Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2020-B-020 Atezolizumab

Stand: März 2020

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

Atezolizumab
[Erstlinienbehandlung des metastasierten NSCLC]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“. Nicht berücksichtigt wurden Arzneimittel mit expliziter Zulassung für das NSCLC mit EGFR-Mutation sowie ALK-Mutation/ Amplifikation
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:** • Pembrolizumab (NSCLC, nicht-plattenepithelial, Kombination mit Pemetrexed und Platin-Chemotherapie): Beschluss vom 19. September 2019 • Pembrolizumab (NSCLC, plattenepithelial, Kombination mit Carboplatin und (nab-) Paclitaxel): Beschluss vom 19. September 2019 • Dabrafenib (NSCLC mit BRAF-V600-Mutation): Beschluss vom 19. Oktober 2017 • Trametinib (NSCLC mit BRAF-V600-Mutation): Beschluss vom 19. Oktober 2017 • Pembrolizumab (NSCLC, PD-L1 Expression: TPS ≥ 50 %): Beschluss vom 03. August 2017 • Necitumumab (EGFR-exprimierendes NSCLC): Beschluss vom 15. September 2016 • Crizotinib (ROS1-positives NSCLC): Beschluss vom 16. März 2017 **Richtlinien:** Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie - Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (Off-Label-Use): • Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie (*Beschluss vom 18. Oktober 2018)*.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Atezolizumab	Geplantes Anwendungsgebiet laut Beratungsanforderung: Atezolizumab als Monotherapie wird angewendet zur Erstlinienbehandlung von erwachsenen Patienten mit metastasiertem nicht-kleinzelligen Lungenkarzinom (NSCLC), deren Tumoren eine PD-L1 Expression ≥ 50 % auf Tumorzellen (TC) oder ≥ 10 % auf tumorinfiltrierenden Immunzellen (IC) aufweisen und keine EGFR-Mutation oder ALK-positives NSCLC haben.
Chemotherapien	
Carboplatin L01XA02 generisch	Off-Label-Indikation für Carboplatin: Kombinationstherapie des fortgeschrittenen NSCLC (palliativ)
Cisplatin L01XA01 generisch	Cisplatin wird angewendet zur Behandlung des: • fortgeschrittenen oder metastasierten nichtkleinzelligen Bronchialkarzinoms. Cisplatin kann als Mono- oder Kombinationstherapie angewendet werden. • […]
Docetaxel L01CD02 generisch	Nicht-kleinzelliges Bronchialkarzinom: Docetaxel ist in Kombination mit Cisplatin zur Behandlung von Patienten mit nicht resezierbarem, lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Bronchialkarzinom ohne vorausgegangene Chemotherapie angezeigt.

(Fortsetzung)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Gemcitabin L01BC05 generisch	Gemcitabin ist in Kombination mit Cisplatin als Erstlinientherapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nichtkleinzelligen Bronchialkarzinom (NSCLC) angezeigt. Eine Gemcitabin-Monotherapie kann bei älteren Patienten oder solchen mit einem Performance Status 2 in Betracht gezogen werden.
Ifosfamid L01AA06 Holoxan®	Nicht-kleinzellige Bronchialkarzinome: Zur Einzel- oder Kombinationschemotherapie von Patienten mit inoperablen oder metastasierten Tumoren.
Mitomycin L01DC03 generisch	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Die intravenöse Anwendung von Mitomycin ist in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei Erwachsenen mit folgenden Erkrankungen angezeigt: • nicht-kleinzelliges Bronchialkarzinom • […].
Paclitaxel L01CD01 generisch	Fortgeschrittenes nicht-kleinzelliges Bronchialkarzinom (NSCLC): Paclitaxel ist in Kombination mit Cisplatin angezeigt zur Behandlung des nicht-kleinzelligen Bronchialkarzinoms (NSCLC) bei Patienten, für die eine potentiell kurative chirurgische Maßnahme und/oder Strahlentherapie nicht in Frage kommt. […]
Nab-Paclitaxel L01CD01 Abraxane®	Abraxane ist in Kombination mit Carboplatin indiziert für die Erstlinienbehandlung des nicht-kleinzelligen Bronchialkarzinoms bei erwachsenen Patienten, bei denen keine potentiell kurative Operation und/oder Strahlentherapie möglich ist. […]
Pemetrexed L01BA04 generisch	Nicht-kleinzelliges Lungenkarzinom • 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. • 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. • […]

(Fortsetzung)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Vindesin L01CA03 Eldesine®	Kombinationschemotherapie: Lokal fortgeschrittenes oder metastasiertes nicht-kleinzelliges Bronchialkarzinom (Stadium IIIB, IV).
Vinorelbin L01CA04 Generisch	Behandlung des nicht kleinzelligen Bronchialkarzinoms (Stadium 3 oder 4). […]
Proteinkinase-Inhibitoren	
Crizotinib L01XE16 Xalkori®	Xalkori wird angewendet bei Erwachsenen zur Behandlung des ROS1-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, NSCLC).
Dabrafenib L01XE23 Tafinlar®	Dabrafenib in Kombination mit Trametinib ist angezeigt zur Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligen Lungenkarzinom mit einer BRAF-V600-Mutation.
Trametinib L01XE25 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 L01XC32 Tecentriq®	Tecentriq wird angewendet in Kombination mit Bevacizumab, Paclitaxel und Carboplatin bei erwachsenen Patienten zur Erstlinienbehandlung des metastasierten nichtkleinzelligen Lungenkarzinoms (NSCLC) mit nicht-plattenepithelialer Histologie. 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). 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. […]

(Fortsetzung)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Bevacizumab L01XC07 Avastin®	Bevacizumab wird zusätzlich zu einer platinhaltigen Chemotherapie zur First-Line-Behandlung von erwachsenen Patienten mit inoperablem fortgeschrittenem, metastasiertem oder rezidivierendem nicht-kleinzelligem Bronchialkarzinom, außer bei vorwiegender Plattenepithel-Histologie, angewendet.
Necitumumab L01XC22 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 L01XC18 Keytruda®	KEYTRUDA ist als Monotherapie zur Erstlinienbehandlung des metastasierenden nicht-kleinzelligen Lungenkarzinoms (NSCLC) mit PD-L1 exprimierenden Tumoren (Tumor Proportion Score [TPS] ≥ 50 %) ohne EGFR oder ALK-positive Tumormutationen bei Erwachsenen angezeigt. KEYTRUDA ist in Kombination mit Pemetrexed und Platin-Chemotherapie zur Erstlinienbehandlung des metastasierenden nicht-plattenepithelialen NSCLC ohne EGFR- oder ALK-positive Tumormutationen bei Erwachsenen angezeigt.

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-020 (Atezolizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	5. Februar 2020

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Adverse event
AFA	Afatinib
ALK	Anaplastic Lymphoma Kinase
ALT	Alanin-Aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartat-Aminotransferase
ATEZO	Atezolizumab
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
Bev	Bevacizumab
BSC	Best supportive care
CIS	Cisplatin
CNS	Zentrales Nervensystem/central nervous system
CTX	Cytotoxic Chemotherapy
DAHTA	DAHTA Datenbank
DCR	Disease Control Rate
DOC	Docetaxel
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organisation for QLQ Research and Treatment of Cancer Quality of Life Questionnaire
EPHPP	Effective Public Health Practice Project Tool
ERL	Erlotinib
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
Gem	Gemcitabin
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation

HR	Hazard Ratio
ICI	Immune-Checkpoint Inhibitor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
k.A.	Keine Angaben
KI	Konfidenzintervall
KRAS	Kirsten rat sarcoma oncogene Mutation
LoE	Level of Evidence
M+	mutation positive (EGFR)
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NINTE	Nintedanib
NIVO	Nivolumab
NSCLC	non-small cell lung cancer
NSQ	Non-Squamous
OR	Odds Ratio
ORR	Objective response rate
OS	Overall Survival
PAX	Paclitaxel
PC	paclitaxel and carboplatin
PD-1	anti-programmed cell death receptor 1
PD-L1	antiprogrammed cell death ligand
PEM	Pemetrexed
PEMBRO	Pembrolizumab
PFS	Progression Free Survival
Pt+B	Platinum plus Bevacizumab
QoL	Quality of Life
RCT	Randomized Controlled Trial
RR	Relatives Risiko
SQ	Squamous

SIGN	Scottish Intercollegiate Guidelines Network
TA	Targeted Agent
TKI	Tyrosinkinsaseinhibitor
TPS	Tumor Proportion Score
TRAE	Treatment related adverse event
TRIP	Turn Research into Practice Database
TTP	Time to Progression
VEGFR	Vascular endothelial growth factor receptor
VTE	Venous Thromboembolism
WHO	World Health Organization
WMD	Weighted mean difference.
WT	Wild Type

1 Indikation

Indikation für die Synopse: Erstlinientherapie bei Patienten mit fortgeschrittenem oder metastasierendem NSCLC.

Hinweis: Erhaltungstherapie wurde ebenfalls mit abgebildet.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *nicht-kleinzelligen Lungenkarzinom* durchgeführt. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, 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 Folgerecherche am 12.10.2019. Die Recherchestrategie der Erstrecherche wurde für die Folgerecherche.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 1472 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. 90 Referenzen wurden in die synoptische Evidenz-Übersicht aufgenommen.

3 Ergebnisse

3.1 G-BA-Beschlüsse/IQWiG-Berichte

G-BA, 2019 [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 – 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

G-BA, 2019 [25].

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.

G-BA, 2019 [12].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Dacomitinib. Vom 17. Oktober.

Anwendungsgebiet

Vizimpro als Monotherapie wird angewendet für die Erstlinienbehandlung erwachsener Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom

(non-small cell lung cancer, NSCLC) mit aktivierenden EGFR-Mutationen (epidermaler Wachstumsfaktor-Rezeptor, epidermal growth factor receptor, EGFR).

Zweckmäßige Vergleichstherapie

a) Erwachsene Patienten mit Erstlinienbehandlung des lokal fortgeschrittenen oder metastasierten NSCLC mit den aktivierenden EGFR-Mutationen L858R1 oder del 192:

- Zweckmäßige Vergleichstherapie: Afatinib oder Gefitinib oder Erlotinib oder Osimertinib

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Dacomitinib gegenüber Gefitinib:

Ein Zusatznutzen ist nicht belegt.

b) Erwachsene Patienten mit Erstlinienbehandlung des lokal fortgeschrittenen oder metastasierten NSCLC mit anderen aktivierenden EGFR-Mutationen als L858R oder del 19:

Zweckmäßige Vergleichstherapie:

eine patientenindividuelle Therapie in Abhängigkeit von der aktivierenden EGFR-Mutation unter Auswahl von:

- Afatinib, Gefitinib, Erlotinib, Osimertinib
- Cisplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel oder Pemetrexed)
- Carboplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel oder Pemetrexed) (vgl. Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie)
- Carboplatin in Kombination mit nab-Paclitaxel

und

- Monotherapie mit Gemcitabin oder Vinorelbin (nur für Patienten mit ECOG-Performance-Status 2 als Alternative zur Platin-basierten Kombinationsbehandlung).

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Dacomitinib gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

G-BA, 2019 [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 4. April 2019 – Duravalumab.

Anwendungsgebiet

IMFINZI ist angezeigt als Monotherapie zur Behandlung des lokal fortgeschrittenen, inoperablen nicht-kleinzelligen Lungenkarzinoms (NSCLC) bei Erwachsenen, deren Tumoren PD-L1 in ≥ 1 % der Tumorzellen exprimieren und deren Krankheit nach einer platinbasierten Radiochemotherapie nicht fortgeschritten ist (siehe Abschnitt 5.1).

Zweckmäßige Vergleichstherapie

Erwachsene Patienten mit lokal fortgeschrittenem, inoperablem nicht-kleinzelligem Lungenkarzinom, deren Tumoren PD-L1 in ≥ 1 % der Tumorzellen exprimieren und deren Krankheit nach einer platinbasierten Radiochemotherapie nicht fortgeschritten ist

- Zweckmäßige Vergleichstherapie: Best-Supportive-Care

Fazit / Ausmaß des Zusatznutzens

Anhaltspunkt für einen beträchtlichen Zusatznutzen.

G-BA, 2019 [22].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Osimertinib (neues Anwendungsgebiet: lokal fortgeschrittenes oder metastasiertes nicht-kleinzelliges Lungenkarzinom, Erstlinientherapie) vom 17. Januar 2019.

Anwendungsgebiet

TAGRISSO® ist als Monotherapie angezeigt zur Erstlinientherapie von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Lungenkarzinom (NSCLC) mit aktivierenden Mutationen des epidermalen Wachstumsfaktor-Rezeptors (Epidermal Growth Factor Receptor, EGFR).

Hinweis: Der vorliegende Beschluss bezieht sich nicht auf Patienten mit einer de novo T790M-Mutation des EGFR. Diese Patienten waren bereits vor der Zulassung des neuen Anwendungsgebietes vom Anwendungsgebiet umfasst (siehe Beschluss über die Nutzenbewertung von Osimertinib vom 15. September 2016).

Zweckmäßige Vergleichstherapie

Erwachsene Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC mit den aktivierenden EGFR-Mutationen L858R[1] oder del 19[2]:

- Afatinib oder Gefitinib oder Erlotinib

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Osimertinib gegenüber Gefitinib oder Erlotinib:

Anhaltspunkt für einen beträchtlichen Zusatznutzen

Zweckmäßige Vergleichstherapie

Erwachsene Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC mit anderen aktivierenden EGFR-Mutationen als L858R L858R1 oder del 192 (außer de novo T790M): eine patientenindividuelle Therapie in Abhängigkeit von der aktivierenden EGFR-Mutation unter Auswahl von:

- Afatinib, Gefitinib, Erlotinib,
- Cisplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel oder Pemetrexed),

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

und

- Monotherapie mit Gemcitabin oder Vinorelbin (nur für Patienten mit ECOG-Performance-Status 2 als Alternative zur Platin-basierten Kombinationsbehandlung).

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Osimertinib gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

[1] Exon 21-Substitutionsmutation
[2] Exon 19-Deletion

G-BA, 2018 [26].

Beschluss über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Alectinib (neues Anwendungsgebiet: Erstlinienbehandlung nicht-kleinzelliges Lungenkarzinom)

vom 21.06.2018

Neues Anwendungsgebiet (laut Zulassung vom 18. Dezember 2017):

Alecensa wird als Monotherapie angewendet zur Erstlinienbehandlung des Anaplastische-Lymphomkinase (ALK)-positiven, fortgeschrittenen nicht-kleinzelligen Lungenkarzinoms (non-small cell lung cancer, NSCLC) bei erwachsenen Patienten.

Zweckmäßige Vergleichstherapie

Crizotinib

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Crizotinib:

Anhaltspunkt für einen nicht-quantifizierbaren Zusatznutzen

G-BA, 2018 [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 1. Februar 2018 – Ceritinib.

Neues Anwendungsgebiet (laut Zulassung vom 23. Juni 2017):

Zykadia wird als Monotherapie angewendet bei erwachsenen Patienten zur Erstlinienbehandlung des fortgeschrittenen, Anaplastische-Lymphomkinase(ALK)-positiven, nicht-kleinzelligen Bronchialkarzinoms (NSCLC).

Vergleichstherapie

Crizotinib

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

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 17.10.2019

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

G-BA, 2017 [21].

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.

G-BA, 2017 [23].

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.

G-BA, 2017 [15].

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.

G-BA, 2017 [24].

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, 2017 [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 15. September 2016 / 19. Oktober 2017- Osimertinib

Anwendungsgebiet

TAGRISSO ist angezeigt zur Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Lungenkarzinom (NSCLC) und einer positiven T790M-Mutation des epidermalen Wachstumsfaktor-Rezeptors (Epidermal Growth Factor Receptor, EGFR).

Hinweis:

Der Beschluss vom 19. Oktober 2017 bezieht sich ausschließlich auf die Bewertung des Zusatznutzens von Osimertinib in der Teilpopulation: Patienten nach Vorbehandlung mit einem EGFR-Tyrosinkinase-Inhibitor, für die eine zytotoxische Chemotherapie infrage kommt.

Über die Nutzenbewertung von Osimertinib im gesamten Anwendungsgebiet laut Zulassung vom 2. Februar 2016 hat der G-BA bereits mit Beschluss vom 15. September 2016 beschlossen. Dabei wurden die Feststellungen zum Zusatznutzen für die oben genannte Teilpopulation (Teilpopulation „1a“ im Beschluss vom 15. September 2016) in ihrer Geltungsdauer zeitlich befristet.

(…)

2) Nicht vorbehandelte Patienten mit einer de novo positiven T790M-Mutation:

Zweckmäßige Vergleichstherapie

- Gefitinib oder Erlotinib oder Afatinib (nur für Patienten mit aktivierenden EGFR-Mutationen)

oder

- 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 der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

(…)

G-BA, 2016 [20].

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. Juni 2016 - Crizotinib (neues Anwendungsgebiet: nicht -kleinzelliges Lungenkarzinom, ROS1 -positiv, Erstlinie)

Zugelassenes Anwendungsgebiet (laut Zulassung vom 23.11.2015):

XALKORI wird angewendet bei Erwachsenen zur Erstlinienbehandlung des Anaplastische-Lymphom-Kinase(ALK)-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, NSCLC).

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 Platin-basierten Kombinationsbehandlung: eine Monotherapie mit Gemcitabin oder Vinorelbin

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

Anhaltspunkt für einen beträchtlichen Zusatznutzen.

G-BA, 2016 [18].

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.

G-BA, 2015 [17].

Beschluss über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Afatinib vom 5. November 2015

Anwendungsgebiet

GIOTRIF als Monotherapie wird angewendet zur Behandlung von EGFR-TKI-naiven erwachsenen Patienten mit lokal fortgeschrittenem und/oder metastasiertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit aktivierenden EGFR-Mutationen.

1) Nicht vorbehandelte Patienten mit ECOG-Performance-Status 0 oder 1

Zweckmäßige Vergleichstherapie

- Gefitinib oder Erlotinib

oder

- 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)

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

a) Patientengruppe mit EGFR-Mutation Del19: Hinweis auf einen erheblichen Zusatznutzen.

b) Patientengruppe mit EGFR-Mutation L858R: Ein Zusatznutzen ist nicht belegt.

c) Patientengruppe mit anderen EGFR-Mutationen: Ein Zusatznutzen ist nicht belegt.

2) Nicht vorbehandelte Patienten mit ECOG-Performance-Status 2:

Zweckmäßige Vergleichstherapie

- Gefitinib oder Erlotinib

oder

- alternativ zu den unter 1) angegebenen platinbasierten Kombinationsbehandlungen: Monotherapie mit Gemcitabin oder Vinorelbin

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

3) Patienten nach Vorbehandlung mit einer Platin-basierten Chemotherapie:

Zweckmäßige Vergleichstherapie

- Gefitinib oder Erlotinib

oder

- Docetaxel oder Pemetrexed

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

3.2 Cochrane Reviews

Greenhalgh J et al., 2016 [27].

assessed as up to date: 1 June 2015

First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer

Fragestellung

To assess the clinical effectiveness of single-agent or combination EGFR therapies used in the first-line treatment of people with locally advanced or metastatic EGFRM+ NSCLC compared with other cytotoxic chemotherapy (CTX) agents used alone or in combination, or best supportive care (BSC). The primary outcome was overall survival. Secondary outcomes included progression-free survival, response rate, toxicity, and quality of life.

Methodik

Population:

- Chemotherapy-naive patients with locally advanced or metastatic (stage IIIB or IV) EGFR M+ NSCLC unsuitable for treatment with curative intent with surgery or radical radiotherapy. We included studies that included or excluded exon 20 T790 in the review.

Intervention/ Komparator:

- EGFRM+ targeted agents, alone or in combination with cytotoxic agents, compared with cytotoxic agents used alone or in combination or BSC.
- We excluded trials comparing single-agent or combinations of cytotoxic chemotherapy without a targeted therapy in either arm and trials with targeted therapy in both arms, and we did not evaluate maintenance or second-line strategies. We also excluded cross-over trials.

Endpunkt:

- Primary outcomes
  - 1. Overall survival
- Secondary outcomes
  - 1. Progression-free survival
  - 2. Tumour response
  - 3. Toxicity and adverse effects of treatment
  - 4. Quality of life (e.g. Functional Assessment of Cancer Therapy - Lung (FACT-L) and Trial Outcome Index (TOI))
  - 5. Symptom palliation

Recherche/Suchzeitraum:

- up to 1 June 2015

Qualitätsbewertung der Studien:

- according to Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions

Ergebnisse

Anzahl eingeschlossener Studien:

- 19 trials, 7 of these exclusively recruited people with EGFR M+ NSCLC (see below); the remainder recruited a mixed population and reported results for people with EGFR M+ NSCLC as subgroup analyses
- four EGFR targeted treatments: erlotinib (eight trials); gefitinib (seven trials); afatinib (two trials); and cetuximab (two trials)
- median length of follow-up (where reported): from 15.9 to 59 months

[1] Wu Y-L, et al. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. Annals of Oncology 2015;26(9):1883–9.
[2] Rosell R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. The Lancet Oncology 2012;13(3):239–46.
[3] Sequist LV, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. Journal of Clinical Oncology 2013;31:1–11.
[4] Geater SL, et al. Symptom and quality of life improvement in LUX-Lung 6: An open-label phase III study of afatinib versus cisplatin/gemcitabine in Asian patients with EGFR mutation-positive advanced non-small-cell lung cancer. Journal of Thoracic Oncology 2015;10(6):883–9.
[5] Maemondo M, et al. Gefitinib or chemotherapy for non-small cell lung cancer with mutated EGFR. The New England Journal of Medicine 2010;362(25):2380–8.
[6] Zhou C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation positive non small cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. The Lancet Oncology 2011;12(8):735–42.
[7] Mitsudomi T, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. The Lancet Oncology 2009;11(2):121–8.

Charakteristika der Population:

- number of participants with EGFR M+ tumours: 2 317, of whom 1 700 were of Asian origin
- median age: from 56 to 77 years; median age of participants in the EGFR M+ only trials: from 56 to 65 years; 2 trials only included people aged over 70 years
- more females in 9 trials; more males in 7 trials; in all of the trials that recruited EGFRM+ patients only, the proportion of females was greater than males
- majority of participants were of good performance status (ECOG or WHO 0 or 1)

Qualität der Studien:

- quality of the evidence: high for all comparisons
- mixed risk of bias across the included trials for the majority of the assessment criteria
  - o two items considered to be at high risk of bias across the trials were related to blinding of treatment allocation for participants and personnel and blinding of outcome assessment

Studienergebnisse:

- Overall survival (OS)
  - o inconsistent results between the included trials that compared EGFR-targeted treatments against cytotoxic chemotherapy or placebo
  - o FASTACT 2 did report a statistically significant OS gain for participants treated with erlotinib plus cytotoxic chemotherapy when compared to cytotoxic chemotherapy alone, result based on a small number of participants (n = 97)
  - o None of the remaining 18 included trials demonstrated any OS benefit of targeted therapy compared with cytotoxic chemotherapy.

  - no OS effect demonstrated in pooled analyses of erlotinib, gefitinib or afatinib
  - no statistically significant OS benefit for cetuximab plus cytotoxic chemotherapy (n = 81)
  - The majority of the included trials of anti-EGFR monotherapy allowed participants to switch treatments on disease progression, which will have a confounding effect on any OS analysis.
- Commonly reported adverse events
  - most commonly reported for TKI monotherapy: rash, diarrhoea, paronychia, stomatitis/mucositis (afatinib), and rash, diarrhoea, and fatigue (erlotinib and gefitinib)
  - for cytotoxic chemotherapy: neutropenia, febrile neutropenia, leukopenia, and fatigue (usually associated with this treatment)
  - rare but serious AE: interstitial lung disease
  - grade 3/4: for afatinib, erlotinib, and gefitinib monotherapy rash and diarrhoea; myelosuppression consistently worse in the chemotherapy arms; fatigue and anorexia also associated with some chemotherapies
- Quality of life and symptom improvement
  - 6 trials reported; different methodologies used
  - erlotinib, gefitinib, and afatinib, showed improvement in one or more indices for the tyrosine-kinase inhibitor (TKI) compared to chemotherapy

Anmerkung/Fazit der Autoren

Erlotinib, gefitinib, and afatinib are all active agents in EGFRM+NSCLC patients, and demonstrate an increased tumour response rate and prolonged progression-free survival compared to cytotoxic chemotherapy. We also found a beneficial effect of the TKI compared to cytotoxic chemotherapy. However, we found no increase in overall survival for the TKI when compared with standard chemotherapy.

Cytotoxic chemotherapy is less effective in EGFRM+NSCLC than erlotinib, gefitinib, or afatinib and is associated with greater toxicity.

There were no data supporting the use of monoclonal antibody therapy.

Kommentare zum Review

- *73 Prozent der Untersuchten waren asiatischer Herkunft. Subgruppenanalysen zur Herkunft liegen nicht vor.*

Santos FN et al., 2015 [70].

Chemotherapy for advanced non-small cell lung cancer in the elderly population

Fragestellung

- To assess the effectiveness and safety of different cytotoxic chemotherapy regimens for previously untreated elderly patients with advanced (stage IIIB and IV) NSCLC.
- To also assess the impact of cytotoxic chemotherapy on quality of life.

Methodik

Population:

- patients 70 years of age and older with previously untreated and histologically confirmed NSCLC, with metastatic disease and/or pleural effusion (stage IIIB or IV).

Intervention/Komparator:

We classified chemotherapy regimens into three categories.

- Non-platinum monotherapy.
- Non-platinum combination therapy.
- Platinum combination therapy.

We considered trials comparing these compounds, whatever the numbers.

Categories were compared according to the following.

- Non-platinum monotherapy versus non-platinum combination therapy.
- Non-platinum therapy (given as a single agent or in combination) versus platinum combination therapy.

Endpunkte:

- Primär:
  - Overall survival
  - QoL
- Sekundär:
  - One-year survival rate (1yOS).
  - Progression-free survival (PFS).
  - Objective response rate (ORR), classified according to Response Evaluation Criteria in Solid Tumors (RECIST), World Healh Organization (WHO) criteria, or individual study criteria.
  - Serious adverse events (grade 3 or above, according to WHO or National Cancer Institute Common Toxicity Criteria (NCI-CTC))

Recherche/Suchzeitraum:

- Bis 2014

Qualitätsbewertung der Studien:

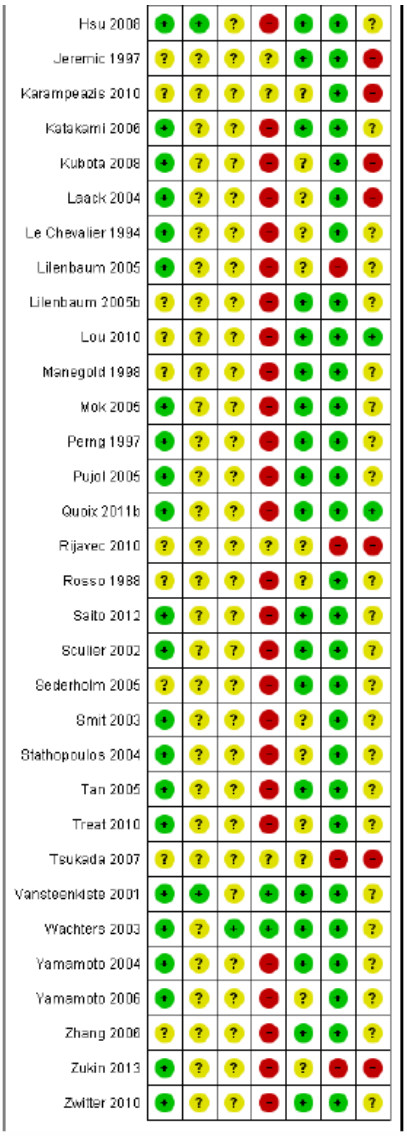
- Cochrane risk of bias tool

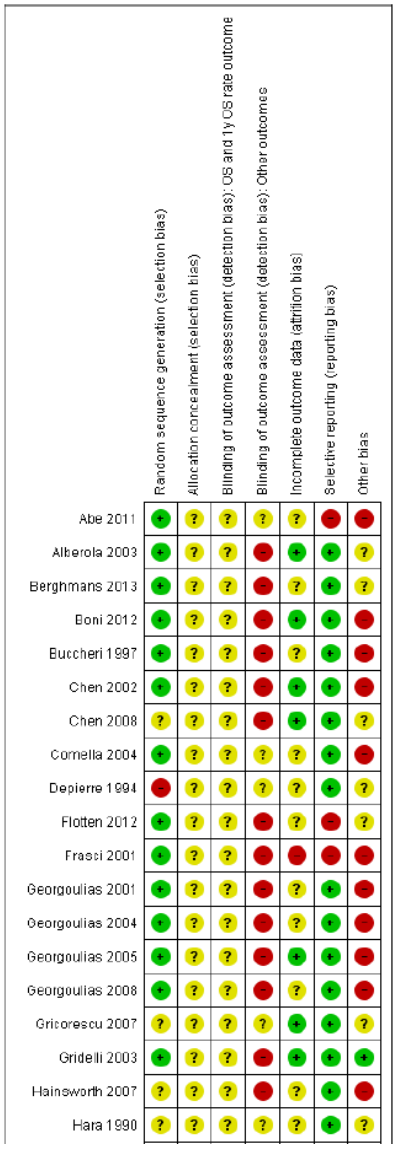
Ergebnisse

Anzahl eingeschlossener Studien:

- 51 (13,103), nur RCTs

Qualität der Studien:



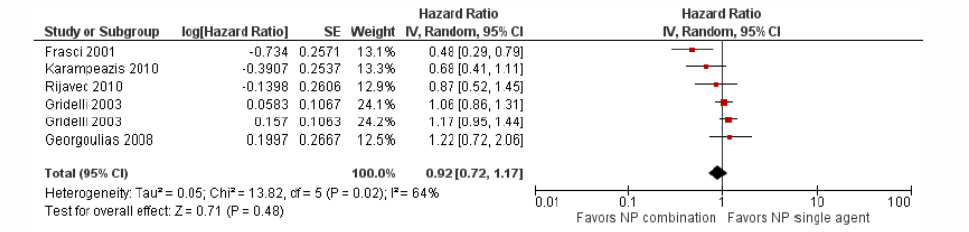


Studienergebnisse:

Non-platinum single-agent versus non-platinum combination therapy

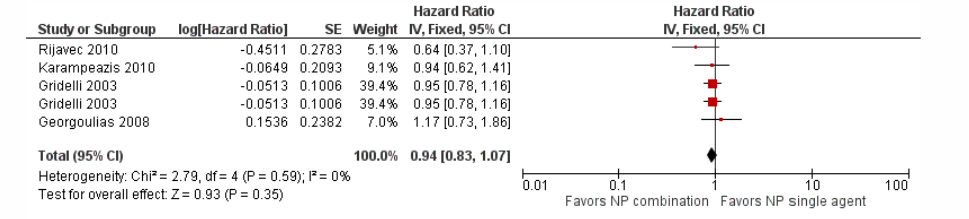
- OS: The meta-analysis of five RCTs involving 1294 participants showed no differences in OS between treatment strategies (hazard ratio (HR) 1.01, 95% confidence interval (CI) 0.89 to 1.15) and significant heterogeneity among trials (I2 = 64%). As a result of the presence of heterogeneity, we performed an analysis using a random-effects model with no impact on effects of the intervention (HR 0.92, 95% CI 0.72 to 1.17)

Figure 4. Forest plot of comparison: 1 Non-platinum single agent vs non-platinum combination, outcome: 1.1 Overall survival (OS).Gridelli 2003 was designed for a separate comparison of each single-agent arm (V arm and G arm) vs the combination arm (VG arm). Therefore, each entry for this trial represents one comparison (V vs VG and G vs VG arm).



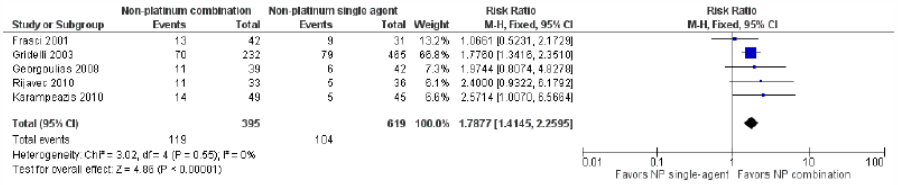
- QoL: Only two RCTs included quality of life (QoL) assessment in the trial design. We were not able to performameta-analysis because of the paucity of available data.
- PFS: The meta-analysis of four RCTs involving 942 participants showed no impact on the PFS of non-platinum combination over nonplatinum single-agent therapy (HR 0.94, 95% CI 0.83 to 1.07) with low heterogeneity among trials (I2 = 0%)

Figure 5. Forest plot of comparison: 1 Non-platinum single-agent vs non-platinum combination, outcome: 1.3 Progression-free survival.



- ORR: The meta-analysis including 1014 participants assessed from five RCTs showed statistically significant improvement in response rate (RR 1.79, 95% CI 1.41 to 2.26; I2 = 0%) with no heterogeneity among trials (I2 = 0%)

Figure 6. Forest plot of comparison: 1 Non-platinum single agent vs non-platinum combination, outcome: 1.6 Overall response rate (ORR).



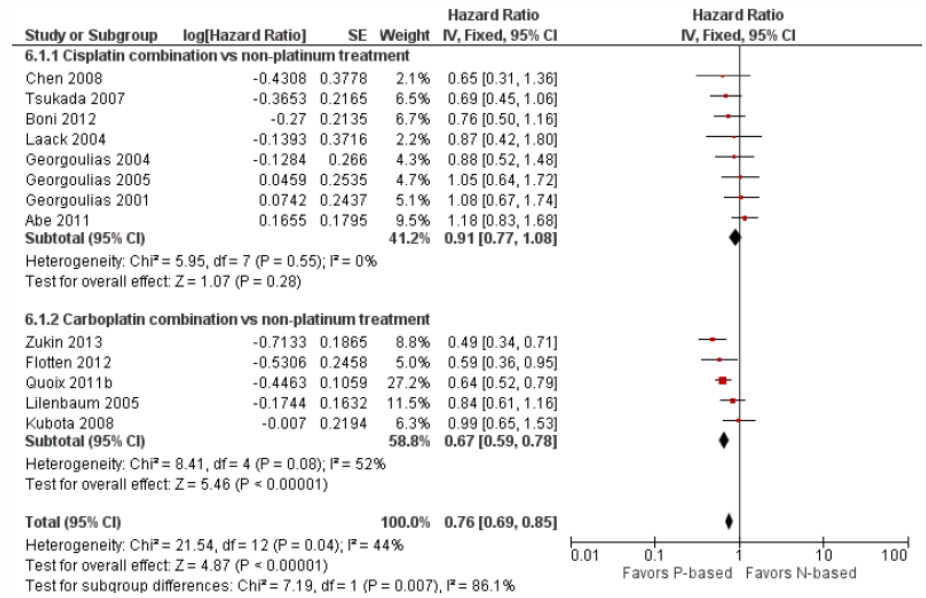
- Toxicity:
  - Grade 3 or higher hematological adverse events: We found no significant differences in risk of anemia (RR 1.18, 95% CI 0.57 to 2.40; participants = 1064; five studies; I2 = 0%), neutropenia (RR 1.19, 95%CI 0.93 to 1.54; participants = 1064; five studies; I2 = 24%), febrile neutropenia (RR 0.34, 95% CI 0.04 to 3.20; participants = 995; four studies; I2 = 0%), or thrombocytopenia (RR 1.58, 95% CI 0.82 to 3.04; participants = 995; four studies; I2 = 0%).
  - Grade 3 or higher non-hematological adverse events: We found no significant differences in risk of fatigue (RR 1.16, 95%CI 0.69 to 1.96; participants = 995; four studies; I2 = 0%) or emesis (RR 1.73, 95% CI 0.68 to 4.43; participants = 995; four studies; I2 = 0%). For diarrhea, constipation, and mucositis, few grade 3 or 4 events were observed in all included trials

Non-platinum therapy versus platinum combination therapy

The meta-analysis of 13 RCTs involving 1705 elderly participants showed improvement in OS in favor of platinum combination treatment (HR 0.76, 95% CI 0.69 to 0.85), with moderate heterogeneity observed among trials (I2 = 44%)

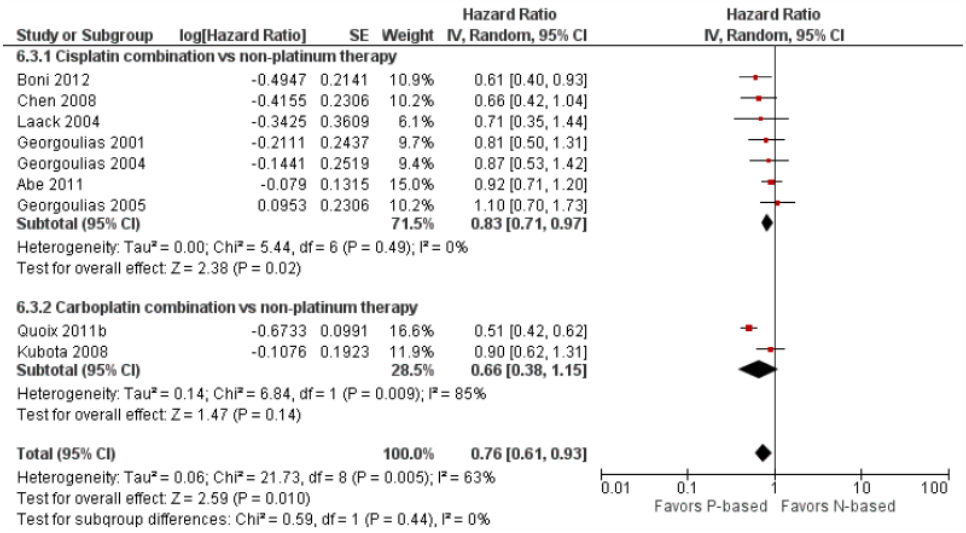
Exploratory analysis by platinum agent showed improvement in OS for carboplatin combination treatment (HR 0.67, 95% CI 0.59 to 0.78) and no significant differences for cisplatin combination treatment (HR 0.91, 95% CI 0.77 to 1.08) over non-platinum therapy. Differences between subgroups reached statistical significance (Chi2= 7.16; P value = 0.007; I2 = 86%), suggesting greater benefit of carboplatin over cisplatin regimens when compared with non-platinum therapy.

Figure 7. Forest plot of comparison: 3 Overall survival analysis for platinum combination by cisplatin or carboplatin combination, outcome: 3.1 Overall survival by platinum agent.



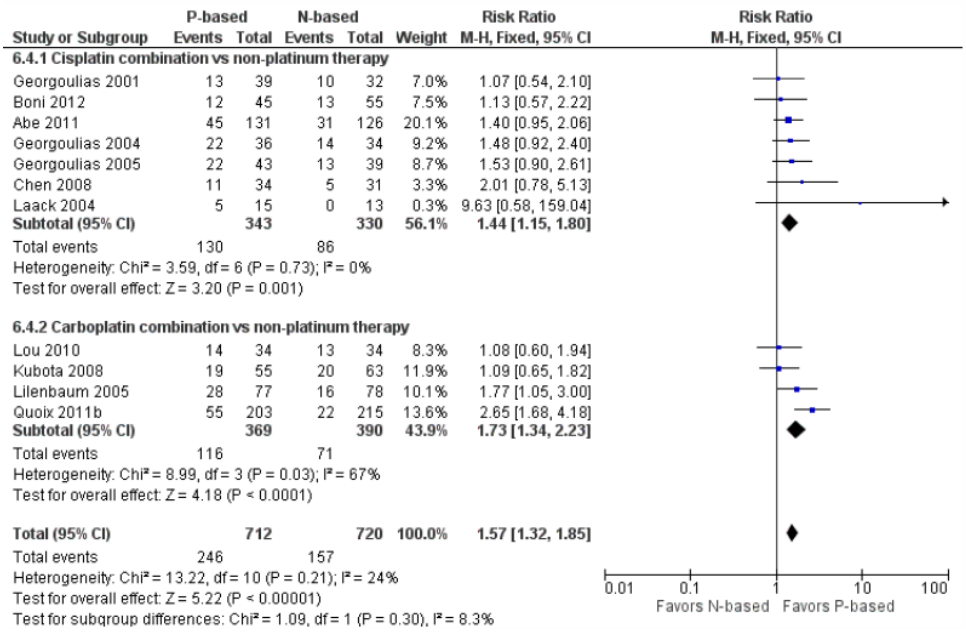
- QoL: Only five RCTs included QoL assessment. However, we were not able to performameta-analysis of these data because of the paucity of data provided.
- PFS: The meta-analysis of nine RCTs with 1273 elderly participants showed significant improvement in PFS in favor of platinum combination over non-platinum therapy (HR 0.70, 95% CI 0.63 to 0.79). In light of the presence of significant heterogeneity (I2 = 63%), we performed an analysis using a random- effects model, while maintaining a significant difference in PFS in favor of platinum combination (HR 0.76, 95% CI 0.61 to 0.93).

Figure 8. Forest plot of comparison: 3 Outcome analysis for platinum combination by cisplatin or carboplatin combination, outcome: 3.3 Progression-free survival by platinum agent.



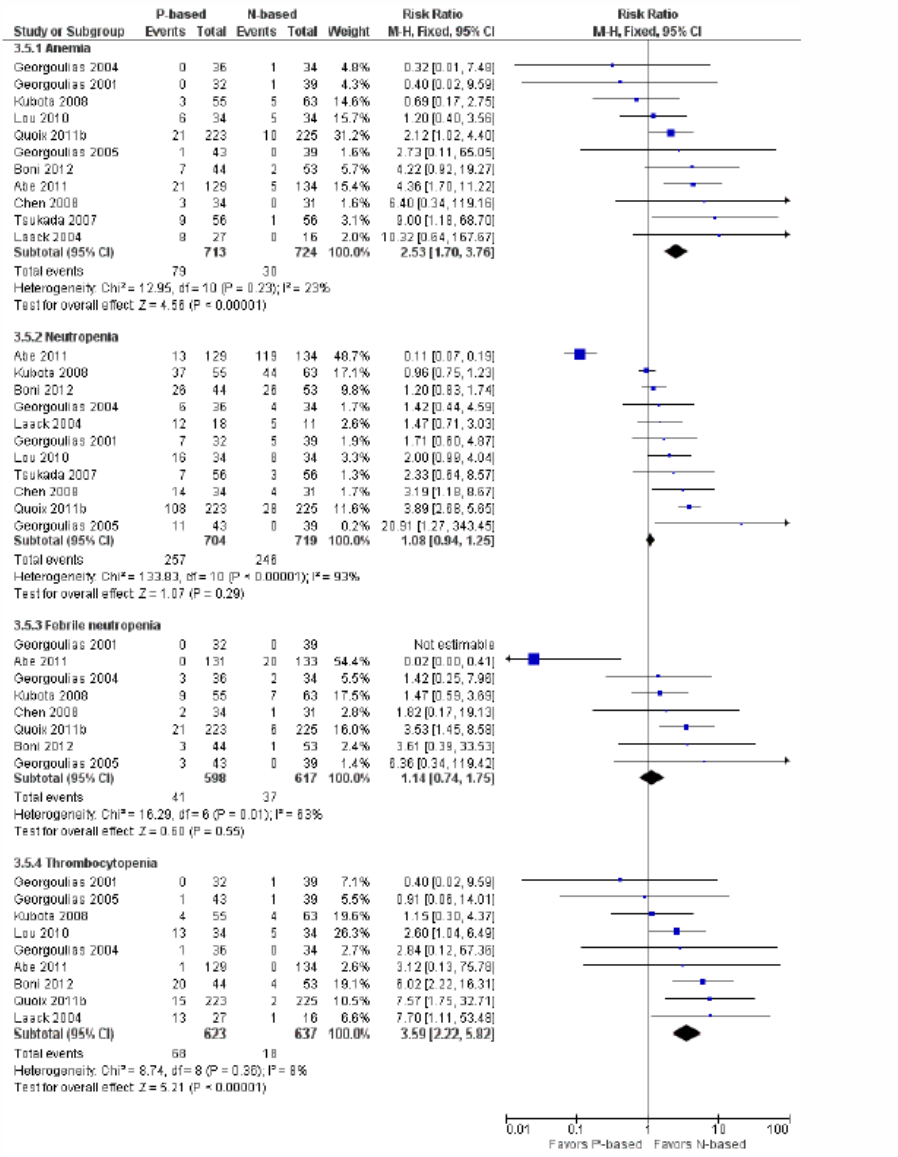
- ORR: The meta-analysis from 11 RCTs with 1432 elderly participants showed benefit in RR in favor of platinum combination over nonplatinum regimens with low heterogeneity among trials (RR 1.57, 95% CI 1.32 to 1.85; I2 = 24%)

Figure 9. Forest plot of comparison: 3 Outcome analysis for platinum combination by cisplatin or carboplatin combination, outcome: 3.4 Objective response rate by platinum agent.



- Toxicity:
  - Hematological grade 3 or higher adverse events: Using a fixed-effect model, we found greater risk of anemia (RR 2.53, 95% CI 1.70 to 3.76; participants = 1437; 11 studies; I2 = 23%) and thrombocytopenia (RR 3.59, 95% CI 2.22 to 5.82; participants = 1260; nine studies; I2 = 8%) for platinum combinations. We found no statistically significant differences in risks of neutropenia (RR 1.08, 95%CI 0.94 to 1.25; participants = 1423; 12 studies; I2 = 93%) and febrile neutropenia (RR 1.14, 95% CI 0.74 to 1.75; participants = 1215; eight studies; I2 = 63%), and results for both were associated with high heterogeneity among trials.

Figure 10. Forest plot of comparison: 4 Non-platinum vs platinum combination therapy, outcome: 4.6 Grade 3 or higher hematological toxicity for platinum therapies.



- Non-hematological grade 3 or higher adverse events: We found higher risk of fatigue (RR 1.56, 95% CI 1.02 to 2.38; participants = 1150; seven studies; I2 = 0%), emesis (RR3.64, 95% CI 1.82 to 7.29), and peripheral neuropathy (RR 7.02, 95% CI 2.42 to 20.41; participants = 776; five studies; I2 = 0%) associated with platinum combination treatment. We found no statistically significant differences in the incidence of diarrhea (RR 1.75, 95% CI 0.91 to 3.38; participants = 1075; seven studies; I2 = 21%) and mucositis (RR 0.93, 95% CI 0.33 to 2.67; participants = 740; five studies; I2 = 0%)

Anmerkung/Fazit der Autoren

Our assessment of treatment effect supports the use of platinum combination for fit elderly patients with advanced NSCLC, with advantages for survival (number needed to treat for an additional beneficial outcome (NNTB) for 1yOS 12.6, 95% CI 7.8 to 34.5) and response rate (NNTB for ORR 8.0, 95% CI 5.0 to 14.3). Nonetheless, such treatment is also associated with greater risk of grade 3 or 4 hematological (number needed to treat for an additional harmful

outcome (NNTH) for anemia 15.6, 95% CI 8.7 to 34.5; NNTH for thrombocytopenia 13.7, 95% CI 7.4 to 28.6) and non-hematological adverse events (NNTH for peripheral neuropathy 32.3, 95% CI 10.1 to 142.9). Exploratory analysis also suggests that carboplatin combinations should be preferred over cisplatin combinations; however, this finding should be interpreted with caution, as it was not based on a direct comparison between cisplatin and carboplatin combinations. For patients who are not candidates for platinum treatment (unfit), our findings suggest an increase in response rate in favor of non-platinum doublets, with similar efficacy for survival. Unfortunately, we also found scarce evidence on the impact of different treatment regimens on quality of life, challenging the process of decision-making.

Kommentare zum Review

- Der Mutationsstatus wurde in diesem CR nicht untersucht
- Gemischte Population (Stadium IIIB und IV): Keine seperaten Ergebnisse (z.B. fortgeschritten vs. metastasiert.

3.3 Systematische Reviews

Zhao, Y. et al., 2019 [88].

Efficacy and safety of first line treatments for patients with advanced epidermal growth factor receptor mutated, non-small cell lung cancer: systematic review and network meta-analysis.

Fragestellung

To compare the efficacy and safety of first line treatments for patients with advanced epidermal growth factor receptor (EGFR) mutated non-small cell lung cancer (NSCLC).

Methodik

Population:

- patients with histologically or cytologically confirmed advanced (stage III/IV/ recurrent) NSCLC with EGFR activating mutations

Intervention/Komparator:

- trials comparing two or more treatments in the first line setting

Endpunkte:

- PFS, OS, ORR, toxcitiy

Recherche/Suchzeitraum:

- PubMed, Embase, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and several international conference databases, from inception to 20 May 2019.

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 18 eligible trials involved 4628 patients and 12 treatments: EGFR tyrosine kinase inhibitors (TKIs; osimertinib, dacomitinib, afatinib, erlotinib, gefitinib, and icotinib), pemetrexed based chemotherapy, pemetrexed free chemotherapy, and combination treatments (afatinib plus cetuximab, erlotinib plus bevacizumab, gefitinib plus pemetrexed based chemotherapy, and gefitinib plus pemetrexed).

Qualität der Studien:

Figure S3. Summary of results from assessment of studies using the Cochrane risk of bias tool.

Studienergebnisse:

- progression free survival:
  - osimertinib yielded not only the best benefit of all EGFR-TKIs monotherapies (versus dacomitinib (hazard ratio 0.74, 95% credible interval 0.55 to 1.00), afatinib (0.52, 0.40 to 0.68), erlotinib (0.48, 0.40 to 0.57), gefitinib (0.44, 0.37 to 0.52), and icotinib (0.39, 0.24 to 0.62)), but also significant benefits versus afatinib plus cetuximab (0.44, 0.28 to 0.71) and gefitinib plus pemetrexed (0.65, 0.46 to 0.92).
  - Gefitinib plus pemetrexed based chemotherapy was shown to be consistent with osimertinib (0.95, 0.72 to 1.24) in providing the best progression free survival.
  - Pemetrexed based chemotherapy significantly prolonged progression free survival compared with pemetrexed free chemotherapy (0.68, 0.50 to 0.91), although both were shown to have the worst progression free survival versus other treatments.
- OS:
  - In terms of overall survival, osimertinib and gefitinib plus pemetrexed based chemotherapy were also consistent (hazard ratio 0.94, 95% credible interval 0.66 to 1.35) in providing the best overall survival benefit; significant differences were also observed when compared with most other monotherapies.
  - Similar efficacy was found between dacomitinib and afatinib, and among erlotinib, gefitinib, icotinib, pemetrexed based chemotherapy, pemetrexed free chemotherapy, and afatinib plus cetuximab, because the hazard ratios were close to 1.
- ORR
  - In terms of objective response rate, no significant difference was observed in any comparable EGFR-TKI monotherapies; however, EGFR-TKIs produced significant objective response rate benefits over chemotherapy.
  - For multiple comparisons, the addition of pemetrexed based chemotherapy to gefitinib significantly increased objective response rate over gefitinib alone (odds ratio 2.75, 95% credible interval 1.41 to 5.43).
  - Furthermore, gefitinib plus pemetrexed based chemotherapy was likely to be the best treatment in achieving an objective response.
- Adverse events:

  - Combination treatments caused more toxicity in general, especially erlotinib plus bevacizumab, which caused the most adverse events of grade 3 or higher. Different toxicity spectrums were revealed for individual EGFR-TKIs.
- Subgroup analyses by the two most common EGFR mutation types indicated that osimertinib was associated with the best progression free survival in patients with the exon 19 deletion, and gefitinib plus pemetrexed based chemotherapy was associated with the best progression free survival in patients with the Leu858Arg mutation.
- Rank probabilities
  - the bayesian ranking profiles of comparable treatments in different populations (with detail ranking results summarised in supplementary table S3). The bayesian ranking results were almost in line with the pooled analyses using hazard and odds ratios. For patients with advanced EGFR mutated NSCLC, osimertinib was most likely to be ranked first for progression free survival (cumulative probability 57%), gefitinib plus pemetrexed based chemotherapy for both overall survival (49%) and objective response rate (75%), and erlotinib plus bevacizumab for adverse events of grade 3 or higher (80%; fig 5). Icotinib had the highest probability (80%) of ranking last in causing adverse events of grade 3 or higher followed by osimertinib. When EGFR mutation types were considered (fig 6), treatments with the greatest probability of being ranked first were different: osimertinib for the exon 19 deletion subgroup (56%) and gefitinib plus pemetrexed based chemotherapy for the Leu858Arg subgroup (98%) in terms of progression free survival; and afatinib for the exon 19 deletion (45%) subgroup and dacomitinib for the Leu858Arg subgroup (36%) in terms of overall survival.

Anmerkung/Fazit der Autoren

In this network meta-analysis, osimertinib and gefitinib plus pemetrexed based chemotherapy appears to be superior first line treatment choices for patients with advanced EGFR mutated NSCLC, and were preferentially recommended to patients with exon 19 deletion or Leu858Arg mutations, respectively. We also found EGFR-TKIs, especially icotinib, were associated with less toxicity, although toxicity risk generally rose when they were combined with other treatments—in particular, erlotinib plus bevacizumab caused the most adverse events of grade 3 or higher. These findings could complement current standard of care and enhance future trial design for advanced EGFR mutated NSCLC.

Kommentare zum Review

- Siehe auch: Zhang, H. et al. 2019 [84] & Franek, J. et al. 2019 [10]

Li, Y. X. et al., 2019 [44]

A meta-analysis of the comparing of the first-generation and next-generation TKIs in the treatment of NSCLC.

Fragestellung

to address this question, and identify the most efficacious drug, by assessing the efficacy and safety of first generation EGFR TKIs and next generation EGFR-TKIs in patients with EGFR-mutant NSCLC.

Methodik

Population:

- NSCLC patients harboring activating mutations in EGFR

Intervention/Komparator:

- Comparing second/third -generation EGFR-TKIs and first -generation EGFR-TKIs

Endpunkte:

- survival, tumor response, toxicity

Recherche/Suchzeitraum:

- PubMed and Embase databases were searched to identify studies. Two investigators independently performed the literature search up to September 2018.

Qualitätsbewertung der Studien:

- Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 RCTs including 3 clinical trials

Charakteristika der Population:

Study	Year	Clinical Trials	Treatment regimen		Patients number		Age(years)	
			Study arm	Comparative arm	Study arm	Comparative arm	Study arm	Comparative arm
J.-C. Soria	2017	FLAURA	osimertinib	gefitinib/erlotinib	279	277	64	64
Keunchil Park	2016	LUX-Lung 7	afatinib	gefitinib	160	159	63	63
L. Paz-Ares	2017	LUX-Lung 7	afatinib	gefitinib	146	151	/	/
Yi-Long Wu	2017	ARCHER 1050	dacomitinib	gefitinib	227	225	62	61
Tony S. Mok	2018	ARCHER 1050	dacomitinib	gefitinib	227	225	62	61

Qualität der Studien:

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

Studienergebnisse:

- Pooling the PFS data from three trials showed that next-generation EGFR-TKIs did prolong the PFS compared with the first-generation EGFR-TKIs
- While, subgroup analyses with EGFR mutations, there are also significant differences with exon 19 deletion (OR = 0.56, 95%CI = 0.41–0.77, P = 0.0003) and exon 21 (L858R) mutation (OR = 0.60, 95%CI = 0.49–0.75, P＜0.00001)
- Pooled data showed that the next-generation EGFR-TKIs had significantly better OS rate than first-generation group, with the pooled OR being 0.76 (95 % CI 0.65–0.90, P = 0.001)
- The pooling ORR data achieved advantage in the next-generation EGFR-TKIs agents (OR = 1.27, 95%CI = 1.01–1.61, P = 0.04)
- Pooling the SAE data show that there is no statistical difference between the two groups

Anmerkung/Fazit der Autoren

In summary, our meta-analysis indicates that next-generation EGFR-TKIs are superior to the first-generation EGFR-TKIs with respect to survival and objective response in the treatment of NSCLC patients with EGFR activating mutations. And the efficacy benefits are found both in exon 19 deletion and exon 21 (L858R) mutation when comparing the next-generation EGFR-TKIs over first -generation EGFR-TKIs. We believe that these results provide additional evidence to help to inform decision-making when choosing the standard treatment option for patients with EGFR mutation- positive NSCLC.

Kommentare zum Review

- Linie unklar

Lv, W. W. et al., 2019 [50].

Safety of combining vascular endothelial growth factor receptor tyrosine-kinase inhibitors with chemotherapy in patients with advanced non-small-cell lung cancer: A PRISMA-compliant meta-analysis.

Fragestellung

A meta-analysis of randomized controlled trials (RCTs) to definite the incidence and the risk of grade ≥3 adverse events (AEs), serious and fatal AEs (SAEs and FAEs), with VEGFR-TKIs in advanced/metastatic NSCLC patients was performed.

Methodik

Population:

- advanced/metastatic NSCLC

Intervention/Komparator:

- either chemotherapy alone or in combination with VEGFR-TKIs

Endpunkte:

- incidence and relative risk of FAEs, included grade ≥3 AEs and SAEs

Recherche/Suchzeitraum:

- published up to December 2017

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- Eighteen RCTs of VEGFR-TKIs plus chemotherapy, involving 8461 advanced NSCLC patients

Charakteristika der Population:

Characteristics of included randomized controlled trials.

First author, year (ref)	Study design	Treatment line	Treatment arms	Number for analysis	Median age, y	Median PFS, mo	Median OS, mo
Heymach et al, 2007[18]	Phase II	Second line	Vandetanib 100 mg + docetaxel	42	61 (30–76)	4.7	13.1
			Vandetanib 300 mg + docetaxel	44	60 (29–82)	4.2	7.9
			Placebo + docetaxel	41	58 (41–78)	4.0	13.4
Heymach et al, 2008[19]	Phase II	First line	Vandetanib 300 mg + carboplatin/ paclitaxel Placebo + carboplatin/paclitaxel	56	60 (36–79)	6.0	10.2
				52	59 (42–83)	5.8	12.6
Goss et al, 2010[20]	Phase II	First line	Cediranib 30 mg/day + paclitaxel/carboplatin	126	60 (36–77)	5.6	NM
			Placebo + paclitaxel/carboplatin	123	58 (39–81)	5.0	
Herbst et al, 2010[21]	Phase II	Second line	Vandetanib 100 mg/day + docetaxel	689	59 (28–82)	4.0	10.6
			Placebo + docetaxel	690	59 (20–82)	3.2	10.0
Scagliotti et al, 2010[22]	Phase III	First line	Sorafenib 400 mg twice a day + carboplatin/paclitaxel	463	62 (34–86)	4.6	10.7
			Placebo + carboplatin/paclitaxel	459	63 (34–82)	5.4	10.6
de Boer et al, 2011[23]	Phase III	Second line	Vandetanib 100 mg/day + pemetrexed	260	60 (28–82)	4.4	10.5
			Placebo + pemetrexed	273	60 (35–83)	3.0	9.2
Paz-Ares et al, 2012[24]	Phase III	First line	Sorafenib 400 mg twice a day + gemcitabine/cisplatin	385	59 (28–81)	6.0	12.4
			Placebo + gemcitabine/cisplatin	384	58 (22–77)	5.5	12.5
Scagliotti et al, 2012[25]	Phase III	First line	Motesanib 125 mg/day + paclitaxel/carboplatin	533	60 (23–87)	5.6	13.0
			Placebo + paclitaxel/carboplatin	539	60 (21–84)	5.4	11.0
Dy et al, 2013[26]	Phase II	First line	Cediranib 30 mg/day + gemcitabine/carboplatin	58	65 (46–81)	6.3	12
			Gemcitabine/carboplatin	29	64 (45–82)	4.5	9.9
Scagliotti et al, 2013[27]	Phase II	First line	Pazopanib 800 mg/day + pemetrexed	61	62 (40–75)	6.2	NM
			Cisplatin + pemetrexed	34	64 (36–74)	5.7	
Belani et al, 2014[28]	Phase II	First line	Axitinib 5 mg bid + pemetrexed/cisplatin	55	62 (30–77)	8.0	17.0
			Pemetrexed/cisplatin	55	59 (42–76)	7.1	15.9
Gridelli et al, 2014[29]	Phase II	First line	Vandetanib 100 mg/day + gemcitabine	61	75 (70–82)	6.1	8.7
			Placebo + gemcitabine	63	75 (70–84)	5.6	10.2
Laurie et al, 2014[30]	Phase III	First line	Cediranib 20 mg/day + paclitaxel/carboplatin	151	63 (23–85)	5.5	12.2
			Placebo + carboplatin/paclitaxel	153	62 (36–77)	5.5	12.1
Novello et al, 2014[31]	Phase III	First line	Motesanib 125 mg/day + carboplatin/paclitaxel	181	62 (31–79)	4.9	11.1
			Placebo + carboplatin/paclitaxel	173	59.5 (32–81)	5.1	10.7
Heist et al, 2014[32]	Phase II	Second line	Pemetrexed + sunitinib 37.5 mg daily	39	63 (38–84)	3.7	6.7
			Pemetrexed	42		4.9	10.5
Reck et al, 2014[33]	Phase III	Second line	Nintedanib 200 mg twice daily + docetaxel Placebo + docetaxel	652	60 (53–67)	3.4 2.7	10.9
				655	60 (54–66)		7.9
Ramalingam et al, 2015[34]	Phase II	First line	Linifanib 7.5 mg + carboplatin/paclitaxel	42	61.5 (35–79)	8.3	11.4
			Linifanib 12.5 mg carboplatin/paclitaxel	47	60 (43–79)	7.3	13.0
			Placebo + carboplatin/paclitaxel	47	61 (44–79)	5.4	11.3
Hanna et al, 2016[35]	Phase III	Second-line	Nintedanib 200 mg twice daily + pemetrexed	347	60 (21–84)	4.4	12.0
			Placebo + pemetrexed	357	59 (26–86)	3.6	12.7

NM = not mentioned, OS = overall survival, PFS = progression-free survival.

Qualität der Studien:

- The quality of the trial was generally good and the risk of bias was low. Of the studies enrolled, 7 trials were considered to be with an excellent quality without bias. The most common problem is that there is no expression of randomization process and allocation concealment (selection bias), and the lack of blinding in the studies by Bellani et al, Dy et al, Heist et al, and Scagliotti et al (performance bias and detection bias).

Studienergebnisse:

- The proportion of patients with grade ≥3 AEs was increased with the addition of VEGFR-TKIs (relative risk, 1.35; 95% confidence interval [CI] 1.19–1.52; incidence, 68.1% vs 50.1%; P<.001).
- The most common grade ≥3 AEs was neutropenia (24.9% vs 15.4%, P<.001). Addition of VEGFR-TKIs was also related to the increased risk of SAEs (relative risk, 1.34; 95% CI 1.14–1.56; incidence, 37.8% vs 27.9%; P<.001) and FAEs (relative risk, 2.16, 95% CI 1.47–3.19; incidence, 3.4% vs 1.8%).
- Subgroup analysis suggested there was no difference in the rates of SAEs and FAEs in the second-line settings.

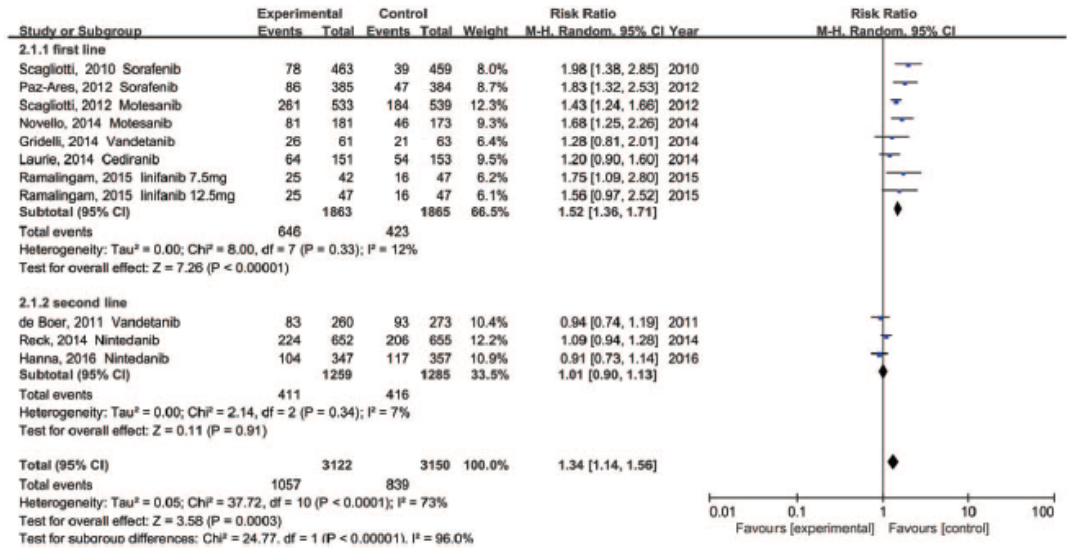


Figure 4. Forest plot and pooled risk ratio for serious adverse events.

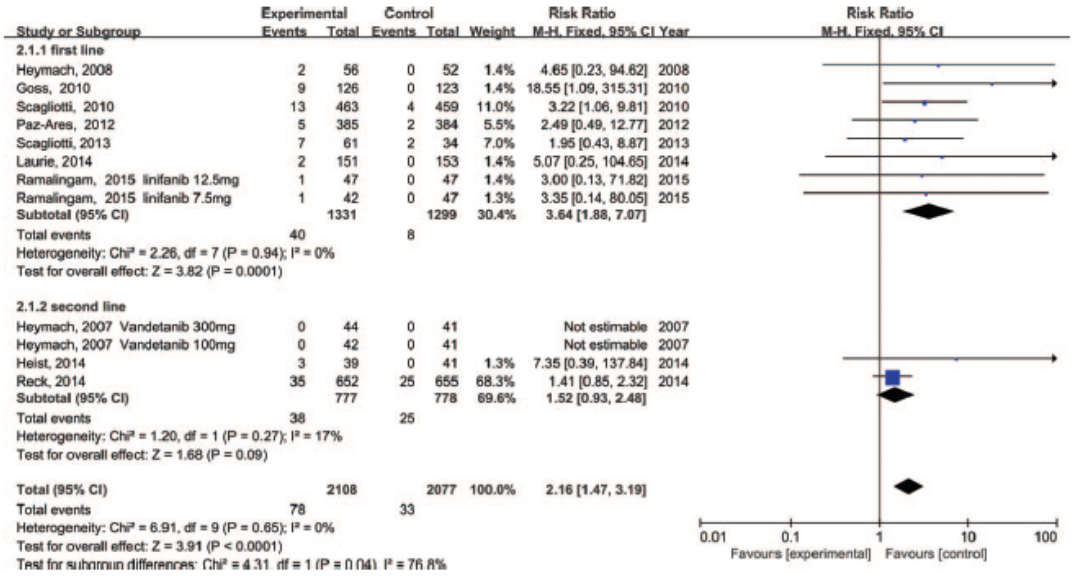


Figure 5. Forest plot and pooled risk ratio for fatal adverse events.

Anmerkung/Fazit der Autoren

This is a comprehensive meta-analysis that specifically evaluated the grade ≥3, serious and fatal toxicities of adding VEGFR-TKIs to chemotherapies in advanced NSCLC patients, and also the most reported specific grade ≥3 AEs. Our results show that the addition of VEGFR-TKIs to chemotherapies in NSCLC significantly increases grade ≥3 toxicity, SAEs, and FAEs compared with traditional chemotherapy alone, especially in the first treatment line. Monitoring AEs, especially haematologic AEs during VEGFR-TKIs therapy, is recommended.

Liu GF et al., 2019 [46].

Efficacy and adverse events of five targeted agents in the treatment of advanced or metastatic non-small-cell lung cancer: A network meta-analysis of nine eligible randomized controlled trials involving 5,059 patients.

Fragestellung

to conduct a comprehensive review for assessing the efficacy and adverse events of erlotinib, gefitinib, vandetanib, dacomitinib, and icotinib in the treatment of NSCLC patients with network meta-analysis.

Methodik

Population:

- patients with advanced or metastatic NSCLC aged between 20 and 95 years

Intervention/Komparator:

- NMA: placebo, erlotinib, gefitinib, vandetanib, dacomitinib, and icotinib

Endpunkte:

- PFS, overall response rate (ORR), disease control rate (DCR), diarrhea, fatigue, rash, and cough

Recherche/Suchzeitraum:

- PubMed and Cochrane Library from inception to May 2016

Qualitätsbewertung der Studien:

- Cochrane risk assessment tool bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 RCTs that satisfy the inclusion criteria were involved in this meta-analysis.
- A total of 5,059 patients with advanced or metastatic NSCLC were involved, in which the number of patients who received erlotinib was relatively larger.

Charakteristika der Population:

- The subjects in five studies included in this network meta-analysis were from the Asians and that in other four enrolled studies were from the Caucasians. In addition, nine included studies were all two-arm trials.

TABLE A1 Baseline characteristics of included studies

First author	Year	Country	Follow-up (year)	Interventions		Sample size			Gender (Male/Female)		Age (years)	
				T1	T2	Total	T1	T2	T1	T2	T1	T2
S. S. Ramalingam	2016	Australia	5.5	B	E	121	55	66	28/27	33/33	62 (34–79)	61 (32–84)
K. Kelly	2015	America	2	A	B	973	350	623	209/141	366/257	61.8 ± 9.34	62.0 ± 9.28
Y. Shi	2013	China	1	C	F	395	196	199	111/85	117/82	57 (50–64)	57 (50–62)
L. Zhang	2012	China	1	A	C	296	148	148	92/56	83/65	55 (20–75)	55 (31–79)
Y. L. Wu	2012	China	3	A	B	125	65	60	42/23	40/20	54 (30–77)	55 (33–73)
J. S. Lee	2012	Korea	2	A	D	924	307	617	147/160	288/329	60 (21–84)	60 (20–85)
S. T. Kim	2012	Korea	2	B	C	96	48	48	7/41	7/41	56 (32–81)	60 (37–83)
R. B. Natale	2011	America	2	B	D	1,240	617	623	393/224	381/242	61 (26–85)	61 (26–92)
F. Cappuzzo	2010	Italy	3	A	B	889	451	438	338/113	321/117	60 (30–81)	60 (33–83)

Note. A, placebo; B, erlotinib; C, gefitinib; D, vandetanib; E, dacomitinib; F, icotinib; NR, not reported; T, treatment.

Qualität der Studien:

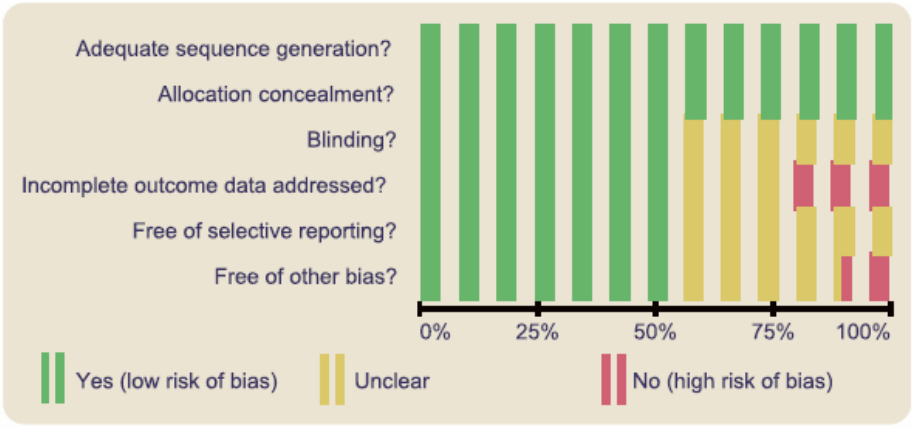


FIGURE A2 Cochrane systematic bias evaluation chart of nine included studies [Color figure can be viewed at wileyonlinelibrary.com]

Studienergebnisse:

- Pairwise meta-analysis of efficacy and adverse events of five targeted drugs
  - In terms of efficacy, the PFS (months) of NSCLC patients treated with gefitinib was relatively shorter when compared with patients treated with icotinib (WMD = −2.50; 95% CI = −3.17 to−1.83); compared with NSCLC patients treated with gefitinib,
  - the PFS of patients treated with placebo and erlotinib was shorter (placebo vs. gefitinib: WMD= −2.20; 95% CI = −2.65 to − 1.75; erlotinib vs. gefitinib: WMD= −1.80; 95% CI = −2.64 to − 0.96);
  - the placebo-related ORR was comparatively lower when compared with gefitinib and erlotinib (gefitinib vs. placebo: OR = 0.02; 95% CI = 0.00–0.16; erlotinib vs. placebo: OR = 0.37; 95% CI = 0.23–0.59);
  - the placebo-related DCR was comparatively low when compared with gefitinib and erlotinib (gefitinib vs. placebo: OR = 0.41; 95% CI = 0.25–0.66; erlotinib vs. placebo: OR = 0.55; 95% CI = 0.42–0.71).
  - In terms of adverse events, compared with erlotinib (OR = 0.16; 95% CI = 0.12–0.21), gefitinib (OR = 0.29; 95% CI = 0.15–0.57), and vandetanib (OR = 0.15; 95% CI = 0.10–0.22),

- the placebo-related incidence of diarrhea was comparatively lower; compared with NSCLC patients treated with vandetanib, patients treated with erlotinib had relatively lower incidence of diarrhea (OR = 0.61; 95% CI = 0.49–0.77);
- placebo-related incidence of fatigue was relatively lower than erlotinib (OR = 0.69; 95% CI = 0.48–0.99);
- compared with NSCLC patients treated with gefitinib, patients treated with erlotinib had relatively higher incidence of fatigue (OR = 10.36; 95% CI = 1.14–363.58);
- compared with erlotinib (OR = 0.06; 95% CI = 0.05–0.08), gefitinib (OR = 0.11; 95% CI = 0.06–0.20) and vandetanib (OR = 0.17; 95% CI = 0.11–0.25), patients treated with placebo had comparatively lower incidence of rash;
- compared with vandetanib, the incidence of rash in patients treated with erlotinib was relatively higher (OR = 1.58; 95% CI = 1.24–2.01);
- compared with gefitinib, placebo was related to comparatively higher incidence of cough (OR = 2.40; 95% CI = 1.05–5.45).

- Network evidence of the population that received five targeted drugs
  - This study included five targeted agents: erlotinib, gefitinib, vandetanib, dacomitinib, and icotinib. Conclusions can be drawn that the number of patients treated with erlotinib, vandetanib, and gefitinib in the treatment of advanced or metastatic NSCLC was relatively larger, and the number of patients treated with dacomitinib and icotinib in the treatment of advanced or metastatic NSCLC was relatively smaller.
  - When compared with placebo, the ORR of patients with advanced or metastatic NSCLC who were treated with gefitinib was comparatively higher (OR = 14.92; 95% CI = 1.62–285.70);
  - the DCR of patients treated with erlotinib and gefitinib was relatively higher than those treated with placebo (erlotinib vs. placebo: OR = 1.82; 95% CI = 1.01–3.21; gefitinib vs. placebo: OR = 2.44; 95% CI = 1.16– 5.16);
  - four targeted drugs (placebo, erlotinib, gefitinib, and icotinib) indicated no significant difference in terms of PFS
  - Compared with placebo, patients with advanced or metastatic NSCLC who were treated with erlotinib, gefitinib, and vandetanib were associated with relatively higher incidences of diarrhea (erlotinib vs. placebo: OR = 5.76, 95% CI = 3.81-10.09; gefitinib vs. placebo: OR = 4.02; 95% CI = 2.00-8.94; vandetanib vs. placebo: OR = 8.45; 95% CI = 4.40-15.48);
  - patients treated with erlotinib suggested relatively higher incidence of fatigue when compared with gefitinib (OR = 14.11; 95% CI= 1.10–442.90);
  - compared with placebo, patients treated with erlotinib, gefitinib, vandetanib, and icotinib indicated relatively higher incidence of rash (erlotinib vs. placebo: OR = 14.79; 95% CI = 9.48–25.70; gefitinib vs. placebo: OR = 9.64; 95% CI = 4.14–22.45; vandetanib vs. placebo: OR = 7.92; 95% CI = 3.89–16.24; icotinib vs. placebo: OR = 6.79; 95% CI = 1 89–23.54);
  - in terms of cough, no significant difference was detected in the incidence of cough among the three targeted agents (placebo, gefitinib, and erlotinib)
- SUCRA value of efficacy and adverse events of five targeted drugs
  - the SUCRA value of five targeted agents for the treatment of advanced or metastatic NSCLC indicated that with regard to efficacy, icotinib has the highest SUCRA value for

PFS (months) and DCR (PFS: 83%; DCR: 77.8%), and the SUCRA value of gefitinib ranked highest with regard to ORR (83.4%) among the five targeted agents. Among the five targeted agents, erlotinib had the lowest SUCRA value in the aspect of adverse events, such as rash, cough, and fatigue (fatigue: 44.5%; rash: 24.2%; cough: 43.5%), and vandetanib had the lowest SUCRA value in terms of diarrhea (28.8%).

Anmerkung/Fazit der Autoren

To briefly conclude, this network meta-analysis revealed that the efficacies of gefitinib and icotinib for advanced or metastatic NSCLC were comparatively better; in terms of adverse events, the toxicities of erlotinib and vandetanib were relatively greater. However, these conclusions need further validation by more fully designed sample parameters and a more comprehensive analysis of multiple factors. In addition, the subjects of enrolled studies regarding the history of any inflammatory disease such as chronic obstructive pulmonary disease (COPD) confine the efficacy to a certain extent. It is also noteworthy that differences between the sample sizes of interventions may lead to the restriction of universal conclusion. Nevertheless, this network metaanalysis could have certain guiding implications for the clinical application and treatment of advanced or metastatic NSCLC. A further study could be designed with larger sample parameters and more involved factors, thereby offering more choice for clinical treatment.

Kommentare zum Review

- Icotinib und Vandetanib sind für dieses Anwendungsgebiet nicht in Deutschland zugelassen.

Hess LM et al., 2018 [31].

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

Sheng M et al., 2016 [74].

Targeted drugs for unselected patients with advanced non-small cell lung cancer: a network meta-analysis

Fragestellung

A systematic review and network meta-analysis of randomized controlled trials comparing the efficacy and safety of first-line chemotherapy and targeted therapy in unselected patients with advanced NSCLC and also estimated the rank probability of each treatment, expecting it will be helpful for making evidence-based clinical decision for physicians

and patients. Methodik

Population:

- patients with confirmed locally advanced or metastatic NSCLC

Intervention/Komparator

- NMA: first-line treatments
  - at least two arms of different treatment regimens, chemotherapy, placebo or targeted therapy

Endpunkte:

- ORR and safety

Recherche/Suchzeitraum:

- from inception to 2015 using PubMed, EMBASE and Cochrane Library

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 24 randomized clinical trials
- Five trials applied bevacizumab (Bev) (9,10,32-34), seven trials applied gefitinib (Gef) (35-41), ten trials applied erlotinib (Erl) (24,42-50) and the other two trials applied cetuximab (Cet)
- A total of 13,060 patients were enrolled, patients median age varied from; 38.2–100% of patients were adenocarcinoma; sixteen trials predominantly enrolled White patients whereas other six had a majority of Asian patients excluding the unreported data.
- For the outcomes of interest, eight different treatment arms were assessed: placebo, CT, Erl, Gef, Erl + CT, Gef + CT, Bev + CT,Cet + CT.

Qualität der Studien:

- 14/24 studies were reported as high quality and the remaining 10 studies as acceptable quality.
- Based on the GRADE criteria, the overall quality of the evidence about ORR, neutropenia, rash and diarrhea were rated as moderate, and the quality of the evidence about thrombocytopenia and anemia were rated as low

Studienergebnisse:

- Pairwise comparisons
  - For unselected patients, Bev + CT (OR =2.19; 95% CI, 1.55–3.11; P<0.001), Erl + CT (OR =1.64; 95% CI, 1.05–2.57; P=0.031) and Cet + CT (OR =1.68; 95% CI, 1.96–2.36; P=0.003) were associated with statistically significantly higher incidence of ORR than CT.
  - The estimated OR for Gef + CT and Gef compared with CT showed a consistent trend for higher ORR, although they did not reach statistical significant. However, Erl was associated with inferior efficacy compared with CT (OR =0.81; 95% CI, 0.23–2.78; P=0.735).
  - In terms of rash and diarrhea, Erl + CT, Gef + CT, Cet + CT and Gef were associated with significantly greater odds compared with CT. While CT showed statistically significantly more incidence of neutropenia and anemia compared to Gef and Erl. The risk of thrombocytopenia did not show any statistically significant difference among all the treatment arms except CT vs. Gef (OR =0.13; 95% CI, 0.03–0.61; P=0.009).
  - An estimate consistent with large heterogeneity >50%) was seen in three comparisons for ORR, two comparisons for rash, one comparison for neutropenia and one comparison for thrombocytopenia, while no large heterogeneity was seen in comparisons concerning anemia and diarrhea.
- Network meta-analysis

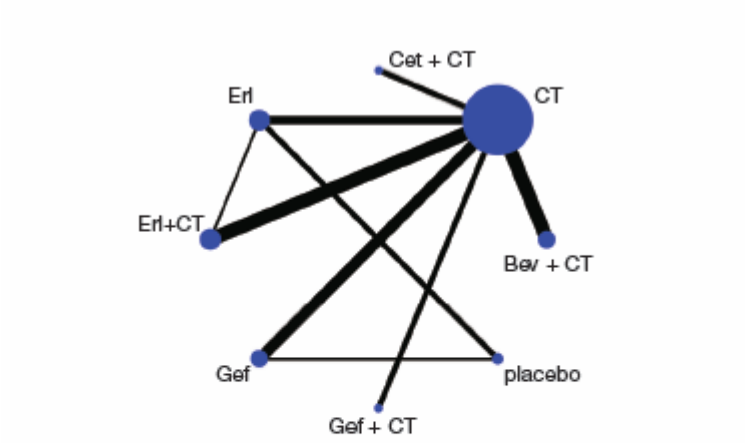


Figure 2 Network of studies comparing objective response rate of different agents for unselected patients with advanced non-small cell lung cancer. Each link represents at least one study, width of each link is number of trials per comparison, size of each node is proportional to the total sample size. CT, chemotherapy; Bev, bevacizumab; Gef, gefitinib; Erl, erlotinib; Cet, cetuximab.

  - showed that Bev + CT had a statistically significantly higher incidence of ORR relative to the other six different treatments, including placebo (OR =6.47; 95% CI, 3.85–10.29), Erl (OR =2.81; 95% CI, 2.08–3.70), CT (OR =1.92; 95% CI, 1.61–2.28), Gef (OR =1.40; 95% CI, 1.10–1.75), Erl + CT (OR =1.46; 95% CI, 1.17–1.80) and Gef + CT (OR =1.75; 95% CI, 1.36–2.22), whereas placebo and Erl were associated with statistically significantly lower incidence of ORR.
  - Trend analyses of rank probability revealed that Bev + CT had the highest probability of being the best treatment arm in term of ORR, followed by Cet + CT.

- o Meanwhile, Cet + CT showed significant severer rash and thrombocytopenia compared with Bev + CT. Gef was probable to be the rank 3 for ORR but was associated with relatively low risk for grade ≥3 toxicities.

Anmerkung/Fazit der Autoren

In summary, our study suggested that the use of bevacizumab in combination with chemotherapy in the treatment of unselected patients with advanced NSCLC may offer a greater ORR and moderate toxicity. We hope this network meta-analysis may guide physicians in the therapeutic decision-making.

Kommentare zum Review

- Cetuximab besitzt für dieses Anwendungsgebiet in Deutschland keine Zulassung.

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). In the subsequent setting, the single use of anti-PD1/PD-L1 monoclonal antibodies (atezolizumab alone, pembrolizumab alone and nivolumab alone) showed significant survival benefit as compared to docetaxel or pemetrexed. The combination of ramucirumab and docetaxel

also resulted in survival advantage when compared to docetaxel (HR: 0.79; 95% CI: 0.64–0.98).

→ Overall, in the subsequent setting, the single use of anti-PD1/PD-L1 monoclonal antibodies appears superior to anti-angiogenic therapies in terms of OS. The use of nivolumab alone was associated with statistically significant survival benefit as compared to the combination of ramucirumab and docetaxel (HR: 0.79; 95%CI: 0.64–0.98), the combination of sunitinib and pemetrexed (HR: 0.49; 95%CI: 0.31–0.78), and the combination of vandetanib and docetaxel (HR: 0.72; 95%CI: 0.58–0.88); the use of pembrolizumab alone (HR: 0.83; 95%CI: 0.65–1.05) and atezolizumab alone (HR: 0.85; 95%CI: 0.7–1.03) were both superior the combination of ramucirumab and docetaxel, although the difference were not statistically significant.

- 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. In the subsequent setting, combination of ramucirumab and docetaxel showed significant increased efficacy compared with docetaxel alone in terms of PFS (HR: 0.74; 95%CI: 0.56–0.98). Although the HR appears to be in favor of pembrolizumab alone and nivolumab alone compared with docetaxel alone, the difference were not statistically significant.
- Toxicity:

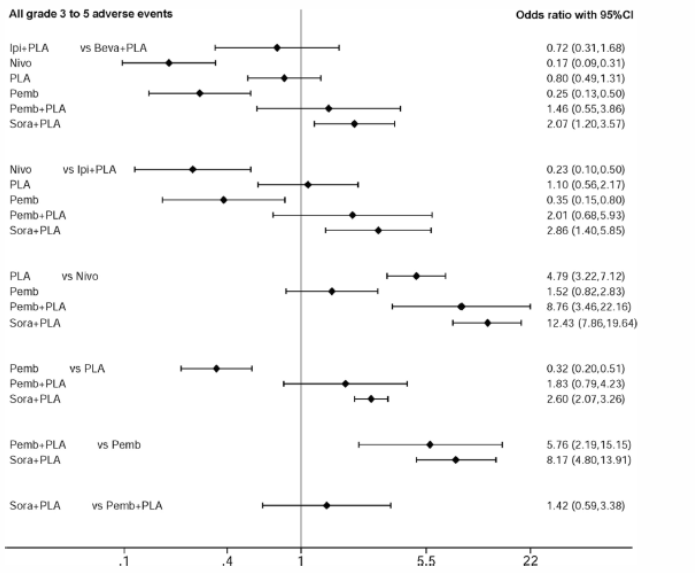


Figure 2. Forest plot of indirect comparison: all grade 3 to 5 adverse events in first line therapy. All individual regimens compared with reference treatment. Odds ratios (OR) and 95% confidence intervals were given. Beva: bevacizumab; Ipi: ipilimumab; Nivo: nivolumab; Pemb: pembrolizumab; Sora: sorafenib;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

Li J et al., 2019 [43].

Meta-analysis of overall incidence and risk of ALK inhibitors-induced liver toxicities in advanced non-small-cell lung cancer.

Fragestellung

We conducted a systematic review of published phase II and III clinical trials, and combined relevant studies for a meta-analysis to evaluate the overall risk of liver toxicity during the administration of ALK inhibitors.

Methodik

Population:

- NSCLC patients assigned to treatment with ALK inhibitors

Intervention:

- ALK inhibitors daily

Komparator:

- placebo or control drug in addition to the same treatment

Endpunkte:

- all-grade and high-grade alanine aminotransferase (ALT) and the increase of aspartate aminotransferase (AST)

Recherche/Suchzeitraum:

- Pubmed, Embase, and the Cochrane Library electronic databases from Jan 2000 to Jan 2018

Qualitätsbewertung der Studien:

- publication bias evaluated by Begg and Egger tests; Jadad scale used to assess the quality of included trials

Ergebnisse

Anzahl eingeschlossener Studien:

- 12 clinical trials (2 418 patients) considered eligible for the meta-analysis
- including 5 Phase III trials [24–28] and 7 Phase II trials [29–35]

Referenzen aus dem Review
[24] Shaw AT, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013;368:2385–94.
[25] Solomon BJ, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014;371:2167–77.
[26] Soria JC, et al. First-line ceritinib versus platinumbased chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet 2017;389:917–29.
[27] Hida T, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet 2017;390:29–39.
[28] Peters S, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med 2017;377:829–38.
[29] Kwak EL, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010;363: 1693–703.
[30] Camidge DR, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol 2012;13:1011–9.
[31] Shaw AT, et al. Ceritinib in ALK-rearranged nonsmall- cell lung cancer. N Engl J Med 2014;370:1189–97.
[32] Shaw AT, et al. Crizotinib in ROS1-rearranged nonsmall- cell lung cancer. N Engl J Med 2014;371:1963–71.
[33] Kim DW, et al. Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. Lancet Oncol 2016;17:452–63.
[34] Ou SH, et al. Alectinib in crizotinib-refractory ALKrearranged non-small-cell lung cancer: a phase II global study. J Clin Oncol 2016;34:661–8.
[35] Shaw AT, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. Lancet Oncol 2016;17:234–42.

Charakteristika der Population:

- baseline Eastern Cooperative Oncology Group performance status: for the majority of patients between 0, 1 and 2
- patients were required to have adequate hepatic, renal and hematological function (inclusion criteria of each trial)

Qualität der Studien:

- all were open-label controlled trials, thus had Jadad score of 3

Studienergebnisse:

- Incidence and relative risk of ALT increase (1 677 patients included in the analysis)

- increase of the ALT was reported in 541 out of 1 677 ALK inhibitors treated patients with an incidence of 26,0% (95% CI: 17,4%–37%)
- Subgroup analysis according to the ALK inhibitors: incidence of ALT associated with ceritinib (56,4%, 95% CI: 38,9%–72,5%) was significantly higher than that of alectinib (13,3%, 95% CI: 9,9%–17,7%) and crizotinib (28,4%, 95% CI: 18,8%–40,5%).
- RR (fixed effect) to develop any grade of ALT increase: 2,37 (95% CI: 1,97–2,86; P<.001) in patients treated with ALK inhibitors compared to chemotherapy (P=,37; I2=0%).
- grade 3 to 4 of the ALT increase (evaluable in 1 884 patients) and the incidence of high grade of ALT increase: 8,4% (95% CI:, 5,1%–13,4%) for ALK inhibitors
- RR to develop grade 3 to 4 of ALT increase: 7,34 (95% CI 3,95–13,63; P<.001) in patients treated with ALK inhibitors compared to chemotherapy
- no significant heterogeneity observed in RR analysis for grade 3 to 4 (P=.27; I2=23,4%)

- Incidence and relative risk of AST increase (1 721 patients included in the analysis)
  - increase of the AST was reported in 466 out of 1721 ALK inhibitors treated patients with an incidence of 23,2% (95% CI: 16,7%–31,4%)
  - Subgroup analysis according to the ALT inhibitors: incidence of AST elevation associated with ceritinib (41,9%, 95% CI: 23,3%–63,1%) was higher than that of alectinib (13,1%, 95% CI: 9,0%–18,6%) and crizotinib (26,3%, 95% CI: 18,6%–35,7%)
  - RR (fixed effect) to develop any grade of,AST increase: 3,27 (95% CI: 2,47–4,34; P<.001) in patients treated with ALK inhibitors compared to controls
  - grade 3 to 4 of the AST increase (evaluable in 1 653 patients) and the incidence of high grade of AST increase: 7,0% (95% CI: 4,8%–10,2%) for ALK inhibitors
  - RR to develop grade 3 to 4 of the AST increase (fixed effect): 11,54 (95% CI : 4,33–30,7; P<.001) in patients treated with ALK inhibitors compared to controls
  - no significant heterogeneity observed with fixed model in the analysis for all grades (P=,12;I2=52,6%) and grade 3 to 4 (p=0,89; I2=0%) of AST increase

Anmerkung/Fazit der Autoren

In conclusion, the findings of the present study offer substantial evidence that ALK inhibitors treatment in advanced NSCLC significantly increases the risk of developing all-grade and high-grade liver toxicities in comparison with controls. Clinicians should recognize liver toxicities promptly as early interventions may alleviate future complications. In addition, more trials are still needed to investigate the potential predictive factors in order to avoid toxicity and premature drug discontinuation.

Lee YC et al., 2019 [39].

Which Should Be Used First for ALK-Positive Non-Small-Cell Lung Cancer: Chemotherapy or Targeted Therapy? A Meta-Analysis of Five Randomized Trials

Fragestellung

This meta-analysis examines whether having targeted therapy as the first- or second-line of therapy affects either progression-free survival (PFS) or overall survival (OS), by pooling evidence from the currently available randomized controlled trials.

Methodik

Population:

- lung cancer patients

Intervention:

- ALK

Komparator:

- chemotherapy

Endpunkte:

- progression-free survival (PFS) or overall survival (OS)

Recherche/Suchzeitraum:

- MEDLINE (EBSCOhost) and PubMed up to 7 May 2018

Qualitätsbewertung der Studien:

- five-point Jadad ranking system on randomization, double-blinding, and withdrawals

Ergebnisse

Anzahl eingeschlossener Studien:

- five articles satisfied the inclusion criteria [1,4–7]

Referenzen aus dem Review
1. Solomon, B.J.; et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N. Engl. J. Med. 2014, 371, 2167–2177.
4. Novello, S.; et al. Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: Results from the phase III ALUR study. Ann. Oncol. 2018, 29, 1409–1416.
5. Soria, J.C.; et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): A randomised, open-label, phase 3 study. Lancet 2017, 389, 917–929.
6. Shaw, A.T.; et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N. Engl. J. Med. 2013, 368, 2385–2394.
7. Shaw, A.T.; et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): A randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2017, 18, 874–886.

Charakteristika der Population:

- 1 404 patients included: 721 assigned to ALK inhibitors, 683 assigned to control arms (Novello et al. [4] randomized patients at a ratio of 2:1 to receive alectinib or chemotherapy)
- median age of the patients: 55
- brain metastasis status: balanced among all studies (between 26 and 74%)
- setting: one study in second line; one study after two prior lines, crizotinib, platinum-based doublet; one Study after 1 or 2 chemotherapy, and crizotinib resistance

Qualität der Studien:

- all were open-label, phase 3 trials
- two of the studies scored 3, two studies scored 2, and one study scored 1
- cross-over after chemotherapy failure allowed in all studies, inverse was not mentioned

Studienergebnisse:

- treatment with ALK inhibitors associated with
  - HR in PFS: 0,48 (95% CI: 0,42–0,55), significant reduction
  - HR in OS: 0,88 (95% CI: 0,72–1,07), no significant reduction
  - no significant heterogeneity found
- sensitivity analysis for first-line ALK targeted therapy from two trials [1,5] (Anmerkung: beide Studien erreichen 2 Punkte nach der Bewertung nach Jadad)
  - pooled HR for PFS: 0,50 (95% C: 0,41–0,60), significant reduction
  - HR for OS 0,77 (95% CI: 0,59–1,02), no significant reduction
  - no significant heterogeneity observed

Anmerkung/Fazit der Autoren

The choice of the first-line treatment for ALK-positive, non-small cell lung cancer needs to take into account cost–benefit considerations and the patient-reported quality of life, as the treatment sequence did not cause a significant difference in overall survival.

Kassem L et al., 2019 [34].

Safety issues with the ALK inhibitors in the treatment of NSCLC: A systematic review

Fragestellung

To adequately describe the exact safety profile of each of those agents we conducted a systematic review of prospective trials testing various ALK inhibitors (ALKi) in NSCLC. We compare common AE with each ALKi along with clinical approach to management.

Methodik

Population:

- patients with non-small cell lung cancer

Intervention:

- ALK inhibitors (i.e. Crizotinib, Alectinib, Ceritinib, Brigatinib, Lorlatinib, Entrectinib, X-396)

Komparator:

- nicht definiert

Endpunkte:

- safety results (for the common AEs)

Recherche/Suchzeitraum:

- PubMed database, ASCO library database, ESMO, IASLC and ELCC meeting abstract databases from January 2005 to August 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- A total of 14 studies with 2 793 patients were included in the final analysis:
  - two phase IB trials, seven phase II trials and five phase III trials

Referenzen aus dem Review

A) Crizotinib (CRZ) trials

Camidge, D.R., et al., 2012. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol. 13 (10), 1011–1019. (PROFILE 1001)

Shaw, A.T., et al., 2013. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N. Engl. J. Med. 368 (25), 2385–2394. (PROFILE 1007)

Solomon, B.J., et al., 2014. First-line crizotinib versus chemotherapy in ALK -Positive lung Cancer. N. Engl. J. Med. 371 (23), 2167–2177. (PROFILE 1014)

Hida, T., et al., 2017. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet [Internet] 390 (10089), 29–39. (Crizotinib arm)

B) Alectinib (ALC) trials

Seto, T., et al., 2013. (RO5424802) for patients with ALK-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1-2 study. CH5424802. Lancet Oncol. 14 (7), 590–598.

Ou S-HI, et al. Alectinib in Crizotinib-Refractory ALK-Rearranged Non-Small-Cell Lung Cancer: A Phase II Global Study. J Clin Oncol. 2018 Mar 1;34(7):661–668. NP28673

Shaw, A.T., et al., 2016. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. Lancet Oncol. 17 (Febuary (2)), 234–242. NP28761, North America

J-Alex (Alectinib arm) Hida et al., 2017

C) Ceritinib (CRT) trials:

Kim, D.W., et al., 2016a. Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. Lancet Oncol. 17 (4), 452–463.

Crino, L., et al., 2016. Multicenter phase II study of whole-body and intracranial activity with ceritinib in patients with ALK-rearranged non-small-cell lung cancer previously treated with chemotherapy and crizotinib: results from ASCEND-2. J. Clin. Oncol. 34 (24), 2866–2873.

Soria, J.-C., et al., 2017. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged nonsmall-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet 4;389 (March (10072)), 917–929.

ASCEND-3 (Felip et al., 2016; Park and Tan, 2015; Felip et al., 2016)

Shaw, A.T., et al., 2017. Ceritinib versus chemotherapy in patients with ALK -rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 18 (July (7)), 874–886.

D) Other ALK inhibitors:

Gettinger, S.N., et al., 2016. Activity and safety of brigatinib in ALK-rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial. Lancet Oncol. 2045 (16), 1–14.

Kim, D., et al., 2017. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase – positive non –small-cell lung Cancer : a randomized, multicenter phase II trial. J. Clin. Oncol. 35 (22).

  - fulltext of ASCEND-3 trial (Felip et al., 2016; Park and Tan, 2015; Felip, 2015) was not published at time of review
- ALK inhibitors used as a monotherapy in all studies
- one study randomized crizotinib versus alectinib (Hida et al., 2017)
- four of the included studies compared an ALK inhibitor to chemotherapy

Charakteristika der Population:

- majority of patients was metastatic
- patients with locally advanced (stage III) disease not eligible for local therapy
- median age: from 48 to 61 years
- most studies allowed prior platinum based chemotherapy for advanced disease

Qualität der Studien:

- Cochrane risk of bias tool not used as the majority of studies was nonrandomized

Studienergebnisse:

- differences in the toxicity patterns between the different ALK inhibitors:
  - more GI and hepatic toxicities with Ceritinib,

  - more visual disorders with Crizotinib,
  - more dysgeusia with crizotinib and Alectinib and
  - possibly more respiratory complications with Brigatinib
- most AEs were low grade
- treatment-related deaths associated with ALK inhibitors: 0–1% of patients
- Gastrointestinal toxicities
  - most common adverse events (AEs) observed with ALK inhibitors
  - nausea (up to 83%), vomiting (up to 67%) and diarrhea (up to 86%),
- Hepatic toxicities
  - elevation of liver enzymes occurred in up to 60%
- Fatigue, Visual disorders and peripheral edema
  - fatigue (up to 43%)
- Hematological toxicities
  - most common haematological toxicities observed with ALK inhibitors: neutropenia, anemia
  - neutropenia much lower than observed with chemotherapy
- Miscellaneous toxicities
  - Brigatinib, has a unique profile of increased early onset pulmonary AEs and hypertension
- Serious AEs (SAEs) and treatment-related deaths
  - occurred in the range of 0% to 25% across all studies
  - discrepancy across different studies mostly due to inconsistent definition of treatment-related versus disease-related SAEs

Anmerkung/Fazit der Autoren

Most of adverse effects of ALKi can be managed efficiently via dose modifications or interruptions. Timely identification of each ALKi pattern of toxicity can prevent treatment-related morbidity and mortality in this palliative setting.

Kommentare zum Review.

- LK received a research grant from Novartis oncology. KSS received a study grant from Dubai Harvard Foundation (DHFMR). Other authors have nothing to declare.

Zhao X et al., 2018 [87].

Ceritinib Alone for Crizotinib-naive Versus Crizotinib-pretreated for Management of Anaplastic Lymphoma Kinase-rearrangement None-Small-cell Lung Cancer: A Systematic Review

Fragestellung

The present systematic review aimed to assess the discrepancies in the efficacy and safety of ceritinib in crizotinib-naive and crizotinib-pretreated patients with ALK-rearrangement NSCLC detected by the whole body and intracranial responses.

Methodik

Population:

- crizotinib-naïve and crizotinib-pretreated patients with ALK-rearrangement NSCLC

Intervention:

- ceritinib

Komparator:

- k.A.

Endpunkte:

- ORR, PFS, DCR, and ORR for intracranial metastasis

Recherche/Suchzeitraum:

- Medline (via PubMed), Embase, Ovid, Web of Science, the Cochrane Library, ClinicalTrials.gov, Science Direct, and conference abstracts, between inception and August 2017

Qualitätsbewertung der Studien:

- Effective Public Health Practice Project Tool (EPHPP) assesses 6 aspects of interventions: selection bias, study design, confounders, blinding, data collection method, and withdrawals and dropouts, all of which is synthesized to calculate a global study rating, identified as strong, moderate, or weak

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 reports (7 trials) with 1 015 participants included, reported from 2014 to 2017
- nine single-arm clinical studies were involved, including 968 patients altogether
  - 4 described ceritinib for crizotinib-naïve patients [18,19,21,22] and
  - 5 described ceritinib for crizotinib-pretreated patients [18-20,23,24]

Referenzen aus dem Review

18. Shaw AT, et al. Ceritinib in ALK-rearranged nonesmall-cell lung cancer. N Engl J Med 2014; 370:1189-97.
19. Kim DW, et al. Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. Lancet Oncol 2016; 17:452-63.
20. Crinò L, et al. Multicenter phase II study of whole-body and intracranial activity with ceritinib in patients with ALK-rearranged non-small-cell lung cancer previously treated with chemotherapy and crizotinib: results from ASCEND-2. J Clin Oncol 2016; 34:2866-73.
21. Felip E, et al. ASCEND-3: a single-arm, open-label, multicentre phase II study of ceritinib in ALKi-naïve adult patients (pts) with ALKrearranged (ALKþ) non-small cell lung cancer (NSCLC). J Clin Oncol 2015; 90:208-17.
22. Soria JC, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet 2017; 389:917-29.
23. Shaw AT, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2017; 18:874-86.
24. Hida T, et al. Ceritinib in patients with advanced, crizotinib-treated, anaplastic lymphoma kinase-rearranged NSCLC: Japanese subset. Jpn J Clin Oncol 2017; 47:618-24.

Charakteristika der Population:

- Mean Age: 45,5-56,0 years
- Female Sex: 50-67%
- Brain Metastases: 31-79%

Qualität der Studien:

- 4 (57%) classified as strong and 3 (43%) as moderate
- selection bias for 6 reports (86%) was rated as strong
- most studies representative of the target population
- blinding for 5 studies (71%) was strong (to blind the assessing researcher in most studies; was not always possible, two reports were rated as moderate because this was not reported)
- confounders and data collection methods were also relatively strong domains, with 4 (57%) and 6 (86%) reports, respectively, rated as strong (reliable and valid data collection methods used, withdrawals and dropouts reported, 1 study insufficiently described the data collection process)

Studienergebnisse:

Effect of NSCLC

- analysis for crizotinib-naive pooled data revealed a pooled ORR of 68,9% (95% CI: 64,3%-73,1%; no heterogeneity observed)
- PFS for crizotinib-naive treatment: 14,62 months (95%CI: 11,99-17,78 months; no heterogeneity observed)
- no evidence of publication bias
- most common types of **adverse events** and their incidence included
  - diarrhea (83.7%), nausea (74.9%), vomiting (61.5%), fatigue (33.3%), decreased weight (27.2%), decreased appetite (40.5%), increased alanine aminotransferase concentration (46.9%), increased aspartate aminotransferase (38.1%), increased blood alkaline phosphatase concentration (22.0%), and increased gammaglutamyltransferase (20.1%).
  - most adverse events were grade 1 or 2, a small proportion were grade 3 or 4

Effect of Brain Metastases

- pooled intracranial ORR with ceritinib used as the initial regimen: 50,4% (95% CI: 41,6%-59.2%; no heterogeneity observed)

Anmerkung/Fazit der Autoren

Ceritinib is an effective agent for both crizotinib-naive and crizotinib-pretreated patients with locally advanced or metastatic ALK-rearranged NSCLC. Ceritinib has significant activity in crizotinib-naïve patients with brain metastases.

Kommentare zum Review

- Phase I, II, III Studien eingeschlossen

Petrelli F et al., 2018 [68].

Efficacy of ALK inhibitors on NSCLC brain metastases: A systematic review and pooled analysis of 21 studies.

Fragestellung

In the current paper, we performed a pooled analysis, including data from ALK positive NSCLC patients with BMs receiving ALK inhibitors.

Methodik

Population:

- ALK positive NSCLC patients with BMs

Intervention:

- treatment with an ALK inhibitor

Komparator:

- k.A.

Endpunkte:

- intracranial objective response rate (IC ORR), intracranial disease control rate (ICC DCR): complete response, partial response, or stable disease for at least 24 weeks
- median PFS, median OS, one-year OS

Recherche/Suchzeitraum:

- PubMed (MEDLINE), EMBASE, The Cochrane Library, Scopus, and Web of Science, between inception and 30th June 2017

Qualitätsbewertung der Studien:

- assessed by Jadad scale for randomized controlled studies and Newcastle-Ottawa Scale (NOS) for retrospective cohort studies

Ergebnisse

Anzahl eingeschlossener Studien:

- 21studies , which included data from 1 016 patients with ALK positive NSCLC and BMs
  - 7 studies evaluated crizotinib [7-13], 5 ceritinib [14-18], 4 alectinib [19-22], 1 both crizotinib and alectinib [23], 1 included different ALK inhibitors [5], 2 evaluated brigatinib [24, 25]
  - in 1, the used ALK inhibitor(s) not specified [26]
  - 4 studies conducted in first line setting [9, 18, 23, 26]

Referenzen aus dem Review
9. Solomon BJ, et al. Intracranial Efficacy of Crizotinib Versus Chemotherapy in Patients With Advanced ALK-Positive Non-Small-Cell Lung Cancer: Results From PROFILE 1014. J Clin Oncol. 2016; 34(24):2858-65.
18. Soria JC, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet. 2017.
23. Peters S, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2017.
26. Doherty MK, et al. Treatment options for patients with brain metastases from EGFR/ALK-driven lung cancer. Radiother Oncol. 2017; 123 (2):195-202.

  - 14 studies included patients pre-treated with at least one line of therapy [5, 7, 8, 12-17, 19-22, 25],
  - 3 a cohort of patients receiving ALK inhibitors in different lines (first or beyond) [10, 11, 24]

Charakteristika der Population:

- No patient of the first-line studies had a previous chemotherapy.
- Between 38 and 100% had a previous local therapy.

Qualität der Studien:

- RCTs (Solomon BJ, et al.; Soria JC, et al.; Peters S, et al.): 4 points on Jadad scale with moderate risk of selection and attrition bias
- Retrospective study (Doherty MK, et al.): 6 points on NOS scale
- no evidence of publication bias observed

Studienergebnisse:

- **IC ORR and IC DCR** available in three out of five studies
- pooled ICC ORR: 39,17% (95%CI 13.1-65,2%), with heterogeneity observed
- pooled IC DCR: 70,3% (95%CI 47,7-86,0%), random effect model
- ICC ORR with alectinib: 59,0% (95%CI 29,3-83,0%),
- ICC ORR with ceritinib: 56,6% (95%CI 33,3-77,4%),
- ICC ORR with crizotinib: 26,0% (95%CI 8,9-55,9%)
- median **PFS** in naive patients: 7,3 months (range 5,9-10,7),
- median **IC PFS** was 13,2 months (range 7,0-15,7)
- median **OS**: 23 months
- pooled **one-year OS:** 64,0% (range 59,0-81,0%), data from two studies

Anmerkung/Fazit der Autoren

In conclusion, there is evidence, albeit of limited quality, that ALK positive NSCLC patients with BMs derive significant clinical benefit from ALK inhibitors with or without previous (whole) brain radiotherapy, and the efficacy is similar to that observed for extracranial systemic disease.

Based on these data, ALK inhibitors are effective in both naive and pre-treated patients with similar IC ORR and IC DCR, irrespective of the line of therapy.

Kommentare zum Review

- Funding: The authors received no specific funding for this work.
- Competing interests: The authors have declared that no competing interests exist.

Liu B et al., 2018 [45].

Incidence and risk of hepatic toxicities associated with anaplastic lymphoma kinase inhibitors in the treatment of non-small-cell lung cancer: a systematic review and meta-analysis

Fragestellung

We conduct a systematic review and meta-analysis of published data associated with ALK-TKIs to investigate the overall incidence and risk of liver toxicities with the administration of these drugs.

Methodik

Population:

- NSCLC patients

Intervention:

- ALK-TKIs

Komparator:

- k.A.

Endpunkte:

- Hepatotoxicity (all grades and grade 3–4)
  - increase of alanine aminotransferase (ALT),
  - increase of aspartate aminotransferase (AST)

Recherche/Suchzeitraum:

- Pubmed (data from Jan 2000 to Jan 2017), Embase (data from Jan 2000 to Jan 2017) and the Cochrane Library electronic databases, abstracts, clinical trial registration website (http://www.ClinicalTrials.gov)

Qualitätsbewertung der Studien:

- assessed by Jadad scale and Newcastle-Ottawa Scale (NOS)

Ergebnisse

Anzahl eingeschlossener Studien:

- 10 prospective trials, a total of 1 908 patients available for meta-analysis
  - 3 phase III [24–26]

Referenzen aus dem Review
24. Shaw AT, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med. 2013; 368:2385–2394.
25. Solomon BJ, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014; 371:2167–2177.
26. Soria JC, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet. 2017; 389:917–929.

  - 7 phase II trials [27–33]

Referenzen aus dem Review
27. Kwak EL, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med. 2010; 363:1693–1703.
28. Camidge DR, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol. 2012; 13:1011–1019.
29. Shaw AT, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med. 2014; 370: 1189–1197.
30. Shaw AT, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med. 2014; 371:1963–1971.
31. Kim DW, et al. Activity and safety of ceritinib in patients with ALK-rearranged nonsmall-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. Lancet Oncol. 2016; 17:452–463.
32. Ou SH, et al. Alectinib in Crizotinib-Refractory ALK-Rearranged Non-Small-Cell Lung Cancer: A Phase II Global Study. J Clin Oncol. 2016; 34:661–668.
33. Shaw AT, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a singlegroup, multicentre, phase 2 trial. Lancet Oncol. 2016; 17:234–242.

Charakteristika der Population:

- Median age (y): 49-54
- Median PFS (m): 3-16,6
- Median OS (m): 20,3 for crizotinib, 22,8 for chemotherapy (one study: Shaw AT, et al.)

Qualität der Studien:

- all of the three randomized controlled trials were open-label controlled trials, thus had Jadad score of 3
- seven non-randomized controlled trials: quality score was high (≥ 6) according to NOS checklists

Studienergebnisse:

- incidences of all-grade
  - aspartate aminotransferase (AST) elevation: 25,2% (95% CI 17,7–34,7%)
  - alanine transaminase (ALT) elevation: were, 26,0% (95% CI 17,8–36,3%)
- incidences of high-grade (grade 3 and 4)
  - AST elevation: 7,0% (95% CI: 5,4–9,0%)
  - ALT elevation: 9,9% (95%CI: 5,6–16,7%)
- sub-group analysis according to ALK-TKIs
  - incidence of liver toxicities associated with ceritinib was higher than that of crizotinib and alectinib
- compared to chemotherapy, ALK-TKIs significantly increased the risk of developing all-grade and high-grade
  - AST elevation (RR 2,30; 95%CI: 1,87–2,83, p < 0,001; RR 10,14; 95% CI: 3,9–26,39, p < 0.001) and
  - ALT elevation (RR 2,37; 95%CI: 1,97–2,86, p < 0.001; RR 7,34; 95% CI: 3,95–13,63, p < 0,001), respectively

Anmerkung/Fazit der Autoren

The use of ALK-TKIs significantly increases the risk of developing all-grade and high-grade liver toxicities in lung cancer patients.

Fan J et al., 2018 [9].

The efficacy and safety of alectinib in the treatment of ALK+ NSCLC: a systematic review and meta-analysis

Fragestellung

We performed this meta-analysis to synthesize the results of different clinical trials to evaluate the efficacy and safety of alectinib.

Methodik

Population:

- ALK+ NSCLC patients

Intervention:

- alectinib at any dose

Komparator:

- k.A.

Endpunkte:

- overall response rate (ORR), disease control rate, progression-free survival, intracranial ORR
- discontinuation rate, rate of dose reduction or interruption due to adverse events, incidence of several adverse events

Recherche/Suchzeitraum:

- PubMed, Web of Science, the Cochrane Library, from the inception through September 5, 2017

Qualitätsbewertung der Studien:

- Cochrane collaboration ROB tool, Newcastle–Ottawa scale (NOS) used

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 studies (2 RCTs and 6 single-arm trials) with 626 patients (255 in the 2 RCTs and 371 in the 6 single-arm trials)
  - 3 studies with ALKi-naïve or untreated patients (Phase II or III)

Referenzen aus dem Review
15. Peters S, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med. 2017; 377(9):829–838.
23. Hida T, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet. 2017;390:29–39.
26. Seto T, et al. CH5424802 (RO5424802) for patients with ALK-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1–2 study. Lancet Oncol. 2013; 14:590–598.

Charakteristika der Population:

- Median age (years): 48-61
- Median duration of follow-up (months): 7,6-18,6

Qualität der Studien:

- Cochrane ROB tool: high risk (2 phase III studies)
- NOS: 6 points (considered to be “moderate”)

Studienergebnisse:

- ORR 70% (95% CI: 57% to 82%),
- disease control rate 88% (95% CI: 82% to 94%),
- progression-free survival 9,36 months (95% CI: 7.38% to 11.34%),
- intracranial ORR 52% (95% CI: 45% to 59%)
- **ALK inhibitor-naïve patients**
  - better responses than crizotinib-pretreated patients (59%, 95% CI: 47% to 71% vs 48%, 95% CI: 38% to 57%)
- aggregate discontinuation rate is 7% (95% CI: 4% to 10%),
- pooled rate of dose reduction or interruption is 33% (95% CI: 24% to 42%)
- incidences of most adverse events were relatively low
- incidences of myalgia (18%) and anemia (25%) higher than with crizotinib

Anmerkung/Fazit der Autoren

Generally, alectinib is a drug with preferable efficacy and tolerable adverse effects, and it is suitable for the treatment of intracranial metastases.

Han S et al., 2018 [28].

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

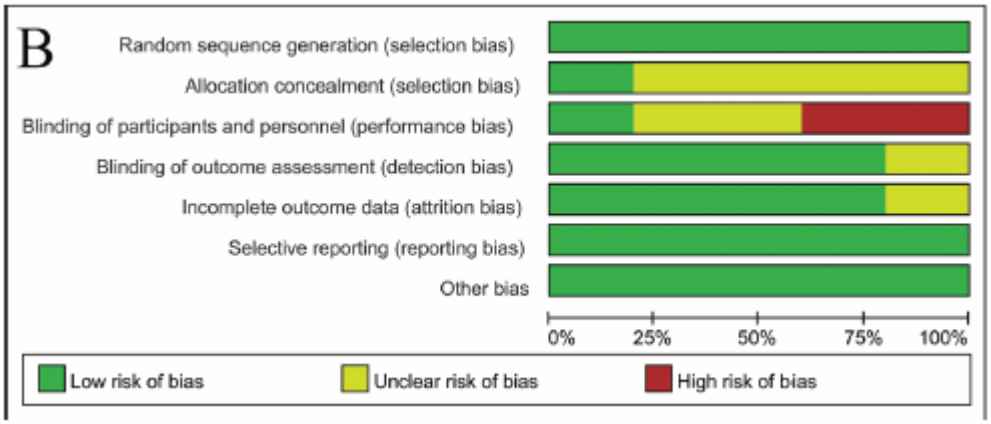
Charakteristika der Population:

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 T:CP+BEV(7.5 mg/kg) T:CP+BEV(15 mg/kg)	32 32 35	adenocarcinoma, large cell carcinoma, squamous cell carcinoma, other	time to disease progression and tumor response rate
Sandler	2006	USA	III	878	C:CP T:CP+BEV(15 mg/kg)	444 434	adenocarcinoma, large cell carcinoma, bronchoalveolar carcinoma, other	overall survival
Soria	2011	Europe	II	85	C:CP T:CP+BEV(15 mg/kg)	41 44	adenocarcinoma, bronchoalveolar carcinoma, large cell carcinoma, other	objective response rate
Niho	2012	Japan	II	180	C:CP T:CP+BEV(15 mg/kg)	59 121	adenocarcinoma, large cell carcinoma, other	progression-free survival
Zhou	2015	China	III	276	C:CP T:CP+BEV(15 mg/kg)	138 138	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.

Zhao S et al., 2018 [86].

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.

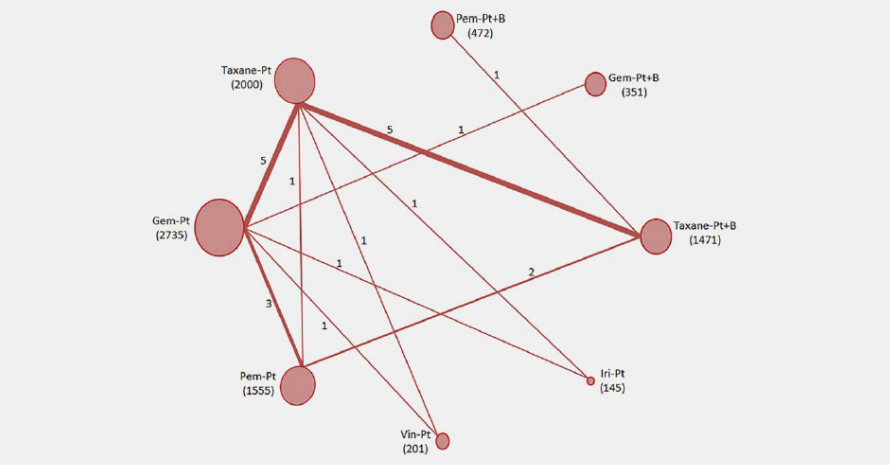


Figure 2. Network of all eligible trials assessing the six treatments in the first-line setting for advanced NS-NSCLC established for the Bayesian network meta-analysis. The size of the nodes is proportional to the number of patients (in parentheses) randomized to receive the treatment. The width of 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.

Sun L et al., 2015 [76].

Efficacy and safety of chemotherapy or tyrosine kinase inhibitors combined with bevacizumab versus chemotherapy or tyrosine kinase inhibitors alone in the treatment of non-small cell lung cancer: a systematic review and meta-analysis

Fragestellung

In the present study, we summarized data from randomized controlled clinical trials comparing chemotherapy or EGFR-TKIs plus bevacizumab with chemotherapy or EGFR-TKIs alone in the first- or second-line treatment of NSCLC to provide evidence for the use of bevacizumab inadvanced NSCLC

Methodik

Population:

- advanced stage IIIB/IV or recurrent NSCLC with ECOG performance status of 0–2 or Karnofsky performance score ≥60)

Intervention/Komparator:

- bevacizumab plus chemotherapy with chemotherapy alone, or comparing bevacizumab plus EGFR-TKIs with TKIs alone, in either first-line or secondline treatment

Endpunkte:

- PFS, OS, ORR, and adverse effects of grade ≥3

Recherche/Suchzeitraum:

- bis 2014

Qualitätsbewertung der Studien:

- Cochrane Collaboration tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Nine studies with 1,779 cases in the bevacizumab group and 1,768 cases in the control group were included in the metaanalysis. Among these studies, there were seven first-line studies including 2,528 cases and two second-line studies including 756 cases.

Qualität der Studien:

- Only two studies were high quality

Studienergebnisse:

- Meta-analysis of the addition of bevacizumab to different lines of treatment:
  - Six first-line studies reported OS results, and all of them compared bevacizumab plus chemotherapy with chemotherapy alone. The results indicated that combination treatment significantly prolonged OS (HRos 0.90, 95 % CIos 0.82–0.99, Pos = 0.029). PFS results were reported in six trials, of which one compared bevacizumab plus erlotinib with erlotinib alone, and the remaining five compared bevacizumab plus chemotherapy with chemotherapy alone. All nine trials analyzed reported ORR results. The results indicated that combination treatment with bevacizumab statistically significantly improved PFS and ORR in the first-line treatment (HRpfs 0.72, 95 % CIpfs 0.66–0.79, Ppfs\0.001; RRorr 1.58, 95 % CIorr 1.28–1.95, Porr\0.001).
  - Two trials reported the survival results of bevacizumab in the second-line treatment of NSCLC, comparing bevacizumab plus chemotherapy to chemotherapy alone, and bevacizumab plus erlotinib to erlotinib alone, respectively. Pooled analysis showed that the addition of bevacizumab to standard second-line treatment did not decrease the risk of death, but it significantly improved PFS and ORR (HRpfs: 0.62, 95 % CI 0.52–0.74, Ppfs<0.001 / RRorr 1.33, 95 % CIorr 1.11–1.60, Porr = 0.002, respectively)

Anmerkung/Fazit der Autoren

In conclusion, the addition of bevacizumab to chemotherapy or erlotinib can significantly improve PFS and ORR in the first- and second-line treatment of advanced NSCLC, with an acceptable and tolerated risk of bleeding events, hypertension, proteinuria, and rash. Bevacizumab plus chemotherapy can also provide an OS benefit; however, whether bevacizumab plus erlotinib can prolong OS needs further validation.

Kommentare zum Review

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

Luo W et al., 2018 [49].

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.

Kommentare zum Review

- Einige Endpunkte sind Laborparameter

Zhou Y et al., 2018 [89].

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 [72].** 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	squamous 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

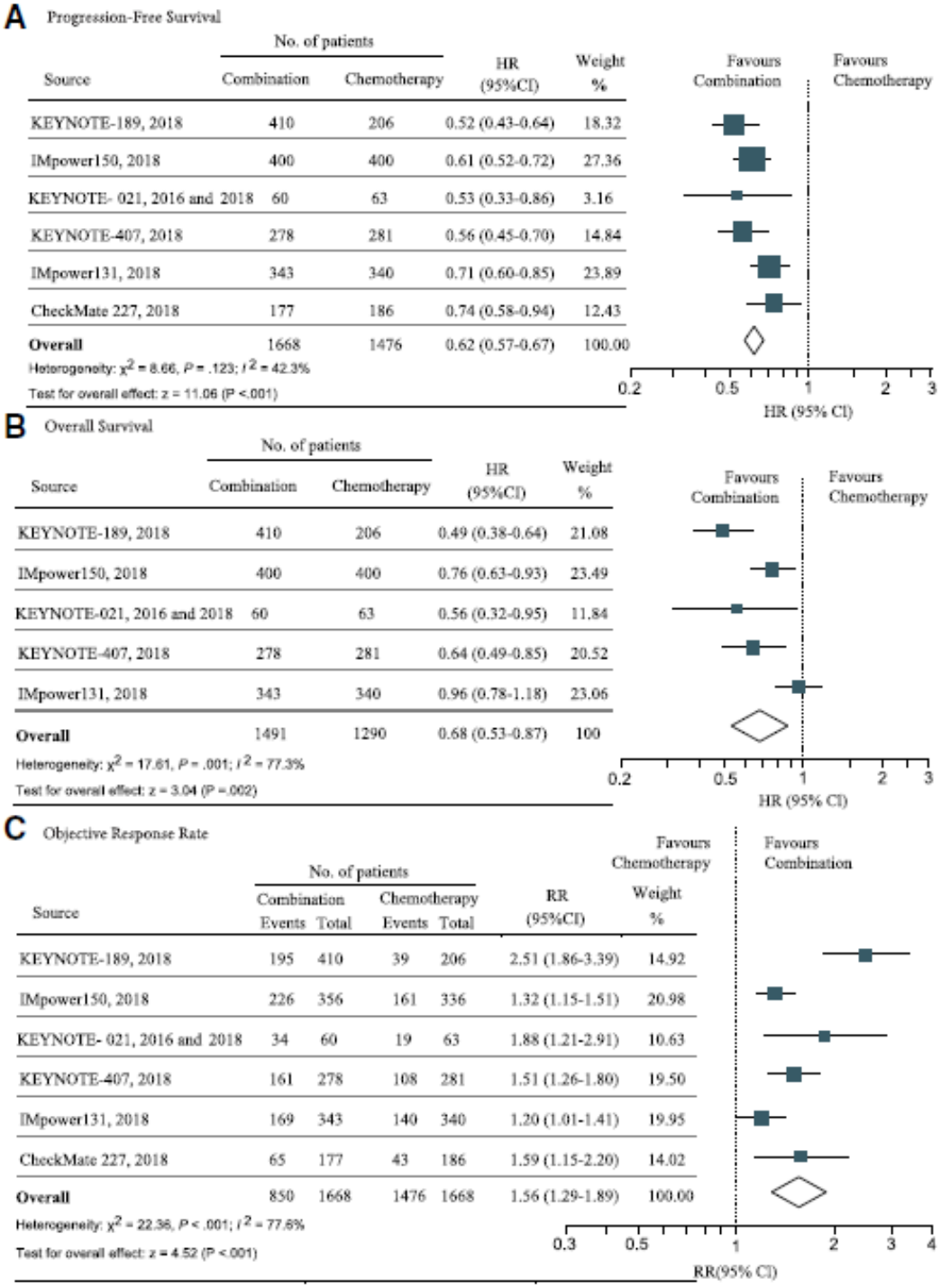


Fig. 1 Forest plot of hazard ratios and risk ratios comparing (a) progression-free survival, (b) overall survival, and (c) objective response rate in patients who received IO-Chemotherapy vs Chemotherapy alone. Squares represent study-specific effect size (HR or RR). The area of square is inversely proportional 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

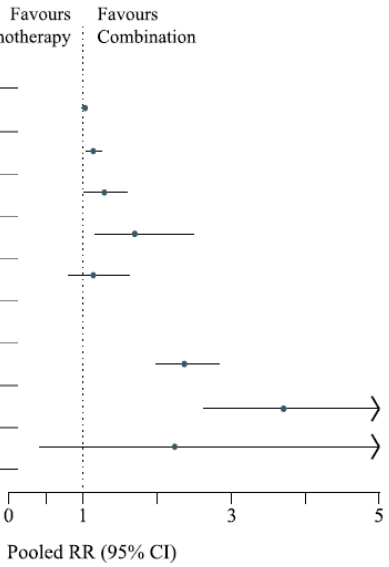


Fig. 4 Forest plot of risk ratios comparing treatment-related adverse events in patients who received IO-Chemotherapy vs Chemotherapy alone. The horizontal line crossing the dot represents the 95%CI of the pooled risk ratio in each subgroup-analysis. No. of trials refers to the number of trials included 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.

Khan M et al., 2018 [35].

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 und Wu TW, 2019 [67].** 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:

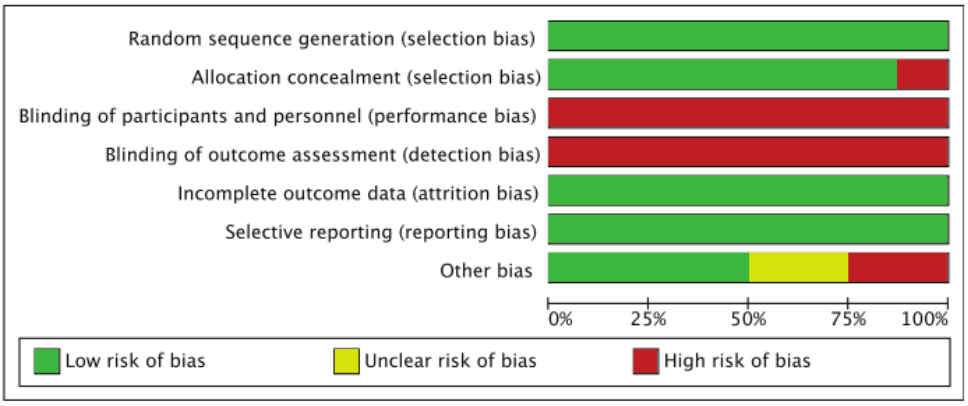


Figure 2. Risk of bias graph. +: low risk of bias; −: high risk of bias; ?: unclear risk of bias.

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.

Chen S, Hu B und Li H, 2018 [5].

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.

Roviello G et al., 2018 [69].

Are EGFR tyrosine kinase inhibitors effective in elderly patients with EGFR-mutated non-small cell lung cancer?

Fragestellung

Therefore, the aim of this study is to perform a systematic review of the available clinical data from randomized trials (RCTs) in order to evaluate the efficacy of anti-EGFR therapies in elderly patients with advanced EGFR-mutated NSCLC.

Methodik

Population:

- Patients ≥ 65 years old (**EGFR-mutated NSCLC**)

Intervention:

- anti-EGFRbased therapy

Komparator:

- chemotherapy, placebo, or other anti-EGFR therapy

Endpunkte:

- PFS

Recherche/Suchzeitraum:

- bis April 2016 (Systematisch in PubMed, the Cochrane Library, and the American Society of Clinical Oncology (ASCO) Meeting)

Qualitätsbewertung der Studien:

- Jadad 5-item scale

Ergebnisse

Anzahl eingeschlossener Studien:

- N=5 (1368 Patienten, 814 were <65 years of age and 597 cases were ≥65) → 4 Phase III-Studien, 1 Phase IIb-Studie)

Charakteristika der Population:

Table 1 Characteristics of the analysed trials

Study	Phase	Primary endpoint	Number of patients experimental arm	Number of patients control arm	Line	Experimental drug	Control arm	Jaded Score
OPTIMAL 2011	III	PFS	82	72	1st	Erlotinib	Gemcitabine + carboplatin	5
EURTAC 2012	III	PFS	86	87	1st	Erlotinib	Standard chemotherapy	5
Lux-Lung 6 2014	III	PFS	242	122	1st	Afatinib	Gemcitabine + cisplatin	5
Lux-Lung 7 2015	IIB	PFS/TTF/ OS	160	159	1st	Afatinib	Gefitinib	4
WJTONG 5108L	III	PFS	185	186	2nd	Erlotinib	Gefitinib	5

- Three studies compared a single EGFR TKI to chemotherapy [7, 9, 12], whist two studies directly compared two EGFR TKIs, afatinib and gefitinib in a head-to-head fashion [18, 19].

Qualität der Studien:

- The median Jadad score was 5, showing a good quality of the included studies

Studienergebnisse:

- The pooled analysis revealed an overall significant improvement in PFS (HR = 0.44, 95% CI 0.28–0.69; p = 0.0004) with the use of EGFR TKIs in EGFR-mutated NSCLC.
- The subgroup analysis, according to the age status, revealed the major effect of EGFR TKIs on PFS has been detected in elderly patients with HR 0.39 (p = 0.008) compared to young patients HR = 0.48 (p = 0.04).

Anmerkung/Fazit der Autoren

Our results suggest that EGFR TKIs had a significant effect in slowing down disease progression in elderly patients with advanced EGFR-mutated NSCLC. Although this family of targeted therapies seems to be more effective in patients in their 70s and older, further analyses of this hypothesis in randomized clinical trials specifically designed to investigate this subset of the population are warranted.

Sheng Z et al., 2017 [75].

The Efficacy of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Non–Small Cell Lung Cancer Harboring Wild-type Epidermal Growth Factor Receptor A Meta-analysis of 25 RCTs.

Siehe auch: Li G et al., 2016 [42].

Fragestellung

To determine the efficacy of first-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) in advanced non–small cell lung cancer (NSCLC) patients with wild-type (WT) EGFR tumors.

Methodik

Population:

- advanced NSCLC, defined as inoperable locally advanced (stage IIIB) or metastatic or recurrent disease (stage IV)

Intervention:

- first-generation EGFR-TKIs (erlotinib or gefitinib).

Komparator:

- standard chemotherapy or placebo

Endpunkt:

- progression-free survival (PFS), and (or) overall survival (OS)

Recherche/Suchzeitraum:

- Medline, Embase, the Cochrane controlled trials register and the Science Citation Index: up to September 2014 and written in English

Qualitätsbewertung der Studien:

- (1) generation of allocation concealment, (2) description of dropouts, (3) masking of randomization, intervention, outcome assessment, (4) intention-to-treat analyses.

Ergebnisse

Anzahl eingeschlossener Studien:

- 25 RCTs enrolling more than 4467 patients
- 14 trials of EGFR-TKIs versus chemotherapy (5 for first-line treatment, 9 for second/third-line), 6 trials of EGFR-TKIs versus placebo (1 for first-line treatment, 2 for second/thirdline treatment, 3 for maintenance treatment)

Charakteristika der Population:

TABLE 1. Demographic Characteristics of Patients

Study Name (y)	No. Wild EGFR	Therapy Regimen	EGFR Assessment Method
EGFR-TKIs vs. chemotherapy			
First-line therapy			
First-SIGNAL (2012)[14]	54	Gefitinib vs. CisG	Direct sequencing
IPASS (2009)[15,16]	176	Gefitinib vs. CP	ARMS
GTOWG† (2010)[17]	75	Erlotinib vs. CV	Direct sequencing
TORCH (2012)[18]	236	Erlotinib vs. CisG	Direct sequencing/Fragment analysis/MS
ML 20322 (2012)[19]	36	Erlotinib vs. vinorelbine	Direct sequencing
Second/third-line therapy			
V-15-32 (2008)[20]	26	Gefitinib vs. D	Direct sequencing
INTEREST (2008)[21,22]	253	Gefitinib vs. D	Direct sequencing
KCSG-LU08-01 (2012)[23]	38	Gefitinib vs. Pem	Direct sequencing
CTONG-0806 (2013)[24]	157	Gefitinib vs. Pem	Direct sequencing
TAILOR (2013)[25]	219	Erlotinib vs. D	Direct sequencing + fragment analysis
DELTA (2014)[26]	199	Erlotinib vs. D	PCR-based method
TITAN (2012)[27]	149	Erlotinib vs. pemetrexed or D	Direct sequencing
NCT01565538 (2014)[28]	123	Erlotinib vs. pemetrexed	ARMS
CT/06.05 (2013)[29]	112	Erlotinib vs. pemetrexed	Direct sequencing
EGFR-TKIs vs. placebo			
First-line therapy			
TOPICAL (2010)[30,31]	362	Erlotinib vs. placebo	SequenomOncoCarta Panel
Second/third			
ISEL (2005)[32]	189	Gefitinib vs. Placebo	Direct sequencing, ARMS
BR21 (2005)[33,34]	170	Erlotinb vs. Placebo	Direct sequencing, ARMS
Maintenance therapy			
IFCT-GFPC 0502* (2012)[35]	106	Erlotinib vs. Placebo	NA
INFORM (2011)[36]	49	Gefitinib vs. Placebo	NA
SATURN (2010)[37]	388	Erlotinib vs. Placebo	Direct sequencing
EGFR-TKIs + chemotherapy vs. chemotherapy alone			
First-line therapy			
INTACT 1 (2004)[38,39]	280	Gefitinib + CisG vs. CisG	Direct sequencing
INTACT 2 (2004)[40,39]		Gefitinib + CP vs. CP	
TALENT (2007)[41,42]	NA	Erlotinib + CisG vs. CisG	NA
TRIBUTE (2005)[43]	198	Erlotinib + CP vs. CP	Direct sequencing
Maintenance therapy			
ATLAS (2013)[44]	295	Erlotinib + B vs. B	NA

*EGFR mutation based on exon 19 and exon 21 only.
†Trials reported in abstract format.
ARMS indicates amplification refractory mutation system; B, bevacizumab; CG, carboplatin-gemcitabine; CisD, cisplatin-docetaxel; CisG, cisplatin-gemcitabine; CisPem, cisplatin-pemetrexed; CP, carboplatin-paclitaxel; CV, carboplatinvenorelbine; D, docetaxel; EGFR+, presence of epidermal growth factor receptor mutation; EGFR−, absence of epidermal growth factor receptor mutation; G, gemcitabine; MS, mass spectrometry; NA, not available; PCR, polymerase chain reaction; PEM, pemetrexed; TKI, tyrosine kinase inhibitor.

Qualität der Studien:

- All included trials were open-labeled. Random sequence generation and allocation concealment were performed adequately in most of the trials. None was blinded. Only 1 trial that was exclusively designed for WT EGFR patients reported intention-to-treat analyses, and description of dropouts.25

Effect of EGFR-TKIs vs Chemotherapy on PFS:

- significantly shorter PFS with EGFR-TKIs than with chemotherapy in the patients with WT (wild type) EGFR (HR, 1.37; 95% confidence interval [CI]: 1.10, 1.72; P = 0.006) → statistically significant heterogeneity was noted in this analysis (I2 = 77%, P < 0.001). The funnel plot asymmetry can also be explained by the 3 outlying small trials of <50 patients with WT EGFR (ML 20322, V-15-32, KCSG-LU08-01) that caused heterogeneity, rather than by a publication bias.
- To strengthen the results of the present meta-analysis and decrease the heterogeneity, the inclusion criteria were strictly set in the subgroup analysis. Three small trials including <50 patients with WT EGFR were excluded, so the effect of EGFR-TKIs versus chemotherapy could be clearly evaluated further. Both these trials of first-line treatment (HR, 2.15; 95% CI: 1.68, 2.76; P< 0.001) and those of second-line/third-line treatment (HR, 1.35; 95% CI: 1.13, 1.61) showed significant improvement in PFS with chemotherapy over TKIs, but the subgroup difference reached the level of statistical significance in meta-regression analysis (P= 0.018) → However, the heterogeneity was relative low within each subgroup (I2 =40% or 43%, P= 0.17 or 0.12, respectively).
- In the other 2 predefined subgroup analyses by kinds of TKI agents and EGFR mutation analysis methods, the treatment effects were similar between the subgroups.

Effect of Combination of EGFR-TKIs and Chemotherapy vs Chemotherapy Alone on PFS:

- The pooled results of the 4 trials showed that the patients treated with a combination of EGFR-TKIs and chemotherapy had a more pronounced PFS benefit than those treated with chemotherapy alone (HR, 0.83; 95% CI: 0.71, 0.96; P = 0.01). And, this benefit was consistent across those trials (heterogeneity: I2 = 0%, P = 0.72). Three of the 4 trials were conducted using EGFR-TKIs in combination with standard platinum doublet chemotherapy for previously untreated patients with WT EGFR. When pooling them, the therapeutic advantage for the concurrent addition of EGFR-TKIs to standard first-line platinum doublet chemotherapy was still statistically significant (HR, 0.82; 95% CI: 0.68, 0.98; P = 0.03).

Indirection Comparison of EGFR-TKIs Combined With Chemotherapy vs EGFR-TKIs Alone:

- Compared with standard platinum doublet chemotherapy as first-line treatment, EGFR-TKIs alone were inferior in terms of PFS (HR, 2.15; 95% CI: 1.68, 2.76; P < 0.001) in WT EGFR patients. For patients with WT EGFR tumors, indirection comparison of EGFR-TKIs combined with chemotherapy versus EGFR-TKIs alone showed a PFS benefit (HR, 0.38; 95% CI: 0.32, 0.46; P < 0.001) when using standard platinum-based doublet chemotherapy as the common comparator in the first-line setting.

Effect of EGFR-TKIs vs Control on OS

- No statistically significant difference was observed in terms of OS (HR, 0.99; 95% CI: 0.91, 1.08; P = 0.87). The summary HRs were 1.08 (95% CI: 0.97, 1.21; P = 0.87) for EGFR-TKIs versus chemotherapy, 0.93 (95% CI: 0.77, 1.12; P = 0.45) for EGFR-TKIs versus placebo,

0.91 (95% CI: 0.77, 1.07; P = 0.26) for EGFR-TKIs added to chemotherapy versus chemotherapy alone, respectively.

TABLE 2. Subgroup Analyses for EGFR-TKIs Versus Chemotherapy

			Progression-free Survival		Heterogeneity Within Subgroups	
	No. Trials	No. Patients With Wild EGFR	HR (95% CI)	*P*	I^2 (%)	*P*
Trials of more than 50 patients with WT EGFR (N = 10)						
Line of treatment						
First-line	4	541	2.15 (1.68, 2.76)	<0.001	40	0.17
Second/third-line	6	1100	1.35 (1.13, 1.61)	<0.001	43	0.12
Subgroup heterogeneity (*P* = 0.018)						
Kinds of agents						
Erlotinib	6	1001	1.47 (1.17, 1.86)	0.001	65	0.01
Gefitinib	4	640	1.79 (1.19, 2.68)	0.005	80	0.002
Subgroup heterogeneity (*P* = 0.396)						
EGFR analysis method						
Direct sequencing only	5	688	1.51 (1.21, 1.89)	<0.001	41	0.15
More sensitive platform	5	953	1.63 (1.17, 2.29)	0.004	83	<0.001
Subgroup heterogeneity (*P* = 0.772)						
All included trials (N = 13)						
Line of treatment						
First-line	5	577	1.65 (1.06, 2.58)	0.03	82	<0.001
Second/third-line	8	1164	1.25 (1.02, 1.53)	0.03	55	0.03
Subgroup heterogeneity (*P* = 0.236)						
Kinds of agents						
Erlotinib	7	1037	1.33 (1.01, 1.76)	0.04	75	<0.001
Gefitinib	6	704	1.40 (0.92, 2.14)	0.12	81	<0.001
Subgroup heterogeneity (*P* = 0.801)						
EGFR analysis method						
Direct sequencing only	8	788	1.19 (0.88, 1.62)	0.26	70	0.002
More sensitive platform	5	953	1.63 (1.17, 2.29)	0.004	83	<0.001
Subgroup heterogeneity (*P* = 0.249)						

CI indicates confidence interval; HR, hazard ratio; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; WT, wild-type.

Anmerkung/Fazit der Autoren

We found that in patients with advanced NSCLC harboring WT EGFR, EGFR-TKIs were inferior to standard chemotherapy both for first-line treatment and for second-line/third-line treatment.

Kommentare zum Review

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

Zhang M et al., 2016 [85].

Efficacy of epidermal growth factor receptor inhibitors in combination with chemotherapy in advanced non-small cell lung cancer: A meta-analysis of randomized controlled trials.

Fragestellung

we performed a meta-analysis of randomized controlled trials to comprehensively examine the efficacy and safety of EGFR-TKIs in combination with chemotherapy for the treatment of advanced NSCLC and to find the most effective combinatorial strategy

Methodik

Population:

- advanced NSCLC

Intervention:

- combination of EGFR-TKI and chemotherapy

Komparator:

- chemotherapy or EGFR-TKI alone

Endpunkte:

- OS, PFS and ORR

Recherche/Suchzeitraum:

- Bis September 2015 (Systematische Recherche in PubMed, EMBASE, and Cochrane databases)

Qualitätsbewertung der Studien:

- JADAD score

Ergebnisse

Anzahl eingeschlossener Studien:

- N=15 Studien (5861 advanced NSCLC)

Charakteristika der Population:

Study	Year	Phase	Line of treatment	Drug delivery	Dominant ethnicity	Treatment comparison	Number of patients	Median age (years)	Female	Never smoker	Activating EGFR-mutant	Jadad score
Aerts	2013	II	Second line	Intercalated	Caucasian	E+DOC or E+PEM	116	62.5	43	9	NA	3
						E	115	64	40	7	NA	
Auliac	2014	II	Second line	Intercalated	Caucasian	E+DOC	75	59.1	14	9	NA	3
						DOC	76	59.7	18	2	NA	
Boutsikou	2013	III	First line	Concurrent	Caucasian	E+DOC+CBP	52	62.5	12	8	NA	3
						DOC+CBP	61	65	4	8	NA	
Dittrich	2014	II	Second line	Concurrent	Caucasian	E+PEM	76	64	30	10	NA	3
						PEM	83	61	34	14	NA	
Gatzemeier	2007	III	First line	Concurrent	Caucasian	E+GEM+DDP	580	60	125	NA	NA	3
						E	579	59.1	142	NA	NA	
Giaccone	2004	III	First line	Concurrent	Caucasian	G+GEM+DDP	365	59	85	NA	NA	4
						G	363	61	101	NA	NA	
Herbst	2004	III	First line	Concurrent	Caucasian	G+TAX+CBP	345	61	146	NA	NA	3
						G	345	63	133	NA	NA	
Herbst	2005	III	First line	Concurrent	Caucasian	E+TAX+DDP	539	62.7	217	72	NA	4
						E	540	62.6	207	44	NA	
Hirsch	2011	II	First line	Intercalated	Caucasian	E+TAX+CBP	71		31	21	12	3
						E	72	NA	44	19	10	
Janne	2012	II	First line	Concurrent	Caucasian	E+TAX+CBP	100	60	58	79	33	3
						E	81	58	49	64	33	
Lee	2013	II	Second line	Intercalated	Asian	E+PEM	78	55.8	58	78	NA	3
						E or PEM	162	54.9	99	162	NA	
Mok	2009	II	First line	Intercalated	Asian	E+GEM+DDP or CBP	76	57.5	22	24	2	3
						GEM+DDP or CBP	78	57	24	28	5	
Soria	2015	III	Second line	Concurrent	Asian	G+PEM	133	60	87	88	127	5
						PEM	132	58	84	91	134	
Wu	2013	III	First line	Intercalated	Asian	E+GEM+DDP or CBP	226	59	94	112	49	5
						GEM+DDP or CBP	225	57.3	85	107	48	
Yu	2014	II	First line	Intercalated	Asian	G+PEM+DDP	58	55.3	25	29	14	3
						PEM+DDP	59	54.9	34	39	18	

Abbreviations: E: erlotinib; G: gefitinib;,DOC: doctaxel; Pem: pemetrexed; TAX: paclitaxel; Gem: gemcitabine; CBP: carboplatin; DDP: cisplatin; NA: not available.

Qualität der Studien:

- Jaded Score 3-5

Studienergebnisse:

- **PFS (14 Studien)**
  - EGFR-TKI combinations significantly reduced the risk of disease progression compared with EGFR-TKIs or chemotherapy alone (HR = 0.80; 95% CI = 0.71–0.9; *P* < 0.001)
  - Subgroup analysis showed that the EGFR-TKI combination was associated with a lower risk of disease progression in never smokers (HR = 0.51; 95% CI = 0.40–0.65; *P* < 0.001). However, EGFR-TKIs did not show a treatment advantage in smoking patients. In addition, the combination group showed a significant improvement in PFS compared to the group receiving chemotherapy alone (HR = 0.76; 95% CI = 0.63–0.91; *P* < 0.002), but this difference was not statistically significant compared to EGFR-TKIs alone (HR = 0.94; 95% CI = 0.86–1.01; *P* = 0.10)
- **OS (13 Studien)**
  - the EGFR-TKI combination treatment of advanced NSCLC patients did not significantly reduce mortality risk compared with EGFR-TKI or chemotherapy alone (HR = 0.96; 95% CI = 0.90–1.03; P = 0.25). No significant heterogeneity in the HR of individual trials (I2 = 34%; P = 0.11).
  - Subgroup analysis demonstrated improvements in patients with EGFR mutations (HR = 0.55; 95% CI = 0.34–0.89; P = 0.01)
  - patients with advanced NSCLC (mainly the never smokers, patients receiving second-line treatment or intercalated therapy and Asian-dominant groups) would benefit from EGFR-TKI combination therapy. The combination group showed no significant difference in OS compared to the group receiving chemotherapy alone (HR = 0.92; 95% CI = 0.81–1.05; P = 0.23) or EGFR-TKIs alone (HR = 0.98; 95% CI = 0.83–1.16.; P = 0.83)
- **Objective response rate (15 Studien)**
  - The meta-analysis demonstrated that the ORR of the EGFR-TKI plus chemotherapy group was significantly higher than the EGFR-TKI- or chemotherapy-alone group (RR = 1.35, 95% CI = 1.14–1.59; p < 0.001)
- **Toxicity analysis results**
  - compared with the EGFR-TKIs or chemotherapy alone group, the combination group showed a higher incidence of grade 3–4 leucopoenia, neutropenia, febrile neutropenia, anaemia, rash, fatigue and diarrhoea.

Anmerkung/Fazit der Autoren

In summary, our study indicated that EGFR-TKIs combined with chemotherapy present a viable therapy for patients with advanced NSCLC. Importantly, the present study suggests that there is a larger magnitude of benefit for Asians, never smokers, and EGFR mutation patients and further suggests that intercalated therapy is the most effective combinatorial strategy.

Yan H et al., 2015 [83].

Systems assessment of intercalated combination of chemotherapy and EGFR TKIs versus chemotherapy or EGFR TKIs alone in advanced NSCLC patients

Fragestellung

we sought to perform a systematic assessment to verify whether the intercalated combination of chemotherapy and EGFR TKIs is superior to chemotherapy alone or EGFR TKIs alone in the treatment of NSCLC

Methodik

Population:

- patients had advanced NSCLC (III/IV)

Intervention:

- EGFR TKIs orally between cycles of chemotherapy

Komparator:

- EGFR TKIs or chemotherapy alone

Endpunkte:

- OS, PFS, and time to disease progression (TTP)

Recherche/Suchzeitraum:

- Bis Februar 2015

Qualitätsbewertung der Studien:

- RoB- Cochrane Handbook

Ergebnisse

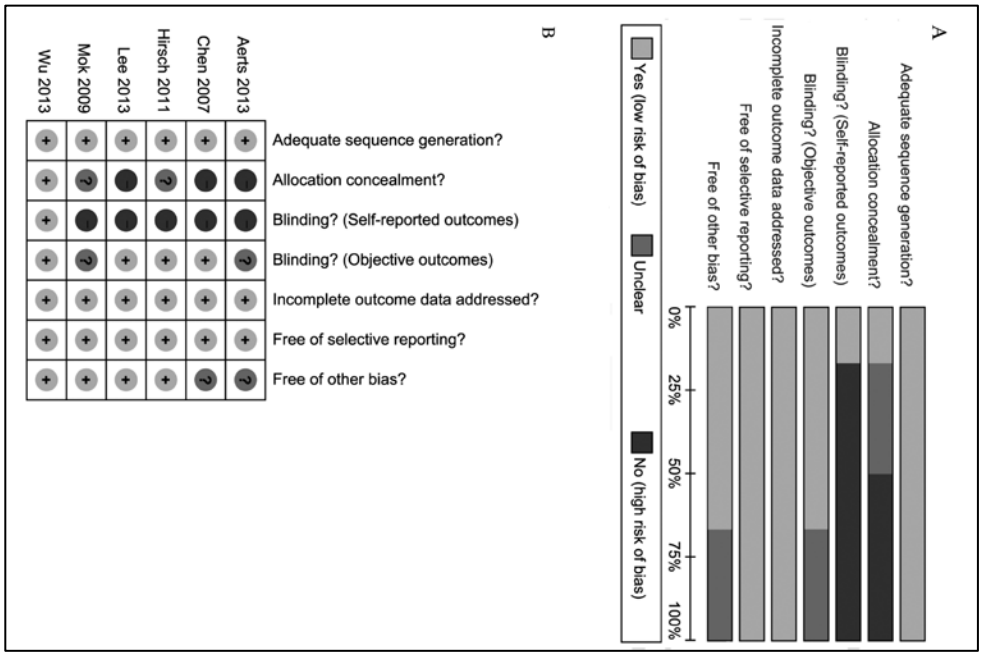
Anzahl eingeschlossener Studien:

- 10 Studien (N=1660)
- compared the intercalated combination of chemotherapy and EGFR TKIs to chemotherapy alone or EGFR TKIs alone

Charakteristika der Population:

Author	Year	Phase	Country	Treatments of experimental and control group	No. of patients	CR+PR (%)	OS (m)	PFS (m)	TTP (m)
Auliac *et al.* (GFPC 10.02)[19]	2014	II	Global	docetaxel 75 mg/m² d1, erlotinib 150 mg d2-16	73	12.30	6.5	2.2	—
				docetaxel 75 mg/m² d1	74	6.60	8.3	2.5	—
Chen *et al.*[4]	2007	II	China	Vinorelbine 15 mg/m² D1; gefitinib 250 mg/d, D2–14	21	52.38	23.4	—	12.8
				Gefitinib 250 mg/d	27	55.56	13.3	—	7.1
Guo *et al.*[20]	2012	II	China	gemcitabine1250 mg/m² on days 1 and 8, cisplatin 25 mg/m², gefitinib 250 mg/d days 10–24	36	36.10	12.1	7.3	—
				gemcitabine1250 mg/m² on days 1 and 8,cisplatin 25 mg/m²	35	14.30	10.8	5.8	—
Jia *et al.*[22]	2014	II	China	pemetrexed 500 mg/m² day 1 or docetaxel 75 mg/m² d1, gefitinib 250 mg/d days 2–20	33	9.10	10.4	4.2	—
				pemetrexed 500 mg/m² day 1 or docetaxel 75 mg/m² d1,	33	6.45	7.9	3.3	—
Lee *et al.*[16]	2013	II	Global	Pemetrexed 500 mg/m² D1; erlotinib 150 mg/d D2–14	78	44.74	20.5	7.4	—
				Pemetrexed, 500 mg/m² D1	80	10. 00	17.7	4.4	—
				erlotinib 150 mg daily	82	29.27	22.8	3.8	
Mok *et al.* (FAST-ACT)[3]	2009	II	Asian Pacific	Gemcitabine 1250 mg/m² D1 & 8; cisplatin 75 mg/m² D1 or carboplatin AUC 5 D1; erlotinib 150 mg/d, D15–28	76	35.55	17.29	6.86	—
				Gemcitabine 1250 mg/m² D1 & 8; cisplatin 75 mg/m² or carboplatin AUC 5 D1	78	24.36	17.66	5.46	—
Yu *et al.*[21]	2014	II	China	pemetrexed 500 mg/m² day 1,ciplatin 75 mg/m² or carboplatin AUC = 5, gefitinib 250 mg/d days 3–16	58	50.00	25.4	7.9	—
				pemetrexed 500 mg/m² day 1,ciplatin 75 mg/m² or carboplatin AUC = 5	59	47.40	20	7	—
Wu *et al.* (FASTACT-2)[15]	2013	III	Asia	Gemcitabine 1250 mg/m² D1 & 8; carboplatin AUC 5 or cisplatin 75 mg/m² D1; erlotinib 150 mg/d D15–28	226	42.92	18.3	7.6	—
				Gemcitabine 1250 mg/m² D1 & 8; carboplatin AUC 5 or cisplatin 75 mg/m² D1	225	18.22	15.2	6	—
Hirsch *et al.*[17]	2011	II	Global	Paclitaxel 200 mg/m²; carboplatin AUC 6; erlotinib 150 mg, D2–15	67	22.38	11.43	4.57	—
				Erlotinib 150 mg/d	69	11.59	16.7	2.69	—
Aerts *et al.* (NVALT-10)[18]	2013	II	Netherlands	Erlotinib 150 mg D2–16; docetaxel 75 mg/m² D1 or pemetrexed 500 mg/m² D1	116	12.93	7.8	6.1	—
				Erlotinib 150 mg/d	115	6.96	5.5	4.9	—

Qualität der Studien:



Studienergebnisse:

- **intercalated combination of chemotherapy and EGFR TKIs versus chemotherapy alone (7 Studien)**
  - Compared to the chemotherapy alone group, the pooled hazard ratios (HRs) for **OS and PFS** in the group of EGFR TKI administration between chemotherapy cycles showed significantly reduced risks of death and disease progression (OS: HR = 0.83, 95% confidence interval (CI): 0.70–0.98, P = 0.027; PFS: HR = 0.65, 95% CI: 0.51–0.84, P = 0.001)
  - Compared to chemotherapy alone, the statistical results showed that the **ORR** was significantly improved in the chemotherapy plus interval TKIs group (risk ratio (RR) = 1.90, 95% CI: 1.22–2.98, P = 0.005).
  - The **disease control rates (DCRs**) of the two different treatment patterns were reported by six RCTs, and there was heterogeneity between two studies (I2 = 57.0%, P = 0.040). The pooled RR for DCR showed that regardless of the treatment pattern used for NSCLC treatment, no significant difference existed between the two groups (RR = 1.14, 95% CI: 0.97–1.34, P = 0.116).
  - For the first-line treatment of NSCLC, 3 RCTs reported the HRs of **OS and PFS**. The risk of disease progression was significantly lower in the group of EGFR TKI administration between chemotherapy cycles compared to the chemotherapy alone group (HR = 0.60, 95% CI: 0.45–0.79, P < 0.001), but OS was not different between the two groups (HR = 0.84, 95% CI: 0.70–1.01, P = 0.068)
  - Four RCTs presented data on **ORR**, which compared the intercalated combination of chemotherapy and EGFR TKIs to chemotherapy alone for the first-line treatment of NSCLC, and no difference in ORR was found (RR = 1.63, 95% CI: 0.97–2.72, P = 0.063)
  - The data on **DCR** were available in three RCTs. The addition of EGFR TKIs to chemotherapy did not improve DCR for the first-line treatment of NSCLC (RR = 1.15, 95% CI: 0.91–1.45, P = 0.245)
- **The intercalated combination of chemotherapy and EGFR TKIs versus EGFR TKIs monotherapy (4 Studien)**
  - Compared to the EGFR TKIs monotherapy group, there was no significant improvement in OS in the group of EGFR TKI administration between chemotherapy cycles (HR = 0.87, 95% CI: 0.70–1.08, P = 0.218), but PFS was significantly prolonged (HR = 0.75, 95% CI: 0.62–0.91, P = 0.004)
  - Because there was no heterogeneity among the four RCTs, the FEM was applied in the analysis of ORR and DCR: In the group of EGFR TKI administration between chemotherapy cycles, the ORR (RR = 1.49, 95% CI: 1.12–2.00, P = 0.007) and DCR (RR = 1.33, 95% CI: 1.15–1.54, P < 0.001) were significantly higher than in the EGFR TKIs alone group.
  - For the first-line treatment of NSCLC, 3 RCTs reported the HRs of OS, ORR and DCR. ORR and DCR were higher in patients who received the intercalated combination of chemotherapy and EGFR TKIs than in patients who received EGFR TKI monotherapy (ORR: RR = 1.68, 95% CI: 1.19–2.36, P = 0.003; DCR: RR = 1.37, 95% CI: 1.16–1.61, P < 0.001), but no survival benefit of chemotherapy plus interval EGFR TKIs was found (HR = 0.92, 95% CI: 0.63–1.33, P = 0.656)

Anmerkung/Fazit der Autoren

In conclusion, we found that the intercalated combination of chemotherapy and EGFR TKIs significantly improved OS, PFS, and ORR compared to chemotherapy alone for the treatment of advanced NSCLC and significantly improved PFS and ORR compared to EGFR TKI monotherapy. However, there are some limitations to this systematic review. In regards to patient selection, this study was not based on individual cases but, rather, was a pooled analysis of previously published data. Moreover, not all of the included studies provided EGFR mutation status and histological type. To obtain more convincing data, rigorous phase III clinical trials should be performed to further explore the potential benefits of chemotherapy combined with EGFR TKIs in advanced NSCLC patients.

Yan H et al., 2015 [82].

The Efficacy of Synchronous Combination of Chemotherapy and EGFR TKIs for the First-Line Treatment of NSCLC: A Systematic Analysis.

Fragestellung

This systematic review was conducted to compare the efficacy and safety of the synchronous combination of these two treatments with EGFR TKIs or chemotherapy alone in advanced NSCLC.

Methodik

Population:

- patients with pathologically diagnosed NSCLC

Intervention:

- combination of EGFR TKIs and chemotherapy by synchronous

Komparator:

- EGFR TKIs or chemotherapy alone

Endpunkte:

- OS or PFS

Recherche/Suchzeitraum:

- EMBASE (1974 to January 2015), PubMed (1966 to January 2015), the CENTAL database, ESMO, the annual meetings of the ASCO and CNKI were searched.

Qualitätsbewertung der Studien:

- Cochrane Handbook

Ergebnisse

Anzahl eingeschlossener Studien:

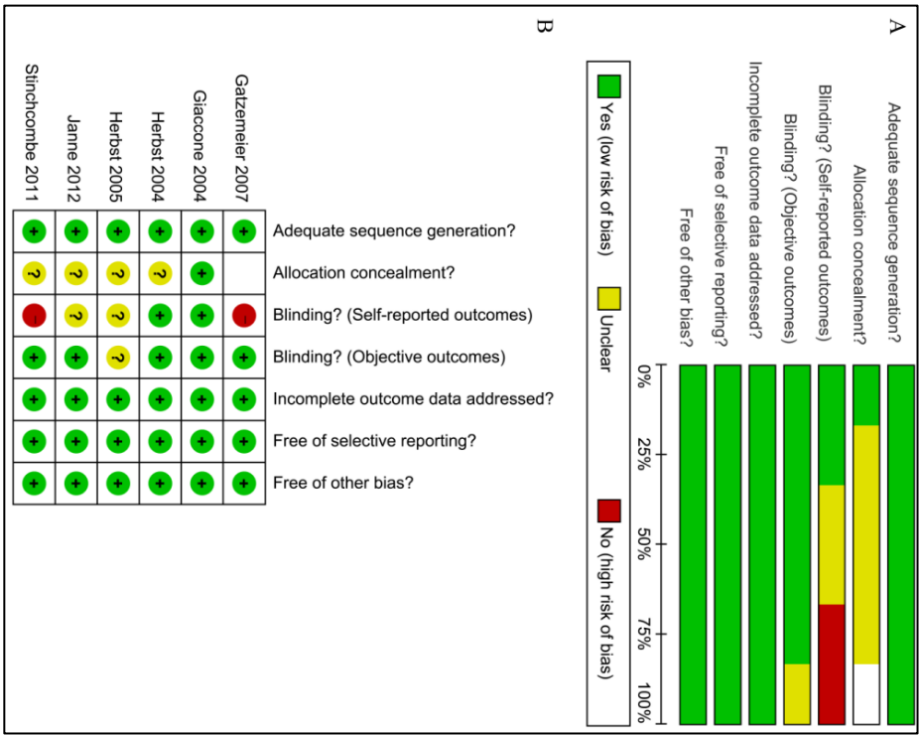
- 6 Studien

Charakteristika der Population:

Table 1. Characteristics of included studies.

Clinical Trials	year	phase	country	group	Primary endpoint	No. of patients	CR +PR (%)	OS (m)	PFS (m)	TTP (m)
TALENT: Gatzemeier et al.	2007	III	Europe, Canada, South America, and Australasia	erlotinib 150 mg/d daily, gemcitabine 1,250 mg/m^2 D1 and D8, cisplatin 80 mg/m^2 D1	OS	580	31.5	10.3	NE	5.7
				gemcitabine 1,250 mg/m^2 D1 and 8 and cisplatin 80 mg/m^2 D1		579	29.9	10	NE	5.5
NTACT 1: Giaccone et al.	2004	III	European, America, Asia, South Africa	cisplatin 80 mg/m^2 D1, gemcitabine 1,250 mg/m^2 D1 and D8, gefitinib 500 mg/d daily	OS	365	49.7	9.9	5.5	NE
				cisplatin 80 mg/m^2 D1, gemcitabine 1,250 mg/m^2 D1 and D8, gefitinib 250 mg/d daily		365	50.3	9.9	5.8	NE
				cisplatin 80 mg/m^2 D1, gemcitabine 1,250 mg/m^2 D1 and D8, placebo daily		363	44.8	109	6	NE
INTACT 2: Herbst et al.	2004	III	United States	paclitaxel 225 mg/m^2 D1, carboplatin AUC 6 D1, gefitinib 500 mg/ d daily	OS	347	30	8.7	NE	4.6
				paclitaxel 225 mg/m^2 D1, carboplatin AUC 6 D1, gefitinib 250 mg/ d daily		345	30.4	9.8	NE	5.3
				paclitaxel 225 mg/m^2 D1, carboplatin AUC 6 D1		345	28.7	9.9	NE	5
TRIBUTE: Herbst et al.	2005	III	Global	paclitaxel 200mg/m^2 D1, carboplatin AUC 6 D1, erlotinib 150mg/day daily	OS	526	21.5	11	NE	6.6
				paclitaxel 200mg/m^2 D1, carboplatin AUC 6 D1		533	19.3	11	NE	4.3
Stinchcombe et al.	2011	II	United States	gemcitabine 1000 mg/m^2 D1 and D8, erlotinib 100 mg/d daily	NE	51	21	5.6	4.1	NE
				gemcitabine 1000 mg/m^2 D1		44	7	6.8	3.7	NE
				erlotinib 150 mg/d daily		51	0	5.8	2.8	NE
CALGB 30406: Jänne et al.	2012	II	Global	paclitaxel 200mg/m^2 D1, carboplatin AUC 6 D1,erlotinib 150 mg/d daily	PFS	100	46	20	6.6	NE
				erlotinib 150 mg/d daily		81	35	25	5	NE

Qualität der Studien:



Synchronous combination of chemotherapy and TKIs vs. chemotherapy alone (5 Studien)

- **OS (5 Studien)**
  - No significant difference in OS between the synchronous combination group and chemotherapy group (HR1.05, 95%CI: 0.98–1.12, P = 0.18)
- **PFS (1 Studie)**
  - no significant difference between the two groups (HR = 0.77, 95%CI: 0.51–1.17, P = 0.217)
- **TTP (4 Studien)**
  - pooled HR was 0.94 and 95% CI is 0.89 to 1.00 indicating a similar TTP in the two groups (P = 0.054)
- **ORR (5 Studien)**
  - no significant advantage of combination therapy over chemotherapy (RR = 1.07, 95%CI: 0.98–1.17, P = 0.112)
- Four studies reported OS and ORR of the platinum-containing chemotherapy combined with EGFR TKIs vs. chemotherapy alone → no significant difference in OS and ORR between the two groups (OS: HR = 1.05, 95%CI: 0.98–1.13, P = 1.60; ORR:RR = 1.06, 95%CI: 0.97–1.16, P = 0.173)

Synchronous combination of chemotherapy and TKIs vs. EGFR TKI alone (2 Studien)

- **OS (2 Studien)**
  - no significant difference in OS between the two groups (HR = 1.10, 95% CI: 0.83–1.46, P = 0.492)
- **PFS (2 Studien)**
  - TKIs synchronous, combined with chemotherapy had significantly lower risk of progression, compared with EGFR TKI alone (HR = 0.86, 95%CI: 0.67–1.10, P = 0.228)
- **ORR**
  - Due to incomplete data, the systematic review of the ORR comparing the synchronous combination of TKIs and chemotherapy vs. TKIs alone has not been completed

Grade 3–4 toxicity analysis

- Compared with chemotherapy alone in patients with advanced NSCLC, the patients who received synchronous combination of chemotherapy and EGFR TKIs presented a significant increase in the incidence of grade 3/4 anemia and rash (anemia: RR = 1.40, 95%CI = 1.10–1.79, P = 0.007; rash: RR = 7.43, 95%CI = 4.56–12.09, P<0.001). No difference between the two groups in the incidence of other grade 3/4 toxicity reactions including: leukopenia, neutropenia, thrombocytopenia, fatigue, nausea, vomiting and diarrhea
- Compared with EGFR TKIs and monotherapy, the patients who received synchronous combination therapy presented with a significant increase in the incidence of grade 3/4 anemia and fatigue (anemia: RR = 6.71, 95%CI = 1.25–35.93, P = 0.026; fatigue: RR = 9.60, 95%CI = 2.28–40.86 P = 0.002). For neutropenia, thrombocytopenia, rash and diarrhea, the incidence of the two groups were similar

Anmerkung/Fazit der Autoren

In conclusion, we found that the synchronous combination of chemotherapy and TKIs did not obtain satisfactory results. To obtain more convincing data, rigorous phase III clinical trials are needed to further explore the potential benefits of the efficacy of chemotherapy combined with TKIs in advanced NSCLC patients.

Kuan FC et al., 2015 [37].

Overall survival benefits of first-line EGFR tyrosine kinase inhibitors in EGFR-mutated non-small-cell lung cancers: a systematic review and meta-analysis

Fragestellung

meta-analysis of current RCTs was performed by separating patients who received three different TKIs (gefitinib, erlotinib, and afatinib) into exon 19 deletions and L858R EGFR mutations.

Methodik

Population:

- local advanced or metastatic (IIIB or IV) stage NSCLC with first-line monotherapy of EGFR-TKIs.
- NSCLC patients with specific EGFR mutation (exon 19 deletions or L858R).

Intervention:

- EGFR-TKIs

Komparator:

- conventional chemotherapy

Endpunkte:

- PFS, OS

Recherche/Suchzeitraum:

- Bis Januar 2015 (MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL)

Qualitätsbewertung der Studien:

- Cochrane Collaboration tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 Studien

Charakteristika der Population:

Table 1. Characteristics of included trials for meta-analysis for PFS

Lead author (year)	Trial name (phase)	TKI	Chemotherapy	EGFR mutation	Sample size (TKI/ chemotherapy)	HR for PFS (TKI *vs* chemotherapy) mean (95% CI)
Mok *et al* (2009)	IPASS (III)	Gefitinib 250 mg per day	Carboplatin (AUC = 5 or 6) Paclitaxel (200 mg m^{-2}) every 3 weeks for ⩽6 cycles[a]	Del 19 L858R	Not available Not available	0.38 (0.26–0.56) 0.55 (0.35–0.87)
Maemondo *et al* (2010)	NEJ002 (III)	Gefitinib 250 mg per day	Carboplatin (AUC = 6) Paclitaxel (200 mg m^{-2}) every 3 weeks for ⩾3 cycles	Del 19 L858R	58/59 49/48	0.35 (0.23–0.52) 0.32 (0.20–0.50)
Mitsudomi *et al* (2010, 2012)	WJTOG3405 (III)	Gefitinib 250 mg per day	Cisplatin (80 mg m^{-2}) Docetaxel (60 mg m^{-2}) every 3 weeks for 3 to 6 cycles	Del 19 L858R	50/37 36/49	0.45 (0.27–0.77) 0.51 (0.29–0.90)
Zhou *et al* (2011, 2012)	OPTIMAL (III)	Erlotinib 150 mg per day	Carboplatin (AUC = 5) on day 1 Gemcitabine (1000 mg m^{-2}) on day 1 and 8, every 3 weeks for 4 cycles	Del 19 L858R	43/39 39/33	0.13 (0.07–0.25) 0.26 (0.14–0.49)
Rosell *et al* (2012)	EURTAC (III)	Erlotinib 150 mg per day	Cisplatin (75 mg m^{-2}) on day 1 Docetaxel (75 mg m^{-2}) on day 1 or gemcitabine (1250 mg m^{-2}) on day 1 and 8, every 3 weeks for 4 cycles[b]	Del 19 L858R	57/58 29/29	0.30 (0.18–0.50) 0.55 (0.29–1.02)
Wu *et al* (2013)	EUSURE (III)	Erlotinib 150 mg per day	Cisplatin (75 mg m^{-2}) on day 1 Gemcitabine (1250 mg m^{-2}) on day 1 and 8, every 3 weeks for 4 cycles	Del 19 L858R	Not available Not available	0.20 (0.12–0.33) 0.54 (0.32–0.90)
Sequist *et al* (2013)	LUX-Lung 3 (III)	Afatinib 40 mg per day	Cisplatin (75 mg m^{-2}) Pemetrexed (500 mg m^{-2}) every 3 weeks for ⩽6 cycles	Del 19 L858R	112/57 91/47	0.28 (0.18–0.44) 0.73 (0.46–1.17)
Wu *et al* (2014)	LUX-Lung 6 (III)	Afatinib 40 mg per day	Cisplatin (75 mg m^{-2}) on day 1 Docetaxel (75 mg m^{-2}) on day 1 or gemcitabine (1000 mg m^{-2}) on day 1 and 8, every 3 weeks for ⩽6 cycles	Del 19 L858R	124/62 92/46	0.20 (0.13–0.33) 0.32 (0.19–0.52)

Abbreviations: AUC = area under curve; CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.
[a]AUC is the dose equivalent to an area under the concentration-time curve.
[b]Patients who were ineligible for cisplatin treatment received intravenous carboplatin chemotherapy instead (3-week cycles of AUC 6 on day 1 with 75 mg m^{-2} docetaxel on day 1, or AUC 5 on day 1 with 1000 mg m^{-2} gemcitabine on days 1 and 8).

Qualität der Studien:

- All the included trials had a low risk of bias when appraised using the Cochrane Collaboration's tool

Studienergebnisse:

- **PFS (8 Studien)**
  - TKI treatment demonstrated consistent PFS benefits both in patients with exon 19 deletions (HR: 0.27, 95% CI: 0.21–0.35) and L858R (HR: 0.45, 95% CI: 0.35–0.58
  - Subgroup analyses of reversible (gefitinib and erlotinib) and irreversible (afatinib) TKIs revealed statistically significant PFS in patients with exon 19 deletions (reversible TKIs, HR: 0.28, 95% CI: 0.20–0.40; irreversible TKI, HR: 0.24, 95% CI: 0.17–0.33; Figure 3A). Moreover, reversible TKIs also had significant PFS in patients with L858R (HR: 0.44, 95% CI: 0.34–0.57). However, L858R patients treated with irreversible TKI had only marginal PFS benefit (HR: 0.48, 95% CI: 0.22–1.09).
  - When stratified by chemotherapy (including cisplatin- or carboplatin-based regimen), both reversible and irreversible TKIs were associated with significant PFS in patients with exon 19 deletions (HR: 0.27, 95% CI: 0.20–0.36) and L858R (HR: 0.44, 95% CI: 0.33–0.58
- **OS (5 Studien)**
  - Patients with exon 19 deletions had significant OS benefits from TKI treatment (HR: 0.72, 95% CI: 0.60–0.88).

- Subgroup analyses revealed that irreversible TKIs, but not reversible TKI, had statistically significant OS benefit in patients with exon 19 deletions (irreversible TKI, HR: 0.59, 95% CI: 0.47–0.73; reversible TKIs, HR: 0.84, 95% CI: 0.69–1.02)).
- But patients with L858R demonstrated no OS benefit regardless of the TKI used (HR: 1.15, 95% CI: 0.95–1.39).
- When stratified between cisplatin- or carboplatin-based chemotherapy, TKI treatment was associated with significant OS benefits in patients with exon 19 deletions compared with those with cisplatin-based chemotherapy (cisplatin, HR: 0.59, 95% CI: 0.47–0.73; carboplatin, HR: 0.81, 95% CI: 0.64–1.02). In patients with L858R, TKI treatment showed no OS benefit over cisplatin- or carboplatin-based chemotherapy (HR: 1.18, 95% CI: 0.94–1.48)

Anmerkung/Fazit der Autoren

Accumulating evidence suggests that exon 19 deletions and L8585R are two different disease entities. Therapeutic strategies should differ when treating lung adenocarcinoma harbouring exon 19 deletions or L858R mutations. This study reveals that in patients with advanced NSCLC harbouring exon 19 deletions, both reversible and irreversible TKIs are associated with better OS compared with conventional chemotherapy. Future clinical trials should take exon 19 deletions and L858R as distinct disease entities and evaluate treatment efficacy separately

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Chen J et al., 2016 [3].

Efficacy of targeted agents in the treatment of elderly patients with advanced non-small-cell lung cancer: a systematic review and meta-analysis.

Fragestellung

The efficacy of targeted agents (TAs) in the treatment of elderly patients with advanced non-small-cell lung cancer (NSCLC) remains controversial. We aimed to assess the efficacy of TAs in the treatment of advanced NSCLC in this setting.

Methodik

Population:

- patients were pathologically confirmed of NSCLC and ≥65 years

Intervention/Komparator:

- Chemotherapies with or without TAs

Endpunkte:

- OS, PFS

Recherche/Suchzeitraum:

- PubMed, Embase, and Cochrane Library to June 2015

Qualitätsbewertung der Studien:

- Jadad score

Ergebnisse

Anzahl eingeschlossener Studien:

- A total of 4,093 elderly patients from 17 randomized controlled trials
- 14 trials were performed in first-line settings and three in second-line settings
- 13 trials were RCTs Phase III trials; three were randomized Phase II trials.

Qualität der Studien:

- The quality of each included study was roughly assessed according to Jadad scale, and six trials had Jadad score of 5, and eleven trials had Jadad score of 3.

Studienergebnisse:

- The addition of TAs to chemotherapy significantly improved PFS (hazard ratio [HR] 0.85, 95% confidence interval [CI]: 0.75–0.96, P=0.01) when compared to chemotherapy alone.
- There was also a tendency to improve OS in the combination groups (n.s.).
- Subgroup analysis based on treatment line indicated that TAs plus chemotherapy as first-line chemotherapy in elderly patients with advanced NSCLC significantly improved PFS (HR 0.80, 95% CI: 0.68–0.95, P=0.01) and OS (HR 0.91, 95% CI: 0.83–0.99, P=0.037)
- The use of TA-containing regimens as second-line therapy in these patients did not significantly improve PFS and OS in comparison with chemotherapy alone.

Anmerkung/Fazit der Autoren

This is the first meta-analysis specifically assessing the efficacy of adding TAs to chemotherapy in elderly patients with advanced NSCLC. The results of our study suggest that the addition of TAs to first-line chemotherapy in elderly patients with NSCLC offers an improved PFS and OS, when compared to chemotherapy alone. With present available data from randomized clinical trials, we could not clearly set the role of TAs in the second-line treatment for elderly patients with advanced NSCLC. Further studies are recommended to assess the efficacy of adding TAs to second-line chemotherapy for advanced NSCLC in this setting.

Kommentare zum Review

- Only elderly patients included
- Which TA would be the best choice not studied

Xu JL et al., 2015 [80].

Chemotherapy plus Erlotinib versus Chemotherapy Alone for Treating Advanced Non-Small Cell Lung Cancer: A Meta-Analysis

Fragestellung

This study aimed to summarize the currently available evidence and compare the efficacy and safety of chemotherapy plus erlotinib versus chemotherapy alone for treating advanced NSCLC.

Methodik

Population:

- patients with NSCLC, keine Erhaltungstherapie

Intervention:

- erlotinib plus standard chemotherapy

Komparator:

- standard chemotherapy alone

Endpunkte:

- OS, PFS

Recherche/Suchzeitraum:

- bis 10 / 2014

Qualitätsbewertung der Studien:

- Cochrane Handbook for Systematic Reviews of Interventions, which appraised sequence generation, allocation concealment, performance bias, detection bias, attrition bias, reporting bias, and other biases.

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 / 3599 (RCT)

Charakteristika der Population:

Table 1. Summary of Characteristics of the Included Studies. Abbreviations: E: erlotinib, Carb: carboplatin, Cisp: cisplatin, Pac: paclitaxel, Gem: Gemcitabine, Pem: Pemetrexed, NA: Not available

Study	Number of points	Dominant ethnicity	Female	Age (range)	Drug delivery	Treatment comparison	Non-smoker	EGFR-mutant	EGFR-wild-type
Herbst, 2005	1079	Caucasian/934	424	24–84	Continuous	E+Carb+Pac vs. Carb+Pac +Placebo	116	29	198
Gatzemeier, 2007	1159	Caucasian/1064	267	26–84	Continuous	E+Gem+Cisp vs. Gem +Cisp+Placebo	NA	NA	NA
Mok, 2009	154	Asian/145	46	27–79	Intercalated	E+Gem+Cisp or Carb vs. Gem+Cisp or Carb +Placebo	52	NA	NA
Thomas, 2013	146	NA	73	69–90	Continuous	E+Gem vs. E vs. Gem	240	24	19
Lee, 2013	240	Asian/240	157	NA	Intercalated	E+Pem vs. E vs. Pem	219	97	136
Wu, 2013	451	Asian/451	179	31–96	Intercalated	E+Gem+Cisp or Carb vs. Gem+Cisp or Carb +Placebo	219	97	136
Dittrich, 2014	165	Caucasian/157	64	31–84	Continuous	E+Pem vs. E vs Pem	24	NA	NA
Auliac, 2014	151	NA	115	NA	Intercalated	E+docetaxel vs. E vs. docetaxel	11	NA	98
Michael, 2014	54	Caucasian/49	22	38–86	Intercalated	E+Gem vs. Gem	8	NA	NA

Qualität der Studien:

- Although all nine eligible trials reported that the participants were randomized into different treatment arms, three of them did not provide details about random sequence generation. Only one trial showed concealment procedures. Five trials were open-label; they did not mask either participants or personnel. Five trials had independent persons who performed

the outcome assessment, and one trial did not show details about the blinding of outcome assessment. Six eligible trials conducted efficacy analysis on an intention-to-treat basis; one trial missed two cases in both arms [10]; and one trial missed three patients who were still in treatment [9]. We believe that the outcomes were unlikely to have been affected in these instances. Six trials did not selectively report data, while the protocols of three trials were not available. Therefore, we could not judge whether these three trials selectively reported data.

Studienergebnisse:

- Progression free survival
  - This meta-analysis showed a longer PFS in patients who received a combination of erlotinib and chemotherapy treatment (HR = 0.76 [95% CI 0.62, 0.92], P = 0.006). The heterogeneity between studies was significant [$\chi 2$ = 14.28, df = 4 (P = 0.006); I2 = 72%]. The pooled HR meta-analysis for intercalated erlotinib plus chemotherapy showed an improvement in PFS (HR = 0.67 [95% CI 0.50, 0.91], P = 0.009). Meanwhile, continuous erlotinib plus chemotherapy treatment failed to show an improvement in PFS.
  - Subgroup analysis demonstrated improvements in PFS in never smoking patients (HR = 0.46 [95% CI 0.37, 0.56], P<0.00001) and patients with EGFR mutant tumors (HR = 0.31 [95% CI 0.17, 0.58], P = 0.0002). No significant difference was shown in PFS between the chemotherapy plus erlotinib group and the chemotherapy group in patients with EGFR wild-type tumors.
- Overall survival
  - HRs for OS data were available from 8 trials. No statistically significant improvement was shown in OS, and there was no significant heterogeneity [$\chi 2$ = 10.36, df = 7 (P = 0.17); I2 = 32%].
  - Intercalated erlotinib plus chemotherapy treatment showed a modest but statistically significant improvement in OS (HR = 0.82 [95% CI 0.69, 0.98], P = 0.03).
  - Continuous erlotinib plus chemotherapy treatment failed to show an improvement in OS. (…) Additionally, a statistically significant improvement in OS was observed in patients with EGFR mutant tumors (HR = 0.52 [95% CI 0.30, 0.88], P = 0.01).
  - No significant difference in OS was noted in patients with EGFR wild-type tumors.
- Adverse events
  - Data for the grade 3 or 4 adverse events were available in five studies. There were more incidences of grade 3 or 4 anemia (OR = 1.48 [95% CI 1.12, 1.97], P = 0.006), rash (OR = 12.34 [95% CI 5.65, 26.95], P<0.00001), and diarrhea (OR = 4.25 [95% CI 2.16, 8.38], P<0.0001) in the erlotinib and chemotherapy combination treatment.
  - However, there was no difference in incidences of grade 3 or 4 neutropenia, leucopoenia, or thrombocytopenia.

Anmerkung/Fazit der Autoren

Combination of chemotherapy and erlotinib is a viable treatment option for patients with NSCLC, especially for patients who never smoked and patients with EGFR mutation-positive disease. In addition, intercalated administration is an effective combinatorial strategy.

However, for patients with EGFR mutation-positive NSCLC, the current standard care is EGFR TKI alone. OPTIMAL study showed that compared with chemotherapy, erlotinib demonstrated a significant benefit in patients with advanced EGFR mutation-positive NSCLC, and median

PFS was 13.1 months for erlotinib-treated patients versus 4.6 months for patients receiving chemotherapy. In FASTACT-2, patients with EGFR mutation derived benefit from the combination treatment, and median PFS was 16.8 months. We didn't address whether a combination treatment was better than erlotinib alone for patients with EGFR mutation-positive NSCLC. A head-to-head study is needed to answer this question. In this systematic review, we analyzed the efficacy of different schedules of erlotinib in combination with chemotherapy, and led to a conclusion that the intercalated schedule showed an improvement in PFS and OS, while the continuous schedule did not.

Kommentare zum Review

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

Xu W et al., 2015 [81].

A meta-analysis of erlotinib versus docetaxel for advanced non small-cell lung cancer with poor prognosis

Fragestellung

to compare the efficacy of erlotinib with docetaxel for different patients with advanced NSCLC

Methodik

Population:

- patients with historically or cytologically confirmed stage

Intervention:

- erlotinib

Komparator:

- docetaxel

Endpunkte:

- ORR, PFS, OS

Recherche/Suchzeitraum:

- Cochrane Library, PubMed, CNKI from February 2003 to June 2015

Qualitätsbewertung der Studien:

- Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 Studies included

Charakteristika der Population:

Study	Intervention	Participants	Gender (male/ female)	Age median years (range)	Performance status					Histological classification			Smoking			Jadad's quality scores
					0	1	2	≥3	Not started	NSCC	SCC	Others	Yes	No	Not recorded	
Krawczyk, 2012	Erlotinib	102	65/37	61 (33-81)	-*	-	-	-	-	47	55	-	75	27	-	2
	Docetaxel	102	75/27	61 (43-76)	-	-	-	-	-	34	68	-	94	8	-	
Kawaguchi, 2014	Erlotinib	150	108/42	68 (37-82)	77	67	6	-	-	104	29	17	111	39	-	3
	Docetaxel	151	107/44	67 (31-85)	78	67	6	-	-	103	32	16	114	37	-	
Popat, 2008	Erlotinib	100	59/41	67 (34-86)	0	21	41	7	31	48	28	24	90	10	-	2
	Docetaxel	100	63/37	61 (41-79)	0	57	28	4	11	48	30	22	89	10	1	
Garassino, 2013	Erlotinib	109	77/32	66 (40-81)	52	48	9			70	31	8	90	19	-	2
	Docetaxel	110	73/37	65 (35-83)	53	50	7			84	23	3	80	30	-	
Ng, 2008	Erlotinib	53	32/21	58 (41-77)	-	-	-	-	-	-	38	15	31	22	-	2
	Docetaxel	74	46/28	59 (35-77)	-	-	-	-	-	-	42	32	47	27	-	
Ma, 2015	Erlotinib	145	77/68	63.6 (27-84)	116	29	-	-	-	130	-	15	107	38	-	3
	Docetaxel	49	22/27	63.8 (27-84)	46	3	-	-	-	32	-	17	65	27	-	

*Not reported in the publication. NSCC=Nonsmall-cell carcinoma; SCC=Small-cell carcinoma

Qualität der Studien:

- Four studies had a Jadad Score of 2 & two studies had a Jadad Score of 3

Studienergebnisse:

→ Fokus bei der Ergebnisdarstellung auf OS, PFS und Toxizität

- Overall survival
  - Due to the comparing results of 4 trails, the pooled HRs for OS showed significant difference between erlotinib and docetaxel groups [HR = 1.66, 95% CI = 1.43–1.92, P = 0.00].
  - For OS analysis showed that erlotinib comparing docetaxel in the treatment of advanced NSCLC has obvious advantages
- Progression-free survival
  - According to these 4 trials, the HRs for PFS were derived from the supportive adjusted model. The pooled HR for PFS showed significant difference between erlotinib and docetaxel group [HR = 1.57. 95% CI = 1.47–1.69, P = 0.00], suggesting an erlotinib advantage over docetaxel for patients with advanced NSCLC.
- Toxicity
  - As expectancy, docetaxel resulted in more grades 3 or 4 common toxicity criteria than erlotinib. The pooled odds ratio (OR) was 4.92 [95% CI = 3.60–6.72, P = 0.00], indicating less toxicity of erlotinib compared with docetaxel. However, a great heterogeneity (I2 = 97%) was exhibited between erlotinib and docetaxel, even though a random-effect model was performed. Kawaguchi's trial was the source of heterogeneity. After excluding the data of Kawaguchi's trial, I2 = 88% [OR = 1.79, 95% CI = 1.20–2.69].

Anmerkung/Fazit der Autoren

In this meta-analysis, we performed a high efficacy and longer PFS and OS of erlotinib than docetaxel, although similar ORR. In terms of toxicity, erlotinib still shows an advantage than docetaxel. Therefore, erlotinib is a potential and valid treatment alternative for patients with advanced NSCLC with poor prognosis. With the development of biomarkers prediction, clinical factors should be introduced into the analysis for more confirmative results and better-personalized medication.

Ma H et al., 2016 [51].

The Efficacy of Erlotinib Versus Conventional Chemotherapy for Advanced Nonsmall-Cell Lung Cancer: A PRISMA-Compliant Systematic Review With Meta-Regression and Meta-Analysis.

Fragestellung

A meta-analysis to compare the efficacy of erlotinib and chemotherapy for advanced NSCLC

Methodik

Population:

- All the patients who were diagnosed as advanced NSCLC using pathology and cytology tests were eligible for the systematic review.

Intervention / Komparator:

- the intervention is erlotinib alone, the comparison is conventional chemotherapy regardless any regimens or cycles.

Endpunkt:

- OS, ORR, PFS, and 1-year survival rate (OSR)

Recherche/Suchzeitraum:

- bis 2015

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 14 studies which involved a total of 3559 participants, met the inclusion criteria and were thus included in the final analysis, all 14 trials were open-label

Charakteristika der Population:

TABLE 1. The Main Study Characteristics

Study	Phase	Line of Treatment	Intervention Regimen	Control Regimen	Participants	EGFR Mutation Testing	EGFR Mutants (N)
Lilenbaum et al[31]	II	NA	E 150 mg/day	Ca (AUC = 6) plus Pa (200 mg/m^2)	52/51	Yes	NA/5
Zhou et al[34,37]	III	1	E 150 mg/day	G 1000 mg/m^2 D1,8 plus C (AUC = 5) D1	82/72	Yes	82/72
Stinchcombe[39]	II	1	E 150 mg/day	G 1200 mg/m^2 D1,8	51/44	No	NA
Ciuleanu et al[25]	III	2	E 150 mg/day	Standard D or Pe dosing schedule	203/221	Yes	7/4
Gridelli et al[26]	III	1	First-line E 150 mg/day, second-line (Ci plus G)	First-line (Ci plus G), second-line E 150 mg/day	380/380	Yes	18/18
Perol et al[32]	III	2	E 150 mg/day	G 1250 mg/m^2 D1,8 q21d	155/154	Yes	29/29
Rosell et al[33]	III	1	E 150 mg/day	75 mg/m^2 Ci plus 75 mg/m^2 D D1 or 75 mg/m^2 Ci D1 plus 1250 mg/m^2 G D1,8	86/87	Yes	86/87
Chen et al[38]	II	NA	E 150 mg/day	Vi 60 mg/m^2 on D1,8 q21d	57/56	Yes	9/15
Kelly et al[30]	II	2	E 150 mg/day	Pr 190 mg/m^2 on D1,15 q28d	101/100	No	NA
Karampeazis et al[28]	III	2 or 3	E 150 mg/day	Pe 500 mg/m^2 D1	166/166	Yes	61/62
Lee et al[24]	II	2	E 150 mg/day	Pe 500 mg/m^2 D1	82/80	No	NA
Heigener et al[27]	II	1	E 150 mg/day	Ca AUC = 5 D1 plus Vi 25 mg/m^2 D1,8	144/140	Yes	6/4
Kawaguchi et al[29]	III	2 or 3	E 150 mg/day	D 60 mg/m^2 q21d	150/151	Yes	21/30
Wu et al[36]	III	1	E 150 mg/day	Ci 75 mg/m^2 G and 1250 mg/m^2 D1,8 q21d	110/107	Yes	110/107

Ca = carboplatin; Ci = cisplatin; D = docetaxel; E = erlotinib; EGFR = epidermal growth factor receptor; G = gemcitabine; NA = not available; ORR = objective response rate; OSR = 1-year survival rates; Pa = paclitaxel; Pe = pemetrexed; Pr = pralatrexate; V = vinorelbine.

Qualität der Studien:

- The overall methodological quality of the included trials was generally good and fair

Studienergebnisse:

- PFS:

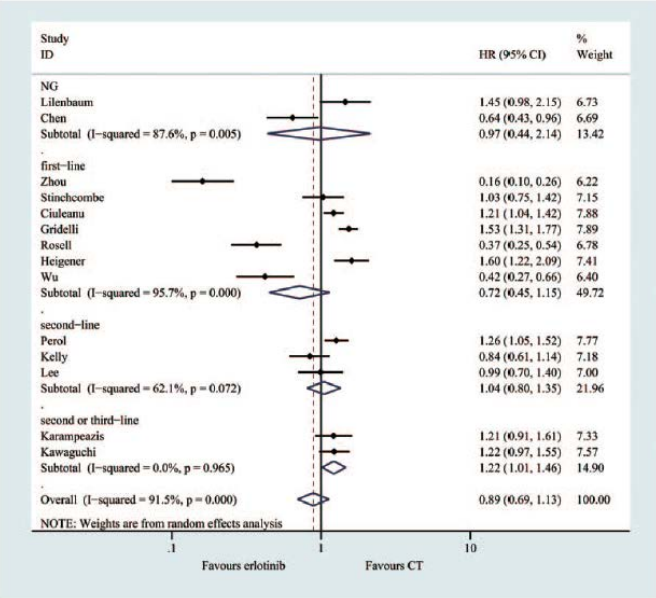
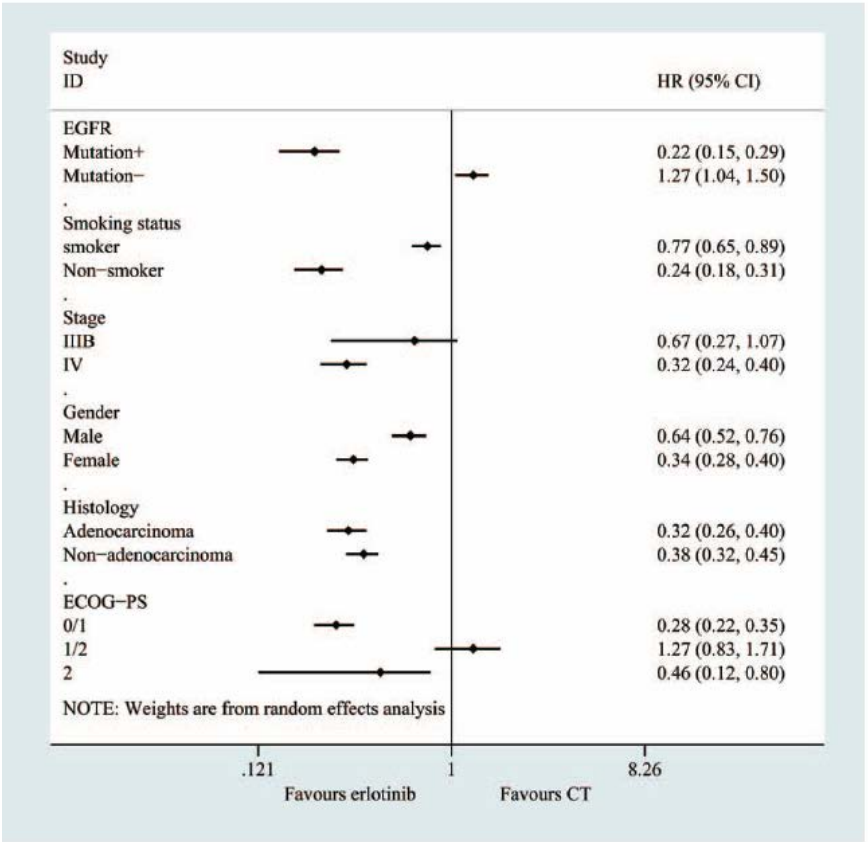
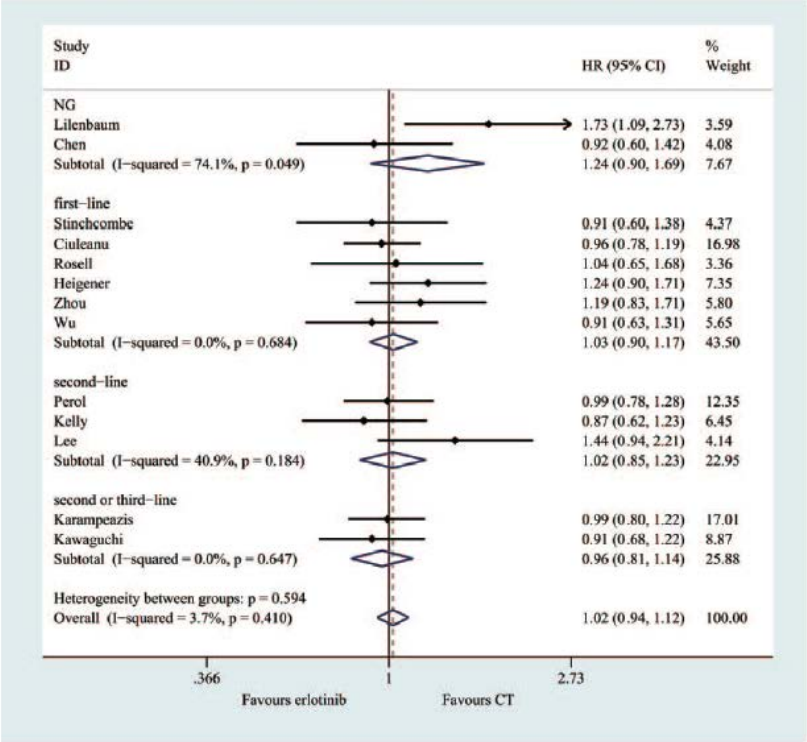


FIGURE 4. Meta-analysis results of the progression-free survival.

- Subgroup and meta-regression analyses of the PFS:

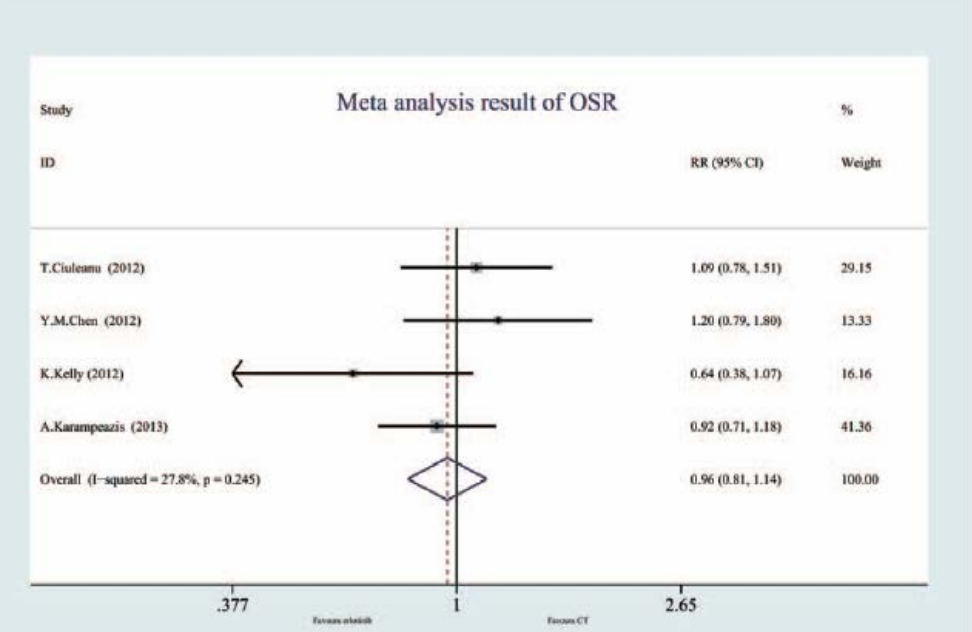


- OS:

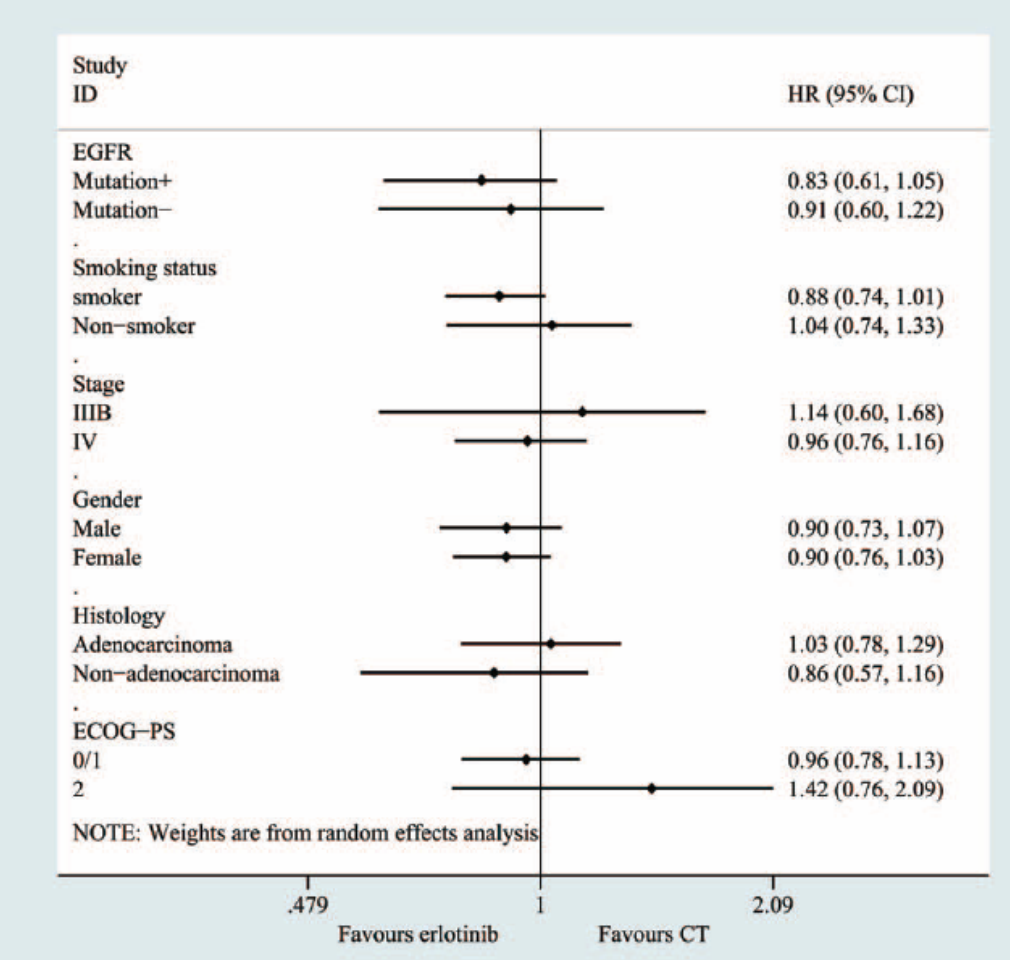


alysis results of the overall survival.

- 1-year Survival rate:



- Subgroup and meta-regression analyses of the OS:



Anmerkung/Fazit der Autoren

In conclusion, the present systematic review and metaanalysis suggested that erlotinib did not improve the ORR, PFS, OS, or the 1-year survival rate for whole patients with or without EGFR mutation test. Nevertheless, the subgroup analysis revealed that erlotinib did not affect the OS regardless of EGFR mutation status, however, the agent prolonged PFS in subjects with EGFR mutation, but not in those without EGFR mutation. […]

Kommentare zum Review

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

He X et al., 2015 [30].

Efficacy and safety of docetaxel for advanced non-small-cell lung cancer: a meta-analysis of Phase III randomized controlled trials.

Fragestellung

to conduct a meta-analysis to compare the efficacy and safety of docetaxel and pemetrexed or docetaxel and vinca alkaloid for non-small-cell lung cancer.

Methodik

Population:

- advanced NSCLC

Intervention:

- docetaxel

Komparator:

- pemetrexed or vinca alkaloid

Endpunkte:

- overall response rate (ORR), median survival time, PFS, disease control rate, and toxicities

Recherche/Suchzeitraum:

- bis 01/ 2015

Qualitätsbewertung der Studien:

- Jadad scoring system

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 / 2080 (RCT, phase III)

Charakteristika der Population:

Table 1 Characteristics of the seven eligible Phase III randomized trials in this meta-analysis

Study	Study region	Intervention	Number	Median age (years)	Male (%)	Stage	Outcome	Jadad score
Rodrigues-Pereira et al[20]	Argentina	Doc (75 mg/m²) + Carb	105	58.9	47.6	Stage IIIB/IV	SWT, OS, PFS	3
		Pem (500 mg/m²) + Carb	106	60.1	60.4			
Karampeazis et al[23]	Greece	Doc (38 mg/m²)	66	75.5	92.4	Stage IIIB/IV	OS, ORR, TTP, Toxl	4
		Vin (25 mg/m²)	64	77	93.8			
Vergnenegre et al[21]	France	Doc (75 mg/m²)	75	64	85.3	Stage IIIB/IV	OS, PFS, ORR, Toxl	3
		Pem (500 mg/m²)	75	62	82.7			
Krzakowski et al[25]	France	Doc (75 mg/m²)	275	60	75.3	Stage III/IV	PFS, ORR, OS	4
		Vfl (320 mg/m²)	262	61.9	75			
Kudoh et al[24]	Japan	Doc (60 mg/m²)	88	76	77.5	Stage IIIB/IV	OS, PFS, ORR, Toxl	3
		Vin (25 mg/m²)	91	76	74.7			
Hanna et al[22]	United States	Doc (75 mg/m²)	288	57	75.3	Stage III/IV	OS, PFS, ORR, Toxl	3
		Pem (500 mg/m²)	283	59	68.6			
Kubota et al[26]	Japan	Doc (60 mg/m²) + Cis	151	63	64.2	Stage IV	OS, ORR, Toxl	3
		Vds (3 mg/m²) + Cis	151	64	68.2			

Abbreviations: Doc, docetaxel; Carb, carboplatin; Pem, pemetrexed; Vin, vinorelbine; Vfl, vinflunine; Vds, vindesine; Cis, cisplatin; SWT, survival without grade 3 or 4 toxicity; OS, overall survival; PFS, progression-free survival; ORR, overall response rate; TTP, time to tumor progression; Toxl, toxicity indexes.

Qualität der Studien:

- The Jadad score was used to assess the quality of the included trials. Overall, two trials scored 4, while the others scored 3.

Studienergebnisse:

- Overall survival
  - We performed subgroup analysis in first-line and second-line, respectively, in order to distinguish the efficacy of the different lines of treatment. Five trials provided HR results of overall survival (OS). No significant difference was found in the pooled HR for OS between docetaxel and pemetrexed as both first-line and second-line treatment (HR 1.10, 95% CI: 0.76–1.59, P=0.62; HR 1.05, 95% CI: 0.88–1.24, P=0.60, respectively). Results were similar in the comparison of docetaxel with vinca alkaloid. OS for docetaxel versus vinca alkaloid as first-line treatment was not statistically different (HR 0.78, 95% CI: 0.56–1.08, P=0.14). In addition, there was also no difference in OS between docetaxel and vinca alkaloid as second-line treatment (HR 0.97, 95% CI: 0.80–1.18, P=0.78).
- PFS
  - HR results of PFS were offered by four clinical trials.20,22,24,25 Similar to the result of OS, there was no significant difference in PFS between docetaxel and pemetrexed as both first-line and second-line treatment (HR 1.10, 95% CI: 0.81–1.49, P=0.54; HR 1.03, 95% CI: 0.86–1.23, P=0.74, respectively). In terms of docetaxel with vinca alkaloid as first-line treatment, there was a significant statistical difference in PFS (HR 0.63, 95% CI: 0.45–0.82, P=0.001). However, docetaxel was associated with no significant improvement in PFS compared with vinca alkaloid as second-line treatment (HR 1.00, 95% CI: 0.83–1.19, P=0.96).
- Toxicity:

Table 2 Comparison of grade 3/4 toxicity between docetaxel and pemetrexed as first-line treatment

Grade 3/4 toxicity symptom	Docetaxel	Pemetrexed	OR (95% CI)	P-value
Hematologic events				
Neutropenia	68/105	35/106	3.73 (2.11, 6.59)	<0.00001
Anemia	2/105	13/106	0.14 (0.03, 0.63)	0.01
Thrombocytopenia	3/105	10/106	0.28 (0.08, 1.06)	0.06
Leukopenia	42/105	17/106	3.49 (1.82, 6.68)	0.0002
Febrile neutropenia	9/105	0/106	20.97 (1.20, 365.10)	0.04
Non-hematologic events				
Diarrhea	4/105	1/106	4.16 (0.46, 37.84)	0.21
Nausea	1/105	1/106	1.01 (0.06, 16.36)	0.99
Vomiting	0/105	1/106	0.33 (0.01, 8.28)	0.50

Table 3 Comparison of grade 3/4 toxicity between docetaxel and pemetrexed as second-line treatment

Grade 3/4 toxicity symptom	Docetaxel	Pemetrexed	Heterogeneity		OR (95% CI)	P-value
			P-value	I^2		
Hematologic events						
Neutropenia	137/351	20/340	0.24	29%	9.57 (5.08, 18.03)	<0.00001
Anemia	13/351	16/340	0.15	53%	0.60 (0.12, 2.94)	0.53
Thrombocytopenia	2/351	10/340	1.00	0%	0.19 (0.04, 0.87)	0.03
Febrile neutropenia	35/276	5/265	–	–	7.55 (2.91, 19.59)	<0.0001
Non-hematologic events						
Diarrhea	7/276	1/265	–	–	6.87 (0.84, 56.22)	0.07
Nausea	7/351	9/340	0.74	0%	0.75 (0.28, 2.04)	0.57
Vomiting	5/351	6/340	0.79	0%	0.81 (0.24, 2.68)	0.73

Table 4 Comparison of grade 3/4 toxicity between docetaxel and vinca alkaloid as first-line treatment

Grade 3/4 toxicity symptom	Docetaxel	Vinca alkaloid	Heterogeneity		OR (95% CI)	P-value
			P-value	I^2		
Hematologic events						
Neutropenia	165/305	171/306	0.0001	89%	0.67 (0.19, 2.32)	0.53
Anemia	18/305	44/306	0.97	0%	0.37 (0.20, 0.65)	0.0007
Thrombocytopenia	1/305	0/306	–	–	3.02 (0.12, 74.72)	0.50
Leukopenia	120/239	149/242	0.003	89%	0.71 (0.23, 2.22)	0.56
Febrile neutropenia	12/154	11/155	0.91	0%	1.14 (0.48, 2.71)	0.77
Non-hematologic events						
Diarrhea	19/305	3/306	0.83	0%	5.94 (1.88, 18.73)	0.002
Nausea	23/305	15/306	0.72	0%	1.59 (0.82, 3.10)	0.17
Vomiting	13/305	8/306	0.31	4%	1.64 (0.68, 3.97)	0.27

Table 5 Comparison of grade 3/4 toxicity between docetaxel and vinca alkaloid as second-line treatment

Grade 3/4 toxicity symptom	Docetaxel	Vinca alkaloid	OR (95% CI)	P-value
Hematologic events				
Neutropenia	82/277	90/274	0.86 (0.60, 1.23)	0.41
Anemia	8/277	20/274	0.38 (0.16, 0.87)	0.02
Thrombocytopenia	1/277	6/274	0.16 (0.02, 1.35)	0.09
Leukopenia	59/277	64/274	0.89 (0.59, 1.33)	0.56
Febrile neutropenia	13/277	9/274	1.45 (0.61, 3.45)	0.40
Non-hematologic events				
Diarrhea	5/277	2/274	2.50 (0.48, 13.00)	0.28
Nausea	3/277	4/274	0.74 (0.16, 3.33)	0.69
Vomiting	3/277	5/274	0.59 (0.14, 2.49)	0.47

Anmerkung/Fazit der Autoren

Docetaxel leads to a better result than vinca alkaloid in effectiveness and safety on patients with advanced non-small-cell lung cancer as first-line therapy. Docetaxel also causes lower toxicity as second-line therapy compared with vinca alkaloid. However, the differences in efficacy and safety between docetaxel and pemetrexed are not obvious. Further clinical study with more details, such as sex, age, histology, and so on, should be considered for illustrating the differences between these two drugs.

Kommentare zum Review

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

Xiao HQ et al., 2016 [79].

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).

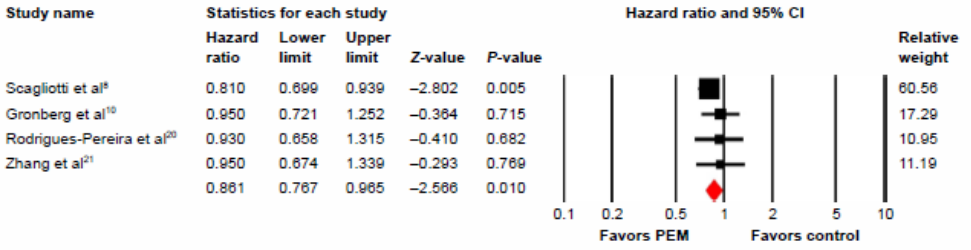


Abbildung 1: Fixed-effects model of HR (95% CI) of OS associated with PEM plus platinum versus other platinum-based chemotherapy.

- 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 ($I2$=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.

Wang S et al., 2015 [78].

Are VEGFR-TKIs effective or safe for patients with advanced non-small cell lung cancer?

Fragestellung

The overall efficacy and safety of VEGFR-TKIs are undetermined. In this study, we performed a pooled analysis of currently published RCTs to summarize the up to-date evidence.

Methodik

Population:

- Advanced NSCLC

Intervention:

- VEGFR-TKIs

Komparator:

- non-VEGFR-TKIs

Endpunkte:

- Primary endpoint: PFS

- Secondary endpoints: OS, ORR, DCR and AEs

Recherche/Suchzeitraum:

- PubMed, EMBASE, Cochrane Library databases as well as Web of science, Meeting abstracts on 5 December 2014

Qualitätsbewertung der Studien:

- Jadad Scale

Ergebnisse

Anzahl eingeschlossener Studien:

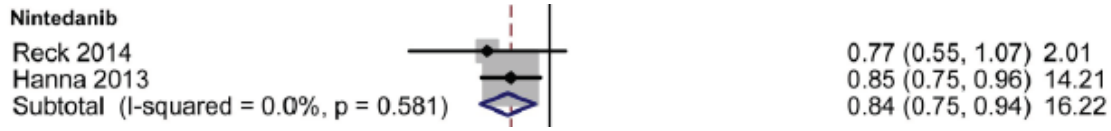
- 23 RCTs with 12,520 patients
- 3 were on cediranib; 1 on motesanib; 2 on Nintedanib; 1 on pazopanib; 4 on sorafenib ; 3 on sunitinib and 9 on vandetanib
- Nur Nintedanib als Komparator in Deutschland zugelassen
  - 17. Reck M, Kaiser R, Mellemgaard A, Douillard JY4, Orlov S, Krzakowski M, von Pawel J, Gottfried M, Bondarenko I, Liao M, Gann CN, Barrueco J, Gaschler-Markefski B, et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. Lancet Oncol. 2014;15:143-155.
  - 18. Nasser H. Hanna RK, Richard N, Sullivan, Osvaldo Rudy Aren, Myung-Ju Ahn, Beatrice Tiangco, Zanete Zvirbule, Carlos H. Barrios, Ahmet Demirkazik, Birgit Gaschler-Markefski, Isabelle Voccia, et al. A multicenter, randomized, double-blind, phase III study of nintedanib plus pemetrexed versus placebo plus pemetrexed in patients with advanced nonsquamous non-small cell lung cancer (NSCLC) after failure of first-line chemotherapy. J Clin Oncol. 31, 2013 (suppl; abstr 8034).

Qualität der Studien:

- Reck [17] Jadad Score: 5
- Hanna [18] Jadad Score: 4

Studienergebnisse:

- Subgroups analyses were performed based on the individual VEGFR-TKI
  - PFS: 2 Studies statistically significant improvement was favouring Nintedanib



  - OS, PFS, DCR: no significant benefit with Nintedanib
- AE: no subgroup analysis performed fort he individual VEGFR-TKI

Anmerkung/Fazit der Autoren

In summary, this study provides proof of principle that VEGFR-TKIs have an advantage in terms of PFS, ORR and DCR, compared with control therapies. However, advanced NSCLC patients treated with VEGFR-TKIs have high risks of AEs. Thus, the monitoring AEs during VEGFR-TKIs

therapy is recommended. The risk and benefit of VEGFR-TKIs must be evaluated carefully to select patients who utmost benefit from VEGFR-TKIs treatment.

Kommentare zum Review

- Es wurden ausschließlich die Ergebnisse für Nintedanib dargestellt, da dies der einzige in Deutschland zugelassene Komparator ist.

Kulkarni S et al., 2016 [38].

The Use of Systemic Treatment in the Maintenance of Patients with Non–Small Cell Lung Cancer: A Systematic Review

Fragestellung

to examine the use of systemic treatment in the maintenance of patients with NSCLC.

Methodik

Population:

- Patients with stage IIIB or IV NSCLC

Intervention/Komparator:

- maintenance systemic treatment against another systemic treatment or placebo

Endpunkte:

- response rate, PFS, OS, quality of life, and adverse effects

Recherche/Suchzeitraum:

- To 2014

Qualitätsbewertung der Studien:

- GRADE system

Ergebnisse

Anzahl eingeschlossener Studien:

- Fourteen randomized controlled trials with 22 publications were included

Qualität der Studien:

- For the fully published papers, the randomization method was either unclear or not reported in three studies. Blinding was either open label or not reported in four studies. Losses to follow-up were not reported in four studies and the role of the funder was unclear in five studies.

Studienergebnisse:

- OS:
  - The overall survival benefit was strongest for maintenance therapy with pemetrexed for patients with nonsquamous NSCLC (HR= 0.74, 95% CI: 0.64–0.86) but not significant for patients with squamous NSCLC.

  - There was also an overall survival benefit with maintenance therapy with epidermal growth factor receptor tyrosine kinase inhibitors, but the magnitude of the benefit was smaller than with pemetrexed HR = 0.84, 95% CI: 0.75–0.94).
  - Docetaxel or gemcitabine as maintenance chemotherapies did not have an impact on overall survival.
- PFS:
  - Patients with a histologic diagnosis of nonsquamous cell carcinoma who received pemetrexed as maintenance therapy had longer PFS (HR = 0.51, 95% CI: 0.41–0.63, p < 0.00001) compared with those who did not receive pemetrexed as maintenance therapy.
  - A significant interaction was found between EGFR mutation status and treatment for PFS, with a larger improvement in PFS for patients with EGFR mutations (EGFR positive: HR = 0.22, 95% CI: 0.10–0.46, EGFR wild type: HR = 0.82; 95% CI: 0.71–0.96, p = 0.0007)

Anmerkung/Fazit der Autoren

In conclusion, in patients with advanced, stage IIIB/IV NSCLC whose disease has not progressed (i.e., those with a complete response, partial response, or stable disease) after at least four cycles of platinum-based chemotherapy, there is evidence for a beneficial effect of OS with few adverse events to support the use of pemetrexed and EGFR TKI maintenance therapy. For pemetrexed, the evidence is strongest for patients with nonsquamous NSCLC. There is insufficient evidence to recommend either gemcitabine or docetaxel for maintenance therapy, and they should be considered an option in the management of patients with a histologic diagnosis of nonsquamous cell carcinoma.

Shan F et al., 2018 [71].

The Role of Combination Maintenance with Pemetrexed and Bevacizumab for Advanced Stage Nonsquamous Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis.

Fragestellung

to evaluate combination maintenance therapy with bevacizumab plus pemetrexed.

Methodik

Population:

- patients with histologically or cytologically proven stage IIIB or IV NSCLC

Intervention:

- combination maintenance with pemetrexed plus bevacizumab

Komparator:

- any other maintenance therapy or no maintenance therapy

Endpunkte:

- progression-free survival (PFS), overall survival (OS), and treatment-related toxicities (adverse event grade ≥ 3, AEs)

Recherche/Suchzeitraum:

- Embase, PubMed, Cochrane, and Web of Science from1 January 1960 to 29 October 2016

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool for assessing risk of bias/GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 3 randomized controlled trials
- 3 included randomized controlled trials evaluated 5 maintenance regimens with a total of 1302 patients enrolled.

Qualität der Studien:

- All three trials were multicenter with adequate randomization. One of them reported concealment of allocation by central randomization.None used double blindmethod and the blinding of assessors is not informed in all included trials. All RCTs provided complete outcome data and none reported outcomes selectively.

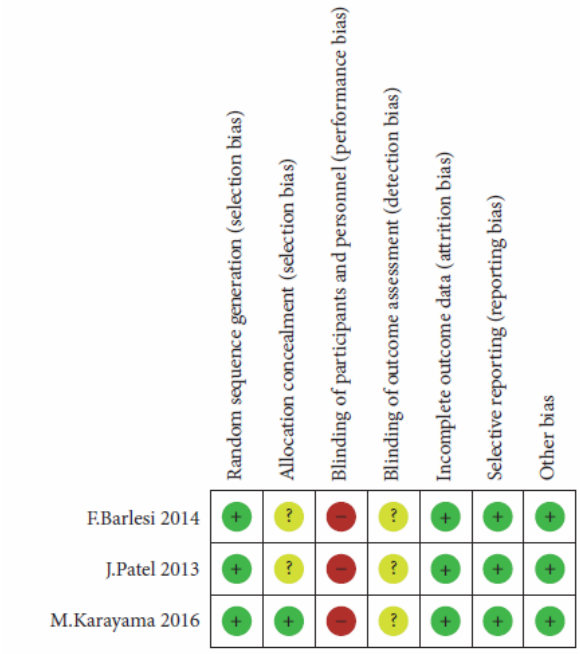


FIGURE 2: Risk of bias assessment in each item. -: high risk of bias; ?: unclear risk of bias; +: low risk of bias.

Studienergebnisse:

- An evident PFS improvement (HR = 0.73, 95% CI = 0.63–0.83, <0.01) was observed in patients with pemetrexed and bevacizumab combination maintenance therapy compared with single-agent maintenance therapy, yet it did not subsequently lead to a significant improvement in OS (HR = 0.97, 95% CI = 0.84–1.10, P = 0.66).
- statistically increased risks for provoking grade 3-4 adverse events in patients managed using pemetrexed plus bevacizumab combination (RR = 1.59, 95% CI = 1.07–2.36, P = 0.022).
- Subgroupanalyses

- Patients managed using the combination strategy appeared to be at an advantage with regard to PFS compared with patients receiving other maintenance regimens when based on subset factors of age, ECOG score, and smoking history. And, remarkably, lower hazard ratios were observed in patients with younger age (< 65, HR = 0.64, 95% CI =0.39–0.90, P < 0.01), better physical status (ECOG score =0, HR = 0.60, 95% CI = 0.32–0.87, P < 0.01), and no smoking history (never smoked, HR = 0.45, 95% CI = 0.27–0.63, P <0.01).
- As for overall survival, a clear trend for longer OS was observed in patients with age < 65 years, ECOG score = 0, or never smoked. However, no statistically significant improvement was detected in all three subsets.

Anmerkung/Fazit der Autoren

Our study suggests that the double maintenance of pemetrexed and bevacizumab is associated with significantly prolonged PFS but not OS and is accompanied by increased risks of grade 3-4 adverse events. Given the current limitation of existing studies and this meta-analysis, further studies like ECOG 5508 are expected to report a fundamental strategy and provide a powerful clinical evidence.

Kommentare zum Review

- heterogeneity across included trials

Hu J et al., 2019 [32].

Efficacy and toxicities of combination maintenance therapy in the treatment of advanced non-small-cell lung cancer: an up-to-date meta-analysis.

Fragestellung

meta-analysis of all available randomized controlled trials (RCTs) to determine the overall efficacy and toxicities of doublet maintenance therapy in advanced NSCLC patients.

Methodik

Population:

- NSCLC patients

Intervention/Komparator:

- comparing doublet versus single agent maintenance therapy

Endpunkte:

- survival and toxicities

Recherche/Suchzeitraum:

- PubMed, Web of Science, and Cochrane library. K.A. Suchzeitraum.

Qualitätsbewertung der Studien:

- Cochrane approach / Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- total of 1950 advanced NSCLC patients from six trials

Charakteristika der Population:

Table 1 Baseline characteristics of six included trials

Authors/years	Population	Induction therapy	Treatment group	Maintenance regimen	No. of patients	Median age	Median PFS	Median OS	Jadad score
Barlesi F. et al./2013	CT-naïve, Stage IIIB–IV, non-squamous, ECOG PS 0–2	Pemetrexed +cisplatin +bevacizumab	Experimental arm (doublet)	Bevacizumab +pemetrexed	128	NR	7.4 (0.48, 0.35–0.66	19.8 (0.88, 0.63–1.21)	3
			Control arm (single agent)	Bevacizumab	125	NR	3.7	15.9	
Johnson B.E. et al./2013	CT-naïve, Stage IIIB–IV, or recurrent, ECOG PS 0–1	Chemotherapy +bevacizumab	Experimental arm (doublet)	Bevacizumab erlotinib	370	64	4.8 (0.71, 0.58–0.86	14.4 (0.92, 0.70–1.21)	5
			Control arm (single agent)	Bevacizumab placebo	373	64	3.7	13.3	
Patel J.D. et al./2013	CT-naïve, non-squamous, Stage IIIB–IV, or recurrent, ECOG PS 0–1	Chemotherapy +bevacizumab	Experimental arm (doublet)	Bevacizumab +pemetrexed	292	63.8	6 (0.73, 0.71–0.96	12.6 (1, 0.86–1.16)	3
			Control arm (single agent)	Bevacizumab	298	64.3	5.6	13.4	
Karayama M. et al./2016	CT-naïve, non-squamous, Stage IIIB–IV, or recurrent, ECOG PS 0–1	Pemetrexed +carboplatin +bevacizumab	Experimental arm (doublet)	Bevacizumab +pemetrexed	45	66	11.5 (0.73, 0.44–1.19	24.4, 0.87, 95% CI: 0.49e1.54	3
			Control arm (single agent)	Pemetrexed	35	65	7.3	21.3	
Ciuleanu T.E. et al./2017	CT-naïve, Stage IV, or recurrent, ECOG PS 0–1	Platinum-based chemotherapy	Experimental arm (doublet)	Linsitinib +erlotinib	102	62	125, 1.09 (0.788–1.507)	381, 1.20 (0.777, 1.853)	5
			Control arm (single agent)	Placebo +erlotinib	103	60	129	421	
Niho S. et al./2017	CT-naïve, Stage IIIB–IV, or recurrent, ECOG PS 0–1	Platinum-based chemotherapy	Experimental arm (doublet)	S-1+bevacizumab	39	61	4.6 (0.64, 0.45–0.91	19.9 (0.65, 0.41–1.02)	3
			Control arm (single agent)	Bevacizumab	40	65	2.6	11.0	

Abbreviations: CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; NR, not reported; OS, overall survival; PFS, progression-free survival; PS, performance status.

Qualität der Studien:

- two of the six RCTs were double-blind placebo-controlled trials, thus had Jadad score of 5. Other three trials were an open-label controlled trial, thus had Jadad score of 3.

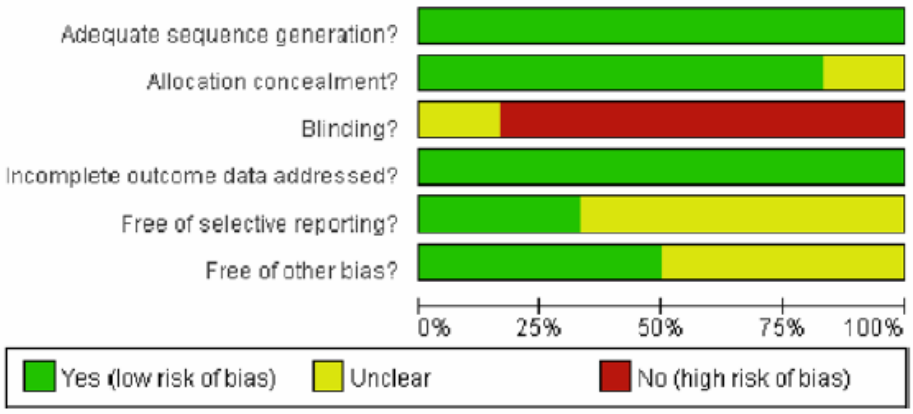


Figure 2. Random-effect model of hazard ratio (95%CI) of PFS in NSCLC treated doublet versus single agent maintenance therapy

Studienergebnisse:

- The use of doublet maintenance therapy in NSCLC patients significantly improved PFS (HR 0.74, 95%CI: 0.59–0.93, P = 0.010), but not for OS in comparison with single agent maintenance therapy.
  - Similar results were observed in sub-group analysis according to treatment regimens.
- In addition, there was no significantly risk difference between doublet and single agent maintenance therapy in terms of grade 3/4 hematologic and non-hematologic toxicities.

Anmerkung/Fazit der Autoren

Our study suggests that doublet maintenance therapy in advanced NSCLC patients demonstrates a PFS benefits, but not for OS benefits in comparison with single agent maintenance therapy. In addition, doublet maintenance therapy does not significantly increase the risk of severe toxicities when compared with single agent maintenance therapy. Future trials are suggested to assess the long-term clinical benefit of doublet maintenance treatment in NSCLC patients and its impact on health-related QOL.

Kommentare zum Review

- Limitation von Autoren: … ‘‘we could not answer which regimen is the best choice’’

Hu X et al., 2016 [33].

Role of Gemcitabine and Pemetrexed as Maintenance Therapy in Advanced NSCLC: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.

Fragestellung

to assess the role of gemcitabine and pemetrexed in the maintenance treatment of non-small-cell lung carcinoma (NSCLC).

Methodik

Population:

- patients were pathologically diagnosed with advanced chemotherapy-naïve NSCLC

Intervention:

- gemcitabine or pemetrexed as a single agent was applied in maintenance therapy after 4 to 6 cycles of induction chemotherapy

Komparator:

- no restrictions were imposed and included BSC/observation, cytotoxic agents, vascular endothelial growth factor receptor (VEGFR), EGFR-TKI or any other therapeutic drugs.

Endpunkte:

- PFS and OS, risk ratios (RR) of grade 3–4 adverse events (AEs)

Recherche/Suchzeitraum:

- PubMed, EMBASE and Cochrane library databases from their inceptions to September 16, 2015.

Qualitätsbewertung der Studien:

- GRADE system / Cochrane risk of bias tool

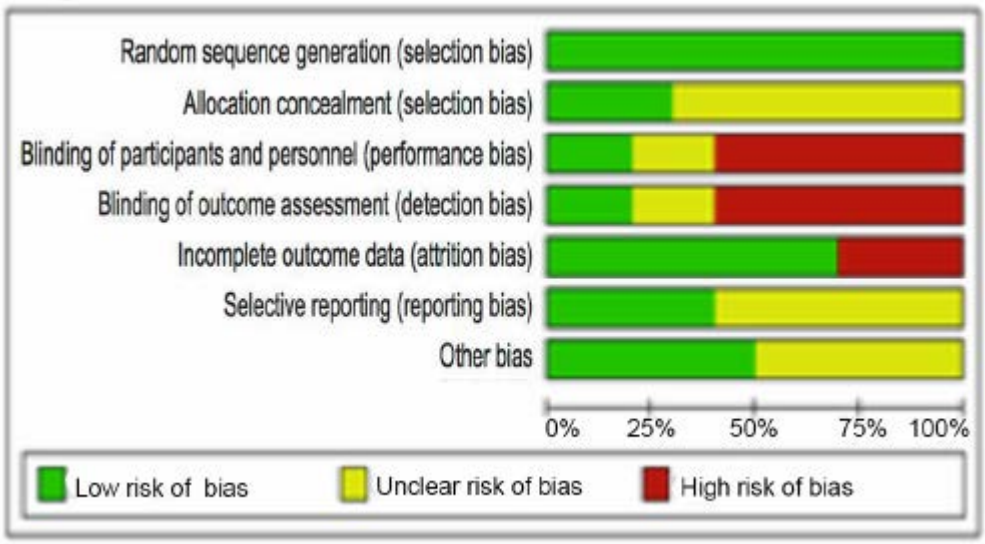
Ergebnisse

Anzahl eingeschlossener Studien:

- Eleven randomized controlled trial (RCT) studies

Qualität der Studien:

- Risk of bias:



- Regarding the grade, the GRADE system indicated that the gemcitabine group was "MODERATE", the pemetrexed group was "HIGH", and both the pemetrexed + bevacizumab vs. bevacizumab groups and pemetrexed vs. B groups were "LOW".

Studienergebnisse:

- Ten studies were included in the meta-analysis and divided into the following 4 groups: gemcitabine vs. best supportive care (BSC)/observation, pemetrexed vs. BSC/placebo, pemetrexed + bevacizumab vs. bevacizumab and pemetrexed vs. bevacizumab.
  - Gemcitabine exhibited significantly improved progression-free survival (PFS) compared with BSC (hazard ratio (HR) = 0.62, p = 0.000).
  - Pemetrexed exhibited significantly improved PFS (HR = 0.54, p = 0.000) and OS (HR = 0.75, p = 0.000) compared with BSC.
  - Pemetrexed + bevacizumab almost exhibited significantly improved PFS (HR = 0.71, p = 0.051) compared with bevacizumab.
  - Pemetrexed exhibited no improvement in PFS or overall survival (OS) compared with bevacizumab.

    Adverse events: Thus, in the gemcitabine vs. BSC/observation group, the pooled HR was 4.70 (2.87–7.69, p = 0.000; I2 = 14.6%, p = 0.279). In the pemetrexed vs. BSC ± placebo group, the pooled HR was 3.27 (1.56–6.83, p = 0.002; I2 = 63.8%, p = 0.063). In the pemetrexed + bevacizumab vs. bevacizumab group, the HR was 1.25 (1.08–1.45, p =

0.002; I2 = 62.1%, p = 0.104). In the pemetrexed vs. bevacizumab group, the HR was 0.79 (0.49–1.29, p = 0.343; I2 = 65.7, p = 0.088).

Anmerkung/Fazit der Autoren

In our article, we confirmed that gemcitabine significantly improved PFS compared with BSC, pemetrexed significantly improved PFS and OS compared with BSC ± placebo, and pemetrexed + bevacizumab approached a significantly improved PFS compared with bevacizumab alone. The incidence of grade 3–4 AEs was significantly increased in the maintenance therapy arm compared with the control arm. Additional trials are required to confirm the impact of pemetrexed + bevacizumab vs. bevacizumab and pemetrexed vs. bevacizumab. In particular, randomized, controlled double-blind trials are required. Randomized, controlled double-blind trials are also needed for gemcitabine vs. BSC studies. In pemetrexed + bevacizumab vs. bevacizumab or pemetrexed vs. bevacizumab studies, the contribution of maintenance therapy to the outcomes should be separately evaluated. Finally, regarding the socioeconomic impact, the problems of maintenance therapy must identify new solutions.

Wang Q et al., 2016 [77].

Single-agent maintenance therapy for advanced non-small cell lung cancer (NSCLC): a systematic review and Bayesian network meta-analysis of 26 randomized controlled trials.

Fragestellung

network meta-analysis to assess the comparative treatment efficacy of several single-agent maintenance therapy regimens for stage III/IV NSCLC.

Methodik

Population:

- patients were pathologically or cytologically-diagnosed with non-resectable stage III or IV NSCLC

Intervention/Komparator:

- single-agent maintenance therapy and placebo, observation, or another single-agent maintenance regimen

Endpunkte:

- OS, PFS, averse events

Recherche/Suchzeitraum:

- from inception to November 09, 2015

Qualitätsbewertung der Studien:

- For each included trial, the following domains of bias were judged and ranked into ``low risk,'' ``high risk,'' or ``unclear risk'': generation of random sequence, allocation concealment, blinding, incomplete outcome data, selective reporting of outcome, and other biases.
- GRADE system

Ergebnisse

Anzahl eingeschlossener Studien:

- total of 26 trials covering 7,839 patients, of which 24 trials were included in the OS analysis, while 23 trials were included in the PFS analysis.

Qualität der Studien:

- Since direct data comparing different maintenance therapy regimens was available for only two couples of regimens, measurement of inconsistencies between direct and indirect data was limited. In general, the most common reasons for lowering the quality of evidence were limitations in trial design and imprecision in some studies. Data suggested that evidence on switchdocetaxel, continue-paclitaxel and switch-vinorelbine were rated as limited quality, while evidence on switch-pemetrexed, switch-belagenpumatucel-L and switch-racotumomabalum was rated as higher quality.

Studienergebnisse:

No maintenance control was set as the reference in all analyses.

- In total, 24 trials were included in the OS analysis: Based on assessment of model fit, results calculated by random effects models are presented in this section.
- Several maintenance therapy regimens yielded longer OS than no-maintenance, although differences were not statistically significant in some regimens. Switch-docetaxel, continue-paclitaxel, switch-sunitinib, switch-vandetanib, switch-carboxyaminoimidazole (CAI), and switch-vinorelbine did not improve OS. Switch-maintenance therapy with racotumomab-alum vaccine showed excellent efficacy compared to no-maintenance with a HR D 0.64 [95% credible intervals (CrI), 0.45-0.92]
- In PFS analysis, we included 23 trials: Continue-paclitaxel, switch-belagenpumatucel-L, or switch-CAI did not yield longer PFS than no-maintenance. Switch-pemetrexed and switch-gefitinib showed excellent efficacy compared to no-maintenance with HRs D 0.54 (95% CI [0.26-1.04]) and 0.60 (95% CI [0.40-0.90]).
- Ranking which indicated the probability of the best regimen in descending order, among all treatments
  - Based on OS): switch-racotumomab-alum vaccine had the greatest probability as the best regimen (52%), with switch-pazopanib ranked second (32%), and switch-pemetrexed ranked third (6%).
  - Based on PFS, switch-pemetrexed ranked first (34%), followed by switch-sunitinib (19%), with switch-pazopanib ranked third (12%).
- Adverse events:
  - Maintenance chemotherapy (including pemetrexed, gemcitabine, docetaxel, paclitaxel, and vinorelbine) was commonly associated with hematologic events such as neutropenia, thrombocytopenia, and anemia. Maintenance tyrosine kinase inhibitor (TKI) (including EGFR-TKI and other TKIs) commonly caused more skin and gastrointestinal AEs, such as rash, nausea, and vomiting. Maintenance vaccine (including belagenpumatucel-L, racotumomab-alum, and L-BLP25) was commonly associated with injection site reaction and flu-like symptoms. The main AE of CAI was nausea.

Anmerkung/Fazit der Autoren

In conclusion, our NMA demonstrates that several single-agent maintenance therapy regimens may prolong OS and PFS for stage III/IV NSCLC. Racotumomab-alum vaccine has shown potential survival benefit in unselected NSCLC population but should be confirmed with additional clinical evidence.

Sheng J et al., 2015 [73].

Efficacy of Addition of Antiangiogenic Agents to Taxanes-Containing Chemotherapy in Advanced Non small-Cell Lung Cancer

Fragestellung

We summarized the current evidences from relevant phase II/III randomized controlled trials (RCTs) by performing this meta-analyses.

Methodik

Population:

- Adults patient with pathologically confirmed, squamous or nonsquamous, recurrent or metastatic NSCLC that untreated before or progressed after a single platinum-based chemotherapy regimen.

Intervention + Komparator:

- comparing the efficacy and safety profile of adding AA to TCC with TCC alone

Endpunkt:

- OS, PFS, ORR, DCR, Toxizität

Recherche/Suchzeitraum:

- bis 2015

Qualitätsbewertung der Studien:

- Cochrane Collaboration /Jadad Score

Ergebnisse

Anzahl eingeschlossener Studien:

- 14 studies with 9703 patients met the inclusion criteria and were finally included for OS analyses.

Qualität der Studien:

- All studies were scored 3 to 5, and evaluated as high quality except 1 study.

Studienergebnisse:

OS:

- According to the original data, 2 trials reported statistically significant improvement on OS. The pooled result showed that the combination with AA was associated with the significant

improved OS (HR 0.92, 95% CI 0.87–0.97, P=0.002) compared with standard TCC. No apparent heterogeneity was detected among the recruited studies (P=0.34, I2=11%).

- Subgroup analyses indicated that slightly OS improvement was observed in first-line application (HR 0.96, 95% CI 0.87–1.06, P= 0.39). However, the practice in second-line application was associated with the significant prolonged OS (HR 0.91, 95% CI 0.85–0.96, P=0.002). Other clinical factors directing significant OS improvement by the combination strategy included histologically nonsquamous cancer (HR 0.90, 95% CI 0.84–0.96, P=0.002), nonsmokers (HR 0.81, 95% CI 0.70–0.94, P=0.0005), or female (HR 0.87, 95% CI 0.77–0.98, P=0.02). Only monoclonal antibodies (HR 0.89, 95% CI 0.82–0.96, P=0.004) were proved efficient in combination with TCC. However, indirect analyses failed to validate the superiority of monoclonal antibodies (HR 0.94, 95% CI 0.84–1.04, P¼0.22).

Secondary Measure: PFS, ORR, DCR, and Toxicity:

- Thirteen studies reported the original data of PFS and ORR. Compared with TCC alone, the combination of AA and TCC resulted in significant improvement on PFS (HR 0.79, 95% CI 0.71–0.87, P<0.0001) and high response rate (RR 1.69, 95% CI 1.47–1.95, P<0.0001). The DCR was also improved by this combination strategy (RR 1.19, 95% CI 1.08–1.32, P<0.00001). In general, grade _3 adverse events occurring more frequently in the combination arms versus the TCC arms, such as hypertension, hemorrhage, proteinuria, thromboembolic events and diarrhea for anti-VEGF-induced events and neutropenia, leukopenia, and fatigue for chemotherapy-induced events. Moreover, it had been reported that addition of AA to chemotherapy lead to more treatment-induced death. However, the combination therapy had a safety profile compared with that of AA such as bevacizumab taken individually. In addition, various AAs had their own toxicity profiles. On the whole, the toxicities were greater but generally mild or moderate in severity and manageable in the combination group.

Anmerkung/Fazit der Autoren

In summary, the addition of AAs to TCC could improve prognosis of NSCLC patients. Furthermore, proper selection of patient population and AAs is crucial for clinical trials design and clinical practice in the future.

Kommentare zum Review

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

Dafni U et al., 2019 [6].

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 [47].

Zhou Y et al., 2019 [90].

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

Fragestellung

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

Methodik

Population:

- advanced NSCLC

Intervention/Komparator:

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

Endpunkte:

- OS, PFS, ORR

Recherche/Suchzeitraum:

- before November 1, 2018

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool

Ergebnisse

Anzahl eingeschlossener Studien:

- five trials involving 1289 patients

Charakteristika der Population:

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

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

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

Qualität der Studien:

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

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

Studienergebnisse:

- Direct metaanalysis:
  - Significant difference of ORR was observed in favor of pembrolizumab plus chemotherapy versus chemotherapy (RRpem + chemo/chemo 2.16, 95% CI 1.66–2.82; P < 0.001; heterogeneity, P = 0.441). And for pembrolizumab vs chemotherapy, the pooled RRpem/chemo was 1.33 (95% CI 1.11–1.58; P = 0.002).
  - For PFS, pembrolizumab plus chemotherapy significantly reduced the risk of disease progression compared with chemotherapy (HRpem + chemo/chemo, 0.36; 95% CI 0.27–0.48; z = 7.03, P < 0.001).
  - While pembrolizumab monotherapy failed to demonstrate significant improvement in PFS (HRpem/chemo, 0.65; 95% CI 0.40–1.04; z = 1.82, P = 0.069)
  - In terms of OS, both pembrolizumab plus chemotherapy (HRpem+ chemo/chemo, 0.51; 95% CI 0.35–0.72; z = 3.71, P < 0.001) and pembrolizumab monotherapy (HRpem/chemo, 0.67; 95% CI 0.56–0.80; z = 4.57, P < 0.001) significantly decreased the risk of death compared with chemotherapy.
- Indirect meta-analysis
- The results indicated that patients treated with pembrolizumab plus chemotherapy had better clinical outcomes including ORR (RRpem + chemo/pem 1.62, 95% CI 1.18–2.23; P = 0.003) and PFS (HRpem + chemo/pem 0.55, 95% CI 0.32–0.97; P = 0.037) than those treated with pembrolizumab alone. However, there was only a trend towards improved OS with the three-drug combination therapy.

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

- Siehe auch: Kim R et al. 2019 [36] & Liu Y et al. 2019 [48].
- Unklar Anteil metastasierte Patienten

3.4 Leitlinien

National Institute for Health and Care Excellence (NICE), 2019 [60].

Lung cancer: diagnosis and management

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

Siehe auch: National Institute for Health and Care Excellence (NICE), 2018 [56]; National Institute for Health and Care Excellence (NICE), 2018 [55]; National Institute for Health and Care Excellence (NICE), 2017 [62]; National Institute for Health and Care Excellence (NICE), 2016 [57]; National Institute for Health and Care Excellence (NICE), 2015 [61].

Leitlinienorganisation/Fragestellung

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

Methodik

Grundlage der Leitlinie

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

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

Recherche/Suchzeitraum:

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

LoE

- trifft nicht zu (sieh sonstige methodische Hinweise)

GoR

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

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

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

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

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

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

Updates-Kennzeichnung:

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

Empfehlungen

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

EGFR-TK mutation

- 1.4.45 For guidance on treatment for stage IIIB and IV non-squamous NSCLC in people with the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation:
  - for initial treatment, see the NICE technology appraisal guidance on afatinib [54], erlotinib [58] and gefitinib [59].

    (…)
  - if people do not immediately progress after chemotherapy, see the NICE technology appraisal guidance on pemetrexed maintenance after pemetrexed and pemetrexed maintenance after other platinum doublet chemotherapy [65], [66]

ALK gene rearrangement

- 1.4.46 For guidance on treatment for stage IIIB and IV non-squamous NSCLC in people with the anaplastic lymphoma kinase-positive gene rearrangement:
  - for first-line systemic treatment, see the NICE technology appraisal guidance on crizotinib, ceritinib and alectinib [55], [56], [57]

    (…)

- if people do not immediately progress after chemotherapy, see the NICE technology appraisal guidance on pemetrexed maintenance after pemetrexed and pemetrexed maintenance after other platinum doublet chemotherapy [65], [66]

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 [63] and pembrolizumab combination [64]

    (…)
  - if people do not immediately progress after chemotherapy, see the NICE technology appraisal guidance on pemetrexed maintenance after pemetrexed and pemetrexed maintenance after other platinum doublet chemotherapy [65], [66]

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. [57]
  - if people do not immediately progress after chemotherapy, see the NICE technology appraisal guidance on pemetrexed maintenance after pemetrexed and pemetrexed maintenance after other platinum doublet chemotherapy

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 [64] and pemetrexed with cisplatin or offer pemetrexed with carboplatin or other platinum doublet chemotherapy.
  - if people do not immediately progress after chemotherapy, see the NICE technology appraisal guidance on pemetrexed maintenance after pemetrexed and pemetrexed maintenance after other platinum doublet chemotherapy [65], [66]

Squamous non-small-cell lung cancer

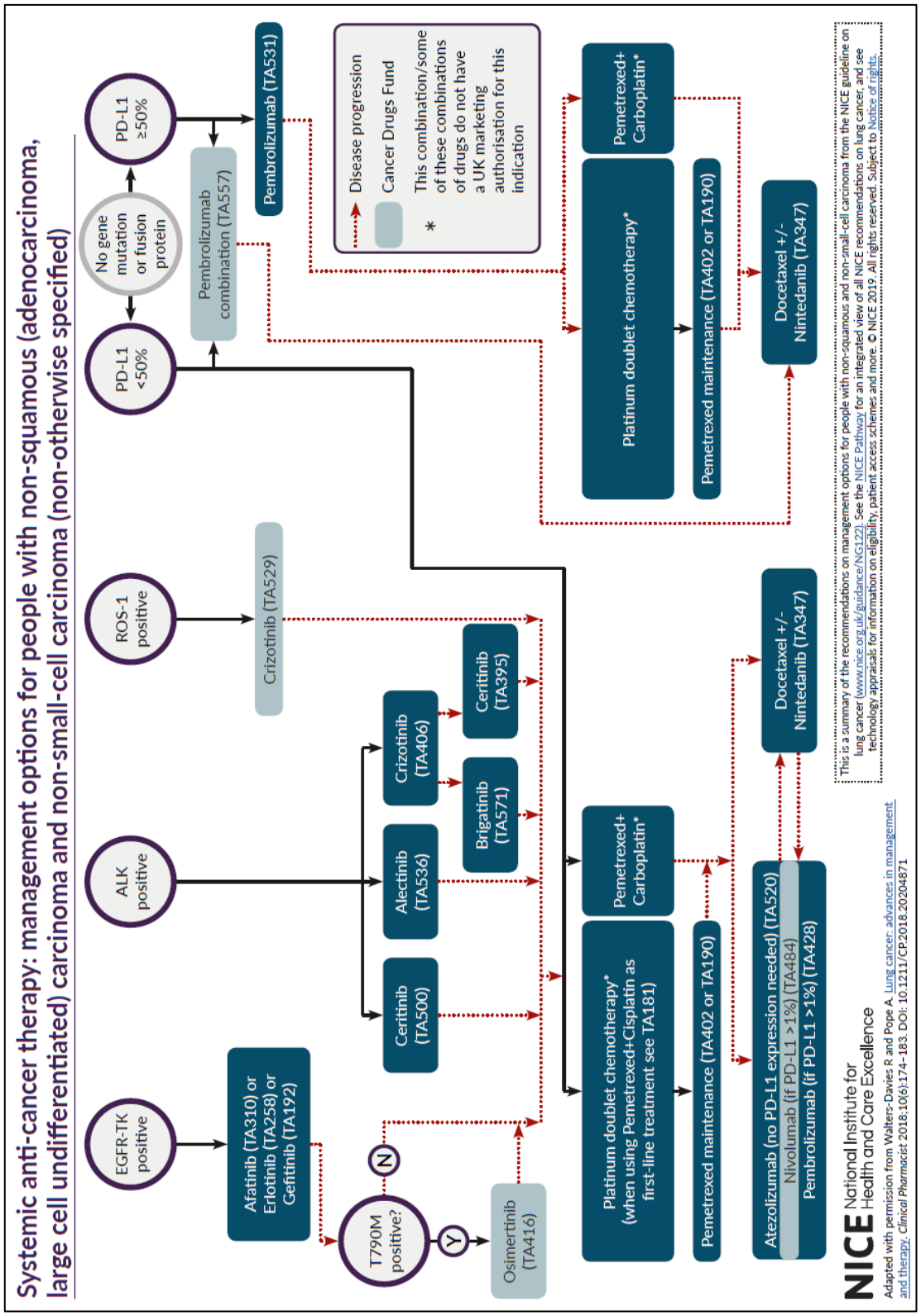
PDL1≥50%

- 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 [63]

PDL1<50%

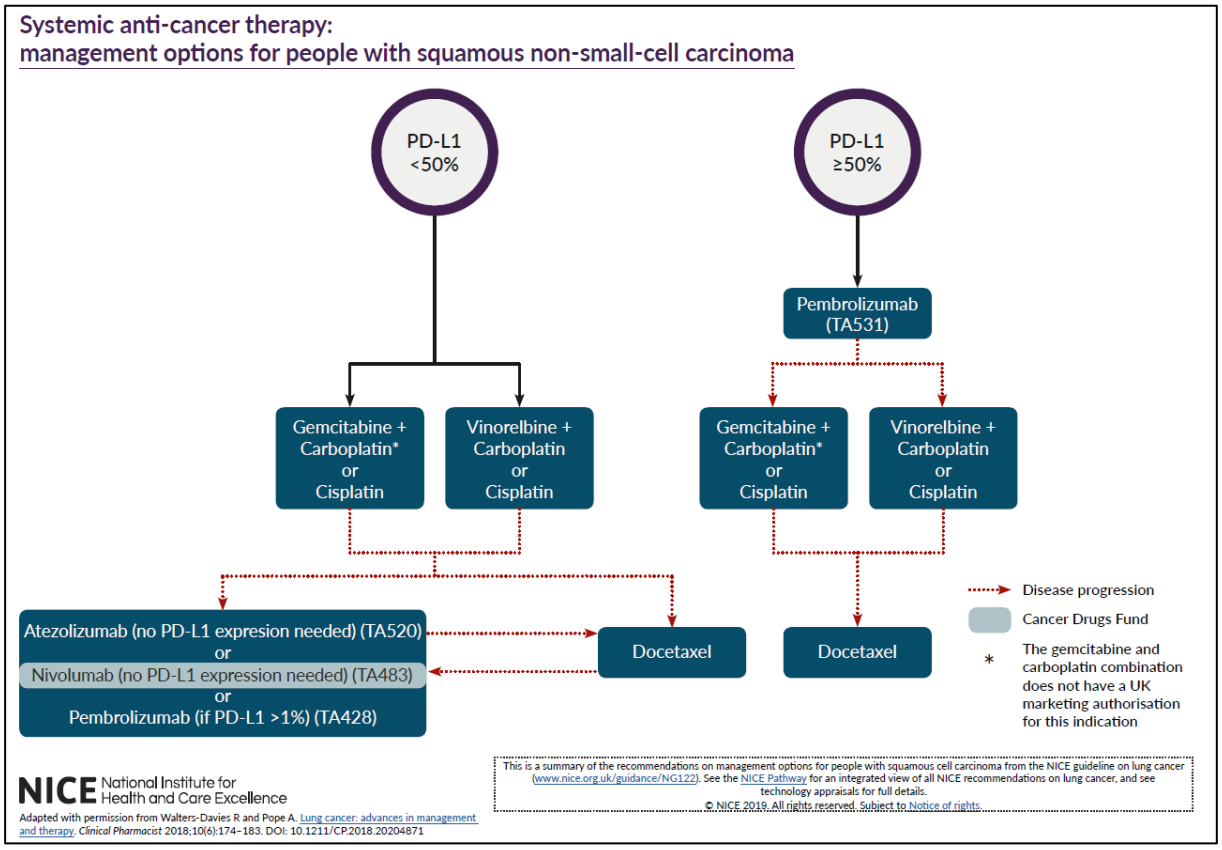
- 1.4.51 For guidance on treatment for squamous NSCLC in people whose tumours express PD-L1 below 50%:
  - for initial treatment, offer gemcitabine or vinorelbine and cisplatin[6] or carboplatin.

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 [41].

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

Siehe auch: Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft (DKG), et al., 2018 [40].

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):

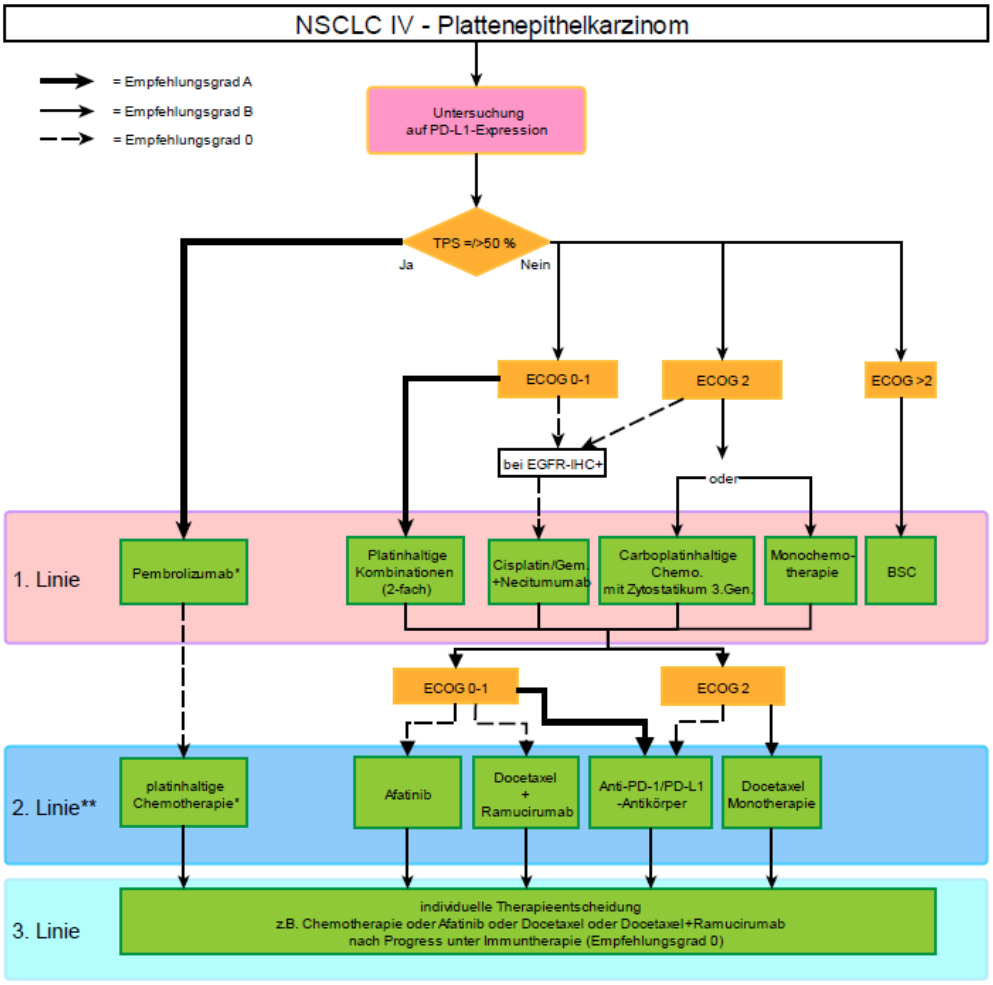
Unter dem Stichwort „Personalisierte Therapie“ oder „Stratifizierende Therapie“ hatten sich die Prinzipien insbesondere der Chemotherapie im metastasierten Stadium tiefgreifend geändert. Dieses galt in 2013 insbesondere für die Erstlinien-Chemotherapie bei Nachweis einer EGFR-Mutation sowie für die Zweitlinien-Chemotherapie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

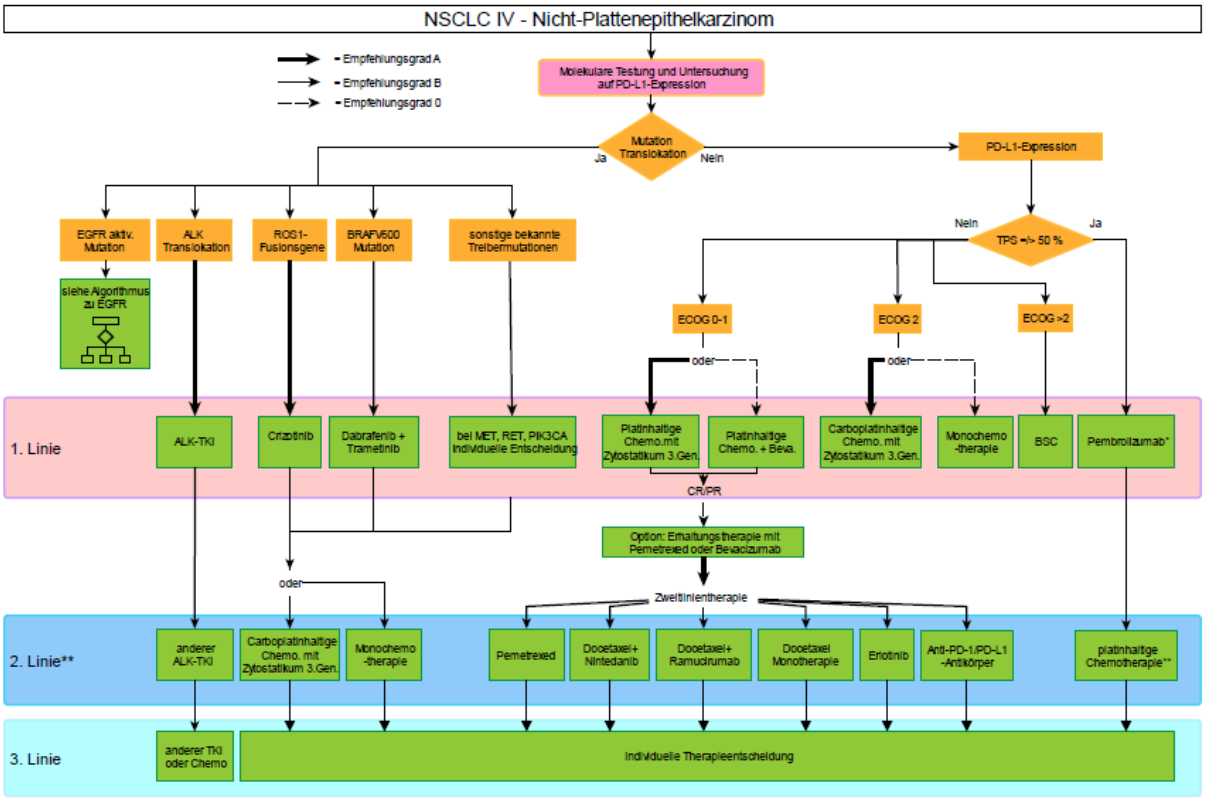
Empfehlungen

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



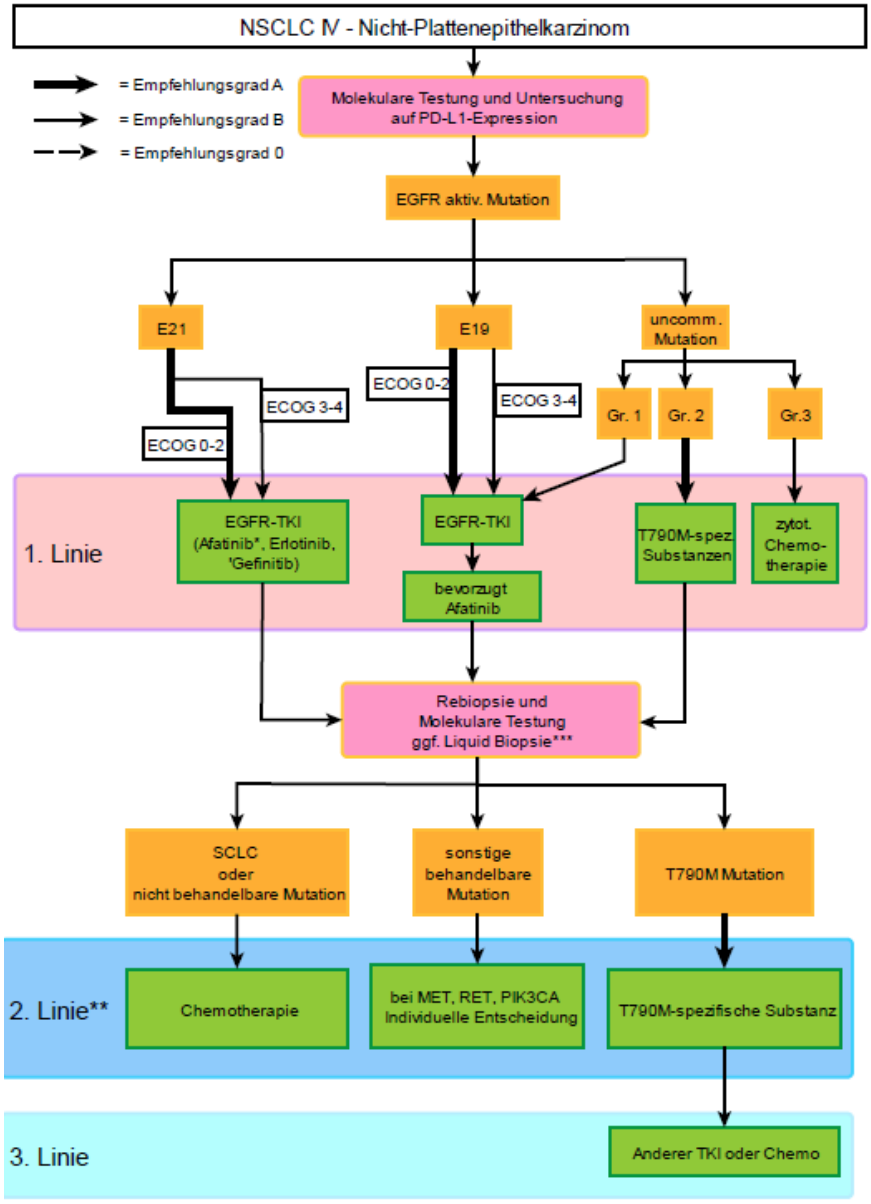
Legende:
* Die Systemtherapie nach Erstlinientherapie mit Pembrolizumab erfolgt nach den Kriterien einer Erstlinien -Chemotherapie
** Grundsätzlich gilt, dass bei Nachweis einer therapierbaren molekularen Veränderung auch im Falle eines Tumorprogresses unter Berücksichtigung von Resistenzmechanismen 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 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. Nach der Erstlinientherapie kann bei fehlendem Krankheitsprogress und bei guter Verträglichkeit der Therapie eine Erhaltungstherapie mit Necitumumab angeboten werden.	
Level of Evidence 1b	Literatur : [798-800]	
	Konsensstärke: 96 %	

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

8.71.	Evidenzbasiertes Statement	2018
Level of Evidence 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 A	Bei Patienten mit ECOG 2 ohne wesentliche Komorbiditäten sollen platinbasierte Kombinationen, z.B. Carbo/Pacli oder Carbo/Pem angeboten werden.	
Level of Evidence 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 %	

Stellenwert von Erhaltungstherapien

8.74.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad 0	Patienten mit nicht-plattenepithelialem Lungenkarzinom im Stadium IV in gutem Allgemeinzustand kann bei Ansprechen auf die und guter Verträglichkeit der Chemotherapie nach Abschluss von 4 Zyklen einer Erstlinientherapie eine Erhaltungstherapie (switch maintenance) mit Pemetrexed angeboten werden.	
Level of Evidence 1b	Literatur: [820]	
	Konsensstärke: 93%	

8.75.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad B	Bei Patienten mit nicht-plattenepithelialem Lungenkarzinom im Stadium IV in gutem Allgemeinzustand sollte bei Ansprechen auf die Cis/Pem-Chemotherapie und guter Verträglichkeit der Chemotherapie nach Abschluss von 4 Zyklen einer Erstlinientherapie eine Erhaltungstherapie (continuation maintenance) mit Pemetrexed angeboten werden.	
Level of Evidence 1b	Literatur: [805, 821-824]	
	Konsensstärke: 88%	

8.76.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad B	Patienten mit Plattenepithelkarzinom, sollte nach Erstlinienchemotherapie keine Erhaltungstherapie angeboten werden. Ausgenommen von dieser Empfehlung sind Patienten, die Necitumumab in der Erstlinientherapie erhalten haben.	
Level of Evidence 4	Literatur: [771]	
	Konsensstärke: 100%	

Systemtherapie bei Patienten mit aktivierender Mutation des EGF-Rezeptors (ECOG 0-4)

8.90.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad A	Bei Vorliegen einer aktivierenden EGFR Mutation soll bei Patienten mit ECOG 0-2 in der Erstlinientherapie ein EGFR-TKI abgeboten werden.	
Level of Evidence 1a	Literatur: [850-862]	
	Konsensstärke: 100 %	

8.91.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad B	Aufgrund der Überlebensdaten sollte bei Exon 19 deletierten Tumoren Afatinib angeboten werden.	
Level of Evidence 1b	Literatur: [859]	
	Konsensstärke: 88 %	

8.92.	Evidenzbasierte Empfehlung	2018
EK	Bei Vorliegen einer aktivierenden EGFR Mutation sollte bei Patienten mit ECOG 3-4 in der Erstlinientherapie ein EGFR-TKI angeboten werden.	
	Konsensstärke: 96 %	

8.92.	Evidenzbasierte Empfehlung	2018
EK	Bei Vorliegen einer aktivierenden EGFR Mutation sollte bei Patienten mit ECOG 3-4 in der Erstlinientherapie ein EGFR-TKI angeboten werden.	
	Konsensstärke: 96 %	

8.93.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad B	Bei Patienten mit seltenen EGF-R Tumormutationen der Gruppe 1 sollten TKI angeboten werden. Die Datenlage spricht für den bevorzugten Einsatz von Afatinib.	
Level of Evidence 1b	Literatur: [861]	
	Konsensstärke: 89 %	

8.94.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad A	Bei Patienten mit seltenen EGF-R Tumormutationen der Gruppen 2 sollen T790M spezifische Substanzen angeboten werden.	
Level of Evidence 1b	Literatur: [863]	
	Konsensstärke: 89 %	

8.95.	Konsensbasierte Empfehlung	2018
EK	Patienten mit seltenen EGF-R Tumormutationen der Gruppe 3 sollten - bis zur Verfügbarkeit von spezifischen Substanzen - wie EGFR-Wildtyp-Patienten behandelt werden.	
	Konsensstärke: 92 %	

8.96.	Evidenzbasiertes Statement	2018
Level of Evidence 2	Eine Erstlinientherapie mit Erlotinib und Bevacizumab bei EGFR-mutierten Patienten wurde in einer kleinen japanischen Studie untersucht. Aktuell kann nicht beurteilt werden, ob diese Kombinationstherapie für ein größeres Patientenkollektiv z.B. auch bei Kaukasiern in Frage kommt.	
	Literatur: [869]	
	Konsensstärke:89 %	

Systemtherapie bei Patienten mit ALK-Translokation oder weiteren bekannten Treibermutationen (ECOG 0-4)

8.100.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad A	NSCLC-Patienten mit einer ALK-Translokation soll in der Erstlinientherapie ein ALK-Inhibitor angeboten werden.	
Level of Evidence 1b	Literatur: [849, 871]	
	Konsensstärke: 100 %	

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

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

Systemtherapie bei Patienten mit BRAF-V600-Mutation

8.107.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad B	NSCLC IV- Patienten mit nachgewiesener BRAF-V600-Mutation sollte eine Kombination aus Dabrafenib und Trametinib angeboten werden.	
Level of Evidence 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.

Department of Health, 2017 [53].

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

A Cochrane review (Greenhalgh et al., 2016) and a phase III trial (Solomon et al., 2014) addressed the effectiveness of first-line targeted therapy in patients with advanced NSCLC. The Guideline Development Group highlighted this as a rapidly evolving area of research.

Recommendation 2.6.4.1	Grade
Effectiveness of first-line cytotoxic chemotherapy 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 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 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 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 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

Recommendation 2.6.4.6	Grade	Resource implication:
Effectiveness of first-line targeted therapy Crizotinib should be considered as first-line therapy in patients with ALK positive NSCLC tumours.	B	Crizotinib is licensed for this indication in the Republic of Ireland but is not currently reimbursed. The HSE reimbursement application is expected to be submitted in 2017.

Good practice point
Ensure patients are offered participation in a clinical trial when available and appropriate.

Good practice point
Patients should be referred for assessment by the palliative care service.

Referenzen aus Leitlinien

Greenhalgh, J., et al. 2016. First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer. Cochrane Database Syst Rev, Cd010383.
Solomon, B. J.,et al. 2014. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med, 371, 2167-77.

Maintenancetherapy:

	2.6.5.1 In patients with stage IV non-squamous NSCLC who do not experience disease progression and have a preserved performance status after 4-6 cycles of platinum-based therapy, treatment with maintenance pemetrexed is suggested.	**(B)**
	2.6.5.2 In patients with stage IV NSCLC, switch maintenance therapy with chemotherapy agents other than pemetrexed has not demonstrated an improvement in overall survival and is **not** recommended.	**(B)**
	2.6.5.3 In patients with stage IV NSCLC who do not experience disease progression after 4-6 cycles of platinum-based double agent chemotherapy, there is insufficient evidence to recommend maintenance therapy with erlotinib.	**(B)**

Hanna N et al., 2017 [29].

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

Siehe auch: Masters GA et al., 2015 [52].

Fragestellung

For patients with stage IV NSCLC in certain histologic or molecular subgroups (including EGFR, EGFR-positive T790M, ALK, ROS1, PD-L1/PD-1), what is the most effective first-line therapy?

Methodik

Grundlage der Leitlinie

Update der Version von 2015 (Masters GA, et al. Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update)

- 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:

- February 2014 to December 2016

LoE

Rating	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (e.g., balance of benefits versus harms) and further research is very unlikely to change either the magnitude or direction of this net
Intermediate	Intermediate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect, however it might alter the magnitude of the net effect.

Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change the magnitude and/or
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. Reliance on consensus opinion of experts may be reasonable to provide guidance on the topic until better

GoR

Type of Recommendation	**Definition**
Evidence-based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
Formal Consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak"). The results of the formal consensus process are
Informal Consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength
No Recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of

First-Line Treatment for Patients

Recommendations

First-Line Treatment for Patients

- Patients with non–squamous cell carcinoma without a tumor *EGFR*-sensitizing mutation or *ALK* or *ROS1* gene rearrangement and with a performance status (PS) of 0 or 1 (and appropriate PS of 2):
  - With high PD-L1 expression (tumor proportion score [TPS] ≥ 50%) and no contraindications, single-agent pembrolizumab is recommended (Evidence quality: high; Strength of recommendation: strong).
  - With low PD-L1 expression (TPS < 50%), a variety of combination cytotoxic chemotherapies (with or without bevacizumab if patients are receiving carboplatin and paclitaxel) are recommended (Platinum based [Evidence quality: high; Strength of recommendation: strong]; Non–platinum based [Evidence quality: intermediate; Strength of recommendation: weak]).
  - There is insufficient evidence to recommend bevacizumab in combination with pemetrexed plus carboplatin.
  - Other checkpoint inhibitors, combination checkpoint inhibitors, or immune checkpoint therapy with chemotherapy are not recommended.
  - With PS of 2, combination or single-agent therapy or palliative care alone may be used (chemotherapy [Evidence quality: intermediate; Strength of recommendation: weak]; palliative care [Evidence quality: intermediate; Strength of recommendation: strong]).
- Patients with squamous cell carcinoma without a tumor *EGFR*-sensitizing mutation or *ALK* or *ROS1* gene rearrangement and with a PS of 0 or 1 (and appropriate PS of 2):
  - With high PD-L1 expression (TPS ≥ 50%) and no contraindications, single-agent pembrolizumab is recommended (Evidence quality: high; Strength of recommendation: strong).
  - With low PD-L1 expression (TPS < 50%), a variety of combination cytotoxic chemotherapies are recommended (Platinum based [Evidence quality: high; Strength of recommendation: strong]; Non–platinum based [Evidence quality: low; Strength of recommendation: weak]).
  - Other checkpoint inhibitors, combination checkpoint inhibitors, or immune checkpoint therapy with chemotherapy are not recommended.
  - With PS of 2, combination or single-agent therapy or palliative care alone may be used (chemotherapy [Evidence quality: intermediate; Strength of recommendation: weak]; palliative care [Evidence quality: intermediate; Strength of recommendation: strong]).
  - With squamous NSCLC treated with cisplatin and gemcitabine, the Panel neither recommends for nor recommends against the addition of necitumumab to chemotherapy.
- With sensitizing *EGFR* mutations, afatinib, erlotinib, or gefitinib is recommended (Evidence quality: high; Strength of recommendation: strong for each).
- With *ALK* gene rearrangements, crizotinib is recommended (Evidence quality: strong; Strength of recommendation: high).
- With *ROS1* rearrangement, crizotinib is recommended (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Ellis PM et al., 2016 [7].

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

- nach 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:

- Cisplatin-based combinations
  - Cisplatin plus docetaxel
  - Cisplatin plus paclitaxel
  - Cisplatin plus pemetrexed
  - Cisplatin plus vinorelbine
  - *Cisplatin plus gemcitabine*
- Carboplatin-based combinations
  - Carboplatin plus albumin-bound (nab) –paclitaxel
  - Carboplatin plus paclitaxel
  - Carboplatin plus pemetrexed
  - Carboplatin plus docetaxel
  - *Carboplatin plus gemcitabine*
- 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.

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. 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. 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:

- Cisplatin-based combinations
  - Cisplatin plus docetaxel
  - Cisplatin plus gemcitabine
  - Cisplatin plus paclitaxel
  - Cisplatin plus vinorelbine
- Carboplatin-based combinations
  - Carboplatin plus gemcitabine
  - Carboplatin plus paclitaxel
  - Carboplatin plus nab-paclitaxel
  - Carboplatin plus docetaxel
- 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 an EGFR-sensitizing mutation and PS 0 to 1 or possibly PS 2?

Recommendation A4

If patients have stage IIIB/IV NSCLC and a sensitizing *EGFR* mutation, first-line afatinib, erlotinib, or gefitinib is recommended.

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?

Recommendation A5

If patients have stage IIIB/IV NSCLC and *ALK* rearrangements, first-line crizotinib is recommended.

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.

What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with negative or unknown EGFR/ALK status and large-cell neuroendocrine carcinoma?

Recommendation A7

Patients with large-cell neuroendocrine carcinoma may receive the same treatment as other patients with NSCC or treatment with etoposide in platinum combinations.

What is the optimal treatment for patients with stable disease or response after four cycles of cytotoxic chemotherapy?

Recommendation A9
This clinical question was covered by the recent PEBC 7-22 guideline [2]. The recommendations from this guideline are as follows: Maintenance therapy is recommended as an option for therapy as described below: • Maintenance therapy with pemetrexed should be considered an option for patients with non-squamous NSCLC. Maintenance therapy with pemetrexed is not recommended for patients with squamous NSCLC. • Maintenance therapy with EGFR tyrosine kinase inhibitors (TKIs) may be considered an option. No recommendation can be made with respect to the choice of gefitinib or erlotinib. Any decision should be made in conjunction with discussion with the patient. • There is insufficient evidence to recommend docetaxel or gemcitabine as maintenance chemotherapies. • In patients who elect to have a break following first-line therapy, second-line therapy should be considered at the time of progression. *Qualifying statements* • These recommendations apply both to patients who previously received pemetrexed- or non-pemetrexed-containing platinum-doublet chemotherapy. • Trials have evaluated both erlotinib and gefitinib, but no trials directly compared these two agents as maintenance therapy. However, the strongest data would support the use of erlotinib in this setting, although the OS advantage was modest for both agents. • The recommendation for EGFR TKIs applies to both *EGFR* mutation-positive and wild-type patients. • Since the cut-off date of the review of the literature, a notification has been released by Health Canada based on the results of the IUNO trial [3,4]. While the results are not available in the public domain, Health Canada has recommended that EGFR TKI maintenance therapy should not be used in patients with EGFR wild-type advanced NSCLC [3]. • In patients receiving maintenenance bevacizumab, it is unclear whether the addition of maintenance pemetrexed improves OS.
Key Evidence for Recommendation A9
Readers should refer to the PEBC 7-22 guideline for additional information [2].
Interpretation of Evidence for Recommendation A9
Readers should refer to the PEBC 7-22 guideline for additional information [2].

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

1. Develop a structured clinical question in PICO format
2. Search for existing relevant guidelines and SR answering the clinical question
3. Perform systematic review process (systematic review protocol and systematic literature search strategy for each PICO question; Body evidence table of all included literature)
4. Summarise the relevant data
5. Assess the body of evidence and formulate recommendations
6. 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. 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. 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. 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. 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. 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. 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. 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. 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. 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. 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.
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. Last reviewed September 2017	I	[1], [4]
3G platinum-based monotherapy (vinorelbine, paclitaxel, docetaxel, or gemcitabine) improves survival compared with best supportive care. 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. 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. 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. Last reviewed September 2017	I	[1]
Triplet chemotherapy regimens are associated with greater grade 3 /4 toxicities. 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. 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. 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. 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. 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. 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. 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. 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. ^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. 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. 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. 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. 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. 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 . 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. 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. 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. 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 first-line maintenance therapy for treatment of stage IV inoperable NSCLC?

Recommendation	Grade
In unselected patients with stable or responsive advanced NSCLC after four cycles of initial platinum doublet chemotherapy, "switch maintenance" therapy to an alternative agent is recommended to delay tumour progression. Options for delaying tumour progression in unselected patients, include erlotinib or docetaxel, whilst in patients with non-squamous cell carcinoma histology, pemetrexed or erlotinib. Options most proven for prolongation of survival include erlotinib or pemetrexed. In the case of patients with known EGFR-gene activating mutations treated initially with chemotherapy, switch maintenance erlotinib is recommended. Last reviewed December 2015	A

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. 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. 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) . 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. 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.

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.

What is the optimal systemic therapy regimen for elderly patients for treatment of stage IV inoperable NSCLC?

Evidence summary	Level	References
First-line single agent vinorelbine (30 mg/m2 on days one and eight, Q3 weekly) in patients over 70 years of age improves survival and reduces disease related symptoms. Last reviewed December 2015	II	[1]
In patients over 70 years of age, first line single agent docetaxel 60 mg/m2 (day one) compared to vinorelbine 25 mg/m2 (days one and eight) every 21 days, improves response rate, progression free survival and disease related symptoms, but not overall survival and is associated with more G3/4 neutropaenia. Last reviewed December 2015	II	[2]
In patients over 65 years of age, gemcitabine doublet chemotherapy improves response rate compared with single agent 3G chemotherapy, but does not improve survival and is associated with greater thrombocytopaenia. Last reviewed December 2015	I	[4]
In patients over 70 years of age, first-line carboplatin/weekly paclitaxel combination improves survival compared with 3G monotherapy (weekly vinorelbine or gemcitabine) but, is associated with more neutropaenia. Last reviewed December 2015	II	[5]

+ Evidence-based recommendation?	Grade
Suitably fit patients over 65 years of age, can be offered first-line mono-chemotherapy with a 3G single agent (vinorelbine (25-30 mg/ m2 day one, eight Q3 weekly), docetaxel (60 mg/m2 day one, Q3 weekly) or gemcitabine (1150 mg/m2 days one and eight, Q3 weekly). Last reviewed December 2015	B

+ Evidence-based recommendation?	Grade
In elderly patients, first-line gemcitabine doublet chemotherapy is not recommended. Last reviewed December 2015	B

+ Evidence-based recommendation?	Grade
In fit elderly patients, first-line carboplatin/weekly paclitaxel may be offered instead of 3G monotherapy, but at the expense of greater neutropaenia. Last reviewed December 2015	B

The age criterion for designation of “elderly” has varied somewhat across NSCLC studies with the elderly groups commonly defined as those patients either 65 or 70 years of age or older. Several randomised controlled trials (RCTs) have been conducted within this subgroup. As a group elderly patients are considered at higher risk of treatment related toxicity, due to possible age physiologic effects on drug handling and high proportion of co-morbidities. Gridelli et al first reported findings to indicate benefit from monotherapy with vinorelbine in patients over 70, with improvement seen in OS 0.65 (95% CI = 0.45–0.93) and fewer reported lung cancer related symptoms in a RCT of 161 patients[1] Kudoh et al, subsequently compared

docetaxel 60 mg/m2 (day one) to vinorelbine 25 mg/m2 (days one and eight) every 21 days for four cycles, in a RCT of 182 Japanese patients over 70 years of age.[2] There was no statistical difference in the primary endpoint of median OS with docetaxel versus vinorelbine (14.3 months versus 9.9 months; HR 0.780; 95% CI 0.561 - 1.085; P = 0.138).[2] However, median PFS (5.5 months versus 3.1 months; P = 0.001), RR (22.7% versus 9.9%; P = 0.019) and disease-related symptoms favoured docetaxel over vinorelbine (odds ratio, 1.86; 95% CI, 1.09 - 3.20). Docetaxel was associated with more grade 3/4 neutropaenia (82.9% for docetaxel; 69.2% for vinorelbine; P = 0.031).[2]

Hainsworth et al, randomised 350 patients over 65 years of age to first line single-agent weekly docetaxel versus the combination of docetaxel and gemcitabine.[3] There was no difference in OS with the combination treatment compared with single agent weekly docetaxel.[3] Russo et al reported a literature-based meta-analysis of RCTs that compared a gemcitabine based doublet regimen with a 3G single agent in elderly patients (> 65).[4] This meta-analysis included the study by Hainsworth et al. Four trials evaluating 1436 patients were included in the meta-analysis. A significant difference in RR was seen favouring gemcitabine doublet therapy over single 3G agents (OR 0.65; 95% CI 0.51-0.82, p < .001), whereas one-year survival rate was not significantly different (OR, 0.78; 95% CI, 0.57-1.06, P = 0.169). Only Grade ¾ thrombocytopaenia was greater with combination therapy (OR, 1.76; 95% CI, 1.12-2.76, P= 0.014).

More recently, Quoix et al reported findings from a RCT of that compared a carboplatin and paclitaxel doublet chemotherapy regimen with 3G monotherapy in 451 elderly patients (age 70-89) with advanced NSCLC.[5] Patients were treated with carboplatin AUC 6 on day one and 90 mg/m. paclitaxel on days 1, 8, and 15 Q4 weekly or 3G monotherapy with either 25 mg/m2. vinorelbine on days one and eight or 1150 mg/m2 gemcitabine on days one and eight, Q3 weekly.[5] Overall survival was in favour of the combination (median 10.3 months for doublet chemotherapy versus 6.2 months for 3G monotherapy (HR 0.64, 95% CI 0.52–0.78; p<0.0001)).[5] Toxicity was more frequent in the doublet chemotherapy group than in the monotherapy group (neutropaenia (48.4% vs 12.4%); asthenia (10.3% versus 5.8%)[5]

What is the optimal systemic therapy regimen in selected patients for treatment of stage IV inoperable NSCLC?

- currently being updated

Facchinetti F et al., 2019 [8].

Italian Association of Medical Oncologyg (AIOM)

Treatment of metastatic non-small cell lung cancer: 2018 guidelines of the Italian Association of Medical Oncology (AIOM).

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:

- Up to 2018

LoE/GoR

- SIGN, GRADE

Table 1. The four levels of strength of clinical recommendations.

Strength of recommendation	Meaning
Strong for	The intervention should be considered as the first treatment option (benefits are higher than risks)
Conditional for	The intervention can be considered as a possible treatment option (not sure that benefits are higher than risks)
Conditional against	The intervention should not be considered as the first treatment option; it could be considered in selected cases after discussion with the patient (not sure that risks are higher than benefits)
Strong against	The intervention should not be considered as a possible treatment option (risks are higher than benefits)

Recommendations

Table 2. Clinical recommendations developed according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) method for the treatment of oncogene-addicted advanced/metastatic non-small cell lung cancer (NSCLC).

Global quality of evidence according to GRADE	Clinical recommendation	Strength of the recommendation
Very low	An EGFR inhibitor (gefitinib, erlotinib, afatinib) should be administered as first-line treatment for patients with NSCLC harboring classic (exon 19 deletions, L858R) *EGFR* mutations[8–15]	Strong for
Very low	An EGFR inhibitor (gefitinib, erlotinib, afatinib) can be considered as first-line treatment for patients with NSCLC harboring uncommon (mutations/duplications in exons 18–21) *EGFR* mutations[20–27]	Conditional for
Very low	An EGFR inhibitor (gefitinib, erlotinib, afatinib) should not be administered as first-line treatment for patients with NSCLC harboring *EGFR* exon 20 insertion or de novo T790M[20–27]	Strong against
Very low	Osimertinib should be administered after progression during gefitinib, erlotinib or afatinib for patients with NSCLC harboring classic (exon 19 deletions, L858R) *EGFR* mutations and T790M mutation (detected through liquid or tumor biopsy)[31]	Strong for
Very low	Compared to chemotherapy, crizotinib should be administered as first-line treatment for patients with NSCLC harboring an *ALK* rearrangement[36]	Strong for
Very low	Compared to crizotinib, alectinib should be administered as first-line treatment for patients with NSCLC harboring an *ALK* rearrangement[45,48]	Strong for
Very low	After progression during crizotinib, ceritinib or alectinib should be administered as second-line treatment for patients with NSCLC harboring an *ALK* rearrangement[38,41]	Strong for
Very low	Crizotinib should be considered as first-line treatment for patients with NSCLC harboring a *ROS1* rearrangement[52,53]	Strong for

Table 3. Treatment recommendations developed according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) method for the treatment of advanced/metastatic non-oncogene-addicted non-small cell lung cancer (NSCLC).

Global quality of evidence according to GRADE	Clinical recommendation	Strength of the recommendation
Low	Pembrolizumab should be administered as first-line treatment for patients with NSCLC, without *EGFR* mutations or *ALK* rearrangements, with PD-L1 expression ⩾50%[61]	Strong for
Low	Maintenance therapy with pemetrexed can be considered for nonsquamous NSCLC patients with good ECOG performance status (0–1) and whose disease is not progressed during/after first-line platinum-based chemotherapy[90–92]	Conditional for
Very low	Immunotherapy with nivolumab, atezolizumab, or pembrolizumab (the latter only if PD-L1 ⩾1%) can be considered for NSCLC patients as second-line treatment after first-line chemotherapy[100–103]	Conditional for
Very low	Nintedanib/docetaxel combination can be considered in patients with lung adenocarcinoma as second-line treatment, especially if progression after first-line chemotherapy occurs within nine months since its beginning[104]	Conditional for

Table 4. Treatment recommendations developed according to the Scottish Intercollegiate Guidelines Network (SIGN) method for the treatment of non-advanced/metastatic oncogene-addicted non-small cell lung cancer (NSCLC).

Quality of evidence according to SIGN	Clinical recommendation	Strength of the recommendation
A	In patients with NSCLC candidate to first-line chemotherapy, platinum-based doublets should be administered. Cisplatin should be preferred, while carboplatin should be considered as an appropriate option in case of contraindications to cisplatin.[73–77]	Strong for
A	Based on the subgroup analysis of a single randomized study, cisplatin/pemetrexed regimen can be considered for patients with nonsquamous NSCLC, given its favorable risk/benefit profile compared to cisplatin/gemcitabine.[79]	Conditional for
A	Bevacizumab combined with a platinum-based doublet can be considered for patients with nonsquamous NSCLC, although the survival benefit has been documented only in case of carboplatin/paclitaxel association.[80]	Conditional for
A	Single-agent first-line chemotherapy should be considered in elderly, nonselected population of NSCLC.[81,82]	Strong for
A	Carboplatin-based first-line chemotherapy doublets can be considered in selected elderly patients with NSCLC.[83–86]	Conditional for
A	Patients with NSCLC with ECOG performance status 2 can be candidate either to single-agent chemotherapy or to a platinum-based doublet with reduced dose, after careful clinical selection.[87,89]	Conditional for

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 10 of 12, October 2019) am 12.10.2019

#	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 Oct 2014 to present

Systematic Reviews in Medline (PubMed) am 12.10.2019

#	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-

#	Suchfrage
	analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
7	((#6) AND ("2014/10/01"[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 12.10.2019

#	**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 ("2014/04/01"[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: • Non-randomised, experimental trial • Cohort study • Case-control study • 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: • Non-randomised, experimental trial • Cohort study • Case-control study
III-3	A comparative study without concurrent controls: • Historical control study • Two or more single arm study • 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: • Historical control study • 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)