of cetuximab to chemotherapy increases response rate and improves overall survival. This overall benefit was modest and observed only in the phase III trial using cisplatin/vinorelbine .<br>Last reviewed September 2017 | I | [12], [13] |

| + Evidence-based recommendation? | Grade |
|---|---|
| In patients with advanced NSCLC whose tumours have been shown to express EGFR by immunohistochemistry, cetuximab may be considered in addition to cisplatin/vinorelbine chemotherapy to improve response rate and overall survival.<br>Last reviewed September 2017 | B |

| Evidence summary | Level | References |
|---|---|---|
| In patients with stage IV squamous carcinoma, necitumumab improves overall survival at the cost of increased toxicity when added to cisplatin and gemcitabine.<br>Last reviewed September 2017 | II | [16] |

| + Evidence-based recommendation? | Grade |
|---|---|
| In patients with stage IV squamous carcinoma, necitumumab may be considered in addition to cisplatin and gemcitabine, to improve overall survival.<br>Last reviewed September 2017 | B |

There have been two phase III and one phase II RCT of chemotherapy +/- bevacizumab as first-line therapy in patients with stage IV NSCLC.[1][2][3] The first study, a randomised phase II study by Johnston et al showed promising activity with bevacizumab but found an unexpectedly high incidence of pulmonary haemorrhage in patients with SCC.[3] The study by Sandler et al examined carboplatin and paclitaxel +/- bevacizumab, whilst the study by Reck et al examined cisplatin and gemcitabine +/- bevacizumab.[1][2] Consequently both subsequent PIII studies excluded patients with the following: SCC histologic type, brain metastases, clinically significant hemoptysis,inadequate organ function, ECOG PS of 1, therapeutic anticoagulation, clinically significant cardiovascular disease, tumours invading or abutting major blood vessels or medically uncontrolled hypertension. The overall safety and efficacy of chemotherapy and bevacizumab has been summarised in a meta-analysis of four trials with 2101 patients by Yang et al.[4] Bevacizumab has been studies at high dose (HD: 15 mg/kg) or low dose (LD: 7.5 mg/kg) every three weeks with chemotherapy.

Yang et al found that neither HD or LD bevacizumab improved one-year survival when added to chemotherapy.[4] However, the addition of HD bevacizumab increased two-year overall survival (OS) (RR 1.24; 95% CI 1.04 – 1.49) and tumour response rate (RR 1.69; 95% CI 1.21-2.35).[4] However in an independent systematic review by Botrel et al, although an OS benefit was observed with HD bevacizumab (HR 0.89, 95% CI 0.8 – 1.0, p =0.04), there was moderate statistical heterogeneity (Chi2 = 5.09, 3df, p = 017; I2 = 41%), making this finding less certain. Progression free survival (PFS) was improved with both LD bevacizumab (HR 0.76; 95%; CI 0.64-0.90) and HD bevacizumab (HR 0.73; 95%CI 0.65-0.81).[4][5] However, HD bevacizumab was associated with an increase in treatment related deaths (RR 2.07, 95%; CI 1.19-3.59). Patients treated with HD bevacizumab experienced more hypertension, headaches, haemoptysis, neutropaenia and rash than patients on chemotherapy alone.[4] In the phase III trials bevacizumab was continued if tolerated until disease progression.

In the 2nd line setting, Garon et al found that ramucirumab + docetaxel improved overall survival compared to docetaxel + placebo in patients with stage IV NSCLC.[6] However, only 14-15% of patients in this study had previously received bevacizumab, limiting the applicability of the results.

With regard to the small molecule TKIs, Scagliotti et al reported the outcomes of their phase III RCT evaluating the efficacy and safety of sorafenib, in combination with carboplatin and paclitaxel in chemotherapy-naïve patients.[7] The study was

terminated after the interim analysis concluded that the study was highly unlikely to meet its primary end point for OS. A pre-specified exploratory analysis revealed that patients with squamous cell histology had greater mortality in arm A than in arm B (HR 1.85; 95%; CI 1.22 to 2.81).

Chemotherapy and anti-EGFR TKIs

Following the discovery of the first generation EGFR TKIs gefitinib and erlotinib, four first-line placebo controlled RCTS were undertaken, evaluating the efficacy of the addition of these agents to two commonly used chemotherapy regimens (carboplatin/paclitaxel and cisplatin/gemcitabine)[8][9][10][11] In all four trials the addition of the EGFR TKIs, gefitinib or erlotinib to a standard chemotherapy regimen did not improve outcomes (OS, RR or time to progression (TTP) compared with chemotherapy alone.

Chemotherapy and anti-EGFR with the Mab cetuximab

The first monoclonal antibody to EGFR to enter the clinic was cetuximab. Two meta-analyses have summarised the evidence for the addition of cetuximab to standard chemotherapy, from four RCTs with 2018 patients with advanced NSCLC (selected by the presence of EGFR-positive tumor as measured by immunohistochemistry (IHC), two of which were phase III RCTs.[12][13][14][15] Both meta-analsyses concur in finding that overall survival was improved by the addition of cetuximab to chemotherapy (HR 0.87; 95%CI, 0.79–0.96; p = 0.004)[13] and overall response rate was increased (50% increase (odds ratio (OR) = 1.48; (CI = 1.22–1.80); p < 0.0001). PFS whilst improved with the addition of cetuximab to chemotherapy was not significantly better than chemotherapy alone (HR, 0.91; 95%CI, 0.83–1.00; p = 0.06).[12][13] Of the two Phase III trials, only the Pirker study which added cetuximab to cisplatin/vinoerlbine was positive for survival, whilst the Lynch study, which added cetuximab to carboplatin/paclitaxel showed improved RR but not PFS or OS.[14][15] The addition of cetuximab was associated with increased grade 3/4 rash and infusion reactions.[12][13] In the phase III trials cetuximab was continued if tolerated until disease progression.

## What is the optimal chemotherapy regimen for overall quality of life for patients in the treatment of stage IV inoperable NSCLC?

✓ Practice point?

As overall quality of life does not seem to differ across the different chemotherapy regimens, the choice of chemotherapy in an individual patient may involve discussion regarding expected toxicities and the patient's preferences.

Last reviewed September 2017

Many of the aforementioned clinical trials have formally included patient rated QOL evaluation usually as a secondary endpoint. The overall effect of common chemotherapy regimens on health related QOL in NSCLC is probably best summarised in the meta-analysis by Tanvetyanon et al.[1] This study identified 14 RCTs from 1998 – 2005 with 6665 patients to determine differences in QOL between the regimens studies. Of these, 13 trials using a validated QOL instrument were included for review. The meta-analsysis found QOL reporting/analysis techniques were heterogeneous. Nine RCTs reported the rate of completedbaseline assessment and compliance survivors at analysis of greaterthan 50%, for data synthesis.[1] Of these, only one trial found a significant difference in QOL between the comparator arms: paclitaxelplus cisplatin was better than teniposide plus cisplatin. However, teniposide is not used in practice today. Based on this review, it seems unlikely that a major difference exists in the global QOL associated with standard chemotherapy regimens for advanced NSCLC.[1] Furthermore, the authors concluded that although the available QOL reporting formats are largely acceptable, a lack of uniformity in analysis and a poor compliance to QOL assessment made between-trial comparisons difficult.[1]

A large single RCT of 926 patients (not included in the Tanvetyanon meta-analysis[1]) comparing docetaxel and cisplatin (DC) or carboplatin (DCb) with cisplatin /vinorelbine (VC) also examined QOL using the Lung Cancer Symptom Scale (LCSS) and the general EuroQol five-dimensional questionnaire (EQ-5D).[2] DCband DC were superior to VC in the QoL outcomes assessed except for the difference between DC and VC in LCSS ''QOL today'', which was not significant.[2]

There does not appear to be any major difference evident in the global quality of life associated with standard chemotherapy regimens for advanced NSCLC.[1]

What is the optimal systemic therapy regimen for patients with poor performance status of stage IV inoperable NSCLC?

| Evidence summary | Level | References |
|---|---|---|
| In patients with poor performance status (PS 2), first-line monotherapy with 3G chemotherapy (vinorelbine, gemcitabine, paclitaxel or docetaxel) may improve survival and/or quality of life.<br>Last reviewed September 2017 | I, II | [3], [4], [5], [6], [7], [2] |

| + Evidence-based recommendation? | Grade |
|---|---|
| First-line monotherapy with 3G chemotherapy could be offered to selected patients with PS2 for symptom improvement and possible survival gain, who are willing to accept treatment toxicity.<br>Last reviewed September 2017 | B |

| Evidence summary | Level | References |
|---|---|---|
| There is evidence for benefit with erlotinib 150 mg daily as second or third-line therapy in unselected poor performance status patients (PS2 or 3) .<br>Last reviewed September 2017 | II | [8] |

| + Evidence-based recommendation? | Grade |
|---|---|
| Poor performance status patients having received 1 or 2 lines of prior therapy, may be offered erlotinib 150 mg daily.<br>Last reviewed September 2017 | B |

| ✓ Practice point? |
|---|
| Decision-making on treatment in poor performance status patients may weigh up benefits against toxicity and patient preferences. Whilst a single agent 3G chemotherapy is an option in unselected patients, patients with known activating EGFR MTs should be considered for first line EGFR TKIs as the magnitude of benefit is greater and toxicity profile more favourable.<br>Last reviewed September 2017 |

Most studies with cytotoxic chemotherapy have been evaluated in “fit” patients, predominantly with PS 0 or 1. Patients with PS 2 are generally considered a poor prognostic group and at higher risk of toxicity, particularly from cytotoxic chemotherapy. Attempts to improve outcomes in this poor performance group population (PS 2) of patients with advanced NSCLC have been challenging with trials focused on the use of less toxic regimes or monotherapy with 3G agents or anti-EGFR TKIs.

Liu et al undertook a systematic review of phase II and II studies to examine the safety and efficacy of EGFR TKI monotherapy versus single-agent chemotherapy using third-generation cytotoxics as first-line treatment for patients with advanced non-small cell lung cancer and poor performance status.[1] No randomised controlled trials (RCTs) were identified. Fifteen single arm phase II studies (1425 patients) were evaluated to determine pooled estimates for RR and safety. The pooled RR (95% CI) to EGFR TKIs for unselected populations was 6% (3–8%), which compares with 9% (6–13%) reported by single-agent 3G chemotherapy trials. By summary comparison only, toxicity profiles were more favourable for the EGFR TKIs than chemotherapy. This study confirms the feasibility of treatment in the poor PS population but does not provide information on the overall benefit of such treatment.

Baggstrom et al reported a meta-analysis of five trials (n =1029 patients) compared 3G single agents with BSC. Four of the trials included a BSC control arm, and one trial included 5-fluorouracil (5FU)/ leucovorin as the control arm.[2] Response rates for the 3G agents ranged from 12% to 20%. One-year survival favored the 3G agents over BSC with risk difference of 7% (95% CI: 2% to 12%).[2] The number needed to treat for one patient to realise a benefit in the probability of one-year survival was 14.[2] These five trials evaluated single agent vinorelbine, paclitaxel, docetaxel and gemcitabine.[3][4][5][6][7] The study by Crawford et al of single agent vinorelbine included 50% of patients with low PS, the vinoerlbine study by Gridelli et al in patients over 70 included 24% of patients with PS 2, the paclitaxel study by Ranson et al included 15% PS 2 patients, the docetaxel study by Roszkowski et al, included 20% PS 2 patients whilst the gemcitabine study by Anderson et al was mainly in low PS patients.[3][4][5][6][7] The study by Anderson et al of gemcitabine versus best supportive care evaluated QOL as its primary endpoint and confirmed better QOL and reduced disease-related symptoms compared with those receiving best supportive care alone, although breathlessness was least well palliated and OS was no different.[5] Quality of life was also in favour of paclitaxel, docetaxel and vinorelbine (versus best supportive care) in the respective studies.[4][6][7]

In the second-line setting, several of the key RCTs that evaluated the efficacy of EGFR TKIs have included PS 2 or greater patients.[8][9][10] Both the placebo controlled trials of gefitinib and erlotinib enrolled > 30 % of patients with PS 2, whilst the study by Kim et al comparing gefitinib to docetaxel included 11% of PS 2 patients. In the BR21 study, analysis of benefit by the PS 2 and 3 subgroups that received erlotinib versus placebo demonstrated a benefit in OS (HR 0.8; 95% CI 05-1.1 (PS 2); 0.4-1.3 (PS 3)), which compares with OS HR 0.7 for the overall population. (0.6-0.9).[8] Thatcher et al, demonstrated the direction of benefit to be in favour of gefitinib over placebo in the OS analysis by sub-populations (30% of patients with PS2).[9]. In the small PS2 sub-population in the study by Kim et al comparing gefitinib with docetaxel, the direction of benefit favoured gefitinib but the confidence limits were wide.[10] Overall. confident conclusions cannot be made for benefit from gefitinib in unselected PS 2 or more patients. However, given the magnitude of benefit observed with gefitinib in first line patients with activating EGFR gene mutations (GMT+, ,described in the section below)[11], it would be reasonable to expect that EGFR GMT + "selected" patients may still potentially benefit from an EGFR TKI , even if of poor performance status, given the size of the observed benefit and relatively low toxicity.

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**Passiglia F et al., 2020 [40].**

*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 [10]

LoE/GoR

- GRADE

The global quality of evidence was defined as follow:

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

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

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

## Recommendations

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 |
| Moderate | For patients with advanced NSCLC who experienced disease progression after first-line chemotherapy, immunotherapy with nivolumab, or atezolizumab, or pembrolizumab (PD-L1 TPS ≥ 1 %), should be considered as a treatment of choice | Strong for |
| Very low | For patients with advanced lung adenocarcinoma who experienced disease progression after first-line chemotherapy, the combination of nintedanib plus docetaxel could be considered as a treatment option. | Conditional for |

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

| | | |
|---|---|---|
| Very low | For patients with metastatic NSCLC harboring *ROS1* rearrangements, first-line therapy with crizotinib should be considered as treatment of choice. | Strong for |

# 4 Detaillierte Darstellung der Recherchestrategie

**Cochrane Library - Cochrane Database of Systematic Reviews (Issue 5 of 12, May 2020) am 15.05.2020**

| # | Suchfrage |
|---|---|
| 1 | [mh “Carcinoma, Non-Small-Cell Lung”] |
| 2 | (((non NEXT small) OR nonsmall) NEXT cell NEXT lung):ti,ab,kw |
| 3 | (cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesions*):ti,ab,kw |
| 4 | (advanced OR metastat* OR metastas* OR recurren* OR relaps*):ti,ab,kw |
| 5 | {AND #2, #3, #4} |
| 6 | nsclc*:ti,ab,kw |
| 7 | {OR #1, #5, #6} |
| 8 | #7 with Cochrane Library publication date from May 2015 to present |

**Systematic Reviews in Medline (PubMed) am 15.05.2020**

| # | 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 neoplasm*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesions*[tiab] |
| 4 | (#2 AND #3) OR #1 |
| 5 | (#4) AND ((((advanced[tiab]) OR metastat*[tiab]) OR metastas*[tiab]) OR recurren*[tiab] or relaps*[tiab]) |
| 6 | (#5) 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 studies[pt] OR validation studies[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 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 |

| # | Suchfrage |
|---|---|
| | 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])))))) |
| 7 | ((#6) AND ("2015/05/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp])) |

**Leitlinien in Medline (PubMed) am 15.05.2020**

| # | **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 neoplasm*[Tiab]) OR sarcoma*[Tiab]) OR cancer*[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])* |
| 10 | (((#9) AND ("2015/05/01"[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])) |

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# Anhang

| Level | Intervention | Diagnosis | Prognosis | Aetiology | Screening |
|---|---|---|---|---|---|
| I | A systematic review of level II studies | A systematic review of level II studies | A systematic review of level II studies | A systematic review of level II studies | A systematic review of level II studies |
| II | A randomised controlled trial | A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation | A prospective cohort study | A prospective cohort study | A randomised controlled trial |
| III-1 | A pseudo-randomised controlled trial (i.e. alternate allocation or some other method) | A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation | All or none | All or none | A pseudo-randomised controlled trial (i.e. alternate allocation or some other method) |
| III-2 | A comparative study with concurrent controls:<br>• Non-randomised, experimental trial<br>• Cohort study<br>• Case-control study<br>• Interrupted time series with a control group | A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence | Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial | A retrospective cohort study | A comparative study with concurrent controls:<br>• Non-randomised, experimental trial<br>• Cohort study<br>• Case-control study |
| III-3 | A comparative study without concurrent controls:<br>• Historical control study<br>• Two or more single arm study<br>• Interrupted time series without a parallel control group | Diagnostic case-control study | A retrospective cohort study | A case-control study | A comparative study without concurrent controls:<br>• Historical control study<br>• Two or more single arm study |
| IV | Case series with either post-test or pre-test/post-test outcomes | Study of diagnostic yield (no reference standard) | Case series, or cohort study of patients at different stages of disease | A cross-sectional study | Case series |

*Abbildung 2: NHMRC Evidence Hierarchy (Australian Government Cancer Council Australia)*

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

**2020-B-134**

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Indikation gemäß Beratungsantrag

Erstlinienbehandlung des metastasierten nicht-kleinzelligen Lungenkarzinoms (NSCLC) ohne EGFR- oder ALK-positive Tumormutationen bei Erwachsenen

**Was ist der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz bei der Erstlinienbehandlung des metastasierten, nicht-kleinzelligen Lungenkarzinoms (NSCLC) ohne EGFR- oder ALK-positive Tumormutationen bei Erwachsenen? Wie sieht die Versorgungspraxis in Deutschland aus?**

Zusammenfassung

Standard in der Erstlinientherapie von Patienten mit zuvor unbehandeltem, lokal fortgeschrittenem, inoperablem oder metastasierten, nichtkleinzelligem Lungenkarzinom (NSCLC) ist die systemische Therapie, als

- gezielte Therapie bei Nachweis prädiktiver genetischer Aberrationen (Treibermutationen)
- Immunchemo- oder Immuntherapie bei Fehlen prädiktiver genetischer Aberrationen

Bei Patienten ohne Nachweis einer aktivierenden, genetischen Aberration besteht der Standard in der Kombination eines PD-1- oder PD-L1-Immuncheckpoint-Inhibitors mit platinhaltiger Chemotherapie über 4-6 Zyklen, gefolgt von einer Erhaltungstherapie mit dem Immuncheckpoint-Inhibitor. Beim Einsatz der optimalen Chemotherapie wird nach der Histologie, d. h. zwischen Plattenepithel- und Nichtplattenepithelkarzinom differenziert. Bei Nachweis einer hohen Expression von PD-L1 ($\geq$50%) kann die Therapie allein mit einem Immuncheckpoint-Inhibitor durchgeführt werden. Bei Kontraindikationen gegen eine Immuntherapie wird eine platinhaltige Chemotherapie empfohlen.

Die Empfehlung zur gezielten Therapie bei Nachweis prädiktiver genetischer Aberrationen bezieht sich nicht nur auf *EGFR* und *ALK*. Auch bei Patienten mit aktivierenden Aberrationen von *BRAF V600*, *ROS1* und *NTRK* wird eine gezielte Erstlinientherapie eingesetzt, jeweils in Abwägung gegenüber den anderen zugelassenen Therapieoptionen.

Behandlungsstandard als Basis der vergleichenden Bewertung eines neuen Arzneimittels in der Erstlinientherapie des metastasierten, nicht-kleinzelligen Lungenkarzinoms (NSCLC) ohne EGFR- oder ALK-positive Tumormutationen ist die Kombination aus einem Immuncheckpoint-Inhibitor und platinhaltiger Chemotherapie, bei Patienten mit hoher PD-L1-Expression auch die Monotherapie mit einem Immuncheckpoint-Inhibitor.

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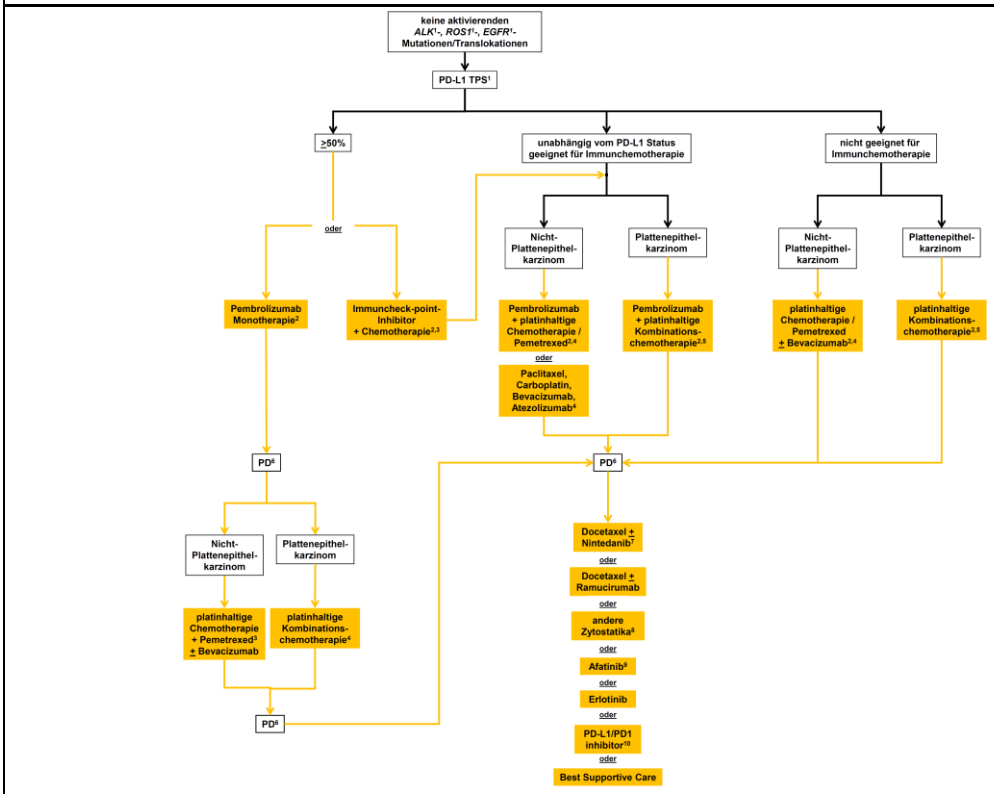
Indikation gemäß Beratungsantrag

Erstlinienbehandlung des metastasierten nicht-kleinzelligen Lungenkarzinoms (NSCLC) ohne EGFR- oder ALK-positive Tumormutationen bei Erwachsenen

Stand des Wissens

35 – 40 % der Patienten mit nicht-kleinzelligem Lungenkarzinom werden im Stadium IV diagnostiziert. Bei der Mehrzahl der Patienten ist der Therapieanspruch palliativ [1, 2, 3]. Ausnahme sind Patienten im neu definierten Stadium M1b, z. B. mit solitären Nebennieren-, ZNS-, Lungen-, Leber- oder Knochenmetastasen, bei denen ein potenziell kurativer Therapieansatz in Frage kommt. Bei Patienten mit multiplen Metastasen ist das Therapieziel palliativ. Die mediane Überlebenszeit lag noch vor wenigen Jahren zwischen 8 und 12 Monaten. Die aktuellen Therapie-Empfehlungen basieren auf prädiktiven histologischen, immunhistochemischen und genetischen Markern. Ein Algorithmus für die Erstlinientherapie bei Patienten ohne prädiktive Treibermutation ist in Abbildung 1 dargestellt.

***Abbildung 2: Algorithmus für die nicht-molekular stratifizierte medikamentöse Therapie in fortgeschrittenen Stadien***



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Pneumologisch-Onkologische Arbeitsgemeinschaft der Deutschen Krebsgesellschaft (POA)

Indikation gemäß Beratungsantrag

Erstlinienbehandlung des metastasierten nicht-kleinzelligen Lungenkarzinoms (NSCLC) ohne EGFR- oder ALK-positive Tumormutationen bei Erwachsenen

Legende: ; [1]PD-L1 TPS - Expression von PD-L1 auf Tumorzellen, quantifiziert nach dem Tumor Progression Score (TPS); [2] wenn für Immuntherapie geeignet und keine relevanten Kontraindikationen bestehen; [3] Kombination aus einem Anti-PD1 Antikörper und Chemotherapie, differenziert nach der Histologie; [4] Kombination aus Cis- oder Carboplatin mit Pemetrexed; [5] Kombination von Carboplatin mit Paclitaxel oder nabPaclitaxel; [6] CR – komplette Remission, PR – partielle Remission, SD – stabile Erkrankung, PD – progrediente Erkrankung; [7] Nintedanib nur bei Adenokarzinom; [8] Zytostatikum der 3. Generation: Gemcitabin, Pemetrexed, Vinorelbin; Pemetrexed nur bei Nicht-Plattenepithelkarzinom; [9] Afatinib nur bei Plattenepithelkarzinom; [10] PD-1/PD-L1 Inhibitor: Azetolizumab, Nivolumab, Pembrolizumab (TPS ≥1%); der Nachweis der Wirksamkeit ist nicht geführt bei Patienten, die in der Erstlinientherapie mit einem Immuncheckpoint-Inhibitor vorbehandelt sind; [11] PD-1/PD-L1 Inhibitor: Azetolizumab, Nivolumab, Pembrolizumab (TPS ≥1%);

Die Therapieindikation richtet sich nach dem Allgemeinzustand, der Vorbehandlung, der Symptomatik, spezifischer Komorbidität und der Patientenpräferenz. Die Auswahl der Substanzen wird bestimmt durch die histologische Klassifikation des Tumors, molekularpathologische Alterationen (molekular-stratifizierte Therapie) und den Grad der PD-L1-Expression auf den Tumorzellen. Das Wissen um die therapeutischen Optionen ermöglicht ein optimales Patientenmanagement.

Bei Patienten ohne genetische Aberrationen, für die zielgerichtete Arzneimittel zugelassen sind, gelten folgende Empfehlungen:

- Expression des Immunmarkers PD-L1 auf ≥50% der Tumorzellen
    - Die Monotherapie mit dem Anti-PD1-Antikörper Pembrolizumab führt gegenüber platinhaltiger Chemotherapie zur Verlängerung der Gesamtüberlebenszeit (Hazard Ratio 0,63; 30,2 vs 14 Monate), zur Verlängerung des progressionsfreien Überlebens (HR 0,50 Median 4,3 Monate) und zu einer Senkung der Rate schwerer Nebenwirkungen [4, 5]. Daten eines Vergleichs von Pembrolizumab Monotherapie gegenüber Pembrolizumab + Kombinationschemotherapie liegen bisher nicht vor.
    - Die Kombination eines Immuncheckpoint-Inhibitors mit Chemotherapie ist eine Alternative, siehe unten. Bei Patienten mit nicht-plattenepithelialer Histologie war die Kombinationstherapie der Monotherapie im indirekten Vergleich in Bezug auf die Gesamtüberlebenszeit überlegen. Bei Patienten mit plattenepithelialer Histologie waren die Kombinations- und die Monotherapie im indirekten Vergleich in Bezug auf die Gesamtüberlebenszeit etwa gleichwertig. Die Zahl der Patienten mit plattenepithelialer Histologie in der Zulassungsstudie zur Pembrolizumab-Monotherapie war niedrig. Patienten mit einer hohen Tumorlast und einem hohen Remissionsdruck könnten besonders von einer Kombinationstherapie profitieren.
- unabhängig von der PD-L1 Expression auf den Tumorzellen
    - Bei Nicht-Plattenepithelkarzinomen führt die Kombination von Pembrolizumab mit

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Chemotherapie (Platin/Pemetrexed) gegenüber Chemotherapie zur Verlängerung der Gesamtüberlebenszeit (HR 0,56; Median 11,3 Monate) und zur Verlängerung des progressionsfreien Überlebens (HR 0,48; Median 3,9 Monate) [6]. Der relative Gewinn durch Pembrolizumab steigt mit dem Grad der PD-L1-Expression, ist aber auch in der Gruppe der PD-L1 negativen Patienten signifikant in Bezug auf die Gesamtüberlebenszeit (HR 0,52).

- Bei Nicht-Plattenepithelkarzinomen führt die Kombination von Atezolizumab mit Carboplatin / Paclitaxel / Bevacizumab (BCP): gegenüber BCP zur Verlängerung der Gesamtüberlebenszeit (HR 0,78; Median 5,5 Monate) und des progressionsfreien Überlebens (HR 0,62; Median 1,5 Monate) [7, 8].
- Bei Plattenepithelkarzinomen wird durch die Kombination von Pembrolizumab mit Chemotherapie (Platin/Paclitaxel) gegenüber Chemotherapie eine Verlängerung der Gesamtüberlebenszeit (HR 0,63; Median 4,6 Monate) und des progressionsfreien Überlebens (HR 0,56; Median 1,6 Monate) erreicht [9].

- Bei Entscheidung für eine ausschließliche Chemotherapie ist die Kombinationschemotherapie mit zwei Zytostatika wirksamer als Monotherapie in Bezug auf die Remissionsrate, die progressionsfreie und die Gesamtüberlebenszeit. Kombinationen sind mit einer höheren Therapie-assoziierten Toxizität belastet. Die meisten Erfahrungen liegen mit platinhaltigen Kombinationen vor. Mit Cisplatin werden signifikant höhere Remissionsraten als mit Carboplatin erreicht. In Bezug auf die Gesamtüberlebenszeit sind die beiden Platinderivate äquieffektiv [10]. Die Wahl orientiert sich vor allem an der beim individuellen Patienten zu erwartenden Toxizität. Nicht-platinhaltige Kombinationen haben niedrigere Remissionsraten als platinhaltige Kombinationen.
- Bei stabiler Erkrankung (Stable Disease) sollte die platinhaltige Erstlinientherapie nach 4 Zyklen beendet werden. Bei Ansprechen sollten Kombinationstherapien nach 4-6 Zyklen beendet werden.
- Bei mindestens stabiler Erkrankung kann die Therapie mit Einzelsubstanzen fortgesetzt werden. In einigen randomisierten Studien wurde die Überlebenszeit im Vergleich zu Kontrollen signifikant verlängert. Optionen sind [1, 2, 3]
  - Pemetrexed bei Nicht-Plattenepithelkarzinom
  - TPS $\geq$50%: Pembrolizumab – Monotherapie alle 3 Wochen; in der Zulassungsstudie wurde Pembrolizumab bis zu 35 Zyklen gegeben
  - TPS <50% und Nicht-Plattenepithelkarzinom: Pembrolizumab + Pemetrexed alle 3 Wochen im Anschluss an die Kombinations-Immunchemotherapie; in der Zulassungsstudie wurde Pembrolizumab bis zu 35 Zyklen gegeben.

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**Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Erstlinienbehandlung des metastasierten nicht-kleinzelligen Lungenkarzinoms (NSCLC) ohne EGFR- oder ALK-positive Tumormutationen bei Erwachsenen die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

Ja

- Bei Patienten in sehr reduziertem Allgemeinzustand, vor allem aufgrund von Komorbidität, wird die Therapieintensität angepasst oder als Best Supportive Care durchgeführt.
- Bei Patienten mit einer solitären Organmetastase oder bis zu 3 solitären ZNS Metastasen (oligometastasierte Erkrankung) kann ein Therapiekonzept mit einem potentiell kurativen Ansatz angeboten werden [2, 3]. Hier wird ein multimodales Therapiekonzept empfohlen. Dieses kann eine systemische Induktionstherapie entsprechend dem o. a. Vorgehen enthalten, gefolgt von einer optimalen, organbezogenen Lokaltherapie.
- Bei der Immuntherapie wird nach dem Grad der PD-L1 Expression differenziert, siehe oben.
- Bei der Chemotherapie wird nach der Histologie differenziert (Pemetrexed beim Nicht-Plattenepithelkarzinom)

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