Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2019-B-218 Entrectinib

Stand: Juni 2020

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

Entrectinib
[zur Behandlung des ROS1-positiven fortgeschrittenen NSCLCs]

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“* • Arzneimittel zur Behandlung des NSCLCs mit aktivierenden EGFR-Mutationen wurden nicht berücksichtigt. • Arzneimittel zur Behandlung des NSCLCs mit ausschließlich plattenepithelialer Histologie wurden ebenfalls nicht berücksichtigt.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	*Nicht angezeigt.*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	**Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:** • Pembrolizumab (NSCLC, Erstlinie, Kombination): Beschluss vom 19.09.2019 • Brigatinib (ALK-positives NSCLC, nach Crizotinib): Beschluss vom 04.07.2019 • Durvalumab (NSCLC): Beschluss vom 04.04.2019 • Alectinib (ALK-positives NSCLC, Erstlinie): Beschluss vom 21.06.2018 • Alectinib (ALK-positives NSCLC, nach Crizotinib): Beschluss vom 19.10.2017 • Atezolizumab (NSCLC): Beschluss vom 16.03.2018 • Ceritinib (ALK-positives NSCLC, Erstlinie): Beschluss vom 01.02.2018 • Dabrafenib (NSCLC mit BRAF-V600-Mutation): Beschluss vom 19.10.2017 • Trametinib (NSCLC mit BRAF-V600-Mutation): Beschluss vom 19.10.2017 • Pembrolizumab (NSCLC, Erstlinie, Monotherapie): Beschluss vom 03.08.2017 • 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): Beschluss vom 16.03.2017 • Pembrolizumab (NSCLC, nach Chemotherapie): Beschluss vom 02.02.2017 • Crizotinib (ALK-positives NSCLC): Beschluss vom 15.12.2016 • Nivolumab (NSCLC, nicht-plattenepitheliale Histologie): Beschluss vom 20.10.2016

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Entrectinib [zur Behandlung des ROS1-positiven fortgeschrittenen NSCLCs]	
Kriterien gemäß 5. Kapitel § 6 VerfO	
	• Ramucirumab (NSCLC): Beschluss vom 01.09.2016 • Nintedanib (NSCLC): Beschluss vom 18.06.2015 **Richtlinien:** Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie (Stand: 4.9.2019) - Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (Off-Label-Use): • Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie
Die Vergleichstherapie soll nach dem allgemein anerkannten 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:	
Entrectinib L01XE56 Rozlytrek®	Zu prüfendes Anwendungsgebiet: 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.
Chemotherapien:	
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.
Gemcitabin L01BC05 generisch	Gemcitabin ist in Kombination mit Cisplatin als Erstlinientherapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nichtkleinzelligen Bronchialkarzinom (NSCLC) angezeigt. Eine Gemcitabin-Monotherapie kann bei älteren Patienten oder solchen mit einem Performance Status 2 in Betracht gezogen werden.
Ifosfamid L01AA06 Holoxan®	Nicht-kleinzellige Bronchialkarzinome: Zur Einzel- oder Kombinationschemotherapie von Patienten mit inoperablen oder metastasierten Tumoren.
Mitomycin L01DC03 generisch	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Bei intravenöser Gabe ist es in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei folgenden metastasierenden Tumoren wirksam: […] nicht-kleinzelliges Bronchialkarzinom […].
Paclitaxel	Fortgeschrittenes nicht-kleinzelliges Bronchialkarzinom (NSCLC): Paclitaxel ist, in Kombination mit Cisplatin, zur Behandlung des nicht-kleinzelligen Bronchialkarzinoms bei Patienten angezeigt, für die

L01CD01 generisch	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:	
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.
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: • 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.
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.
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: • 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.
Trametinib L01XE25 Mekinist®	Trametinib in Kombination mit Dabrafenib ist angezeigt zur Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligen Lungenkarzinom mit einer BRAF-V600-Mutation.

Antikörper:	
Atezolizumab L01XC32 Tecentriq®	Tecentriq 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. Tecentriq wird angewendet in Kombination mit Bevacizumab, Paclitaxel und Carboplatin bei erwachsenen Patienten zur Erstlinienbehandlung des metastasierten nichtkleinzelligen Lungenkarzinoms (NSCLC) mit nicht-plattenepithelialer Histologie. Bei Patienten mit EGFR-Mutationen oder ALKpositivem NSCLC ist Tecentriq in Kombination mit Bevacizumab, Paclitaxel und Carboplatin nur nach Versagen der entsprechenden zielgerichteten Therapien anzuwenden. 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.
Bevacizumab L01XC07 Avastin®	Bevacizumab wird zusätzlich zu einer platinhaltigen Chemotherapie zur First-Line-Behandlung von erwachsenen Patienten mit inoperablem fortgeschrittenem, metastasiertem oder rezidivierendem nicht-kleinzelligem Bronchialkarzinom, außer bei vorwiegender Plattenepithel-Histologie, angewendet.
Nivolumab L01XC17 Opdivo®	Nicht-kleinzelliges Lungenkarzinom (NSCLC) OPDIVO ist als Monotherapie zur Behandlung des lokal fortgeschrittenen oder metastasierten nichtkleinzelligen Lungenkarzinoms nach vorheriger Chemotherapie bei Erwachsenen indiziert.
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.
Pembrolizumab L01XC18 KEYTRUDA®	KEYTRUDA ist als Monotherapie zur Erstlinienbehandlung des metastasierenden nicht-kleinzelligen Lungenkarzinoms (NSCLC) mit PD-L1 exprimierenden Tumoren (Tumor Proportion Score [TPS] ≥ 50 %) ohne EGFR oder ALK-positive Tumormutationen bei Erwachsenen angezeigt. KEYTRUDA ist als Monotherapie zur Behandlung des lokal fortgeschrittenen oder metastasierenden NSCLC mit PD-L1 exprimierenden Tumoren (TPS ≥ 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. 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.
Ramucirumab L01XC21	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.

Cyramza®	

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2019-B-218 (Entrectinib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	24. September 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

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

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

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

1 Indikation

Behandlung des fortgeschrittenen (Stadium IIIB und höher) nicht-kleinzelligen Lungenkarzinoms.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation nicht-kleinzelliges Lungenkarzinom durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 12.04.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, 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.

Die Recherche ergab 1304 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Nachträglich wurden drei G-BA-Dokumente identifiziert und in die Synopse aufgenommen. Insgesamt ergab dies 82 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA-Beschlüsse/IQWiG-Berichte

G-BA, 2019 [13].

Beschluss über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Pembrolizumab vom 19. September 2019.

Anwendungsgebiet

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

Zweckmäßige Vergleichstherapie

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

- 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

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

Fazit / Ausmaß des Zusatznutzens

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

- 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):

- Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Pembrolizumab in Kombination mit Pemetrexed und Platin-Chemotherapie gegenüber Pembrolizumab als Monotherapie:
  - Anhaltspunkt für einen nicht-quantifizierbaren Zusatznutzen

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G-BA, 2019 [12].

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, 2019 [18].

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

Anwendungsgebiet (laut Zulassung vom 21. September 2018):

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).

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

Vergleichstherapie

Best-Supportive-Care

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

Anhaltspunkt für einen beträchtlichen Zusatznutzen.

G-BA, 2018 [29].

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

vom 21.06.2018

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

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

Zweckmäßige Vergleichstherapie

Crizotinib

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Crizotinib:

Anhaltspunkt für einen nicht-quantifizierbaren Zusatznutzen

G-BA, 2018 [14].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. Februar 2018 - Ceritinib

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

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

Vergleichstherapie

Crizotinib

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

G-BA, 2018 [23].

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

1) 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 ≥ 1 %))

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Docetaxel

Hinweis auf einen beträchtlichen Zusatznutzen

Anwendungsgebiet

2) 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

Zweckmäßige Vergleichstherapie

Best-Supportive-Care

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

Ein Zusatznutzen ist nicht belegt.

G-BA, 2019 [11] .

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (sog. Off-Label-Use). Teil A, Ziffer III: Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) - Kombinationstherapie; Stand 04.09.2019.

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

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

1. Hinweise zur Anwendung von Carboplatin gemäß § 30 Abs. 1

a) Nicht zugelassenes Anwendungsgebiet (Off-Label-Indikation): Fortgeschrittenes nicht-kleinzelliges Bronchialkarzinom (NSCL) -Kombinationstherapie

b) Behandlungsziel: palliativ

c) Folgende Wirkstoffe sind für die Indikation fortgeschrittenes nicht-kleinzelliges Bronchialkarzinom (NSCL) -Kombinationstherapie zugelassen:

− Cisplatin

− Docetaxel

− Erlotinib

− Etoposid
− Gemcitabin
− Ifosfamid
− Mitomycin
− Paclitaxel
− Pemetrexed
− Vindesin
− Vinorelbin

d) Spezielle Patientengruppe: Patienten mit einem erhöhten Risiko für cisplatininduzierte Nebenwirkungen im Rahmen einer Kombinationstherapie (z. B. vorbestehende Neuropathie oder relevante Hörschädigung, besondere Neigung zu Übelkeit, Niereninsuffizienz, Herzinsuffizienz)

e) Patienten, die nicht behandelt werden sollten:

− Patienten, für die zugelassene Behandlungen in Frage kommen
− Monotherapie

…

G-BA, 2017 [21].

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

Zugelassenes Anwendungsgebiet (laut Zulassung vom 25.08.2016):

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

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

Zweckmäßige Vergleichstherapie

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

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

  oder

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

- Patienten mit ECOG-Performance-Status 2:

  alternativ zur platinbasierten Kombinationsbehandlung: Monotherapie mit Gemcitabin oder Vinorelbin

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

Ein Zusatznutzen ist nicht belegt.

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, 2017 [26].

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

Anwendungsgebiet

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

1) Patienten ohne Vorbehandlung:

Zweckmäßige Vergleichstherapie:

- Patienten mit ECOG-Performance-Status 0, 1 oder 2:
  Cisplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel oder Pemetrexed) unter Beachtung des Zulassungsstatus
  oder
  Carboplatin in Kombination mit einem Drittgenerationszytostatikum (nur für Patienten mit erhöhtem Risiko für Cisplatin-induzierte Nebenwirkungen im Rahmen einer Kombinationstherapie; vgl. Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie)
  oder
  Carboplatin in Kombination mit nab-Paclitaxel
- Patienten mit ECOG-Performance-Status 2:
  alternativ zur platinbasierten Kombinationsbehandlung: eine Monotherapie mit Gemcitabin oder Vinorelbin

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

2) Patienten mit Vorbehandlung:

Zweckmäßige Vergleichstherapie:

- Für die eine Therapie mit Docetaxel oder Pemetrexed angezeigt ist:
  Docetaxel oder Pemetrexed
- Für die eine Therapie mit Docetaxel und Pemetrexed nicht angezeigt ist:
  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, 2017 [17].

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

Anwendungsgebiet

KEYTRUDA ist als Monotherapie zur Erstlinienbehandlung des metastasierenden nicht-kleinzelligen Lungenkarzinoms (NSCLC) mit PD-L1 exprimierenden Tumoren (Tumor Proportion Score [TPS] ≥ 50 %) ohne EGFR oder ALK-positive Tumormutationen bei Erwachsenen angezeigt.

Zweckmäßige Vergleichstherapie

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

oder

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

oder

Carboplatin in Kombination mit nab-Paclitaxel

- Patienten mit ECOG-Performance-Status 2:
  alternativ zur Platin-basierten Kombinationsbehandlung: eine Monotherapie mit Gemcitabin oder Vinorelbin

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie

Hinweis auf einen beträchtlichen Zusatznutzen.

G-BA, 2017 [27].

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

Anwendungsgebiet

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

1) Patienten ohne Vorbehandlung:

Zweckmäßige Vergleichstherapie

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

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

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

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

2) Patienten mit Vorbehandlung:

Zweckmäßige Vergleichstherapie

- Für die eine Therapie mit Docetaxel oder Pemetrexed angezeigt ist:
  - Docetaxel oder Pemetrexed
- Für die eine Therapie mit Docetaxel und Pemetrexed nicht angezeigt ist:
  - 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, 2017 [25].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 19. 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 [22].

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 – Ceritinib

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, 2017 [16].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 2. Februar 2017 – Pembrolizumab

Anwendungsgebiet

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

1) Patienten, für die eine Therapie mit Docetaxel, Pemetrexed oder Nivolumab angezeigt ist:

Zweckmäßige Vergleichstherapie

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

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:

Zweckmäßige Vergleichstherapie:

- Best-Supportive-Care

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

Ein Zusatznutzen ist nicht beleg

G-BA, 2016 [19].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. 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, 2016 [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 20. Oktober 2016 - Nivolumab

Zugelassenes Anwendungsgebiet (laut Zulassung vom 04.04.2016):

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.]

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)

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:

Zweckmäßige Vergleichstherapie

- Best-Supportive-Care

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

Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [15].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. September 2016 - Ramucirumab

Zugelassenes Anwendungsgebiet (laut Zulassung vom 25.01.2016):

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)

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Docetaxel:

Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [20].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 16. Juni 2016 - Crizotinib (neues Anwendungsgebiet: nicht -kleinzelliges Lungenkarzinom, ROS1 -positiv, Erstlinie)

Zugelassenes Anwendungsgebiet (laut Zulassung vom 23.11.2015):

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

Vergleichstherapie

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

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

oder

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

- Patienten mit ECOG-Performance-Status 2:

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

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

Anhaltspunkt für einen beträchtlichen Zusatznutzen.

G-BA, 2015 [24].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 18. Juni 2015 – Nintedanib.

Anwendungsgebiet

Nintedanib (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.

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)

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer Chemotherapie mit Docetaxel:

- Hinweis für einen geringen Zusatznutzen

3.2 Cochrane Reviews

Santos FN et al., 2015 [65].

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

Fragestellung

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

Methodik

Population:

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

Intervention/Komparator:

We classified chemotherapy regimens into three categories.

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

We considered trials comparing these compounds, whatever the numbers.

Categories were compared according to the following.

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

Endpunkte:

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

Recherche/Suchzeitraum:

- Bis 2014

Qualitätsbewertung der Studien:

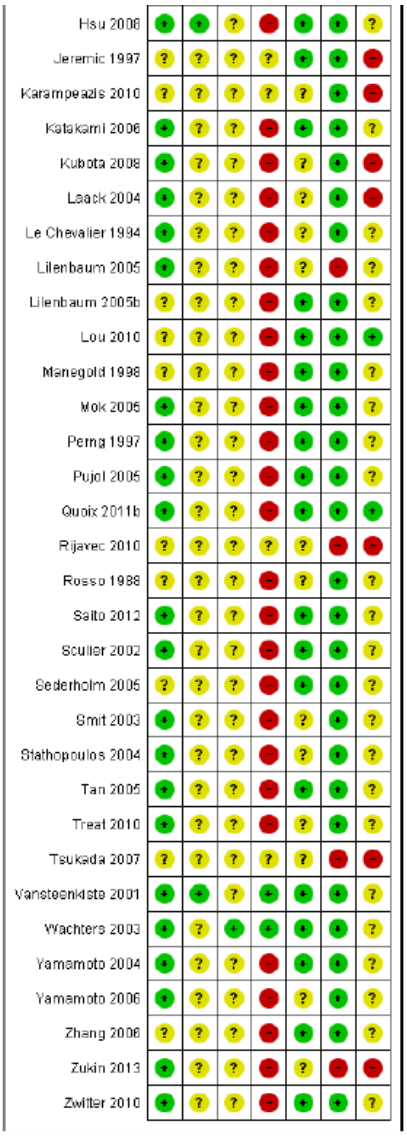
- Cochrane risk of bias tool

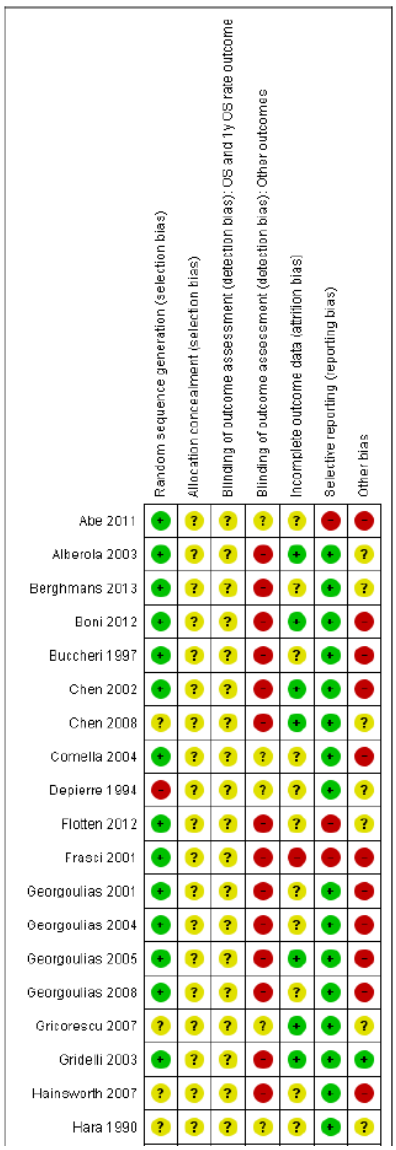
Ergebnisse

Anzahl eingeschlossener Studien:

- 51 (13,103), nur RCTs

Qualität der Studien:



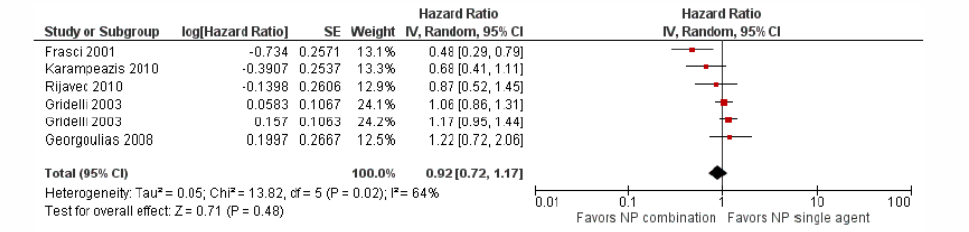


Studienergebnisse:

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

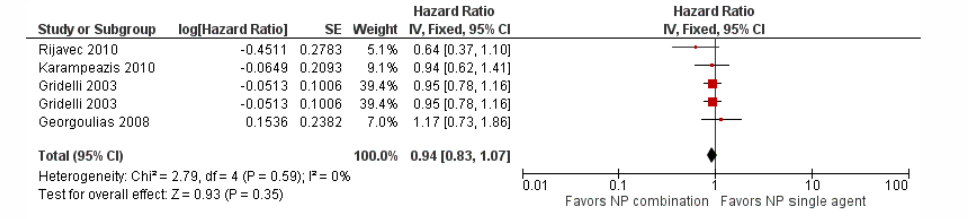
- OS: The meta-analysis of five RCTs involving 1294 participants showed no differences in OS between treatment strategies (hazard ratio (HR) 1.01, 95% confidence interval (CI) 0.89 to 1.15) and significant heterogeneity among trials (I2 = 64%). As a result of the presence of heterogeneity, we performed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

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



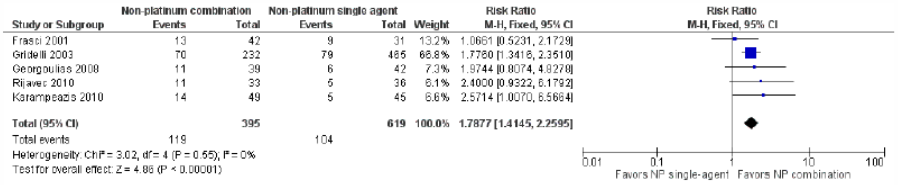
- QoL: Only two RCTs included quality of life (QoL) assessment in the trial design. We were not able to performameta-analysis because of the paucity of available data.
- PFS: The meta-analysis of four RCTs involving 942 participants showed no impact on the PFS of non-platinum combination over nonplatinum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

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



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

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



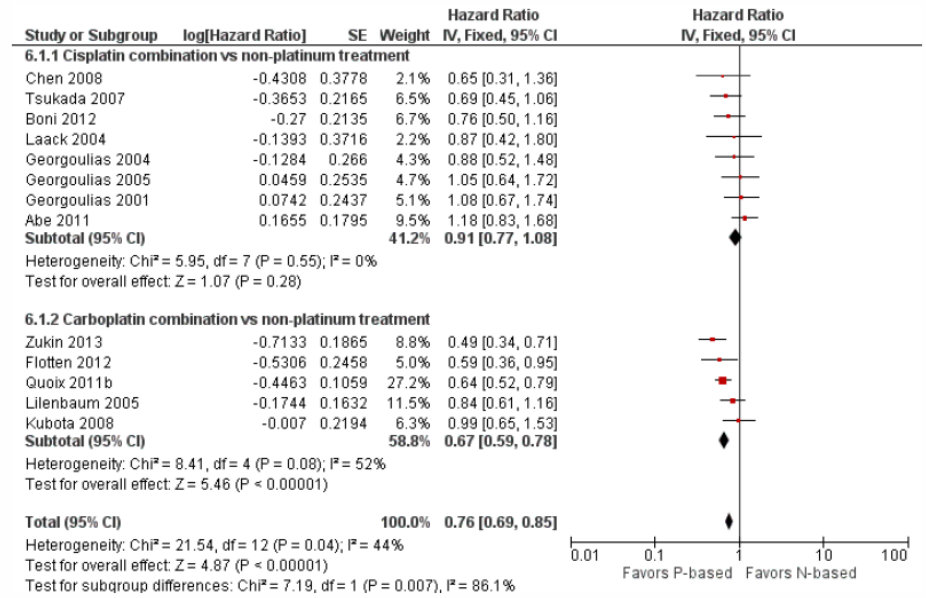
- Toxicity:
  - Grade 3 or higher hematological adverse events: We found no significant differences in risk of anemia (RR 1.18, 95% CI 0.57 to 2.40; participants = 1064; five studies; I2 = 0%), neutropenia (RR 1.19, 95%CI 0.93 to 1.54; participants = 1064; five studies; I2 = 24%), febrile neutropenia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

Non-platinum therapy versus platinum combination therapy

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

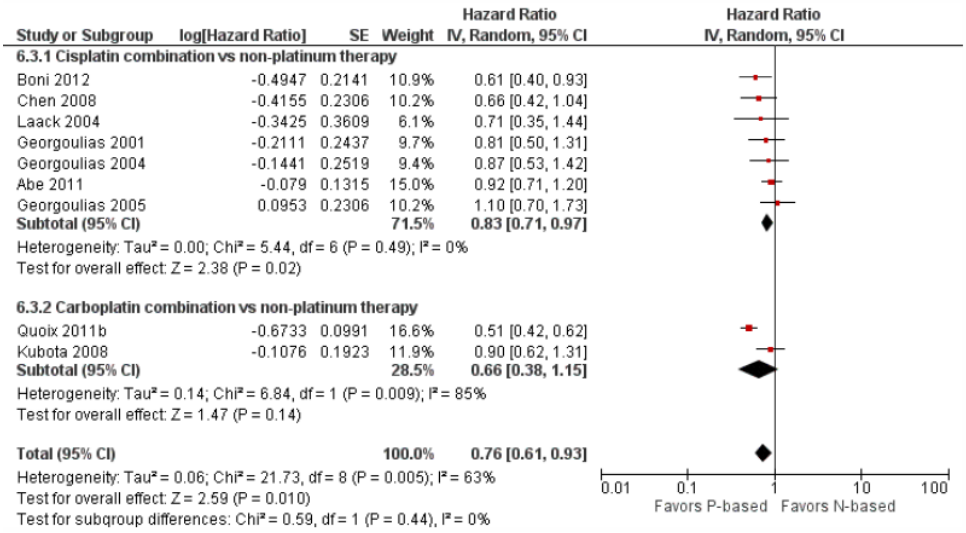
Exploratory analysis by platinum agent showed improvement in OS for carboplatin combination treatment (HR 0.67, 95% CI 0.59 to 0.78) and no significant differences for cisplatin combination treatment (HR 0.91, 95% CI 0.77 to 1.08) over non-platinum therapy. Differences between subgroups reached statistical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

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



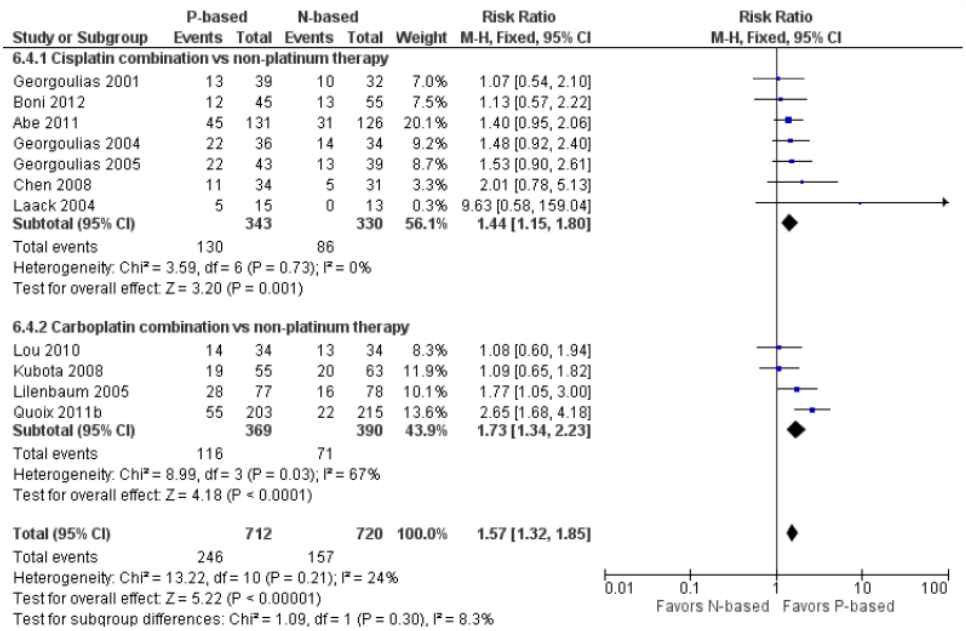
- QoL: Only five RCTs included QoL assessment. However, we were not able to performameta-analysis of these data because of the paucity of data provided.
- PFS: The meta-analysis of nine RCTs with 1273 elderly participants showed significant improvement in PFS in favor of platinum combination over non-platinum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

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



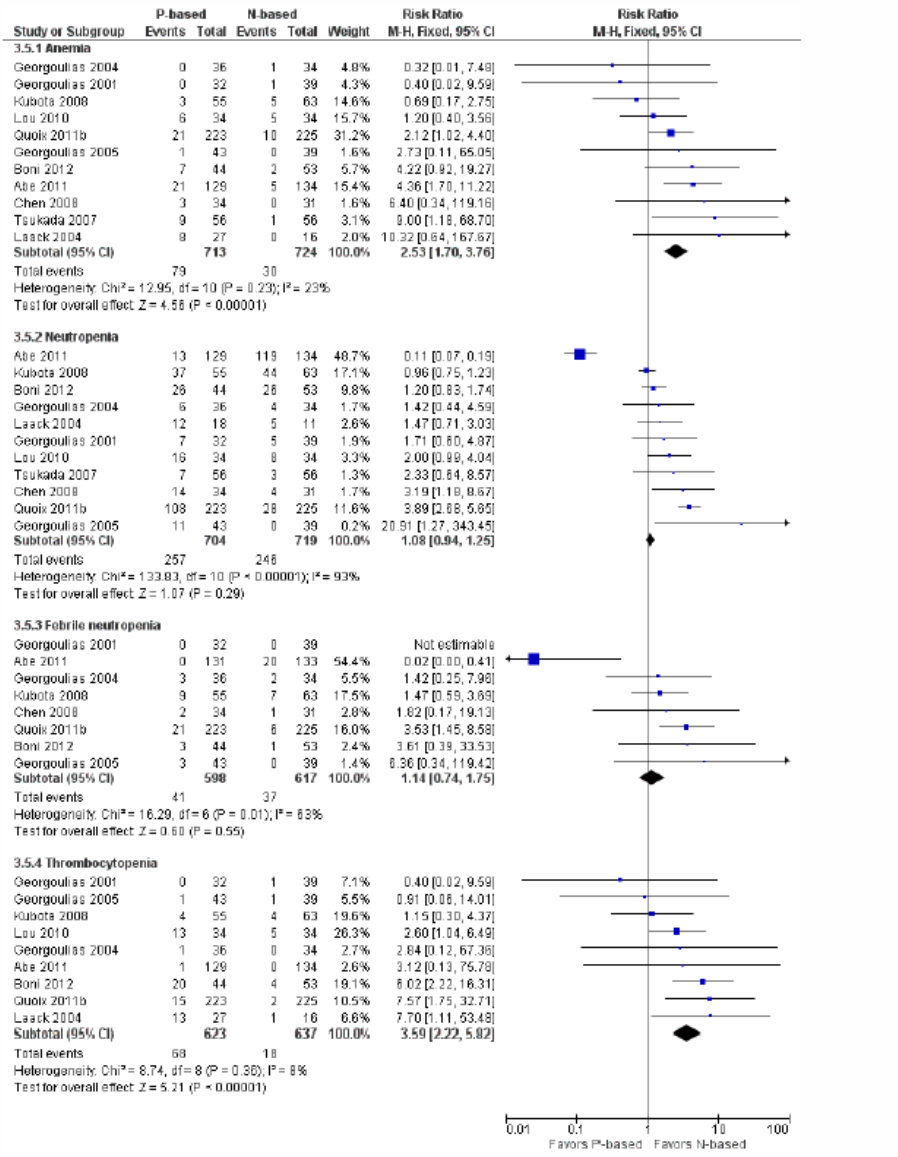
- ORR: The meta-analysis from 11 RCTs with 1432 elderly participants showed benefit in RR in favor of platinum combination over nonplatinum regimens with low heterogeneity among trials (RR 1.57, 95% CI 1.32 to 1.85; I2 = 24%)

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



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

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



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

Anmerkung/Fazit der Autoren

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

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

Kommentare zum Review

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

3.3 Systematische Reviews

Liu GF et al., 2019 [48].

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

Fragestellung

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

Methodik

Population:

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

Intervention/Komparator:

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

Endpunkte:

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

Recherche/Suchzeitraum:

- PubMed and Cochrane Library from inception to May 2016

Qualitätsbewertung der Studien:

- Cochrane risk assessment tool bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

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

Charakteristika der Population:

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

TABLE A1 Baseline characteristics of included studies

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

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

Qualität der Studien:

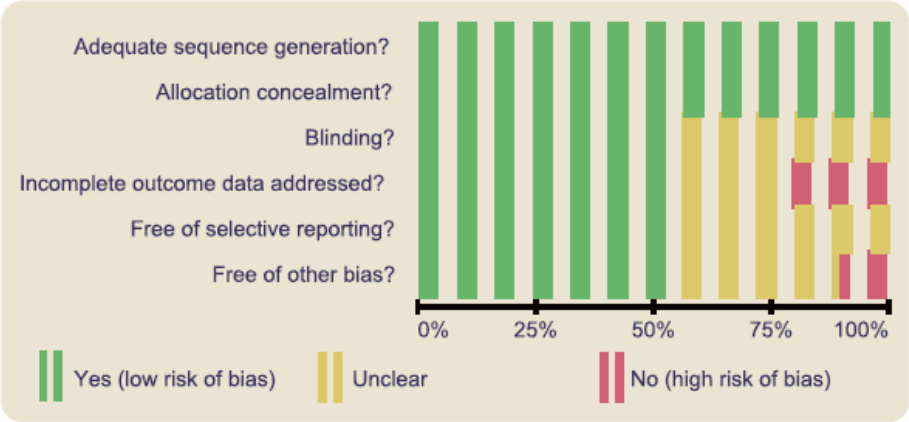


FIGURE A2 Cochrane systematic bias evaluation chart of nine included studies [Color figure can be viewed at wileyonlinelibrary.com]

Studienergebnisse:

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

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

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

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

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

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

Hess LM et al., 2018 [33].

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

Fragestellung

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

Methodik

Population:

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

Intervention/ Komparator:

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

Endpunkte:

- OS, PFS, QOL, and toxicity outcome

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

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

Charakteristika der Population:

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

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

Qualität der Studien:

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

Studienergebnisse:

- **OS (8 Studien)**
  - All comparators, with the exception of carbo + S-1, were associated with a higher HR than neci + gem + cis. A very wide CrI for OS was observed in one study
  - When including carbo + S-1, the probability of neci + gem + cis being the highest ranked treatment option was 22.0%, whereas the probability for carbo + S-1 was 45.2%. Neci + carbo + tax had a 17.3% probability, gem + docetaxel + vinorelbine had a 9.8% probability, and all others had less than a 5% probability of being the highest ranked OS option.
  - When excluding the carbo + S-1 regimen because this agent is not available beyond Asia and may not be a relevant comparator worldwide, neci + gem + cis had a 35.4% probability of being ranked first for OS, neci + carbo + tax had a 30.8% probability, gem + docetaxel + vinorelbine had a 18.5% probability, and nab-tax + carbo had a 10.8% probability.
- **PFS (9 Studien)**
  - Neci + gem + cis demonstrated longer PFS compared with all other comparators.
  - The probability of neci + gem + cis being the highest ranked for PFS in the HR analysis was 63.0%. Nab-tax + carbo had an 11.1% probability, carbo + S-1 had an 11.0% probability, and gem + docetaxel + vinorelbine had a 6.5% probability. All other comparators had less than a 5% probability of being the highest ranked
  - When excluding carbo + S-1, neci + gem + cis had a 70.8% probability of being the highest ranked option for PFS, nab-tax + carbo had a 12.7% probability, gem + docetaxel + vinorelbine had a 7.0% probability, and all other comparators had less than a 5% probability.
- **Adverse events and Quality of life**
  - No analyses

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

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

Armoiry X et al., 2018 [2].

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.

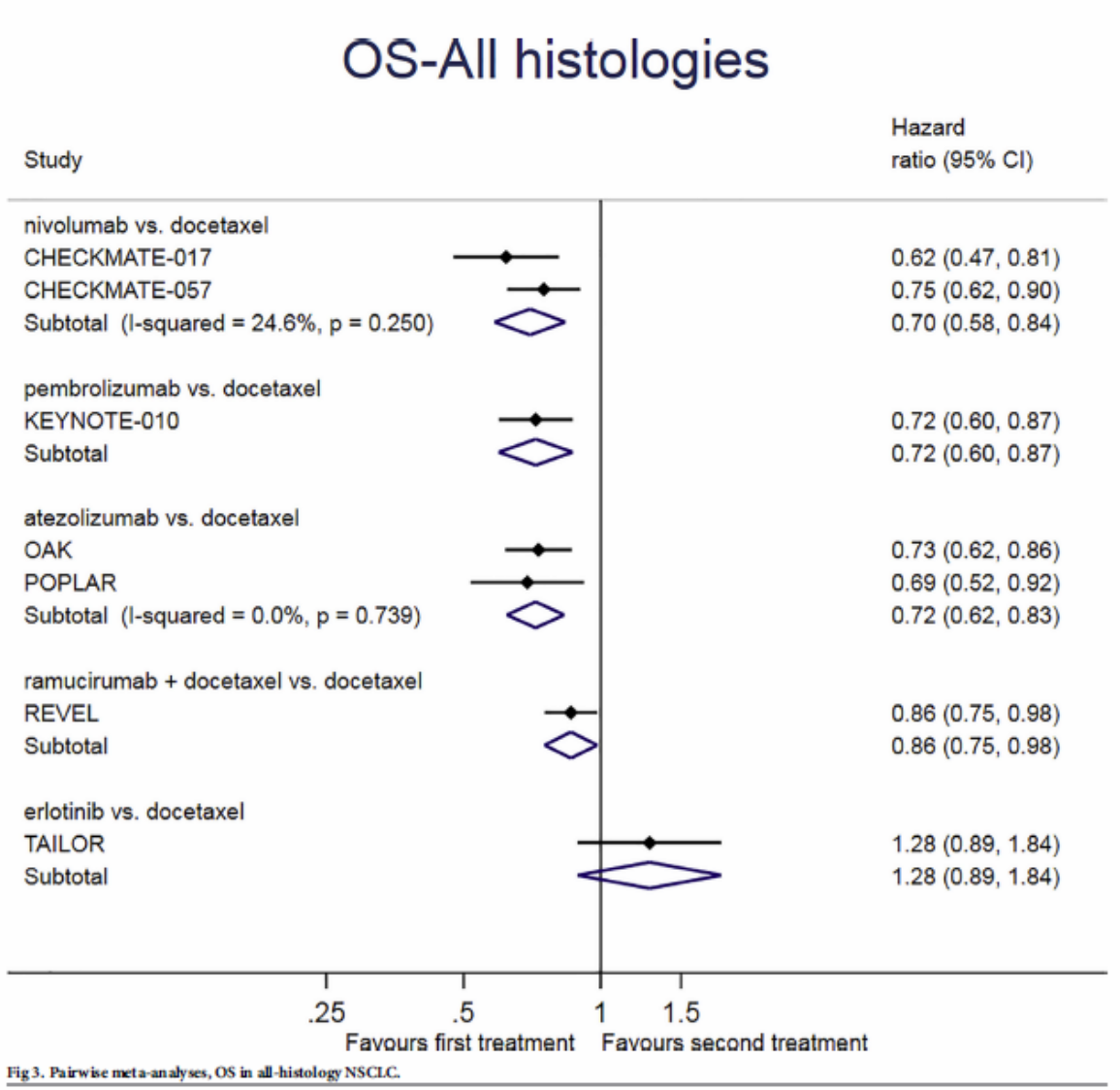


Fig 3. Pairwise meta-analyses, OS in all-histology NSCLC.

  - 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.

Sheng M et al., 2016 [67].

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

Fragestellung

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

and patients. Methodik

Population:

- patients with confirmed locally advanced or metastatic NSCLC

Intervention/Komparator

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

Endpunkte:

- ORR and safety

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

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

Qualität der Studien:

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

Studienergebnisse:

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

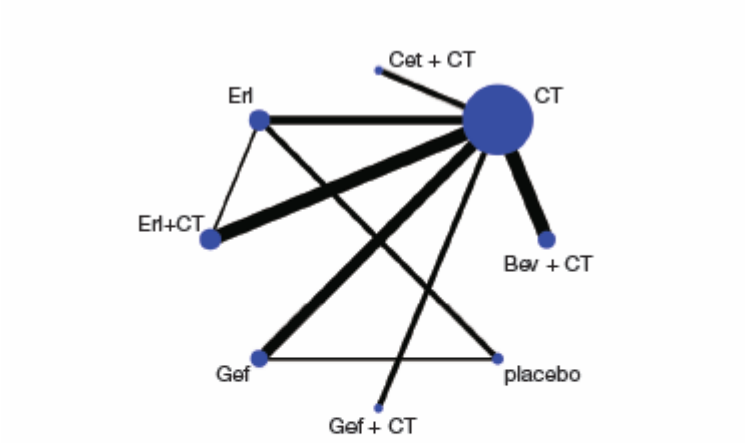


Figure 2 Network of studies comparing objective response rate of different agents for unselected patients with advanced non-small cell lung cancer. Each link represents at least one study, width of each link is number of trials per comparison, size of each node is proportional to the total sample size.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

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

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

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

- Cetuximab besitzt für dieses Anwendungsgebiet in Deutschland keien Zulassung.

Wu D et al., 2017 [72].

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 ($I2 = 0\%$ 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 seperaten Analysen/Ergebnisse zum Stadium oder Status (z.B. fortgeschritten vs. metastasierte Patienten).

Créquit P et al., 2017 [7].

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

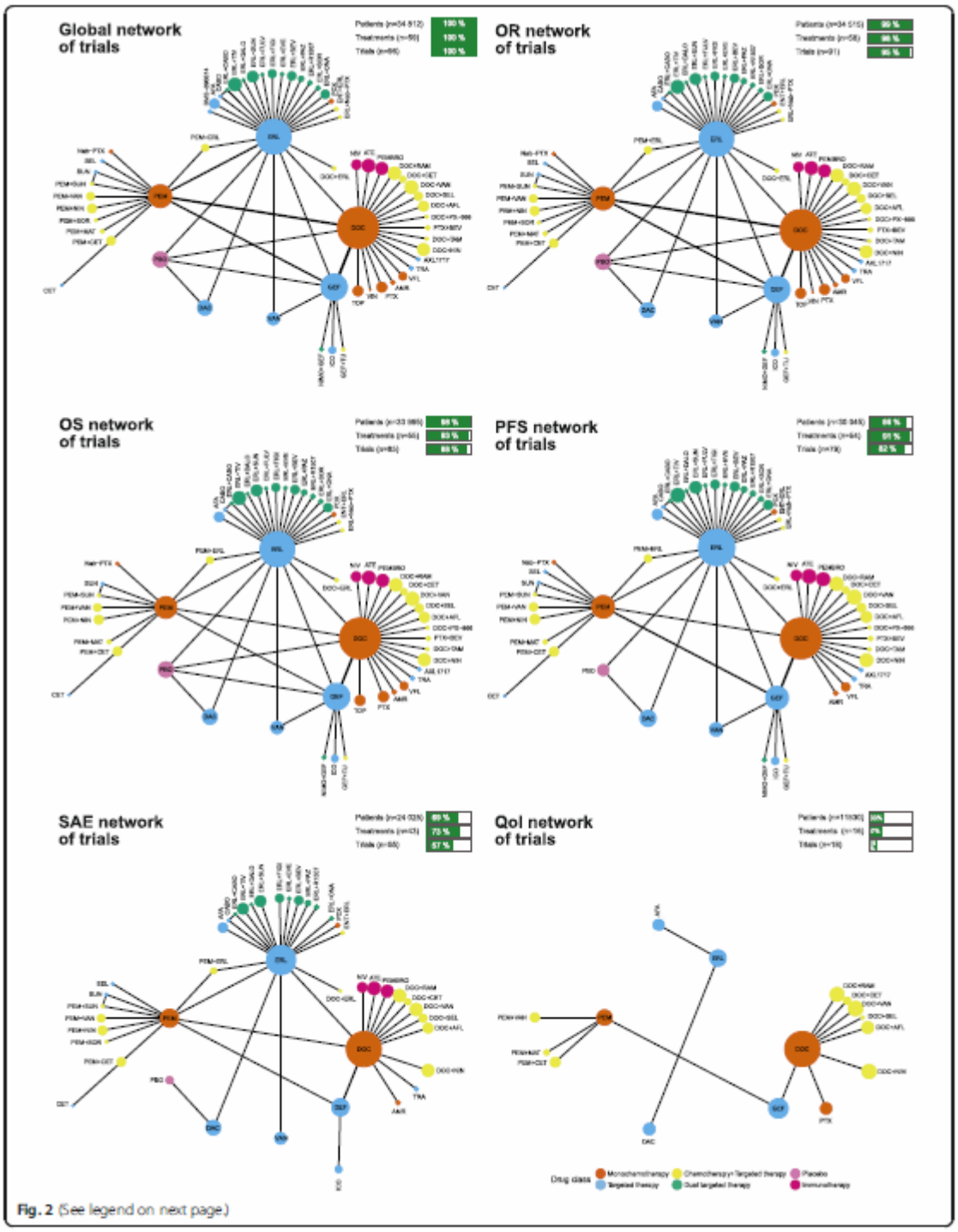

Fig. 2 Network graphs of trials assessing second-line treatments in advanced NSCLC with wild-type or unknown status for EGFR for all eligible trials, ObR, OS, PFS, SAEs, and QoL. The five trials with chemotherapy (i.e., docetaxel or pemetrexed) at the investigators' discretion and the HANSHIN trial were 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.

<u>Charakteristika der Population:</u>

- 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

Chen JH et al., 2018 [5].

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

Fragestellung

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

Methodik

Population:

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

Intervention/Komparator:

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

Endpunkte:

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

Recherche/Suchzeitraum:

- up to July 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

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

Qualität der Studien:

- The quality of the included RCTs were generally good with low risk of bias. The most common bias was the lack of blinding in about 38% of included trials with open-label designed. In the

domain of other risk of bias, one trial by Wang Y. et al. was at high risk of bias due to single center design.

Studienergebnisse:

- Overall survival (OS):
  - The results of pairwise meta-analysis of direct comparisons of OS: In the first line setting, use of pembrolizumab significantly prolonged OS (HR: 0.60; 95%CI: 0.41–0.88; p = 0.010; heterogeneity: single trial). In the subsequent setting, the use of nivolumab (HR: 0.67; 95%CI: 0.55–0.82; p = 0.0001; heterogeneity: p = 0.24; I_2 = 27%), pembrolizumab (HR: 0.71; 95%CI: 0.58–0.87; p = 0.001; heterogeneity: single trial), atezolizumab (HR: 0.73; 95%CI: 0.63–0.84; p < 0.0001; heterogeneity: p = 1.00; I_2 = 0%) and ramucirumab plus docetaxel (HR: 0.86; 95%CI: 0.75–0.98; p = 0.02; heterogeneity: p = 1.00; I_2 = 0%) showed significant OS benefit versus standard chemotherapy.
  - Indirect comparison of OS: For the first line setting, both use of pembrolizumab alone (HR: 0.6; 95%CI: 0.4–0.91) and the combination of bevacizumab and doublet platinum-base therapy (HR: 0.86; 95%CI: 0.75–0.99) showed significant survival benefit as compared to doublet platinum therapy. Overall, anti-PD1 monoclonal antibodies appears superior to anti-angiogenic therapies in terms of OS. The use of pembrolizumab alone was associated with statistically significant survival benefit as compared to the combination of axitinib and doublet platinum-based therapy (HR: 0.41; 95%CI: 0.22–0.78), the combination of sorafenib and doublet platinum-based therapy (HR: 0.57; 95%CI: 0.36–0.89), and the combination of vandetanib and doublet platinum-based therapy (HR: 0.52; 95%CI: 0.28–0.96); it was also superior to the combination of ramucirumab and doublet platinum-based therapy (HR: 0.58; 95%CI: 0.32–1.05) and the combination of bevacizumab and doublet platinum-based therapy, although these difference did not reach statistical significance. In addition, the use of pembrolizumab alone resulted in significant survival advantage when compared to nivolumab alone, regardless of PD-1/PD-L1 expression level (HR: 0.59; 95%CI: 0.36–0.97). In the subsequent setting, the single use of anti-PD1/PD-L1 monoclonal antibodies (atezolizumab alone, pembrolizumab alone and nivolumab alone) showed significant survival benefit as compared to docetaxel or pemetrexed. The combination of ramucirumab and docetaxel also resulted in survival advantage when compared to docetaxel (HR: 0.79; 95% CI: 0.64–0.98).

    → Overall, in the subsequent setting, the single use of anti-PD1/PD-L1 monoclonal antibodies appears superior to anti-angiogenic therapies in terms of OS. The use of nivolumab alone was associated with statistically significant survival benefit as compared to the combination of ramucirumab and docetaxel (HR: 0.79; 95%CI: 0.64–0.98), the combination of sunitinib and pemetrexed (HR: 0.49; 95%CI: 0.31–0.78), and the combination of vandetanib and docetaxel (HR: 0.72; 95%CI: 0.58–0.88); the use of pembrolizumab alone (HR: 0.83; 95%CI: 0.65–1.05) and atezolizumab alone (HR: 0.85; 95%CI: 0.7–1.03) were both superior the combination of ramucirumab and docetaxel, although the difference were not statistically significant.
- PFS:
  - In the first line setting, statistically significant improvement of PFS were shown in the combination of bevacizumab and doublet platinum-based therapy (HR: 0.62; 95%CI: 0.47–0.82; p = 0.0009; heterogeneity: p = 0.0002; I2 = 84%), the combination of pembrolizumab and doublet platinum-based therapy (HR: 0.53; 95%CI: 0.31–0.91; p =

0.02; heterogeneity: single trial), and pembrolizumab alone (HR: 0.50; 95%CI: 0.37–0.68; p < 0.00001; heterogeneity: single trial) versus standard doublet platinum-based therapy. In the subsequent setting, statistically significant benefit of PFS were shown in the combination of ramucirumab and docetaxel (HR: 0.75; 95%CI: 0.67–0.84; p < 0.00001; heterogeneity: p = 0.65; I2 = 0%), the combination of nintedanib and docetaxel (HR: 0.79; 95%CI: 0.68–0.92; p = 0.002; heterogeneity: single trial), the combination of aflibercept and docetaxel (HR: 0.82; 95%CI:0.72–0.94; p = 0.004; heterogeneity: single trial), and the combination of vandetanib and docetaxel (HR: 0.78; 95%CI: 0.70–0.87; p < 0.00001; heterogeneity: p = 0.44; I2 = 0%) versus docetaxel.

- Indirect comparison: In the first line setting, pembrolizumab alone (HR: 0.5; 95%CI: 0.32–0.79) and combination of bevacizumab and doublet platinum-based therapy (HR: 0.64; 95%CI: 0.52–0.78) showed significantly increased efficacy compared with doublet platinum-based therapy.

  → Overall, pembrolizumab showed increased efficacy compared with anti-angiogenic therapies, although statistical significance did not reach in some comparisons: pembrolizumab vs combination of bevacizumab and doublet platinum-based therapy, pembrolizumab vs combination of ramucirumab and doublet platinum-based therapy, pembrolizumab vs combination of sorafenib and doublet platinum-based therapy (HR: 0.54; 95%CI: 0.32–0.91), and pembrolizumab vs combination of vandetanib and doublet platinum-based therapy. In the subsequent setting, combination of ramucirumab and docetaxel showed significant increased efficacy compared with docetaxel alone in terms of PFS (HR: 0.74; 95%CI: 0.56–0.98). Although the HR appears to be in favor of pembrolizumab alone and nivolumab alone compared with docetaxel alone, the difference were not statistically significant.

- Toxicity:

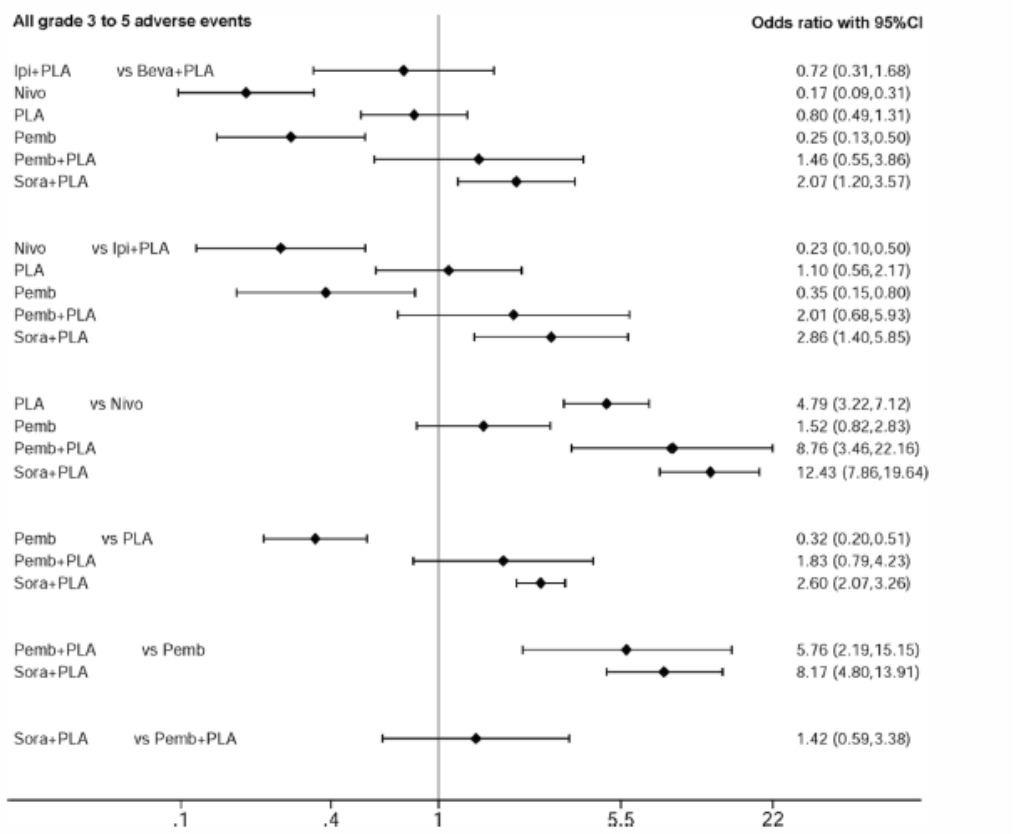

Figure 2. Forest plot of indirect comparison: all grade 3 to 5 adverse events in first line therapy. All individual regimens compared with reference treatment. Odds ratios (OR) and 95% confidence intervals were given. Beva: bevacizumab; Ipi: ipilimumab; Nivo: nivolumab; Pemb: pembrolizumab; Sora: sorafenib;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

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

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

Li J et al., 2019 [46].

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

Fragestellung

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

Methodik

Population:

- NSCLC patients assigned to treatment with ALK inhibitors

Intervention:

- ALK inhibitors daily

Komparator:

- placebo or control drug in addition to the same treatment

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

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

Ergebnisse

Anzahl eingeschlossener Studien:

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

Referenzen aus dem Review

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

Charakteristika der Population:

- baseline Eastern Cooperative Oncology Group performance status: for the majority of patients between 0, 1 and 2

- patients were required to have adequate hepatic, renal and hematological function (inclusion criteria of each trial)

Qualität der Studien:

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

Studienergebnisse:

- Incidence and relative risk of ALT increase (1 677 patients included in the analysis)
  - increase of the ALT was reported in 541 out of 1 677 ALK inhibitors treated patients with an incidence of 26,0% (95% CI: 17,4%–37%)
  - Subgroup analysis according to the ALK inhibitors: incidence of ALT associated with ceritinib (56,4%, 95% CI: 38,9%–72,5%) was significantly higher than that of alectinib (13,3%, 95% CI: 9,9%–17,7%) and crizotinib (28,4%, 95% CI: 18,8%–40,5%).
  - RR (fixed effect) to develop any grade of ALT increase: 2,37 (95% CI: 1,97–2,86; P<.001) in patients treated with ALK inhibitors compared to chemotherapy (P=,37; I2=0%).
  - grade 3 to 4 of the ALT increase (evaluable in 1 884 patients) and the incidence of high grade of ALT increase: 8,4% (95% CI:, 5,1%–13,4%) for ALK inhibitors
  - RR to develop grade 3 to 4 of ALT increase: 7,34 (95% CI 3,95–13,63; P<.001) in patients treated with ALK inhibitors compared to chemotherapy
  - no significant heterogeneity observed in RR analysis for grade 3 to 4 (P=.27; I2=23,4%)
- Incidence and relative risk of AST increase (1 721 patients included in the analysis)
  - increase of the AST was reported in 466 out of 1721 ALK inhibitors treated patients with an incidence of 23,2% (95% CI: 16,7%–31,4%)
  - Subgroup analysis according to the ALT inhibitors: incidence of AST elevation associated with ceritinib (41,9%, 95% CI: 23,3%–63,1%) was higher than that of alectinib (13,1%, 95% CI: 9,0%–18,6%) and crizotinib (26,3%, 95% CI: 18,6%–35,7%)
  - RR (fixed effect) to develop any grade of,AST increase: 3,27 (95% CI: 2,47–4,34; P<.001) in patients treated with ALK inhibitors compared to controls
  - grade 3 to 4 of the AST increase (evaluable in 1 653 patients) and the incidence of high grade of AST increase: 7,0% (95% CI: 4,8%–10,2%) for ALK inhibitors
  - RR to develop grade 3 to 4 of the AST increase (fixed effect): 11,54 (95% CI : 4,33–30,7; P<.001) in patients treated with ALK inhibitors compared to controls
  - no significant heterogeneity observed with fixed model in the analysis for all grades (P=,12;I2=52,6%) and grade 3 to 4 (p=0,89; I2=0%) of AST increase

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

- Endpunkte sind Laborparameter, Patientenrelevanz ist zu diskutieren

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Lee YC et al., 2019 [43].

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 [38].

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

Fragestellung

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

Methodik

Population:

- patients with non-small cell lung cancer

Intervention:

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

Komparator:

- nicht definiert

Endpunkte:

- safety results (for the common AEs)

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

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

Referenzen aus dem Review

A) Crizotinib (CRZ) trials

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

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

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

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

B) Alectinib (ALC) trials

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

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

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

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

C) Ceritinib (CRT) trials:

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

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

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

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

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

D) Other ALK inhibitors:

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

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

  - fulltext of ASCEND-3 trial (Felip et al., 2016; Park and Tan, 2015; Felip, 2015) was not published at time of review

- ALK inhibitors used as a monotherapy in all studies
- one study randomized crizotinib versus alectinib (Hida et al., 2017)
- four of the included studies compared an ALK inhibitor to chemotherapy

Charakteristika der Population:

- majority of patients was metastatic

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

Qualität der Studien:

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

Studienergebnisse:

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

Anmerkung/Fazit der Autoren

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

Kommentare zum Review.

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

Zhao X et al., 2018 [78].

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

Fragestellung

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

Methodik

Population:

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

Intervention:

- ceritinib

Komparator:

- k.A.

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

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

Ergebnisse

Anzahl eingeschlossener Studien:

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

Referenzen aus dem Review
18. Shaw AT, et al. Ceritinib in ALK-rearranged nonesmall-cell lung cancer. N Engl J Med 2014; 370:1189-97.
19. Kim DW, et al. Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. Lancet Oncol 2016; 17:452-63.
20. Crinò L, et al. Multicenter phase II study of whole-body and intracranial activity with ceritinib in patients with ALK-rearranged non-small-cell lung cancer previously treated with chemotherapy and crizotinib: results from ASCEND-2. J Clin Oncol 2016; 34:2866-73.
21. Felip E, et al. ASCEND-3: a single-arm, open-label, multicentre phase II study of ceritinib in ALKi-naïve adult patients (pts) with ALKrearranged (ALKþ) non-small cell lung cancer (NSCLC). J Clin Oncol 2015; 90:208-17.

22. Soria JC, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet 2017; 389:917-29.
23. Shaw AT, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2017; 18:874-86.
24. Hida T, et al. Ceritinib in patients with advanced, crizotinib-treated, anaplastic lymphoma kinase-rearranged NSCLC: Japanese subset. Jpn J Clin Oncol 2017; 47:618-24.

Charakteristika der Population:

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

Qualität der Studien:

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

Studienergebnisse:

- **Effect of NSCLC**
- analysis for crizotinib-naive pooled data revealed a pooled ORR of 68,9% (95% CI: 64,3%-73,1%; no heterogeneity observed)
- PFS for crizotinib-naive treatment: 14,62 months (95%CI: 11,99-17,78 months; no heterogeneity observed)
- no evidence of publication bias
- most common types of **adverse events** and their incidence included
  - diarrhea (83.7%), nausea (74.9%), vomiting (61.5%), fatigue (33.3%), decreased weight (27.2%), decreased appetite (40.5%), increased alanine aminotransferase concentration (46.9%), increased aspartate aminotransferase (38.1%), increased blood alkaline phosphatase concentration (22.0%), and increased gammaglutamyltransferase (20.1%).
  - most adverse events were grade 1 or 2, a small proportion were grade 3 or 4
- **Effect of Brain Metastases**
- pooled intracranial ORR with ceritinib used as the initial regimen: 50,4% (95% CI: 41,6%-59.2%; no heterogeneity observed)

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

- Phase I, II, III Studien eingeschlossen

Petrelli F et al., 2018 [62].

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

Fragestellung

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

Methodik

Population:

- ALK positive NSCLC patients with BMs

Intervention:

- treatment with an ALK inhibitor

Komparator:

- k.A.

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

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

Ergebnisse

Anzahl eingeschlossener Studien:

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

Referenzen aus dem Review

9. Solomon BJ, et al. Intracranial Efficacy of Crizotinib Versus Chemotherapy in Patients With Advanced ALK-Positive Non-Small-Cell Lung Cancer: Results From PROFILE 1014. J Clin Oncol. 2016; 34(24):2858-65.
18. Soria JC, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet. 2017.

23. Peters S, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2017.
26. Doherty MK, et al. Treatment options for patients with brain metastases from EGFR/ALK-driven lung cancer. Radiother Oncol. 2017; 123 (2):195-202.

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

Charakteristika der Population:

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

Qualität der Studien:

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

Studienergebnisse:

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

Anmerkung/Fazit der Autoren

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

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

Kommentare zum Review

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

Liu B et al., 2018 [47].

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

Fragestellung

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

Methodik

Population:

- NSCLC patients

Intervention:

- ALK-TKIs

Komparator:

- k.A.

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

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

Ergebnisse

Anzahl eingeschlossener Studien:

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

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

  - 7 phase II trials [27–33]

Referenzen aus dem Review
27. Kwak EL, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med. 2010; 363:1693–1703.
28. Camidge DR, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol. 2012; 13:1011–1019.

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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 [10].

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**
  - o better responses than crizotinib-pretreated patients (59%, 95% CI: 47% to 71% vs 48%, 95% CI: 38% to 57%)
- aggregate discontinuation rate is 7% (95% CI: 4% to 10%),
- pooled rate of dose reduction or interruption is 33% (95% CI: 24% to 42%)
- incidences of most adverse events were relatively low
- incidences of myalgia (18%) and anemia (25%) higher than with crizotinib

Anmerkung/Fazit der Autoren

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

Han S et al., 2018 [30].

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

Fragestellung

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

Methodik

Population:

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

Intervention/Komparator:

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

Endpunkte:

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

Recherche/Suchzeitraum:

- up to May 2017

Qualitätsbewertung der Studien:

- Cochrane Collaboration tool

Ergebnisse

Anzahl eingeschlossener Studien:

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

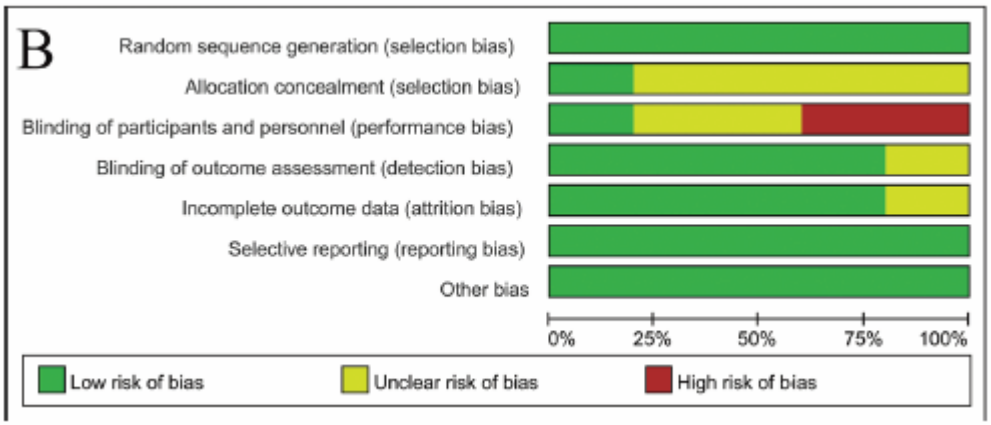
Charakteristika der Population:

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

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

Qualität der Studien:

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



Studienergebnisse:

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

Anmerkung/Fazit der Autoren

Our meta-analysis demonstrated that Bev significantly prolonged the PFS, OS and RR when combined with PC as first-line therapy in patients with non-squamous advanced NSCLC. This combination caused more adverse events and slightly increased the risk of treatment-related death. Thus, Bev plus PC can be considered a good option for reasonably selected target patients. Importantly, the patient's own value, complicated diseases and expected toxicity profile should be considered before making a treatment decision.

Kommentare zum Review

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

Zhao S et al., 2018 [77].

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.

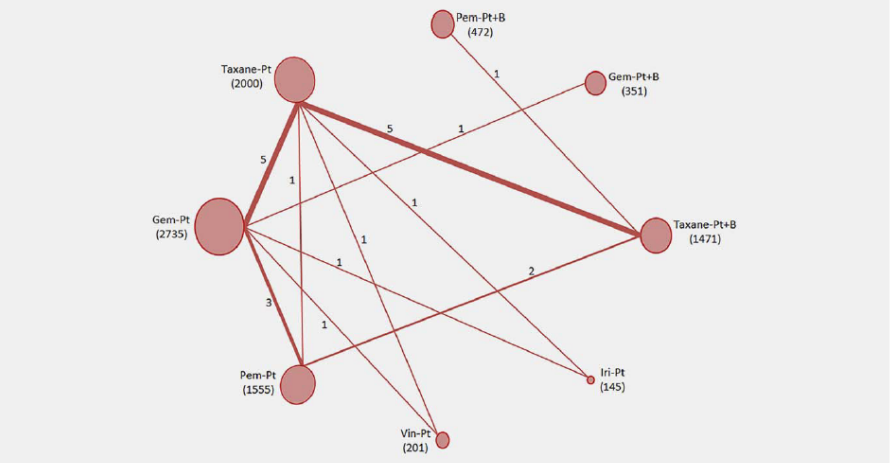


Figure 2. Network of all eligible trials assessing the six treatments in the first-line setting for advanced NS-NSCLC established for the Bayesian network meta-analysis. The size of the nodes is proportional to the number of patients (in parentheses) randomized to receive the treatment. The width of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

Lai XX et al., 2016 [41].

Risk of adverse events with bevacizumab addition to therapy in advanced non-small-cell lung cancer: a meta-analysis of randomized controlled trials.

Fragestellung

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor ligand, has shown survival benefits in the treatment of many types of malignant tumors, including non-small-cell lung cancer (NSCLC). We conducted this systematic review and meta-analysis to investigate the risk of the most clinically relevant adverse events related to bevacizumab in advanced NSCLC.

Methodik

Population:

- advanced NSCLC

Intervention/Komparator:

- treatment with or without bevacizumab in addition to concurrent chemotherapy and/or biological agent

Endpunkte:

- AEs classified as grade ≥ 3 by the National Cancer nstitute – Common Toxicity Criteria (CTAE)

Recherche/Suchzeitraum:

- 2004 - 01/2014

Qualitätsbewertung der Studien:

- Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 (3745)

Charakteristika der Population:

Table 1 Baseline characteristics of nine trials included for analysis

Name of clinical trial	Author/year	Phase	Line of treatment	No of patients	Treatment regimens	Median age, y	Median PFS, m
NR	Johnson et al/2004	II	First line	99	Bevacizumab 2.5 mg/kg/wk + PTX + CBP	NR	4.3
					Bevacizumab 5 mg/kg/wk + PTX + CBP	NR	7.4
					PTX + CBP	NR	4.2
NR	Sandler et al/2006	III	First line	878	Bevacizumab 5 mg/kg/wk + PTX + CBP	NR	6.2
					PTX + CBP	NR	4.5
AVAil	Reck et al/2009	III	First line	1,043	Bevacizumab 5 mg/kg/wk + GEM + DDP	59	6.7
					Bevacizumab 2.5 mg/kg/wk + GEM + DDP	57	6.5
					Placebo + GEM + DDP	59	6.1
BeTa	Herbst et al/2011	III	Second line	636	Bevacizumab 5 mg/kg/wk + erlotinib	64.8	3.4
					Placebo + erlotinib	65	1.7
JO19907	Niho et al/2012	II	First line	180	Bevacizumab 5 mg/kg/wk + PTX + CBP	61	6.9
					PTX + CBP	60	5.9
JO25567	Seto et al/2014	II	First line	154	Bevacizumab 5 mg/kg/wk + erlotinib	67	16
					Placebo + erlotinib	67	9.7
ERACLE	Galetta et al/2015	III	First line	118	Bevacizumab 5 mg/kg/wk + PEM + DDP maintenance with bevacizumab	62	8.3
					PEM + DDP maintenance with PEM	60	8.1
BEYOND	Zhou et al/2015	III	First line	276	Bevacizumab 5 mg/kg/wk + PTX + CBP	57	9.2
					PTX + CBP	56	6.5
PRONOUNCE	Zinner et al/2015	III	First line	361	Bevacizumab 5 mg/kg/wk + PEM + DDP maintenance with bevacizumab	65.4	5.49
					PEM + DDP maintenance with PEM	65.8	4.44

Abbreviations: y, year; PFS, progression-free survival; m, month; NR, not reported; wk, week; PTX, paclitaxel; CBP, carboplatin; GEM, gemcitabine; DDP, cisplatin; PEM, pemetrexed.

Qualität der Studien:

- Three trials were double-blinded, randomized, placebo-controlled trials and had a Jadad score of 5. The other six trials had a Jadad score of 3.

Studienergebnisse:

- No observed heterogeneity for VTEs, GI perforation, hypertension, proteinuria, hemorrhagic events, or fatal AEs was found except for ATEs (I^2=78.3%, P=0.003; Table 2). We thus used the random-effects model to pool the risk of ATEs related to bevacizumab.

Table 2 Relative risk of adverse outcomes for clinical trials included in the meta-analysis

Adverse outcome (grade ≥3)	Trials (n)	No of patients (n)		Incidence, % (95%)		I^2	Relative risk (95%)	P-value
		Bevacizumab, events/total	Controls, events/total	Bevacizumab	Controls			
ATEs	4	32/1,079	16/877	2.6 (0.8%–7.9%)	1.0 (0.2%–5.6%)	78.3	2.83 (0.32–25.45)	0.35
VTEs	7	58/1,919	30/1,470	1.6 (0.5%–4.5%)	1.8 (0.6%–5.6%)	14.0	0.98 (0.64–1.51)	0.92
GI perforation	2	2/799	2/461	0.3 (0.1%–1.5%)	0.6 (0.2%–1.9%)	30.9	0.60 (0.09–4.10)	0.60
Hypertension	8	162/1,870	22/1,428	8.2 (3.5%–17.8%)	1.7 (0.7%–4.2%)	0	5.34 (3.49–8.16)	<0.001
Proteinuria	6	32/1,491	0/1,083	2.5 (1.2%–5.3%)	0	0	7.55 (2.26–25.22)	0.001
Hemorrhagic events	9	72/2,051	17/1,607	3.6 (2.5%–5.0%)	1.4 (0.9%–2.2%)	0	2.61 (1.57–4.35)	<0.001
Fatal adverse events	8	89/1,977	51/1,530	4.6 (3.1%–6.7%)	2.5 (1.2%–5.2%)	43.9	1.21 (0.85–1.73)	0.29

Note: I^2≥50% suggests high heterogeneity across studies.
Abbreviations: ATEs, arterial thromboembolic events; VTEs, venous thromboembolic events; GI, gastrointestinal.

- Summary RRs showed a statistically significant bevacizumab-associated increased risk in three of the adverse outcomes studied: proteinuria (RR =7.55), hypertension (RR =5.34), and hemorrhagic events (RR =2.61). No statistically significant differences were found for gastrointestinal perforation (P=0.60), arterial and venous thromboembolic events (P=0.35 and P=0.92, respectively), or fatal events (P=0.29).

Anmerkung/Fazit der Autoren

The addition of bevacizumab to therapy in advanced NSCLC did significantly increase the risk of proteinuria, hypertension, and hemorrhagic events but not arterial/venous thromboembolic events, gastrointestinal perforation, or fatal adverse events.

Kommentare zum Review

- Eine der eingeschlossenen Primärstudien untersuchte Patienten in der 2. Linie, alle anderen bezogen sich auf die 1. Linie.
- Der EGFR- oder ALK-Mutationsstatus der Patienten ist nicht untersucht/ dargestellt.

Sun L et al., 2015 [69].

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

Fragestellung

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

Methodik

Population:

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

Intervention/Komparator:

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

Endpunkte:

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

Recherche/Suchzeitraum:

- bis 2014

Qualitätsbewertung der Studien:

- Cochrane Collaboration tool

Ergebnisse

Anzahl eingeschlossener Studien:

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

Qualität der Studien:

- Only two studies were high quality

Studienergebnisse:

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

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

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

Su Q et al., 2017 [68].

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 [36].** Anti-PD-1/PD-L1 antibodies versus docetaxel in patients with previously treated non-small-cell lung cancer
- **Huang G et al., 2018 [34].** 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 [82].** 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 [63].** 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 [8].** Immune Checkpoint Inhibitors for Patients With Advanced Non-Small-Cell Lung Cancer: A Systematic Review
- **Zhou GW et al., 2016 [80].** 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 [64].** Efficacy and Safety of Addition of Anti-PD1 to Chemotherapy in Treatment of Non-Small Cell Lung Cancer
- **Lee CK et al., 2018 [42].** 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 [37].** 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 [49].** 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 [70].** 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:

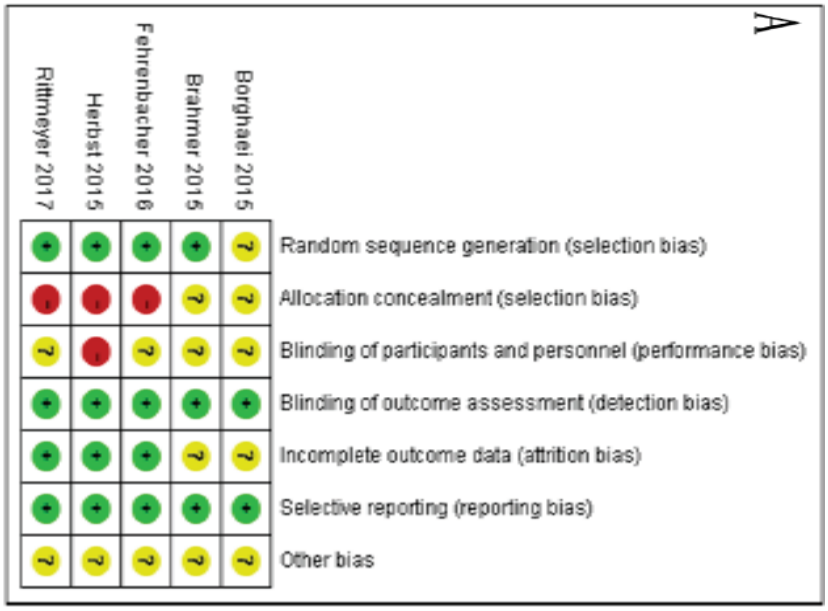
- one had data from SQ-NSCLC patients, while another one had data from NSQ-NSCLC patients, and the remaining three studies had data from both SQ and NSQ NSCLC patients.

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:



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; I2 = 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; I2 = 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.

Referenzen

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18. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, Molina J, Kim JH, Arvis CD, Ahn MJ, Majem M, Fidler MJ, de Castro G, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomized controlled trial. Lancet. 2016; 387: 1540-50.
19. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, Gadgeel SM, Hida T, Kowalski DM, Dols MC, Cortinovis DL, Leach J, Polikoff J, et al. Atezolizumab versus docetaxel in patients with previously treated nonsmall- cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017; 389: 255-65.

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 seperaten Angaben zum Stadium oder Status (z.B. fortgeschritten vs. metastasierte Patienten.

Passiglia F et al., 2018 [59].

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 [74].** 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 [40].** 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

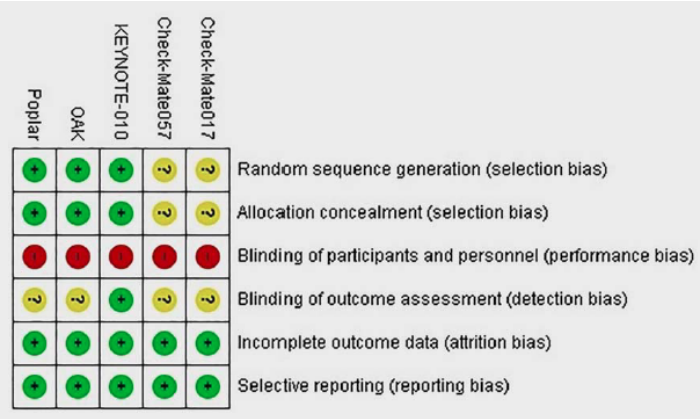
Anzahl eingeschlossener Studien:

- 5 RCTs

Charakteristika der Population:

- Siehe Su Q et al., 2017 [68] oder Zhao Q et al., 2018 [76].

Qualität der Studien:

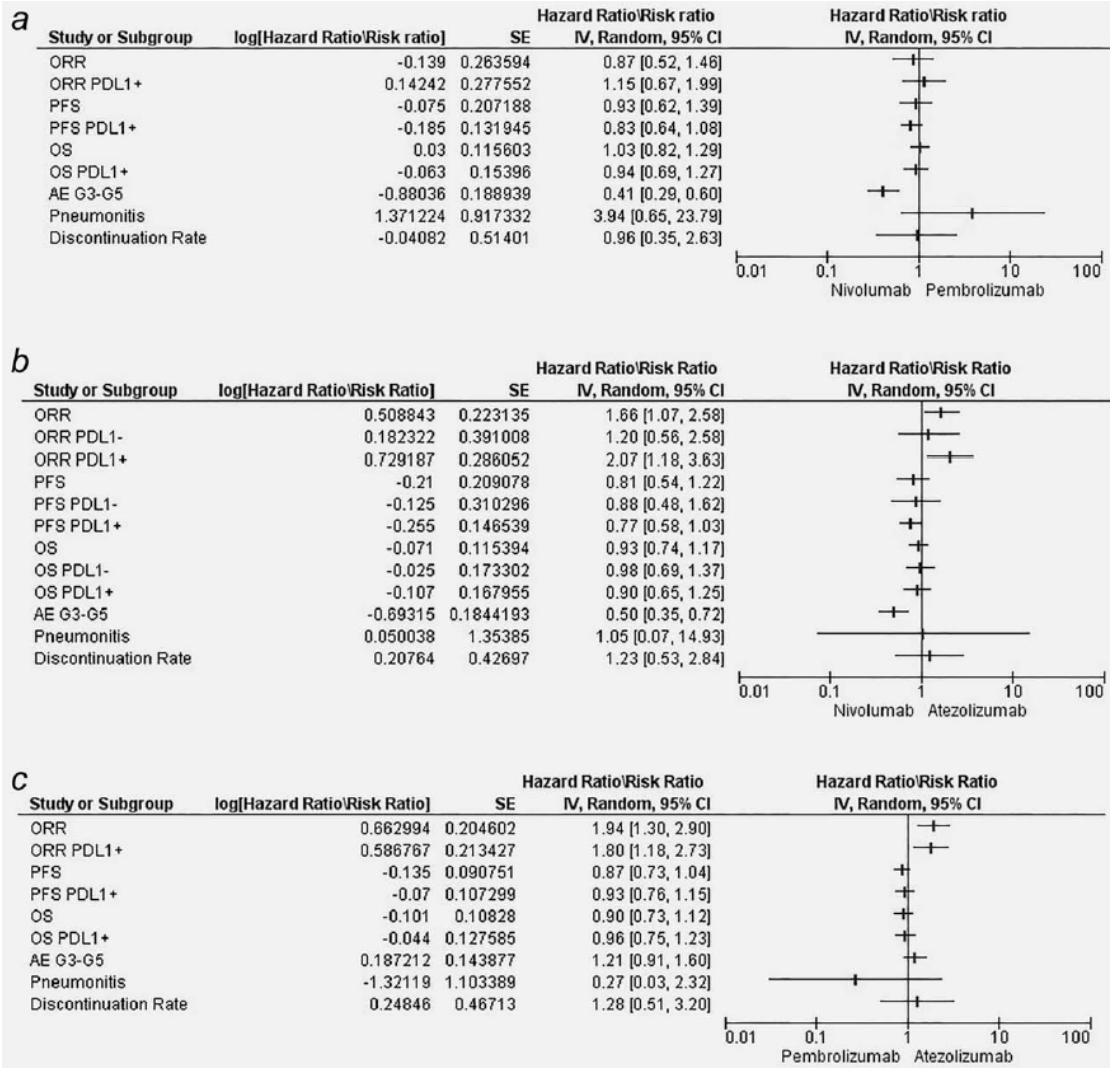


Studienergebnisse:

- 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), regalrdless 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 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 [76].

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 [35].** 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.

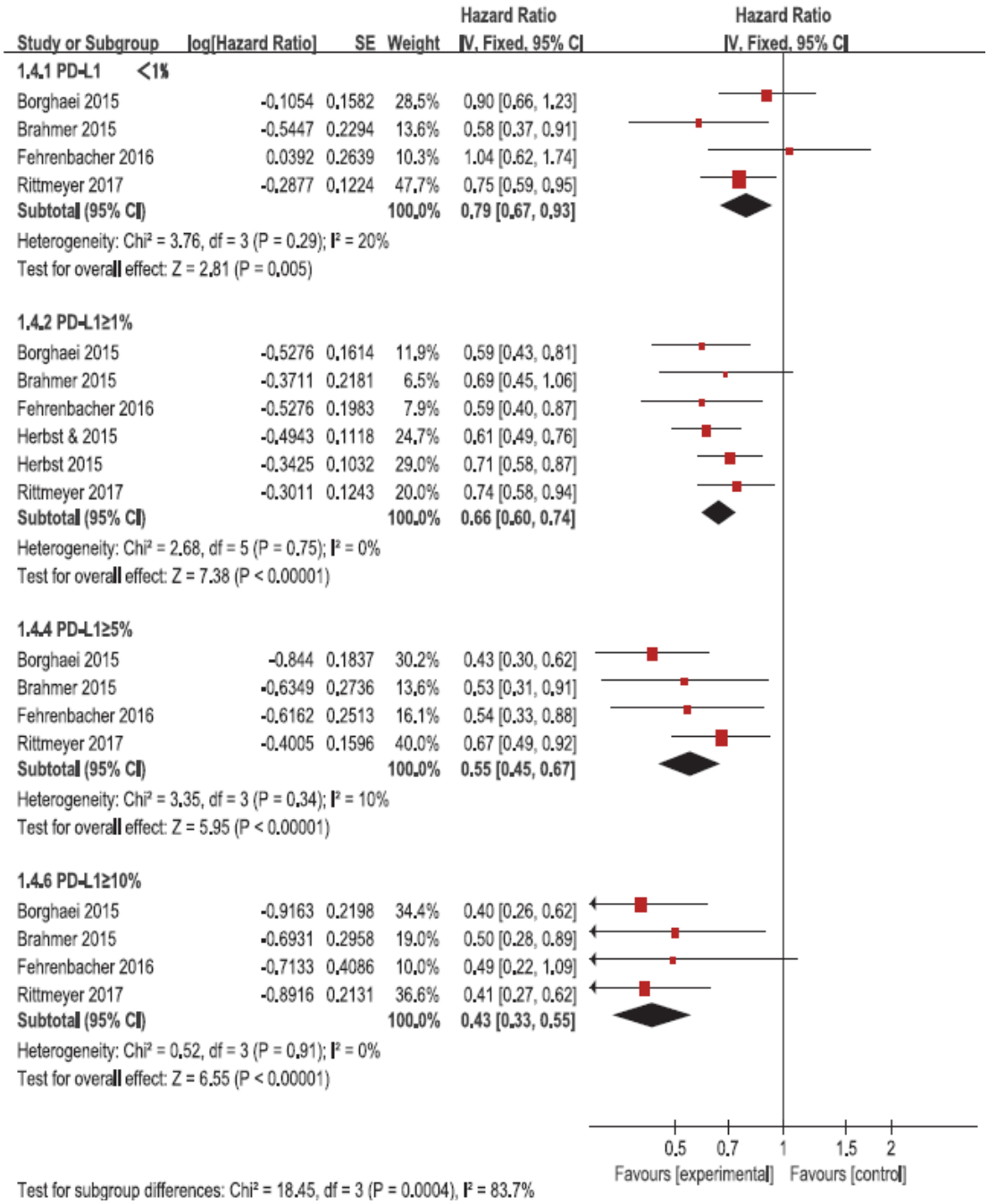
Study	Year	Study type	Intervention	Treatment regimens	No. of patients
Brahmer	2015	Phase III	Nivolumab	3mg/kg ivgtt q2w	135
			Docetaxel	75mg/m^2 ivgtt q3w	137
Borghaei	2015	Phase III	Nivolumab	3mg/kg ivgtt q2w	292
			Docetaxel	75mg/m^2 ivgtt q3w	290
Herbst	2015	Phase III	Pembrolizumab	2mg/kg ivgtt q3w	344
			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 toconfirmthese results and to improve theoptimal dosage for PD-1/PD-L1 inhibitors in NSCLC.

Luo W et al., 2018 [50].

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

Fragestellung

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

Methodik

Population:

- patients with lung cancer

Intervention:

- PD-1/PD-L1 inhibitor

Komparator:

- Chemotherapy

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Cochrane Collaboration’s risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs with 4413 patients

Charakteristika der Population:

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

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

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

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

Qualität der Studien:

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

Studienergebnisse:

Table 2 Incidence and RR of summary toxic events

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

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

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

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

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

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

- Einige Endpunkte sind Laborparameter

Zhou Y et al., 2018 [81].

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

Ähnliche Reviews zu dem Thema:

- **Shen K et al., 2018 [66].** Effectiveness and safety of PD-1/PD-L1 or CTLA4 inhibitors combined with chemotherapy as a first-line treatment for lung cancer: A meta-analysis

Fragestellung

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

Methodik

Population:

- patients with advanced NSCLC.

Intervention:

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

Komparator:

- chemotherapy

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Cochrane Collaboration’s risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 RCTs with 3144 patients

Charakteristika der Population:

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

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

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

Qualität der Studien:

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

Studienergebnisse:

- PFS, OS, ORR

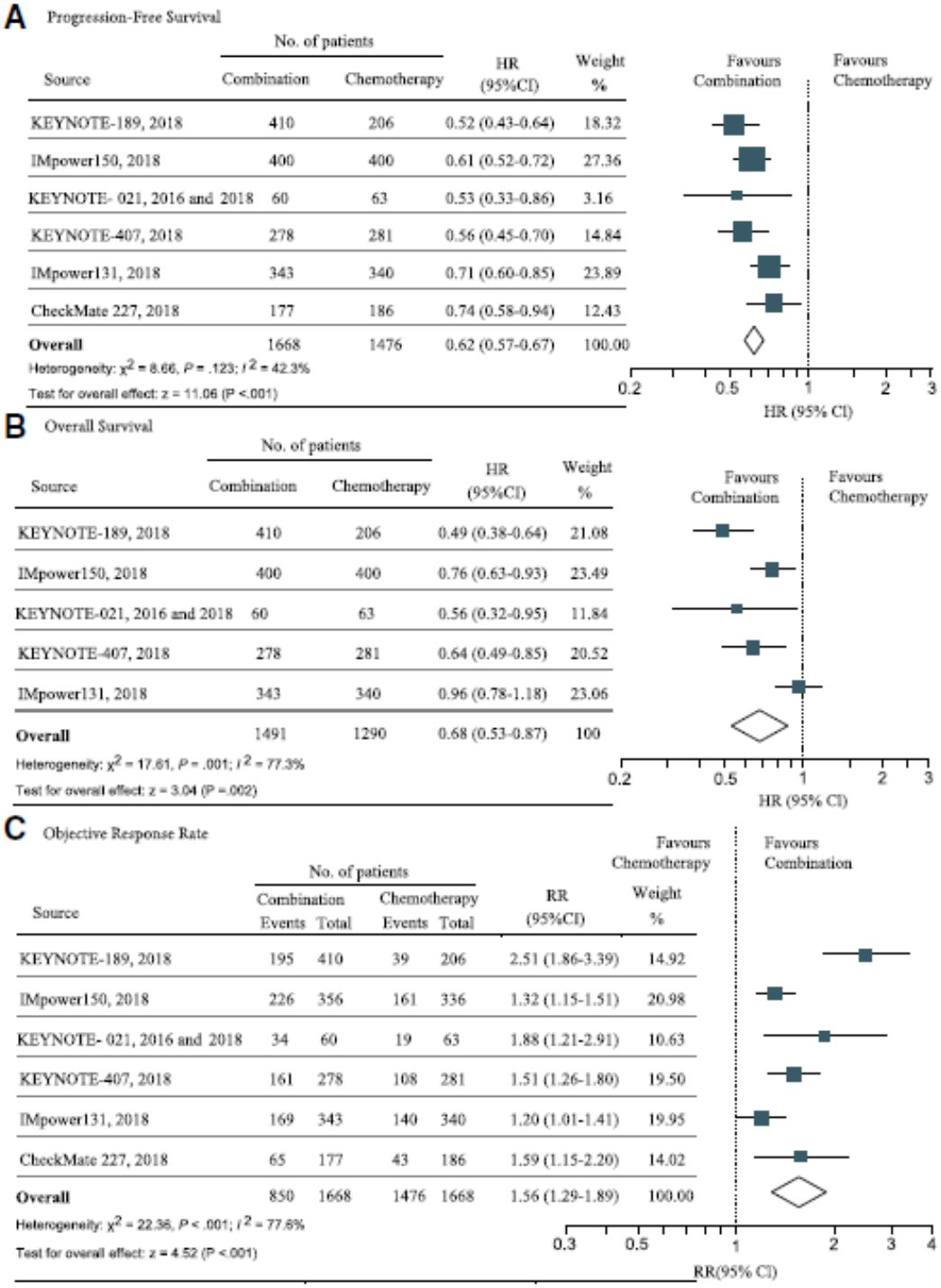


Fig. 1 Forest plot of hazard ratios and risk ratios comparing (a) progression-free survival, (b) overall survival, and (c) objective response rate in patients who received IO-Chemotherapy vs Chemotherapy alone. Squares represent study-specific effect size (HR or RR). The area of square is inversely proportional to the standard error of the study (and therefore indirectly to the sample size) and larger area indicates greater weight in the calculation of the pooled effect size. The horizontal line crossing the square represents the 95% CI. The diamonds represent the estimated overall effect, based on the meta-analysis. HR, hazard ratio; RR, relative risk; CI, confidence interval

- Subgroup Analysis
  - PD-1/PD-L1 inhibitor plus chemotherapy led to statistically longer PFS across all tested subgroups of PD-L1 expression level, including those with a PD-L1 TPS of less than 1% (HR, 0.76; 95% CI, 0.67–0.86; P < .001; heterogeneity, P = .952), a score of 1 to 49%

(HR, 0.60; 95% CI, 0.51–0.71; P < .001; heterogeneity, P = .635), and a score of at least 50% (HR, 0.38; 95% CI, 0.31–0.47; P < .001; heterogeneity, P = .928). The magnitude of PFS benefit was significantly different among subgroups of PD-L1 TPS (P < .001).

- For patients in whom the PD-L1 TPS was less than 1%, the pooled HR for OS was 0.76 (95% CI, 0.64– 0.91; P = .002; heterogeneity, P = .378), compared with the HR of 0.78 (95% CI, 0.51–1.19; P = .244; heterogeneity, P = .050) in those with a score of 1 to 49% and 0.57 (95% CI, 0.44–0.73, P < .001; heterogeneity, P = .487) in those with a score of 50% or greater. The difference of OS benefit across PD-L1 subgroups obtained a near-significant trend (P = .057).
- The response rate was the highest in patients with a PD-L1 TPS of at least 50% (RR, 1.95; 95% CI 1.34–2.82; P < .001; heterogeneity, P = .093). In the subgroup with a score between 1 and 49%, the pooled RR was 1.39 (95% CI 0.98–1.96; P = .062; heterogeneity, P = .079). In the subgroup with a score of less than 1%, the pooled RR was 1.54 (95% CI 1.16–2.05; P = .003; heterogeneity, P = .064). There was no significant interaction between treatment effect in terms of ORR and PD-L1 expression level (P = .232).

- Adverse Events

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

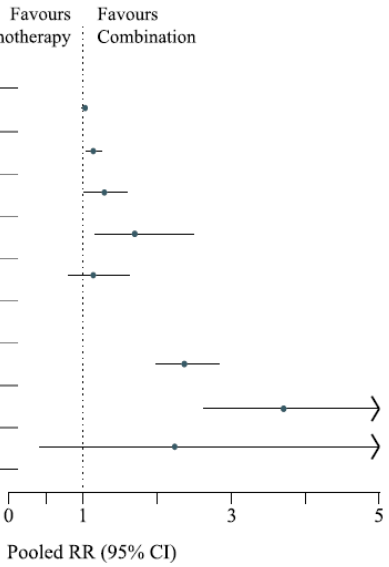


Fig. 4 Forest plot of risk ratios comparing treatment-related adverse events in patients who received IO-Chemotherapy vs Chemotherapy alone. The horizontal line crossing the dot represents the 95%CI of the pooled risk ratio in each subgroup-analysis. No. of trials refers to the number of trials included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

Anmerkung/Fazit der Autoren

In conclusion, PD-1/PD-L1 inhibitor plus chemotherapy, compared with chemotherapy, significantly prolonged PFS and OS in first-line of treatment for advanced NSCLC, irrespective of PD-L1 expression level. Future studies are needed to explore reliable predictors of treatment efficacy and to determine which chemotherapeutic modality will improve patient's survival in combination with PD-1/PD-L1 inhibitor. Finally, the trade-off between benefits and risk of side effects as well as treatment costs should be considered in clinical practice.

Kommentare zum Review

- Keine Ergebnisdarstellung für die einzelnen Arzneimittel.

Khan M et al., 2018 [39].

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 [61].** Efficacy of PD-1/PD-L1 inhibitors in patients with advanced non-small cell lung cancer: A meta-analysis of randomized clinical trials

Fragestellung

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

Methodik

Population:

- Advanced non-small cell lung cancer.

Intervention/Komparator:

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

Endpunkte:

- OS, PFS, ORR, TRAEs

Recherche/Suchzeitraum:

- until December 2017

Qualitätsbewertung der Studien:

- Cochrane Collaboration Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- seven RCTs (n=3867)

Qualität der Studien:

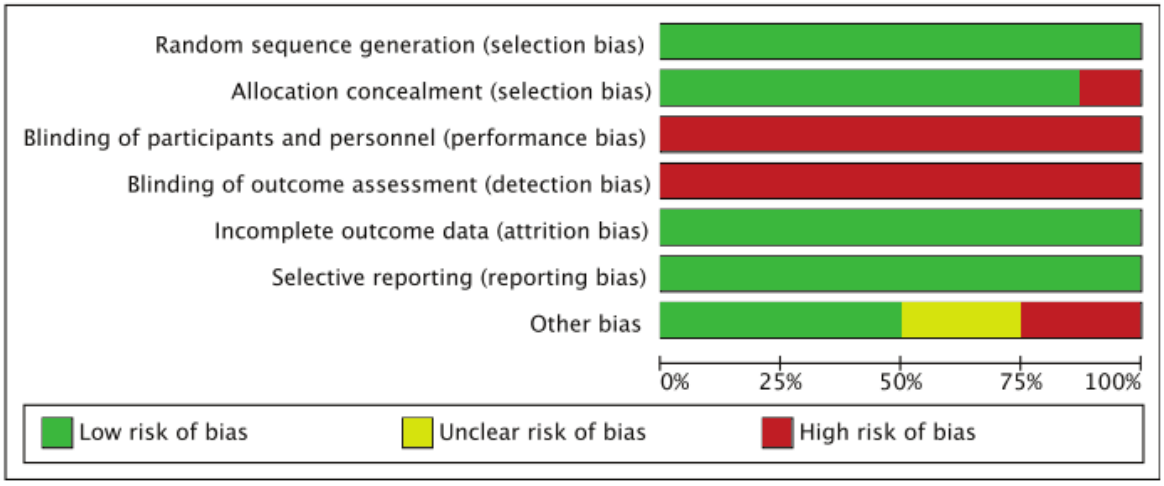


Figure 2. Risk of bias graph. +: low risk of bias; −: high risk of bias; ?: unclear risk of bias.

Studienergebnisse:

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

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

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

Peng TR et al., 2017 [60].

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:

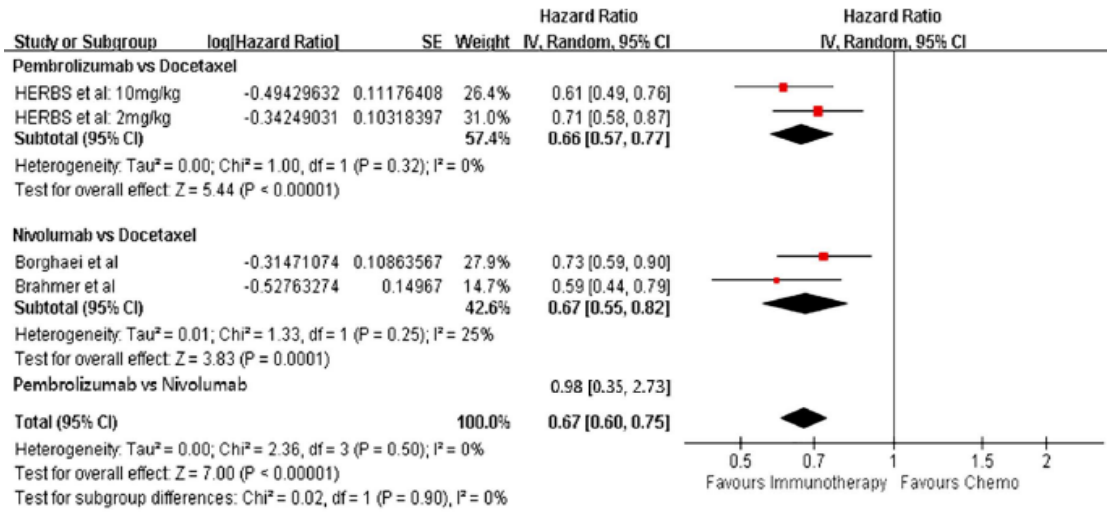
Table 2
The quality assessment of three randomized controlled trials included.

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

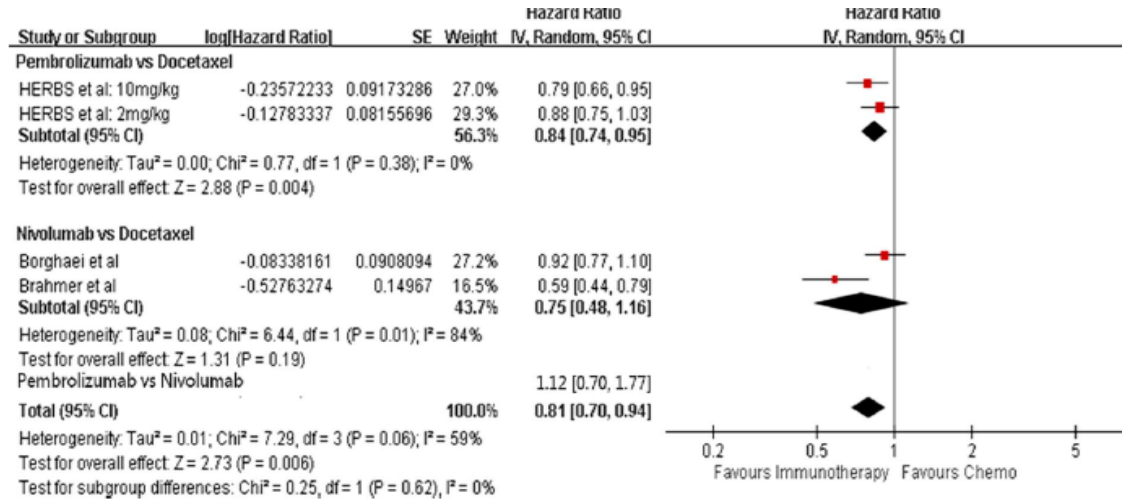


Fig. 3. Meta-analysis results of (A) OS and (B) PFS.

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 seperaten Analysen/Ergebnisse zum Stadium oder Status (z.B. fortgeschritten vs. metastasierte Patienten).

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

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

Fragestellung

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

Methodik

Population:

- advanced NSCLC

Intervention:

- Nivolumab plus chemotherapy

Komparator:

- Chemotherapy

Endpunkte:

- OS, PFS, ORR, and SAE

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

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

Ergebnisse

Anzahl eingeschlossener Studien:

- 3 RCTs with 1,395 patients

Charakteristika der Population:

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

Study	Year	Trial name	Trial phase	Stage	Histology	PD-L1 tumor expression level	Study arm (N)	Comparative arm (N)
Brahmer et al[15]	2015	CheckMate 017	3	IIIb/IV	Squamous	≥1%, ≥5%, and ≥10%	Nivolumab 3 mg/kg every 2 weeks (n=135)	Docetaxel 75 mg/m² 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/m² 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.

Chen J et al., 2016 [4].

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

Fragestellung

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

Methodik

Population:

- patients were pathologically confirmed of NSCLC and ≥65 years

Intervention/Komparator:

- Chemotherapies with or without TAs

Endpunkte:

- OS, PFS

Recherche/Suchzeitraum:

- PubMed, Embase, and Cochrane Library to June 2015

Qualitätsbewertung der Studien:

- Jadad score

Ergebnisse

Anzahl eingeschlossener Studien:

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

Qualität der Studien:

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

Studienergebnisse:

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

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

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

He X et al., 2015 [32].

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

Fragestellung

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

Methodik

Population:

- advanced NSCLC

Intervention:

- docetaxel

Komparator:

- pemetrexed or vinca alkaloid

Endpunkte:

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

Recherche/Suchzeitraum:

- bis 01/ 2015

Qualitätsbewertung der Studien:

- Jadad scoring system

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 / 2080 (RCT, phase III)

Charakteristika der Population:

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

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

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

Qualität der Studien:

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

Studienergebnisse:

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

95% CI: 0.86–1.23, P=0.74, respectively). In terms of docetaxel with vinca alkaloid as first-line treatment, there was a significant statistical difference in PFS (HR 0.63, 95% CI: 0.45–0.82, P=0.001). However, docetaxel was associated with no significant improvement in PFS compared with vinca alkaloid as second-line treatment (HR 1.00, 95% CI: 0.83–1.19, P=0.96).

- Toxicity:

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

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

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

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

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

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

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

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

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

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

Xiao HQ et al., 2016 [73].

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

Fragestellung

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

Methodik

Population:

- chemotherapy-naïve advanced nonsquamous NSCLC patients

Intervention:

- pemetrexed plus platinum doublet chemotherapy

Komparator:

- platinum plus other first-line chemotherapy

Endpunkte:

- ORR, PFS; OS

Recherche/Suchzeitraum:

- Systematische Literaturrecherche zwischen 1990 und 2015

Qualitätsbewertung der Studien:

- Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

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

Charakteristika der Population:

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

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

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

Qualität der Studien:

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

Studienergebnisse:

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

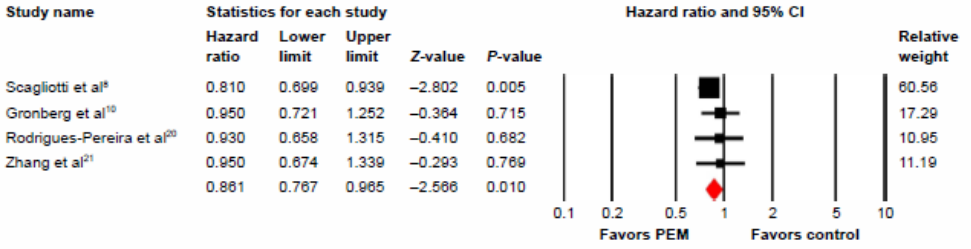


Abbildung 1: Fixed-effects model of HR (95% CI) of OS associated with PEM plus platinum versus other platinum-based chemotherapy.

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

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

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

Zhang N et al., 2018 [75].

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 ($I2 = 92.0\%$, $p < 0.001$), 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

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Wang S et al., 2015 [71].

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

Fragestellung

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

Methodik

Population:

- Advanced NSCLC

Intervention:

- VEGFR-TKIs

Komparator:

- non-VEGFR-TKIs

Endpunkte:

- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, DCR and AEs

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Jadad Scale

Ergebnisse

Anzahl eingeschlossener Studien:

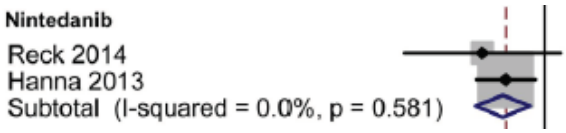
- 23 RCTs with 12,520 patients
- 3 were on cediranib; 1 on motesanib; 2 on Nintedanib; 1 on pazopanib; 4 on sorafenib ; 3 on sunitinib and 9 on vandetanib
- Nur Nintedanib als Komparator in Deutschland zugelassen
  - 17. Reck M, Kaiser R, Mellemgaard A, Douillard JY4, Orlov S, Krzakowski M, von Pawel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

Qualität der Studien:

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

Studienergebnisse:

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



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

Anmerkung/Fazit der Autoren

In summary, this study provides proof of principle that VEGFR-TKIs have an advantage in terms of PFS, ORR and DCR, compared with control therapies. However, advanced NSCLC patients treated with VEGFR-TKIs have high risks of AEs. Thus, the monitoring AEs during VEGFR-TKIs therapy is recommended. The risk and benefit of VEGFR-TKIs must be evaluated carefully to select patients who utmost benefit from VEGFR-TKIs treatment.

Kommentare zum Review

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

Zhong et al., 2015 [79].

The efficacy and safety of pemetrexed-based doublet therapy compared to pemetrexed alone for the second-line treatment of advanced non-small-cell lung cancer: an updated meta-analysis.

Fragestellung

Pemetrexed is currently recommended as the second-line treatment for patients with advanced non-small-cell lung cancer (NSCLC). However, it is unclear whether pemetrexed-based doublet therapy improves treatment efficacy and safety. Thus, this meta-analysis was performed to resolve this controversial question.

Methodik

Population:

- patients diagnosed pathologically with NSCLC and treated previously

Intervention:

- single-agent pemetrexed

Komparator:

- pemetrexed-based doublet therapy

Endpunkte:

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

Recherche/Suchzeitraum:

- bis 03/ 2015

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool for assessing risk of bias; Jadad Score

Ergebnisse

Anzahl eingeschlossener Studien:

- 10/ 2519 (randomized Phase II and III RCTs)

Qualität der Studien:

- three trials scored 5, two scored 4, four scored 3, and one scored 2.

Studienergebnisse:

- OS and PFS
  - The pooled HR for OS revealed that there were no significant differences between pemetrexed-based doublet therapy and pemetrexed alone.
  - In addition, no significant interstudy heterogeneity was found.
  - Regarding PFS, the pooled HR demonstrated that pemetrexed-based doublet therapy was associated with a 14% reduced risk of progression compared to pemetrexed alone (HR, 0.86; 95% CI, 0.75–0.99; P=0.038). There was some heterogeneity among the included studies (I2=47.5%).
- Safety
  - There were significantly higher incidences of grade 3–4 neutropenia and thrombocytopenia in the pemetrexed-based doublet arm compared with the single-agent pemetrexed arm. However, there were no significant differences in the incidence of grade 3–4 anemia, fatigue, or leukopenia between groups. Except for the grade 3–4 anemia and leukopenia, no significant interstudy heterogeneity was observed.

Anmerkung/Fazit der Autoren

In conclusion, the treatment of advanced NSCLC patients using pemetrexed-based doublet therapy improved PFS and ORR, but not OS, and it also increased toxicity. Thus, the use of pemetrexed-based combination chemotherapy as second-line treatment for NSCLC patients should be considered carefully. Additional RCTs with larger samples are warranted to confirm these findings. The effectiveness of other chemotherapy drugs in combination with pemextred needs to be evaluated for the treatment of NSCLC.

Kommentare zum Review

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

3.4 Leitlinien

National Institute for Health and Care Excellence (NICE), 2019 [56].

Lung cancer: diagnosis and management

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

Siehe auch: National Institute for Health and Care Excellence (NICE), 2018 [54]; National Institute for Health and Care Excellence (NICE), 2018 [53]; National Institute for Health and Care Excellence (NICE), 2017 [58]; National Institute for Health and Care Excellence (NICE), 2016 [55]; National Institute for Health and Care Excellence (NICE), 2015 [57].

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

Combination treatment for non-small-cell lung cancer

1.4.32 Consider chemoradiotherapy for people with stage II or III NSCLC that are not suitable for or decline surgery. Balance potential benefit in survival with the risk of additional toxicities. [2011]

1.4.33 Ensure that all people for whom multimodality treatment is potentially suitable (surgery, radiotherapy and chemotherapy in any combination) are assessed by a thoracic oncologist and by a thoracic surgeon. [2011]

1.4.34 Offer postoperative chemotherapy to people with good performance status (WHO 0 or 1) and T1a–4, N1–2, M0 NSCLC. [2011]

1.4.35 Consider postoperative chemotherapy for people with good performance status (WHO 0 or 1) and T2b–4, N0, M0 NSCLC with tumours greater than 4 cm in diameter. [2011]

1.4.36 Offer a cisplatin-based combination chemotherapy regimen for adjuvant chemotherapy. [2011]

1.4.37 For people with stage I–II NSCLC that are suitable for surgery, do not offer neoadjuvant treatment outside a clinical trial. [2011, amended 2019]

1.4.38 Ensure eligible people have the benefit of detailed discussion of the risks and benefits of adjuvant chemotherapy. [2011]

1.4.39 Treat Pancoast tumours in the same way as other types of NSCLC. Offer multimodality therapy according to resectability, stage of the tumour and performance status of the person. [2011]

1.4.40 For people with operable stage IIIA–N2 NSCLC who can have surgery and are well enough for multimodality therapy, consider chemoradiotherapy with surgery. [2019]

1.4.41 Discuss the benefits and risks with the person before starting chemoradiotherapy with surgery, including that: chemoradiotherapy with surgery improves progression-free survival chemoradiotherapy with surgery may improve overall survival. [2019]

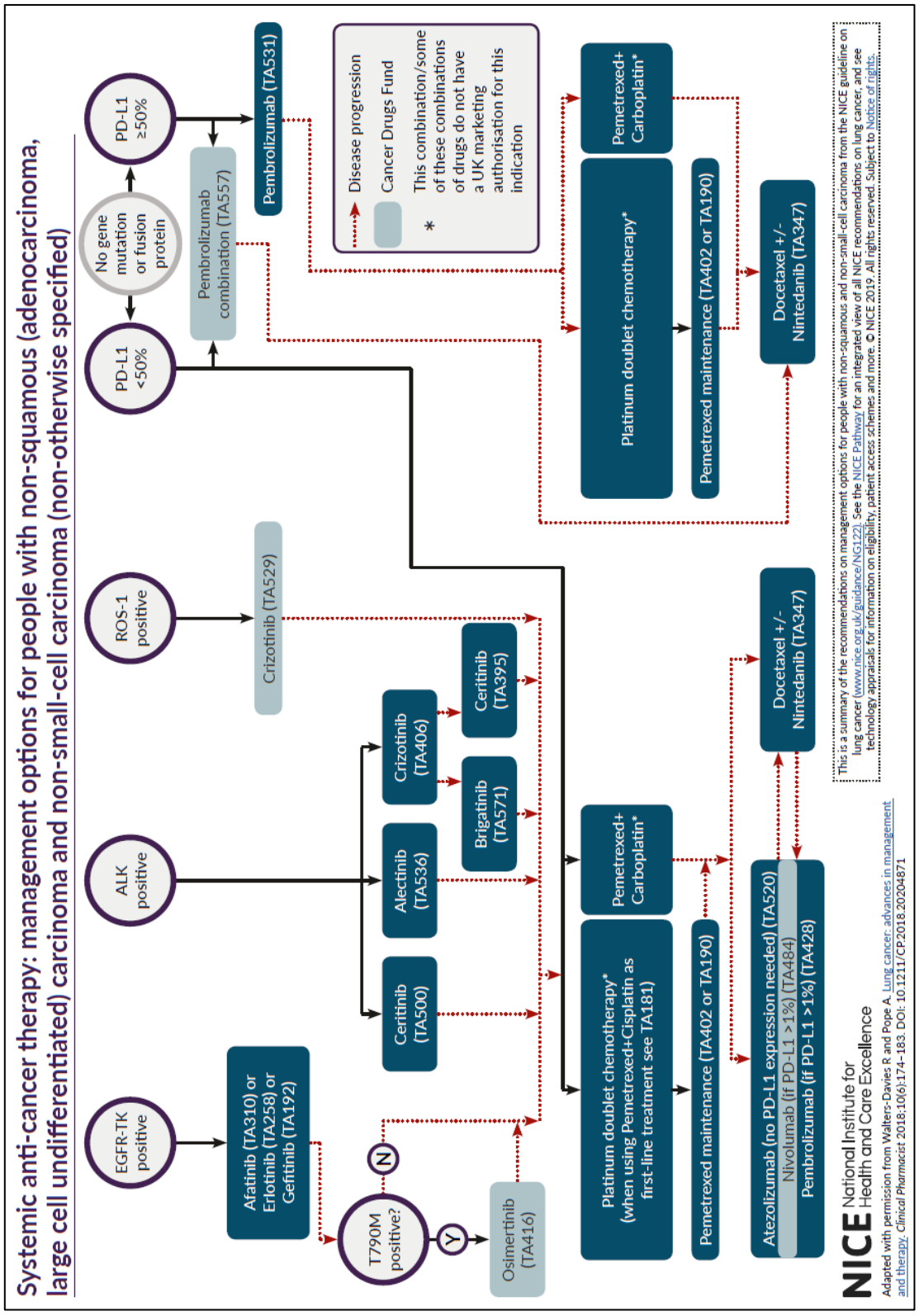
1.4.42 For people with stage IIIA–N2 NSCLC who are having chemoradiotherapy and surgery, ensure that their surgery is scheduled for 3 to 5 weeks after the chemoradiotherapy. [2019]

1.4.43 Multidisciplinary teams that provide chemoradiotherapy with surgery should have expertise in the combined therapy and in all of the individual components. [2019]

1.4.44 Centres performing lung resections for lung cancer should validate their data for the Lung Cancer Clinical Outcomes publication and the National Lung Cancer Audit. [2019]

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

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



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[s]
- 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≥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[s]
- 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[s]
- 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[s]
- 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]**

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft (DKG), et al., 2018 [45].

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

Siehe auch: Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft (DKG), et al., 2018 [44].

Fragestellung

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

- …
- Therapie des NSCLC im Stadium IV
- …

Methodik

Grundlage der Leitlinie

Update: gezielte Aktualisierung der Originalversion von 2010

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

Recherche/Suchzeitraum:

- 1. Aktualisierung für den Zeitraum 2013-2018

LoE

- entsprechend der Vorgaben des Oxford Centre for Evidence-Based Medicine

GoR

- Stärke der aktualisierten Empfehlung (gekennzeichnet mit „2018“) unterschieden in A/B/0, die sich auch in der Formulierung der Empfehlungen widerspiegeln

Sonstige methodische Hinweise (Zitat aus dem Leitlinienreport):

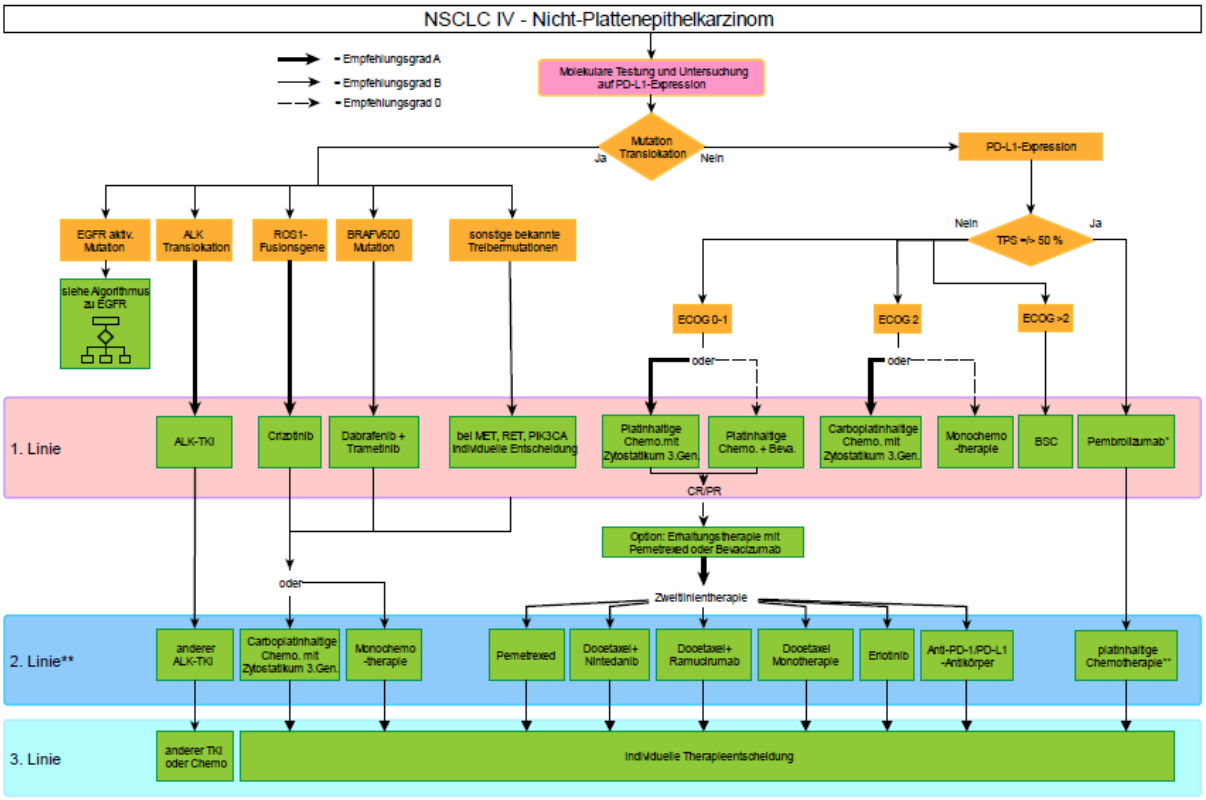
Unter dem Stichwort „Personalisierte Therapie“ oder „Stratifizierende Therapie“ hatten sich die Prinzipien insbesondere der Chemotherapie im metastasierten Stadium tiefgreifend geändert. Dieses galt in 2013 insbesondere für die Erstlinien-Chemotherapie bei Nachweis einer EGFR-Mutation sowie für die Zweitlinien-Chemotherapie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

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

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

Empfehlungen

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



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

Therapie bei sonstigen Treibermutationen beim NSCLC

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

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

Hintergrund

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.

888. Schildhaus, H.U., et al., MET amplification status in therapy-naive adeno- and squamous cell carcinomas of the lung. Clin Cancer Res, 2015. 21(4): p. 907-15.

889. Camidge, D.R., et al., Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer (NSCLC). Journal of Clinical Oncology, 2014. 32(15_suppl): p. 8001-8001.

Patienten mit PD-L1-Expression von ≥ 50 %

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

8.6.2.2. Patienten mit PD-L1-Expression von <50 % und ECOG 0-1

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

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

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

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 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: - 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	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. Therapieoptionenen sind: - 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	Patienten mit Nicht-Plattenepithelkarzinom mit ECOG 2 und keinen Kontraindikationen gegen eine Immuncheckpoint-Inhibitor-Therapie kann ein PD1 Antikörper in der Zweitlinientherapie angeboten werden.	
Level of Evidence 1b	Literatur: [842, 843]	
	Konsensstärke: 93 %	

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

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

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 %	

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 %	

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 %	

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

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

Zweitlinientherapie (bei Crizotinib-Versagen)

8.106.	Konsensbasierte Empfehlung	2018
EK	Bei Progress unter Therapie mit Crizotinib und fehlender Möglichkeit des Einschlusses 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 %	

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 %	

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 Symptom-kontrolle eine weitere Antitumortherapie auch nach der Drittlinienbehandlung angeboten werden.	
	Konsensstärke: 100 %	

Department of Health, 2017 [52].

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

Diagnosis, staging and treatment of patients with lung cancer

Leitlinienorganisation/Fragestellung

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

Methodik

Grundlage der Leitlinie

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

- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

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

LoE/GoR

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

Empfehlungen

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

Effectiveness of first-line targeted therapy

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

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

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

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

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

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

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

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

Hanna N et al., 2017 [31].

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

Siehe auch: Masters GA et al., 2015 [51].

Fragestellung

For patients with stage IV NSCLC in certain histologic or molecular subgroups (including EGFR, EGFR-positive T790M, ALK, ROS1, PD-L1/PD-1), what is the most effective first-line therapy? What is the most effective second-line therapy? Is there a role for third-line or later therapy?

Methodik

Grundlage der Leitlinie

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

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

Recherche/Suchzeitraum:

- February 2014 to December 2016

LoE

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

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

GoR

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

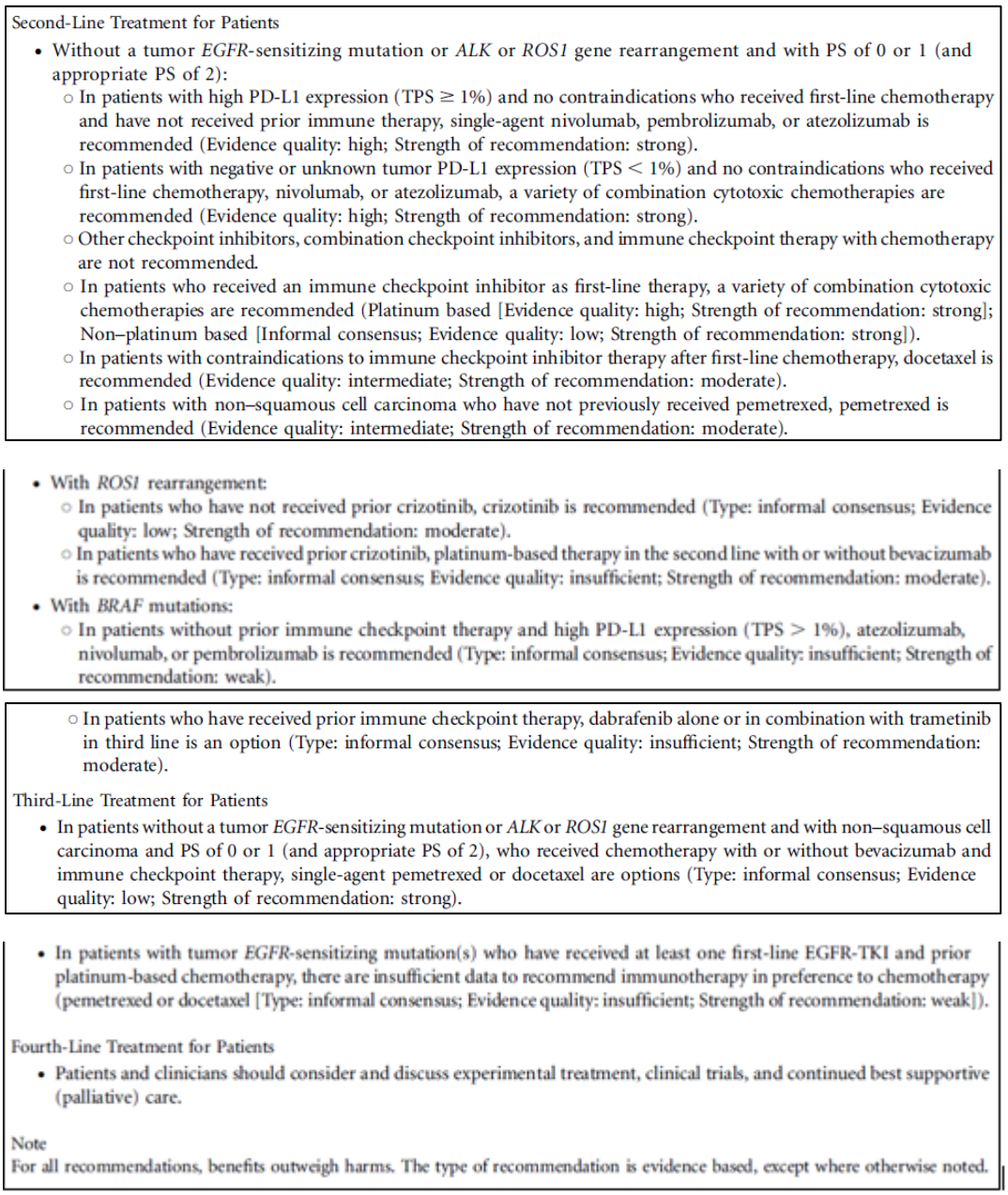
First-Line Treatment for Patients

Recommendations

First-Line Treatment for Patients

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

Second-Line Treatment for Patients



Second-Line Treatment for Patients

- Without a tumor *EGFR*-sensitizing mutation or *ALK* or *ROS1* gene rearrangement and with PS of 0 or 1 (and appropriate PS of 2):
  - In patients with high PD-L1 expression (TPS ≥ 1%) and no contraindications who received first-line chemotherapy and have not received prior immune therapy, single-agent nivolumab, pembrolizumab, or atezolizumab is recommended (Evidence quality: high; Strength of recommendation: strong).
  - In patients with negative or unknown tumor PD-L1 expression (TPS < 1%) and no contraindications who received first-line chemotherapy, nivolumab, or atezolizumab, a variety of combination cytotoxic chemotherapies are recommended (Evidence quality: high; Strength of recommendation: strong).
  - Other checkpoint inhibitors, combination checkpoint inhibitors, and immune checkpoint therapy with chemotherapy are not recommended.
  - In patients who received an immune checkpoint inhibitor as first-line therapy, a variety of combination cytotoxic chemotherapies are recommended (Platinum based [Evidence quality: high; Strength of recommendation: strong]; Non–platinum based [Informal consensus; Evidence quality: low; Strength of recommendation: strong]).
  - In patients with contraindications to immune checkpoint inhibitor therapy after first-line chemotherapy, docetaxel is recommended (Evidence quality: intermediate; Strength of recommendation: moderate).
  - In patients with non–squamous cell carcinoma who have not previously received pemetrexed, pemetrexed is recommended (Evidence quality: intermediate; Strength of recommendation: moderate).
- With *ROS1* rearrangement:
  - In patients who have not received prior crizotinib, crizotinib is recommended (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
  - In patients who have received prior crizotinib, platinum-based therapy in the second line with or without bevacizumab is recommended (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).
- With *BRAF* mutations:
  - In patients without prior immune checkpoint therapy and high PD-L1 expression (TPS > 1%), atezolizumab, nivolumab, or pembrolizumab is recommended (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: weak).
  - In patients who have received prior immune checkpoint therapy, dabrafenib alone or in combination with trametinib in third line is an option (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Third-Line Treatment for Patients

- In patients without a tumor *EGFR*-sensitizing mutation or *ALK* or *ROS1* gene rearrangement and with non–squamous cell carcinoma and PS of 0 or 1 (and appropriate PS of 2), who received chemotherapy with or without bevacizumab and immune checkpoint therapy, single-agent pemetrexed or docetaxel are options (Type: informal consensus; Evidence quality: low; Strength of recommendation: strong).
- In patients with tumor *EGFR*-sensitizing mutation(s) who have received at least one first-line EGFR-TKI and prior platinum-based chemotherapy, there are insufficient data to recommend immunotherapy in preference to chemotherapy (pemetrexed or docetaxel [Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: weak]).

Fourth-Line Treatment for Patients

- Patients and clinicians should consider and discuss experimental treatment, clinical trials, and continued best supportive (palliative) care.

Note

For all recommendations, benefits outweigh harms. The type of recommendation is evidence based, except where otherwise noted.

Ellis PM et al., 2016 [9].

Cancer Care Ontario (CCO)

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

Fragestellung

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

Methodik

Grundlage der Leitlinie

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

- Gremium aus Onkologie, Radiologie, Chirurgie (ohne Patientenvertretung);
- Interessenkonflikte dargelegt und finanzielle Unabhängigkeit nicht erklärt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Ableitung der Empfehlung und Konsensusprozesse nicht beschrieben und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- 1996 Present (February 16, 2016)

LoE

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

GoR

- nach ASCO (siehe oben) durch Fomulierung abgebildet

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

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

Empfehlungen

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

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

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

Recommendation A2
For patients who have the characteristics described in Clinical Question A2 and who have non-squamous histology, the following options are acceptable: ● Cisplatin-based combinations ● Cisplatin plus docetaxel ● Cisplatin plus paclitaxel ● Cisplatin plus pemetrexed ● Cisplatin plus vinorelbine ● *Cisplatin plus gemcitabine* ● Carboplatin-based combinations ● Carboplatin plus albumin-bound (nab) –paclitaxel ● Carboplatin plus paclitaxel ● Carboplatin plus pemetrexed ● Carboplatin plus docetaxel ● *Carboplatin plus gemcitabine* ● Nonplatinum doublets
Key Evidence from ASCO for Recommendation A2
This recommendation was supported by high-quality evidence for cisplatin-based and carboplatin-based combination therapies and intermediate-quality evidence for therapies with nonplatinum doublets from ASCO's reviews [1,5]. ASCO's systematic reviews found that two-drug combinations were superior to single-agent therapy for OS. Also, platinum-based two-drug combinations were slightly superior to nonplatinum combinations for OS, and cisplatin was slightly superior to carboplatin for survival. Individual patient decisions should reflect the balance among improved survival, increased toxicity, and patient preference.
Interpretation of Evidence for Recommendation A2
The Working Group agreed with the interpretation of the evidence provided by ASCO, except the Working Group wanted to add the cisplatin plus gemcitabine and carboplatin and gemcitabine combinations as acceptable options. The evidence for platinum-based chemotherapy plus gemcitabine that was included in ASCO's review was conflicting [1]. Scagliotti et al. [6] found inferior efficacy with cisplatin plus gemcitabine compared with cisplatin plus pemetrexed for patients with NSCC, and Gronberg et al. [7] found no difference in efficacy according to histology for patients who received carboplatin plus gemcitabine compared with carboplatin plus pemetrexed. Based on the lack of consistency, the Working Group decided not to exclude platinum-based chemotherapies combined with gemcitabine as options.
Implementation Considerations for Recommendation A2
Nonplatinum doublets will be a funding gap for Ontario.

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

Recommendation A2.a.1
For patients receiving carboplatin plus paclitaxel, the addition of bevacizumab 15 mg/kg once every three weeks is recommended, except for patients with squamous cell carcinoma (SCC) histologic type, clinically significant hemoptysis, a *known bleeding disorder,* inadequate organ function, Eastern Cooperative Oncology Group PS > 1, clinically significant cardiovascular disease, or medically uncontrolled hypertension. *Caution should be exercised in patients with brain metastases.* Bevacizumab may be continued, as tolerated, until disease progression. *An alternative treatment strategy for patients who are eligible for carboplatin, paclitaxel, and bevacizumab would include cisplatin or carboplatin plus pemetrexed and maintenance pemetrexed.*
Key Evidence from ASCO for Recommendation A2.a.1
This recommendation was supported by intermediate quality evidence from one large phase III randomized controlled trial (RCT) from ASCO's systematic review, which reported a statistically significant increase in OS when bevacizumab was added to carboplatin plus paclitaxel in first-line therapy for patients meeting the above criteria [1,8]. These criteria were chosen to exclude patients with a potential increased risk of toxicity associated with the addition of bevacizumab. Subgroup analysis also suggested that the elderly population may be at increased risk for adverse events with no improvement in OS. The trial also excluded patients with hemorrhagic disorders as well as patients with central nervous system metastases due to risk of bleeding [8]. However, one retrospective study found that bevacizumab may be safe and effective in patients with brain metastases, especially in patients with small lesions that are less likely to hemorrhage [9]. However, the authors do suggest that bevacizumab should be used with caution in these patients. A more recent trial published after the search cut-off date of the ASCO review, found that carboplatin plus paclitaxel and bevacizumab and maintenance bevacizuamb compared with carboplatin plus pemetrexed and maintenance pemetrexed had similar progression-free survival (PFS) and grade IV toxicity [10].
Interpretation of Evidence for Recommendation A2.a.1
The Working Group agreed with the interpretation of the evidence, but wanted to add any known bleeding disorder as a contraindication since patients with hemorrhagic disorders were excluded. Furthermore, low-quality data from one study suggested that bevacizumab may be effective in patients with brain metastases; therefore, the Working Group recommended caution when prescribing bevacizumab to patients with brain metastases. The Working Group also wanted to add another treatment strategy in response to the recently published trial by Zinner et al. (2015) [10].
Implementation Considerations for Recommendation A2.a.1
There is no funding for bevacizumab in Ontario.
Recommendation A2.a.2
There is insufficient evidence (for or against) to recommend pemetrexed in combination with bevacizumab plus carboplatin for patients who do not have contraindications to bevacizumab.

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

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

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

Recommendation A5
If patients have stage IIIB/IV NSCLC and *ALK* rearrangements, first-line crizotinib is recommended.

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

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

- What is the 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.

- 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.
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].

- 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.

- 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.

- 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.

- 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 [3].

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 1)

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.
- Keine formalen Konsentierungsprozesse

Empfehlungen - Stage IV inoperable NSCLC

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

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

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

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

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

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

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

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

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

Evidence summary and recommendations

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

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

✓ Practice point?

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

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

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

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

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

Evidence summary and recommendations

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

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

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

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

✓ Practice point?

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

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

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

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

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

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

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

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

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

Evidence summary and recommendations

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Evidence summary and recommendations

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

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

✓ Practice point?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Chemotherapy and anti-EGFR TKIs

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

Chemotherapy and anti-EGFR with the Mab cetuximab

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

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

✓ Practice point?

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

Last reviewed September 2017

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

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

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

1) 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/m2 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 ¾ 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 ¾ 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 ¾ neutropaenia and thrombocytopaenia 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]

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

Evidence summary and recommendations

Evidence summary	Level	References
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. Last reviewed September 2017	II	[4]

+ Evidence-based recommendation?	Grade
In fit, previously treated patients with advanced NSCLC who have received two lines of therapy, single agent docetaxel administered 3 weekly can be considered. Last reviewed September 2017	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.

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

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

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

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

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

✓ Practice point[?]

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

Last reviewed September 2017

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

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

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

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

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

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

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

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

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

The age criterion for designation of “elderly” has varied somewhat across NSCLC studies with the elderly groups commonly defined as those patients either 65 or 70 years of age or older. Several randomised controlled trials (RCTs) have been conducted within this subgroup. As a group elderly patients are considered at higher risk of treatment related toxicity, due to possible age physiologic effects on drug handling and high proportion of co-morbidities. Gridelli et al first reported findings to indicate benefit from monotherapy with vinorelbine in patients over 70, with improvement seen in OS 0.65 (95% CI = 0.45–0.93) and fewer reported lung cancer related symptoms in a RCT of 161 patients[1] Kudoh et al, subsequently compared docetaxel 60 mg/m2 (day one) to vinorelbine 25 mg/m2 (days one and eight) every 21 days for four cycles, in a RCT of 182

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

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

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

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

currently being updated

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 4 of 12, 2019) am 12.04.2019

#	Suchfrage
1	[mh “Carcinoma, Non-Small-Cell Lung”]
2	(((non NEXT small) OR nonsmall) NEXT cell NEXT lung):ti,ab,kw
3	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesions*):ti,ab,kw
4	(advanced OR metastat* OR metastas* OR recurren* OR relaps*):ti,ab,kw
5	{AND #2, #3, #4}
6	nsclc*:ti,ab,kw
7	{OR #1, #5, #6}
8	#7 with Cochrane Library publication date from Apr 2014 to present

Systematic Reviews in Medline (PubMed) am 12.04.2019

#	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 neoplasm*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesions*[tiab]
4	(#2 AND #3) OR #1
5	(#4) AND ((((advanced[tiab]) OR metastat*[tiab]) OR metastas*[tiab]) OR recurren*[tiab] OR relaps*[tiab])
6	(#5) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR

	studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
7	((#6) AND ("2014/04/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 12.04.2019

#	**Suchfrage**
1	Carcinoma, Non-Small-Cell Lung[mh]
2	Lung Neoplasms/*therapy/drug therapy
3	Medical Oncology/methods/*standards
4	((((non[tiab]) AND small[tiab]) OR nonsmall[tiab]) AND cell[tiab]) AND lung[tiab]
5	(((((((tumor[Tiab]) OR tumors[Tiab]) OR tumour*[Tiab]) OR carcinoma*[Tiab]) OR adenocarcinoma*[Tiab]) OR neoplasm*[Tiab]) OR sarcoma*[Tiab]) OR cancer*[Tiab]
6	lung[ti] AND #5
7	(#4 AND #5) OR #6
8	#1 OR #2 OR #3 OR #7
9	(#8) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
10	(((#9) AND ("2014/04/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))

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Anhang

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

Abbildung 1: NHMRC Evidence Hierarchy (Australian Government Cancer Council Australia)