

**Kriterien zur Bestimmung der zweckmäßigen
Vergleichstherapie**

und

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

und

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

Vorgang: 2020-B-256 Tepotinib

Stand: November 2020

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

Tepotinib

[Behandlung des fortgeschrittenen NSCLC mit MET-Tyrosinkinase-Rezeptor-Exon-14- (METex14-)Skipping-Veränderungen]

Kriterien gemäß 5. Kapitel § 6 VerfO

Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.

Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“

Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.

Nicht angezeigt.

Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen

Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:

- Afatinib: Beschlüsse vom 05.11.2015 und 20.10.2016
- Alectinib (ALK-positives NSCLC, Erstlinie): Beschluss vom 21.06.2018
- Alectinib (ALK-positives NSCLC, nach Crizotinib): Beschluss vom 19.10.2017
- Atezolizumab (Erstlinien): Beschlüsse vom 02.04.2020
- Atezolizumab: Beschluss vom 16.03.2018
- Brigatinib (ALK-positives NSCLC): Beschlüsse vom 04.07.2019 und 15.10.2020
- Ceritinib (ALK-positives NSCLC, Erstlinie): Beschluss vom 01.02.2018
- Ceritinib (ALK-positives NSCLC, nach Crizotinib): Beschluss vom 16.03.2017
- Crizotinib (ALK-positives NSCLC, Erstlinie): Beschluss vom 16.06.2016
- Crizotinib (ROS1-positives NSCLC): Beschlüsse vom 16.03.2017
- Crizotinib (ALK-positives NSCLC): Beschluss vom 15.12.2016
- Dabrafenib (NSCLC mit BRAF-V600-Mutation): Beschluss vom 19.10.2017
- Dacomitinib (NSCLC mit EGFR-Mutation): Beschluss vom 17.10.2019
- Durvalumab (lokal fortgeschritten, nach Radiochemotherapie): Beschluss vom 04.04.2019
- Lorlatinib (ALK-positives NSCLC): Beschluss vom 22.11.2019
- Necitumumab: Beschluss vom 15.09.2016
- Nintedanib (NSCLC): Beschluss vom 18.06.2015

	<ul style="list-style-type: none"> • Nivolumab (NSCLC mit plattenepithelialer Histologie): Beschluss vom 04.02.2016 • Nivolumab (NSCLC mit nicht-plattenepithelialer Histologie): Beschluss vom 20.10.2016 • Osimertinib (NSCLC mit EGFR-Mutation): Beschlüsse vom 15.09.2016, 19.10.2017 und 17.01.2019 • Pembrolizumab (Erstlinie, plattenepitheliale Histologie): Beschluss vom 19.09.2019 • Pembrolizumab (Erstlinie, nicht-plattenepitheliale Histologie): Beschluss vom 19.09.2019 • Pembrolizumab (Erstlinie): Beschluss vom 03.08.2017 • Pembrolizumab (nach Chemotherapie): Beschluss vom 02.02.2017 • Trametinib (NSCLC mit BRAF-V600-Mutation): Beschluss vom 19.10.2017 • Ramucirumab: Beschluss vom 01.09.2016 • Ramucirumab (NSCLC mit EGFR-Mutation, Erstlinie): Beschluss vom 20.08.2020 <p>Richtlinien: Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie - Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (Off-Label-Use):</p> <ul style="list-style-type: none"> • Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff ATC-Code Handelsname	Anwendungsgebiet (Text aus Beratungsanforderung/Fachinformation)
Zu prüfendes Arzneimittel:	
Tepotinib L01EX21 TEPMETKO	<u>Anwendungsgebiet laut Fachinformation</u> TEPMETKO als Monotherapie wird angewendet bei erwachsenen Patienten mit einem fortgeschrittenen nicht-kleinzelligen Bronchialkarzinom (NSCLC) mit Veränderungen, die zu METex14-Skipping (Exon-14-Skipping im mesenchymal-epithelialen Transitionsfaktor-Gen) führen, die eine systemische Therapie nach Platin-basierter Chemotherapie und/oder einer Behandlung mit Immuntherapie benötigen.
Zytostatika:	
Carboplatin L01XA02 generisch	Off-Label-Indikation für Carboplatin: Kombinationstherapie des fortgeschrittenen NSCLC (palliativ)
Cisplatin L01XA01 generisch	Cisplatin wird angewendet zur Behandlung des fortgeschrittenen oder metastasierten nichtkleinzelligen Bronchialkarzinoms. Cisplatin kann als Mono- oder Kombinationstherapie angewendet werden.
Docetaxel L01CD02 generisch	Nicht-kleinzelliges Bronchialkarzinom: Docetaxel ist in Kombination mit Cisplatin zur Behandlung von Patienten mit nicht resezierbarem, lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Bronchialkarzinom ohne vorausgegangene Chemotherapie angezeigt. Docetaxel ist zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Bronchialkarzinom nach Versagen einer vorausgegangenen Chemotherapie angezeigt.
Etoposid L01CB01 Riboposid®	Kombinationstherapie folgender Malignome: – Palliative Therapie des fortgeschrittenen, nicht-kleinzelligen Bronchialkarzinoms bei Patienten mit gutem Allgemeinzustand (Karnofsky-Index > 80 %), [...]
Gemcitabin L01BC05 generisch	Gemcitabin ist in Kombination mit Cisplatin als Erstlinientherapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nichtkleinzelligen Bronchialkarzinom (NSCLC) angezeigt. Eine Gemcitabin-Monotherapie kann bei älteren Patienten oder solchen mit einem Performance Status 2 in Betracht gezogen werden.
Ifosfamid	Nicht-kleinzellige Bronchialkarzinome:

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff ATC-Code Handelsname	Anwendungsgebiet (Text aus Beratungsanforderung/Fachinformation)
L01AA06 Holoxan®	Zur Einzel- oder Kombinationschemotherapie von Patienten mit inoperablen oder metastasierten Tumoren.
Mitomycin L01DC03 generisch	Mitomycin wird in der palliativen Tumorthherapie eingesetzt. Bei intravenöser Gabe ist es in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei folgenden metastasierenden Tumoren wirksam: [...] nicht-kleinzelliges Bronchialkarzinom [...].
Paclitaxel L01CD01 generisch	Fortgeschrittenes nicht-kleinzelliges Bronchialkarzinom (NSCLC): Paclitaxel ist, in Kombination mit Cisplatin, zur Behandlung des nicht-kleinzelligen Bronchialkarzinoms bei Patienten angezeigt, für die potentiell kurative chirurgische Maßnahmen und/oder eine Strahlentherapie nicht in Frage kommen.
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	Pemetrexed ist in Kombination mit Cisplatin angezeigt zur first-line Therapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie. Pemetrexed in Monotherapie ist angezeigt für die Erhaltungstherapie bei lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie bei Patienten, deren Erkrankung nach einer platinbasierten Chemotherapie nicht unmittelbar fortgeschritten ist. Pemetrexed in Monotherapie ist angezeigt zur Behandlung in Zweitlinientherapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nichtkleinzelligen Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie.
Vindesin L01CA03 Eldesine®	Kombinationschemotherapie: Lokal fortgeschrittenes oder metastasiertes nicht-kleinzelliges Bronchialkarzinom (Stadium IIIB, IV).
Vinorelbin L01CA04 generisch	Behandlung des nicht kleinzelligen Bronchialkarzinoms (Stadium 3 oder 4).

Proteinkinase-Inhibitoren:	
Afatinib L01XE13 Giotrif®	GIOTRIF als Monotherapie wird angewendet zur Behandlung von: <ul style="list-style-type: none"> – epidermaler Wachstumsfaktorrezeptor (EGFR, epidermal growth factor receptor)-Tyrosinkinaseinhibitor (TKI)-naiven erwachsenen Patienten mit lokal fortgeschrittenem und/oder metastasiertem nicht-kleinzelligen Lungenkarzinom (NSCLC, non-small cell lung cancer) mit aktivierenden EGFR-Mutationen; – erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC mit Plattenepithel-Histologie, das unter oder nach Platin-basierter Chemotherapie fortschreitet (siehe Abschnitt 5.1).
Alectinib L01XE36 Alecensa®	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. Alecensa wird als Monotherapie angewendet zur Behandlung des Anaplastische-Lymphomkinase (ALK)-positiven, fortgeschrittenen nicht-kleinzelligen Bronchialkarzinoms (non-small cell lung cancer, NSCLC) bei erwachsenen Patienten, die zuvor mit Crizotinib behandelt wurden.
Brigatinib L01XE43 Alunbrig®	Alunbrig ist als Monotherapie bei erwachsenen Patienten mit anaplastischer-Lymphomkinase (ALK)-positivem, fortgeschrittenen, nicht-kleinzelligen Lungenkarzinom (NSCLC) angezeigt, die zuvor mit Crizotinib behandelt wurden. Alunbrig ist als Monotherapie bei erwachsenen Patienten mit anaplastischer-Lymphomkinase (ALK)-positivem, fortgeschrittenem, nicht-kleinzelligem Lungenkarzinom (NSCLC) angezeigt, die zuvor nicht mit einem ALK-Inhibitor behandelt wurden.
Ceritinib L01XE28 Zykadia®	Zykadia wird als Monotherapie angewendet bei erwachsenen Patienten zur Erstlinienbehandlung des fortgeschrittenen, Anaplastische-Lymphomkinase (ALK)-positiven, nichtkleinzelligen Bronchialkarzinoms (NSCLC). Zykadia wird angewendet bei erwachsenen Patienten zur Behandlung des fortgeschrittenen, Anaplastische-Lymphomkinase (ALK)-positiven, nicht-kleinzelligen Bronchialkarzinoms (NSCLC), die mit Crizotinib vorbehandelt wurden.
Crizotinib L01XE16 Xalkori®	XALKORI als Monotherapie wird angewendet bei: <ul style="list-style-type: none"> – Erwachsenen zur Erstlinienbehandlung des Anaplastische-Lymphom-Kinase (ALK)-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, NSCLC) – Erwachsenen zur Behandlung des vorbehandelten Anaplastische-Lymphom-Kinase (ALK)-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, NSCLC) – 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.

Dacomitinib L01XE47 Vizimpro®	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).
Entrectinib L01XE56 Rozlytrek®	Rozlytrek als Monotherapie wird zur Behandlung von Erwachsenen und pädiatrischen Patienten ab 12 Jahren mit soliden Tumoren mit neurotropher Tyrosinrezeptorkinase (NTRK)-Genfusion angewendet, <ul style="list-style-type: none"> – bei denen eine lokal fortgeschrittene oder metastasierte Erkrankung vorliegt oder eine Erkrankung, bei der eine chirurgische Resektion wahrscheinlich zu schwerer Morbidität führt, und – die bisher keinen NTRK-Inhibitor erhalten haben – für die keine zufriedenstellenden Therapieoptionen zur Verfügung stehen (siehe Abschnitte 4.4 und 5.1). Rozlytrek als Monotherapie wird angewendet bei erwachsenen Patienten mit ROS1-positivem, fortgeschrittenem nicht-kleinzelligem Lungenkarzinom (NSCLC), die zuvor keine Behandlung mit ROS1-Inhibitoren erhalten haben.
Erlotinib L01XE03 Tarceva®	<u>Nicht-kleinzelliges Lungenkarzinom (NSCLC)</u> Tarceva ist zur First-Line-Behandlung bei Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit aktivierenden EGFR-Mutationen angezeigt. Tarceva ist auch für eine Wechsel-Erhaltungstherapie (switch maintenance treatment) bei Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC mit aktivierenden EGFR-Mutationen und unverändertem Krankheitszustand nach First-Line-Chemotherapie angezeigt. Tarceva ist auch zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC angezeigt, bei denen mindestens eine vorausgegangene Chemotherapie versagt hat. Bei Patienten mit Tumoren ohne aktivierende EGFR-Mutationen ist Tarceva angezeigt, wenn andere Therapieoptionen als ungeeignet erachtet werden.
Gefitinib L01XE02 Iressa®	IRESSA ist als Monotherapie angezeigt zur Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Lungenkarzinom (NSCLC) mit aktivierenden Mutationen der EGFR-TK (siehe Abschnitt 4.4).
Lorlatinib L01XE44 Lorviqua	Lorviqua als Monotherapie wird angewendet zur Behandlung erwachsener Patienten mit Anaplastische-Lymphomkinase (ALK)-positivem, fortgeschrittenen nicht-kleinzelligen Lungenkarzinom (non-small cell lung cancer, NSCLC), deren Erkrankung fortgeschritten ist nach: <ul style="list-style-type: none"> – Alectinib oder Ceritinib als erste Therapie mit ALK-Tyrosinkinase-Inhibitoren (TKI); oder – Crizotinib und mindestens einem anderen ALK-TKI.
Nintedanib L01XE31 Vargatef®	Vargatef wird angewendet in Kombination mit Docetaxel zur Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem, metastasiertem oder lokal rezidiviertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit Adenokarzinom-Histologie nach Erstlinienchemotherapie.
Osimertinib L01XE35	TAGRISSO ist als Monotherapie angezeigt zur:

Tagrisso®	<ul style="list-style-type: none"> – 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) – Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem EGFR-T790M-mutationspositivem NSCLC.
Trametinib L01XE25 Mekinist®	Trametinib in Kombination mit Dabrafenib ist angezeigt zur Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligem Lungenkarzinom mit einer BRAF-V600-Mutation.
Antikörper:	
Atezolizumab L01XC32 Tecentriq®	<p><u>Nicht-kleinzelliges Lungenkarzinom</u></p> <p>Tecentriq wird angewendet in Kombination mit Bevacizumab, Paclitaxel und Carboplatin bei erwachsenen Patienten zur Erstlinienbehandlung des metastasierten nicht-kleinzelligen Lungenkarzinoms (NSCLC) mit nicht-plattenepithelialer Histologie. Bei Patienten mit 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).</p> <p>Tecentriq als Monotherapie wird angewendet bei erwachsenen Patienten zur Behandlung des lokal fortgeschrittenen oder metastasierten NSCLC nach vorheriger Chemotherapie. Patienten mit EGFR-Mutationen oder ALK-positivem NSCLC sollten vor der Therapie mit Tecentriq zudem auch bereits entsprechende zielgerichtete Therapien erhalten haben (siehe Abschnitt 5.1).</p> <p>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 (siehe Abschnitt 5.1).</p>
Bevacizumab L01XC07 Avastin®	<p>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.</p> <p>Bevacizumab wird in Kombination mit Erlotinib zur First-Line-Behandlung von erwachsenen Patienten mit inoperablem fortgeschrittenem, metastasiertem oder rezidivierendem nicht-kleinzelligem Nicht-Platten-epithel-Bronchialkarzinom mit Mutationen, die den epidermalen Wachstumsfaktorrezeptor (EGFR) aktivieren, angewendet (siehe Abschnitt 5.1).</p>
Durvalumab L01XC28 Imfinzi®	IMFINZI ist angezeigt als Monotherapie zur Behandlung des lokal fortgeschrittenen, inoperablen nicht-kleinzelligen Lungenkarzinoms (NSCLC) bei Erwachsenen, deren Tumoren PD-L1 in ≥ 1 % der Tumorzellen exprimieren und deren Krankheit nach einer platinbasierten Radiochemotherapie nicht fortgeschritten ist.
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.
Nivolumab	Nicht-kleinzelliges Lungenkarzinom (NSCLC)

L01XC17 Opdivo®	OPDIVO ist als Monotherapie zur Behandlung des lokal fortgeschrittenen oder metastasierten nichtkleinzelligen Lungenkarzinoms nach vorheriger Chemotherapie bei Erwachsenen indiziert.
Pembrolizumab L01XC18 KEYTRUDA®	<p>KEYTRUDA ist als Monotherapie zur Erstlinienbehandlung des metastasierenden nicht-kleinzelligen Lungenkarzinoms (NSCLC) mit PD-L1 exprimierenden Tumoren (Tumor Proportion Score [TPS] \geq 50 %) ohne EGFR oder ALK-positive Tumormutationen bei Erwachsenen angezeigt.</p> <p>KEYTRUDA ist als Monotherapie zur Behandlung des lokal fortgeschrittenen oder metastasierenden NSCLC mit PD-L1 exprimierenden Tumoren (TPS \geq 1 %) nach vorheriger Chemotherapie bei Erwachsenen angezeigt. Patienten mit EGFR- oder ALK-positiven Tumormutationen sollten vor der Therapie mit KEYTRUDA ebenfalls eine auf diese Mutationen zielgerichtete Therapie erhalten haben.</p> <p>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.</p> <p>KEYTRUDA ist in Kombination mit Carboplatin und entweder Paclitaxel oder nab-Paclitaxel zur Erstlinienbehandlung des metastasierenden plattenepithelialen NSCLC bei Erwachsenen angezeigt.</p>
Ramucirumab L01XC21 Cyramza®	<p><u>Nicht-kleinzelliges Lungenkarzinom</u></p> <p>Cyramza ist in Kombination mit Erlotinib indiziert zur Erstlinien-Therapie von erwachsenen Patienten mit einem metastasierten nicht-kleinzelligen Lungenkarzinom mit aktivierenden epidermalen Wachstumsfaktorrezeptor-(epidermal growth factor receptor = EGFR-) Mutationen (siehe Abschnitt 5.1).</p> <p>Cyramza ist in Kombination mit Docetaxel indiziert zur Behandlung von erwachsenen Patienten mit einem lokal fortgeschrittenen oder metastasierten nicht-kleinzelligen Lungenkarzinom mit Tumorprogress nach platinhaltiger Chemotherapie.</p>

Quellen: AMice-Datenbank, Fachinformationen

Abteilung Fachberatung Medizin

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

Vorgang: 2020-B-256 (Tepotinib)

Auftrag von: Abt. AM
Bearbeitet von: Abt. FB Med
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Abkürzungsverzeichnis

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

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

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

1 Indikation

Anwendungsgebiet laut Beratungsanforderung: Behandlung des fortgeschrittenen nicht-kleinzelligen Bronchialkarzinoms (NSCLC) mit MET-Tyrosinkinase-rezeptor-Exon-14- (METex14-) Skipping-Veränderungen bei Erwachsenen.

Indikation für die Synopse: Behandlung von erwachsenen Patienten mit fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkrebs (NSCLC).

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *NSCLC* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 20.07.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 1975 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 129 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA-Beschlüsse/IQWiG-Berichte

G-BA, 2020 [27].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Ramucirumab (neues Anwendungsgebiet: NSCLC, 1. Linie, EGFR-Mutation, Kombination mit Erlotinib) vom 20. August 2020

Anwendungsgebiet

Cyramza ist in Kombination mit Erlotinib indiziert zur Erstlinien-Therapie von erwachsenen Patienten mit einem metastasierten nicht-kleinzelligen Lungenkarzinom mit aktivierenden epidermalen Wachstumsfaktorrezeptor-(epidermal growth factor receptor = EGFR-) Mutationen.

Zweckmäßige Vergleichstherapie & Ausmaß des Zusatznutzens

a) Erwachsene Patienten mit metastasiertem NSCLC mit den aktivierenden EGFR Mutationen L858R¹ oder del 19²; Erstlinientherapie:

- Afatinib oder Gefitinib oder Erlotinib oder Osimertinib

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Ramucirumab in Kombination mit Erlotinib gegenüber Erlotinib:

- Ein Zusatznutzen ist nicht belegt.

b) Erwachsene Patienten mit metastasiertem NSCLC mit anderen aktivierenden EGFR Mutationen als L858R¹ oder del 19²; Erstlinientherapie:

- 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-Paclitaxelund
 - 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 Ramucirumab in Kombination mit Erlotinib gegenüber der zweckmäßigen Vergleichstherapie:

- Ein Zusatznutzen ist nicht belegt.

¹ Exon 21-Substitutionsmutation

² Exon 19-Deletion

G-BA, 2020 [49].

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 Pemetrexed und Platin-Chemotherapie) vom 19. September 2019 / 28. Januar 2020.

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 [48].

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 \geq 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, 2020 [25].

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

Anwendungsgebiet

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

Zweckmäßige Vergleichstherapie

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

- Pembrolizumab als Monotherapie
- b) Erwachsene Patienten mit einem metastasierten nicht-kleinzelligen Lungenkarzinom mit nicht-plattenepithelialer Histologie und einem Tumor Proportion Score [TPS] von < 50 % (PD-L1-Expression) und ohne EGFR- oder ALK-positive Tumormutationen; Erstlinientherapie
- Cisplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel oder Pemetrexed) oder
- Carboplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel oder Pemetrexed) vgl. Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie oder
- Carboplatin in Kombination mit nab-Paclitaxel oder
- Pembrolizumab in Kombination mit Pemetrexed und Platin-Chemotherapie

Fazit / Ausmaß des Zusatznutzens

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

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

- Ein Zusatznutzen ist nicht belegt

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

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

- Ein Zusatznutzen ist nicht belegt.

G-BA, 2020 [24].

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

Anwendungsgebiet

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

Zweckmäßige Vergleichstherapie

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

- Pembrolizumab als Monotherapie
- b) Erwachsene mit einem metastasierten nicht-kleinzelligen Lungenkarzinom mit nichtplatteneithelialer Histologie; und einem Tumor Proportion Score [TPS] von < 50 % (PD-L1-Expression); Erstlinientherapie; oder einem EGFR-mutierten oder ALKpositiven NSCLC unabhängig vom Tumor Proportion Score [TPS] nach Vorbehandlung mit einer entsprechenden zielgerichteten Therapie
- Cisplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel oder Pemetrexed) unter Beachtung des Zulassungsstatus oder
- Carboplatin in Kombination mit einem Drittgenerationszytostatikum (nur für Patienten mit erhöhtem Risiko für Cisplatin-induzierte Nebenwirkungen im Rahmen einer Kombinationstherapie; vgl. Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie)
Oder
- Carboplatin in Kombination mit nab-Paclitaxel
Oder
- Pembrolizumab in Kombination mit Pemetrexed und platinhaltiger Chemotherapie (nur für Patienten ohne EGFR- oder ALK-positive Tumormutationen)

Fazit / Ausmaß des Zusatznutzens

- a) Erwachsene mit einem metastasierten nicht-kleinzelligen Lungenkarzinom mit nichtplatteneithelialer Histologie und einem Tumor Proportion Score [TPS] von ≥ 50 % (PD-L1-Expression) und ohne EGFR-Mutationen oder ALK-Translokationen; Erstlinientherapie
- Ein Zusatznutzen ist nicht belegt.
- b) Erwachsene mit einem metastasierten nicht-kleinzelligen Lungenkarzinom mit nichtplatteneithelialer Histologie; und einem Tumor Proportion Score [TPS] von < 50 % (PD-L1-Expression); Erstlinientherapie; oder einem EGFR-mutierten oder ALKpositiven NSCLC unabhängig vom Tumor Proportion Score [TPS] nach Vorbehandlung mit einer entsprechenden zielgerichteten Therapie
- Ein Zusatznutzen ist nicht belegt.

G-BA, 2019 [43].

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 17. Oktober 2019 – Dacomitinib

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 [32].

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 – Durvalumab.

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, 2017 [37].

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 – Osimertinib (Neubewertung nach Fristablauf: nicht-kleinzelliges Lungenkarzinom, T790M-EGFR-Mutation)

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).

Zweckmäßige Vergleichstherapie

1) Patienten nach Vorbehandlung mit einem EGFR-Tyrosinkinase-Inhibitor:

- eine zytotoxische Chemotherapie nach Maßgabe des Arztes (unter Beachtung des Zulassungsstatus in Verbindung mit der Verordnungsfähigkeit von Arzneimitteln in Off-Label-Indikationen gemäß Anlage VI der Arzneimittel-Richtlinie)

oder gegebenenfalls

- Best-Supportive-Care für Patienten, die bereits eine zytotoxische Chemotherapie erhalten haben als Alternative für eine weitere zytotoxische Chemotherapie.

b) für Patienten, für die eine zytotoxische Chemotherapie nicht infrage kommt:

- Best-Supportive-Care

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

- 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

3) Patienten nach Vorbehandlung mit einer Platin-basierten Chemotherapie und einer *de novo* positiven T790M-Mutation:

- Docetaxel oder Pemetrexed (Pemetrexed: außer bei überwiegend plattenepithelialer Histologie)
oder
- Gefitinib oder Erlotinib (nur für Patienten mit aktivierenden EGFR-Mutationen, die noch nicht mit Gefitinib oder Erlotinib vorbehandelt wurden)
- Patienten, für die eine Therapie mit Docetaxel, Pemetrexed, Gefitinib und Erlotinib nicht angezeigt ist: Best-Supportive-Care

Fazit / Ausmaß des Zusatznutzens

1) Patienten nach Vorbehandlung mit einem EGFR-Tyrosinkinase-Inhibitor:

- Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie: Ein Zusatznutzen ist nicht belegt.

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

- Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie: Ein Zusatznutzen ist nicht belegt.

3) Patienten nach Vorbehandlung mit einer Platin-basierten Chemotherapie und einer *de novo* positiven T790M-Mutation:

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie: Ein Zusatznutzen ist nicht belegt.

G-BA, 2019 [42].

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 17. Januar 2019 –Osimertinib (neues Anwendungsgebiet: nicht-kleinzelliges Lungenkarzinom, Erstlinientherapie).

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 L858R¹ oder del 19²:

- 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, 2020 [23].

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 26. Juni 2020.

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

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

b) Behandlungsziel: palliativ

c) Folgende Wirkstoffe sind zugelassen:

- Cisplatin
- Docetaxel
- Etoposid

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

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

e) Patienten, die nicht behandelt werden sollten:

- Monotherapie

G-BA, 2016 [36].

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 - Necitumumab

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 [34].

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 5. November 2015 – Afatinib

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.

G-BA, 2016 [29].

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. September 2016 – Ramucirumab.

Anwendungsgebiet

„Ramucirumab (Cyramza®) ist in Kombination mit Docetaxel indiziert zur Behandlung von erwachsenen Patienten mit einem lokal fortgeschrittenen oder metastasierten nicht-kleinzelligen Lungenkarzinom mit Tumorprogress nach platinhaltiger Chemotherapie.“

Zweckmäßige Vergleichstherapie

- Docetaxel oder Pemetrexed (Pemetrexed: außer bei überwiegend plattenepithelialer Histologie)

oder

- Gefitinib oder Erlotinib (nur für Patienten mit aktivierenden EGFR-Mutationen, die noch nicht mit Afatinib, Gefitinib oder Erlotinib vorbehandelt wurden)

oder

- Crizotinib (nur für Patienten mit aktivierenden ALK-Mutationen, die noch nicht mit Crizotinib vorbehandelt wurden)

Fazit / Ausmaß des Zusatznutzens

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Docetaxel: Ein Zusatznutzen ist nicht belegt.

G-BA, 2018 [41].

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 2018 – Atezolizumab.

Anwendungsgebiet

Tecentriq als Monotherapie wird angewendet bei erwachsenen Patienten zur Behandlung des lokal fortgeschrittenen oder metastasierten nicht-kleinzelligen Lungenkarzinoms (NSCLC) nach vorheriger Chemotherapie. Patienten mit aktivierenden EGFR-Mutationen oder ALK-positiven Tumormutationen sollten vor der Therapie mit Tecentriq bereits eine auf diese Mutationen zielgerichtete Therapie erhalten haben.

Zweckmäßige Vergleichstherapie

Atezolizumab als Monotherapie für die Behandlung erwachsener Patienten mit fortgeschrittenem nicht-kleinzelligen Lungenkarzinom, für die eine Therapie mit Docetaxel, Pemetrexed, Nivolumab oder Pembrolizumab nach vorheriger Chemotherapie angezeigt ist:

- Docetaxel oder Pemetrexed oder Nivolumab oder Pembrolizumab (Pemetrexed: außer bei überwiegend plattenepithelialer Histologie, Pembrolizumab: nur für Patienten mit PD-L1 exprimierenden Tumoren (TPS \geq 1 %))

Atezolizumab als Monotherapie für die Behandlung erwachsener Patienten mit fortgeschrittenem nicht-kleinzelligen Lungenkarzinom, für die eine Therapie mit Docetaxel, Pemetrexed, Nivolumab und Pembrolizumab nach vorheriger Chemotherapie nicht angezeigt ist:

- Best-Supportive-Care

Fazit / Ausmaß des Zusatznutzens

(...) für die eine Therapie mit Docetaxel, Pemetrexed, Nivolumab oder Pembrolizumab nach vorheriger Chemotherapie angezeigt ist:

- Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Docetaxel: Hinweis auf einen beträchtlichen Zusatznutzen

(...) für die eine Therapie mit Docetaxel, Pemetrexed, Nivolumab und Pembrolizumab nach vorheriger Chemotherapie nicht angezeigt ist:

- Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care: Ein Zusatznutzen ist nicht belegt.

G-BA, 2017 [30].

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 2. Februar 2017 - Pembrolizumab

Anwendungsgebiet

„KEYTRUDA ist zur Behandlung des lokal fortgeschrittenen oder metastasierenden nichtkleinzelligen Lungenkarzinoms (NSCLC) mit PD-L1 exprimierenden Tumoren nach vorheriger Chemotherapie bei Erwachsenen angezeigt. Patienten mit EGFR- oder ALKpositiven Tumormutationen sollten vor der Therapie mit KEYTRUDA bereits eine für diese Mutationen zugelassene Therapie erhalten haben.

Zweckmäßige Vergleichstherapie

- 1) Patienten, für die eine Therapie mit Docetaxel, Pemetrexed oder Nivolumab angezeigt ist:
 - Docetaxel oder Pemetrexed oder Nivolumab (Pemetrexed: außer bei überwiegend plattenepithelialer Histologie)

- 2) Patienten, für die eine Therapie mit Docetaxel, Pemetrexed und Nivolumab nicht angezeigt ist:
 - Best-Supportive-Care

Fazit / Ausmaß des Zusatznutzens

- 1) Patienten, für die eine Therapie mit Docetaxel, Pemetrexed oder Nivolumab angezeigt ist:
 - Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Docetaxel: Hinweis auf einen beträchtlichen Zusatznutzen.

- 2) Patienten, für die eine Therapie mit Docetaxel, Pemetrexed und Nivolumab nicht angezeigt ist:
 - Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-SupportiveCare: Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [51].

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 20. Oktober 2016 – Nivolumab.

Anwendungsgebiet

„OPDIVO ist zur Behandlung des lokal fortgeschrittenen oder metastasierten nicht-kleinzelligen Lungenkarzinoms (NSCLC) nach vorheriger Chemotherapie bei Erwachsenen indiziert.“

[Hinweis: Der vorliegende Beschluss bezieht sich nur auf die Behandlung von Patienten mit nicht-plattenepithelialer Histologie. Über den Zusatznutzen von Nivolumab bei Patienten mit plattenepithelialer Histologie informiert der Beschluss zu Nivolumab vom 4. Februar 2016.]

Zweckmäßige Vergleichstherapie

1) Patienten, für die eine Therapie mit Docetaxel, Pemetrexed, Gefitinib, Erlotinib oder Crizotinib angezeigt ist: Zweckmäßige Vergleichstherapie:

- Docetaxel oder Pemetrexed

oder

- Gefitinib oder Erlotinib (nur für Patienten mit aktivierenden EGFR-Mutationen, die noch nicht mit Afatinib, Gefitinib oder Erlotinib vorbehandelt wurden)

oder

- Crizotinib (nur für Patienten mit aktivierenden ALK-Mutationen, die noch nicht mit Crizotinib vorbehandelt wurden)

2) Patienten, für die eine Therapie mit Docetaxel, Pemetrexed, Gefitinib, Erlotinib und Crizotinib nicht angezeigt ist:

- Best-Supportive-Care

Fazit / Ausmaß des Zusatznutzens

1) Patienten, für die eine Therapie mit Docetaxel, Pemetrexed, Gefitinib, Erlotinib oder Crizotinib angezeigt ist:

- Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Docetaxel: Hinweis auf einen beträchtlichen Zusatznutzen.

2) Patienten, für die eine Therapie mit Docetaxel, Pemetrexed, Gefitinib, Erlotinib und Crizotinib nicht angezeigt ist:

- Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-SupportiveCare: Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [33].

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. Februar 2016 – Nivolumab.

Anwendungsgebiet

OPDIVO ist zur Behandlung des lokal fortgeschrittenen oder metastasierten nichtkleinzelligen Lungenkarzinoms (NSCLC) mit plattenepithelialer Histologie nach vorheriger Chemotherapie bei Erwachsenen indiziert.

Zweckmäßige Vergleichstherapie

1) Patienten, für die eine Behandlung mit Docetaxel angezeigt ist: Docetaxel

2) Patienten, für die eine Behandlung mit Docetaxel nicht angezeigt ist: Best-Supportive-Care

Fazit / Ausmaß des Zusatznutzens

1) Patienten, für die eine Behandlung mit Docetaxel angezeigt ist: Hinweis auf einen beträchtlichen Zusatznutzen.

2) Patienten, für die eine Behandlung mit Docetaxel nicht angezeigt ist: Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care: Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [50].

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 20. Oktober 2016 - Afatinib (neues Anwendungsgebiet: nicht-kleinzelliges Lungenkarzinom, Plattenepithel-histologie).

Anwendungsgebiet

Giotrif® als Monotherapie wird angewendet zur Behandlung von lokal fortgeschrittenem oder metastasiertem NSCLC mit Plattenepithel-Histologie, das unter oder nach Platin-basierter Chemotherapie fortschreitet.

Zweckmäßige Vergleichstherapie

- a) Patienten mit lokal fortgeschrittenem und/oder metastasiertem NSCLC mit PlattenepithelHistologie mit Progression während oder nach einer platinbasierten Chemotherapie, für die eine Therapie mit Docetaxel angezeigt ist: Docetaxel
- b) Patienten mit lokal fortgeschrittenem und/oder metastasiertem NSCLC mit PlattenepithelHistologie mit Progression während oder nach einer platinbasierten Chemotherapie, für die eine Therapie mit Docetaxel nicht angezeigt ist: Best-Supportive-Care

Fazit / Ausmaß des Zusatznutzens

- a) Patienten mit lokal fortgeschrittenem und/oder metastasiertem NSCLC mit PlattenepithelHistologie mit Progression während oder nach einer platinbasierten Chemotherapie, für die eine Therapie mit Docetaxel angezeigt ist:
 - Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Docetaxel: Ein Zusatznutzen ist nicht belegt.
- b) Patienten mit lokal fortgeschrittenem und/oder metastasiertem NSCLC mit PlattenepithelHistologie mit Progression während oder nach einer platinbasierten Chemotherapie, für die eine Therapie mit Docetaxel nicht angezeigt ist:
 - Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care: Ein Zusatznutzen ist nicht belegt.

G-BA, 2015 [44].

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 18. Juni 2015 – Nintedanib.

Anwendungsgebiet

Nintedanib (Vargatef®) wird angewendet in Kombination mit Docetaxel zur Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem, metastasiertem oder lokal rezidiertem nichtkleinzelligem Lungenkarzinom (NSCLC) mit Adenokarzinom-Histologie nach Erstlinienchemotherapie.

Zweckmäßige Vergleichstherapie

- Eine Chemotherapie mit Docetaxel oder Pemetrexed
oder
- Gefitinib oder Erlotinib (nur für Patienten mit aktivierenden EGFR-Mutationen)
oder
- Crizotinib (nur für Patienten mit aktivierenden ALK-Mutationen)

Fazit / Ausmaß des Zusatznutzens

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer Chemotherapie mit Docetaxel: Hinweis für einen geringen Zusatznutzen.

G-BA, 2017 [46].

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-kleinzelligem 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 [31].

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] \geq 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 [47].

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 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, 2018 [28].

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, 2017 [39].

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.

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

Vergleichstherapie:

- Patienten, für die eine Behandlung mit Docetaxel oder Pemetrexed infrage kommt:
Docetaxel oder Pemetrexed
- Patienten, für die eine Behandlung mit Docetaxel oder Pemetrexed nicht infrage kommt:
Best-Supportive-Care

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Docetaxel oder Pemetrexed:

Ein Zusatznutzen ist nicht belegt.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive- Care:

Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [38]

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, 2019 [53].

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 22. November 2019 - Lorlatinib (nicht-kleinzelliges Lungenkarzinom, ALK+, vorbehandelte Patienten)

Anwendungsgebiet

Lorviqua als Monotherapie, wird angewendet zur Behandlung erwachsener Patienten mit Anaplastische-Lymphomkinase (ALK)-positivem, fortgeschrittenen nicht-kleinzelligen Lungenkarzinom (non-small cell lung cancer, NSCLC), deren Erkrankung fortgeschritten ist nach: Alectinib oder Ceritinib als erste Therapie mit ALK-Tyrosinkinase-Inhibitoren (TKI); oder Crizotinib und mindestens einem anderen ALK-TKI.

Zweckmäßige Vergleichstherapie

a) Patienten mit ALK-positivem, fortgeschrittenem NSCLC, deren Erkrankung fortgeschritten ist nach Alectinib oder Ceritinib als erste ALK-TKI-Therapie oder Crizotinib und mindestens einem anderen ALK-TKI; für die eine weitere antineoplastische systemische Therapie infrage kommt:

- Eine patientenindividuelle Therapie unter Berücksichtigung der ALK-Inhibitoren Alectinib und Ceritinib sowie von Kombinations- oder Mono-Chemotherapien

b) Patienten mit ALK-positivem, fortgeschrittenem NSCLC, deren Erkrankung fortgeschritten ist nach Alectinib oder Ceritinib als erste ALK-TKI-Therapie oder Crizotinib und mindestens einem anderen ALK-TKI; für die eine weitere antineoplastische systemische Therapie nicht infrage kommt:

- Best-Supportive-Care

Fazit / Ausmaß des Zusatznutzens

a) Patienten mit ALK-positivem, fortgeschrittenem NSCLC, deren Erkrankung fortgeschritten ist nach Alectinib oder Ceritinib als erste ALK-TKI-Therapie oder Crizotinib und mindestens einem anderen ALK-TKI; für die eine weitere antineoplastische systemische Therapie infrage kommt:

- Ein Zusatznutzen ist nicht belegt.

b) Patienten mit ALK-positivem, fortgeschrittenem NSCLC, deren Erkrankung fortgeschritten ist nach Alectinib oder Ceritinib als erste ALK-TKI-Therapie oder Crizotinib und mindestens einem anderen ALK-TKI; für die eine weitere antineoplastische systemische Therapie nicht infrage kommt:

- Ein Zusatznutzen ist nicht belegt.

G-BA, 2017 [45].

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 – Alectinib.

Anwendungsgebiet

Alecensa wird als Monotherapie angewendet zur Behandlung des Anaplastische-Lymphomkinase (ALK)-positiven, fortgeschrittenen nicht-kleinzelligen Bronchialkarzinoms (non-small cell lung cancer, NSCLC) bei erwachsenen Patienten, die zuvor mit Crizotinib behandelt wurden.

a) Patienten, für die eine Behandlung mit Docetaxel oder Pemetrexed oder Ceritinib infrage kommt:

Zweckmäßige Vergleichstherapie

Docetaxel oder Pemetrexed oder Ceritinib

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Docetaxel oder Pemetrexed:

Anhaltspunkt für einen geringen Zusatznutzen.

b) Patienten, für die eine Behandlung mit Docetaxel oder Pemetrexed oder Ceritinib nicht infrage kommt:

Zweckmäßige Vergleichstherapie

Best-Supportive-Care

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care:

Ein Zusatznutzen ist nicht belegt.

G-BA, 2017 [40].

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 / 19. Oktober 2017 – Crizotinib

Anwendungsgebiet

Zykadia wird angewendet bei erwachsenen Patienten zur Behandlung des fortgeschrittenen, Anaplastische-Lymphomkinase (ALK)-positiven, nicht-kleinzelligen Bronchialkarzinoms (NSCLC), die mit Crizotinib vorbehandelt wurden.

Zweckmäßige Vergleichstherapie

a.) Für Patienten, für die eine Behandlung mit Docetaxel oder Pemetrexed infrage kommt.

- Docetaxel oder Pemetrexed

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Docetaxel oder Pemetrexed:

Anhaltspunkt für einen beträchtlichen Zusatznutzen.

Zweckmäßige Vergleichstherapie

b.) Für Patienten, für die eine Behandlung mit Docetaxel oder Pemetrexed nicht infrage kommt

- Best-Supportive-Care

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care:

Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [35].

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. Dezember 2016 – Crizotinib.

Zugelassenes Anwendungsgebiet (laut Zulassung vom 23.10.2012):

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

a) Patienten, bei denen eine Chemotherapie angezeigt ist

Zweckmäßige Vergleichstherapie:

Docetaxel oder Pemetrexed zur Behandlung von Patienten, bei denen eine Chemotherapie angezeigt ist (dies können insbesondere Patienten mit ECOG-Performance-Status 0, 1 und gegebenenfalls 2 sein).

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der Chemotherapie mit Docetaxel oder Pemetrexed:

Anhaltspunkt für einen beträchtlichen Zusatznutzen.

b) Patienten, bei denen eine Chemotherapie nicht angezeigt ist

Zweckmäßige Vergleichstherapie:

Best-Supportive-Care zur Behandlung von Patienten, bei denen eine Chemotherapie nicht angezeigt ist (dies können insbesondere Patienten mit ECOG-Performance-Status 4, 3 und gegebenenfalls 2 sein).

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care:

Ein Zusatznutzen ist nicht belegt.

G-BA, 2019 [26].

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 – Brigatinib vom 4. Juli 2019.

Anwendungsgebiet

Alunbrig ist als Monotherapie bei erwachsenen Patienten mit anaplastischer-Lymphomkinase (ALK)-positivem, fortgeschrittenen, nicht-kleinzelligen Lungenkarzinom (NSCLC) angezeigt, die zuvor mit Crizotinib behandelt wurden.

Zweckmäßige Vergleichstherapie

Ceritinib oder Alectinib

Fazit / Ausmaß des Zusatznutzens

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Brigatinib gegenüber Ceritinib:

- Ein Zusatznutzen ist nicht belegt.

G-BA, 2018 [52].

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 21. Juni 2018 - Alectinib (neues Anwendungsgebiet: Erstlinienbehandlung nicht-kleinzelliges Lungenkarzinom)

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

3.2 Cochrane Reviews

Vasconcellos VF et al., 2020 [105].

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

Fragestellung

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

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

Methodik

Population:

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

Intervention/Komparator:

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

Endpunkte:

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

Recherche/Suchzeitraum:

- Bis Januar 2019

Qualitätsbewertung der Studien:

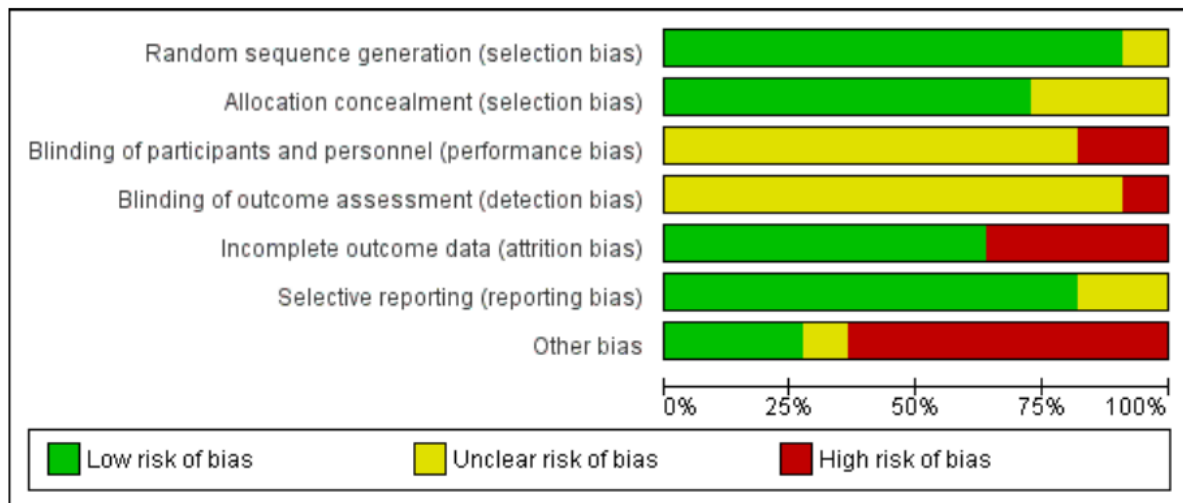
- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

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

Qualität der Studien:



Studienergebnisse:

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

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

- Gemischte Population; keine Subgruppenanalysen zu Therapielinie oder Stadium

Sim, E. H. A. et al., 2018 [100].

Gefitinib for advanced non-small cell lung cancer.

Fragestellung

To determine the effectiveness and safety of gefitinib as first-line, second-line or maintenance treatment for advanced NSCLC.

Methodik

Population:

- Eligible trials included adult participants aged 18 years or older of either sex with histologically or cytologically confirmed NSCLC (stage IIIB/IV) not curable with surgery

Intervention:

- Any dosage of gefitinib as first or second-line therapy or maintenance therapy

Komparator:

- placebo or best supportive care, chemotherapeutic agents, gefitinib combined with a chemotherapy regimen, Gefitinib at any dose in combination with chemotherapeutic agents versus the same chemotherapy agents alone, Gefitinib at any dose in combination with chemotherapeutic agents versus a different combination of chemotherapeutic agents

Endpunkte:

- OS, PFS, Toxicity, Ansprechen, QoL

Recherche/Suchzeitraum:

- CENTRAL, MEDLINE and Embase from inception to 17 February 2017

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

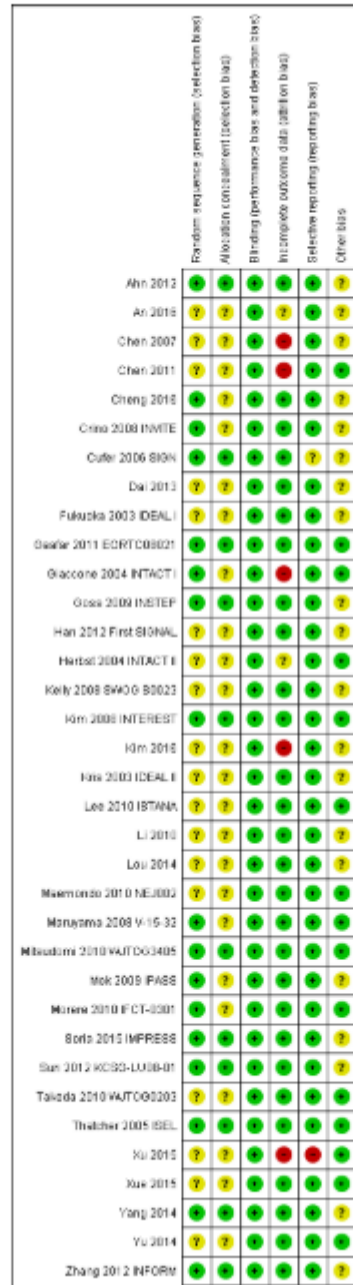
Ergebnisse

Anzahl eingeschlossener Studien:

- 35 eligible randomised controlled trials (RCTs), which examined 12,089 patients

Qualität der Studien:

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Studienergebnisse:

- Gefitinib did not statistically improve overall survival when compared with placebo or chemotherapy in either first- or second-line settings.
 - Second-line gefitinib prolonged time to treatment failure (TTF) (hazard ratio (HR) 0.82, 95% confidence interval (CI) 0.75 to 0.90, P < 0.0001) when compared with placebo.
 - Maintenance gefitinib improved progression-free survival (HR 0.70, 95% CI 0.53 to 0.91, P = 0.007) after first-line therapy.

- Studies in patients of Asian ethnicity or that conducted subgroup analyses:
 - Second-line gefitinib prolonged overall survival over placebo (HR 0.66, 95% CI 0.48 to 0.91, $P = 0.01$). In the first-line setting, progression-free survival was improved with gefitinib over chemotherapy alone (HR 0.65, 95% CI 0.43 to 0.98, $P = 0.04$, moderate quality of evidence). Gefitinib given in combination with a chemotherapy regimen improved progression-free survival versus either gefitinib alone or chemotherapy alone (HR 0.69, 95% CI 0.49 to 0.96, $P = 0.03$; HR 0.69, 95% CI 0.62 to 0.77, $P < 0.00001$, respectively). In the second-line setting, progression-free survival was superior in patients given gefitinib over placebo or chemotherapy (HR 0.69, 95% CI 0.52 to 0.91, $P = 0.009$; HR 0.71, 95% CI 0.57 to 0.88, $P = 0.002$; moderate quality of evidence, respectively). Combining gefitinib with chemotherapy in the second-line setting was superior to gefitinib alone (HR 0.65, 95% CI 0.43 to 0.97, $P = 0.04$). As maintenance therapy, gefitinib improved progression-free survival when compared with placebo (HR 0.42, 95% CI 0.33 to 0.54, $P < 0.00001$).
- Patients with EGFR mutation-positive tumours:
 - Studies in patients with EGFR mutation-positive tumours showed an improvement in progression-free survival in favour of gefitinib over first-line and second-line chemotherapy (HR 0.47, 95% CI 0.36 to 0.61, $P < 0.00001$; HR 0.24, 95% CI 0.12 to 0.47, $P < 0.0001$, respectively). Gefitinib as maintenance therapy following chemotherapy improved overall and progression-free survival (HR 0.39, 95% CI 0.15 to 0.98, $P = 0.05$; HR 0.17, 95% CI 0.07 to 0.41, $P < 0.0001$, respectively) in one phase III study when compared to placebo. Toxicities from gefitinib included skin rash, diarrhoea and liver transaminase derangements. Toxicities from chemotherapy included anaemia, neutropenia and neurotoxicity. In terms of quality of life, gefitinib improved Functional Assessment of Cancer Therapy-Lung (FACT-L) (standardised mean difference (SMD) 10.50, 95% CI 9.55 to 11.45, $P < 0.000001$), lung cancer subscale (SMD 3.63, 95% CI 3.08 to 4.19, $P < 0.00001$) and Trial Outcome Index (SMD 9.87, 95% CI 1.26 to 18.48, $P < 0.00001$) scores when compared with chemotherapy.

Anmerkung/Fazit der Autoren

This systematic review shows that gefitinib, when compared with standard first- or second-line chemotherapy or maintenance therapy, probably has a beneficial effect on progression-free survival and quality of life in selected patient populations, particularly those with tumours bearing sensitising EGFR mutations.

Patients with EGFR mutations lived longer when given maintenance gefitinib than those given placebo.

One study conducted subgroup analysis and showed that gefitinib improved overall survival over placebo in the second-line setting in patients of Asian ethnicity. All other studies did not detect any benefit on overall survival. The data analysed in this review were very heterogenous. We were limited in the amount of data that could be pooled, largely due to variations in study design. The risk of bias in most studies was moderate, with some studies not adequately addressing potential selection, attrition and reporting bias. This heterogeneity may have an impact on the applicability of the results.

Combining gefitinib with chemotherapy appears to be superior in improving progression-free survival to either gefitinib or chemotherapy alone, however further data and phase III studies in these settings are required.

Gefitinib has a favourable toxicity profile when compared with current chemotherapy regimens. Although there is no improvement in overall survival, gefitinib compares favourably with cytotoxic chemotherapy in patients with EGFR mutations with a prolongation of progression-free survival and a lesser side effect profile.

3.3 Systematische Reviews

Zhou, K. et al., 2020 [126].

Efficacy and safety of erlotinib combined with bevacizumab in the treatment of non-small cell lung cancer: A systematic review and meta-analysis.

Fragestellung

To determine the efficacy and safety of erlotinib and bevacizumab for NSCLC, we conducted a meta-analysis and systematic review of randomized controlled trials.

Methodik

Population:

- patients aged 18 years or older; histologically or cytologically confirmed NSCLC

Intervention/Komparator:

- Erlotinib vs erlotinib combined with bevacizumab, or bevacizumab vs erlotinib combined with bevacizumab

Endpunkte:

- OS, PFS, or ORR, and incidence of adverse events

Recherche/Suchzeitraum:

- PubMed, Embase, Web of Science, and Cochrane databases On June 2, 2019

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 included studies involved 1960 participants

Charakteristika der Population:

Table 1

Summary of studies included in the final meta-analysis.

Author	Year	Group	Number	Male/ Female	Race (White/ Asian or Pacific Island/Other)	Smoking history (Never/previous/ current)	ECOGPS (0/1/2)	Histology (large- cell carcinoma/ squamous/other)	Clinical stage (IIIB/IV/Other)	Region	Line of treatment
Herbst et al ^[26]	2007	B+E	39	17/22	29/3/7	NR	19/20/0	0/32/0/7	NR	USA	Second
		B+chemo	40	23/17	34/2/4	NR	19/21/0	9/30/0/1	NR		
Herbst et al ^[21]	2011	B+E	319	171/148	264/23/32	34/237/48	129/166/23	23/242/11/43/38	NR	USA	Second
		E+placebo	317	170/147	257/18/42	33/212/72	121/176/20	25/235/14/40	NR		
Ciuleanu et al ^[25]	2013	B+E	63	37/26	NR	21/20/11	28/35/0	NR	NR	Romania	First
		B+gem	61	36/25	NR	23/14/24	20/41/0	NR	NR		
Johnson et al ^[22]	2013	B+E	370	193/177	293/43/34	61/180/129	180/190/0	30/301/11/28	32/317/21	USA	Second
		B+placebo	373	196/177	290/45/38	66/178/129	173/198/1	26/309/6/32	37/310/25		
Seto et al ^[23]	2014	B+E	75	30/45	NR	42/9/24	43/32/0	0/74/1/0	1/60/14	Japan	First
		E	77	26/51	NR	45/6/26	41/36/0	1/76/0/0	0/62/15		
Saito et al ^[24]	2019	B+E	112	41/71	NR	65/6/41	64/48/0	1/110/0/1	8/82/22	Japan	First
		E	112	39/73	NR	64/7/41	68/42/2	0/112/0/0	8/84/20		

B = bevacizumab; chemo = chemotherapy; E = erlotinib; gem = gemcitabine; NR = not reported.

Table 2

Number of patients with different epidermal growth factor receptor mutation status.

Study	Year	Grouping	EGFR mutation status				EGFR FISH status		EGFR IHC status	
			Mutant	Wild type	Exon 19 deletion	Exon21 Leu858Arg mutation	Positive	Negative	Positive	Negative
Herbst et al	2007	B+E	1	8						
		B or E	0	13						
Herbst et al	2011	B+E	12	173			33	69	135	49
		B or E	18	152			43	59	119	42
Ciuleanu et al	2013	B+E	2	19			12	7	15	4
		B or E	0	11			6	5	5	5
Seto et al	2014	B+E			40	35				
		B or E			40	37				
Saito et al	2019	B+E			28	24				
		B or E			32	33				

B = bevacizumab; E = erlotinib; EGFR = epidermal growth factor receptor; FISH = fluorescent in situ hybridization; IHC = immunohistochemistry.

Qualität der Studien:

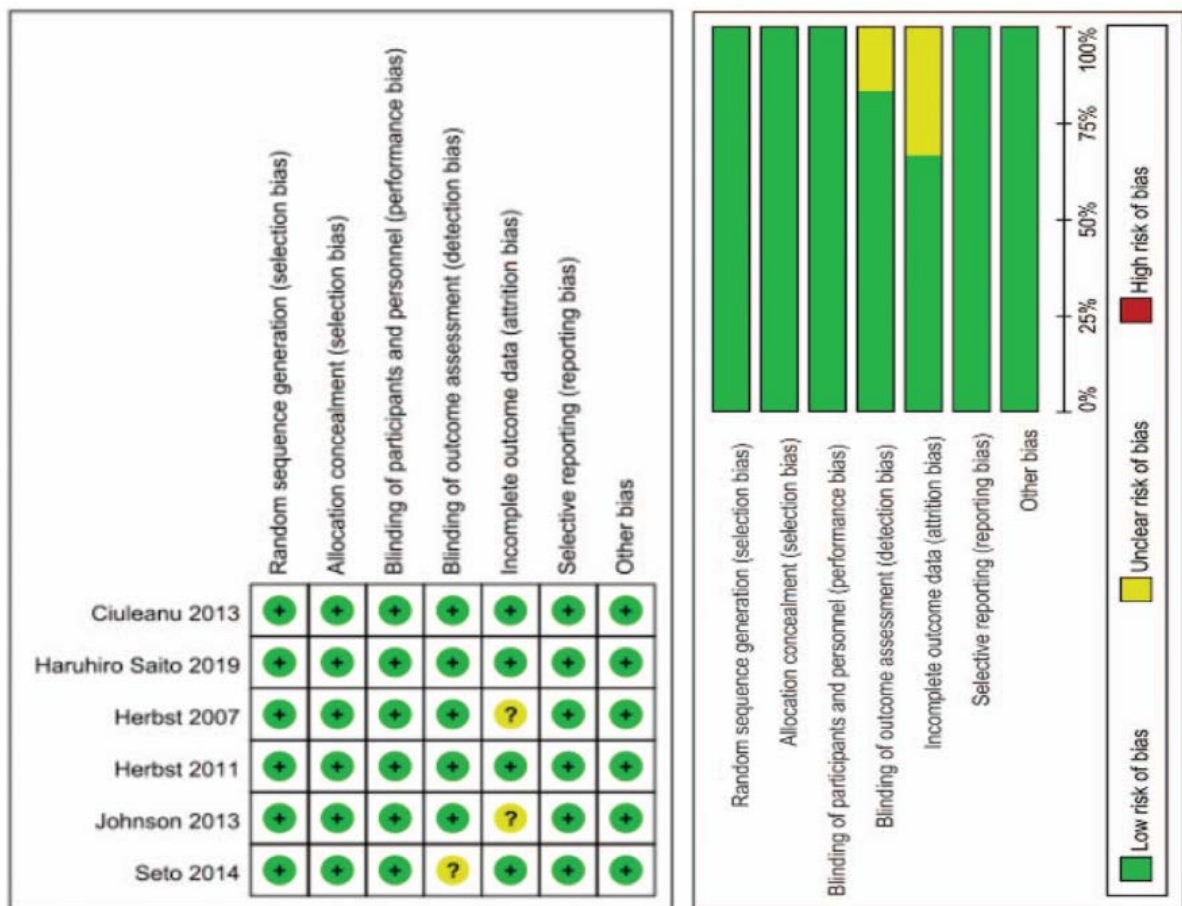


Figure 2. Methodological quality of studies included in meta-analysis.

Studienergebnisse:

- Compared with erlotinib or bevacizumab alone, the combined treatment did not significantly prolong OS (95% confidence interval [CI]=0.84–1.11; P=.62) or increase the ORR (95% CI=0.91–1.20; P=.52), but significantly improved PFS (95% CI=0.58– 0.73; P<.001).
- This improvement was especially notable in patients with the following characteristics: Eastern Cooperative Oncology Group Performance Status score of 0 or 1, female, no

smoking history, adenocarcinoma, and EGFR Exon19 deletion or Exon21 Leu858Arg mutation.

- Combination therapy significantly increased incidence of grade 1–2 hypertension (20.3% vs 6.3%, 95% CI 1.73–5.88; $P < .01$) and severe diarrhea (10% vs 3.2%, 95% CI 1.36–6.60; $P = .01$).

Anmerkung/Fazit der Autoren

Combining erlotinib and bevacizumab did not improve OS and ORR of patients with NSCLC but did prolong PFS. Subgroup analysis confirmed that combination therapy prolonged PFS without causing severe incurable complications in female patients, as well as those with ECOG-PS0 or ECOG-PS1, no smoking history, adenocarcinoma, and an EGFR Exon19 deletion or Exon21 Leu858Arg mutation. Therefore, we particularly recommend combination therapy for these patients. Our findings can help resolve existing controversies surrounding the benefits of erlotinib+bevacizumab therapy, thus further improving and personalizing patient selection for this treatment.

Elliott, J. et al., 2020 [15].

ALK inhibitors for non-small cell lung cancer: A systematic review and network meta-analysis.

Fragestellung

to assess the relative effects of individual anaplastic lymphoma kinase (ALK) inhibitors for the treatment of non-small cell lung cancer (NSCLC).

Methodik

Population:

- Treatment-naïve or experienced participants with phase III or IV ALK-positive and/or ROS1-positive NSCLC

Intervention:

- ALK inhibitors (e.g, crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, ensartinib, and entrectinib)

Komparator:

- Placebo, chemotherapy, radiotherapy, another ALK inhibitor, or the same ALK inhibitor at a different dose

Endpunkte:

- treatment-related death, overall survival, progression-free survival, and SAEs

Recherche/Suchzeitraum:

- MEDLINE, Embase, Cochrane CENTRAL, and grey literature (July 23, 2019)

Qualitätsbewertung der Studien:

- Cochrane Collaboration's ROB tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 RCTs

Charakteristika der Population:

Table 1. Study characteristics of included randomized controlled trials.

Author, yr, page (study name; NCT no.) (companion publications)	Population	Groups (no. randomized)	Duration of treatment, median (IQR), months	Cross-over between treatment groups allowed?	Reported outcomes of interest to this review	Funding source
Chemotherapy-controlled						
Wu 2018, p. 1549 (PROFILE 1029; NCT01639001)[28, 30]	18–70 years, ALK-positive NSCLC, with ECOG score of 0–2, with no prior systemic treatment	Crizotinib 250 mg BID (104) Chemotherapy (103)	NR	Not reported	TR death; OS; PFS (independent review)*;	Pharma
Shaw 2013, p. 2385 (PROFILE 1007; NCT00932893)[16, 31] (Blackhall 2014[32])	≥ 18 yr, ALK-positive NSCLC, with ECOG score of 0–2, with progressive disease after one prior platinum-based chemotherapy regimen	Crizotinib, 250 mg BID (173) Chemotherapy (174)	NR	Not during study period; participants from the chemotherapy arm could enroll in NCT00932451	TR death; OS; PFS (independent radiologic review)*	Pharma
Solomon 2014, p. 2167[25] (PROFILE 1014; NCT01154140) (Thorne-Nuzzo 2017,[33] Solomon 2016[34], Solomon 2018 [35])	≥ 18 yr, ALK-positive NSCLC, with ECOG score of 0–2, with no prior systemic treatment	Crizotinib 250 mg BID (172) Chemotherapy (171)	10.9 (range 0.4 to 34.3) 4.1 (range 0.7 to 6.2)	Yes; participants in the chemotherapy arm with disease progression could cross to the crizotinib arm provided safety criteria were met	TR death; OS; PFS (independent review)*	Pharma
Zhao 2015, p. 616[18]	≥ 18 yr, ALK-positive NSCLC, Karnofsky performance status (KPS) score ≥ 70, following first- or second-line chemotherapy	Crizotinib, 250 mg BID (14) Chemotherapy (14)	NR	Not reported	TR death; SAEs	Non-pharma
Novello 2018, p. 1409 (ALUR; NCT02604342) [26]	ALK-positive NSCLC, with ECOG score of 0–2; two prior lines of systemic therapy including one line of chemotherapy and one of crizotinib	Alectinib 600 mg BID (72) Chemotherapy (35)	20.1 wk (range 0.4–62.1) 6.0 wk (range 1.9–47.1)	Yes; cross-over from chemotherapy to alectinib was permitted following progression	OS; PFS (investigator-assessed)*	Pharma
Soria 2017, p. 917[24, 36] (ASCEND-4; NCT01828099)	≥ 18 yr, ALK-positive NSCLC, ECOG score of 0–2, previously untreated	Ceritinib 750 mg QD (189) Chemotherapy (187)	66.4 (30.8 to 83.7) 29.9 (13.0 to 62.3)	Yes, participants in the chemotherapy arm could crossover to ceritinib after disease progression	TR death; OS; PFS (independent review)*; SAEs	Pharma
Shaw 2017, p. 874 (ASCEND-5; NCT01828112)[23, 37] (Kiura 2018[38])	≥ 18 yr, ALK-positive NSCLC, with WHO performance status of 0–2, one or two previous chemotherapy regimens and previous crizotinib for at least 21 d	Ceritinib 750 mg QD (115) Chemotherapy (116)	30.3 (13.3 to 54.1) 6.3 (6.0 to 15.1)	Yes, participants in the chemotherapy arm could cross over to the ceritinib group after disease progression	TR death; OS; PFS (independent review)*	Pharma
Head-to-head comparisons of ALK inhibitors						
Zhou 2019, p. 437 (ALESIA; NCT02838420)[29]	≥ 18 yr, ALK-positive NSCLC, ECOG score of 0–2, life expectancy of >12wk, no prior systemic therapy	Crizotinib 250 mg BID (62) Alectinib 600 mg BID (125)	12.6 14.7	No	TR death; OS; PFS (investigator assessed)*; SAEs	Pharma
Camidge 2018, p. 1 (ALTA-1L; NCT02737501)[25]	≥ 18 yr, ALK-positive locally advanced or metastatic NSCLC, with at least one measurable lesion, and no prior ALK-targeted therapy	Crizotinib 250 mg BID (138) Brigatinib 180 mg QD (137)	7.4 (range 0.1 to 19.2) 9.2 (range 0.1 to 18.4)	Yes; patients in the crizotinib group could cross over to brigatinib after disease progression	TR death; OS; PFS (independent review)*	Pharma
Peters 2017, p. 829 (ALEX; NCT02075840)[5, 39] (Camidge 2019[40]; Gadgeel 2018[41])	≥ 18 yr, ALK-positive NSCLC, with ECOG score of 0–2, with no prior systemic treatment	Crizotinib 250 mg BID (151) Alectinib 600 mg BID (152)	17.6 (0.3 to 27.0) 18.6 (0.5 to 29.0)	No	TR death; OS; PFS (investigator assessed)*	Pharma



Hida 2017, p. 29[21] (J-ALEX; JAPICcti-132316)	≥ 20 yr, ALK-positive NSCLC, with ECOG score of 0–2, ALK-inhibitor naïve, chemotherapy-naïve or had received 1 regimen of chemotherapy	Crizotinib 250 mg BID (104) Alectinib 300 mg BID (103)	NR	Not during study period; Treatment crossover after study withdrawal was allowed in both groups	TR death; PFS (independent review)*	Pharma
Hida 2016, p. 1642 (JP28927; JapicCTI-132186)[19] (Nishio 2018[42])	≥ 20 yr, ALK-positive NSCLC, with ECOG score of 0–1; prior treatment, including other ALK inhibitors, was allowed	Cross-over (300 mg BID total for all groups; 35 participants): Alectinib 20/40 mg capsules Alectinib 150 mg capsules Extension: Alectinib 300 mg BID (150 mg capsules)	13.1 (range 11.1 to 15.0)	Yes by design during cross-over phase	TR death	Pharma
Kim 2017 (ALTA, NCT02094573)[22, 43] (Kawata 2019[44])	≥ 18 yr, ALK-positive NSCLC, with ECOG performance status of 0–2, disease progression while receiving crizotinib	Brigatinib 90 mg QD (109) Brigatinib 180 mg QD (110)	NR	Yes, participants in the 90 mg/d group could cross to the 180 mg/d group after disease progression	PFS (independent review), SAEs	Pharma

BID = twice daily, ECOG = Eastern Cooperative Oncology Group, NSCLC = non-small cell lung cancer, OS = overall survival, PFS = progression-free survival, QD = once daily, RCT = randomized controlled trial, SAE = serious adverse event, TR = treatment-related, WHO = World Health Organization.

*Primary outcome.

Table 2. Participants characteristics of included randomized controlled trials.

Author, yr, page (study name; NCT no.)	Group	Age, yr, median (range) ^a	Male, %	Current smoking,%	Never smoked,%	Brain or CNS metastases, %	ECOG0, %	ECOG 1, %	ECOG2, %	Adenocarcinoma, %
Treatment naive										
Zhou 2019[29] (ALESIA; NCT02838420)	Crizotinib	49 (IQR 41–59)	55	5	73	37	98**		2	97
	Alectinib	51 (IQR 43–59)	51	3	67	35	97**		3	94
Wu 2018[28] (PROFILE 1029; NCT01639001)	Chemotherapy	50 (23–69)	42	9	70	31	96**		4	98
	Crizotinib	48 (24–67)	48	7	75	20	96**		4	96
Camidge 2018[25] (ALTA-1L; NCT02737501)	Crizotinib	60 (29–89)	41	5	54	30	96**		4	99
	Brigatinib	58 (27–86)	50	3	61	29	96**		4	92
Soria 2017, p. 917 (ASCEND-4; NCT01828099)	Chemotherapy	54.0 (22–80)	39	8	65	33	37†	56†	6†	98
	Ceritinib	55.0 (22–81)	46	8	57	31	37	57	7	95
Peters 2017[5] (ALEX; NCT02075840)	Crizotinib	54.0 (18–91)	42	3	65	38	93**		7	94
	Alectinib	58.0 (25–88)	45	8	61	42	93**		7	90
Solomon 2014[17] (PROFILE 1014; NCT01154140)	Chemotherapy	54 (19–78)	37	3	65	27	95**		5	94
	Crizotinib	52 (22–76)	40	6	62	26	94**		6	94
Treatment experienced										
Novello 2018[26] (ALUR; NCT02604342)	Chemotherapy	59 (37–80)	49	6	46	74	31	54	14	100
	Alectinib	55.5 (21, 82)	57	3	49	65	40	51	8	100
Hida 2017[21] (J-ALEX; JAPICcti- 132316)	Crizotinib	59.5 (25–84)	39	3	59	28	46	52	2	99
	Alectinib	61.0 (27–85)	40	2	54	14	52	46	2	97
Kim 2017[22] (ALTA; NCT02094573)	BRI 90 QD	50.5 (18–82)	45	NR	63	71	30	63	6	96
	BRI 180 QD	56.5 (20–81)	42	NR	57	67	41	51	8	98
Shaw 2017[23] (ASCEND-5; NCT01828112)	Chemotherapy	54.0 (47.0–64.0) [‡]	47	1	53	59	44†	52†	4†	97
	Ceritinib	54.0 (44.0–63.0) [‡]	41	3	62	57	49	43	8	97
Hida 2016[19] (JP28927; JapicCTI- 132186)	Alectinib (cross-over)	45.0 (21–78)	46	3	60	NR	43	57	NR	100
Zhao 2015[18]	Chemotherapy	58.1 (13.2) [‡]	64	NR	NR	NR	NR	NR	NR	29
	Crizotinib	55.3 (12.7) [‡]	57	NR	NR	NR	NR	NR	NR	43
Shaw 2013[16] (PROFILE 1007; NCT00932893)	Chemotherapy	49 (24–85)	45	5	64	34	37	55	8	94
	Crizotinib	51 (22–81)	43	3	62	35	42	49	9	95

BRI = brigatinib, CNS = central nervous system, ECOG = Eastern Cooperative Oncology Group, IQR = interquartile range, NR = not reported, QD = once daily, SD = standard deviation.

^aUnless otherwise stated.

†WHO performance score.

[‡]Mean (SD).

[‡]Median (IQR).

**ECOG0 or ECOG1.

Qualität der Studien:

- Most RCTs were at low ROB for randomization (62%) and allocation concealment (54%), although 38% and 46% of studies did not report details of randomization and allocation concealment, respectively. Performance and detection bias were of concern for all RCTs because of the open-label design. All RCTs that reported progression-free survival employed an independent review committee to ascertain disease progression; however, the primary outcome in three RCTs was based on unblinded assessment of progression-free survival by trial investigators. The ROB owing to selective reporting was unclear for 23% of RCTs, primarily owing to a lack of available protocol or registration record; two RCTs (15%) were at high ROB owing to differences between the protocol and published manuscript. Other concerns included the potential for participant cross-over between study groups with unclear reporting of outcome data by group allocation.

Studienergebnisse:

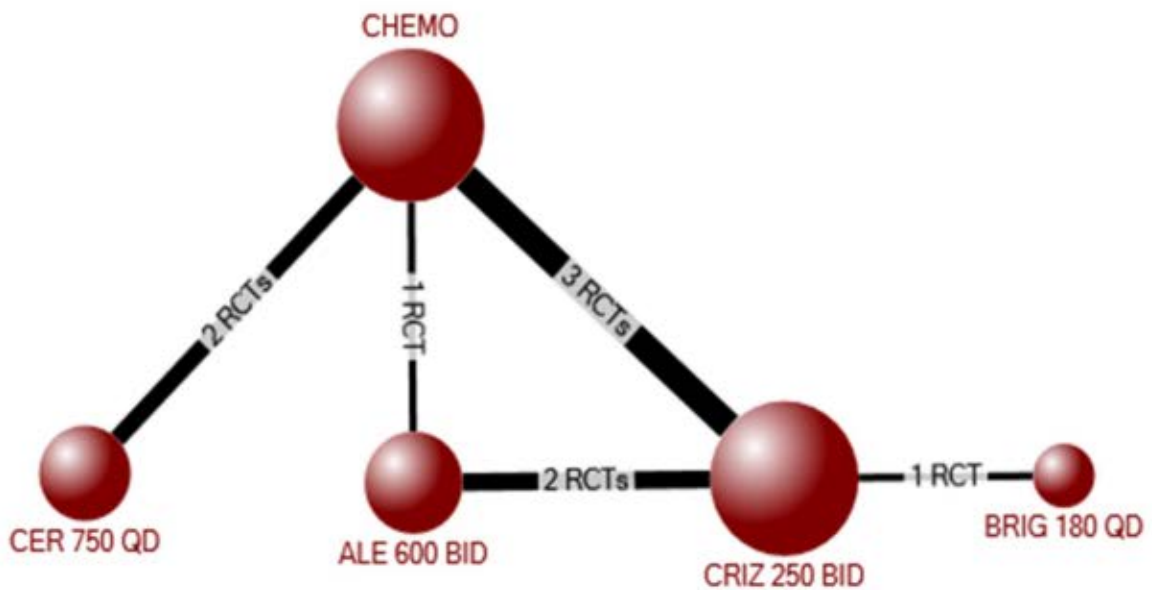


Fig 2. Evidence network for the network meta-analysis of overall survival among all participants (treatment experienced and naïve).

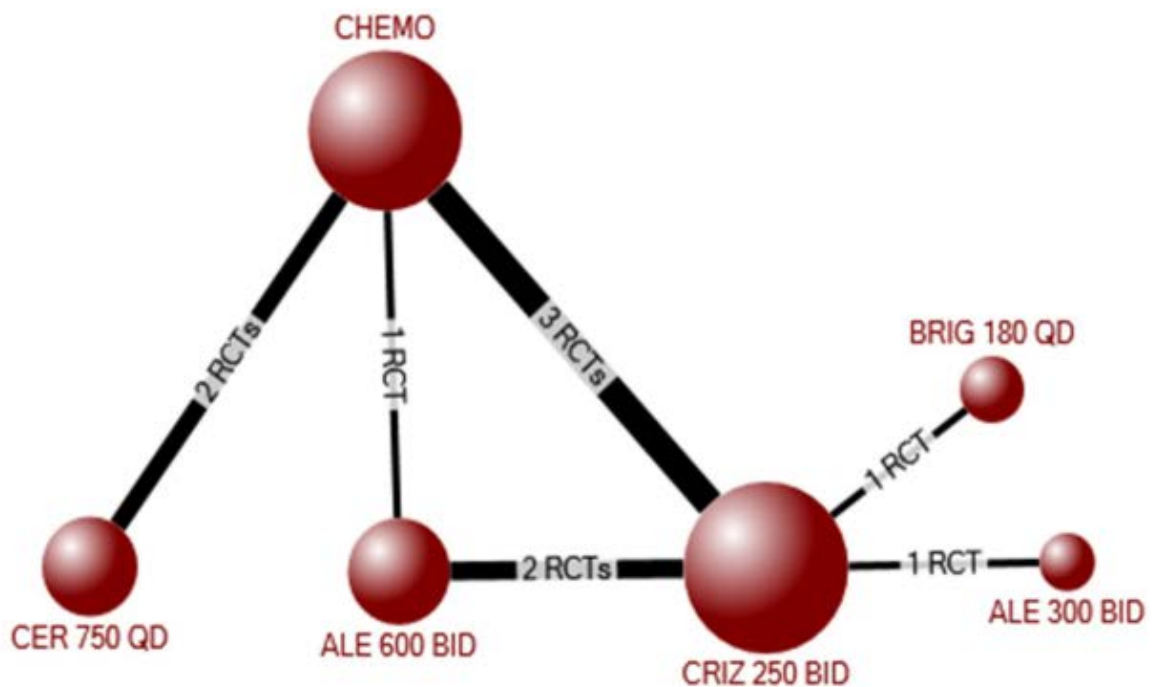


Fig 3. Evidence network for the network meta-analysis of progression-free survival among all participants (treatment experienced and naïve).

- Treatment-related deaths were rare, with 10 deaths attributed to crizotinib (risk difference v. chemotherapy: 0.49, 95% credible interval [CrI] -0.16 to 1.46; odds ratio 2.58 (0.76–11.37).
- All ALK inhibitors improved PSF relative to chemotherapy (hazard ratio [95% CrI]: crizotinib 0.46 [0.39–0.54]; ceritinib 0.52 [0.42–0.64]; alectinib 300 BID 0.16 [0.08–0.33]; alectinib 600 BID 0.23 [0.17–0.30]; brigatinib 0.23 [0.15–0.35]), while alectinib and brigatinib improved PFS over crizotinib and ceritinib (alectinib v. crizotinib 0.34 [0.17–0.70]; alectinib v. ceritinib

0.30 [0.14–0.64]; brigatinib v. crizotinib 0.49 [0.33–0.73]; brigatinib v. ceritinib 0.43 [0.27–0.70]).

- OS was improved with alectinib compared with chemotherapy (HR 0.57 [95% CrI 0.39–0.83]) and crizotinib (0.68 [0.48–0.96]).
- Use of crizotinib (odds ratio 2.08 [95% CrI 1.56–2.79]) and alectinib (1.60 [1.00–2.58]) but not ceritinib (1.25 [0.90–1.74]), increased the risk of serious adverse events compared with chemotherapy.
- Results were generally consistent among treatment-experienced or naïve participants.

Anmerkung/Fazit der Autoren

Treatment-related deaths were infrequent among ALK-positive NSCLC. Among patients with ALK-positive NSCLC, progression-free survival was improved by crizotinib, ceritinib, alectinib, and brigatinib compared with chemotherapy, while alectinib and brigatinib were significantly better than crizotinib and ceritinib. Overall survival was improved only by alectinib; however, the findings are likely confounded by crossover between treatment groups and should be interpreted with caution. Few studies have enrolled participants with ROS1 mutations, and additional research is needed in this area.

Xu, Z. et al., 2019 [111]

Nivolumab provides improved effectiveness and safety compared with docetaxel as a second-line treatment for advanced non-small cell lung cancer: A systematic review and meta-analysis.

Fragestellung

goal of identifying a better second-line therapeutic regimen for patients with advanced NSCLC, we conducted a meta-analysis to compare the anti-tumor efficacy and adverse effects (AEs) between nivolumab and docetaxel.

Methodik

Population:

- patients with stage III/IV NSCLC

Intervention:

- nivolumab

Komparator:

- docetaxel

Endpunkte:

- OS, PFS, objective response rate (ORR), complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), disease control rate (DCR), and AEs.

Recherche/Suchzeitraum:

- PubMed, EMBASE, Ovid MEDLINE, Scopus, Web of Science, Cochrane Library, ScienceDirect, Ovid MEDLINE, and Google Scholar from their inception to 5 June 2018

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- six studies (949 patients)
- four were RCTs (studies 11 and 12 were the two-year and three-year outcomes of studies 9 and 10), and two were retrospective studies.

Charakteristika der Population:

-

Qualität der Studien:

- According to the Cochrane Risk of Bias Tool, all the included studies were of high quality

Studienergebnisse:

- Nivolumab showed better efficacy in terms of the PFS (hazard ratios [HR]: 0.70, P = 0.03), OS (HR: 0.70, P < 0.00001), objective response rate (ORR) (risk ratios [RR]: 1.73, P = 0.0008), total AEs (RR: 0.77, P = 0.006), and grade 3-5 AEs (RR: 0.18, P < 0.00001) than docetaxel.
- The subgroup analysis suggested that the anti-tumor efficacy of nivolumab was superior for squamous NSCLC than for nonsquamous NSCLC in terms of both PFS and OS, and no changes in these endpoints were found among the groups with different ECOG statuses, histological features, and study designs. The anti-tumor efficacy of nivolumab for NSCLC in terms of both PFS and OS was positively correlated with the level of PD-L1 expression.
- In the nivolumab treatment arm, the 10 most-reported AEs were fatigue (15.7%), nausea (10.8%), decreased appetite (10.3%), asthenia (9.8%), diarrhea (7.5%), rash (7.5%), arthralgia (5.4%), vomiting (4.4%), constipation (3.5%), and pyrexia (3.3%).

Anmerkung/Fazit der Autoren

Our results suggested that nivolumab is a better choice than docetaxel-based chemotherapy for advanced NSCLC due to its improved anti-tumor efficacy (PFS, OS, and ORR) and decreased toxicity. The anti-tumor efficacy of nivolumab for NSCLC in terms of both PFS and OS showed a positive correlation with the level of PD-L1 expression. However, due to the inherent limitations of the study, more largescale and high-quality RCTs are needed to support this conclusion. Moreover, the use of a drug combination for lung cancer is also a promising research direction and deserves attention.

Zhao Y et al., 2019 [124].

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, toxicity

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 [120] & Franek, J. et al. 2019 [20]

Li YX et al., 2019 [77].

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 WW et al., 2019 [86].

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

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:

- 18 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	56	60 (36–79)	6.0	10.2
			Placebo + carboplatin/paclitaxel	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
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	63 (38–84)	4.9	10.5
Reck et al, 2014 ^[33]	Phase III	Second line	Nintedanib 200 mg twice daily + docetaxel	652	60 (53–67)	3.4	10.9
			Placebo + docetaxel	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.

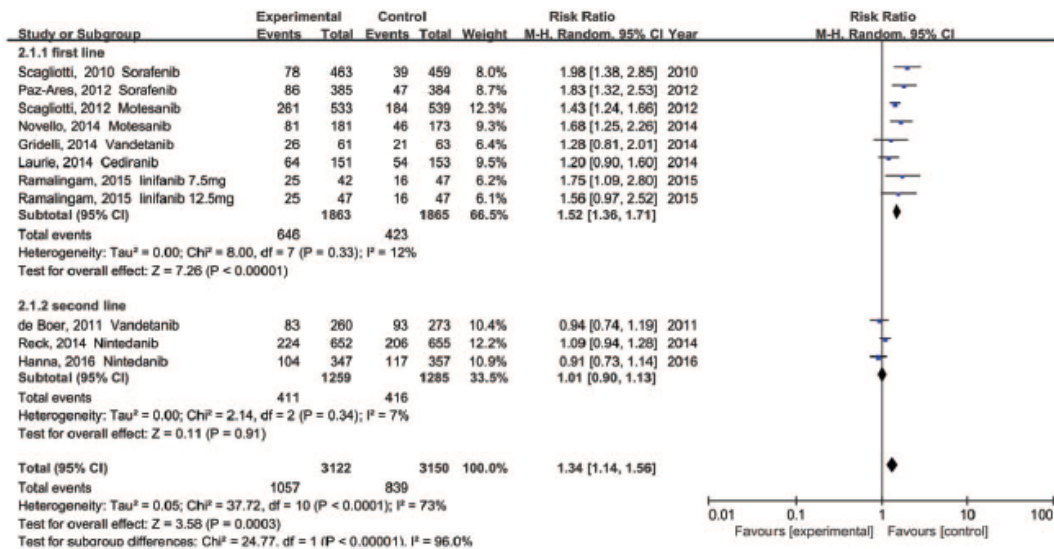


Figure 4. Forest plot and pooled risk ratio for serious adverse events.

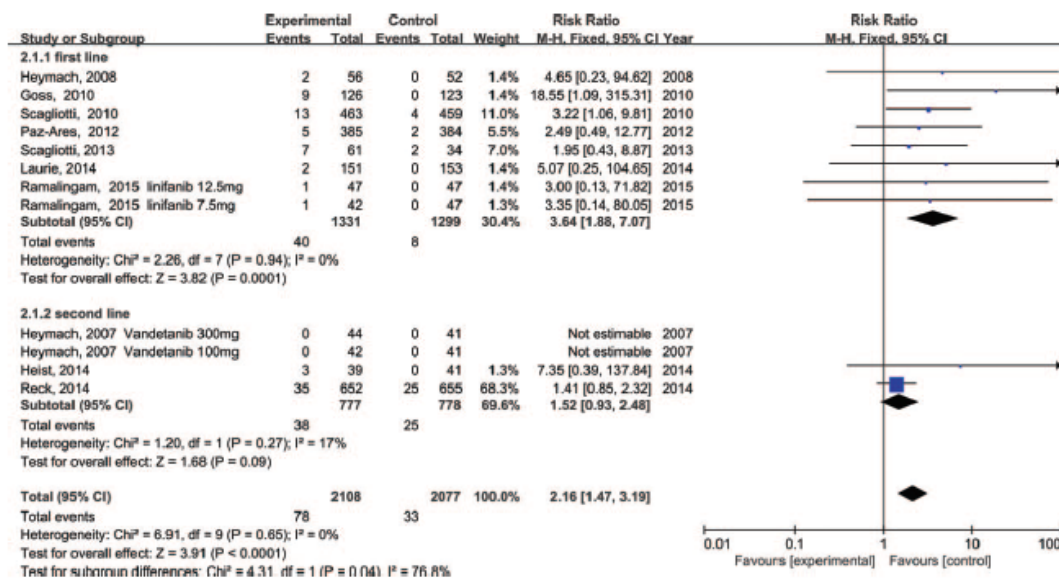


Figure 5. Forest plot and pooled risk ratio for fatal adverse events.

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 [80].

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:

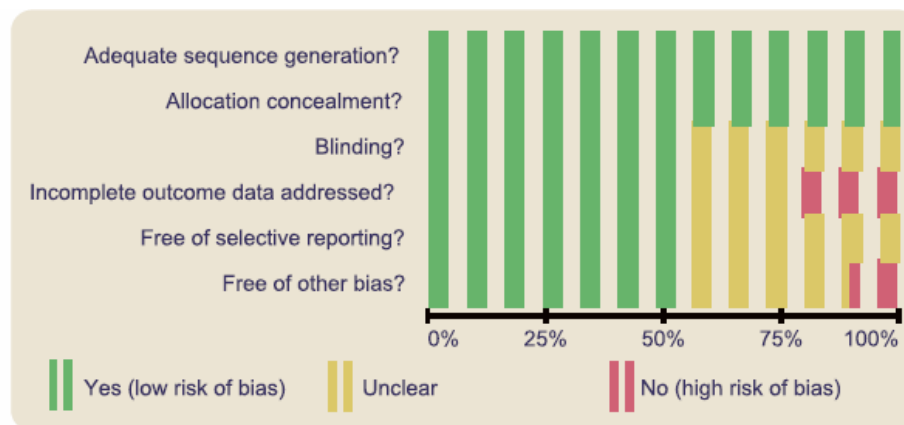


FIGURE A2 Cochrane systematic bias evaluation chart of nine included studies [Color figure can be viewed at wileyonlinelibrary.com]

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.

Hess LM et al., 2018 [58].

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

Fragestellung

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 <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (29)	Erlotinib 150 mg/day	To PD	11 (21.2%)
	Paclitaxel 200 mg/m ² + carboplatin AUC 6	4 cycles	8 (15.7%)
Morabito <i>et al.</i> (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 <i>et al.</i> (31,32)	Cisplatin 80 mg/m ² + vinorelbine 25 mg/m ²	6 cycles	187 (33%)
Gatzemeier <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (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
- Siehe auch: Ilic, I. et al., 2019 [63]

Chen JH et al., 2018 [7].

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: $p = 0.0002$; $I_2 = 84\%$), 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: $p = 0.65$; $I_2 = 0\%$), 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: $p = 0.44$; $I^2 = 0\%$) 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:

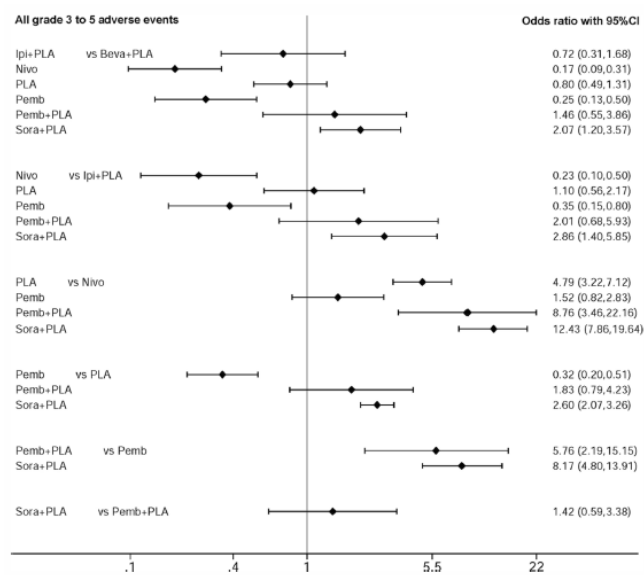


Figure 2. Forest plot of indirect comparison: all grade 3 to 5 adverse events in first line therapy. All individual regimens compared with reference treatment. Odds ratios (OR) and 95% confidence intervals were given. Beva: bevacizumab; Ipi: ipilimumab; Nivo: nivolumab; Pemb: pembrolizumab; Sora: sorafenib; 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 separaten Analysen/Ergebnisse zum Stadium oder Status (z.B. fortgeschritten vs. metastasierte Patienten) bzw. EGFR Status.
- Siehe auch: Shao, J. et al., 2020 [98]

Han S et al., 2018 [55].

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

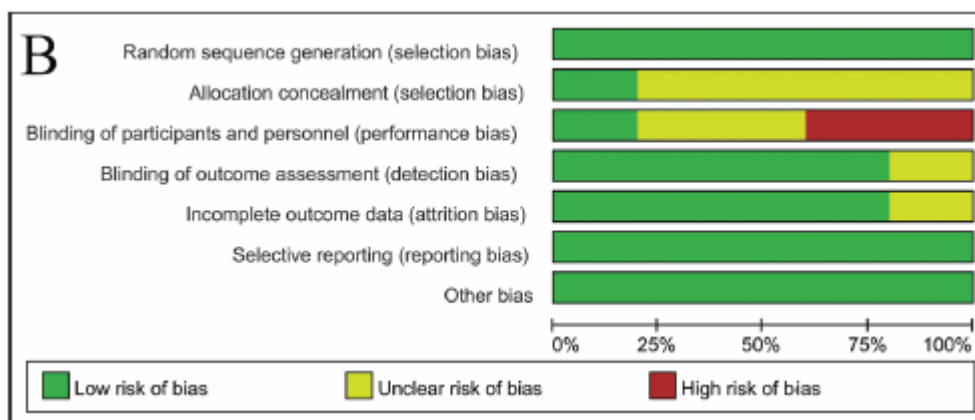
Charakteristika der Population:

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 blinding. 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 [122].

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.

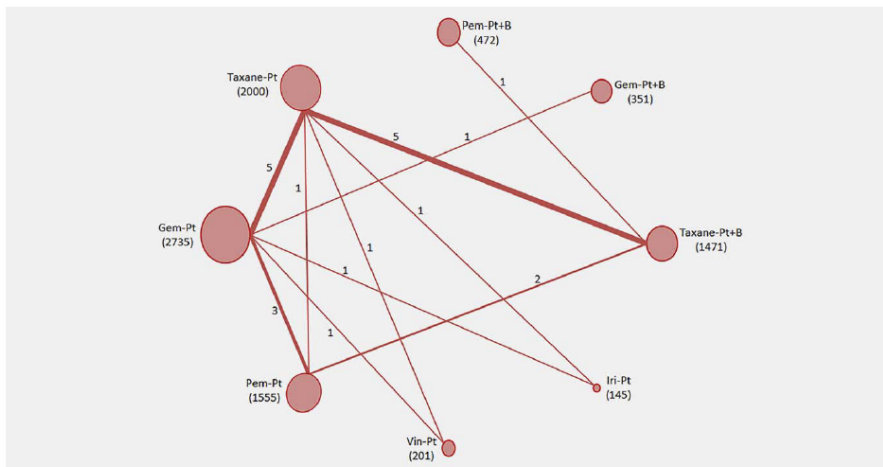


Figure 2. Network of all eligible trials assessing the six treatments in the first-line setting for advanced NS-NSCLC established for the Bayesian network meta-analysis. The size of the nodes is proportional to the number of patients (in parentheses) randomized to receive the treatment. The width of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

Roviello G et al., 2018 [96].

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

Fragestellung

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 \geq 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:

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], whilst 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 [99].

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.

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:

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	Erlotinib 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, carboplatinvinorelbine; 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: $I^2 = 0\%$, $P = 0.72$). 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.

	No. Trials	No. Patients With Wild EGFR	Progression-free Survival		Heterogeneity Within Subgroups	
			HR (95% CI)	<i>P</i>	<i>I</i> ² (%)	<i>P</i>
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).

Dafni U et al., 2019 [14].

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 \geq 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 \leq PD-L1 \leq 49%) Cohort: For the subgroup of PD-L1-intermediate patients, results are more limited (five studies, 972 patients). The only treatments evaluated are the combination of chemotherapy with either pembrolizumab or atezolizumab versus chemotherapy-alone. Both of the combinations are significantly better than chemotherapy-alone (HRpooled=0.55 [0.44-0.70]; HRpooled=0.68 [0.57-0.81]) while not different between them.
- OS-NMA for full study cohort
 - In the overall NMA model for OS, with data from 10 studies, initially nine experimental treatments are compared to the chemotherapy-alone control arm, including an indirect comparison of the bevacizumab combinations. The combinations of chemotherapy with without bevacizumab (NMA estimate: HR=0.75 [0.59-0.94]; HRpooled=0.85 [0.75-0.95], respectively) as well as the pembrolizumab-monotherapy (HR=0.81 [0.71-0.93]) show a significant OS benefit over chemotherapy-alone.
 - Based on the NMA estimates, the combination of pembrolizumab/chemotherapy is estimated to be consistently better than all other treatments evaluated (HRs: 0.51-0.72), while other promising treatments are ABC and pembrolizumab-monotherapy, followed by atezolizumab/ chemotherapy, all no different between them. Pembrolizumab-monotherapy and ABC are also better than the durvalumab/tremelimumab combination, with ABC also better than bevacizumab/chemotherapy. Excluding the non-significant interim analysis results on atezolizumab/chemotherapy combination, similar evidence for the OS benefit is provided (results not shown).
- OS-NMA by histological subtype
 - OS results by histology were similar to the overall cohort regarding the combination of pembrolizumab/chemotherapy being the better treatment choice for both histological types, with also ABC and atezolizumab/chemotherapy in non-squamous. ABC is evaluated only in non-squamous, ipilimumab/chemotherapy only in squamous, while pembrolizumab-monotherapy (among others) could not be evaluated here.
- OS-NMA by PD-L1 category

- PD-L1 < 1% Cohort: The NMA OS analysis for PD-L1-negative patients is based on five trials evaluating four experimental treatments (N=1325). Available immature OS information, from the non-significant interim analysis of IM131 is used for atezolizumab/chemotherapy along with the final OS data from IM130. Both combinations of pembrolizumab and atezolizumab with chemotherapy display a significant benefit over chemotherapy-alone (HR_{pooled}=0.60 [0.45-0.80] and HR_{pooled}=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 [2] & Liu T et al. 2019 [83] & Chen, R. et al., 2019 [8]

Zhou Y et al., 2019 [127]

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 $\geq 50\%$ using indirect comparison meta-analysis.

Methodik

Population:

- advanced NSCLC

Intervention/Komparator:

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

Endpunkte:

- OS, PFS, ORR

Recherche/Suchzeitraum:

- before November 1, 2018

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool

Ergebnisse

Anzahl eingeschlossener Studien:

- five trials involving 1289 patients

Charakteristika der Population:

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

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

^aData 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	Blinding	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 [70] & Liu Y et al. 2019 [84] & Frederickson, A. M. et al., 2019 [21]
- Unklar Anteil metastasierte Patienten

Griesinger F et al., 2019 [54]

Efficacy and safety of first-line carboplatin-versus cisplatin-based chemotherapy for non-small cell lung cancer: A meta-analysis.

Fragestellung

to evaluate the relative efficacy, safety, and health-related quality of life (HRQoL) of carboplatin-versus cisplatin-based chemotherapy in 1L NSCLC.

Methodik

Population:

- treatment-naïve adult patients with advanced NSCLC

Intervention/Komparator:

- carboplatin-based vs. cisplatin-based therapy, in combination with the same chemotherapy agent: gemcitabine, docetaxel, paclitaxel, vinorelbine, irinotecan, or pemetrexed

Endpunkte:

- OS, one-year survival rate, ORR, drug toxicities, or HRQoL

Recherche/Suchzeitraum:

- Searches were run in January 2018 using the following electronic databases: The Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Embase and the Latin American and Caribbean Health Sciences (LILACS) database.

Qualitätsbewertung der Studien:

- Cochrane Collaborations recommended risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Twelve RCTs (2,048 patients)

Qualität der Studien:

- Allocation was adequately concealed in most studies, although no relevant information was provided by Saad et al. Eleven of the RCTs did not report complete information about the blinding process; the study by Schuette et al. (2013) was classified as high risk for selection bias given that it was an open-label study; additionally, this study was designed as a non-comparative trial. Overall, selective reporting was not identified as a main source of bias in the included studies; only Cai et al. (2002) and Rosell et al. (2002) did not report survival data. Phase II studies were identified as high risk for other bias. As explained by de Castria et al. (2013), the study conducted by Rosell et al. (2002) was classified as high risk for other

bias due to the fact that 34% of subjects randomized to carboplatin required a dose reduction and that this may be associated with a lower effectiveness.

Studienergebnisse:

- There were no significant differences in OS and one-year OS between carboplatin- and cisplatin-based chemotherapy.
- A small effect on ORR favouring cisplatin was detected (RR=0.88; CI: 0.78, 0.99).
- Differences in drug-related toxicities were observed between carboplatin- and cisplatin-based chemotherapy for thrombocytopenia, anaemia, neurotoxicity, and the risk of nausea/vomiting.
- Three RCTs comparing HRQoL between carboplatin- and cisplatin-based chemotherapy found no significant differences.

Anmerkung/Fazit der Autoren

This updated evidence base corroborates findings of previous meta-analyses showing no difference in OS between carboplatin- and cisplatin-based chemotherapy, despite a slight benefit in ORR for cisplatin. Toxicity profiles should be considered alongside patients' comorbidities in the choice of therapy.

Zhang, Y. et al., 2017 [119].

Therapeutic Efficacy Comparison of 5 Major EGFR-TKIs in Advanced EGFR-positive Non-Small-cell Lung Cancer: A Network Meta-analysis Based on Head-to-Head Trials.

Fragestellung

to offer additional data about comparisons between these 5 EGFR-TKIs through integrating and indirect methods of network meta-analysis, with the intent that these results can assist physicians and patients in decisionmaking.

Methodik

Population:

- advanced NSCLC patients

Intervention/Komparator:

- EGFR-TKI treatment versus another EGFR-TKI → trials could be performed in chemotherapy-naive or previously treated patients or a combination of the 2 types

Endpunkte:

- ORR, DCR, 1y-PFS, 1y-OS, 2-y OS

Recherche/Suchzeitraum:

- PubMed, Embase, and the Cochrane Central Register of Controlled Trials of the Cochrane Library up to March 2016

Qualitätsbewertung der Studien:

- Jadad score

Ergebnisse

Anzahl eingeschlossener Studien & Charakteristika der Population:

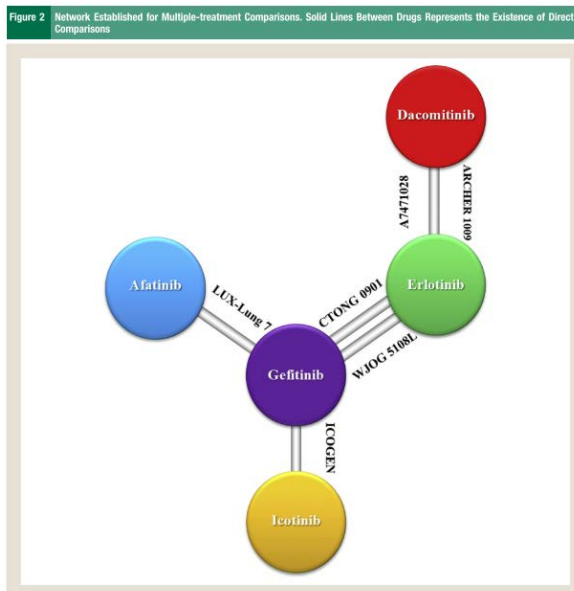
- 6 phase III RCTs were finally enrolled, which involved 1055 patients with advanced NSCLC harboring EGFR mutations

Table 1 Characteristics of Included Studies for Meta-analyses				
Trial	Type	Race	Drug	EGFR Mutations
ICOGEN	Previously treated	Asian	Icotinib	29
WJOG 5108L	Previously treated	Asian	Gefitinib	39
			Erlotinib	150
CTONG 0901	Mixed	Asian	Gefitinib	128
			Erlotinib	128
ARCHER 1009 and A7471028	Previously treated	Mixed	Dacomitinib	53
			Erlotinib	48
LUX-Lung 7	CT naïve	Mixed	Afatinib	160
			Gefitinib	159

Qualität der Studien:

- Studies ranked as low quality level were excluded for the meta-analyses.

Studienergebnisse:



- Multiple treatment comparisons showed that 5 different EGFR-TKIs shared equivalent therapeutic efficacy in terms of all outcome measures.

Table 2 Multiple-treatment Comparisons (MTCs) for Efficacy Based on Network

ORR				
Afatinib	0.60 (0.12, 3.03)	0.53 (0.16, 1.60)	0.51 (0.20, 1.30)	0.69 (0.15, 3.44)
1.67 (0.33, 8.23)	Dacomitinib	0.86 (0.27, 2.63)	0.85 (0.23, 3.16)	1.14 (0.19, 8.27)
1.90 (0.63, 6.16)	1.16 (0.38, 3.64)	Erlotinib	0.99 (0.51, 1.94)	1.35 (0.33, 5.79)
1.94 (0.77, 5.01)	1.17 (0.32, 4.31)	1.01 (0.51, 1.95)	Gefitinib	1.36 (0.41, 5.05)
1.45 (0.29, 6.70)	0.88 (0.12, 5.19)	0.74 (0.17, 3.01)	0.74 (0.20, 2.45)	Icotinib
DCR				
Afatinib	0.67 (0.14, 3.01)	0.50 (0.13, 1.74)	0.14 (0.01, 1.57)	
1.49 (0.33, 7.29)	Erlotinib	0.74 (0.32, 1.76)	0.22 (0.02, 1.95)	
2.00 (0.58, 7.53)	1.35 (0.57, 3.14)	Gefitinib	0.29 (0.02, 2.24)	
7.10 (0.64, 116.30)	4.64 (0.51, 65.04)	3.49 (0.45, 41.59)	Icotinib	
1y-PFS				
Afatinib	2.48 (0.45, 15.68)	1.07 (0.28, 4.03)	0.76 (0.26, 2.23)	1.16 (0.19, 7.16)
0.40 (0.06, 2.25)	Dacomitinib	0.42 (0.12, 1.45)	0.30 (0.07, 1.21)	0.47 (0.06, 3.59)
0.93 (0.25, 3.57)	2.36 (0.69, 8.47)	Erlotinib	0.71 (0.32, 1.50)	1.07 (0.21, 5.49)
1.32 (0.45, 3.92)	3.30 (0.83, 14.98)	1.42 (0.67, 3.17)	Gefitinib	1.53 (0.35, 6.59)
0.86 (0.14, 5.19)	2.15 (0.28, 17.33)	0.93 (0.18, 4.81)	0.65 (0.15, 2.85)	Icotinib
1y-OS				
Dacomitinib	0.75 (0.23, 2.34)	0.52 (0.13, 1.99)	0.71 (0.12, 4.17)	
1.33 (0.43, 4.28)	Erlotinib	0.69 (0.32, 1.46)	0.96 (0.24, 3.67)	
1.94 (0.50, 7.52)	1.46 (0.69, 3.11)	Gefitinib	1.40 (0.43, 4.20)	
1.41 (0.24, 8.43)	1.04 (0.27, 4.13)	0.72 (0.24, 2.35)	Icotinib	
2y-OS				
Dacomitinib	0.71 (0.30, 1.69)	0.55 (0.19, 1.60)	0.44 (0.10, 2.15)	
1.40 (0.59, 3.35)	Erlotinib	0.77 (0.41, 1.45)	0.63 (0.17, 2.22)	
1.82 (0.63, 5.36)	1.29 (0.69, 2.43)	Gefitinib	0.81 (0.27, 2.49)	
2.28 (0.47, 10.08)	1.59 (0.45, 5.74)	1.23 (0.40, 3.69)	Icotinib	

Abbreviations: DCR = Disease control rate; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

- Rank probabilities indicated that dacomitinib and afatinib had potentially better efficacy compared with erlotinib, gefitinib, and icotinib in the EGFRmutated patients.
- When compared with other agents, potential survival benefits (progression-free and overall survival) were observed in dacomitinib, whereas afatinib showed a better rank probability in overall response rate and disease control rate.

Table 3 Rank Probabilities of Each TKI for Different Outcomes Based on Network					
Drug	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
ORR					
Afatinib	0.53	0.29	0.10	0.04	0.03
Dacomitinib	0.18	0.23	0.19	0.14	0.27
Erlotinib	0.02	0.11	0.28	0.36	0.24
Gefitinib	0.01	0.1	0.29	0.34	0.26
Icotinib	0.26	0.27	0.14	0.12	0.21
DCR					
Afatinib	0.70	0.19	0.09	0.02	
Erlotinib	0.24	0.53	0.19	0.04	
Gefitinib	0.03	0.23	0.66	0.08	
Icotinib	0.03	0.05	0.06	0.86	
1y-PFS					
Afatinib	0.08	0.22	0.28	0.23	0.20
Dacomitinib	0.71	0.18	0.06	0.03	0.02
Erlotinib	0.02	0.30	0.36	0.23	0.08
Gefitinib	0	0.02	0.13	0.38	0.47
Icotinib	0.18	0.28	0.17	0.14	0.23
1y-OS					
Dacomitinib	0.54	0.22	0.12	0.12	
Erlotinib	0.16	0.46	0.30	0.07	
Gefitinib	0.02	0.09	0.34	0.55	
Icotinib	0.28	0.23	0.24	0.25	
2y-OS					
Dacomitinib	0.71	0.15	0.09	0.06	
Erlotinib	0.13	0.58	0.20	0.08	
Gefitinib	0.05	0.15	0.54	0.26	
Icotinib	0.11	0.12	0.17	0.61	

Abbreviations: DCR = Disease control rate; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

Anmerkung/Fazit der Autoren

In conclusion, our study indicated a preferable therapeutic efficacy in the second-generation TKIs (dacomitinib and afatinib) when compared with the first-generation TKIs (erlotinib, gefitinib, and icotinib).

Kommentar zum Review:

- Siehe auch Zhang Y. et al., 2017 [118]

Li, Z. et al., 2018 [78].

Chemotherapy with or without pemetrexed as second-line regimens for advanced non-small-cell lung cancer patients who have progressed after first-line EGFR TKIs: a systematic review and meta-analysis.

Fragestellung

to evaluate the chemotherapeutic regimens “with-pemetrexed” versus “non-pemetrexed” in advanced NSCLC patients who had progressed after first-line EGFR-TKIs.

Methodik

Population:

- patients were pathologically confirmed of advanced NSCLC/ patients using EGFR-TKIs as first-line therapy and developed acquired resistance or progression of disease

Intervention/Komparator:

- pemetrexed singlet or pemetrexed-based combination chemotherapy with non-pemetrexed chemotherapy as secondline chemotherapy (with-pemetrexed vs non-pemetrexed)

Endpunkte:

- Response rate (RR), disease control rate (DCR), 1-year survival rate (1-year SR), progression-free survival (PFS), and overall survival (OS)

Recherche/Suchzeitraum:

- PubMed, Embase, Cochrane Library, and the Web of science up to March 2017.

Qualitätsbewertung der Studien:

- Jadad score / modified Newcastle-Ottawa scale

Ergebnisse

Anzahl eingeschlossener Studien:

- One randomized controlled trial (RCT) and three retrospective studies were included in this meta-analysis, covering a total of 354 patients
- 202 in the chemotherapy with-pemetrexed arm and 152 in the chemotherapy non-pemetrexed arm

Charakteristika der Population:

- In these 354 patients, mostly metastatic and stage IV adenocarcinoma, except for 11 patients with stage IIIb in the RCT.
- All of these 354 patients were treated using EGFR-TKIs as first-line therapy, and none of them were treated with any radiation therapy before. After the first-line EGFR-TKIs treatment, the patients presented local progress and distant metastasis, and hence changed to second-line chemotherapy regimens.
- The regimens included in the with-pemetrexed arm are pemetrexed singlet or pemetrexedbased combination chemotherapy. The regimens of the non-pemetrexed arm comprised conventional cytotoxic chemotherapy singlet (eg, docetaxel singlet) or doublet (eg, platinum doublet, navelbine/platinum doublet and platinum+gemcitabine/navelbine/taxotere doublet).

Table 1 Characteristics and data extracted from the studies included in this meta-analysis

Authors/ year	Type	EGFR mutation	Second-line regimens (per arm)	Patients enrolled	RR (%)	DCR (%)	I-year SR (%)	PFS	OS	Jadad/ Ottawa score
Dong et al 2014 ¹⁵	RCT	Yes	Pem, docetaxel	54 55	22.2 25.5	51.9 52.7	25.9 25.5	NA	NA	3
Park et al 2015 ¹⁶	Retrospective	Yes	Pem, platinum doublet	34 26	24 12	91 88	NA	HR: 0.47 95% CI: 0.26–0.84	HR: 0.50 95% CI: 0.22–1.13	6
Tseng et al 2016 ¹⁷	Retrospective	Yes	Pem ± platinum ± beva, NVB/platinum doublet	37 46	32.4 17.4	78.4 50.0	NA	HR: 0.54 95% CI: 0.34–0.86	HR: 0.92 95% CI: 0.50–1.68	6
Yang et al 2016 ¹⁴	Retrospective	Yes	Pem + platinum, platinum + GEM/NVB/TXT	77 25	26 20	54.6 48	60.3 40.9	HR: 0.78 95% CI: 0.51–1.2	HR: 0.47 95% CI: 0.26–0.83	6

Abbreviations: EGFR, epidermal growth factor receptor; RR, response rate; PFS, progression-free survival; OS, overall survival; DCR, disease control rate; I-year SR, I-year survival rate; RCT, randomized controlled trial; HR, hazard ratio; Pem, pemetrexed; Beva, bevacizumab; GEM, gemcitabine; NVB, navelbine; TXT, taxotere; NA, no assessment.

Qualität der Studien:

- Jadad score obtained was 3. Three retrospective studies were used to assess Newcastle-Ottawa scale and the score obtained was 6. All these articles were considered to be of high quality.

Studienergebnisse:

- The results showed that there was no significant difference between with-pemetrexed arm and non-pemetrexed arm in RR, DCR, and 1-year SR.
- But the with-pemetrexed chemotherapeutic regimens significantly improved the PFS (HR 0.61, 95% CI 0.46–0.81, P=0.0005) and OS (HR 0.62, 95% CI 0.42–0.90, P=0.01).

Anmerkung/Fazit der Autoren

Our meta-analysis showed that compared with nonpemetrexed regimens, the second-line with-pemetrexed chemotherapeutic regimens provided significantly longer PFS and OS in the advanced NSCLC patients who had progressed after first-line treatment with EGFR TKIs. This indicates that the with-pemetrexed chemotherapeutic regimen may be an optimal second-line chemotherapeutic regimen for patients with advanced NSCLC after EGFR-TKI failure.

Gao, J. W. et al., 2017 [22].

Erlotinib-based doublet targeted therapy versus erlotinib alone in previously treated advanced non-small-cell lung cancer: a meta-analysis from 24 randomized controlled trials.

Fragestellung

To assess the efficacy profile of erlotinib-based doublet targeted therapy compared with erlotinib monotherapy for previously treated patients with advanced NSCLC, a meta-analysis was performed.

Methodik

Population:

- patients with histologically or cytologically confirmed stage IIIB or stage IV NSCLC and previously treated with at least one chemotherapy

Intervention:

- erlotinib-doublet targeted therapy

Komparator:

- single-agent erlotinib

Endpunkte:

- OS, PFS, ORR, DCR

Recherche/Suchzeitraum:

- PubMed, Embase, and Cochrane) for studies published between inception and February 2, 2016

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 24 articles involving 6,196 patients

Charakteristika der Population:

- Of the 24 randomized trials, the primary end point was PFS in twelve OS in six, ORR in two, ORR plus PFS (coprimary end points) in one, 12-weeks PFS rate in one, 4-month PFS rate in one and DCR
- Six of the included studies were phase III RCTs and the remaining were phase II RCTs. 14 trials employed erlotinib plus placebo as the control arm, while the remaining 10 treated control subjects with single-agent erlotinib. 8 studies tested targeted therapies in molecularly enriched populations in accordance with EGFR status (immunocytochemistry positive; wild-type), KRAS status (wild-type), expression of MET (immunocytochemistry 2+/3+) and histological type (non-adenocarcinoma; nonsquamous cell carcinoma).

Qualität der Studien:

- All the included trials reported “randomization” with 75% and 54% studies providing the conduction details of random sequence generation and allocation concealment, respectively. 10 RCTs were marked with “open-label” and the performance bias was assessed as “high risk”. For other key domains, no high risk of bias was detected.

Studienergebnisse:

- The median OS were 5.7 to 13.3 months in the combination arm versus 4.1 to 14 months in the control arm. Pooled HR for OS estimated from 22 studies was not significant. No significant heterogeneity was detected among the studies included for OS analysis.
- The median PFS of the doublets group and singleagent group were 1.3 to 5.4 months and 1.5 to 3.5 months, respectively. Considering significant heterogeneity among the studies (I² = 58%), a random effect model was employed to estimate the pooled HR for PFS. Pooled PFS of patients treated with erlotinib plus the other targeted agent was superior to those treated with erlotinib alone (HR 0.83, 95% CI 0.75-0.91, p = 0.0002).
- 1-year SR did not significantly improve with doublets compared with single erlotinib.

- However, ORR and DCR were in favor of the doublet targeted therapy (RR 1.28, 95 % CI 1.08-1.52, $p = 0.004$ and RR 1.21, 95% CI 1.13-1.30, $p < 0.00001$)
- Neither phase II nor phase III trials subset analysis of OS revealed significant differences between the erlotinib-based combinations compared with the single agent, whereas both phase II and phase III trials subgroup analysis showed improvement in PFS with doublets regimen over single erlotinib regimen (HR 0.83, 95 % CI 0.73-0.95, $p = 0.007$; I² % CI 0.69-0.96, $p = 0.01$)
- Overall, no significant differences existed in PFS or OS between combining targeted therapy and erlotinib monotherapy, except that patients treated with erlotinib plus antiangiogenesis or anti-MET targeted agents showed improvement in PFS (HR 0.73, 95% CI 0.62-0.86, $p = 0.0002$; I² 0.03; I² = 49%; and HR 0.84, 95% CI: 0.72-0.99, $p = 0.0054$, respectively) and the doublets erlotinib plus cabozantinib (anti-angiogenesis plus anti-MET signaling) group revealed significant improvement in both OS and PFS (HR 0.44, 95 % CI 0.29-0.66, $p < 0.0001$; and HR 0.35, 95 % CI 0.24-0.52, $p < 0.00001$)
- 11 studies provided the detailed analysis of OS in EGFR wild-type population. The pooled HR was 0.89 (95% CI 0.75-1.06, $p = 0.2$). Combining PFS of ten trials involving 2205 NSCLC harboring wild-type EGFR produced a significant improvement from the doublet targeted therapy (HR 0.68, 95% CI 0.57-0.83, $p < 0.0001$)
- No significant differences were observed expect for PFS in EGFR wild-type population mentioned above.
- In patients with KRAS mutations, the pooled HR for OS and PFS for combination arm versus erlotinib arm were 0.95 (95% CI 0.76-1.19, $p = 0.64$; I² = 34%) and 0.23 (95% CI 0.13-0.41, $p < 0.00001$; I² = 0%), respectively. = 0%) and In KRAS wild-type population, the pooled HR for OS and PFS were 0.93 (95% CI 0.82-1.05, $p = 0.23$; I² 0.79 (95% CI 0.64-0.97, $p = 0.03$).

Anmerkung/Fazit der Autoren

From this analysis, we conclude that erlotinib combined with additional targeted agent, especially anti-angiogenesis and anti-MET agent, could provide superior clinical benefit to patients with previously treated advanced NSCLC. The efficacy of combination therapy for particular selected populations, such as EGFR wildtype population, need further investigation. The absence of a biomarker to identify sensitive populations is a major hurdle for optimal utilization.

Kommentar zum Review:

- Siehe auch: Yu, S. et al., 2016 [114]

Yi, L. et al., 2019 [112].

Efficacy and safety of osimertinib in treating EGFR-mutated advanced NSCLC: A meta-analysis.

Fragestellung

synthesized the results of different studies, including the overall response rate (ORR), disease control rate (DCR), PFS, and AEs, to provide more objective data for the optimal clinical use of osimertinib.

Methodik

Population:

- histologically diagnosed with advanced NSCLC

Intervention:

- osimertinib

Komparator:

- siehe Ergebnisteil

Endpunkte:

- response rate, PFS, and toxicity

Recherche/Suchzeitraum:

- PubMed, Web of Science, and the Cochrane Library on May 4, 2018

Qualitätsbewertung der Studien:

- The Newcastle–Ottawa Scale (NOS) / Cochrane Approach

Ergebnisse

Anzahl eingeschlossener Studien:

- A total of 11 clinical trials (three RCTs, eight single-arm trials) involving 3,086 patients with advanced NSCLC (632 in the three RCTs, 2,454 in the eight single-arm trials)

Charakteristika der Population & Qualität der Studien:

- The eligible studies were published from 2015 to 2017, and the sample size of each study ranged from 60 to 1,217.
- The proportion of female patients varied from 62 to 69% in each study, apart from three studies for which this information was not available.
- In the two studies involving first-line treatment, patients with EGFR-TKIsensitizing mutations accounted for 98.5% (334/339).
- All patients in eight of the nine studies involving secondline treatment or beyond were EGFR T790M-positive. The 80 mg dose of osimertinib was used in 8 of 11 studies.

Table 1. Characteristics of the 11 trials included in the meta-analysis

Study (year)	Country	Trial design	Sub-category	EGFR mutant (%)	Treatment line	Age (years)	Sample size (female %)	Dosage and length of osimertinib	Quality assessment
Mok <i>et al.</i> (2017)	China, America, United Kingdom, Korea, Italy	RCT Phase III	AURA3	T790M (100%)	Second	20–90	279 (62%)	80 mg qd, to PD	Cochrane ROB tool: low risk
Soria <i>et al.</i> (2018)	America	RCT Phase III	FLAURA	Ex19del/L858R (100%) ¹	First	26–93	279 (64%)	80 mg qd, to PD	Cochrane ROB tool: low risk
Nie <i>et al.</i> (2017)	China	RCT Phase III	NR	T790M (100%)	Third	18–80	74 (NR)	80 mg qd, to PD	Cochrane ROB tool: medium risk
Janne <i>et al.</i> (2015)	America, China	Single-arm Phase I	AURA	T790M (NR)	≥Second	28–88	163 (NR)	20–240 mg qd, to PD	NOS: 7
Goss <i>et al.</i> (2016)	America	Single-arm Phase II	AURA2	T790M (100%)	≥Second	35–88	210 (69%)	80 mg qd, to PD	NOS: 8
Planchard <i>et al.</i> (2016)	France	NR	NR	T790M (100%)	≥Second	28–92	350 (67%)	NR	NOS: 6
Marinis <i>et al.</i> (2017)	America	Single-arm Phase III b	ASTRIS	T790M (100%)	Second	27–92	1,217 (67%)	80 mg qd, to PD	NOS: 6
Ramalingam <i>et al.</i> (2018)	America	Single-arm Phase I	AURA	Ex19del/L858R (92%) ²	First	38–91	60 (64%)	80 or 160 mg qd, to PD	NOS: 7
Yang <i>et al.</i> (2017)	China	Single-arm Phase II (extension)	AURA	T790M (100%)	≥Second	37–89	201 (61%)	80 mg qd, to PD	NOS: 7
Zhou <i>et al.</i> (2017)	China	Single-arm Phase II	AURA17	T790M (100%)	≥Second	26–82	171 (69%)	80 mg qd, to PD	NOS: 5
Hochmair <i>et al.</i> (2017)	Austria	NR	NR	T790M (100%)	Second	NR	82 (NR)	80 mg qd, to PD	NOS: 4

Abbreviations: EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; NOS, Newcastle–Ottawa Scale; NR, not reported; PD, progression disease; RCT, randomized controlled trial; ROB, risk of bias.

¹T790M (NR)

²T790M (8%).

Studienergebnisse:

- Tumor response
 - About 9 of the 11 studies provided data on second-line treatment or beyond, and the combined ORR on EGFR T790M-positive NSCLC patients treated with osimertinib was 58% (95% CI 46–71%), with obvious heterogeneity ($I^2 = 98\%$, $p < 0.00001$).
 - Nine studies included usable data on DCR, and the pooled DCR was 84% (95% CI 71–97%). The combined DCR of the first-line treatment group was 97% (95% CI 95–99%), ($I^2 = 0\%$, $p = 0.85$), while the pooled DCR for second-line treatment or beyond was 80% (95% CI 63–98%), ($I^2 = 99\%$, $p < 0.00001$).
 - The data on CR, PR, and SD were given by six studies. The pooled CR was 3% (95% CI 1–4%). Subgroup analysis showed that the pooled CR values of the first-line group and the second-line or beyond group were 3% (95% CI 1–4%) ($I^2 = 0\%$, $P = 0.74$) and 3% (95% CI 1–5%), ($I^2 = 79\%$, $P = 0.003$), respectively.
 - The pooled PR was 62% (95% CI 39–84%). Subgroup analysis showed that the pooled PR of the first-line group was 77% (95% CI 72–81%), ($I^2 = 0\%$, $p = 0.51$), while that of the second-line or beyond group was 55% (95% CI 27–84%), ($I^2 = 99\%$, $p < 0.00001$).
 - The pooled SD was 15% (95% CI 9–21%). Subgroup analysis showed that the pooled SD of the first-line group was 17% (95% CI 13–21%), ($I^2 = 0\%$, $p = 0.58$), while the pooled SD of the second-line or beyond group was 14% (95% CI 5–22%), ($I^2 = 94\%$, $p < 0.00001$).
- Progression-free survival
 - The pooled median PFS was 13.06 months (95% CI 10.19– 15.93 months). Subgroup analysis suggested that the pooled median PFS of patients with EGFR-TKI-sensitizing mutations treated with osimertinib was 19.17 months (95% CI 16.88– 21.45 months), ($I^2 = 0\%$, $p = 0.61$). The pooled median PFS of EGFR T790M-positive patients treated with osimertinib was 10.58 months (95% CI 9.20–11.97 months), ($I^2 = 57\%$, $p = 0.07$). The PFS-

6 and PFS-12 were analyzed separately based on the available data from five studies. The pooled PFS-6 was 71% (95% CI 60–82%).

- Subgroup analysis indicated that the pooled PFS-6 of the first-line group was 83% (95% CI 80–87%), with small heterogeneity ($I^2 = 0\%$, $p = 0.97$). The combined PFS-6 of the second-line or beyond group was 63% (95% CI 58–69%), with significant heterogeneity ($I^2 = 55\%$, $p = 0.11$).
- The combined PFS-12 was 45% (95% CI 26–64%). The pooled PFS-12 of the second-line or beyond group was 32% (95% CI 17–47%), with significant heterogeneity ($I^2 = 95\%$, $p < 0.00001$).
- Toxicities
 - The highest-incidence AE among AEs of all grades was diarrhea, and the combined rate from a total of six studies (579/1,303) was 44% (95% CI 36–52%). The second was rash, and the pooled rate from a total of six studies (556/1,303) was 42% (95% CI 33–51%). Aggregated analysis based on AEs of grade \geq III indicated that the highest incidence was a prolonged QT interval on ECG, and the combined rate was 2% (95% CI 1–3%), with two studies included in the analysis (10/489). The second was neutropenia, and the combined rate was 2% (95% CI 1–3%), with two studies (9/489) included in the analysis. Furthermore, the pooled rate of diarrhea with grade \geq III was 1% (95% CI 0–1%). Five studies (12/1,132) provided data on rash with grade \geq III, and the pooled rate was 1% (95% CI 0–1%).

Anmerkung/Fazit der Autoren

The results of our study indicate that most patients with advanced NSCLC harboring T790M mutations after earlier-generation EGFR-TKI therapy would respond to osimertinib treatment or exhibit disease control. Osimertinib has impressive antitumor activity in treatment-naïve advanced NSCLC harboring EGFR-TKI-sensitizing mutations. Additionally, the incidences of AEs such as diarrhea and rash were lower than earlier-generation EGFR-TKIs, and there were no prominent serious AEs. Thus, osimertinib is a drug with favorable efficacy as well as tolerable AEs. Further clinical trials comparing firstline osimertinib treatment with the sequential use of earlier-generation EGFR-TKIs and osimertinib are warranted to update this meta-analysis and provide insight for optimizing the clinical use of osimertinib.

Almutairi AR et al., 2019 [3].

Comparative efficacy and safety of immunotherapies targeting the PD-1/PD-L1 pathway for previously treated advanced non-small cell lung cancer: A Bayesian network meta-analysis.

Fragestellung

A network meta-analysis was conducted to compare efficacy/safety of PD-1/PD-L1 inhibitors.

Methodik

Population:

- Previously treated advanced NSCLC

Intervention/Komparator:

- Netzwerkmetaanalyse: immune checkpoint inhibitors that target PD-1 (nivolumab, pembrolizumab) and its ligand PD-L1 (atezolizumab) in previously treated advanced NSCLC

Endpunkte:

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

Recherche/Suchzeitraum:

- Medline/PubMed, Cochrane Library, and Embase from inception through 31 May 2018

Qualitätsbewertung der Studien:

- Cochrane Collaboration Risk of Bias Assessment tool

Ergebnisse

Anzahl eingeschlossener Studien:

- five trials
- all had docetaxel as the comparator arm and included 3024 patients with advanced NSCLC previously treated with chemotherapy
- The majority of patients had non-squamous NSCLC type, wild type of EGFR, no anaplastic lymphoma kinase (ALK) translocation, PD-L1 expression measured by tumor proportion score (TPS) less than 50%, ECOG performance status score of 1, and one prior line of systemic treatment. Three additional articles provided 2-year and 3-year updates for two nivolumab trials (Checkmate-017, Checkmate-057) (Horn et al., 2017; Vokes et al., 2018) and a 2-year update for an atezolizumab trial (OAK) (Fehrenbacher et al., 2018).

Qualität der Studien:

- All five trials being open-label, they were all considered at high risk of bias in performance and detection. Two studies were rated at high risk of selection bias because they utilized unmasked allocation methods

Studienergebnisse:

- with docetaxel as common comparator there were no differences in OS and PFS between PD-1/PD-L1 inhibitors.
- Pembrolizumab (odds ratio (OR)=2.22, 95%CrI=1.28–3.70) and nivolumab (OR=1.92, 95%CrI=1.15–3.23) had higher ORRs than atezolizumab and at PD-L1 expression $\geq 50\%$ and $\geq 1\%$.
- Probabilistically, pembrolizumab ranked first in OS and ORR, and in OS sub-analyses for adenocarcinoma, EGFR-mutant, ECOG-score-1, male, and age < 65 years.
- Nivolumab ranked first in PFS, and in OS sub-analyses for squamous-cell disease, EGFR-wild-type, and ECOG-score-0.
- Pembrolizumab and nivolumab ranked the best option for most of adverse events.

Anmerkung/Fazit der Autoren

In conclusion, pembrolizumab and nivolumab prevailed in overall OS and ORR benefits over atezolizumab in our overall network metaanalysis. However, our analyses also suggest that

clinical (NSCLC type, ECOG status), genomic (EGFR, PD-L1 expression), and demographic (gender, age) patient characteristics, as well as safety and tolerance, should be considered in treatment decision-making about PD-1 and PDL1 checkpoint inhibitors in previously-treated patients with advanced NSCLC. Real-world evidence is necessary to complement trial evidence under conditions of greater heterogeneity in patients and treatment settings.

Connock M et al., 2019 [12].

Comparative survival benefit of currently licensed second or third line treatments for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) negative advanced or metastatic non-small cell lung cancer: a systematic review and secondary analysis of trials.

Fragestellung

With the aim of gauging patient survival benefit, we conducted a systematic review of randomised controlled trials (RCT) and compared survival outcomes from available licensed treatments for patients with advanced/metastatic NSCLC.

Methodik

Population:

- adult patients with advanced or metastatic (IIIB and/or IV) NSCLC with non-squamous (adenocarcinoma, large cell) or squamous histology who had experienced failure to prior first line chemotherapy (i.e., those receiving second line treatment and beyond); had either predominantly negative or 100% negative expression of anaplastic lymphoma kinase (ALK); had either predominantly negative or 100% negative expression of epidermal growth factor receptor (EGFR).

Intervention/Komparator:

- Docetaxel (DOC), Pemetrexed (PEM), Ramucirumab plus docetaxel (RAM + DOC), Erlotinib (ERL), Nintedanib plus docetaxel (NIN +DOC), Afatinib (AFA), Nivolumab (NIVO), and Pembrolizumab (PEMBRO), Atezolizumab (ATEZO)

Endpunkte:

- overall survival or progression-free survival

Recherche/Suchzeitraum:

- MEDLINE; EMBASE; Web of Science) from January, 2000 up to July, 2017

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 primary RCT studies with 7581 participants
- The 11 RCTs compared nine different drugs with the majority of comparisons were against DOC

Charakteristika der Population:

- Study sample size ranged from 208 to 1314 patients; studies included predominantly people with stage IV NSCLC and performance status 1

Qualität der Studien:

- Nine studies were considered as high-risk of bias due to the lack of blinding of participants and personnel. The five RCTs evaluating checkpoint inhibitors versus DOC were open-label and were considered as high-risk due to performance bias. LUME-LUNG-1 was rated at low risk of bias for all the key domains. Only HORG and TAILOR [18, 22] had public funding, so the remaining studies were rated as high-risk due to “other source bias”.

Studienergebnisse:

- patients regardless of histology groups, targeted drugs (ramucirumab and nintedanib) yielded small overall survival gains of < 2.5 months over docetaxel, erlotinib provided no benefit, while immunotherapies (atezolizumab and pembrolizumab) delivered 5 to 6 months gain.
- Studies with patients stratified by histology confirmed the apparent superiority of immunotherapy (nivolumab and atezolizumab) over targeted treatments (ramucirumab, nintedanib, afatinib) providing between about 4 to 8 months OS gain over docetaxel.
- In network analysis immunotherapies consistently ranked higher than alternatives irrespective of population histology and outcome measure.

Table 2 Mean survival (months) estimates from studies of patients with mixed histologies

TRIAL	Outcome	Intervention (n)	Control (n)	Intervention minus control
REVEL		Ram + Doc (628)	Plac + Doc (625)	
RMS [95% CI]	to 19 mos	11.00 [10.47–11.52]	10.01 [9.48–10.55]	0.99 [0.24–1.73]
Mean total OS	R_{mSext}	15.02	14.31	0.71
Mean total OS	Weibull [95% CI]	14.87 [13.40–16.57]	12.99 [11.71–14.46]	1.88 [–0.22–3.98]
Mean total OS	Weibull formula	14.87	12.98	1.89
LUMELUNG-1		Nin + Doc (655)	Plac + Doc (659)	
RMS [95% CI]	to 19 mos	10.85 [10.35–11.36]	10.38 [9.88–10.87]	0.48 [–0.23–1.18]
Mean total OS	R_{mSext}	14.38	13.57	0.82
Mean total OS	Weibull [95% CI]	14.08 [12.97–15.31]	13.21 [12.17–14.35]	0.87 [–0.73–2.47]
Mean total OS	Weibull formula	14.08	13.20	0.88
POPLAR		Atezolizumab (144)	Docetaxel (143)	
RMS [95% CI]	to 19 mos	11.84 [10.71–12.97]	10.39 [9.33–11.46]	1.45 [–0.11–3.00]
Mean total OS	R_{mSext}	20.76	13.00	7.76
Mean total OS	Weibull [95% CI]	17.89 [13.69–24.31]	12.15 [10.02–15.05]	5.74 [–0.135–11.61]
Mean total OS	Weibull formula	17.93	12.15	5.78
OAK		Atezolizumab (425)	Docetaxel (425)	
RMS [95% CI]	to 19 mos	12.31 [11.65–12.96]	10.68 [10.03–11.33]	1.62 [0.70–2.55]
Mean total OS	R_{mSext}	20.76	12.24	8.52
Mean total OS	Weibull [95% CI]	18.93 [16.54–21.81]	13.59 [12.11–15.32]	5.34 [2.25–8.43]
Mean total OS	Weibull formula	18.98	13.34	5.64
KEYNOTE-010		Pembrolizumab (344)	Docetaxel (343)	
RMS [95% CI]	to 19 mos	11.40 [10.62–12.19]	9.82 [9.05–10.59]	1.58 [0.48–2.68]
Mean total OS	R_{mSext}	20.64	12.74	7.89
Mean total OS	Weibull [95% CI]	16.14 [13.51–19.68]	11.10 [9.68–12.88]	5.04 [1.57–8.52]
Mean total OS	Weibull formula	16.43	10.42	6.01
TAILOR		Erlotinib (109)	Docetaxel (110)	
RMS [95% CI]	to 19 mos	7.66 [6.15–8.81]	9.30 [8.02–10.57]	–1.64 [–3.36–0.08]
Mean total OS	R_{mSext}	8.90	11.16	–2.26
Mean total OS	Weibull [95% CI]	8.67 [6.99–10.86]	11.11 [8.80–14.25]	–2.44 [–5.78–0.90]
Mean total OS	Weibull formula	8.67	11.10	–2.43
HORG		Erlotinib (166)	Pemetrexed (166)	
RMS [95% CI]	to 19 mos	10.18 [9.10–11.26]	9.85 [8.73–10.97]	0.33 [–1.23–1.88]
Mean total OS	R_{mSext}	15.33	14.42	0.91
Mean total OS	Weibull [95% CI]	15.02 [11.94–18.94]	13.86 [11.21–17.35]	1.16 [–3.5–5.82]
Mean total OS	Weibull formula	15.12	13.86	1.25
Hanna		Pemetrexed (283)	Docetaxel (288)	
RMS [95% CI]	to 19 mos	8.80 [8.10–9.50]	8.70 [7.96–9.44]	0.10 [–0.92–1.12]
Mean total OS	R_{mSext}	9.64	8.83	0.81
Mean total OS	Weibull [95% CI]	9.34 [8.30–10.57]	9.35 [8.20–10.74]	–0.01 [–1.71–1.69]
Mean total OS	Weibull formula	9.34	9.34	–0.01

OS overall survival, RMS restricted mean survival; R_{mSext} restricted mean survival exponentially extended from the end of the KM plot, Mean total OS Weibull formula mean OS estimated from Weibull model parameters using the formula published by Davies et al. [13]



Table 3 Estimates of mean survival (months) based on studies of patients with squamous histology

TRIAL	Outcome	Intervention (n)	Control (n)	Intervention minus control
REVEL		Ram + Doc (157)	Plac + Doc (171)	
RMS [95% CI]	to 24 mos	10.89 [19.65–12.13]	9.92 [8.75–11.10]	0.96 [–0.75–2.67]
Mean total OS	R_{mSext}	12.04	11.87	0.17
Mean total OS	Weibull [95% CI]	11.91 [10.01–14.29]	11.08 [9.31–13.29]	0.83 [–2.09–3.75]
Mean total OS	Weibull formula	11.90	11.07	0.83
Lux-lung 8		Afatinib (398)	Erlotinib (397)	
RMS [95% CI]	to 24 mos	10.48 [9.67–11.28]	8.95 [8.23–9.67]	1.52 [0.44–2.61]
Mean total OS	R_{mSext}	10.98	9.87	1.11
Mean total OS	Weibull [95% CI]	11.46 [10.19–12.94]	9.32 [8.39–10.37]	2.14 [0.45–3.83]
Mean total OS	Weibull formula	11.35	9.41	1.94
LUME LUNG-1		Nin + Doc (276)	Docetaxel (279)	
RMS [95% CI]	to 24 mos	10.65 [9.79–11.52]	10.14 [9.26–11.02]	0.51 [–0.72–1.75]
Mean total OS	R_{mSext}	11.76	12.19	–0.43
Mean total OS	Weibull [95% CI]	11.67 [10.42–13.07]	11.73 [10.31–13.38]	–0.06 [–2.09–1.97]
Mean total OS	Weibull formula	11.67	11.72	–0.06
Checkmate_017		Nivolumab (135)	Docetaxel (137)	
RMS [95% CI]	to 24 mos	11.94 [10.48–13.39]	8.33 [7.15–9.52]	3.61 [1.73–5.48]
Mean total OS	R_{mSext}	17.14	9.76	7.37
Mean total OS	Weibull [95% CI]	15.92 [12.79–19.94]	9.41 [7.78–11.41]	6.51 [2.50–10.52]
Mean total OS	Weibull formula	15.95	9.40	6.55
OAK		Atezolizumab (112)	Docetaxel (110)	
RMS [95% CI]	to 24 mos	11.99 [10.37–13.62]	9.73 [8.31–11.14]	2.27 [0.11–4.42]
Mean total OS	R_{mSext}	14.80	10.41	4.40
Mean total OS	Weibull [95% CI]	14.34 [11.31–18.58]	10.26 [8.45–12.52]	4.08 [–0.09–8.25]
Mean total OS	Weibull formula	14.34	10.25	4.09
Hanna		Pemetrexed (78)	Docetaxel (94)	
RMS [95% CI]	to 24 mos	NOT REACHED		
Mean total OS	R_{mSext}	7.40	8.83	–1.43 [–0.75–2.67]
Mean total OS	Weibull [95% CI]	7.22 [5.95–8.75]	8.83 [7.32–10.59]	–1.61 [–5.84–2.62]
Mean total OS	Weibull formula	7.22	8.82	–1.61

OS overall survival, RMS restricted mean survival, R_{mSext} restricted mean survival exponentially extended from the end of the KM plot, Mean total OS Weibull formula mean OS estimated from Weibull model parameters using the formula published by Davies et al. [13]

Table 4 Estimates of mean survival (months) based on studies of patients with non- squamous histology

TRIAL	Outcome	Intervention (n)	Control (n)	Intervention minus control
REVEL		Plac + Doc (465)	Plac + Doc (447)	
RMS [95% CI]	to 27 mos	13.50 [12.60–14.40]	12.10 [11.20–13.00]	1.39 [0.12–2.67]
Mean total OS	R_{mSext}	18.18	14.88	3.31
Mean total OS	Weibull [95% CI]	15.98 [14.16–18.15]	13.56 [12.00–15.41]	2.42 [–0.20–5.04]
Mean total OS	Weibull formula	16.98	13.56	2.43
LUME LUNG-1		Nin+Doc (322)	Plac + Doc (336)	
RMS [95% CI]	to 27 mos	14.18 [13.14–15.21]	12.62 [11.65–13.59]	1.55 [0.14–2.97]
Mean total OS	R_{mSext}	17.84	14.90	2.94
Mean total OS	Weibull [95% CI]	17.29 [15.24–19.68]	14.45 [12.88–16.26]	2.84 [0.05–5.63]
Mean total OS	Weibull formula	17.30	14.45	2.85
Checkmate_057		Nivolumab (292)	Docetaxel (290)	
RMS [95% CI]	to 27 mos	13.93 [12.77–15.09]	11.79 [10.78–12.80]	2.14 [0.61–3.68]
Mean total OS	R_{mSext}	18.29	14.72	3.57
Mean total OS	Weibull [95% CI]	18.04 [15.48–21.07]	13.32 [11.73–15.18]	4.72 [1.44–8.00]
Mean total OS	Weibull formula	18.13	13.31	4.82
OAK		Atezolizumab (313)	Docetaxel (315)	
RMS [95% CI]	to 27 mos	15.62 [14.5–16.72]	13.07 [11.99–14.15]	2.55 [1.00–4.09]
Mean total OS	R_{mSext}	23.76	13.09	10.67
Mean total OS	Weibull [95% CI]	20.70 [17.64–24.51]	15.02 [13.05–17.43]	5.68 [1.61–9.75]
Mean total OS	Weibull formula	20.79	15.01	5.77
Hanna		Pemetrexed (205)	Docetaxel (194)	
RMS [95% CI]	to 27 mos	na	na	na
Mean total OS	R_{mSext}	12.54	10.72	1.82
Mean total OS	Weibull [95% CI]	11.88 [10.27–13.82]	10.53 [9.11–12.20]	1.35 [–1.00–3.70]
Mean total OS	Weibull formula	11.87	10.52	1.35

OS overall survival, RMS restricted mean survival, R_{mSext} restricted mean survival exponentially extended from the end of the KM plot, Mean total OS Weibull formula mean OS estimated from Weibull model parameters using the formula published by Davies et al. [13]

Anmerkung/Fazit der Autoren

Based on our review, NIVO, PEMBRO and ATEZO exhibit superior benefit compared to other licensed drugs indicated for people with non-specific late stage NSCLC. The patient survival gains over chemotherapy from these drugs appear to be fairly substantial in the context of an expected average survival with DOC of less than 1 year for people with squamous histology and a little over a year for those with non-squamous histology.

Tartarone A et al., 2019 [103].

Anti-PD-1 versus anti-PD-L1 therapy in patients with pretreated advanced non-small-cell lung cancer: a meta-analysis.

Fragestellung

The aim of this meta-analysis is an indirect comparison between anti-PD-1 and anti-PD-L1 inhibitors in terms of efficacy and tolerability in pretreated patients with advanced NSCLC.

Methodik

Population:

- patients with NSCLC who progress after a first-line therapy

Intervention:

- immune checkpoint agent (anti-PD-1 or anti-PD-L1)

Komparator:

- docetaxel

Endpunkte:

- OS, PFS, AEs

Recherche/Suchzeitraum:

- PubMed, Embase and Web of Sciences up to 30 September 2018

Qualitätsbewertung der Studien:

- Jadad Scale

Ergebnisse

Anzahl eingeschlossener Studien:

- Seven studies were included in the analysis
- A total of 4664 patients were analyzed, among these 2735 cases in the experimental group and 1929 cases in the control group.
- All the studies were Phase III (6/7) or Phase II RCTs (1/7).

Charakteristika der Population:

Table 1. Main characteristics of the included studies.						
Clinical trials	Experimental arm	Control arm	Primary end points	Number of patients (experimental/docetaxel)	Patient selection based on PD-L1 status	Ref.
Javelin	Avelumab	Docetaxel	OS	396/396	No	[12]
OAK	Atezolizumab	Docetaxel	OS	425/425	No	[7]
POPLAR	Atezolizumab	Docetaxel	OS	144/143	No	[11]
CheckMate 017	Nivolumab	Docetaxel	OS	135/137	No	[4]
CheckMate 057	Nivolumab	Docetaxel	OS	292/290	No	[5]
KEYNOTE 010	Pembrolizumab	Docetaxel	OS, PFS	345; 346/343	TPS \geq 1%	[6]
CheckMate 078	Nivolumab	Docetaxel	OS	338/166	No	[25]

OS: Overall survival; PFS: Progression-free survival; TPS: Tumor proportion score.

Qualität der Studien:

- The median Jadad score was five, confirming a high level of quality.

Studienergebnisse:

- Considering the overall survival ICIs showed very robust efficacy over docetaxel, while in terms of progression-free survival the therapy with ICIs is slightly favored.
- Anti-PD-1 gives a more significant benefit than anti-PD-L1; however, excluding the KEYNOTE 010 trial that enrolled only PD-L1-positive patients, the subgroup difference remains only in terms of progression-free survival.

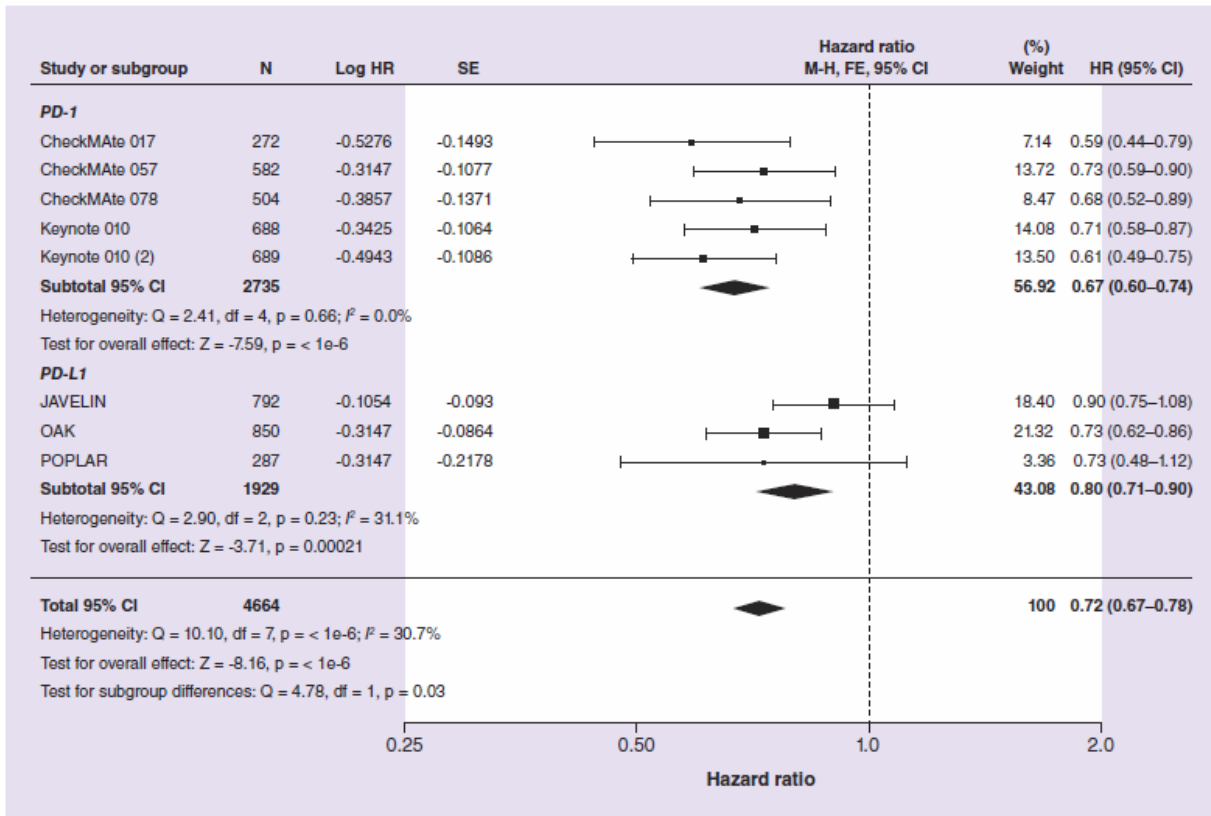


Figure 2. Forest plots of hazard ratios for overall survival comparing anti PD-1 and anti PD-L1 to docetaxel in all the collected non-small-cell lung cancer trials.
HR: Hazard ratio; SE: Standard error.

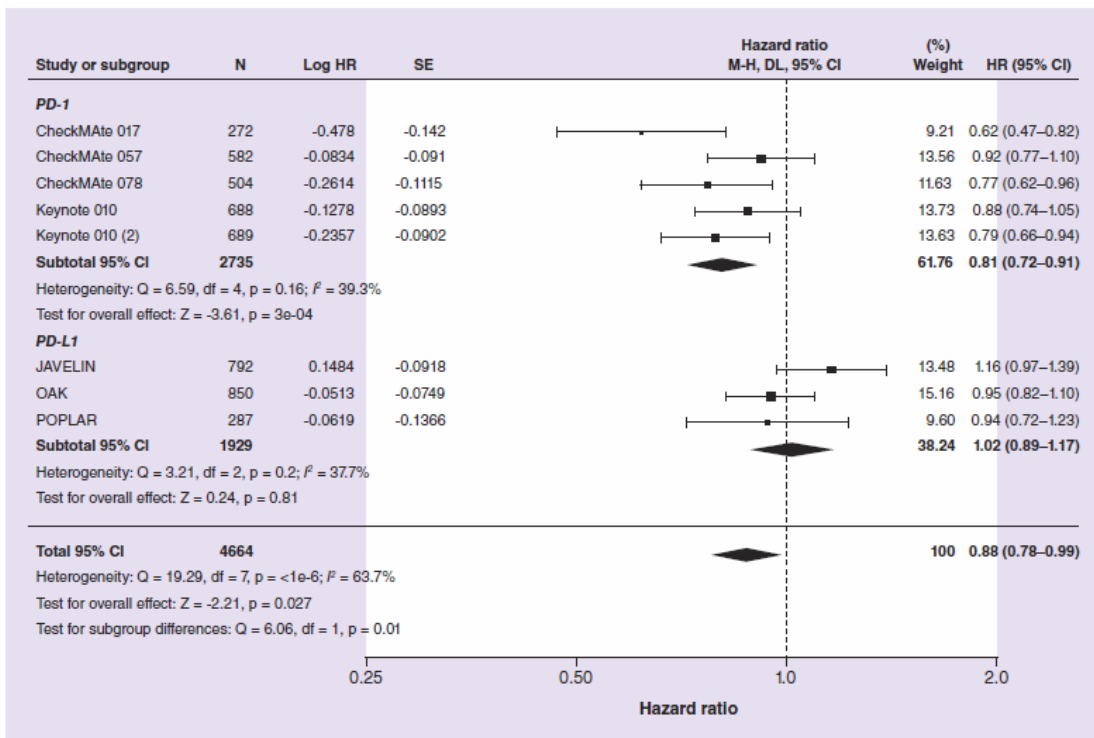


Figure 3. Forest plots of hazard ratios for progression free survival comparing anti PD-1 and anti PD-L1 to docetaxel in all the collected non-small-cell lung cancer trials.
HR: Hazard ratio; SE: Standard error.

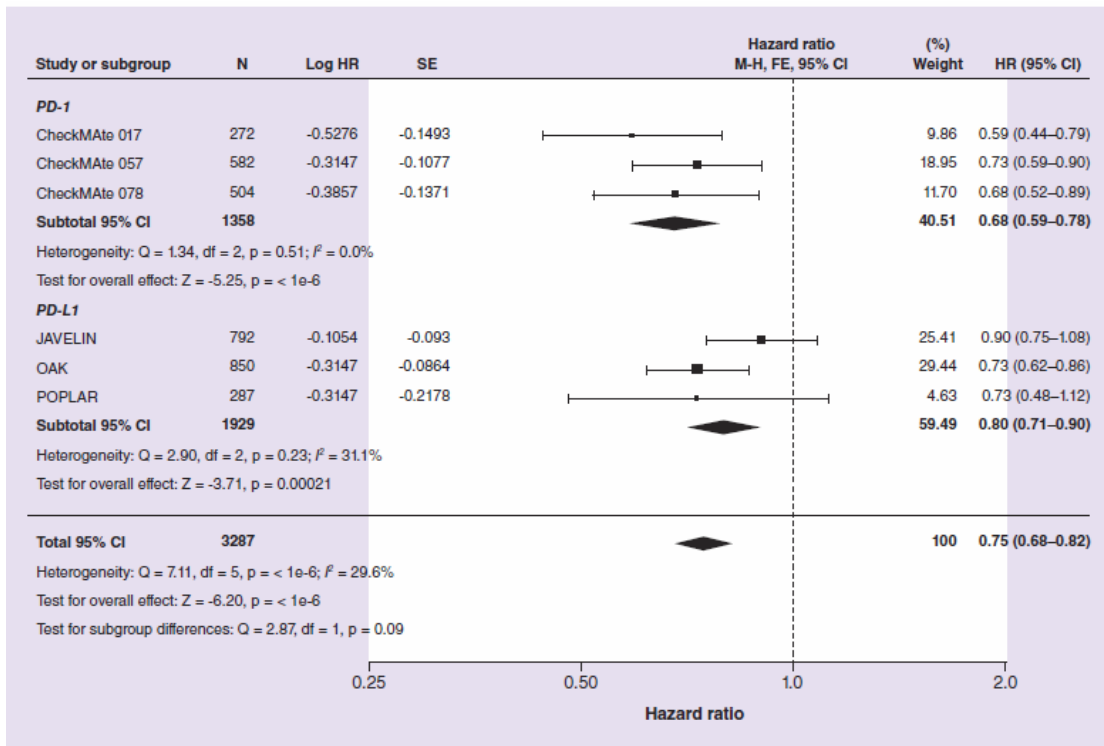


Figure 4. Forest plots of hazard ratios for overall survival comparing anti PD-1 and anti PD-L1 to docetaxel in NSCLC in all trials but without the KEY010 trial that enrolled only PD-L1-positive patients.
HR: Hazard ratio; SE: Standard error.

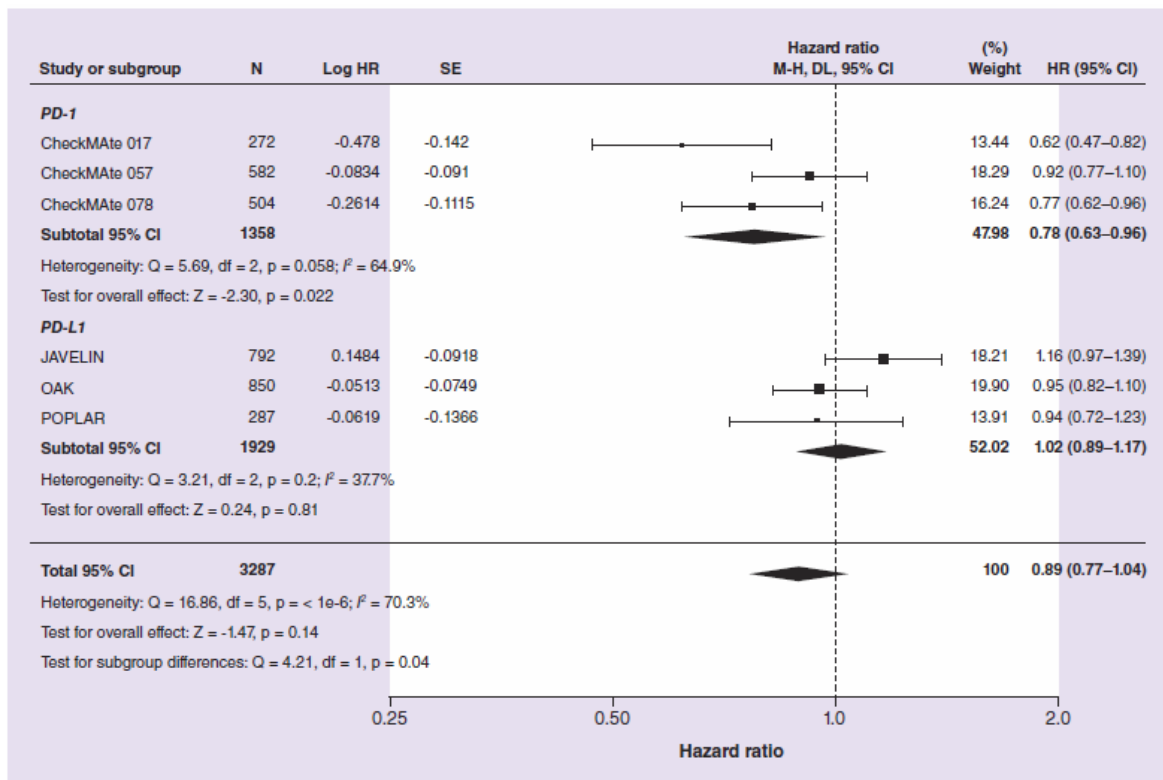


Figure 5. Forest plots of hazard ratios for progression free survival comparing anti PD-1 and anti PD-L1 to docetaxel in non-small-cell lung cancer in all trials but without the KEY010 trial that enrolled only PD-L1-positive patients.
HR: Hazard ratio; SE: Standard error.

Anmerkung/Fazit der Autoren

The advent in clinical practice of ICIs determined a major breakthrough in the battle against solid tumors, including NSCLC. At present, in view of the results obtained in large Phase III studies, two anti-PD-1 (nivolumab and pembrolizumab) and one anti-PD-L1 (atezolizumab) can be used interchangeably in pretreated NSCLC patients. Considering that so far, no published trials have compared anti-PD-1 to anti-PD-L1 therapies, some differences between these agents could emerge from the analysis of the data available in the literature. Our meta-analysis, based on seven studies including more than 4000 patients, as well as confirming the superiority in terms of efficacy and tolerability of ICIs versus docetaxel, would indicate a slight benefit from anti-PD-1 than from anti-PD-L1 inhibitors, always keeping in mind the possible biases of this indirect comparison.

Kommentar zum Review:

- Siehe auch: Khunger, M. et al., 2018 [68] & Tan, P. S. et al., 2018 [102]

Vickers AD et al., 2019 [106].

Relative efficacy of interventions in the treatment of second-line non-small cell lung cancer: a systematic review and network meta-analysis.

Fragestellung

a systematic review and network meta-analysis (NMA) of second-line treatments in all subgroup combinations determined by histology, programmed death ligand 1 (PD-L1) expression, and epidermal growth factor receptor (EGFR) mutation.

Methodik

Population:

- Patients with locally advanced or metastatic NSCLC who had progressed after first-line chemotherapy.

Intervention/Komparator:

- regimens containing the following interventions: docetaxel (any dose), erlotinib (150mg), gefitinib (250mg), gemcitabine (any dose), nintedanib (200mg), nivolumab (3 mg/kg), pembrolizumab (any dose), pemetrexed (500 mg/m²), ramucirumab (10 mg/kg), vinorelbine (any dose), and best supportive care, S-1 (40mg/m²), bevacizumab (15 mg/kg) and pembrolizumab

Endpunkte:

- OS, PFS

Recherche/Suchzeitraum:

- MEDLINE, PubMed, EMBASE, Biosciences Information Service (using the Dialog Platform), Cochrane Library, and abstracts from scientific meetings were searched for RCTs published up to September 2015

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 30 studies containing 17 different treatment regimens

Qualität der Studien:

- The bias assessment showed that a high proportion of studies were open label, with physicians and patients not blinded to treatment.



(nivolumab) studied showed superior efficacy in the populations exhibiting high PD-L1 expression.

Table 2 Summary of interventions that showed a significant ($P < 0.05$) benefit over single-agent docetaxel (75 mg/m^2): fixed-effects NMA

Histology	PD-L1 expression	EGFR mutation	Occurrence (Non-Asian)	Occurrence (Asian)	OS (Hazard ratio NMA)	PFS (Fractional polynomial NMA)
Non-squamous	< 5%	Negative	32.8%	21.2%	Docetaxel + nintedanib: 2.6 (0.1, 5.6) Docetaxel + ramucirumab: 2.3 (0.3, 4.6)	Docetaxel + ramucirumab: 1.2 (0.6, 1.9)
Squamous	< 5%	Negative	21.0%	20.2%	Nivolumab: 5.5 (0.7, 12.4) Docetaxel + ramucirumab: 2.0 (0.3, 4.0)	Nivolumab: 2.6 (0.0, 5.8) ^a Docetaxel + ramucirumab: 1.2 (0.6, 1.9)
Non-squamous	≥ 5%	Negative	20.5%	13.3%	Nivolumab: 12.9 (5.6, 23.8) Docetaxel + nintedanib: 2.6 (0.1, 5.6) Docetaxel + ramucirumab: 2.3 (0.3, 4.6)	Nivolumab: 5.0 (2.2, 8.2) Docetaxel + ramucirumab: 1.2 (0.6, 1.9)
Squamous	≥ 5%	Negative	13.2%	12.7%	Nivolumab 8.0 (1.6, 17.8) Docetaxel + ramucirumab: 2.0 (0.3, 4.0)	Nivolumab: 5.7 (1.8, 10.1) Docetaxel + ramucirumab: 1.2 (0.6, 1.9)
Non-squamous	< 5%	Positive	7.2%	18.8%	Docetaxel + erlotinib: 13.4 (4.8, 27.0) Erlotinib + pemetrexed: 8.0 (0.3, 28.5) Erlotinib: 7.4 (2.5, 14.9) Gefitinib: 4.4 (0.8, 10.5) Docetaxel + nintedanib: 2.6 (0.1, 5.6) Docetaxel + ramucirumab: 2.3 (0.3, 4.6)	Docetaxel + erlotinib: 8.1 (4.9, 10.9) Erlotinib + pemetrexed: 7.0 (1.2, 14.6) Erlotinib: 6.8 (3.4, 11.3) Gefitinib: 5.4 (2.7, 8.6) Docetaxel + ramucirumab: 1.2 (0.6, 1.9)
Squamous	< 5%	Positive	0.5%	1.3%	Docetaxel + erlotinib: 11.9 (4.2, 23.8) Erlotinib: 6.5 (2.2, 13.2) Nivolumab: 5.5 (0.7, 12.4) Gefitinib: 3.9 (0.7, 9.3) Docetaxel + ramucirumab: 2.0 (0.3, 4.0)	Docetaxel + erlotinib: 8.1 (4.9, 10.9) Erlotinib: 6.8 (3.4, 11.3) Gefitinib: 5.4 (2.7, 8.6) Nivolumab: 2.6 (0.0, 5.8) ^a Docetaxel + ramucirumab: 1.2 (0.6, 1.9)
Non-squamous	≥ 5%	Positive	4.5%	11.8%	Docetaxel + erlotinib: 13.4 (4.8, 27.0) Nivolumab: 12.9 (5.6, 23.8) Erlotinib + pemetrexed: 8.0 (0.3, 28.5) Erlotinib: 7.4 (2.5, 14.9) Gefitinib: 4.4 (0.8, 10.5) Docetaxel + nintedanib: 2.6 (0.1, 5.6) Docetaxel + ramucirumab: 2.3 (0.3, 4.6)	Docetaxel + erlotinib: 8.1 (4.9, 10.9) Erlotinib + pemetrexed: 7.0 (1.2, 14.6) Erlotinib: 6.8 (3.4, 11.3) Gefitinib: 5.4 (2.7, 8.6) Nivolumab: 5.0 (2.2, 8.2) Docetaxel + ramucirumab: 1.2 (0.6, 1.9)
Squamous	≥ 5%	Positive	0.3%	0.8%	Docetaxel + erlotinib: 11.9 (4.2, 23.8) Nivolumab 8.0 (1.6, 17.8) Erlotinib: 6.5 (2.2, 13.2) Gefitinib: 3.9 (0.7, 9.3) Docetaxel + ramucirumab: 2.0 (0.3, 4.0)	Docetaxel + erlotinib: 8.1 (4.9, 10.9) Erlotinib: 6.8 (3.4, 11.3) Nivolumab: 5.7 (1.8, 10.1) Gefitinib: 5.4 (2.7, 8.6) Docetaxel + ramucirumab: 1.2 (0.6, 1.9)

Docetaxel = docetaxel (75 mg/m^2) 3 times a week; difference in mean survival relative to docetaxel (75 mg/m^2) after colon with 95% credible intervals in parentheses. Treatments shown in bold indicate relatively better performance in a group; (typically, the highest predicted mean survival) and performed better than one or more other treatments in the same group ($P < 0.05$). Occurrence of each tumor subgroup are only approximate and based on the following: 65% nonsquamous, 35% squamous [5]; non-Asian: 18% EGFR mutation positive in nonsquamous tumors; Asian: 47% EGFR mutation in nonsquamous tumors [76]; 8 times more likely to be EGFR positive if nonsquamous compared to squamous [77] and 38.5% PD-L1 ≥ 5% (combined data from Borghaei et al. [39]; Brahmer et al. [40]). Predictions from the NMA assumed relationships for each factor are the same across any other factor. This allowed predictions to be made across all subgroups, but where subgroups are rare, there may be little actual direct evidence for that patient population
^aBorderline significance ($P = 0.0508$)

Anmerkung/Fazit der Autoren

New treatments for NSCLC are being developed and studied; these treatments often are specific to particular biomarkers. This will add further complexity to NMAs conducted in this disease area. However, the results from this study should help inform the decision-making process for prescribing currently available treatments and could be used to help power future trials. Results also may be used to serve as a reference for the efficacy of existing treatments for patients with a particular tumor type, where only mixed population evidence so far exists. As far as we know, this is the only NMA in which investigators have attempted to model the treatment covariate interactions present in NSCLC for second-line treatment after disease progression has occurred.

Wan N et al., 2019 [107].

A pooled meta-analysis of PD-1/L1 inhibitors incorporation therapy for advanced non-small cell lung cancer.

Fragestellung

This meta-analysis summarized recent developments in four combination regimens of PD-1/L1 inhibitors.

Methodik

Population:

- advanced NSCLC patients

Intervention/Komparator:

- anti-PD1/L1 antibody with CTLA-4 inhibitors/chemotherapy/EGFR-TKIs/IDO inhibitors

Endpunkte:

- ORR, PFS, OS and safety

Recherche/Suchzeitraum:

- PubMed, the Cochrane Library and the Embase database up to July 2018

Qualitätsbewertung der Studien:

- Risks of bias within studies without comparable arms were assessed using the methodological item for non-randomized studies (MINORS) / Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- Seventeen trials / 1,222 NSCLC patients
- Six studies involved research into the combination therapy of anti-PD-1/L1 antibody and chemotherapy involving 700 patients. Four studies reported the combination therapy of anti-PD-1/L1 antibody with EGFR-TKIs, and 95 patients were enrolled. One study reported the combination of pembrolizumab with epacadostat involving 43 patients.

Qualität der Studien:

Table S1 Bias risk evaluation of the studies without comparable arms in the meta-analysis

Reference	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow up less than 5%	Prospective calculation of the study size	Score
Patnaik [2015] ¹	1	2	0	2	0	0	1	1	7
Gubens [2016] ²	1	2	0	2	0	2	2	1	10
Antonia [2014] ³	1	2	0	2	0	2	2	1	10
Hellmann [2017] ⁴	2	2	2	2	0	2	2	2	14
Antonia [2016] ⁵	2	2	1	2	0	2	2	2	13
Gadgeel [2016] ⁶	1	2	0	2	0	2	2	1	10
Kanda [2016] ⁷	2	2	2	2	0	2	2	1	13
Liu [2015] ⁸	1	2	0	2	0	0	2	1	8
Rizvi [2016] ⁹	2	2	2	2	0	2	2	2	14
Gettinger [2014] ¹⁰	1	2	0	2	0	2	2	1	10
Gibbons [2016] ¹¹	1	2	0	2	0	0	2	1	8
Ma [2016] ¹²	1	2	0	2	0	2	2	2	11
Ahn [2016] ¹³	2	2	0	2	0	0	2	1	9
Gangadhar [2017] ¹⁴	1	1	0	2	0	0	2	1	7

Table S2 Bias risk evaluation of the randomized controlled trials included in the meta-analysis

Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
Hellmann [2018] ¹⁵	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	High risk	Unclear risk
Langer [2016] ¹⁶	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Unclear risk
Gandhi [2018] ¹⁷	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	unclear risk

Studienergebnisse:

- Pooled ORR of combination therapy for first/second or more line therapy
 - Second-Line Therapy: A total of 5 eligible trials^{24,27,28,34,39} involving 125 patients were included to evaluate the efficacy of anti-PD -1/L1 antibody combination therapy in the

second or more line setting for NSCLC patients, and the ORR ranged from 17% to 55%. The combined ORR was 32.0% (95% CI: 23–42%) (Figure 4B). The pooled ORR of anti-PD-1/L1 antibody combination therapy with anti-CTLA-4 antibody/chemotherapy/EGFR-TKIs/IDO inhibitors in the second or more line setting for NSCLC patients was 36% (95% CI: 8–65%), 17% (95% CI: –13–46%), 39% (95% CI:19–59%) and 35% (95% CI:20–50%), respectively.

- The pooled 6-month progression-free survival rate (6m PFSr) and 1-year overall survival rate (1y OSr) for combination therapy of PD-1/L1 inhibitors with CTLA-4 inhibitors or chemotherapy were 35% or 65% (6m PFSr) and 31% or 70% (1y OSr) respectively. Anti-PD-1/L1 drugs combined with anti-CTLA-4 drugs exhibited a more potent efficacy on PD-L1 positive patients (OR=0.33, 95%CI: 0.12–0.88). This trend was not observed in patients receiving combination therapy of PD-1/L1 inhibitors with chemotherapy (OR=0.96, 95%CI: 0.51–1.78).

Anmerkung/Fazit der Autoren

In summary, the four combination regimens involving PD-1/L1 inhibitors with CTLA-4 inhibitors, chemotherapy, EGFR-TKIs and IDO inhibitors were potential treatment strategies and well tolerated for NSCLC patients. Further, the therapy lines and PD-L1 expression status were correlated with treatment efficacy.

Kommentare zum Review

- Gemischte Population u.a. hinsichtlich Linie und advanced/metastasiert

Zhang L et al., 2020 [115].

The Effect of Next-Generation TKI in Non-Small Cell Lung Cancer after Failure of First-Line Treatment: a Meta-Analysis.

Fragestellung

We performed this meta-analysis by including relevant trials which have been designed to determine its efficacy and toxicity with EGFR TKIs and focus primarily on whether next-generation EGFR-TKIs was superior in pre-treated NSCLC with first-line EGFR-TKI therapy.

Methodik

Population:

- Patient with treatment-refractory advanced NSCLC after failure of first-generation EGFR-TKIs

Intervention/Komparator:

- next-generation EGFR-TKIs vs. chemotherapy

Endpunkte:

- overall survival, progression-free survival, tumor response, toxicity

Recherche/Suchzeitraum:

- Pubmed, Embase, and Cochrane Database of Systematic Reviews from their inception to September, 2018

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- three RCTs

Charakteristika der Population:

The Effect of Next-Generation TKI in Non-Small Cell Lung Cancer after Failure of First-Line Treatment: a...

Table 1 Detailed description of included trails

Study	Year	Treatment regimen		Patients number		Age(years)	
		Study arm	Comparative arm	Study arm	Comparative arm	Study arm	Comparative arm
V.A. Miller	2012	afatinib plus best supportive care	Placebo plus best supportive care	390	195	58	59
T.S. Mok	2016	osimertinib	intravenous pemetrexed plus either carboplatin or cisplatin	279	140	62	63
Keke Nie	2018	osimertinib	docetaxel plus bevacizumab	74	73	49.4	48.6

Qualität der Studien:

- keine weiteren Angaben über Studiendesign hinaus

Studienergebnisse:

- PFS: benefit was found between next-generation EGFR-TKIs and chemotherapy (OR = 0.34,95%CI = 0.29–0.40, P < 0.00001).
- OS: no significant statistical difference of OS when comparing the two groups
- ORR: there is advantage between two groups (OR = 10.48,95%CI = 3.87–28.34, P < 0.00001)
- AEs: diarrhoea, rash/acne, nausea, vomiting, and anemia were included → data did not reach a statistically significant level (P>0.05).
- DCR: data did show advantage in the next generation EGFR-TKIs groups (OR = 6.03,95%CI = 4.41–8.25, P < 0.00001)

Anmerkung/Fazit der Autoren

Acquired resistance refers to disease progression after response to first-generation EGFR-TKI is complicated; and the survival result is gloomy if resistance occurs. Our data showed that, next-generation EGFR-TKI could prolong PFS and better response rate in NSCLC patients after failed to firstgeneration EGFR-TKI.

Relevant clinical studies have been developed to study the paradigm of “personalized” medicine in the treatment of NSCLC, at least in a subset of patients with oncogenic driven; examples include mutations in the EGFR gene. From an efficacy standpoint, further trials into bio- markers that will benefit patients by subtype, which can be instructive in driving treatment decisions,

while conferring with manageable adverse events. It is important to consider the risk of AEs when choosing treatment, particularly in patients with underlying immune dysfunction.

Armoiry X et al., 2018 [4].

Comparative efficacy and safety of licensed treatments for previously treated non-small cell lung cancer: A systematic review and network meta-analysis

Fragestellung

This systematic review with network meta-analysis compared the efficacy and safety of currently licensed second-line treatments in patients with late stage non-small cell lung cancer (NSCLC).

Methodik

Population:

- advanced/metastatic NSCLC (IIIB or IV) NSCLC of squamous, non-squamous, or mixed histology who experienced failure to prior first-line chemotherapy → Hinweis: Study populations had to have negative or predominantly negative expressions of ALK and EGFR

Intervention/Komparator:

- Docetaxel (DOC), Pemetrexed (PEM), Ramucirumab plus docetaxel (RAM + DOC), Erlotinib (ERL), Nintedanib plus docetaxel (NINTE + DOC), Afatinib (AFA), Nivolumab (NIVO), Pembrolizumab (PEMBRO), and Atezolizumab (ATEZO)

Endpunkte:

- overall survival (OS), progression-free survival (PFS), and drug-related grade 3±5 adverse-events (AEs)

Recherche/Suchzeitraum:

- from January, 2000 to July, 2017

Qualitätsbewertung der Studien:

- Cochrane RoB tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 RCTs (7,581 participants) comparing nine drugs
- Six RCTs included only people receiving second-line treatment, while four others included those receiving both second- and third-lines

Charakteristika der Population:

- All studies included predominantly people with stage IV NSCLC and performance status 1.

Qualität der Studien:

- Nine studies were considered at high risk of bias for PFS and OS (due to the lack of blinding of participants and personnel). The five RCTs evaluating immunotherapies were open-label and therefore were rated as high-risk on the domain of performance bias. The only study at

low RoB for all the domains was LUME-LUNG 1. The majority of studies were rated as high-risk on 'other domains of bias' due to being funded by industry.

Studienergebnisse:

- Overall survival:
 - Four drugs (NIVO, ATEZO, PEMBRO, and RAMU+DOC) showed a significant improvement on OS compared to DOC in head-to-head comparisons.

OS-All histologies

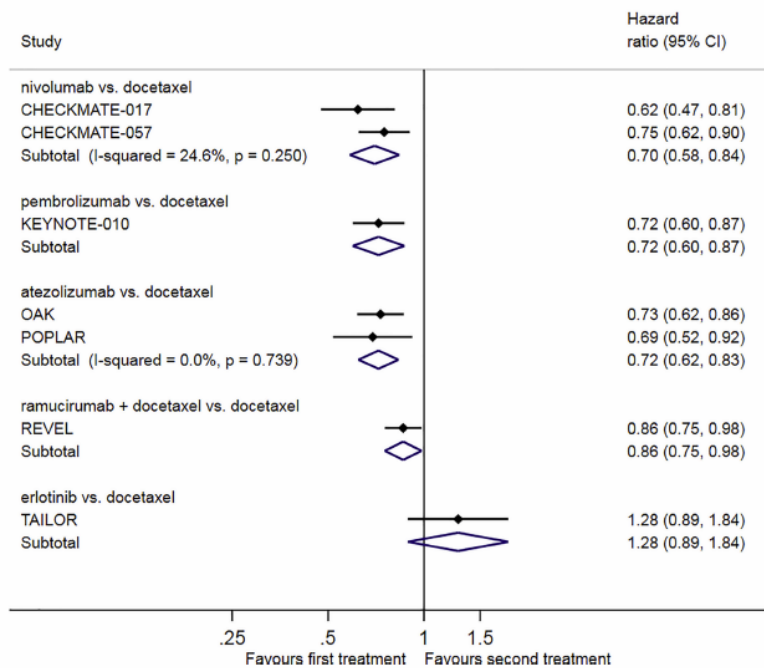


Fig 3. Pairwise meta-analyses, OS in all-histology NSCLC.

- Indirect comparisons of drugs superior to DOC showed greater SUCRA values for the checkpoint inhibitors NIVO (0.82), ATEZO (0.77), PEMBRO (0.77) than for RAMU+DOC (0.42). There was no significant difference in OS across three highest ranking drugs (HR = 0.98, 95% CI 0.79, 1.21 for NIVO vs ATEZO; HR = 0.98, 95% CI 0.77, 1.25 for NIVO vs PEMBRO).
- Progression-free survival:
 - In head-to-head comparisons, only RAMU+DOC showed a significant improvement in PFS compared to DOC. Only the RAMU+DOC vs ERLO and NIVO vs ERLO indirect comparisons reached statistical significance. The SUCRA rankings suggested RAMU+DOC (0.84) as the best intervention followed by NIVO (0.81), PEMBRO (0.57), ATEZO (0.45), DOC (0.31) and ERLO (0.02) which ranked last.
- Drug-related grade 3±5 adverse events:
 - Direct comparisons showed significantly reduced risk of drug-related grade 3±5 AE with NIVO, ATEZO, PEMBRO, and ERLO compared to DOC alone. The same drugs were associated with reduced risk of these AEs compared to RAMU+DOC in indirect comparisons.
 - The SUCRA values for the checkpoint inhibitors were higher (range: 0.63±1.00) than for ERLO (0.49). Of the three highest ranking drugs (NIVO, ATEZO, PEMBRO), the safety

profile of NIVO was significantly better than that of ATEZO (RR = 0.55, 95% CI 0.38, 0.79) and PEMBRO (0.52, 95% CI 0.34, 0.81).

- Discontinuation due to drug-related AE:
 - No NMA could be conducted for this outcome, because unlike for the previous outcome the RR estimates from direct comparisons were not stable across different points of study follow-up.
- Overall results (cluster rank analysis):
 - Overall, NIVO, ATEZO and PEMBRO exhibited dominance in efficacy and safety over alternative therapies. According to the cluster rank analysis, NIVO was the drug with both the highest probability of being the most effective (overall survival) and the safest (drug-related grade 3±5 AEs) followed by ATEZO and PEMBRO.
- Efficacy outcomes by histology subgroups:
 - The NMA for safety outcomes could not be performed due to sparse data.
 - Non-squamous histology:

Based on the SUCRA rankings for OS), checkpoint inhibitors (PEMBRO, ATEZO, and NIVO) were the best interventions (0.94, 0.75, and 0.67, respectively) followed by PEM (0.59), NINTE + DOC (0.46), RAMU+DOC (0.46), and DOC (0.15), with ERLO (0.0) ranking the last.

Among the four drugs with the highest rankings on OS, no significant difference was observed.

For PFS, the network plot included one closed loop allowing a mixed treatment comparison between DOC, ERLO, and PEME. There was no evidence of inconsistency for the mixed treatment comparison (DOC, ERLO, PEME comparisons) within this loop (p = 0.07).

The SUCRA rankings from the NMA suggested that RAMU+DOC (0.85) and NINTE+DOC (0.83) were the best interventions followed by PEMBRO (0.58) and NIVO (0.49), PEME (0.49), and DOC (0.16), with ERLO (0.10) ranking the last. Among the four drugs with the highest rankings on PFS, no significant difference was observed.

Anmerkung/Fazit der Autoren

In this review, we advanced the existing knowledge by comparing drugs approved in people with non-specific late-stage NSCLC. Our results indicate that the use of immunotherapies in people diagnosed with non-specific late stage NSCLC should be promoted. Amongst our included studies, more than 3,500 patients received licensed dosing of DOC, which proved relatively unsuccessful on both survival and safety. The use of DOC may now be judged irrelevant as a comparator intervention for approval of new drugs for second line treatment of NSCLC.

Wu D et al., 2017 [110].

Which treatment is preferred for advanced non-small-cell lung cancer with wild-type epidermal growth factor receptor in second-line therapy? A meta-analysis comparing immune checkpoint inhibitor, tyrosine kinase inhibitor and chemotherapy

Fragestellung

We compared the efficacy of PD-1/PD-L1 antibody, first-generation EGFR-TKI and chemotherapy in second- or third-line setting with Bayesian indirect method that allowed for combining direct and indirect evidence, aiming to identify the optimum treatment that could provide best survival benefit for advanced NSCLC patients with WT EGFR tumors.

Methodik

Population:

- pre-treated patients with advanced NSCLC, defined as unresectable locally advanced, metastatic or recurred disease (stage IIIB or IV).

Intervention + Komparator:

- two or more treatments among standard chemotherapy, first-generation EGFR-TKI and PD-1/PD-L1

Endpunkt:

- hazard ratios (HRs) with 95% confidence intervals (CIs) for OS and/or PFS

Recherche/Suchzeitraum:

- PubMed, Cochrane databases and EMBASE January 2017, with no date and language restriction

Qualitätsbewertung der Studien:

- Cochrane collaboration method

Ergebnisse

Anzahl eingeschlossener Studien:

- 12 open-labeled, randomized Phase II/III trials accruing 6462 patients with advanced NSCLC were finally included in this meta-analysis. 3341 patients bearing WT EGFR tumors

Charakteristika der Population:

- Eastern Cooperative Oncology Group or World Health Organization performance status of 0 to 2
- All the four trials containing PD-1/PD-L1 antibody arm used FDA-approved dose. Three of them were performed in second- or third-line setting, the other one were second- setting [26].
- All 12 trials containing chemotherapy arm used recommended drugs (single-agent docetaxel or pemetrexed is standard second- or higher- line treatment) with standard dosing schedule.
- All the 8 trials containing EGFR-TKI arm used standard dosing schedule (erlotinib, 150 mg orally daily; gefitinib, 250 mg orally daily). Among these trials, five were second-line setting, and three were second- or third-line setting.
- Five trials majorly comprised of white patients, while the other three majorly included Asian patients.

Qualität der Studien:

- The included trials were overall low risk

- Sequence was adequately generated in all trials.
- Allocation concealment was adequately performed in nine trials, not detailed in one trials and undone in two trials.
- Though all trials were designed as open-labeled, six of them blinded assessment of outcome by independent, central radiologic reviews or independent review committee.
- The reasons for excluding patients in all trials were sufficient and ITT principle was followed. No evidence of selective reporting was found.
- Additionally, other source of bias was found in two trials: one were halted prematurely, two had biased baseline characteristics, and the other one had imbalanced number of patients underwent crossover.

Studienergebnisse:

Overall survival

- no evidence of significant inter-study heterogeneity for OS or PFS was identified ($I^2 = 0\%$ and 27% , respectively).
- The pooled fixed-effect models showed that treatment of PD-1/PDL1 antibody was more effective in improving OS and PFS than chemotherapy in WT EGFR patients, with an estimated HR of 0.67 (95% CI 0.60-0.75, $p < 0.001$)
- no significant difference for OS was identified between chemotherapy and EGFR-TKI.

Progression-free survival

- 9 out of 12 trials accruing 2454 patients.[17-19, 24, 26, 28-30, 32, 33]
- Treatment of PD-1 antibody significantly improved PFS compared with chemotherapy (HR 0.83 95% CI 0.73-0.95, $p = 0.007$)
- treatment of chemotherapy significantly improved PFS compared with TKI (HR 0.75 95% CI 0.66-0.84, $p < 0.001$).

Subgroup analysis

- there was a trend to favor chemotherapy than TKI in second-line setting, though the p value did not reach a significance threshold (HR 0.85, 95% CI 0.71-1.01, $p = 0.06$).

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Anmerkung/Fazit der Autoren

For pretreated WT EGFR patients, PD-1/PD-L1 antibody can be a preferable option. For the ones who are not candidates for PD-1/PD-L1 antibody therapy, chemotherapy is preferred. TKI may be only considered for the ones who have bad performance status.

Kommentare zum Review

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

Créquit P et al., 2017 [13].

Comparative efficacy and safety of secondline treatments for advanced non-small cell lung cancer with wild-type or unknown status for epidermal growth factor receptor: a systematic review and network metaanalysis.

Fragestellung

to assess the comparative effectiveness and tolerability of all second-line treatments for advanced NSCLC with wild-type or unknown status for EGFR by a systematic review and network meta-analysis.

Methodik

Population:

- patients with advanced NSCLC (stage IIIB unsuitable for radical radiotherapy or surgery and stage IV) with wild-type or unknown status for EGFR

Intervention/Komparator:

- Indirect comparison to assess second-line treatments

- Trials in which patients in the control arm received chemotherapy (e.g., docetaxel or pemetrexed) at the investigators' discretion were included for the secondary analysis considering treatment categories. We also considered trials including both second- and third-line therapy, because there is no clinical reason to presume that these minority patients in third-line could not be randomized to any of the treatments. If a multi-arm trial compared one drug to two different dosages of another drug, we retained the usual treatment dosage or that corresponding to the 3-week scheme of administration.

Endpunkte:

- OS, PFS, objective response (ObR), SAEs, QoL

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, CENTRAL, ClinicalTrials.gov, and the US Food and Drug Administration website, as well as other sources, were searched for available reports up to June 6, 2017

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 102 RCTs involving 36,058 patients

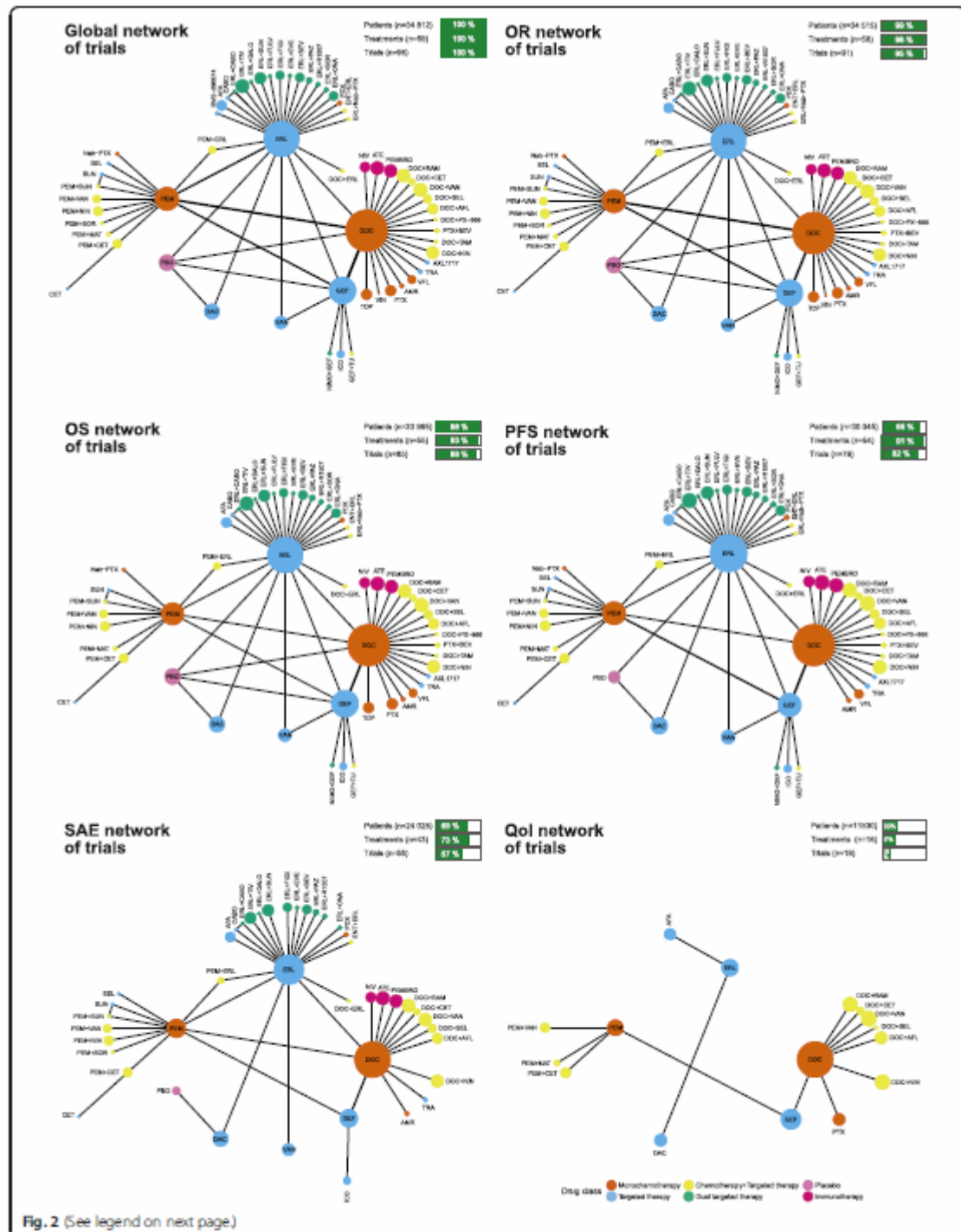


Fig. 2 Network graphs of trials assessing second-line treatments in advanced NSCLC with wild-type or unknown status for EGFR for all eligible trials, ObR, OS, PFS, SAEs, and QoL. The five trials with chemotherapy (i.e., docetaxel or pemetrexed) at the investigators' discretion and the HANSHIN trial were excluded from these networks. The thickness of the lines is proportional to the number of trials evaluating each comparison. The size of the nodes is proportional to the number of patients allocated to the corresponding treatment.

Charakteristika der Population:

- 62% male, median age 61 years, 81% with stage IV cancer, 80% smokers, and 92% with performance status 0–1

Qualität der Studien:

- Only 47 trials (46%) described an adequate random sequence generation and 37 (36%) an adequate treatment allocation concealment. Patients and care providers were blinded in 29 trials (28%), and outcome assessors in 41 trials (40%).

Studienergebnisse:

- *Note:* Half of the trials reported safety outcomes and less than 20% quality of life.
- For OS
 - nivolumab was more effective than docetaxel (hazard ratio (HR) 0.69, 95% credible interval (CrI) 0.56–0.83), pemetrexed (0.67, 0.52–0.83), erlotinib (0.68, 0.53–0.86), and gefitinib (0.66, 0.53–0.83).
 - Pembrolizumab, atezolizumab, and pemetrexed plus erlotinib were also significantly more effective than docetaxel, pemetrexed, erlotinib, and gefitinib.
- For PFS
 - erlotinib plus cabozantinib was more effective than docetaxel (HR 0.39, 95% CrI 0.18–0.84), pemetrexed (0.38, 0.18–0.82), erlotinib (0.37, 0.18–0.78), and gefitinib (0.38, 0.18–0.82).
 - Cabozantinib and pemetrexed plus erlotinib were also significantly more effective than the four recommended treatments.
- For ObR
 - no treatment was significantly more effective. The effectiveness of the four recommended treatments was similar and they were ranked among the 25 less-effective treatments.
- For safety, evidence is insufficient to draw certain conclusions.

Anmerkung/Fazit der Autoren

Our comparative effectiveness review of second-line treatments for advanced NSCLC with wild-type or unknown status for EGFR compared 61 treatments assessed in 102 trials (36,058 patients). Our NMA revealed that immunotherapy (nivolumab, pembrolizumab, and atezolizumab) and pemetrexed plus erlotinib might be more efficacious for OS than the four recommended treatments (docetaxel, pemetrexed, erlotinib, and gefitinib) and highlighted the relatively poor performance of these four treatments. The assessment of safety and patient reporting outcomes was uncertain because of a lack of reporting.

Kommentare zum Review

- The authors did not distinguish between the different types of data; namely, they considered the 11 trials (11%) only identified through a conference abstract as the same level of evidence as published trials in the quantitative analysis
- No formal assessment of the assumption of transitivity possible because, for most of treatment comparisons, there are very few trials included

Su Q et al., 2017 [101].

PD-1/PD-L1 antibodies efficacy and safety versus docetaxel monotherapy in advanced NSCLC patients after first-line treatment option: systems assessment

Ähnliche Reviews zu dem Thema:

- **Jiang Qi et al., 2018 [64].** Anti-PD-1/PD-L1 antibodies versus docetaxel in patients with previously treated non-small-cell lung cancer
- **Huang G et al., 2018 [60].** The efficacy and safety of anti-PD-1/PD-L1 antibody therapy versus docetaxel for pretreated advanced NSCLC: a meta-analysis
- **Zhuansun Y et al., 2017 [129].** Anti-PD-1/PD-L1 antibody versus conventional chemotherapy for previously-treated, advanced non-small-cell lung cancer: a meta-analysis of randomized controlled trials
- **Ramos-Esquivel A et al., 2017 [95].** Anti-PD-1/anti-PD-L1 immunotherapy versus docetaxel for previously treated advanced non-small cell lung cancer: a systematic review and meta-analysis of randomised clinical trials
- **Ellis PM et al., 2017 [16].** Immune Checkpoint Inhibitors for Patients With Advanced Non-Small-Cell Lung Cancer: A Systematic Review
- **Zhou GW et al., 2016 [125].** Anti-PD-1/PD-L1 antibody therapy for pretreated advanced nonsmall-cell lung cancer A meta-analysis of randomized clinical trials
- **Ru CH et al., 2018 [97].** Efficacy and Safety of Addition of Anti-PD1 to Chemotherapy in Treatment of Non-Small Cell Lung Cancer
- **Lee CK et al., 2018 [71].** Clinical and Molecular Characteristics Associated With Survival Among Patients Treated With Checkpoint Inhibitors for Advanced Non-Small Cell Lung Carcinoma: A Systematic Review and Meta-analysis
- **Jiang T et al., 2018 [65].** Impact of Clinicopathologic Features on the Efficacy of PD-1/PD-L1 Inhibitors in Patients With Previously Treated Non-small-cell Lung Cancer
- **Liu J et al., 2018 [82].** Efficacy and safety of PD1/PDL1 blockades versus docetaxel in patients with pretreated advanced non-small-cell lung cancer: a meta-analysis
- **Wang S et al., 2018 [109].** Efficacy and safety of immune checkpoint inhibitors in non-small cell lung cancer

Fragestellung

We conducted a meta-analysis of randomized clinical trials (RCTs) to determine the efficacy and safety of PD-1 or PD-L1 antibodies compared with standard second-line therapy docetaxel alone and to assess the possible association between the level of PD-L1 and the prognosis of PD-1/PD-L1 antibodies in patients of advanced NSCLC.

Methodik

Population:

- histological confirmed SQ and/or NSQ non-small cell lung cancer

Intervention:

- PD-1/PD-L1

Komparator:

- Docetaxel

Endpunkt:

- OS, PFS, ORR, PD-L1 expression rate and adverse events (AEs) with grades 1-4 and 3/4.

Recherche/Suchzeitraum:

- Cochrane library, Embase, PubMed, China hospital knowledge database, China National Knowledge Infrastructure, Wangfang Data and Weipu Data from January 1990 to January 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 RCTs (n=3579)

Charakteristika der Population:

- one had data from SQ-NSCLC patients, while another one had data from NSQ-NSCLC patients, and the remaining three studies had data from both SQ and NSQ NSCLC patients.

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

study[year]	Study type	histology	endpiont	Treatment arms	Patients	CR+PR(%)	OS(m)	PFS(m)
Borghaei et al. [2015]	RCT III	NSQ	OS	nivolumab 3mg/kg q2w	292	56(19%)	12.2	2.3
				DOX 75mg/m2 q3w	290	36(12%)	9.4	4.2
Brahmer et al. [2015]	RCT III	SQ	OS	nivolumab 3mg/kg q2w	135	27(20%)	9.2	3.5
				DOX 75mg/m2 q3w	137	12(9%)	6.0	2.8
Fehrenbacher[2016]	RCT II	SQ and NSQ	OS	atezolizumab 1200mg q3w	144	21(14.6%)	12.6	2.7
				DOX 75mg/m2 q3w	143	21(14.7%)	9.7	3.0
Herbst et al. [2015]1	RCT III	SQ and NSQ	OS	pembrolizumab 2mg/kg q2w	344	62(18.0%)	10.4	3.9
				DOX 75mg/m2 q3w	343	32(9.3%)	8.5	4.0
Herbst et al. [2015]2	RCT III	SQ and NSQ	OS	pembrolizumab 10mg/kg q2w	346	64(18.5%)	12.7	4.0
				DOX 75mg/m2 q3w	343	32(9.3%)	8.5	4.0
Rittmeyer et al.[2017]	RCT II	SQ and NSQ	OS	atezolizumab 1200mg q3w	425	58(13.6%)	13.8	2.8
				DOX 75mg/m2 q3w	425	57(13.4%)	9.6	4.0

RCT: randomized controlled trials; SQ: Squamous non small cell lung cancer; NSQ: Non-squamous non small cell lung cancer; DOX: docetaxel

Qualität der Studien:

	Rittmeyer 2017	Herbst 2015	Fehrenbacher 2016	Brahmer 2015	Borghaei 2015	
Random sequence generation (selection bias)	+	+	+	+	?	
Allocation concealment (selection bias)	-	-	-	?	?	
Blinding of participants and personnel (performance bias)	?	-	?	?	?	
Blinding of outcome assessment (detection bias)	+	+	+	+	+	
Incomplete outcome data (attrition bias)	+	+	+	?	?	
Selective reporting (reporting bias)	+	+	+	+	+	
Other bias	?	?	?	?	?	

A

Studienergebnisse:

Overall survival:

- Compared with docetaxel, we observed a significant decrease (31%) in the risk of death in PD-1/ PD-L1 antibody group (HR 0.69, 95% CI: 0.63-0.75, $p < 0.001$; $I^2 = 0\%$).

Progression free survival analysis

- The PD-1/PD-L1 antibodies displayed significant improvement in PFS of advanced NSCLC patients, with HR value of 0.87 (95% CI: 0.80-0.94; $p < 0.001$).

Overall response rate (ORR)

- overall RR value of 1.53, (95% CI: 1.16-2.01, $P = 0.003$; $I^2 = 59.2\%$) in favor of PD-1/PD-L1 antibodies

Adverse events analysis

- PD-1/PD-L1 antibodies showed significant increase in the incidence rate of grade 1-4 adverse events (AEs). The overall RR value for AE was 0.77 (95% CI: 0.74-0.79; $P = 0.000$).
- Patients receiving PD-1/PD-L1 antibodies showed significant decrease in grade 3-4 AEs with overall RR value of 0.33; 95% CI: 0.22-0.51, $P < 0.001$.

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Anmerkung/Fazit der Autoren

Our meta-analysis study indicated that PD-1/PD-L1 antibodies treatment indeed has beneficial effects on advanced NSCLC patients in comparison to docetaxel monotherapy, along with displaying few adverse events.

Kommentare zum Review

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

Passiglia F et al., 2018 [90].

Looking for the best immune-checkpoint inhibitor in pre-treated NSCLC patients: An indirect comparison between nivolumab, pembrolizumab and atezolizumab

Ähnliche Reviews zu dem Thema:

- **You W et al., 2018 [113].** A Network Meta-analysis Comparing the Efficacy and Safety of Anti-PD-1 with Anti-PD-L1 in Non-small Cell Lung Cancer
- **Kim J et al., 2018 [69].** Relative Efficacy of Checkpoint Inhibitors for Advanced NSCLC According to Programmed Death-Ligand-1 Expression: A Systematic Review and Network Meta-Analysis

Fragestellung

In absence of direct comparisons among these ICIs, it remains crucial identify any differences in both efficacy and toxicity profiles which may help clinicians to select the best drug for each patient. Therefore, we performed a systematic review and meta-analysis of all Phase II/III randomized clinical trials comparing PD1/PDL1 inhibitors versus docetaxel in pre-treated NSCLC patients.

Methodik

Population:

- Advanced NSCLC

Intervention:

- PD1/PDL1 inhibitors: nivolumab, pembrolizumab and atezolizumab

Komparator:

- Docetaxel

Endpunkte:

- OS, PFS, ORR, G3–G5 AEs, pneumonitis and discontinuation rate

Recherche/Suchzeitraum:

- Medline (PubMed), Embase-databases and Cochrane-Library up to February 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 RCTs

Charakteristika der Population:

- Siehe Su Q et al., 2017 [101] oder Zhao Q et al., 2018 [128].

Qualität der Studien:

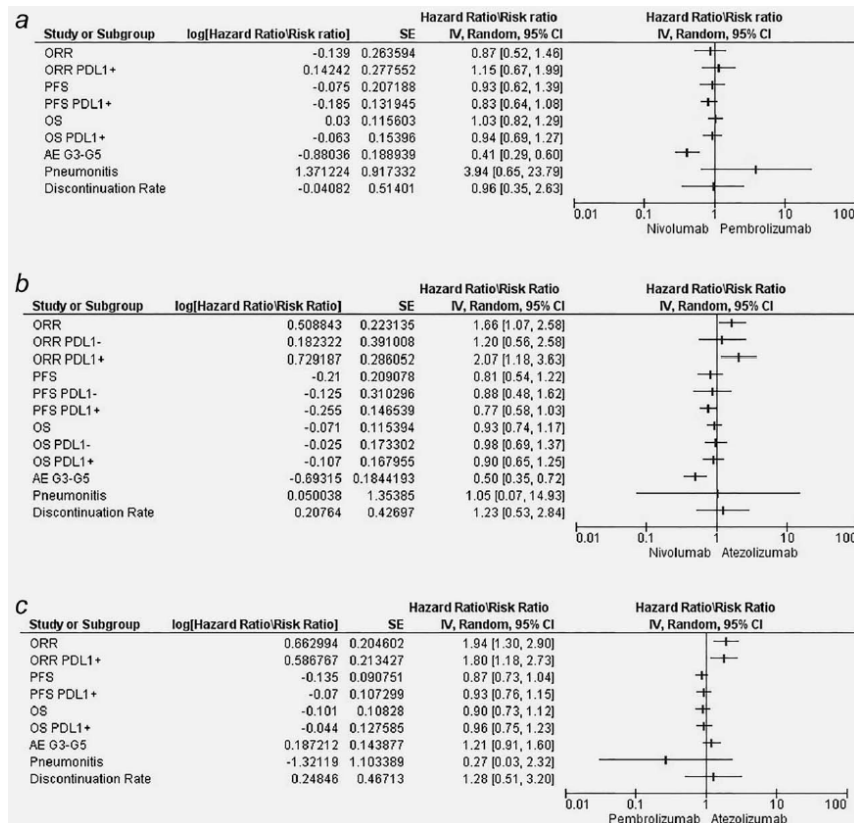
Poplar	OAK	KEYNOTE-010	Check-Mate057	Check-Mate017	
+	+	+	?	?	Random sequence generation (selection bias)
+	+	+	?	?	Allocation concealment (selection bias)
-	-	-	-	-	Blinding of participants and personnel (performance bias)
?	?	+	?	?	Blinding of outcome assessment (detection bias)
+	+	+	+	+	Incomplete outcome data (attrition bias)
+	+	+	+	+	Selective reporting (reporting bias)

Studienergebnisse:

- Direct comparisons:
 - Nivolumab versus docetaxel 2 RCTs (Check-Mate017 and Check-Mate057) 854 patients: statistically significant differences in favor of nivolumab in terms of both OS (HR 0.68, 95% CI 0.57–0.80) and ORR (RR 1.68, 95% CI 1.21–2.34). PFS was not significantly different. nivolumab was associated with a lower incidence of both G3/G5 AEs (RR 0.17, 95% CI 0.13–0.24) and treatment discontinuation (RR 0.48, 95% CI 0.25–0.94) compared to Docetaxel. Conversely a significant higher risk of pneumonitis was observed in the nivolumab arm as compared with chemotherapy arm (RR 9.22, 95% CI 1.73–49.10). Splitting ORR, PFS and OS according to the tumor PD-L1 expression, we also noted a significant benefit in favor of nivolumab for all the above mentioned endpoints in the PD-L1+ population, whereas no benefit has been observed in the PD-L1- patients.
 - Pembrolizumab versus docetaxel: 1 Phase III KEYNOTE-010 with 1,034 patients, 3 arms: pembrolizumab was significantly superior to docetaxel in OS (HR 0.66, 95% CI 0.57–0.77), PFS (HR 0.83, 95% CI 0.74–0.94) and ORR (RR 1.96, 95% CI 1.48–2.59). As for nivolumab, pembrolizumab cohort reported a significant benefit regarding the risk of G3/G5 AEs (RR 0.41, 95% CI 0.33–0.50) while the incidence of pneumonitis was significantly higher as compared to docetaxel arm (RR 2.34, 95% CI 1.21–4.52)
 - Atezolizumab versus docetaxel: 2 Trials with 1137 NSCLC Patients: no significant improvements in terms of ORR and PFS, while only OS resulted significantly longer with atezolizumab in the overall population (HR 0.73, 95% CI 0.63–0.85), regardless of tumor PD-L1 expression status. significant lower incidence of G3/G5 AEs (RR 0.34, 95% CI

0.28–0.41) and discontinuation rate (RR 0.43, 95% CI 0.30–0.62), and an increased risk for pneumonitis (RR 8.77, 95% CI 1.12–68.92)

- Indirect Comparisons: Forest plots for all indirect comparisons among immunecheck-point inhibitors in pre-treated NSCLC patients: nivolumab vs. pembrolizumab (a); nivolumab vs. atezolizumab (b); pembrolizumab vs. atezolizumab (c).



Anmerkung/Fazit der Autoren

However, despite some limitations, the results of our meta-analysis first revealed some additional differences among these agents, which could guide clinicians in their treatment decisions. Particularly PD1 inhibitors nivolumab and pembrolizumab could be preferred options for patients with higher tumor burden or symptomatic disease, to whom the decrease of tumor volume represents a primary objective. Nivolumab seems to be generally better tolerated than the other two agents.

Considering the limitations and the potential bias related to indirect comparisons, these evidences should not be considered as a decisional tool to establish the superiority of one drug to another. However, they could only serve as a scientific support to help the oncologists in their clinical decisions in order to select the best drug for each patient.

Zhao Q et al., 2018 [121].

Anti-PD-1/PD-L1 Antibody Therapy for Pretreated Advanced or Metastatic Nonsmall Cell Lung Carcinomas and the Correlation between PD-L1 Expression and Treatment Effectiveness: An Update Meta-Analysis of Randomized Clinical Trials

Ähnliche Reviews zu dem Thema:

- **Abdel-Rahman O et al., 2016 [1].** Correlation between PD-L1 expression and outcome of NSCLC patients treated with anti-PD-1/PD-L1 agents: A meta-analysis.
- **Huang Q et al., 2018 [62].** Impact of PD-L1 expression, driver mutations and clinical characteristics on survival after anti-PD-1/PD-L1 immunotherapy versus chemotherapy in non-small-cell lung cancer: A meta-analysis of randomized trials

Fragestellung

The aim of this meta-analysis is to further evaluate the efficacy and safety of anti-PD-1/PD-L1 agents in advanced NSCLC patients. A subgroup analysis was performed to determine the correlation between PD-L1 expression level and clinical outcome and to establish guidelines for PD-L1 antibody treatment in patients with low or negative PD-L1 levels.

Methodik

Population:

- Pretreated advanced or metastatic NSCLC

Intervention:

- nivolumab” or “pembrolizumab,” or “atezolizumab.”

Komparator:

- Docetaxel

Endpunkte:

- primary endpoint was overall survival rate.
- Secondary endpoints included PFS, objective response rate (ORR), and safety (grade 3-5 adverse events (AEs), including fatigue, decreased appetite, nausea, vomiting, diarrhea, constipation, anemia, neutropenia, and febrile neutropenia)

Recherche/Suchzeitraum:

- PubMed, Embase, and Cochrane Library electronic databases up to March 2017

Qualitätsbewertung der Studien:

- 5-item Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 RCTS with 3,025 patients

Charakteristika der Population:

TABLE 2: Baseline characteristics of RCTs included in the analysis.

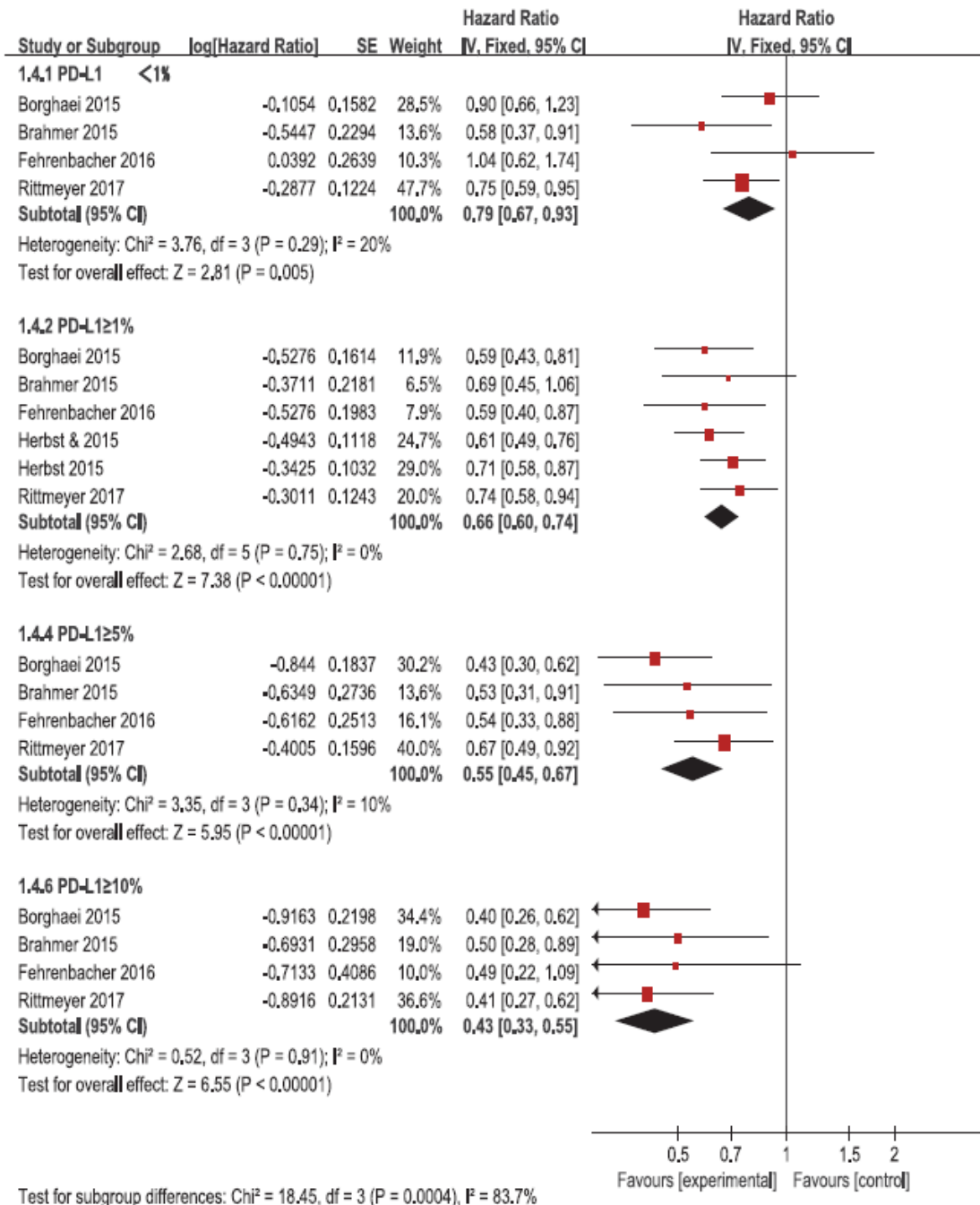
Study	Year	Study type	Intervention	Treatment regimens	No. of patients
Brahmer	2015	Phase III	Nivolumab	3mg/kg ivgtt q2w	135
			Docetaxel	75mg/m ² ivgtt q3w	137
Borghaei	2015	Phase III	Nivolumab	3mg/kg ivgtt q2w	292
			Docetaxel	75mg/m ² ivgtt q3w	290
			Pembrolizumab	2mg/kg ivgtt q3w	344
Herbst	2015	Phase III	Pembrolizumab	10mg/kg ivgtt q3w	346
			Docetaxel	75mg/m ² ivgtt q3w	343
Fehrenbacher	2016	Phase II	Atezolizumab	1200mg ivgtt q3w	144
			Docetaxel	75mg/m ² ivgtt q3w	143
Rittmeyer	2017	Phase III	Atezolizumab	1200mg ivgtt q3w	425
			Docetaxel	75mg/m ² ivgtt q3w	425

Qualität der Studien:

- All included trials were considered high-quality data, as they were randomized (Jadad Score: 3)

Studienergebnisse:

- OS/PFS: anti-PD- 1/PD-L1 antibodies significantly improved the OS (HR=0.69, 95%CI: 0.63-0.75, P<0.0001, and P=0.67) and PFS (HR=0.87, 95%CI: 0.81-0.94, P=0.0004, and P=0.11)
- ORR: Anti-PD-1/PD-L1 antibodies resulted in higher ORR than docetaxel (RR=1.53, 95% CI: 1.16-2.01, P=0.003, and P=0.03)
- Safety: The meta-analysis showed that the rates of overall grade 3-5 adverse events (AEs) for the anti- PD-1/PD-L1 therapy were significantly lower than those of docetaxel. For any grade 3-5 AEs, the rates of hematological AEs (anemia and neutropenia), febrile neutropenia, fatigue, and diarrhea were all significantly lower for anti-PD- 1/PD-L1 antibodies than for docetaxel.
- Subgroup Analyses PD-L1 expression: this meta-analysis indicates that anti-PD- 1/PD-L1 agents exhibited high efficacy in the treatment of advanced NSCLC. Anti-PD-1/PD-L1 therapy also had considerable activity for NSCLC and was superior to docetaxel in the PD-L1<1% population. PD-1/PD-L1 inhibitors tended to be associated with PD-L1 expression level. Higher PD-L1 expression was likely to be associated with increased benefit from anti-PD-1/PD-L1 agents.



Anmerkung/Fazit der Autoren

In conclusion, we analyzed five RCTs and systemically verified favorable OS, PFS, and ORR of anti-PD-1/PD-L1 therapy for pretreated advanced or metastatic NSCLC and demonstrated higher efficacy and safety for these agents than for docetaxel. More importantly, the results of this metaanalysis suggested that anti-PD-1/PD-L1 antibodies could also improve overall survival even when PD-L1<1%, which has not been recommended by previous studies. Our results could be of great value in guiding selection of clinical therapeutic regimens. More prospective studies are necessary to confirm these results and to improve the optimal dosage for PD-1/PD-L1 inhibitors in NSCLC.

Luo W et al., 2018 [85].

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 Docetaxel	131 129	62 64	Minimum 11	4.0
2	Borghaei, 2015	III	Open-label	Non-squamous NSCLC	Nivolumab Docetaxel	287 268	61 64	Minimum 13.2	4.0
3	Carbone, 2017	III	Open-label	NSCLC	Nivolumab Platinum-based chemotherapy	267 263	63 65	Median 13.5	4.0
4	Fehrenbacher, 2016	II	Open-label	NSCLC	Atezolizumab Docetaxel	142 135	62 62	Median; 14.8 for Atezolizumab; 15.7 for Docetaxel	4.0
5	Rittmeyer, 2017	III	Open-label	NSCLC	Atezolizumab Docetaxel	609 578	63 64	median 21	4.0
6*	Herbst, 2016 (1)	II/III	Open-label	NSCLC	Pembrolizumab 2 mg/kg Docetaxel	339 309	63 62	Median 13.1	4.0
7*	Herbst, 2016 (2)	II/III	Open-label	NSCLC	Pembrolizumab 10 mg/kg Docetaxel	343 309	63 62	Median 13.1	4.0
8	Reck, 2016	III	Open-label	NSCLC	Pembrolizumab Platinum-based chemotherapy	154 150	64.5 66	MEDIAN 11.2	4.0

*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.

Khan M et al., 2018 [67].

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 [93].** 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 efficacy 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:

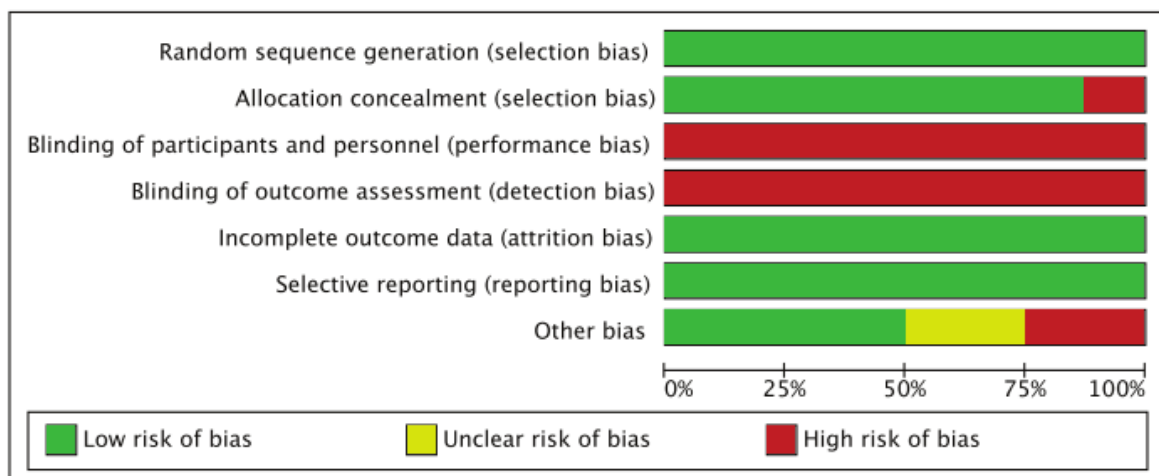


Figure 2. Risk of bias graph. +: low risk of bias; -: high risk of bias; ?: unclear risk of bias.

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, EGFR wild 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 separaten Angaben zum Stadium oder Status (z.B. fortgeschritten vs. metastasierte Patienten).

Peng TR et al., 2017 [92].

Indirect comparison between pembrolizumab and nivolumab for the treatment of non-small cell lung cancer: A meta-analysis of randomized clinical trials

Fragestellung

The purpose of this study is to evaluate the efficacy and adverse effects of nivolumab and pembrolizumab for the treatment of advanced non-small-cell lung cancer (NSCLC) by meta-analysis.

Methodik

Population:

- advanced NSCLC after first-line chemotherapy

Intervention:

- anti-PD-1 antibody

Komparator:

- other

Endpunkt:

- Objective response rate (ORR), overall survival (OS), and progression-free survival (PFS).

Recherche/Suchzeitraum:

- PubMed, Embase, ASCO abstracts, clinicaltrial.gov. and Cochrane Databases: August 31, 2016, limited to the English language

Qualitätsbewertung der Studien:

Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 3 RCTs

Charakteristika der Population:

- A total of 2 studies compared nivolumab therapy versus docetaxel chemotherapy and 1 study compared pembrolizumab therapy versus docetaxel chemotherapy
- Borghaed, 2015: Stage IIIB or IV, recurrent non-squamous NSCLC after radiation therapy or surgical resection; Nivolumab: 2mg/kg; Docetaxel: 75mg/m² Q3W
- Brahmer, 2015: Stage IIIB or IV squamous-cell NSCLC who had disease recurrence after one prior platinum-containing regimen were eligible for participation in study. Nivolumab: 2mg/kg; Docetaxel: 75 mg/m² Q3W
- Herbst, 2016: Patients, with progression, after two or more cycle of platinum-doublet chemotherapy, PD-L1 expression on at least 1% tumor cells. Pembrolizumab: 2mg/kg, 10mg/kg; Docetaxel: 75mg/m² Q3W

Qualität der Studien:

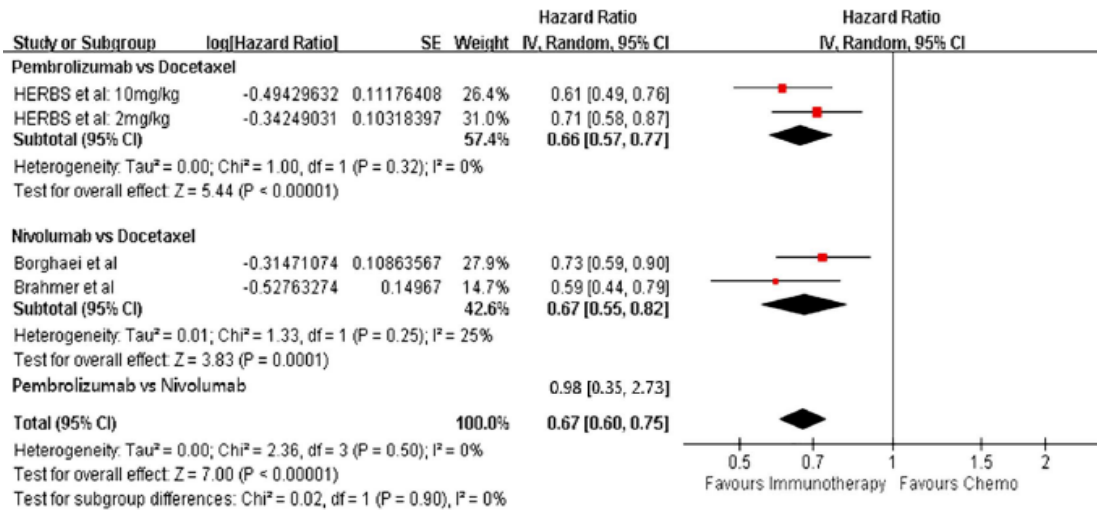
Table 2
The quality assessment of three randomized controlled trials included.

Reference	Patients (N)	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Free of other bias*
Herbs et al.	1034	Yes	Yes	No	Yes	Yes	Yes
Borghaei et al.	582	Yes	Unclear	No	Yes	Yes	Yes
Brahmer et al.	272	Yes	Unclear	No	Yes	Yes	Yes

Note: *Other bias refers to selective bias and measurement bias.

Studienergebnisse:

Overall survival



Progression-free survival

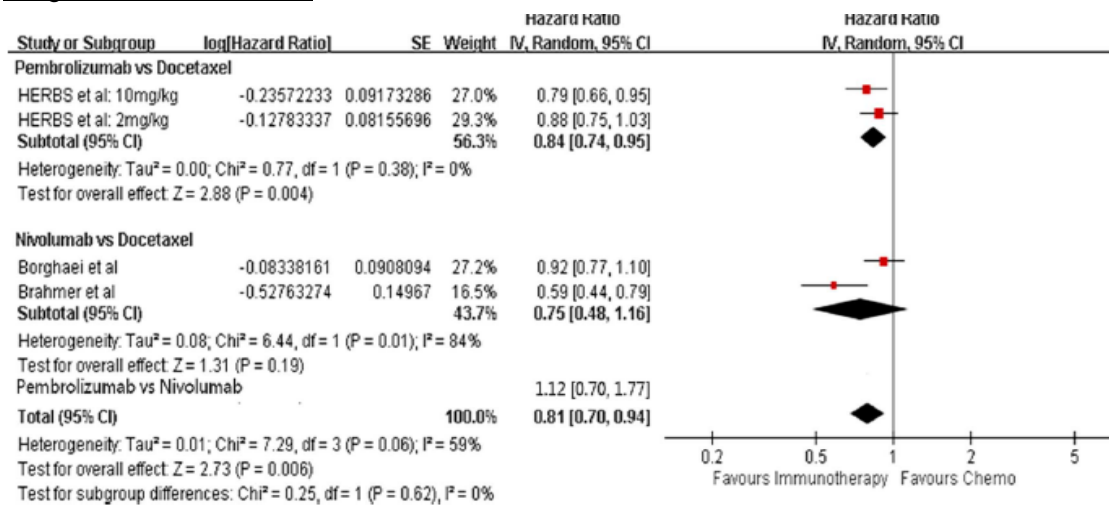


Fig. 3. Meta-analysis results of (A) OS and (B) PFS.

Any grade AEs and grade 3/4/5 AEs

- The OR of adverse events of grades 3 or higher for immunotherapy versus docetaxel is 0.16 (95% CI, 0.08–0.34). The result shows that the rates of adverse events of grades 3 or higher in immunotherapy are lower than those of docetaxel.
- The indirect estimate of the OR of adverse events of grades 3 or higher, showed that pembrolizumab was more common than nivolumab (OR: 3.44, 95% CI, 1.87–6.32). But the rates of pneumonitis and hypothyroidism of any grade were occurred not significantly difference between two group (OR: 0.25, 95% CI, 0.03–1.74, OR: 1.46, 95% CI, 0.06–33.7, respectively)

Referenzen

[8] J. Brahmer, K.L. Reckamp, P. Baas, et al., Nivolumab versus docetaxel in advanced squamous-cell non-smallcell lung cancer, N. Engl. J. Med. 373 (2015) 123–135.

[9] H. Borghaei, L. Paz-Ares, L. Horn, et al., Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer, *N. Engl. J. Med.* 373 (2015) 1627–1639.

[17] R.S. Herbst, P. Bass, D.W. Kim, et al., Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KETNOTE-010): a randomized controlled trial, *Lancet* 387 (10027) (2016) 1540–1550.

Anmerkung/Fazit der Autoren

In conclusion, PD-1 inhibitors have a statistical superiority of survival and safety benefit over docetaxel in patients with advanced, previously treated squamous or nonsquamous-cell NSCLC. Pembrolizumab and nivolumab have demonstrated similar survival benefits in patients with advanced NSCLC after chemotherapy, whereas nivolumab may have an advantage for its lower chances of serious adverse events and economic superiority over pembrolizumab.

Kommentare zum Review

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

Chen S et al., 2018 [10].

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 I 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.*
- Siehe auch: Huang, J. et al., 2016 [61]

Zhang M et al., 2016 [116].

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 leucopenia, 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.

Zhang N et al., 2018 [117].

Systematic review and meta-analysis of third-line salvage therapy for the treatment of advanced non-small-cell lung cancer: A meta-analysis of randomized controlled trials.

Fragestellung

to investigate the efficacy of third-line treatment for advanced non-small-cell lung cancer (NSCLC)

Methodik

Population:

- NSCLC patients

Intervention:

- patients received second or later-line therapy; and available survival data regarding thirdline treatment in advanced NSCLC patients (siehe Details im Ergebnisteil)

Endpunkte:

- OS, PFS

Recherche/Suchzeitraum:

- PubMed, EMBASE, and the Cochrane library (up to May 30, 2017)

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool / Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 randomized controlled trials for analysis
- Five randomized trials compared erlotinib-based doublet versus erlotinib as third-line therapy in advanced NSCLC while the remaining trials investigated single targeted agent versus docetaxel/placebo as third-line therapy for advanced NSCLC.
- A total of 1.958 patients received third-line therapy

Qualität der Studien:

- Jadad Scale: six of the eleven randomized controlled trials were double-blind placebo controlled trials, thus had Jadad score of 5. Another seven trials were an open-label controlled trials, thus had Jadad score of 3.
- Risk of bias: All of the included studies (100%) described random sequence generation. five studies (45%) described adequate allocation concealment. Seven studies (63.6%) described blinding of participants and personnel. Four studies had high risk of bias about blinding of participants and personnel because these four studies were open label trial. Nine studies had a low risk of incomplete outcome data. Although some researches had dropout, the effect of intervention was not affected due to due to the small scale of dropout. Ten studies had low risk of selectively reporting results.

Studienergebnisse:

- Single agent therapy as third-line therapy
 - Three trials reported PFS data of single agent third therapy in NSCLC patients. The pooled hazard ratio for PFS demonstrated that the single agent third therapy in advanced NSCLC patients did not significantly improved PFS, in comparison with docetaxel/placebo. There was significant heterogeneity between trials ($I^2 = 92.0\%$, $p < 0.001$), and the pooled HR for PFS was performed by using random-effects model.
 - Six trials reported OS data of single targeted agent as third-line therapy in this patient population. The pooled hazard ratio for OS showed that the use of single targeted agent as third therapy did not significantly improved OS, in comparison with docetaxel/placebo.
 - Sub-group analysis according to controlled therapy showed that the use of single targeted agent as third therapy did not significantly improved OS in comparison with docetaxel.
- Erlotinib-based combination as third therapy
 - Four included trials comparing erlotinib-based doublet versus erlotinib alone as third-line therapy reported survival data.
 - The pooled hazard ratio for PFS demonstrated that erlotinib-based doublet combination therapy in heavily treated NSCLC patients did not significantly improved PFS and when compared to erlotinib alone.

Anmerkung/Fazit der Autoren

In conclusion, this is the first-meta-analysis specifically assessing the efficacy of third-line therapy in the treatment of advanced NSCLC patients. The results of our study suggest that the efficacy of single novel targeted agent is comparable to that of docetaxel alone in terms of PFS and OS for heavily pretreated NSCLC patients. In addition, no survival benefits are obtained from erlotinib-based doublet therapy, thus single agent erlotinib could be recommended as third-line treatment for unselected advanced NSCLC patients. Further studies are recommended to specifically investigate the efficacy and toxicities of third-line therapy in the treatment of advanced NSCLC patients.

Kommentare zum Review

- None of the included trials report the toxicities of third-line therapy in heavily pretreated NSCLC patients
- Different targeted agents, including EGFR-TKIs and immune check point inhibitors, are included for analysis in the present study

Hu J et al., 2019 [59].

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.

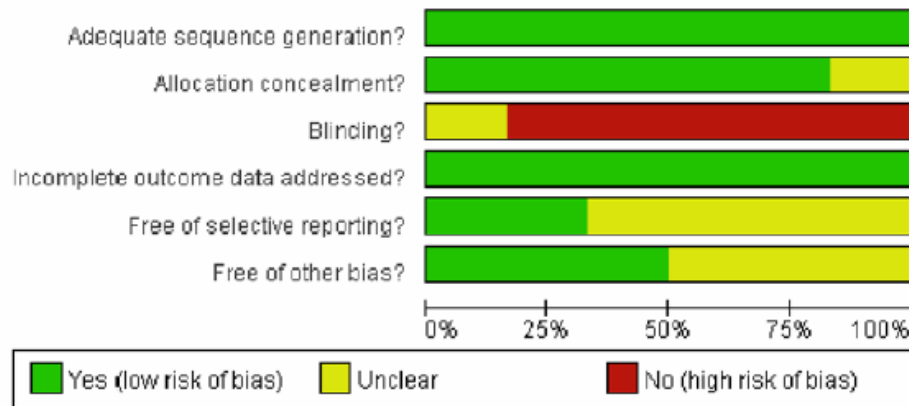


Figure 2. Random-effect model of hazard ratio (95%CI) of PFS in NSCLC treated doublet versus single agent maintenance therapy

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”

Li J et al., 2019 [75].

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 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.
- [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 non-small-cell lung cancer. *N Engl J Med* 2014;370:1189–97.
- [32] Shaw AT, et al. Crizotinib in ROS1-rearranged non-small-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 ALK-rearranged 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 ALK 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 (evaluative 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 [72].

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 [66].

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 (February (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 [123].

Ceritinib Alone for Crizotinib-naïve 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-naïve 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 non-small-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 ALK-rearranged (ALK+) 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-naïve pooled data revealed a pooled ORR of 68,9% (95% CI: 64,3%-73,1%; no heterogeneity observed)

- PFS for crizotinib-naïve 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-naïve 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 [94]

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:

- 21 studies, 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]
- Three 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 [79].

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

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 [19].

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.

Liu J et al., 2020 [81]

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

Fragestellung

to compare these approved first-line treatments for advanced NSCLC

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

Methodik

Population:

- advanced non-small cell lung carcinoma patients

Intervention/Komparator:

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

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Cochrane Collaboration's risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Ten trials, involving 6,124 patients

Charakteristika der Population:

Table 1. Study characteristics.

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

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

Qualität der Studien:

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

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

Studienergebnisse:

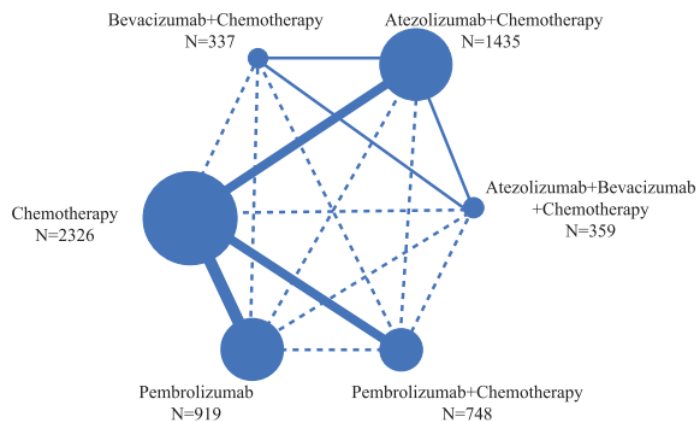


Figure 2. Network structure for all the included trials. Each circular node represents a treatment type. The circle size is proportional to the total number of patients. The width of lines is proportional to the number of studies performing head-to-head comparisons in the same study, and the dotted line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

- NMA for non-squamous NSCLC

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

- For PFS, ABC appears superior to PC; however,; these intervention strategies were both significantly more effective than Pembrolizumab alone (HR 0.37, 95% CI 0.19–0.75 for ABC; HR 0.51, 95% CI 0.31–0.76 for PC), BC (HR 0.33, 95% CI 0.22–0.51 for ABC; HR 0.45, 95% CI 0.24–0.86 for PC) and chemotherapy alone (HR 0.27, 95% CI 0.13–0.52 for ABC; HR 0.36, 95% CI 0.25–0.52 for PC). AC was significantly superior to BC (HR 0.63, 95% CI 0.43–0.92) and chemotherapy alone (HR 0.50, 95% CI 0.35–0.71). Pembrolizumab alone was marginally superior to BC (HR 0.89, 95% CI 0.51–1.50), but was substantially more effective than chemotherapy alone (HR 0.71, 95% CI 0.60–0.83).
- For OS, PC performed significantly better than BC (HR 0.38, 95% CI 0.16–0.87) and chemotherapy alone (HR 0.42, 95% CI 0.26–0.68). Pembrolizumab alone performed significantly better than chemotherapy alone (HR 0.67, 95% CI 0.57–0.78). Although there

were no statistically significant difference between treatment groups, except for those previously mentioned.

Intermediate PD-L1 ($1\% \leq \text{PD-L1} < 50\%$) cohort

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

PD-L1 < 1% cohort

- For PD-L1-low patients, the PFS-NMA was based on four trials and OS-NMA on three. ORR-NMA was not analyzed due to the missing AC connection, for the same reason as for the PD-L1-high expression analysis. Pembrolizumab alone was also not analyzed due to the lack of data.
- For PFS, ABC appears to provide a significant improvement compared with AC (HR 0.68, 95% CI 0.50–0.93), PC (HR 0.56, 95% CI 0.34–0.93), BC (HR 0.75, 95% CI 0.60–0.94) and chemotherapy alone (HR 0.42, 95% CI 0.29–0.61). AC (HR 0.62, 95% CI 0.50–0.75) performed significantly better than chemotherapy and appears superior to PC. Although PC appears inferior to BC while being superior to chemotherapy alone. BC was significantly more effective than chemotherapy alone (HR 0.56, 95% CI 0.42–0.75).
- PC appears superior to chemotherapy in terms of OS (HR 0.59, 95% CI 0.38–0.92). However, there was no significant difference among other interventions in terms of overall survival.
- NMA for squamous non-small cell lung cancer
 - For PD-L1-high patients with squamous NSCLC, the ORR NMA, PFS-NMA, and OS-NMA were both based on separate five trials.
 - For ORR: PC (OR 1.80, 95% CI 1.30–2.70) and Pembrolizumab alone (OR 1.30, 95% CI 1.10–1.60) performed significantly better than chemotherapy alone. PC and AC also appear superior to Pembrolizumab alone.
 - For PFS: PC was significantly more effective than Pembrolizumab alone (HR 0.53, 95% CI 0.33–0.84) and chemotherapy alone (HR 0.37, 95% CI 0.24–0.58). Pembrolizumab appears to provide a significant benefit compared to chemotherapy alone (HR 0.71, 95% CI 0.60–0.84). AC on the other hand appears inferior to PC, yet superior to Pembrolizumab alone.

- For OS: PC appears superior to Pembrolizumab alone. Both AC (HR 0.56, 95% CI 0.32–0.99) and Pembrolizumab alone (HR 0.67, 95% CI 0.57–0.80) performed significantly more effectively than chemotherapy alone.
- For patients with intermediate PD-L1 expression, AC (HR 0.70, 95% CI 0.53–0.92) and PC (HR 0.56, 95% CI 0.39–0.80) were significantly more effective than chemotherapy in terms of PFS and PC appears significantly superior to both chemotherapy alone (HR 0.57, 95% CI 0.36–0.90) and AC in terms of overall survival. For PD-L1-negative patients, PC appears significantly superior to chemotherapy alone in terms of ORR (OR 1.50, 95% CI 1.20–2.10), PFS (HR 0.68, 95% CI 0.47–0.98) and OS (HR 0.61, 95% CI 0.38–0.98). There was no identifiable difference among the other regimens included.
- NMA for safety analysis
 - Patients with low grade and grade 3–5 AEs perhaps benefit more from PC and Pembrolizumab alone compared to BC (OR 0.95, 95% CI 0.91–0.99 for PC, OR 0.69, 95% CI 0.64–0.74 for Pembrolizumab alone for grade 1–5 AEs; OR 0.73, 95% CI 0.61–0.88 for PC, OR 0.33, 95% CI 0.26–0.42 for Pembrolizumab alone for grade 3–5 AEs). ABC and AC appear significantly less safe than PC with an OR 1.60 (95% CI 1.30–1.90 for grade 3–5 AEs for ABC) and an OR 1.20 (95% CI 1.10–1.30 for grade 3–5 AEs for AC). Pembrolizumab alone appears to be the safest intervention among the regimens analyzed.

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

- Siehe auch: Wang, C. et al., 2020 [108] & Chen, Y. et al., 2019 [11] & Tun, A. M. et al., 2019 [104] & Cao, R. et al., 2019 [6]

Chen RL et al., 2019 [9]

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

Fragestellung

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

Methodik

Population:

- patients with advanced squamous NSCLC

Intervention/Komparator:

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

Endpunkte:

- OS and/or PFS

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Jadad scoring system

Ergebnisse

Anzahl eingeschlossener Studien:

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

Charakteristika der Population:

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

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

Qualität der Studien:

- Siehe Charakteristika der Population (Tabelle 1)

Studienergebnisse:

- PD-1/PD-L1 inhibitors demonstrated significant superiority to chemotherapy in overall survival (OS) (hazard ratio [HR]: 0.74; $p < 0.001$) and progression-free survival (PFS) (HR: 0.66; $p < 0.001$) for squamous NSCLC.
- The OS and PFS benefits of PD-1/PD-L1 inhibitors for squamous NSCLC were similar in subgroup analyses of line settings, PD-L1 expression and different study methodologies.

- No advantage in OS was found in advanced squamous NSCLC patients treated with atezolizumab (HR: 0.87; p = 0.087).

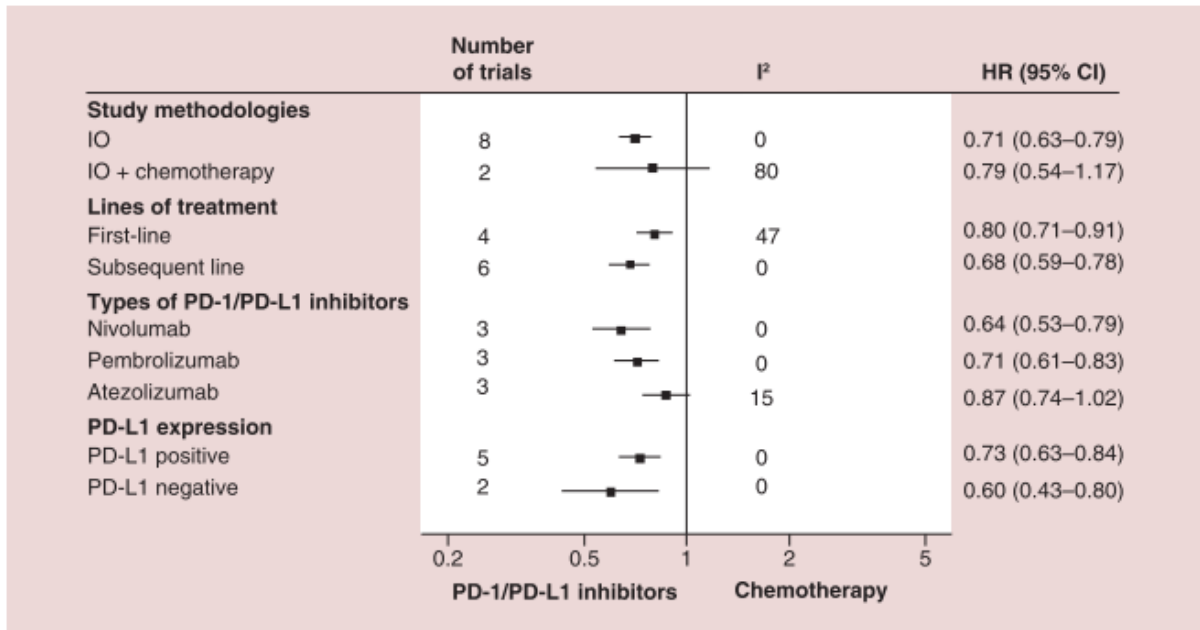


Figure 4. Subgroup analyses on overall survival according to study methodologies, lines of treatment, types of PD-1/PD-L1 inhibitors and PD-L1 expression.

HR: Hazard ratio; IO: Immunotherapy; IO+Chemotherapy: The combination of immunotherapy and chemotherapy; PD-1: Programmed death-1; PD-L1: Programmed death-ligand-1.

Anmerkung/Fazit der Autoren

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

Kommentar zum Review:

- Siehe auch: Li, S. et al., 2019 [76]

3.4 Leitlinien

National Institute for Health and Care Excellence (NICE), 2019 [89].

Lung cancer: diagnosis and management

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

Leitlinienorganisation/Fragestellung

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

Methodik

Grundlage der Leitlinie

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

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

Recherche/Suchzeitraum:

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

LoE

- trifft nicht zu (sieh sonstige methodische Hinweise)

GoR

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

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

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

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

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

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

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

Updates-Kennzeichnung:

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

Empfehlungen

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

EGFR-TK mutation

- 1.4.45 For guidance on treatment for stage IIIB and IV non-squamous NSCLC in people with the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation:
 - for initial treatment, see the NICE technology appraisal guidance on afatinib, erlotinib and gefitinib.
 - on progression for people with the EGFR T790M mutation, see the NICE technology appraisal guidance on osimertinib.
 - on progression after afatinib, erlotinib, gefitinib or osimertinib, 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
 - on progression after first-line chemotherapy, see the NICE technology appraisal guidance on atezolizumab, nivolumab, pembrolizumab and nintedanib with docetaxel or offer docetaxel monotherapy. [2019]

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

- on progression after first-line crizotinib, see the NICE technology appraisal guidance on ceritinib and brigatinib for second-line treatment
- on progression, offer pemetrexed with carboplatin or other platinum doublet chemotherapy [5]
- 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
- on progression after first-line chemotherapy, see the NICE technology appraisal guidance on atezolizumab, nivolumab, pembrolizumab and nintedanib with docetaxel or offer docetaxel monotherapy. [2019]

PDL1 \geq 50% and no gene mutation or fusion protein

- 1.4.47 For guidance on treatment for stage IIIB and IV non-squamous NSCLC in people whose tumours express PD-L1 at 50% or above and who have no gene mutation or fusion protein:
 - for initial treatment, see the NICE technology appraisal guidance on pembrolizumab and pembrolizumab combination
 - on progression after pembrolizumab, offer pemetrexed with carboplatin or other platinum doublet chemotherapy [5]
 - 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
 - on progression after first-line chemotherapy or pembrolizumab combination, see the NICE technology appraisal guidance on nintedanib with docetaxel or offer docetaxel monotherapy. [2019]

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
 - on progression offer pemetrexed with carboplatin or other platinum doublet chemotherapy [5]
 - 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
 - on progression after first-line chemotherapy see the NICE technology appraisal guidance on atezolizumab, nivolumab, pembrolizumab and nintedanib with docetaxel or offer docetaxel monotherapy. [2019]

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

- 1.4.49 For guidance on treatment for stage IIIB and IV non-squamous NSCLC in people who do not have a gene mutation, fusion protein or biomarker:

- see the NICE technology appraisal guidance on pembrolizumab combination and pemetrexed with cisplatin or offer pemetrexed with carboplatin or other platinum doublet chemotherapy.
- 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
- on progression after first-line chemotherapy see the NICE technology appraisal guidance on atezolizumab, nivolumab, pembrolizumab and nintedanib with docetaxel or offer docetaxel monotherapy
- on progression after pembrolizumab combination, see the NICE technology appraisal guidance on nintedanib with docetaxel or offer docetaxel monotherapy. [2019]

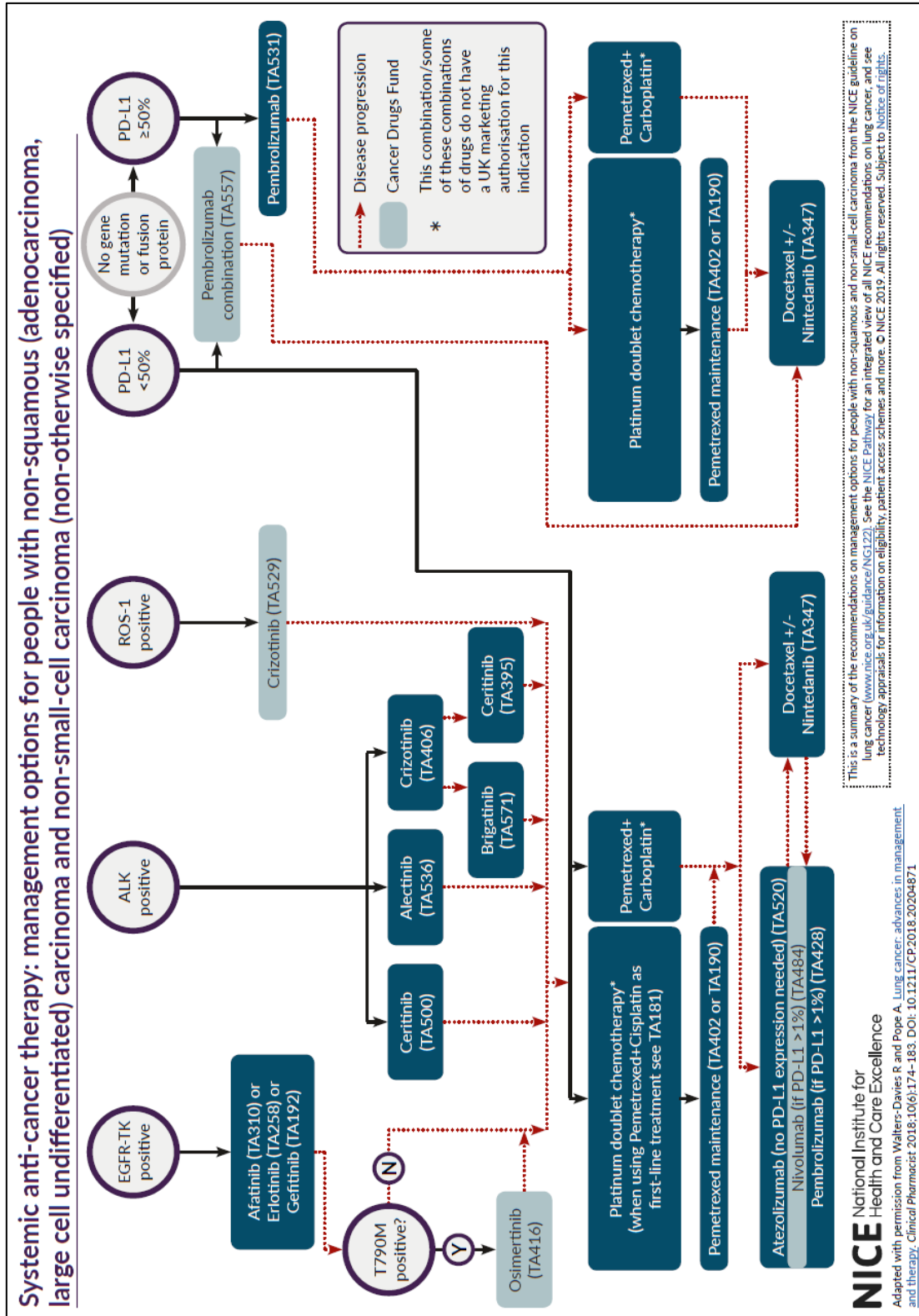
Squamous non-small-cell lung cancer

- PDL1 \geq 50%: For guidance on treatment for squamous NSCLC in people whose tumours express PD-L1 at or above 50%:
 - for initial treatment, offer gemcitabine or vinorelbine and cisplatin or carboplatin
 - on progression, offer gemcitabine or vinorelbine and cisplatin or carboplatin
 - on progression after first-line chemotherapy, offer docetaxel monotherapy. [2019]

PDL1<50%

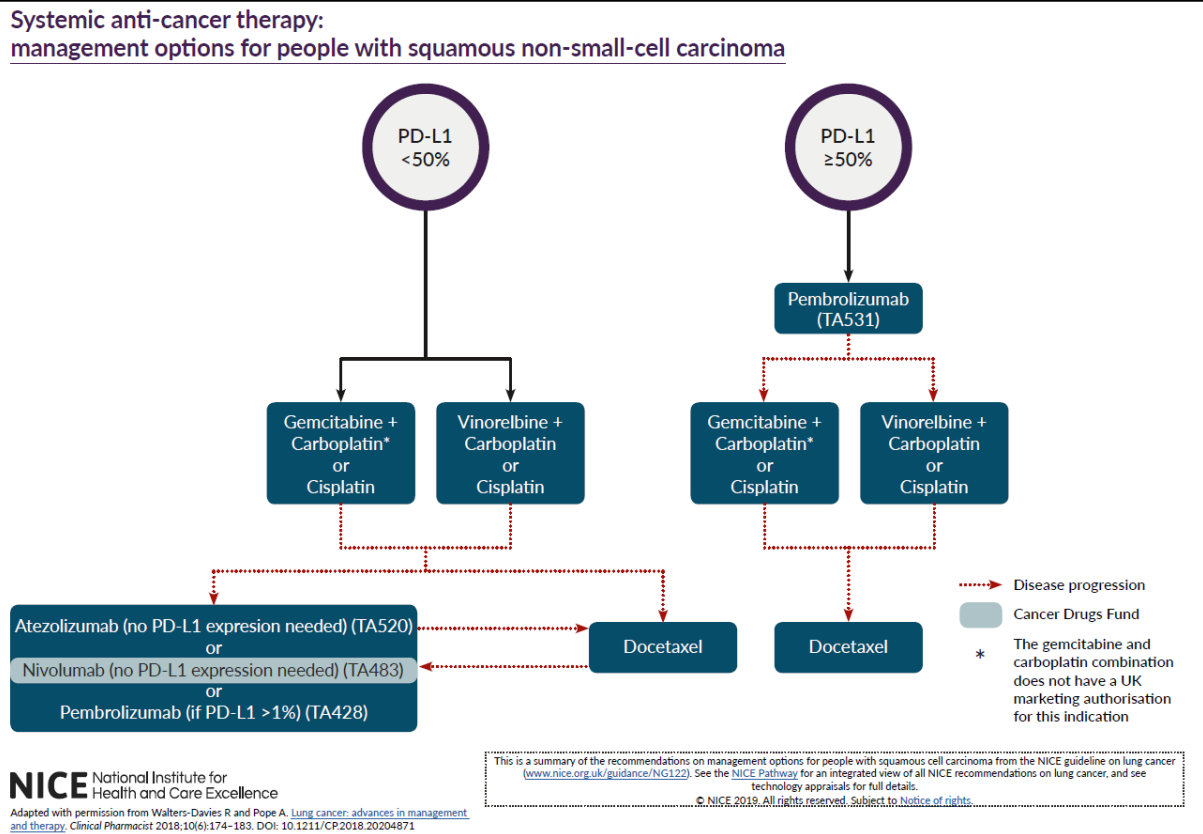
- 1.4.51 For guidance on treatment for squamous NSCLC in people whose tumours express PD-L1 below 50%:
 - for initial treatment, offer gemcitabine or vinorelbine and cisplatin or carboplatin.
 - on progression after first-line chemotherapy, see the NICE technology appraisal guidance on atezolizumab, nivolumab and pembrolizumab, or offer docetaxel monotherapy. [2019]

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 [74].

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

Siehe auch: Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft (DKG), et al., 2018 [73].

Fragestellung

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

- ...
- Therapie des NSCLC im Stadium IIB & 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 Erkenntnissen war die sog. Erhaltungstherapie: 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

Empfehlungen zur molekularen Testung (siehe Kapitel 6.6.10)	
EK	<p>Anhand des zur Verfügung stehenden Tumorgewebes / der Tumorzellen von allen nicht kurativ behandelbaren nichtplatteneithelialen NSCLC sollen molekularpathologische Untersuchungen hinsichtlich aller therapeutisch relevanten molekularer Veränderungen (nach gegenwärtigem Stand vor Erstlinientherapie als Mindestanforderung EGFR-Mutationen in den Exonen 18-21, ALK-Fusionen und ROS1-Fusionen, BRAF V600 Mutationen) eingeleitet werden.</p> <p>Dies gilt ebenfalls für Plattenepithelkarzinome von Nie-Rauchern/Leichtrauchern.</p>
EK	<p>In den Gewebeproben von Therapie-naiven Patienten im Stadium IV soll parallel zu den molekularpathologischen Untersuchungen eine immunhistochemische Untersuchung auf PD-L1-Expression durchgeführt werden*.</p> <p>Das Ergebnis ist als Prozentsatz membranös positiver Tumorzellen (sog. Proportion Score) anzugeben. Eine externe Qualitätssicherung im Rahmen von Ringversuchen soll nachgewiesen werden.</p> <p>* Die Empfehlung zur Untersuchung der PD-L1-Expression gilt für alle histologischen NSCLC-Typen (siehe auch Therapiealgorithmus NSCLC IV).</p>

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:	

Patienten mit PD-L1-Expression von <50 % und ECOG 0-1
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 Komorbiditäten, 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 %	

Zweitlinientherapie bei Patienten mit Plattenepithelkarzinom und ohne Mutationsnachweis

8.78.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad A	Patienten mit Plattenepithelkarzinom in gutem Allgemeinzustand (ECOG 0,1) mit einer Erkrankungsprogression nach primärer Kombinations-Chemotherapie soll eine Zweitlinientherapie bis zum Progress oder Auftreten von Toxizitäten angeboten werden.	
Level of Evidence 1b	Literatur: [835-841]	
	Konsensstärke: 96 %	

8.79.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad A	Patienten mit Plattenepithelkarzinom in gutem Allgemeinzustand (ECOG 0,1) und keinen Kontraindikationen gegen eine Immuncheckpoint-Inhibitor-Therapie soll ein PD1-Antikörper in der Zweitlinientherapie angeboten werden.	
Level of Evidence 1b	Literatur: [840]	
	Konsensstärke: 75 %	

8.80.	Konsensbasierte Empfehlung	2018
EK	Bei Patienten mit Plattenepithelkarzinom mit ECOG 2 und keinen Kontraindikationen gegen eine Immuncheckpoint-Inhibitor-Therapie kann ein PD1-Antikörper in der Zweitlinientherapie angeboten werden.	
	Konsensstärke: 81 %	

8.81.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad 0	Patienten mit Plattenepithelkarzinom in gutem Allgemeinzustand (PS 0,1) und keinen Kontraindikationen gegen einen Angiogenese-Inhibitor kann eine Zweitlinientherapie mit Docetaxel und Ramucirumab angeboten werden.	
Level of Evidence 1b	Literatur: [841]	
	Konsensstärke: 83 %	

8.82.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad 0	Patienten mit Plattenepithelkarzinom in gutem Allgemeinzustand (PS 0,1) kann eine Zweitlinientherapie mit Afatinib angeboten werden.	
Level of Evidence 1b	Literatur: [839]	
	Konsensstärke: 85 %	

8.83.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad 0	Bei Patienten mit Plattenepithelkarzinom, die als Zweitlinientherapie eine Immuncheckpoint-Inhibitorthherapie erhalten haben und keine Kontraindikationen gegen eine Drittlinientherapie aufweisen, kann Docetaxel oder Docetaxel/Ramucirumab oder Afatinib angeboten werden.	
Level of Evidence 1b	Literatur: [840, 842]	
	Konsensstärke: 81 %	

8.84.	Evidenzbasierte Empfehlung	2018
EK	Bei der Verfügbarkeit von mehreren Therapieoptionen kann Patienten mit Plattenepithelkarzinom und gutem Allgemeinzustand nach Versagen einer Immuntherapie bei Progress die Durchführung einer Chemotherapie angeboten werden.	
	Konsensstärke: 86 %	

Zweitlinientherapie bei Patienten mit nicht-Plattenepithelkarzinom ohne Mutationsnachweis

8.85.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad B	Patienten mit Nicht-Plattenepithelkarzinom ohne Treibermutation und bei nachgewiesener PDL1-Positivität sollte in der Zweitlinientherapie eine Therapie mit einem PD1-Inhibitor angeboten werden.	
Level of Evidence 1b	Literatur: [842, 843]	
	Konsensstärke: 96 %	

8.86.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad A	Bei Patienten (ECOG 0-1) mit Nicht-Plattenepithelkarzinom und PDL1-Negativität soll eine 2. Linientherapie angeboten werden. Therapieoption sind:	
	<ul style="list-style-type: none"> - Docetaxel-Nintedanib, - Docetaxel-Ramucirumab, - Pemetrexed, - Docetaxel, - Erlotinib - Nivolumab. 	
Level of Evidence 1b	Literatur: [835-838, 841-845]	
	Konsensstärke: 88 %	

8.87.	Konsensbasierte Empfehlung	2018
EK	Bei Patienten mit Nicht-Plattenepithelkarzinom und PDL-1-Negativität sollten in die Entscheidung der Positionierung der Therapie in die Zweit- oder Drittlinie klinische Faktoren wie Rezidivzeitpunkt, Raucherstatus, Tumordynamik, Mutationsstatus, Komorbiditäten, und die Verträglichkeit der Erstlinientherapie einbezogen werden.	
	Konsensstärke: 100%	

8.88.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad B	<p>Patienten mit Nicht-Plattenepithelkarzinom, die als Zweitlinientherapie eine Immuncheckpoint-Inhibitor-Therapie erhalten haben und keine Kontraindikationen gegen eine Drittlinientherapie aufweisen, sollte eine weitere Therapielinie angeboten werden.</p> <p>Therapieoptionen sind:</p> <ul style="list-style-type: none"> - Docetaxel - Pemetrexed - Docetaxel mit Ramucirumab/Nintedanib - Erlotinib. 	
Level of Evidence 1b	Literatur: [835-838, 841, 844, 845]	
	Konsensstärke: 96 %	

8.89.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad 0	<p>Patienten mit Nicht-Plattenepithelkarzinom mit ECOG 2 und keinen Kontraindikationen gegen eine Immuncheckpoint-Inhibitor-Therapie kann ein PD1 Antikörper in der Zweitlinientherapie angeboten werden.</p>	
Level of Evidence 1b	Literatur: [842, 843]	
	Konsensstärke: 93 %	

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

8.90.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad A	<p>Bei Vorliegen einer aktivierenden EGFR Mutation soll bei Patienten mit ECOG 0-2 in der Erstlinientherapie ein EGFR-TKI abgeboten werden.</p>	
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 %	

Resistenzmechanismen und Zweitlinientherapie bei EGFR mutierten Patienten

8.97.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad A	Bei Nachweis einer erworbenen EGFR-TKI-Resistenz durch Akquisition einer EGFR-T790M-Mutation soll eine T790M spezifische Substanz angeboten werden.	
Level of Evidence 1b	Literatur: [863, 870]	
	Konsensstärke: 100 %	

8.98.	Konsensbasierte Empfehlung	2018
Empfehlungsgrad EK	Bei fehlendem Nachweis einer erworbenen EGFR-T790M-Mutation und fehlendem Nachweis von weiteren therapierbaren genetischen Alterationen sollte analog zur Erstlinientherapie - Wildtyp vorgegangen werden.	
	Konsensstärke: 96 %	

8.99.	Evidenzbasierte Empfehlung	2018
EK	Bei Resistenzmechanismen, die potentiell therapierbar sind, sollten Patienten in Studien eingeschlossen werden. Falls dies nicht möglich ist, sollte der Einsatz von potentiell wirksamen Substanzen unabhängig vom Zulassungstatus erwogen werden.	
	Konsensstärke: 100 %	

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

8.6.6.1. Erstlinientherapie bei Chemotherapie-naiven Patienten

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 %		

8.6.6.2. Zweitlinientherapie nach Versagen einer platinbasierten Standardchemotherapie

8.101.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad A	ALK positiven NSCLC-Patienten mit Progress nach platinbasierter Standardchemotherapie, die in der Erstlinie keinen ALK-Inhibitor erhalten haben, soll Crizotinib angeboten werden.	
Level of Evidence 1b	Literatur: [875]	
Konsensstärke: 100 %		

8.6.6.3. Therapie nach Crizotinib-Versagen

8.102.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad A	ALK-Inhibitoren der zweiten Generation sollen ALK positiven NSCLC Patienten bei Crizotinib/ALK-TKI Versagen angeboten werden.	
Level of Evidence 1b	Literatur: [876]	
Konsensstärke: 85 %		

8.6.6.4. Therapie nach Versagen der zugelassenen ALK-Inhibitoren Crizotinib und Ceritinib

8.103.	Evidenzbasierte Empfehlung	2018
EK	ALK positive NSCLC-Patienten mit Versagen von zugelassenen ALK-Inhibitoren sollten nach Möglichkeit in klinische Studien oder Compassionate-Use-Programme mit weiteren ALK-Inhibitoren eingeschlossen werden. Falls dies nicht möglich ist, werden sie mit Chemotherapie entsprechend Wildtyp-Patienten behandelt. Pemetrexed hat die höchste intrinsische Effektivität bei ALK + Tumoren.	
	Konsensstärke: 100 %	

8.104.	Evidenzbasierte Empfehlung	2018
EK	Bei Zulassung neuer-ALK Inhibitoren sollte eine Rebiopsie in Analogie zur akquirierten EGFR-Resistenz erfolgen.	
	Konsensstärke: 84 %	

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

8.6.7.1. Erstlinientherapie

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 %	

8.6.7.2. Zweitlinientherapie (bei Crizotinib-Versagen)

8.106.	Konsensbasierte Empfehlung	2018
EK	Bei Progress unter Therapie mit Crizotinib und fehlender Möglichkeit des Einschusses in eine Studie mit einem Nächstgenerations-ROS1-Inhibitor sollte, abhängig vom Allgemeinzustand des Patienten, entweder mit einer platinbasierten Kombinationschemotherapie oder einer Monotherapie angeboten werden (siehe Kapitel Chemotherapie).	
	Konsensstärke: 100 %	

8.6.8. 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

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 zu MET-Amplifikation:

(...) High-level MET-Amplifikationen oder aktivierende Mutationen im Exon 14 des MET-Gens wurden ebenfalls als Treibermutationen beschrieben. Sie kommen in ca. 2-4 % der Adenokarzinome und ca. 1-2 % der Plattenepithelkarzinome der Lunge vor [888]. Verschiedene MET-Inhibitoren werden in klinischen Studien evaluiert. Bei Behandlung von Patienten mit MET-Amplifikation mit dem ALK/ROS/MET Inhibitor Crizotinib wurde in der Zwischenanalyse einer Phase-II-Studie Ansprechen in Abhängigkeit von der Höhe der MET-Amplifikation gezeigt (high-level MET Amplifikation: ORR 50% (3/6) (NCT00585195, [889]). Die Endergebnisse dieser Studie stehen noch aus. Laufende Studien evaluieren zahlreiche MET-Inhibitoren in dieser NSCLC-Subgruppe.

Weitere Treibermutationen werden zur Zeit als therapeutische Targets in zahlreichen klinischen Studien evaluiert (z.B. NTRK 1/2/3-Fusionen, DDR2-Mutationen, FGFR1-Mutationen/-amplifikationen u.a).

(...)

Systemtherapie (Drittlinie und ggf. weitere)

8.109.	Konsensbasierte Empfehlung	2018
EK	Bei Patienten in adäquatem Allgemeinzustand (ECOG 0-2), die nach einer Zweitlinientherapie progredient sind, sollte eine Drittlinientherapie angeboten werden.	
	Konsensstärke: 100 %	
8.110.	Konsensbasierte Empfehlung	2018
EK	Patienten mit adäquatem Allgemeinzustand (ECOG 0-2) und mit längerfristigem Krankheitsverlauf kann bei entsprechender klinischer Situation zur Symptomkontrolle eine weitere Antitumorthherapie auch nach der Drittlinienbehandlung angeboten werden.	
	Konsensstärke: 100 %	

National Cancer Control Programme Guideline Development Group (GDG), 2017 [88].

Diagnosis, staging and treatment of patients with lung cancer.

Leitlinienorganisation/Fragestellung

Recommendations for patients with advanced/stage IV NSCLC.

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

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.

Second and third-line therapy:

Recommendation 2.6.7.1	Grade
Second-line systemic anticancer therapy (SACT) with single agent drugs should be considered. The choice of agent to be used should be made on a case by case basis taking into account previous treatment, mutation status and co-morbidities.	B

Hanna N et al., 2020 [56].

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

Fragestellung

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

Methodik

Grundlage der Leitlinie

Update der Version von Hanna N. et al. 2017 [57] & Masters GA, et al. 2015 [87]

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

Recherche/Suchzeitraum:

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

LoE/SoE:

- GRADE

Recommendations

- For patients with high PD-L1 expression (TPS \geq 50%), nonSCC, and PS 0 to 1, clinicians should offer single-agent pembrolizumab (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).
- For patients with high PD-L1 expression (TPS \geq 50%), nonSCC, and PS 0 to 1, clinicians may offer pembrolizumab/ carboplatin/pemetrexed (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).
- For patients with high PD-L1 expression (TPS \geq 50%), nonSCC, and PS 0 to 1, clinicians may offer atezolizumab/ carboplatin/paclitaxel/bevacizumab in the absence of contraindications to bevacizumab (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).
- For patients with high PD-L1 expression (TPS \geq 50%), nonSCC, and PS 0 to 1, clinicians may offer atezolizumab/ carboplatin/nab-paclitaxel (Type: evidence based; Evidence quality: low; Strength of recommendation: weak).
- There are insufficient data to recommend any other checkpoint inhibitors, or to recommend combination checkpoint inhibitors or any other combinations of immune checkpoint inhibitors

with chemotherapy in the first-line setting (Type: evidence based, benefits outweigh harm; Evidence quality: high; Strength of recommendation: strong).

- For patients with negative (0%) and low positive PD-L1 expression (TPS 1% to 49%), non-SCC, and PS 0 to 1, and who are eligible for chemotherapy and pembrolizumab, clinicians should offer pembrolizumab/carboplatin/pemetrexed (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).
- For patients with negative (TPS 0%) and low positive (TPS 1% to 49%) PD-L1 expression, non-SCC, and PS 0 to 1, clinicians may offer atezolizumab/carboplatin/paclitaxel/bevacizumab in the absence of contraindications to bevacizumab (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).
- For patients with negative (TPS 0%) and low positive (TPS 1% to 49%) PD-L1 expression, non-SCC, and PS 0 to 1, clinicians may offer atezolizumab/carboplatin/nab-paclitaxel (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).
- For patients with negative (TPS 0%) and low positive (TPS 1% to 49%) PD-L1 expression, non-SCC, and PS 0 to 1, and who have contraindications to or decline immunotherapy, clinicians should offer standard chemotherapy with platinum-based two-drug combinations as outlined in the 2015 update (Type: evidence based; Evidence quality: high; Strength of recommendation: strong). NOTE. This corresponds to the first part of Recommendation A2.a.iii in 2017: “For patients with low PD-L1 expression (TPS , 50%), clinicians should offer standard chemotherapy with platinum-based two-drug combinations as outlined in the 2015 update (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong) or (see below)”.1(p6)
- For patients with negative (TPS 0%) and low positive (TPS 1% to 49%) PD-L1 expression, non-SCC, and PS 0 to 1, and who have contraindications to or decline immunotherapy and not deemed candidates for platinum-based therapy, clinicians should offer non-platinum-based two-drug therapy as outlined in the 2015 update (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: weak).
- For patients with low positive PD-L1 expression (TPS 1% to 49%), non-SCC, and PS 0 to 1, and who are ineligible for or decline combination of doublet platinum with or without pembrolizumab, clinicians may offer single-agent pembrolizumab (Type: evidence based; Evidence quality: low; Strength of recommendation: weak).

Ellis PM et al., 2016 [17].

Cancer Care Ontario (CCO)

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

Fragestellung

Recommendations for systemic treatment of patients with NSCLC.

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 Formulierung 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%.“

Recommendations

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?

<p>Recommendation A2</p> <p>For patients who have the characteristics described in Clinical Question A2 and who have non-squamous histology, the following options are acceptable:</p> <ul style="list-style-type: none"> ● Cisplatin-based combinations <ul style="list-style-type: none"> ● Cisplatin plus docetaxel ● Cisplatin plus paclitaxel ● Cisplatin plus pemetrexed ● Cisplatin plus vinorelbine ● <i>Cisplatin plus gemcitabine</i> ● Carboplatin-based combinations <ul style="list-style-type: none"> ● Carboplatin plus albumin-bound (nab) -paclitaxel ● Carboplatin plus paclitaxel ● Carboplatin plus pemetrexed ● Carboplatin plus docetaxel ● <i>Carboplatin plus gemcitabine</i> ● Nonplatinum doublets
<p>Key Evidence from ASCO for Recommendation A2</p> <p>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.</p>
<p>Interpretation of Evidence for Recommendation A2</p> <p>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.</p>
<p>Implementation Considerations for Recommendation A2</p> <p>Nonplatinum doublets will be a funding gap for Ontario.</p>

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 bevacizumab 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.

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.

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?

Recommendation A5

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

Clinical Question A6

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.

Clinical Question A7

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.

Clinical Question A8

What is the best chemotherapy for treatment of elderly patients with stage IIIB/IV NSCLC?

Recommendation A8

Decisions on the selection of chemotherapy should not be made or altered based on age alone.

Clinical Question A9

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 maintenance 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].

Clinical Question B1

What is the most effective second-line therapy for patients with stage IIIB/IV NSCLC with negative or unknown *EGFR/ALK* status and NSCC?

Recommendation B1

For patients with advanced NSCLC, NSCC, negative or unknown *EGFR/ALK* status, and adequate PS, when disease has progressed during or after first-line platinum-based therapy, *nivolumab* (in all patients with NSCLC) or *pembrolizumab* (in patients with programmed cell death ligand 1 [PD-L1]-positive tumours) is preferred, if either is available, over docetaxel, erlotinib, gefitinib, or pemetrexed as second-line therapy.

Key Evidence from ASCO and PEBC Reviews for Recommendation B1



High-quality evidence from ASCO's systematic review suggested there were no statistically significant differences in effectiveness as single-agent second-line therapies among docetaxel, erlotinib, gefitinib, or pemetrexed [1]. There was no evidence to suggest that combination therapy was superior to single-agent therapy; however, combination therapy may be more toxic.

Following the publication of ASCO's systematic review, our updated systematic review on immune checkpoint inhibitors found a significant positive OS benefit of nivolumab (hazard ratio [HR], 0.72; 95% confidence interval [CI], 0.60 to 0.77; $p < 0.001$) or pembrolizumab (in patients with PD-L1-positive tumours: pembrolizumab 2 mg/kg: HR, 0.71; 95% CI, 0.58 to 0.88; $p = 0.0008$; pembrolizumab 10 mg/kg: HR, 0.61; 95% CI, 0.49 to 0.75; $p < 0.0001$) compared with docetaxel [11,12]. Furthermore, the adverse effects were higher mainly in the docetaxel group compared with the nivolumab or pembrolizumab group.

Interpretation of Evidence for Recommendation B1

Based on the evidence from our systematic review, the Working Group preferred to recommend nivolumab or pembrolizumab over other single-agent therapies because of the strong positive effect on OS with fewer adverse events.

Implementation Considerations for Recommendation B1

Gefitinib is not approved by Health Canada for this indication. At the time this guideline was developed, nivolumab was still under consideration by Health Canada. Pembrolizumab has not been submitted to Health Canada for approval.

Clinical Question B2

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

Recommendation B2

For patients with advanced NSCLC, SCC, negative or unknown EGFR/ALK status, and adequate PS, when disease has progressed during or after first-line platinum-based therapy, *nivolumab (in all patients with NSCLC) or pembrolizumab (in patients with PD-L1-positive tumours) is preferred*, if either is available, over docetaxel, erlotinib, or gefitinib as second-line therapy.

Key Evidence from ASCO and PEBC Reviews for Recommendation B2

Most of the second-line studies included in the ASCO reviews for recommendation B1 included patients with SCC [1]. Only pemetrexed was excluded as a second-line agent because it was shown to be less effective for patients with SCC.

Following the publication of ASCO's systematic review, our updated systematic review on immune checkpoint inhibitors found a significant positive OS benefit of nivolumab (HR, 0.59; 95% CI, 0.44 to 0.79; $p < 0.001$) or pembrolizumab (in patients with PD-L1-positive tumours: pembrolizumab 2 mg/kg: HR, 0.71; 95% CI, 0.58 to 0.88; $p = 0.0008$; pembrolizumab 10 mg/kg: HR, 0.61; 95% CI, 0.49 to 0.75; $p < 0.0001$) compared with docetaxel [11,13]. Furthermore, the adverse effects were higher mainly in the docetaxel group compared with the nivolumab or pembrolizumab group.

The ASCO review did mention the Brahmer et al. 2015 trial in their review, but it was not yet available when they were developing their recommendations [1,13]. They will consider this new evidence in future updates of their guideline.

Interpretation of Evidence for Recommendation B2

Based on the evidence from our systematic review, the Working Group preferred to recommend nivolumab or pembrolizumab over other single-agent therapies because of the strong positive effect on OS with fewer adverse events.

Implementation Considerations for Recommendation B2



Clinical Question B3.a

What is the most effective second-line therapy for patients with stage IIIB/IV NSCLC with a sensitizing *EGFR* mutation who received a first-line *EGFR* TKI and experienced disease progression?

Recommendation B3.a
For patients with a sensitizing <i>EGFR</i> mutation who did not respond to a first-line <i>EGFR</i> TKI, combination cytotoxic chemotherapy (Recommendation A2) or a <i>third-generation EGFR TKI such as osimertinib in patients shown to have a T790M mutation</i> is recommended, following the first-line recommendations for patients with NSCC.
Key Evidence from ASCO for Recommendation B3.a
Because no studies were found in the ASCO review, this recommendation was based on consensus of the ASCO committee [1].
Interpretation of Evidence for Recommendation B3.a
A more recent trial published after the search cut-off dates of the ASCO and PEBC reviews, found that the overall objective tumour response rate was very high (61%; 95% CI, 52% to 70%) with limited skin and gastrointestinal adverse effects in patients with the T790M mutation who have progressed following treatment with an <i>EGFR</i> TKI and who have received osimertinib [14]. This drug has recently been approved by the Food and Drug Administration and is soon to be approved by Health Canada. Therefore, osimertinib for patients with the T790M mutation was added to the ASCO recommendation.
Implementation Considerations for Recommendation B3.a
Second-line <i>EGFR</i> TKIs are not currently licensed in Ontario.

Clinical Question B3.b

What is the most effective second-line therapy for patients with stage IIIB/IV NSCLC with a sensitizing *EGFR* mutation who received a first-line *EGFR* TKI and experienced disease progression after an initial response?

Recommendation B3.b
Patients who received an <i>EGFR</i> TKI in the first-line setting, had an initial response, and subsequently experienced disease progression may be switched to chemotherapy or a <i>third-generation EGFR TKI such as osimertinib in patients shown to have a T790M mutation</i> as second-line therapy. <i>There is insufficient evidence to recommend the use of other EGFR TKIs, such as afatinib, in previously treated patients, as available data do not demonstrate any improvement in OS.</i>
Key Evidence from ASCO for Recommendation B3.b
Because no studies were found in the ASCO review, this recommendation was based on consensus of the ASCO committee [1].
Interpretation of Evidence for Recommendation B3.b

Osmertinib for patients with the T790M mutation was added to the ASCO recommendation (see interpretation of evidence for Recommendations B3.a). ASCO's recommendation was worded as, "Patients who received an EGFR TKI in the first-line setting, had an initial response, and subsequently experienced disease progression may be switched to chemotherapy or another EGFR TKI as second-line therapy." This could lead a physician to think that if you gave gefitinib than you should use erlotinib or afatinib as second-line therapy. According to the PEBC 7-9 version 2 guideline, the evidence does not support this [15]. Therefore, the recommendation on the use of other EGFR TKIs, such as afatinib, from the PEBC 7-9 version 2 guideline, was added. Readers should refer to the 7-9 version 2 guideline for additional information [15].

Implementation Considerations for Recommendation B3.b

Second-line EGFR TKIs are not currently licensed in Ontario.

Clinical Question B4

What is the most effective second-line therapy for patients with stage IIIB/IV NSCLC with ALK rearrangement with progression after first-line crizotinib?

Recommendation B4

Patients whose tumours have ALK rearrangements and who received crizotinib in the first-line setting may be offered the option of chemotherapy (after first-line recommendations for patients with NSCC [see Recommendation A2]) or ceritinib in the second-line setting.

Implementation Considerations for Recommendation B4

There is a gap in public funding for ceritinib in Ontario at this time.

Clinical Question B5

What is the optimal second-line treatment for elderly patients with stage IIIB/IV NSCLC?

Recommendation B5

The evidence does not support the selection of a specific second-line chemotherapy drug or combination based on age alone. As stated in Recommendation A8, age alone is not a contraindication to chemotherapy for NSCLC.

Clinical Question C

Is there a role for third-line therapy or beyond in the treatment of stage IIIB/IV NSCLC?

Recommendation C1

When disease progresses during or after second-line chemotherapy, treatment with erlotinib may be recommended as third-line therapy for patients with a PS of 0 to 3 who have not received prior erlotinib or gefitinib.

Recommendation C2a

Docetaxel, erlotinib, gefitinib, or pemetrexed may be used in patients with stage IIIB/IV NSCLC with negative or unknown EGFR/ALK status and NSCC after progression on nivolumab or pembrolizumab, although data are limited.

Key Evidence from ASCO and PEBC Reviews for Recommendation C2a

The evidence from the ASCO systematic review suggested that docetaxel, erlotinib, gefitinib, or pemetrexed were effective single-agent second-line therapies. Newer evidence from the PEBC systematic review suggested that nivolumab or pembrolizumab may be more effective than docetaxel as second-line therapies (see key evidence for Recommendations B1).

Interpretation of Evidence for Recommendation C2a

Since nivolumab or pembrolizumab have been recommended as the preferred second-line therapies, the Working Group recommended the use of docetaxel, erlotinib, gefitinib, or pemetrexed as possible third-line therapies because these are established therapies that have been shown to be effective in the second-line setting and may be effective in the third-line setting.

Recommendation C2b

Docetaxel, erlotinib, or gefitinib may be used in patients with stage IIIB/IV NSCLC with negative or unknown EGFR/ALK status and SCC after progression on nivolumab or pembrolizumab, although data are limited.

Key Evidence from ASCO and PEBC Reviews for Recommendation C2b

The evidence from the ASCO systematic review suggested that docetaxel, erlotinib, or gefitinib were effective single-agent second-line therapies. Newer evidence from the PEBC systematic review suggested that nivolumab or pembrolizumab may be more effective than docetaxel as second-line therapies (see key evidence for Recommendations B2).

Interpretation of Evidence for Recommendation C2b

Since nivolumab or pembrolizumab have been recommended as the preferred second-line therapies, the Working Group recommended the use of docetaxel, erlotinib, or gefitinib as possible third-line therapies because these are established therapies that have been shown to be effective in the second-line setting and may be effective in the third-line setting.

Australian Government Cancer Council Australia, 2017 [5].

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
<p>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.</p> <p>Last reviewed September 2017</p>	I	[4], [5]
+ Evidence-based recommendation?		Grade
<p>Platinum-based chemotherapy can be used to extend survival in newly diagnosed patients with stage IV NSCLC.</p> <p>Last reviewed September 2017</p>		A
✓ Practice point?		
<p>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.</p> <p>Last reviewed September 2017</p>		

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
<p>First-line chemotherapy involving cisplatin results in a slightly higher likelihood of tumour response than the same chemotherapy with carboplatin.</p> <p>Last reviewed September 2017</p>	I	[1], [2], [3]
<p>There is no definite overall survival difference between cisplatin or carboplatin based first-line chemotherapy.</p> <p>Last reviewed September 2017</p>	I	[1], [2], [3]
<p>Cisplatin-based chemotherapy is associated with more severe nausea and vomiting and nephrotoxicity; severe thrombocytopenia is more frequent during carboplatin-based chemotherapy.</p> <p>Last reviewed September 2017</p>	I	[1], [2], [3]
+ Evidence-based recommendation?		Grade
<p>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.</p> <p>Last reviewed September 2017</p>		B
✓ Practice point?		
<p>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.</p> <p>Last reviewed September 2017</p>		

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

+ Evidence-based recommendation?	Grade
<p>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.</p> <p>Last reviewed September 2017</p>	A
+ Evidence-based recommendation?	Grade
<p>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.</p> <p>Last reviewed September 2017</p>	B
+ Evidence-based recommendation?	Grade
<p>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.</p> <p>Last reviewed September 2017</p>	B
✓ Practice point?	
<p>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.</p> <p>Last reviewed September 2017</p>	

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, constipation and phlebitis while gemcitabine plus 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).^[6] 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 thrombocytopenia (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 3/4 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
<p>3G platinum-based combination chemotherapy (vinorelbine, paclitaxel, docetaxel, irinotecan or gemcitabine) is superior to 3G agent monotherapy.</p> <p>Last reviewed September 2017</p>	I	[1], [4]
<p>3G platinum-based monotherapy (vinorelbine, paclitaxel, docetaxel, or gemcitabine) improves survival compared with best supportive care.</p> <p>Last reviewed September 2017</p>	I	[2]
+ Evidence-based recommendation?		Grade
<p>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.</p> <p>Last reviewed September 2017</p>		A
+ Evidence-based recommendation?		Grade
<p>Patients unfit for combination chemotherapy could be considered for 3G monotherapy with vinorelbine, paclitaxel, docetaxel or gemcitabine.</p> <p>Last reviewed September 2017</p>		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-analysis 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 3 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 thrombocytopenia 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 paclitaxel 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 al evaluated 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 neutropenia 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, neutropenia, 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 thrombocytopenia, 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 RCTs.^[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
<p>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.</p> <p>Last reviewed September 2017</p>	I	[2], [1]
+ Evidence-based recommendation?		Grade
<p>First-line combination chemotherapy should in most cases be stopped at disease progression or after four cycles in patients with advanced NSCLC.</p> <p>Last reviewed September 2017</p>		B
✓ Practice point?		
<p>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.</p> <p>Last reviewed September 2017</p>		

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; HR 0.75; 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
<p>In carefully selected[^] patients with advanced NSCLC, high dose bevacizumab improves tumour response rate and progression free survival.</p> <p>[^]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.</p> <p>Last reviewed September 2017</p>	I	[4], [5]
<p>In carefully selected^{**} patients with advanced NSCLC, treatment with high dose bevacizumab is associated with an increase in treatment related deaths.</p> <p>Last reviewed September 2017</p>	I	[4]
+ Evidence-based recommendation?		Grade
<p>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.</p> <p>Last reviewed December 2015</p>		B

Evidence summary	Level	References
<p>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.</p> <p>Last reviewed September 2017</p>	II	[8], [9], [11], [10]
+ Evidence-based recommendation?		Grade
<p>The first generation EGFR TKIs gefitinib or erlotinib should not be used in unselected patients in combination with standard chemotherapy.</p> <p>Last reviewed September 2017</p>		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.^{[11][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.^{[11][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 studied 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 = 0.17; 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.^[9] 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-analyses 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/vinorelbine 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 studied. Of these, 13 trials using a validated QOL instrument were included for review. The meta-analysis found QOL reporting/analysis techniques were heterogeneous. Nine RCTs reported the rate of completed baseline assessment and compliance survivors at analysis of greater than 50%, for data synthesis.^[1] Of these, only one trial found a significant difference in QOL between the comparator arms: paclitaxel plus cisplatin was better than teniposide plus cisplatin. However, teniposide is not used in practice today. Based on this review, it seems unlikely that a major difference exists in the global QOL associated with standard chemotherapy regimens for advanced NSCLC.^[1] Furthermore, the authors concluded that although the available QOL reporting formats are largely acceptable, a lack of uniformity in analysis and a poor compliance to QOL assessment made between-trial comparisons difficult.^[1]

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

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

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

Evidence summary	Level	References
In patients with poor performance status (PS 2), first-line monotherapy with 3G chemotherapy (vinorelbine, gemcitabine, paclitaxel or docetaxel) may improve survival and/or quality of life. 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 regimens or monotherapy with 3G agents or anti-EGFR TKIs.

Liu et al undertook a systematic review of phase II and III 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 vinorelbine 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 0.5-1.1 (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
<p>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.</p> <p>Last reviewed December 2015</p>	II	[1]
<p>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.</p> <p>Last reviewed December 2015</p>	II	[2]
<p>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 thrombocytopenia.</p> <p>Last reviewed December 2015</p>	I	[4]
<p>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.</p> <p>Last reviewed December 2015</p>	II	[5]

+ Evidence-based recommendation?	Grade
<p>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).</p> <p>Last reviewed December 2015</p>	B
+ Evidence-based recommendation?	Grade
<p>In elderly patients, first-line gemcitabine doublet chemotherapy is not recommended.</p> <p>Last reviewed December 2015</p>	B
+ Evidence-based recommendation?	Grade
<p>In fit elderly patients, first-line carboplatin/weekly paclitaxel may be offered instead of 3G monotherapy, but at the expense of greater neutropaenia.</p> <p>Last reviewed December 2015</p>	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 3/4 thrombocytopenia 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

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

Evidence summary	Level	References
In previously treated patients with advanced NSCLC, single agent docetaxel 75 mg/m ² improves survival compared with best supportive care or vinorelbine and ifosfamide. Last reviewed September 2017	II	[1], [2]
In previously treated patients with advanced NSCLC not suitable for immunotherapy, single agent pemetrexed has similar efficacy but fewer side effects than three-weekly docetaxel. Last reviewed September 2017	II	[5]
In previously treated patients with advanced NSCLC, compared with docetaxel, pemetrexed appears to have greater efficacy in non-squamous cell carcinoma histology, and inferior efficacy in squamous cell carcinoma. Last reviewed September 2017	I	[7]
+ Evidence-based recommendation?		Grade
In unselected patients previously treated for advanced NSCLC not suitable for immunotherapy, chemotherapy with docetaxel or pemetrexed may be used as second-line therapy. Pemetrexed is preferred in non-squamous cell carcinoma histology, and docetaxel is preferred in squamous cell carcinoma. Last reviewed September 2017		B

Evidence summary	Level	References
Doublet therapy as second-line treatment of advanced NSCLC increases response rate and progression free survival, but is more toxic and does not improve overall survival compared with single agent chemotherapy. Last reviewed September 2017	I	[10], [11]
+ Evidence-based recommendation?		Grade
Doublet therapy is not recommended as second-line treatment of advanced NSCLC . Last reviewed September 2017		A
Evidence summary	Level	References
Erlotinib is inferior to docetaxel as 2nd line therapy in patients without EGFR activating mutations. Last reviewed September 2017	II	[9], [8]
+ Evidence-based recommendation?		Grade
Erlotinib is not effective in WT EGFR patients. Last reviewed September 2017		B

Monotherapy in unselected patients

Several randomised controlled trials (RCTs) have been reported examining the role of second line systemic therapy in unselected patients. The first studies examined docetaxel, establishing it as a standard of care in suitably fit patients. Subsequent studies examined different schedules of docetaxel, or examined the efficacy of new agents using it as the reference standard.

In 2000, two key RCTs were reported evaluating the efficacy of single agent docetaxel in previously treated NSCLC. Shepherd et al evaluated the efficacy of docetaxel versus best supportive care in 104 patients previously treated with platinum-based chemotherapy.^[1] Compared with best supportive care, docetaxel 75 mg/m² Q three-weekly, improved one-year survival (37% versus 11%; P = 0 .003).^[1] Fossella et al randomised 373 previously treated patients with advanced NSCLC to two dose regimens of docetaxel compared with control arm of vinorelbine or ifosfamide.^[2] one-year survival was significantly greater with docetaxel 75 mg/m² than with the control treatment (32% versus 19%; P = 0.025,). Based on these two studies, docetaxel became the standard of care as second-line treatment of advanced NSCLC. Further supporting the clinical value of docetaxel was the results of the QOL analysis in the Shepherd study, which indicated less deterioration in QOL for docetaxel treated patients compared with best supportive care.^[3]

Bria et al, compared the efficacy of weekly docetaxel with the reference standard of three-weekly, by evaluating data from 1018 patients from six RCTs. No significant differences in OS or RR in favour of the weekly schedule were found, however weekly docetaxel was associated with fewer grade 3/4 neutropaenic events.^[4]

Hanna et al, then compared single agent pemetrexed to three-weekly docetaxel as second line monotherapy of advanced NSCLC.^[5] This study of 571 patients, randomised to three-weekly pemetrexed or docetaxel, showed equivalent efficacy outcomes (PFS, one-year survival) but significantly fewer side effects in favour of pemetrexed.^[5] Consequently, pemetrexed was soon registered as an alternative second-line agent in NSCLC. Scagliotti et al in a post hoc analysis of data from two RCTs of pemetrexed, subsequently showed that pemetrexed increased OS in patients with non-SCC histology (p = 0.047), whereas OS was decreased with pemetrexed in SCC histology (p = 0.018).^[6] A subsequent systematic review has confirmed this treatment-by-histology interaction effect with pemetrexed treatment showing greatest benefit in non-SCC histology.^[7]

Older studies in patients not tested for EGFR activating mutations had indicated that EGFR TKIs were potential 2nd line therapies in patients without EGFR mutations. However, in the TAILOR study of 222 patients, erlotinib and docetaxel were compared as 2nd line therapy in patients with wild type EGFR.^[8] Overall survival was superior for docetaxel (median OS 8.2 vs 5.4 months, HR 0.73, p=0.05). There were some imbalances between the arms of this study, with more squamous tumours and current or former smokers in the erlotinib arm. However, the results were confirmed by the DELTA study, a Japanese study involving 301 patients.^[9] Patients with wild-type EGFR were randomised to docetaxel or erlotinib as 2nd or 3rd line therapy. PFS favoured docetaxel (median 2.9 vs 1.3 months, p=0.01), with no significant difference in overall survival (median 10.1 vs 9.0 months, p=0.91). Note that in this study, docetaxel was administered at a dose of 60mg/m² every 3 weeks, as this is the standard dose in Japan.

Combination therapy in unselected patients

Di Maio et al, examined whether doublet chemotherapy is more effective than single agent chemotherapy as second-line treatment of advanced NSCLC in 847 patients from six RCTs from 1999 – 2005.^[10] Single agents evaluated include docetaxel (three studies), irinotecan, cisplatin, or pemetrexed. Response rate was greater for doublet therapy (15 % versus 7.3 %, p = 0.0004), as was PFS (HR 0.79, 95% CI 0.68 – 0.91).^[10] However, there was no significant difference in OS between single agent and doublet chemotherapy and there were significantly more grade 3/4 haematologic and non-haematologic toxicities with doublet chemotherapy.^[10]

Qi et al, examined whether doublet pemetrexed based therapy is more effective than single agent pemetrexed as second-line treatment of advanced NSCLC in 1,186 patients from five RCTs from 1999 – 2005.^[11] Only one of these studies was a phase III RCT, that of the dual targeted TKI vandetanib (anti-VEGF and anti EGFR).^[12] Here doublet therapy was associated with a greater RR, but did not improve PFS).^[12] The other four phase II RCTs evaluated the addition of carboplatin, and the new agents enzastorurin, matuzumab and bortezomib to pemetrexed.^[11] Overall, there was improvement in RR and PFS with doublet therapy but not survival.^[11] Furthermore, there was more grade 3/4 neutropaenia and thrombocytopenia with the doublet therapy.^[11]

Herbst et al, also evaluated the efficacy of vandetanib. In their double blind RCT, the effect of Vandetanib plus docetaxel was compared with docetaxel as second-line treatment for patients with advanced NSCLC, on PFS in 1391 patients.^[13] Vandetanib plus docetaxel was shown to be an active regimen with significant improvement in PFS versus placebo plus docetaxel (HR 0.79, 97.58% CI 0.70–0.90; p<0.0001).^[13], however, the size of the effect on median PFS was small (4.0 months (vandetanib) versus 3.2 months (placebo), and therefore of questionable clinical significance, and survival benefit not shown.^[13]

What is the optimal third-line therapy in unselected patients with stage IV inoperable NSCLC?

Evidence summary and recommendations		
Evidence summary	Level	References
<p>In unselected previously treated patients with advanced NSCLC who have received two lines of therapy, single agent docetaxel administered 3 weekly is a potential option in fit patients.</p> <p>Last reviewed September 2017</p>	II	[4]
+ Evidence-based recommendation?		Grade
<p>In fit, previously treated patients with advanced NSCLC who have received two lines of therapy, single agent docetaxel administered 3 weekly can be considered.</p> <p>Last reviewed September 2017</p>		B

Few randomised controlled trials (RCTs) have evaluated third line therapy in unselected patients with advanced NSCLC. The aforementioned negative RCT (ISEL) of gefitinib versus placebo in 1692 patients included 847 patients (50%) that had received two previous lines of therapy.^[1] The positive RCT (BR21) of erlotinib versus placebo in 731 patients included approximately 50% of patients having received two previous lines of therapy. Univariate analysis of OS by number of prior regimens found OS remained in favour of erlotinib (compared with placebo) by similar magnitude to the overall study population results (HR 0.80, $p = 0.02$).^[2] The study by Kim et al, comparing gefitinib to docetaxel in previously treated advanced NSCLC, only included 235 (16%) patients that had received two previous lines of therapy. Analysis of OS number of prior regimens found OS more in favour of docetaxel. But as this is a post hoc analysis with small patient numbers, it is not appropriate to draw conclusions.^[3]

The Japanese DELTA study enrolled both 2nd and 3rd line patients, but only 17% of patients were 3rd line in this study.^[4] In this study of 301 patients, PFS favoured docetaxel (median 2.9 vs 1.3 months, $p=0.01$), with no significant difference in overall survival (median 10.1 vs 9.0 months, $p=0.91$). With PD-1 or PD-L1 immunotherapy having been shown to be superior to docetaxel as 2nd line therapy (see immunotherapy section), the DELTA trial and other studies support the use of docetaxel as 3rd line therapy in fit patients.

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

- currently being updated

Passiglia F et al., 2020 [91].

Italian Association of Medical Oncology (AIOM)

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

Leitlinienorganisation/Fragestellung

Evidence-based guideline for the management of lung tumors.

Methodik

Grundlage der Leitlinie

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

- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Medline (PubMed), Embase-databases and Cochrane-Library, up to September 2019.
- Update von Facchinetti F et al., 2019 [18]

LoE/GoR

- GRADE

The global quality of evidence was defined as follow:

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

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

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

Recommendations

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

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

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

Global quality of evidence GRADE	Clinical recommendation	Strength of recommendation
Moderate	For patients with <i>EGFR/ALK</i> wild-type, advanced NSCLC and PD-L1 TPS $\geq 50\%$, first-line therapy with Pembrolizumab should be considered as treatment of choice	Strong for
Low	For patients with advanced, non-squamous NSCLC who completed 4–6 cycles of first-line chemotherapy with platinum-pemetrexed and experienced partial response or stable disease, maintenance therapy with single agent pemetrexed until disease progression or unacceptable toxicities could be considered as a treatment option.	Conditional for
Moderate	For patients with advanced NSCLC who experienced disease progression after first-line chemotherapy, immunotherapy with nivolumab, or atezolizumab, or pembrolizumab (PD-L1 TPS $\geq 1\%$), should be considered as a treatment of choice	Strong for
Very low	For patients with advanced lung adenocarcinoma who experienced disease progression after first-line chemotherapy, the combination of nintedanib plus docetaxel could be considered as a treatment option.	Conditional for

4 Detaillierte Darstellung der Recherchestrategie

**Cochrane Library - Cochrane Database of Systematic Reviews (Issue 17 of 12, July 2020)
am 20.07.2020**

#	Suchfrage
1	[mh "Carcinoma, Non-Small-Cell Lung"]
2	(((non NEXT small) OR nonsmall) NEXT cell NEXT lung):ti,ab,kw
3	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesions* OR malignan*):ti,ab,kw
4	nsclc*:ti,ab,kw
5	#1 OR (#2 AND #3) OR #4
6	#6 Publication date from Jul 2015 to present

Systematic Reviews in Medline (PubMed) am 20.07.2020

#	Suchfrage
1	"Carcinoma, Non-Small-Cell Lung"[mh]
2	(((non[tiab] AND small[tiab]) OR nonsmall[tiab]) AND cell[tiab]) AND lung[tiab]
3	((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesions*[tiab]) OR malignan*[tiab]
4	#1 OR (#2 AND #3)
5	(#4) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT

#	Suchfrage
	(letter[pt] OR newspaper article[pt]) OR Technical Report[ptyp] OR (((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab])) OR (((((((HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab] OR (systematic*[tiab] AND review*[tiab]) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab] OR (meta[tiab] AND analyz*[tiab]) OR (meta[tiab] AND analys*[tiab]) OR (meta[tiab] AND analyt*[tiab])) OR ((review*[tiab] OR overview*[tiab]) AND ((evidence[tiab] AND based[tiab])))))
6	((#5) AND ("2015/07/01"[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 20.07.2020

#	Suchfrage
1	Carcinoma, Non-Small-Cell Lung[mh]
2	(((non[tiab] AND small[tiab]) OR nonsmall[tiab] AND cell[tiab] AND lung[tiab]
3	((((((((tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR sarcoma*[tiab] OR cancer*[tiab] OR lesions*[tiab] OR malignan*[tiab]
4	#1 OR (#2 AND #3)
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
6	(((#5) AND ("2015/07/01"[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]))
7	(#7) NOT (retracted publication [pt] OR retraction of publication [pt])

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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: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • Non-randomised, experimental trial • Cohort study • Case-control study
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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 1: NHMRC Evidence Hierarchy (Australian Government Cancer Council Australia)

**Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6
2020-B-256**

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Arbeitsgemeinschaft Thorakale Onkologie in der Arbeitsgemeinschaft Internistische Onkologie der Deutschen Krebsgesellschaft (DKG)

Indikation gemäß Beratungsantrag

Zur Behandlung des fortgeschrittenen nicht-kleinzelligen Bronchialkarzinoms (NSCLC) mit MET-Tyrosinkinase-Rezeptor-Exon-14- (METex14-)Skipping-Veränderungen bei Erwachsenen.

Was ist der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz in der Behandlung des fortgeschrittenen nicht-kleinzelligen Bronchialkarzinoms (NSCLC) mit MET-Tyrosinkinase-Rezeptor-Exon-14-(METex14-)Skipping-Veränderungen bei Erwachsenen? Wie sieht die Versorgungspraxis in Deutschland aus?

Zusammenfassung

Bei 3-4% aller Patienten mit nicht-kleinzelligem Lungenkarzinom ist genetisch in den Tumorzellen ein *MET* Exon-14-Skipping (METex14-Skipping) nachweisbar. Der Nachweis von METex14-Skipping ist im fortgeschrittenen Krankheitsstadium mit einer ungünstigen Prognose assoziiert.

Bisher gibt es im fortgeschrittenen Stadium keine zugelassene, gezielte Therapie für NSCLC-Patienten mit METex14-Skipping. Der Therapieanspruch ist palliativ. Standard in der Erstlinie ist eine kombinierte Immunchemotherapie, ab der Zweitlinie eine Therapie nach Maßgabe des behandelnden Arztes. Bei Patienten mit einer Therapieindikation gehören dazu vor allem

- in der Erstlinie zugelassene, aber bisher nicht eingesetzte Arzneimittel aus dem Bereich der Chemotherapie und der Immuncheckpoint-Inhibitoren
- Docetaxel, allein oder in Kombination mit Angiogenese-Inhibitoren
- Multikinase-Inhibitoren
- Weitere Zytostatika

Allerdings nimmt die Anzahl an Hinweisen aus Phase I/II-Studien zu, dass eine zielgerichtete Therapie des fortgeschrittenen NSCLC mit METex14-Skipping-Veränderung mittels TKI effektiv zu sein scheint. Bei den Adenosintriphosphat-kompetitiven TKIs Bozitinib, Cabozantinib, Crizotinib, Merestinib, Glesatinib, Capmatinib, Savolitinib und Tepotinib zeigten sich präklinische und klinische Hinweise auf Effektivität. Zurzeit liegen keine Ergebnisse randomisierter, klinischer Studien zu MET-Inhibitoren bei Patienten mit fortgeschrittenem NSCLC und METex14-Skipping-Veränderung vor.

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Fragestellung

Gefragt wird nach dem Standard in der Behandlung von erwachsenen Patienten mit fortgeschrittenem, nichtkleinzelligem Lungenkarzinom (NSCLC) und (METex14-Skippping).

Eine weitere Präzisierung der Fragestellung durch den pharmazeutischen Unternehmer liegt nicht vor, insbesondere nicht zur Therapielinie (Erst- oder spätere Therapielinie).

Stand des Wissens

Das Lungenkarzinom ist bei Frauen der dritt-, bei Männern der zweithäufigste maligne Tumor in den deutschsprachigen Ländern. Das mediane Erkrankungsalter liegt zwischen 68 und 70 Jahren. Hauptrisikofaktor ist Rauchen.

Patienten mit nicht-kleinzelligem Lungenkarzinom haben in frühen und in einem Teil der lokal fortgeschrittenen Stadien einen kurativen Therapieanspruch. Therapieoptionen sind Operation, Bestrahlung, Chemo- und Immuntherapie, meist kombiniert als multimodale Therapie. Für die große Mehrzahl von Patienten im Stadium IIIB/IV ist die Therapie nicht kurativ. In den letzten Jahren hat die Integration von Immuncheckpoint- und Kinase-Inhibitoren im Zusammenhang mit prädiktiven Biomarkern die Prognose vieler Patienten deutlich verbessert. Weiterhin stehen Zytostatika, Angiogenese-Inhibitoren und unterstützende Maßnahmen zur Verfügung.

Bei diesen Patienten ist das Therapieziel palliativ [1 - 4]. Die mediane Überlebenszeit lag noch vor wenigen Jahren zwischen 8 und 12 Monaten. Bei Patienten mit aktivierenden Exon 19- oder Exon 21-Aberrationen sowie einigen der sog. „seltenen (uncommon)“ *EGFR*-Mutationen sowie mit *ALK*-, *ROS1*- und *BRAF V600*- Alterationen unter zielgerichteter Therapie ist sie deutlich länger. Bei *EGFR*-Mutationen oder *ALK*-Translokationen liegen die medianen Überlebenszeiten im Bereich von mehreren Jahren. Die aktuellen Empfehlungen basieren auf prädiktiven histologischen, immunhistochemischen und genetischen Markern. Der Algorithmus für die Erstlinientherapie ist in den Abbildungen 1 – 3 dargestellt.

Abbildung 1: Algorithmus für die medikamentöse Therapie in fortgeschrittenen Stadien – Übersicht [1]

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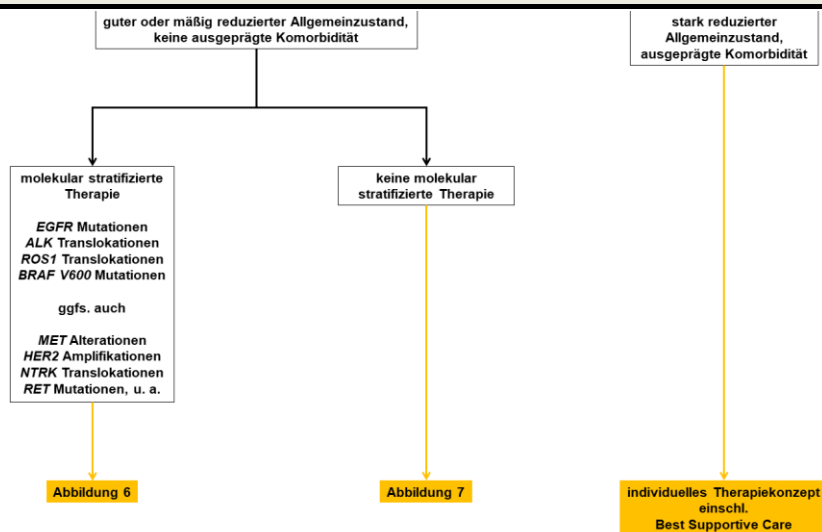


Abbildung 2: Algorithmus für die molekular stratifizierte Therapie in fortgeschrittenen Stadien

Kontaktdaten

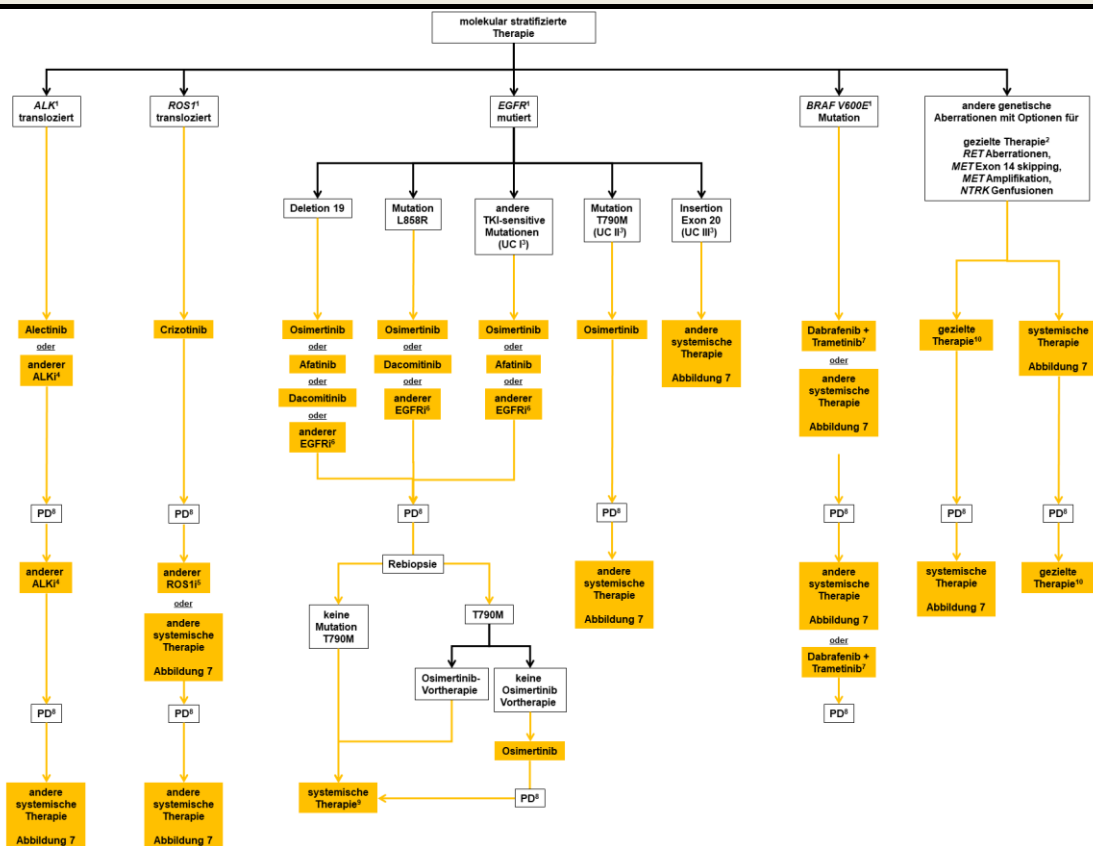
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Legende: ¹ALK – Gen der Anaplastic Lymphoma Kinase; *ROS1* – Gen der Protoonkogen Tyrosinproteinkinase ROS; *EGFR* – Gen des Epidermal Growth Factor Receptor; *BRAFV600E* – Punktmutation im BRAF-Gen; ²andere genetische Aberrationen – *BRAFV600E*; *c-MET Exon 14* skipping mutation; *NTRK* Fusionen; ³UC – uncommon mutations, UC I – Punktmutationen oder Duplikationen in den Exonen 18-21, UCII – Mutation T790M im Exon 20 allein oder in Kombination mit anderen Mutationen, UC III – Exon 20 Insertionen; ⁴ALKi – ALK-Inhibitor: Alectinib, Brigatinib (zugelassen nach Crizotinib), Ceritinib, Crizotinib, Lorlatinib (zugelassen nach Alectinib, Ceritinib und Crizotinib); ⁵ROSi – ROS1-Inhibitor: Ceritinib, Crizotinib, Cabozantinib (nicht in dieser Indikation zugelassen), Lorlatinib (nicht in dieser Indikation zugelassen); ⁶EGFR-TKI – Afatinib, Dacomitinib, Erlotinib, Gefitinib, Osimertinib; ⁷Dabrafenib/Trametinib kann in der Erst- oder der Zweitlinien-therapie eingesetzt werden; ⁸CR – komplette Remission, PR – partielle Remission, SD – stabile Erkrankung, PD – progrediente Erkrankung; ⁹ andere systemische Therapie, z. B. Carboplatin/Paclitaxel/Atezolizumab/Bevacizumab; ¹⁰ jeweils in Abhängigkeit von der Zulassung; Larotrectinib ist zugelassen bei *NTRK*-Genfusionen, wenn keine anderen, zufriedenstellenden Therapieoptionen zur Verfügung stehen; weitere gezielte Arzneimittel sind derzeit in dieser Gruppe nicht zugelassen;

Abbildung 3: Algorithmus für die nicht-molekular stratifizierte medikamentöse Therapie in fortgeschrittenen Stadien

Kontaktadressen

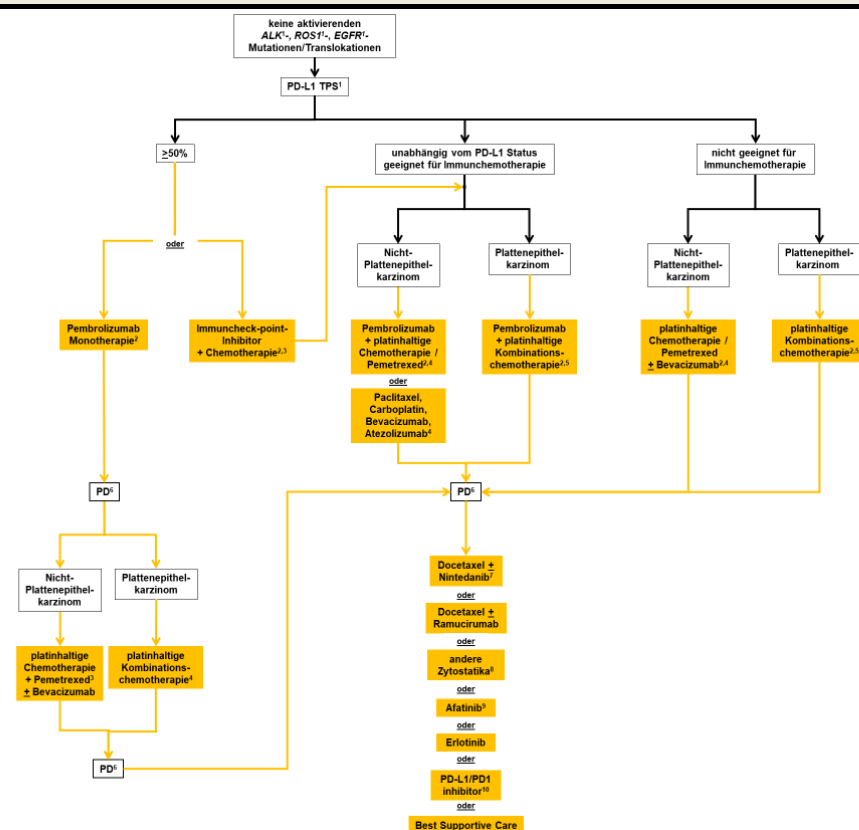
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Legende: ; ¹PD-L1 TPS - Expression von PD-L1 auf Tumorzellen, quantifiziert nach dem Tumor Progression Score (TPS); ²wenn für Immuntherapie geeignet und keine relevanten Kontraindikationen bestehen; siehe auch Onkopedia Lungenkarzinom Zulassung; ³Kombination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

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

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Das *MET* Gen ist auf dem langen Arm von Chromosom 7 lokalisiert und umfasst 21 Exone. *MET* kodiert für eine Rezeptortyrosinkinase, die physiologisch auf epithelialen Zellen, aber auch auf Endothel, Neuronen, Hepatozyten und hämatopoetischen Zellen exprimiert wird. Der natürliche Ligand von *MET* ist HGF, der Hepatocyte Growth Factor. Die Phosphorylierung von *MET* aktiviert unterschiedliche intrazelluläre Signalübertragungswege und induziert Proliferation, Überleben, Mobilisation und Invasion von Zellen. In Tumoren sind unterschiedliche Aberrationen von *MET* nachgewiesen worden. Dazu gehören Mutationen, Amplifikation, Überexpression und Transaktivierung mit anderen Rezeptortyrosinkinasen [5].

Eine der häufigen Aberrationen ist die sog. *MET* Exon-14-Skipping-Mutation (METex14-Skipping). Inzwischen wurde weit über 100 distinkte, genetische Varianten als Ursache einer *MET* Exon-14-Skipping-Mutation identifiziert [6]. Die daraus resultierende In-Frame-Deletion führt zu einem verkürzten Transkript. Der *MET* Rezeptor behält seine Affinität zu HGF und seine transmembranöse Lokalisation mit katalytischer Aktivität. In präklinischen Modellen ist die *MET* Exon-14-Skipping-Mutation ein starker, onkogener Treiber.

METex14-Skipping wird bei 3-4% der NSCLC-Patienten nachgewiesen. Auch beim NSCLC treten unterschiedliche Mutationen auf. Histologisch dominieren Adenokarzinome, METex14-Skipping tritt aber auch in anderen histologischen Formen auf. Das mediane Alter entspricht etwa dem Durchschnittsalter der NSCLC-Patienten, etwa 60% der Patienten sind weiblich [7]. In multivariaten Analysen war METex14-Skipping ein unabhängiger, negativer prognostischer Faktor [8].

Bisher gibt es in der EU keine zugelassene, gezielte Therapie für NSCLC-Patienten mit METex14-Skipping. Allerdings nimmt die Anzahl an Hinweisen aus Phase I/II-Studien zu, dass eine zielgerichtete Therapie des fortgeschrittenen NSCLC mit METex14-Skipping-Veränderung mittels TKI effektiv zu sein scheint. Bei den Adenosintriphosphat-kompetitiven TKIs Bozitinib, Cabozantinib, Crizotinib, Merestinib, Glesatinib, Capmatinib, Savolitinib und Tepotinib zeigten sich präklinische und klinische Hinweise auf Effektivität [9, 10].

Eine multizentrische retrospektive Untersuchung, die das Überleben von Patienten mit fortgeschrittenem NSCLC und METex14-Skipping-Veränderung mittels verschiedenen MET-Inhibitoren untersuchte, fand heraus, dass durch die Behandlung mit einem MET-Inhibitor (Crizotinib, Glesatinib, Capmatinib, Savolitinib, Tepotinib, Cabozantinib oder Merestinib) zu einem medianen Gesamtüberleben (OS) von 24,6 Monaten führte [9]. Dies führte im Vergleich zu einer Therapie ohne MET-Inhibitor zu einer Hazard Ratio (HR) von 0,11 (P = 0.04) - eine Studie, die sowohl Patienten unter Erst- als auch unter Zweitlinientherapie umfasste.

Crizotinib wurde in der Phase I-Studie PROFILE 1001 bei 69 Patienten mit fortgeschrittenem NSCLC und METex14-Skipping-Veränderung durchgeführt [11]. Die objektive Ansprechrates (ORR) lag bei 32%, die mediane Dauer des Ansprechens (DOR) bei 9,1 Monaten und das mediane Progressions-freie Überleben

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(PFS) bei 7,3 Monaten. Die METROS-Studie (Phase II) beobachtete eine ORR von 27%, ein medianes PFS von 4,4 Monaten und ein medianes OS von 5,4 Monaten [12]. Eine weitere Phase II-Studie (AcSé) fand eine ORR von 10,7%, wobei der höchste ORR bei 36% lag [13]. In den USA hat die FDA im Mai 2018 den TKI Crizotinib die Breakthrough Therapy Designation für Patienten mit METex14-Skippling und Progress unter oder nach Platin-basierter Chemotherapie zuerkannt.

Zu Capmatinib wurden erst kürzlich Daten aus der Phase II-Studie GEOMETRY mono-1 veröffentlicht, die bei 69 Patienten in erster oder zweiter Therapielinie eine ORR von 41% und eine ORR von 68% in der Erstlinientherapie fand [14]. Die mediane DOR betrug bei Erst- und Zweitlinien-Patienten 9,7 Monate, während sie bei ausschließlich Erstlinien-Patienten 12,6 Monate lag. Die FDA erteilte dieser Substanz bereits 2019 die Bezeichnung „Breakthrough therapy“. In den USA hat die FDA im Mai 2020 mit Capmatinib den ersten selektiven, kompetitiven MET-Inhibitor zugelassen.

Tepotinib wurde in der Phase II-Studie VISION an 152 Patienten untersucht [15]. Die ORR lag bei 46% und die DOR bei 11,1 Monaten. Es erhielt 2019 die Bezeichnung „Breakthrough therapy“ durch die Amerikanische FDA und wurde seit März 2020 in Japan zugelassen.

Über Cabozantinib wurde vor allem in drei Fallserien berichtet, die in einer Untersuchung auch eine Effektivität bei zerebralen Metastasen zeigten [16 - 18].

Über Savolitinib sind als Abstract publizierte Daten aus einer Phase II-Studie an 31 NSCLC-Patienten mit vornehmlich sarkomatoider Histologie verfügbar, die zeigte, dass 12 Patienten (38%) eine partielle Response, 10 Patienten (32%) eine stabile Erkrankung und zwei Patienten (6%) eine progrediente Erkrankung hatten [19].

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung des fortgeschrittenen nicht-kleinzelligen Bronchialkarzinoms (NSCLC) mit MET-Tyrosinkinase-Rezeptor-Exon-14-(METex14-)Skipping-Veränderungen bei Erwachsenen, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Ja

Unterschieden wird zwischen Erst- und Zweitlinientherapie. Standard in der Erstlinientherapie ist eine Immunchemotherapie. Die Zweitlinientherapie orientiert sich nach dem Ansprechen der Erstlinientherapie, sie ist stärker diversifiziert und individualisiert. Sie umfasst Chemotherapie, Immuntherapie, antiangiogenetisch wirksame Arzneimittel, Multikinase-Inhibitoren und supportive Maßnahmen.

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