Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2018-B-260 Atezolizumab

Stand: Februar 2019

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Atezolizumab **[in Kombination mit nab-Paclitaxel und Carboplatin zur Erstlinienbehandlung des metastasierten NSCLCs mit nicht-plattenepithelialer Histologie und ohne EGFR- oder ALK-Mutationen]** **Kriterien gemäß 5. Kapitel § 6 VerfO**	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	*Nicht angezeigt*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	**Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:** • Crizotinib (ROS1-positives NSCLC): Beschluss vom 16. März 2017 • Pembrolizumab (PD-L1 Expression: TPS ≥ 50 %): Beschluss vom 03. August 2017 • Dabrafenib (NSCLC mit BRAF-V600-Mutation): Beschluss vom 19. Oktober 2017 • Trametinib (NSCLC mit BRAF-V600-Mutation): Beschluss vom 19. Oktober 2017 **Richtlinien:** Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie - Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (Off-Label-Use): • Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie *(Beschluss vom 18. Oktober 2018 über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage VI – Off-Label-Use Teil A Ziffer III: Carboplatin bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie, Aktualisierung; in Kraft getreten: 05.01.19)*
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:	
Atezolizumab L01XC32 Tecentriq®	Geplantes Anwendungsgebiet: Atezolizumab wird in Kombination mit nab-Paclitaxel und Carboplatin bei erwachsenen Patienten zur Erstlinienbehandlung des metastasierten nicht-kleinzelligen Lungenkarzinoms (NSCLC) mit nicht-plattenepithelialer Histologie und ohne EGFR-Mutationen oder ALK-positives NSCLC angewendet.
Chemotherapien:	
Carboplatin L01XA02 generisch	Off-Label-Indikation für Carboplatin: Kombinationstherapie des fortgeschrittenen NSCLC (palliativ)
Cisplatin L01XA01 generisch	Cisplatin wird angewendet zur Behandlung des: fortgeschrittenen oder metastasierten nichtkleinzelligen Bronchialkarzinoms. Cisplatin kann als Mono- oder Kombinationstherapie angewendet werden. (Cisplatin Teva® 1 mg / ml Konzentrat)
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-ratiopharm® 20 mg/ml Konzentrat)
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. (Gemcitabin Kabi 38 mg/ml Konzentrat)
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 […]. (Mitomycin Teva® 1 mg/ml)

Paclitaxel L01CD01 generisch	Fortgeschrittenes nicht-kleinzelliges Bronchialkarzinom (NSCLC): Paclitaxel ist, in Kombination mit Cisplatin, zur Behandlung des nicht-kleinzelligen Bronchialkarzinoms bei Patienten angezeigt, für die potentiell kurative chirurgische Maßnahmen und/oder eine Strahlentherapie nicht in Frage kommen. (Paclitaxel-GRY® 6 mg/ml Konzentrat)
Paclitaxel Nanopartikel 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 Alimta®	Alimta 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. Alimta 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.
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). (Vinorelbin onkovis 10 mg/ml Konzentrat)
Proteinkinase-Inhibitoren:	
Crizotinib L01XE16 Xalkori®	Xalkori wird angewendet bei Erwachsenen zur Behandlung des ROS1-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, NSCLC).
Dabrafenib L01XE23 Tafinlar®	Dabrafenib in Kombination mit Trametinib ist angezeigt zur Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligen Lungenkarzinom mit einer BRAF-V600-Mutation.
Trametinib L01XE25 Mekinist®	Trametinib in Kombination mit Dabrafenib ist angezeigt zur Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligen Lungenkarzinom mit einer BRAF-V600-Mutation.

Antikörper	
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.
Pembrolizumab L01XC18 Keytruda®	Keytruda ist als Monotherapie zur Erstlinienbehandlung des metastasierenden nicht-kleinzelligen Lungenkarzinoms (NSCLC) mit PD-L1 exprimierenden Tumoren (Tumor Proportion Score [TPS] ≥ 50 %) ohne EGFR oder ALK-positive Tumormutationen bei Erwachsenen angezeigt.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2018-B-260 (Atezolizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	14. Dezember 2018

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Adverse event
AFA	Afatinib
ALK	Anaplastic Lymphoma Kinase
ASCO	American Society of Clinical Oncology
ATEZO	Atezolizumab
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
Bev	Bevacizumab
BSC	Best supportive care
CIS	Cisplatin
DAHTA	DAHTA Datenbank
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
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
k.A.	Keine Angaben
KI	Konfidenzintervall
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
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
QoL	Quality of Life
RCT	Randomized Controlled Trial
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TKI	Tyrosinkinsaseinhibitor
TPS	Tumor Proportion Score
TRIP	Turn Research into Practice Database
TTP	Time to Progression
WHO	World Health Organization
WT	Wild Type

1 Indikation

zur Behandlung des metastasierten, nicht-kleinzelligen Lungenkarzinoms (NSCLC).

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *metastasiertes nicht-kleinzelliges Lungenkarzinom (NSCLC)* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 13.03.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, 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 1527 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. Insgesamt ergab dies 63 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

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3 Ergebnisse

3.1 IQWiG Berichte/G-BA Beschlüsse

G-BA, 2018 [18].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 16. März 2018 - Atezolizumab

Anwendungsgebiet

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

Zweckmäßige Vergleichstherapie

Docetaxel oder Pemetrexed oder Nivolumab oder Pembrolizumab

(Pemetrexed: außer bei überwiegend plattenepithelialer Histologie, Pembrolizumab: nur für Patienten mit PD-L1 exprimierenden Tumoren (TPS ≥ 1 %))

Fazit / Ausmaß des Zusatznutzens / Ergebnis

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

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

G-BA, 2017 [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 19. Oktober 2017 - Dabrafenib (BRAF-V600 Mutation)

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:

Vergleichstherapie:

a) 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

b) 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:

Vergleichstherapie

a) Für die eine Therapie mit Docetaxel oder Pemetrexed angezeigt ist:

- Docetaxel oder Pemetrexed

b) Für die eine Therapie mit Docetaxel und Pemetrexed nicht angezeigt ist:

- Best-Supportive-Care

Fazit / Ausmaß des Zusatznutzens / Ergebnis

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 [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 19. Oktober 2018 – 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

Fazit / Ausmaß des Zusatznutzens / Ergebnis

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

Fazit / Ausmaß des Zusatznutzens / Ergebnis

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

Ein Zusatznutzen ist nicht belegt.

G-BA, 2018 [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 21. Juni 2018 - Alectinib (neues Anwendungsgebiet: Erstlinienbehandlung nicht-kleinzelliges Lungenkarzinom)

Anwendungsgebiet

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

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Anhaltspunkt für einen nicht-quantifizierbaren Zusatznutzen

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 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.

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

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

Zweckmäßige Vergleichstherapie

a) Docetaxel oder Pemetrexed

b) Best-Supportive-Care

Fazit / Ausmaß des Zusatznutzens / Ergebnis

a) gegenüber Docetaxel oder Pemetrexed:

Anhaltspunkt für einen beträchtlichen Zusatznutzen.

b) 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 16. März 2017 - Crizotinib (neues Anwendungsgebiet: nicht-kleinzelliges Lungenkarzinom, ROS1-positiv)

Anwendungsgebiet

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:

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

- Cisplatin in Kombination mit

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)

b) Patienten mit ECOG-Performance-Status 2:

- alternativ zur platinbasierten Kombinationsbehandlung: Monotherapie mit Gemcitabin oder Vinorelbin

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Cisplatin 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)

Zweckmäßige Vergleichstherapie

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

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

Fazit / Ausmaß des Zusatznutzens / Ergebnis

a.) gegenüber Docetaxel oder Pemetrexed:

Ein Zusatznutzen ist nicht belegt.

b.) gegenüber Best-Supportive-Care:

Ein Zusatznutzen ist nicht belegt.

G-BA, 2017 [12].

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)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

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

Fazit / Ausmaß des Zusatznutzens / Ergebnis

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

Ein Zusatznutzen ist nicht beleg

G-BA, 2016 [11].

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

Anwendungsgebiet

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

Vergleichstherapie

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

oder

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

oder

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

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [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 20. Oktober 2016 - Nivolumab

Anwendungsgebiet

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

[Hinweis: Der vorliegende Beschluss bezieht sich nur auf die Behandlung von Patienten mit nicht-plattenepithelialer Histologie.]

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

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, 2015 [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 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

Vergleichstherapie

- Eine Chemotherapie mit Docetaxel oder Pemetrexed

oder

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

oder

- Crizotinib (nur für Patienten mit aktivierenden ALK-Mutationen)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Chemotherapie mit Docetaxel: Hinweis für einen geringen Zusatznutzen

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G-BA, 2016 [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 15. Dezember 2016 - Crizotinib

Anwendungsgebiet

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

Zweckmäßige Vergleichstherapie

a) Patienten, bei denen eine Chemotherapie angezeigt ist

- 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).

b) Patienten, bei denen eine Chemotherapie nicht angezeigt ist

- 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).

Fazit / Ausmaß des Zusatznutzens / Ergebnis

a) Patienten, bei denen eine Chemotherapie angezeigt ist

- 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

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

Anwendungsgebiet

XALKORI wird angewendet bei Erwachsenen zur Erstlinienbehandlung des Anaplastische-Lymphom-Kinase(ALK)-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, 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 Platin-basierten Kombinationsbehandlung: eine Monotherapie mit Gemcitabin oder Vinorelbin

Fazit / Ausmaß des Zusatznutzens / Ergebnis

- Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Cisplatin in Kombination mit Pemetrexed oder Carboplatin in Kombination mit Pemetrexed: Anhaltspunkt für einen beträchtlichen Zusatznutzen.

G-BA, 2017 [13].

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.

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

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Hinweis auf einen beträchtlichen Zusatznutzen.

G-BA, 2018 [10].

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.

Anwendungsgebiet

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

Vergleichstherapie

Crizotinib

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

G-BA, 2018 [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 16. Juni 2016 - Crizotinib (neues Anwendungsgebiet)

Anwendungsgebiet

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

Fazit / Ausmaß des Zusatznutzens / Ergebnis

- Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Cisplatin in Kombination mit Pemetrexed oder Carboplatin in Kombination mit Pemetrexed: Anhaltspunkt für einen beträchtlichen Zusatznutzen.

G-BA, 2018 [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 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.

Vergleichstherapie

1) Patienten ohne Vorbehandlung:

- 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

2) Patienten mit Vorbehandlung:

- 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

Patienten mit ECOG-Performance-Status 2:

- alternativ zur platinbasierten Kombinationsbehandlung: eine Monotherapie mit Gemcitabin oder Vinorelbin

Fazit / Ausmaß des Zusatznutzens / Ergebnis

1) Patienten ohne Vorbehandlung: Ein Zusatznutzen ist nicht belegt.

2) Patienten mit Vorbehandlung:
   - o Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Docetaxel oder Pemetrexed: Ein Zusatznutzen ist nicht belegt.
   - o Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best Supportive Care: Ein Zusatznutzen ist nicht belegt.

G-BA, 2014 [9].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage VI - Off-Label-Use, Teil A, Ziffer III: Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) - Kombinationstherapie, Zustimmung eines pharmazeutischen Unternehmers vom 17. Juli 2014

Fazit / Ausmaß des Zusatznutzens / Ergebnis

(…)

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

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

(…)

3.2 Cochrane Reviews

Santos FN et al., 2015 [41].

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:

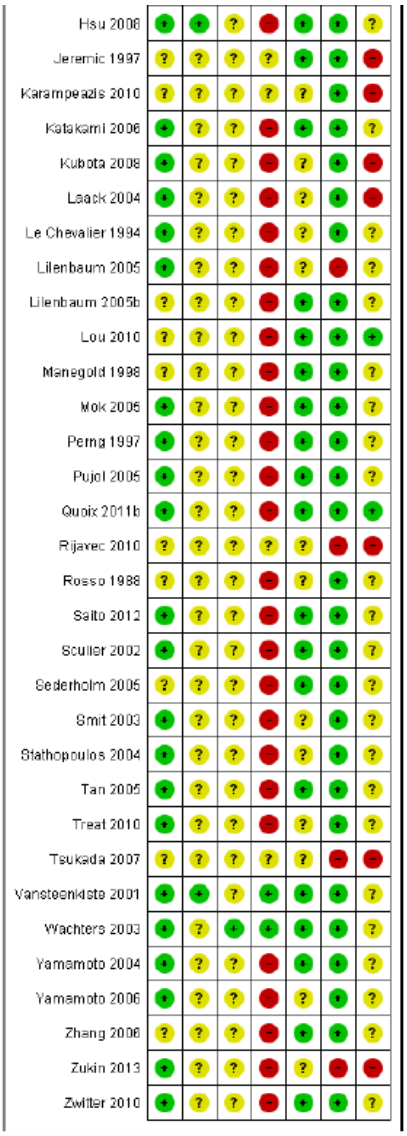
- Cochrane risk of bias tool

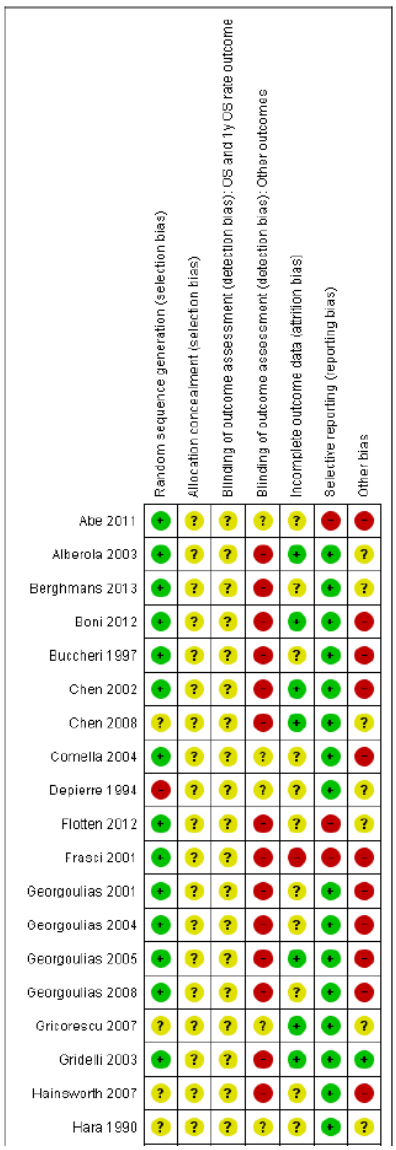
Ergebnisse

Anzahl eingeschlossener Studien:

- 51 (13,103), nur RCTs

Qualität der Studien:



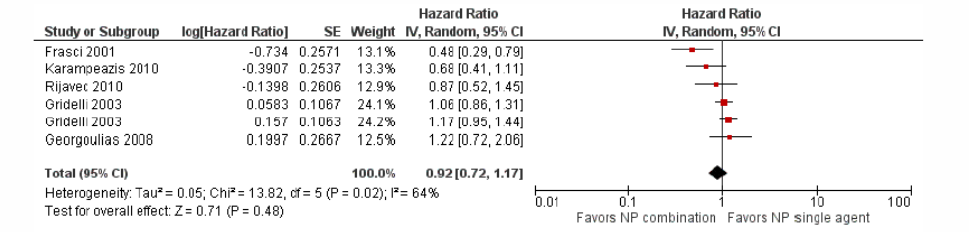


Studienergebnisse:

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

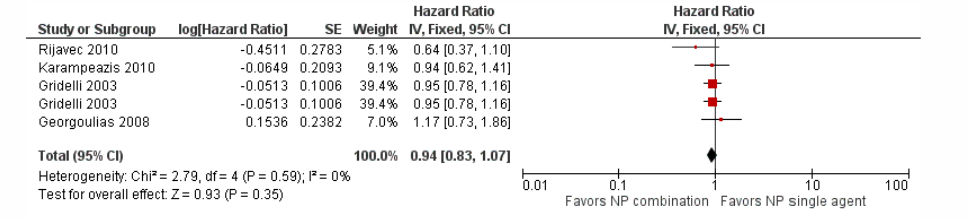
- OS: The meta-analysis of five RCTs involving 1294 participants showed no differences in OS between treatment strategies (hazard ratio (HR) 1.01, 95% confidence interval (CI) 0.89 to 1.15) and significant heterogeneity among trials (I2 = 64%). As a result of the presence of heterogeneity, we performed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



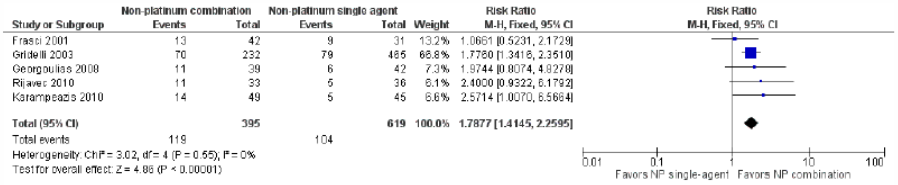
- QoL: Only two RCTs included quality of life (QoL) assessment in the trial design. We were not able to performameta-analysis because of the paucity of available data.
- PFS: The meta-analysis of four RCTs involving 942 participants showed no impact on the PFS of non-platinum combination over nonplatinum 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).



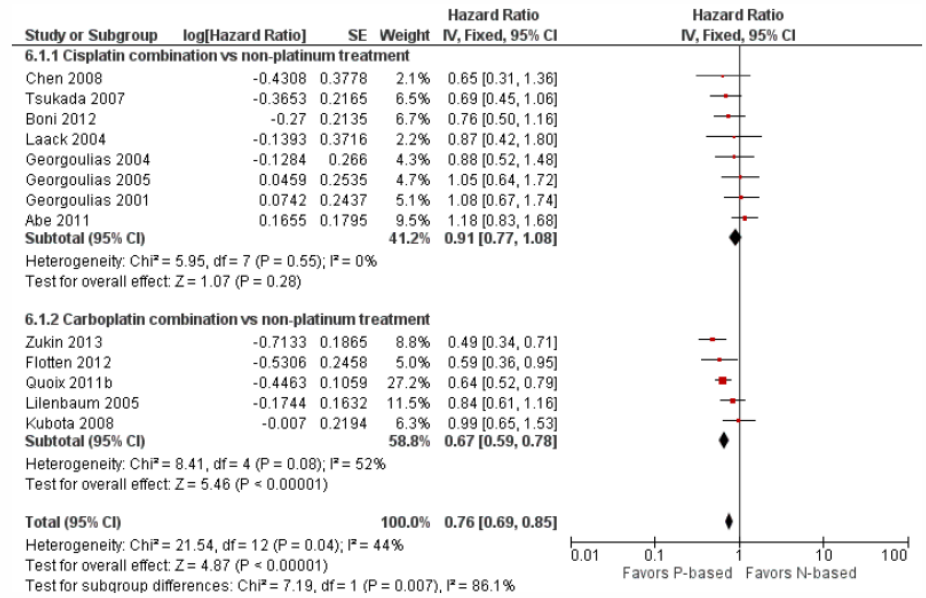
- Toxicity:
  - Grade 3 or higher hematological adverse events: We found no significant differences in risk of anemia (RR 1.18, 95% CI 0.57 to 2.40; participants = 1064; five studies; I2 = 0%), neutropenia (RR 1.19, 95%CI 0.93 to 1.54; participants = 1064; five studies; I2 = 24%), febrile neutropenia (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%)

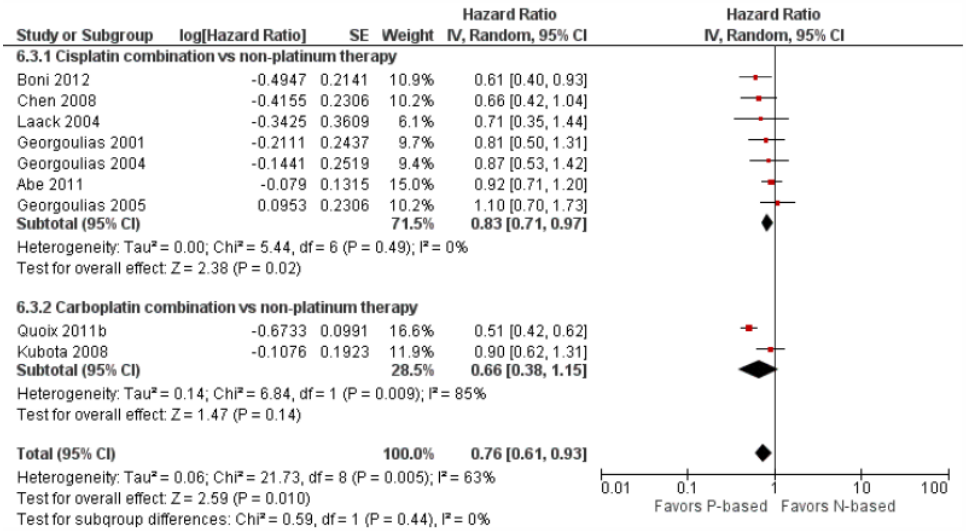
Exploratory analysis by platinum agent showed improvement in OS for carboplatin combination treatment (HR 0.67, 95% CI 0.59 to 0.78) and no significant differences for cisplatin combination treatment (HR 0.91, 95% CI 0.77 to 1.08) over non-platinum therapy. Differences between subgroups reached statistical 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.



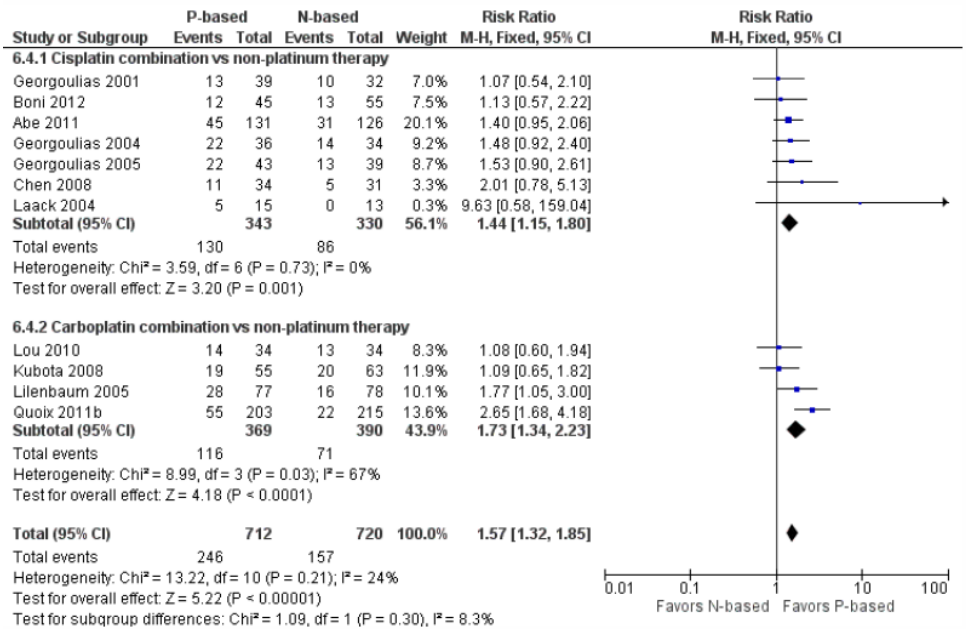
- QoL: Only five RCTs included QoL assessment. However, we were not able to performameta-analysis of these data because of the paucity of data provided.
- PFS: The meta-analysis of nine RCTs with 1273 elderly participants showed significant improvement in PFS in favor of platinum combination over non-platinum 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.



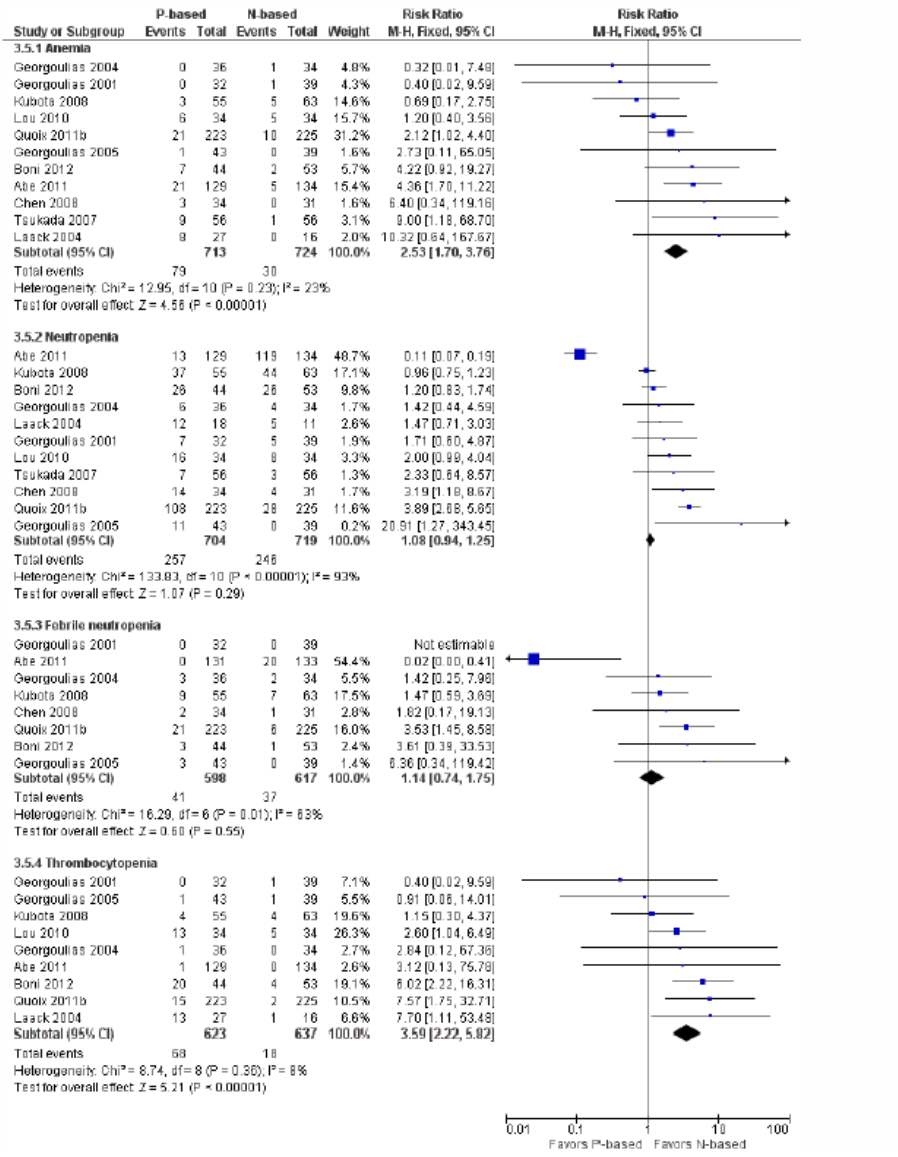
- ORR: The meta-analysis from 11 RCTs with 1432 elderly participants showed benefit in RR in favor of platinum combination over nonplatinum regimens with low heterogeneity among trials (RR 1.57, 95% CI 1.32 to 1.85; I2 = 24%)

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 IIB und IV): Keine seperaten Ergebnisse (z.B. fortgeschritten vs. metastasiert.

3.3 Systematische Reviews

Armoiry 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.

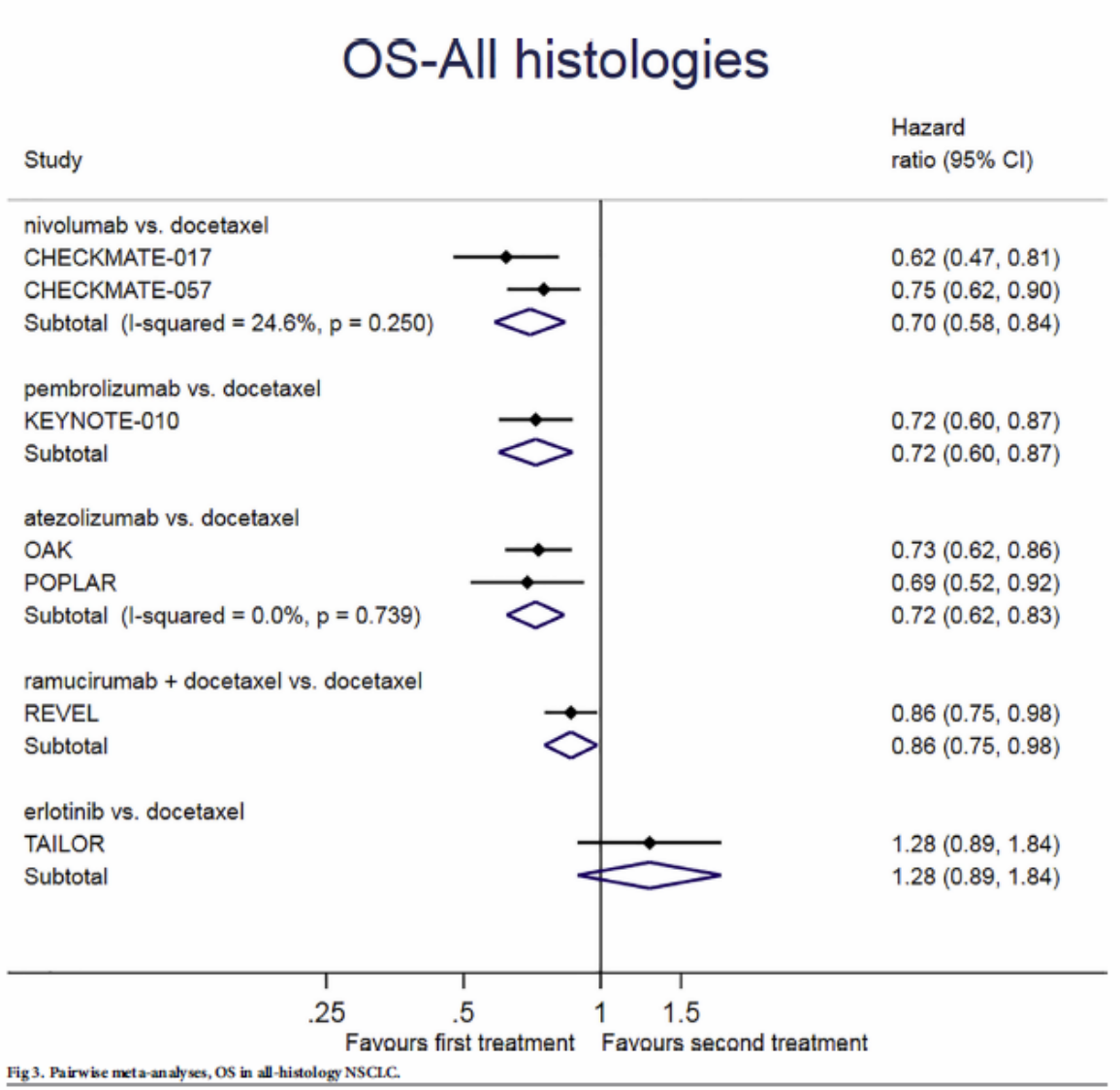


Fig 3. Pairwise meta-analyses, OS in all-histology NSCLC.

  - 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 (Supplementary online material E in S3 File) the RR estimates from direct comparisons were not stable across different points of study follow-up (Supplementary online material F in S3 File).
- 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.

Chen et al., 2018 [4].

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

Fragestellung

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

Methodik

Population:

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

Intervention/Komparator:

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

Endpunkte:

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

Recherche/Suchzeitraum:

- up to July 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

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

Qualität der Studien:

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

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

Studienergebnisse:

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

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

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

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

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

- Toxicity:

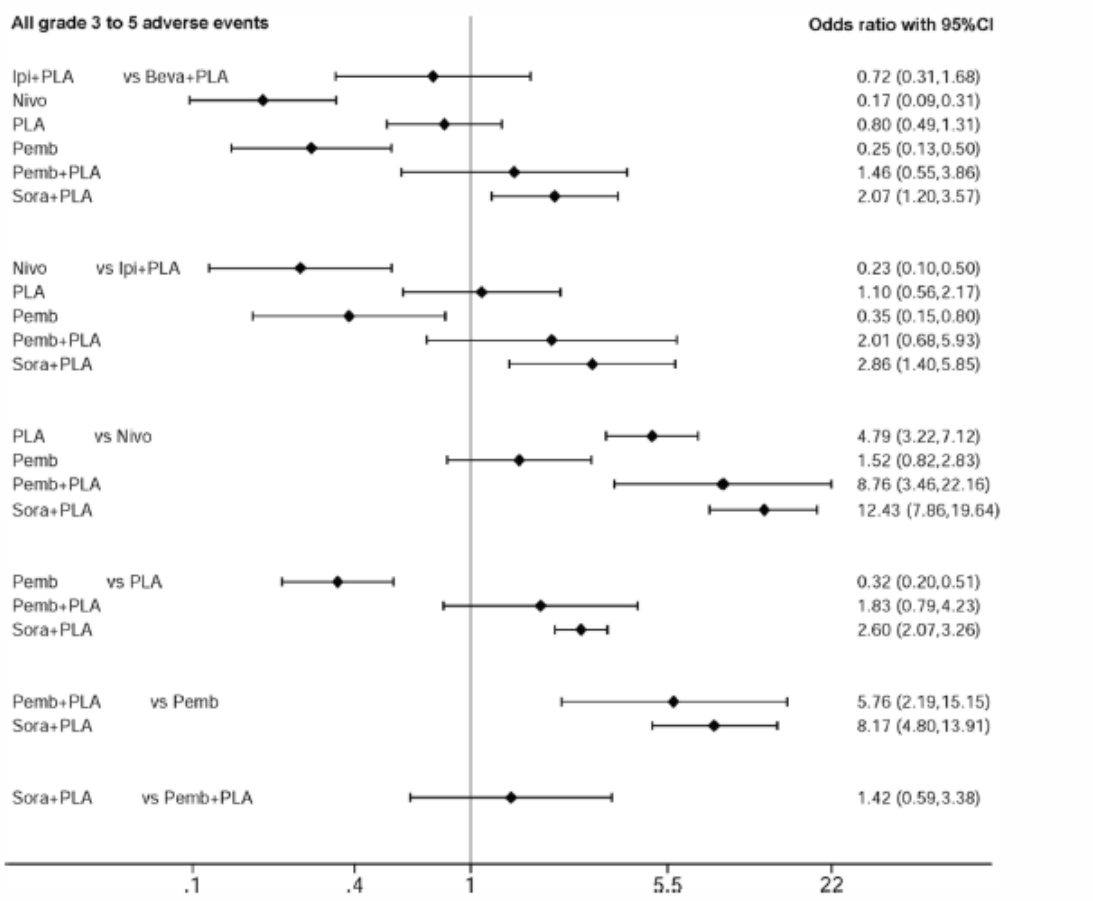


Figure 2. Forest plot of indirect comparison: all grade 3 to 5 adverse events in first line therapy. All individual regimens compared with reference treatment. Odds ratios (OR) and 95% confidence intervals were given. Beva: bevacizumab; Ipi: ipilimumab; Nivo: nivolumab; Pemb: pembrolizumab; Sora: sorafenib;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

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

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

Fan et al., 2018 [8].

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

Fragestellung

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. (siehe Ergebnisteil)

Endpunkte:

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

Recherche/Suchzeitraum:

- through September 5, 2017

Qualitätsbewertung der Studien:

- Cochrane collaboration ROB tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 studies (2 RCTs and 6 single-arm trials) / 626 patients (255 in the 2 RCTs and 371 in the 6 single-arm trials)

Qualität der Studien:

Table 1 Characteristics of the included studies

Citation	Number of patients	Median age (years)	Median duration of follow-up (months)	Alectinib dose and frequency	Trial phase	Baseline	Treatment-line	Quality assessment (NOS unless otherwise stated)
Hida et al[23]	103	61	12	300 mg PO BID	III	ALKi-naïve	Mixed	Cochrane ROB tool: high risk
Peters et al[15]	152	58	18.6	600 mg PO BID	III	Untreated	First-line	Cochrane ROB tool: high risk
Seto et al[26]	46	48	7.6	300 mg PO BID	II	ALKi-naïve	Mixed	6
Gadgeel et al[27]	47	56	4.2	300–900 mg PO BID	I/II	CRZ-pretreated	Mixed	4
Hida et al[24]	35	45	NA	300 mg PO BID	NA	Mixed	Mixed	5
Ou et al[28]	138	52	7	600 mg PO BID	II	CRZ-pretreated	Mixed	6
Shaw et al[29]	87	54	9.9	600 mg PO BID	II	CRZ-pretreated	Mixed	6
Iwama et al[25]	18	72	9.8	600 mg PO BID	II	Mixed	Mixed	3

Abbreviations: ALKi, anaplastic lymphoma kinase inhibitor; BID, twice a day; CRZ, crizotinib; NA, not available; NOS, Newcastle–Ottawa Scale; PO, take orally; ROB, risk of bias.

Studienergebnisse:

- The pooled ORR of ALK+ NSCLC patients treated with alectinib is 70% (95% CI: 57% to 82%).
- Subgroup analysis showed that patients who never received ALKi treatment tend to have higher ORR than crizotinib-pretreated patients (87%, 95% CI: 81% to 92% vs 52%, 95% CI: 46% to 58%).

- The pooled DCR is 88% (95% CI: 82% to 94%), and subgroup analysis showed that patients who never received ALKi treatment tend to have higher DCR than crizotinib-pretreated patients (95%, 95% CI: 89% to 100% vs 83%, 95% CI: 76% to 89%).
- The pooled average PFS is 9.36 months (95% CI: 7.38% to 11.34%).

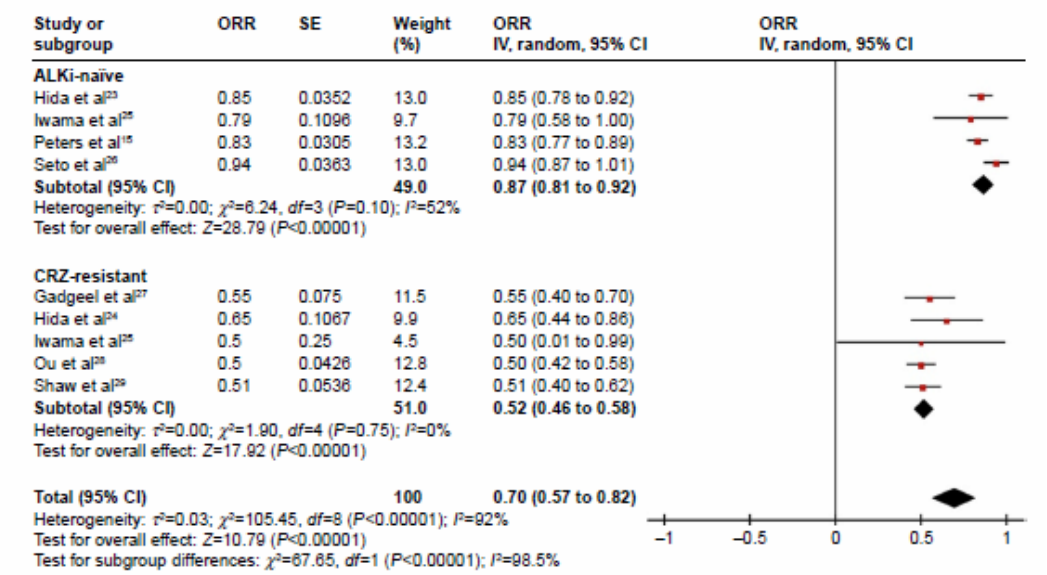


Figure 2 Meta-analysis of the ORR of ALKi-rearranged non-small cell lung cancer treated with alectinib.
Abbreviations: ALKi, anaplastic lymphoma kinase inhibitor; CRZ, crizotinib; ORR, overall response rate; SE, standard error; IV, inverse variance; CI, confidence interval.

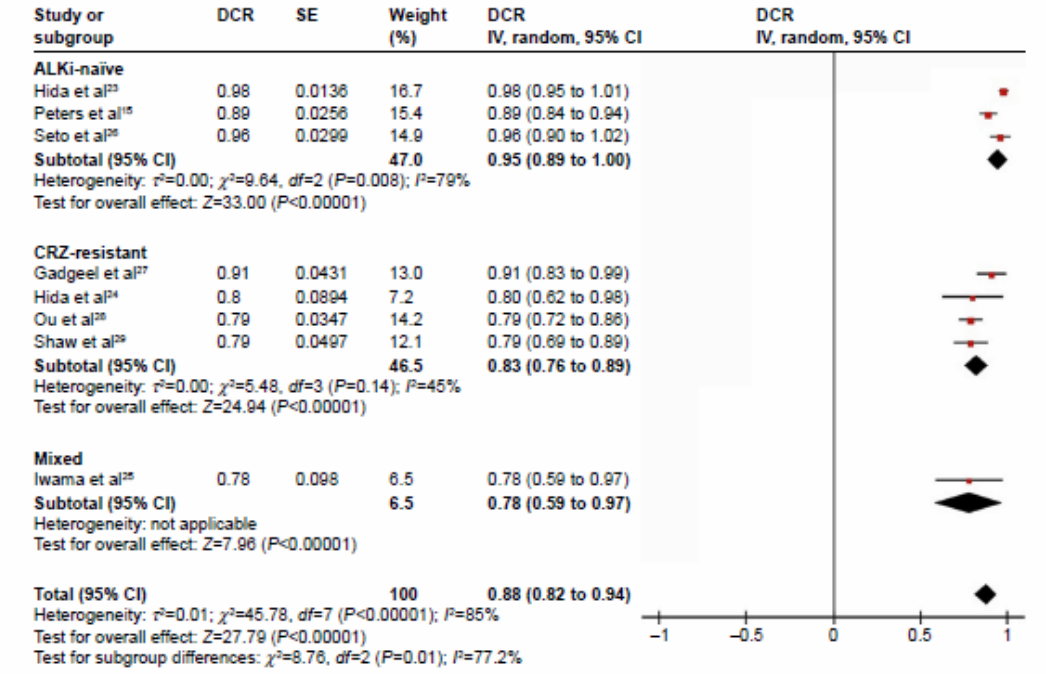


Figure 3 Meta-analysis of the DCR of ALKi-rearranged non-small cell lung cancer treated with alectinib.
Abbreviations: ALKi, anaplastic lymphoma kinase inhibitor; CRZ, crizotinib; DCR, disease control rate; SE, standard error; IV, inverse variance; CI, confidence interval.

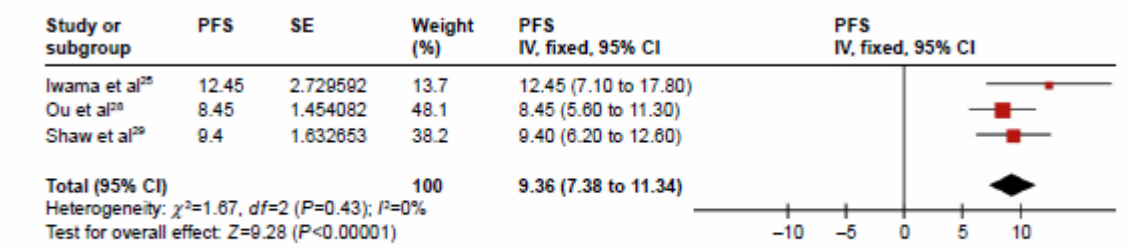


Figure 4 Meta-analysis of the PFS of ALK-rearranged non-small cell lung cancer treated with alectinib.
Abbreviations: ALK, anaplastic lymphoma kinase; PFS, progression-free survival; SE, standard error; IV, inverse variance; CI, confidence interval.

- For the ORR of alectinib-treated ALK+ NSCLC patients with brain metastases, the pooled result is 52% (95% CI: 45% to 59%). Subgroup analysis showed that ALKi-naïve patients tend to have higher ORR than crizotinib-pretreated patients (59%, 95% CI: 47% to 71% vs 48%, 95% CI: 38% to 57%).

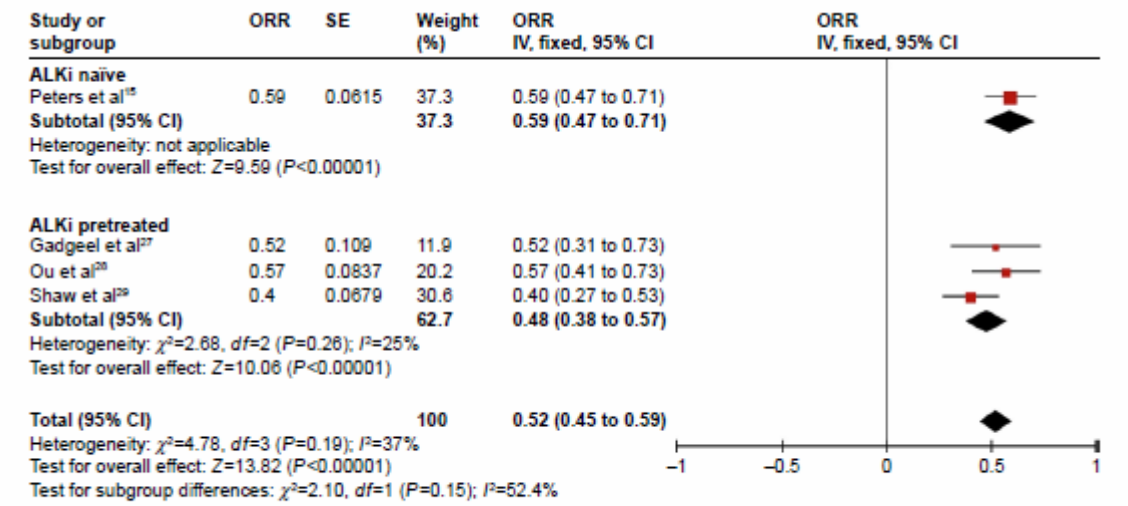


Figure 5 Meta-analysis of the ORR of alectinib-treated ALK-rearranged non-small cell lung cancer with brain metastases.
Abbreviations: ALK, anaplastic lymphoma kinase; ALKi, anaplastic lymphoma kinase inhibitor; CRZ, crizotinib; ORR, overall response rate; SE, standard error; IV, inverse variance; CI, confidence interval.

- The pooled discontinuation rate is 7% (95% CI: 4% to 10%), while the pooled rate of dose reduction or interruption is 33% (95% CI: 24% to 42%).
- The incidences of most adverse events were relatively low, while the incidences of 2 frequently reported adverse events, myalgia (18%) and anemia (25%), were even higher than with the first-generation ALK inhibitor crizotinib.

Anmerkung/Fazit der Autoren

In summary, the results of this meta-analysis suggest that most patients would respond to alectinib treatment, or at least have their disease controlled (DCR: 88% and ORR: 70%). It seems that alectinib is a preferable drug to treat intracranial metastases of ALK+ NSCLC. Patients who never received ALKi treatment tend to have a better response than crizotinib-refractory patients. Generally, alectinib is well tolerated by ALK+ NSCLC patients. However, the incidences of few adverse events, such as myalgia and anemia were even higher in alectinib-treated patients compared with crizotinib-treated counterparts. Further clinical trials are warranted to update our meta-analysis and provide more insightful instructions for the clinical use of alectinib.

Kommentare zum Review

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

Han et al., 2018 [25].

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

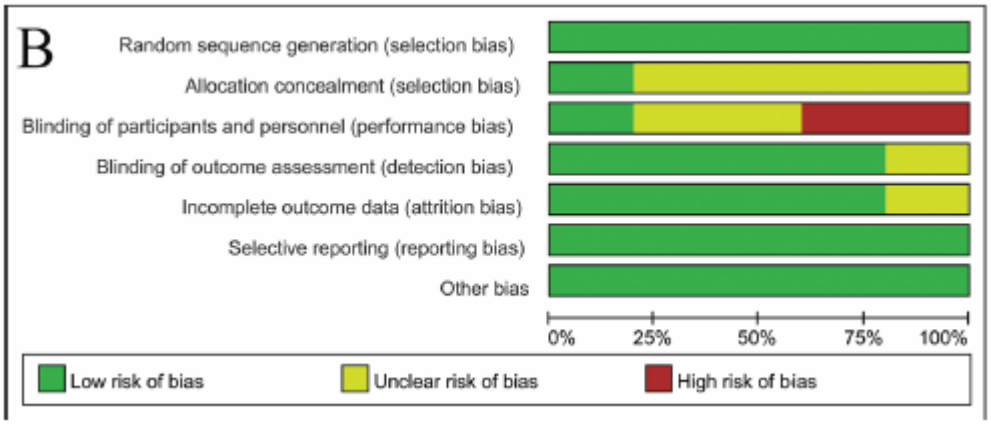
Charakteristika der Population:

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

Khan et al., 2018 [32].

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.

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:

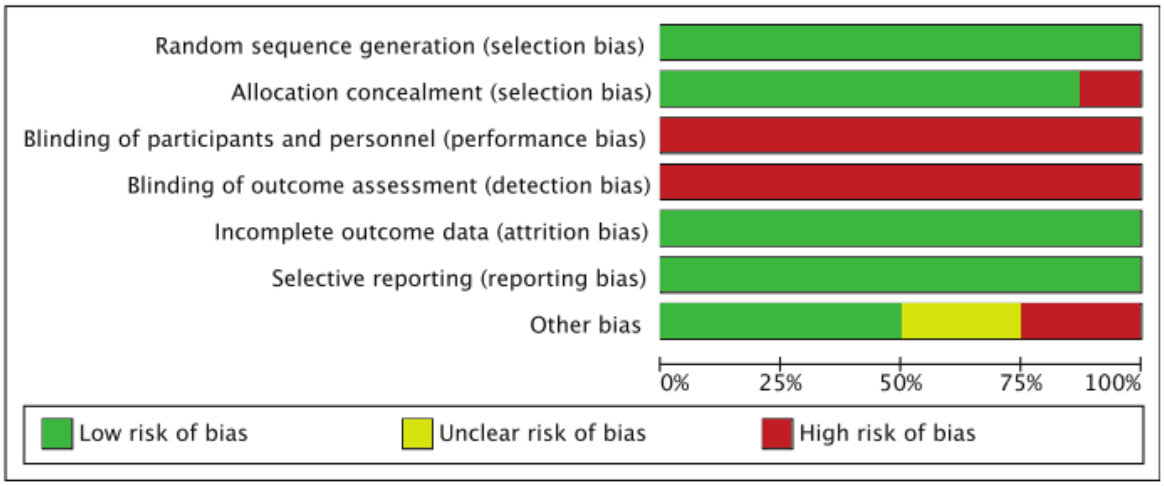


Figure 2. Risk of bias graph. +: low risk of bias; −: high risk of bias; ?: unclear risk of bias.

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.

Zhao et al., 2018 [60].

Ceritinib Alone for Crizotinib-naive Versus Crizotinib-pretreated for Management of Anaplastic Lymphoma Kinase-rearrangement Non-Small-cell Lung Cancer: A Systematic Review.

Fragestellung

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:

- patients with ALK rearrangement NSCLC

Intervention/Komparator:

- ceritinib for ALK-rearrangement NSCLC or metastases to the brain with crizotinib-naive versus crizotinib-pretreated patients → We compared ceritinib treatment for crizotinib-naive versus crizotinib-pretreated patients, with a restriction on treatment history. Thus, the phrase “patients received no previous ALKinhibitor crizotinib treatment and used ceritinib as initial therapy” was used to define the crizotinib-naive group, and the phrase “patients had received previous treatment with crizotinib followed by ceritinib at the time of relapse” was used to define the crizotinib-pretreated group.

Endpunkte:

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

Recherche/Suchzeitraum:

- Until August 2017

Qualitätsbewertung der Studien:

- Effective Public Health Practice Project Tool (EPHPP).

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 reports (7 trials) with 1015 participants

Charakteristika der Population:

Table 1 Primary Characteristics of Selected Studies

Investigator	Mean Age, y	Patients, n	Female Sex, %	Never Smoked, %	Race (White, Asian, Other), %	Trial Phase	Adenocarcinoma, %	Brain Metastases, %	Previous Crizotinib Therapy, n/N (%)	ECOG PS Score ≤ 1, %
Shaw et al[17]	53.0	130	60.0	62.0	75, 22, 3	I	94.0	64.0	Yes, 83/122 (68); no, 39/122 (32)	87.0
Kim et al[a,18]	55.0	83	53.0	99.0	58, 42, 0	I	92.0	31.0	No, 83/246 (34)	65.0
Kim et al[a,18]	52.0	163	54.0	97.0	66, 29, 4 (black, 4)	I	93.0	60.0	Yes, 163/246 (66)	16.0
Crinò et al[20]	51.0	140	50.0	NA	60.0, 37.9, 2.1	II	92.1	71.4	Yes	85.7
Felip et al[21]	56.0	124	60.0	NA	38.7, 59.7, 0	II	NA	40.3	No	NA
Soria et al[22]	55.0	189	54.0	57.0	55, 40, 5	III	95.0	31.0	No, 152/189 (80)	NA
Shaw et al[23]	54.0	115	59.0	62.0	70, 26, 2 (unknown, 2)	III	97.0	57.0	Yes, 115/115 (100)	NA
Hida et al[24]	45.5	24	66.7	NA	0, 95.8, 4.2	NA	91.7	79.2	Yes	79.2

Abbreviations: ECOG = Eastern Cooperative Oncology Group; NA = not available; PS = performance status.
[a]This study included 2 subgroups of trials: 1 of ceritinib for crizotinib-naive patients and 1 of ceritinib for crizotinib-pretreated patients.

Qualität der Studien:

- The quality of the studies was moderate to strong

Studienergebnisse:

- The pooled efficacy parameters were as follows:
  - ORR, 56.9% (95% confidence interval [CI], 53.6%-60.1%); PFS, 8.26 months (95% CI, 6.18-11.07 months); intracranial ORR, 41.3% (95% CI, 35.3%-47.6%); and intracranial disease control rate, 79.8% (95% CI, 73.8%-84.7%).
- The pooled ceritinib for crizotinib-naive showed a trend toward greater ORR and longer PFS compared with ceritinib for crizotinib-pretreated (68.9% and 14.62 months vs. 48.2% and 6.32 months, respectively).
- The intracranial ORR for ceritinib as the initial regimen was 50.6% compared with 33.6% for crizotinib-pretreated.
- The discontinuation and dose reduction rates were 3.1% and 38.4%, respectively. The most common grade 3/4 adverse effects were increased alanine aminotransferase (25.5%), increased g-glutamyltransferase (12.6%), and increased aspartate aminotransferase (11.1%).

Anmerkung/Fazit der Autoren

The results of the present systematic review have shown that the second-generation ALK-TKI ceritinib might be the preferential choice for patients with advanced or metastatic ALK-rearrangement NSCLC, especially crizotinib-naive patients. The adverse events of ceritinib have been mild to moderate. Although further studies are required to determine the optimal approach for the sequence of treatment lines in clinical practice, our findings lend support to the use of ceritinib for crizotinib-naive patients with better results compared with its use for crizotinib-pretreated patients with ALKrearrangement NSCLC.

Ramos-Esquivel et al., 2017 [40].

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.

Fragestellung

To compare the efficacy and toxicity of anti-programmed cell death receptor 1 (PD-1) and antiprogrammed cell death ligand 1 (PD-L1) versus docetaxel in previously treated patients with advanced non-small cell lung cancer (NSCLC).

Methodik

Population:

- patients with advanced non-small cell lung cancer (NSCLC)

Intervention/Komparator:

- chemotherapy versus any anti-PD-1/anti-PD-L1 agent used as monotherapy

Endpunkte:

- OS, PFS

Recherche/Suchzeitraum:

- in May 2017

Qualitätsbewertung der Studien:

- Cochrane Collaboration Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 4 trials that enrolled 2737 patients → majority of patients had wild-type EGFR non-squamous NSCLC.

Charakteristika der Population:

Table 1 General characteristics of the included trials

First author (trial)	Rittmeyer *et al* (OAK)[9]	Herbst *et al* (KEYNOTE-010)[8]	Borghaei *et al* (CheckMate 057)[11]	Brahmer *et al* (CheckMate 017)[10]
Immunotherapy	Atezolizumab	Pembrolizumab	Nivolumab	Nivolumab
Patient's characteristics and definition of treatment				
Median age (years) (range)	64.0 (30–85)	62.66 (56-69)	62 (21–85)	63 (39–85)
Disease stage (n (%))	IIIB and IV (non-specified)	Advanced (non-specified)	IIIB: 44 (8) IV: 538 (92)	IIIB: 53 (19) IV: 217 (80) Not reported: 2 (1)
Performance status (n (%))	ECOG 0: 315 (37) ECOG 1: 535 (63)	ECOG 0: 49 (32) ECOG 1: 102 (67) ECOG 2: 1 (1)	ECOG 0: 179 (31) ECOG 1: 402 (69) Unknown: 1 (<1)	ECOG 0: 64 (24) ECOG 1: 206 (76) Unknown: 1 (<1)
Histology (n (%))	Non-squamous: 628 (74) Squamous: 222 (26)	Non-squamous: 724 (70.1) Squamous: 222 (21.5) Other: 25 (2.4) Unknown: 62 (6.0)	Non-squamous: 582 (100)	Squamous: 272 (100)
EGFR mutation negative (n (%))	628 (74)	875 (84.70)	500 (86)	Not reported
EGFR mutant (n (%))	85 (10) Unknown: 137 (16)	86 (8.32) Unknown: 72 (6.96)	82 (14)	Not reported
Positive ALK translocation (n (%))	2 (<1)	8 (<1)	21 (4)	Not reported
Positive KRAS mutation (n (%))	59 (7)	Not reported	62 (11)	Not reported
Previous treatment	Chemotherapy: 1011 (97.9) Immunotherapy: 4 (<1) EGFR tyrosine kinase inhibitor: 143 (13.8) ALK inhibitor: 10 (<1)	Chemotherapy: 1011 (86.5) Immunotherapy: 4 (<1) EGFR tyrosine kinase inhibitor: 143 (12.24) ALK inhibitor: 10 (<1)	Platinum-based therapy: 582 (100) EGFR tyrosine kinase inhibitor: 53 (9) ALK inhibitor: 3 (1)	Platinum duplet chemotherapy: (Paclitaxel 34%, gemcitabine 44%, etoposide 13%) EGFR tyrosine kinase inhibitor: 3 (1)

(…)

Qualität der Studien:

- All included trials were open-label with high risk of performance and detection bias. Selection bias was likely to occur in one trial due to unmask allocation

Studienergebnisse:

- The use of anti-PD-1/anti-PD-L1 agents (atezolizumab, nivolumab and pembrolizumab) was associated with better OS in comparison with docetaxel alone (HR: 0.69; 95% CI 0.63 to 0.75; p<0.00001).
- Similarly, the PFS and duration of response was significantly longer for patients receiving immunotherapy (HR: 0.85; 95% CI 0.75 to 0.96; p=0.007 and HR: 0.32; 95% CI 0.24 to 0.43; p<0.00001, respectively) versus single agent chemotherapy.
- The overall response rate was also higher for patients who received any anti-PD-1/anti-PD-L1 therapy in comparison with docetaxel (OR: 1.77; 95% CI 1.26 to 2.50; p=0.001).
- Regarding treatment-related side effects grade 3 or higher, patients who received immunotherapy experienced less events than patients allocated to docetaxel (OR: 0.19;
- 95% CI 0.12 to 0.30; p<0.00001)
- Subgroup analyses
  - (…) Patients with wild-type EGFR were more likely to obtain an OS benefit from immunotherapy in contrast to patients with any EGFR mutation (p=0.005). Similarly, patients with high PD-L1 expression on immunohistochemistry had better OS than their counterparts (p=0.0001). Of note, the definition of high PD-L1 expression varied in each trial.

Anmerkung/Fazit der Autoren

In conclusion, our findings show an OS improvement of anti-PD-1/anti-PD-L1 therapy versus docetaxel in previously treated advanced NSCLC. PFS, overall response and duration of response also favoured the use of checkpoint inhibitors when compared with chemotherapy. In terms of side effects, even though the toxicity profile is different between checkpoint inhibitors and chemotherapy, grade 3 or higher adverse events were more likely seen with docetaxel.

Zhao et al., 2018 [59].

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–Pt1B), gemcitabine–platinum plus bevacizumab (Gem–Pt1B) and pemetrexed–platinum plus bevacizumab (Pem–Pt1B)

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–platinum1bevacizumab (Taxane–Pt1B), gemcitabine–platinum1bevacizumab

(Gem–Pt1B) and pemetrexed–platinum1bevacizumab (Pem–Pt1B), 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–Pt1B 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–Pt1B showed no OS benefit compared to any other treatment.
- No significant differences were detected between Pem–Pt1B and Pem–Pt in four outcomes.
- In terms of the benefit-risk ratio, Pem–Pt and Taxane–Pt1B were ranked the first and second, respectively.

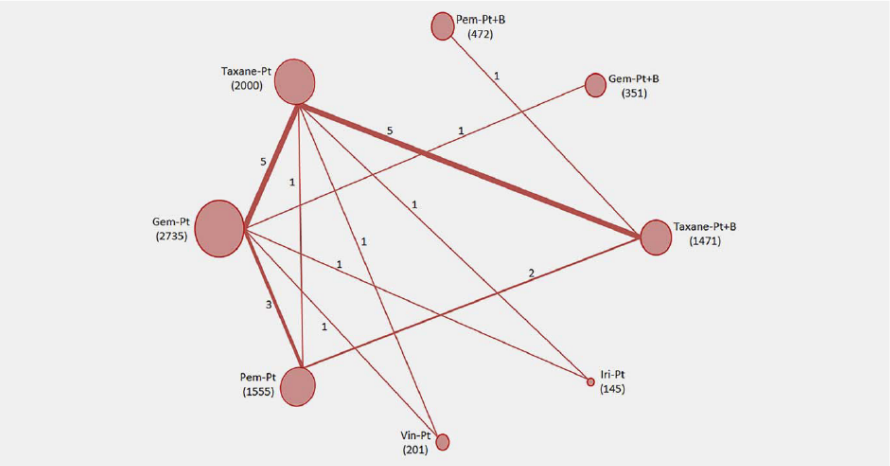


Figure 2. Network of all eligible trials assessing the six treatments in the first-line setting for advanced NS-NSCLC established for the Bayesian network meta-analysis. The size of the nodes is proportional to the number of patients (in parentheses) randomized to receive the treatment. The width of 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–Pt1B are the best and second-best treatment for this population.

Lai et al., 2016 [34].

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.

Xiao et al., 2016 [55].

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:

- 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:

- Overall, a total of 1,565 patients with advanced nonsquamous NSCLC receiving PPC and 986 with other platinum-based doublet chemotherapy were included; the pooled median PFS and OS were 5.7 and 16.05 months, respectively.
- A total of 680 patients from seven trials receiving PPC as first-line chemotherapy were included for ORR analysis. The pooled overall response rate was 37.8% (95% CI: 31.7%–

44.3%). There was significant heterogeneity between the trials ($I2$=56.9%, P=0.031), and the pooled overall response was performed using a random-effects model.

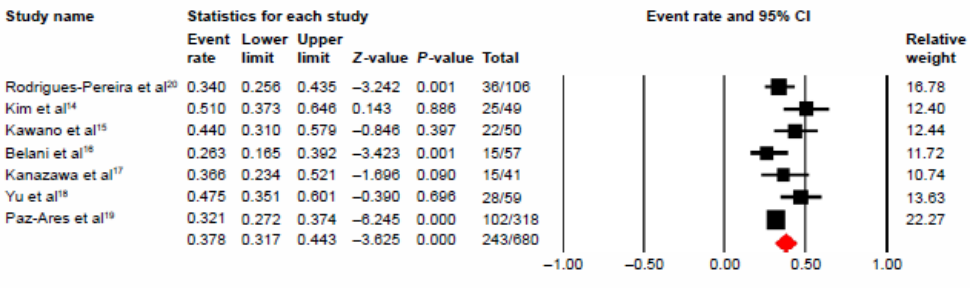


Abbildung 1: Random-effects model of ORR (95% CI) for pemetrexed plus platinum doublet chemotherapy.

- 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 ($I2$=0%, P=0.65).

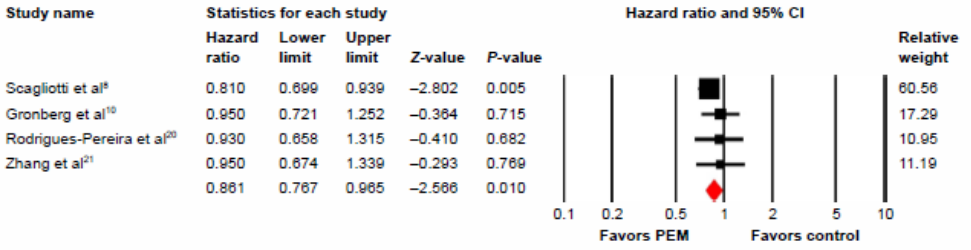


Abbildung 2: Fixed-effects model of HR (95% CI) of OS associated with PEM plus platinum versus other platinum-based chemotherapy.

- Two of four RCTs reported PFS data. The pooled hazard ratio for PFS demonstrated that PPC tends to improve PFS by giving HR 0.90(not significant), compared with other platinum-based doublet chemotherapy in advanced nonsquamous NSCLC patients. There was no significant heterogeneity between trials ($I2$=0%, P=0.95), and the pooled HR for PFS was performed by using fixed-effects model.

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

- Der Mutationsstatus der Patienten in beiden Publikationen ist nicht dargestellt. Es ist daher nicht bekannt ob und in welchem Umfang Patienten mit einer EGFR oder ALK positive Mutation in den zugrunde liegenden Studien eingeschlossen wurden.

Su Q et al., 2017 [48].

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 [31].** Anti-PD-1/PD-L1 antibodies versus docetaxel in patients with previously treated non-small-cell lung cancer
- **Huang, G., 2018 [30].** 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. [63].** 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. [40].** 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, P., 2017 [6].** Immune Checkpoint Inhibitors for Patients With Advanced Non-Small-Cell Lung Cancer: A Systematic Review
- **Zhou G-W., 2016 [62].** Anti-PD-1/PD-L1 antibody therapy for pretreated advanced nonsmall-cell lung cancer A meta-analysis of randomized clinical trials

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

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 RCTs (n=3579)

Charakteristika der Population:

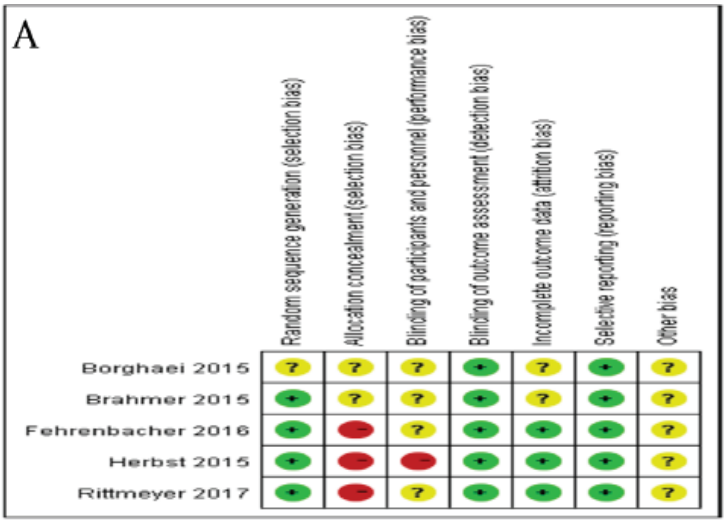
- one had data from SQ-NSCLC patients, while another one had data from NSQ-NSCLC patients, and the remaining three studies had data from both SQ and NSQ NSCLC patients.

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

15. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gainor J, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med. 2015; 373: 123-35.
16. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, Barlesi F, Kohlhaufl M, Arrieta O, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015; 373: 1627-39.
17. Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, Park K, Smith D, Artal- Cortes A, Lewanski C, Braiteh F, Waterkamp D, He P, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet. 2016; 387: 1837-46.
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.

Peng TR et al., 2017 [39].

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:

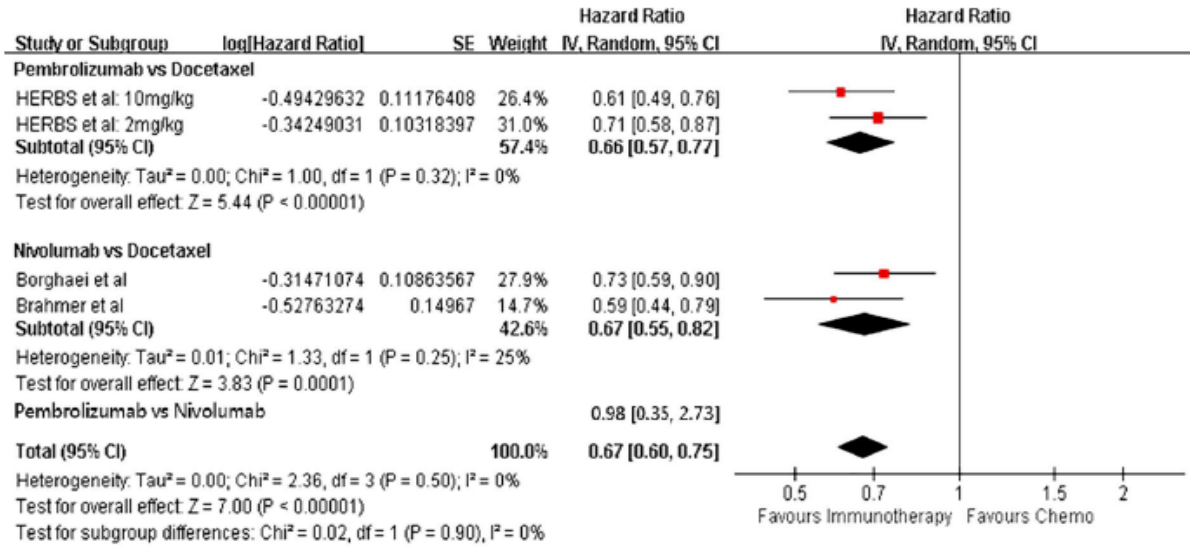
Table 2
The quality assessment of three randomized controlled trials included.

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

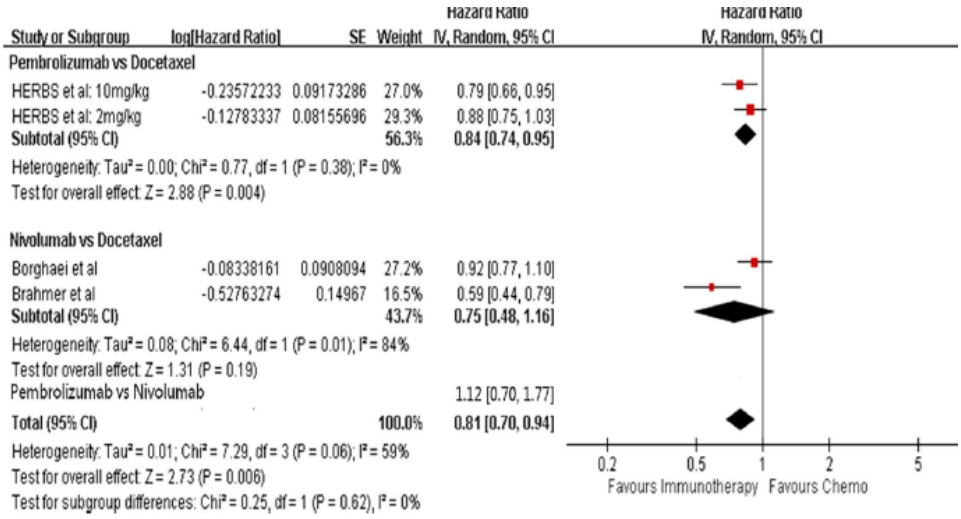


Fig. 3. Meta-analysis results of (A) OS and (B) PFS.

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).

Wu D et al., 2017 [53].

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).

Referenzen

17. Garassino MC, Martelli O, Broggini M, Farina G, Veronese S, Rulli E, Bianchi F, Bettini A, Longo F, Moscetti L, Tomirotti M, Marabese M, Ganzinelli M, et al. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. Lancet Oncol. 2013; 14: 981-8.
18. Kawaguchi T, Ando M, Asami K, Okano Y, Fukuda M, Nakagawa H, Ibata H, Kozuki T, Endo T, Tamura A, Kamimura M, Sakamoto K, Yoshimi M, et al. Randomized phase III trial of erlotinib versus docetaxel as second- or third-line therapy in patients with advanced non-small-cell lung cancer: Docetaxel and Erlotinib Lung Cancer Trial (DELTA). J Clin Oncol. 2014; 32: 1902-8.
19. Zhou Q, Cheng Y, Yang JJ, Zhao MF, Zhang L, Zhang XC, Chen ZH, Yan HH, Song Y, Chen JH, Feng WN, Xu CR, Wang Z, et al. Pemetrexed versus gefitinib as a second-line treatment in advanced nonsquamous nonsmall-cell lung cancer patients harboring wild-type EGFR (CTONG0806): a multicenter randomized trial. Ann Oncol. 2014; 25: 2385 91.
24. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, Barlesi F, Kohlhaufl M, Arrieta O, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015; 373: 1627-39.
25. Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, Park K, Smith D, Artal- Cortes A, Lewanski C, Braiteh F, Waterkamp D, He P, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. The Lancet. 2016; 387: 1837-46.
26. 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. The Lancet. 2016; 387: 1540-50.
27. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiell 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. The Lancet. 2017; 389: 255-65.
28. Kim ES, Hirsh V, Mok T, Socinski MA. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. The Lancet. 2008; 372: 1809-18.
29. Douillard JY, Shepherd FA, Hirsh V, Mok T, Socinski MA, Gervais R, Liao ML, Bischoff H, Reck M, Sellers MV, Watkins CL, Speake G, Armour AA, et al. Molecular predictors of outcome with gefitinib and docetaxel in previously treated non-small-cell lung cancer: data from the randomized phase III INTEREST trial. J Clin Oncol. 2010; 28: 744-52.
30. Ciuleanu T, Stelmakh L, Cicenas S, Miliauskas S, Grigorescu AC, Hillenbach C, Johannsdottir HK, Klughammer B, Gonzalez EE. Efficacy and safety o erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, openlabel, phase 3 study. Lancet Oncol. 2012; 13: 300-8.
31. Karampeazis A, Voutsina A, Souglakos J, Kentepozidis N, Giassas S, Christofillakis C, Kotsakis A, Papakotoulas P, Rapti A, Agelidou M, Agelaki S, Vamvakas L, Samonis G, et al. Pemetrexed versus erlotinib in pretreated patients with advanced non-small cell lung cancer: a Hellenic Oncology Research Group (HORG) randomized phase 3 study. Cancer. 2013; 119: 2754-64.

32. Li N, Ou W, Yang H, Liu QW, Zhang SL, Wang BX, Wang SY. A randomized phase 2 trial of erlotinib versus pemetrexed as second-line therapy in the treatment of patients with advanced EGFR wild-type and EGFR FISHpositive lung adenocarcinoma. Cancer. 2014; 120: 1379-86.
33. Gregorc V, Novello S, Lazzari C, Barni S, Aieta M, Mencoboni M, Grossi F, Pas TD, de Marinis F, Bearz A, Floriani I, Torri V, Bulotta A, et al. Predictive value of a proteomic signature in patients with non-small-cell lung cancer treated with second-line erlotinib or chemotherapy (PROSE): a biomarker-stratified, randomised phase 3 trial. Lancet Oncol. 2014; 15: 713-21.

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).

Sheng Z et al., 2017 [46].

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

Fragestellung

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

Methodik

Population:

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

Intervention:

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

Komparator:

- standard chemotherapy or placebo

Endpunkt:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

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

Ergebnisse

Anzahl eingeschlossener Studien:

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

Qualität der Studien:

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

Studienergebnisse:

- Effect of EGFR-TKIs Versus Chemotherapy on PFS:
  - Using random-effects model, the pooled analysis showed a significantly shorter PFS with EGFR-TKIs than with chemotherapy in the patients with WT EGFR (HR, 1.37; 95% confidence interval [CI]: 1.10, 1.72; P = 0.006) (Fig. 1). A statistically significant heterogeneity was noted in this analysis (I2 = 77%, P < 0.001). The funnel plot asymmetry can also be explained by the 3 outlying small trials of <50 patients with WT EGFR (ML 20322, V-15-32, KCSG-LU08-01) that caused heterogeneity, rather than by a publication bias. To strengthen the results of the present meta-analysis and decrease the heterogeneity, the inclusion criteria were strictly set in the subgroup analysis. Three small trials including <50 patients with WT EGFR were excluded, so the effect of EGFR-TKIs versus chemotherapy could be clearly evaluated further. Both these trials of first-line treatment (HR, 2.15; 95% CI: 1.68, 2.76; P< 0.001) and those of second-line/third-line treatment (HR, 1.35; 95% CI: 1.13, 1.61) showed significant improvement in PFS with chemotherapy over TKIs, but the subgroup difference reached the level of statistical significance in meta-regression analysis (P= 0.018) (Table 2). However, the heterogeneity was relative low within each subgroup (I2 =40% or 43%, P= 0.17 or 0.12, respectively). In the other 2 predefined subgroup analyses by kinds of TKI agents and EGFR mutation analysis methods, the treatment effects were similar between the subgroups.
- Effect of Combination of EGFR-TKIs and Chemotherapy Versus Chemotherapy Alone on PFS:
  - The pooled results of the 4 trials showed that the patients treated with a combination of EGFR-TKIs and chemotherapy had a more pronounced PFS benefit than those treated with chemotherapy alone (HR, 0.83; 95% CI: 0.71, 0.96; P = 0.01). And, this benefit was consistent across those trials (heterogeneity: I2 = 0%, P = 0.72). Three of the 4 trials were conducted using EGFR-TKIs in combination with standard platinum doublet chemotherapy for previously untreated patients with WT EGFR. When pooling them, the therapeutic advantage for the concurrent addition of EGFR-TKIs to standard first-line platinum doublet chemotherapy was still statistically significant (HR, 0.82; 95% CI: 0.68, 0.98; P = 0.03).
- Indirection Comparison of EGFR-TKIs Combined With Chemotherapy Versus EGFR-TKIs Alone:

  - Compared with standard platinum doublet chemotherapy as first-line treatment, EGFR-TKIs alone were inferior in terms of PFS (HR, 2.15; 95% CI: 1.68, 2.76; P < 0.001) in WT EGFR patients. For patients with WT EGFR tumors, indirection comparison of EGFR-TKIs combined with chemotherapy versus EGFR-TKIs alone showed a PFS benefit (HR, 0.38; 95% CI: 0.32, 0.46; P < 0.001) when using standard platinum-based doublet chemotherapy as the common comparator in the first-line setting.
- Effect of EGFR-TKIs Versus Control on OS
  - No statistically significant difference was observed in terms of OS (HR, 0.99; 95% CI: 0.91, 1.08; P = 0.87). The summary HRs were 1.08 (95% CI: 0.97, 1.21; P = 0.87) for EGFR-TKIs versus chemotherapy, 0.93 (95% CI: 0.77, 1.12; P = 0.45) for EGFR-TKIs versus placebo, 0.91 (95% CI: 0.77, 1.07; P = 0.26) for EGFR-TKIs added to chemotherapy versus chemotherapy alone, respectively.

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

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

Créquit P et al., 2017 [5].

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 meta-analysis

Fragestellung

Our objective was 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:

- Advanced NSCLC (stage IIIB unsuitable for radical radiotherapy or surgery and stage IV) with wild-type or unknown status for EGFR; second- and third-line therapy

Intervention:

- docetaxel pemetrexed, erlotinib, and gefitinib

Komparator:

- chemotherapy (e.g., docetaxel or pemetrexed) at the investigators' discretion

Endpunkt:

- overall survival (OS) and progression-free survival (PFS), objective response (ObR), defined as a complete response or a partial response according to the Response Evaluation Criteria in Solid Tumors (RECIST) [11], the number of serious adverse events (SAEs), quality of life

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, CENTRAL, ClinicalTrials.gov, and the US Food and Drug Administration website: up to June 6, 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 102 trials (n=29864)

Charakteristika der Population:

- Overall, 62% of patients were male, the mean age was 61 years, 81% had stage IV cancer, 80% were smokers, and 92% had a performance status score 0–1.
- In all, 26 trials (27%), including 4659 patients (13%), involved only Asians and 78 (76%) were of patients with both SCC or NSCC.
- Second-line only: 50 trials (49%) and second- and third line 41 studies (40%)

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:

Overall survival

- Eighteen treatments were significantly more effective than placebo in terms of OS.
- Nivolumab was more effective than docetaxel (HR 0.69, 95% CrI 0.56–0.83), pemetrexed (HR 0.67, 95% CrI 0.52–0.83), erlotinib (HR 0.68, 95% CrI 0.53–0.86), and gefitinib (HR 0.66, 95% CrI 0.53–0.83).
- Pembrolizumab, atezolizumab, and pemetrexed plus erlotinib were also significantly more effective than docetaxel, pemetrexed, erlotinib, and gefitinib. The τ value was close to 0 (τ = 0.04).
- Erlotinib plus cabozantinib, nivolumab, pembrolizumab, atezolizumab, and pemetrexed plus erlotinib represented the five most effective treatments in terms of OS
- Pairwise meta-analysis suggested a statistically significant OS benefit of nivolumab, atezolizumab, and docetaxel plus ramucirumab against docetaxel and pemetrexed plus erlotinib against pemetrexed.

Progression-free survival

- Pairwise meta-analyses suggested that, for PFS, treatment combinations often performed better when compared to a single treatment for most comparisons, heterogeneity was 0. The largest heterogeneity was for gefitinib versus pemetrexed (τ = 0.51).
- According to the NMA results, erlotinib plus cabozantinib was more effective than docetaxel (HR 0.39, 95% CrI 0.18–0.84), pemetrexed (HR 0.38, 95% CrI 0.18–0.82), erlotinib (HR 0.37, 95% CrI 0.18–0.78), and gefitinib (HR 0.38, 95% CrI 0.18–0.82).
- Cabozantinib and pemetrexed plus erlotinib were also significantly more effective than docetaxel, pemetrexed, erlotinib, and gefitinib. The heterogeneity was larger as compared with OS (τ = 0.15).
- Additionally, combinations of dual-targeted therapies (erlotinib plus pazopanib) or chemotherapy plus targeted therapy (paclitaxel plus bevacizumab) appeared to be among the most effective treatments

Anmerkung/Fazit der Autoren

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

- 81% der Patienten mit Stadium IV, jedoch keine seperaten Analysen.

Ma H et al., 2016 [37].

The Efficacy of Erlotinib Versus Conventional Chemotherapy for Advanced Nonsmall-Cell Lung Cancer

Fragestellung

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

Methodik

Population:

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

Intervention / Komparator:

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

Endpunkt:

- overall survival (OS), objective response (ORR), progress-free survival (PFS), and 1-year survival rate (OSR)

Recherche/Suchzeitraum:

- bis 2015

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

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

Charakteristika der Population:

- All 14 trials were open-label.

TABLE 1. The Main Study Characteristics

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

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

Qualität der Studien:

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

Studienergebnisse:

- PFS:

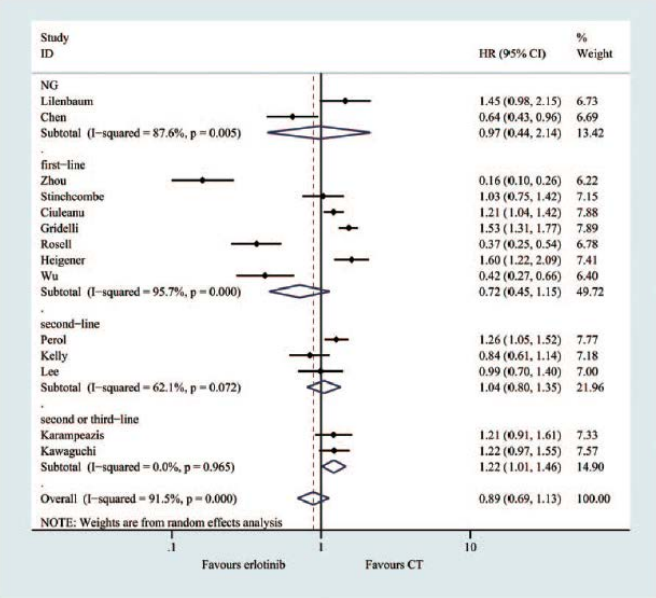
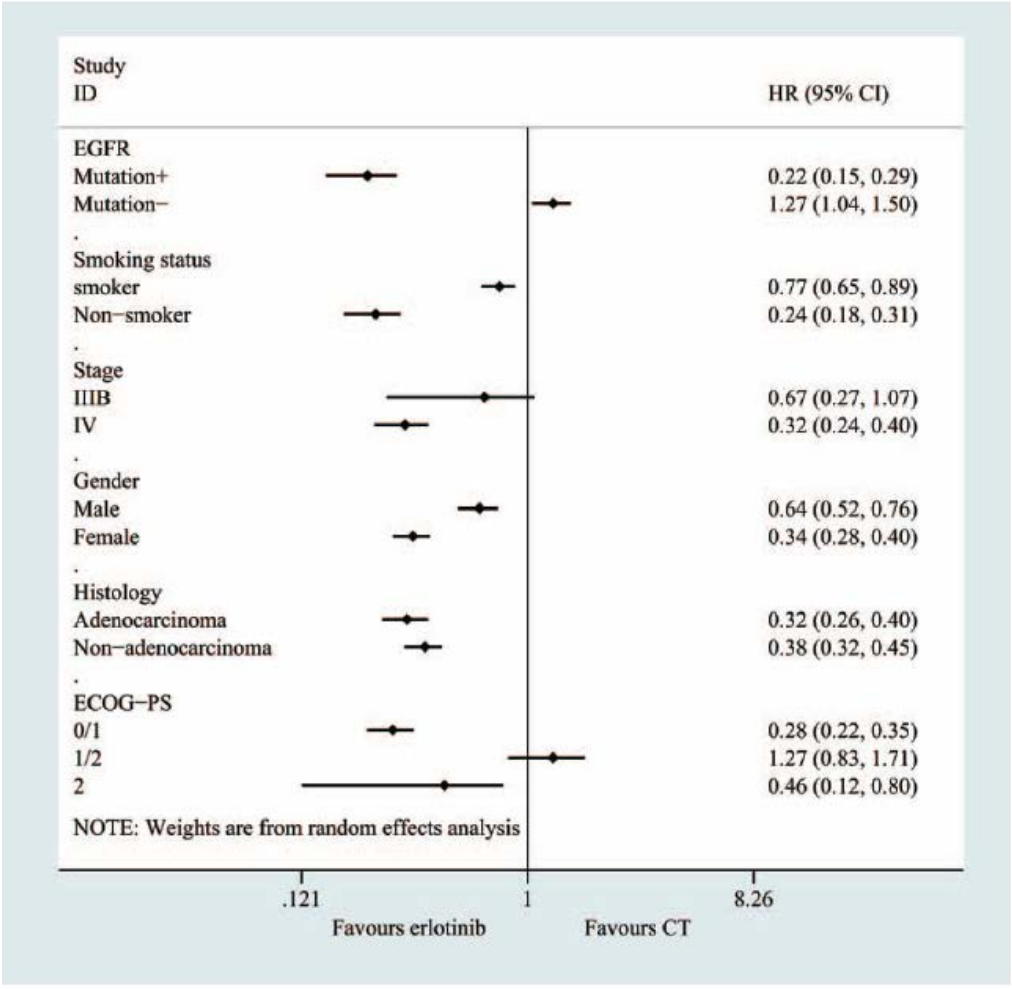
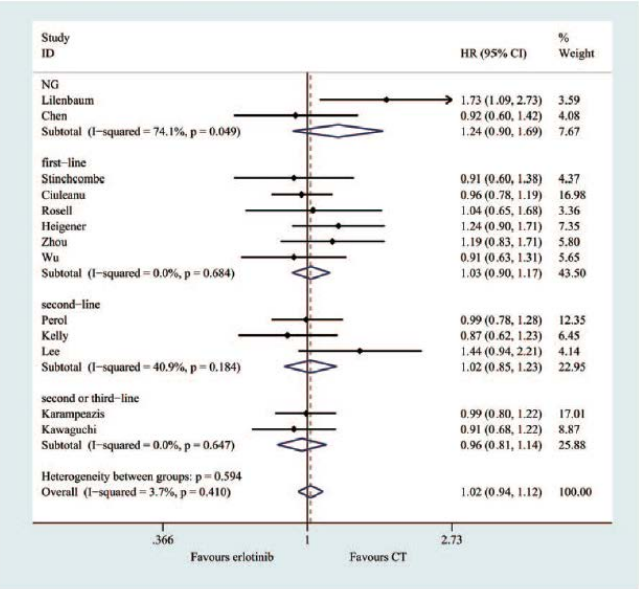


FIGURE 4. Meta-analysis results of the progression-free survival.

- Subgroup and meta-regression analyses of the PFS:

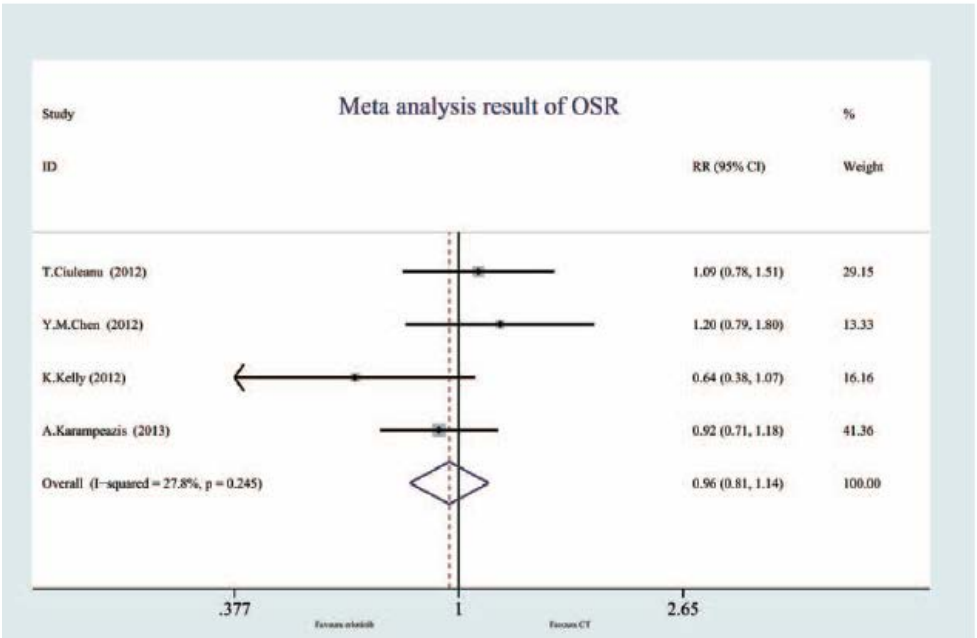


- OS:

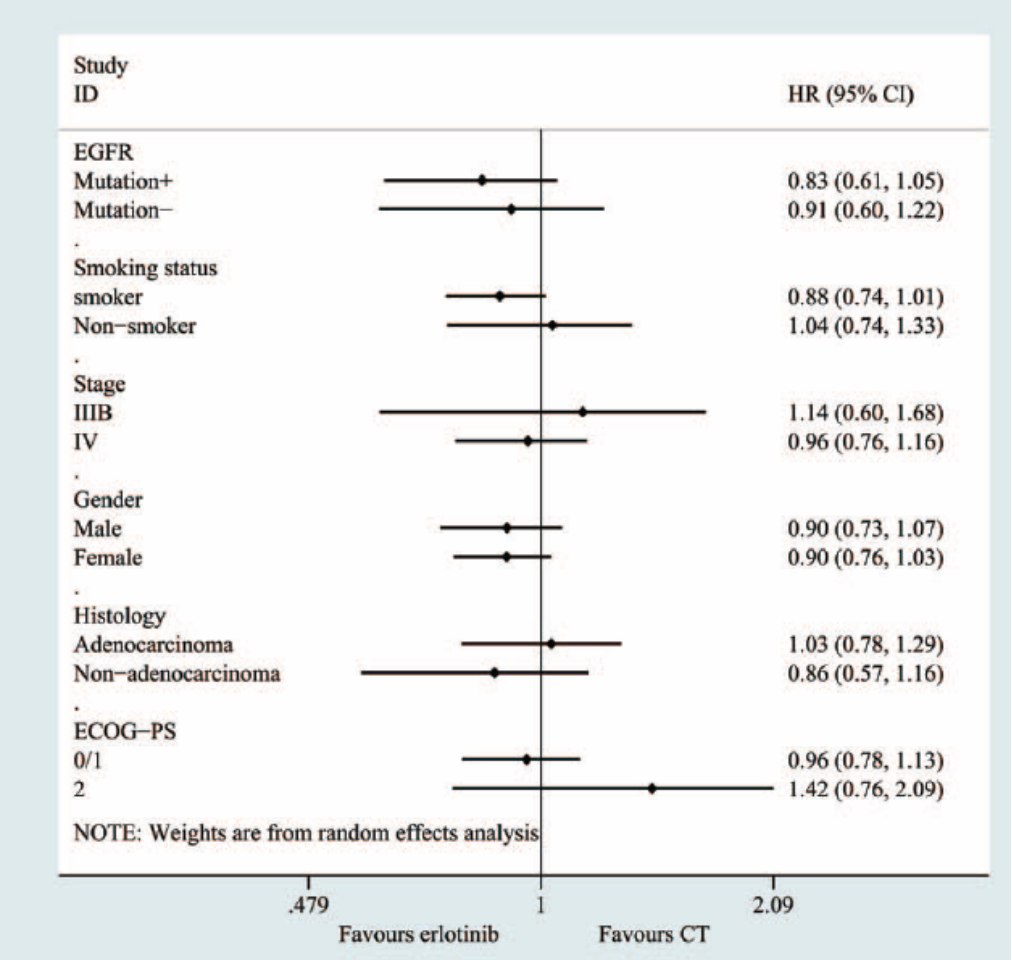


ıalysis results of the overall survival.

- 1-year Survival rate:



- Subgroup and meta-regression analyses of the OS:



Anmerkung/Fazit der Autoren

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

Kommentare zum Review

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

Hong et al. 2015 [28].

Efficacy and safety of angiogenesis inhibitors in advanced non-small cell lung cancer: a systematic review and meta-analysis

Fragestellung

To quantify the overall efficacy and safety of angiogenesis inhibitors in advanced non-small cell lung cancer (NSCLC).

Methodik

Population:

- patients with advanced NSCLC

Intervention + Komparator:

- angiogenesis inhibitors with non-angiogenesis inhibitors

Endpunkt:

- PFS, OS, ORR and DCR

Recherche/Suchzeitraum:

- bis 2014

Qualitätsbewertung der Studien:

- Jadad Score

Ergebnisse

Anzahl eingeschlossener Studien:

- 33 trials included. These trials enrolled a total of 17,396 patients (angiogenesis inhibitors: 8,947; control: 8,449)

Charakteristika der Population:

- Thirteen trials were performed in first-line settings, 17 in ≥second-line settings and three in maintenance. There were differences in the number of studies available for each endpoints because they were not consistently reported in all trials.

Qualität der Studien:

- Jadad Score: 1-5

Studienergebnisse:

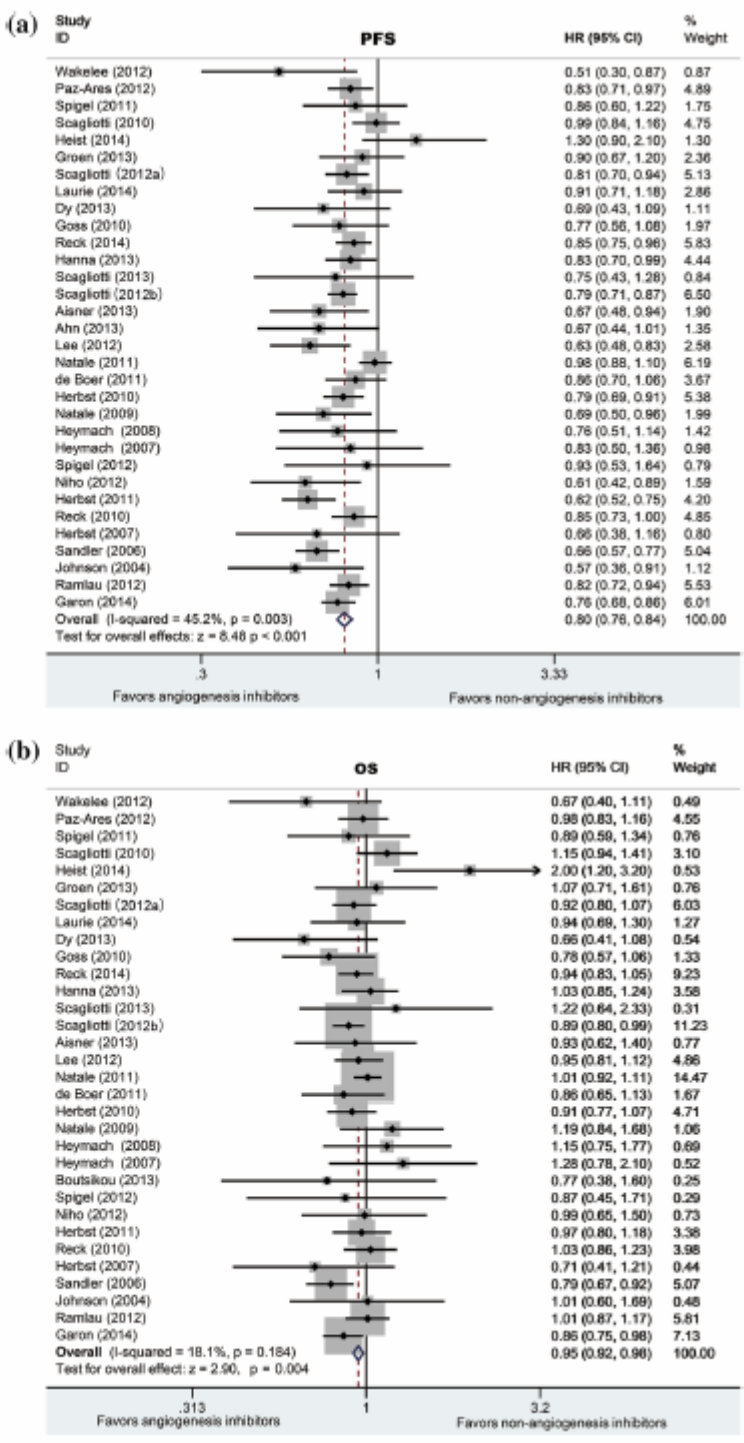


Fig. 2 Relative efficacy of angiogenesis inhibitors in advanced non-small cell lung cancer patients in terms of **a** progression-free survival (PFS) and **b** overall survival (OS). *HR* hazard ratio, *CI* confidence interval

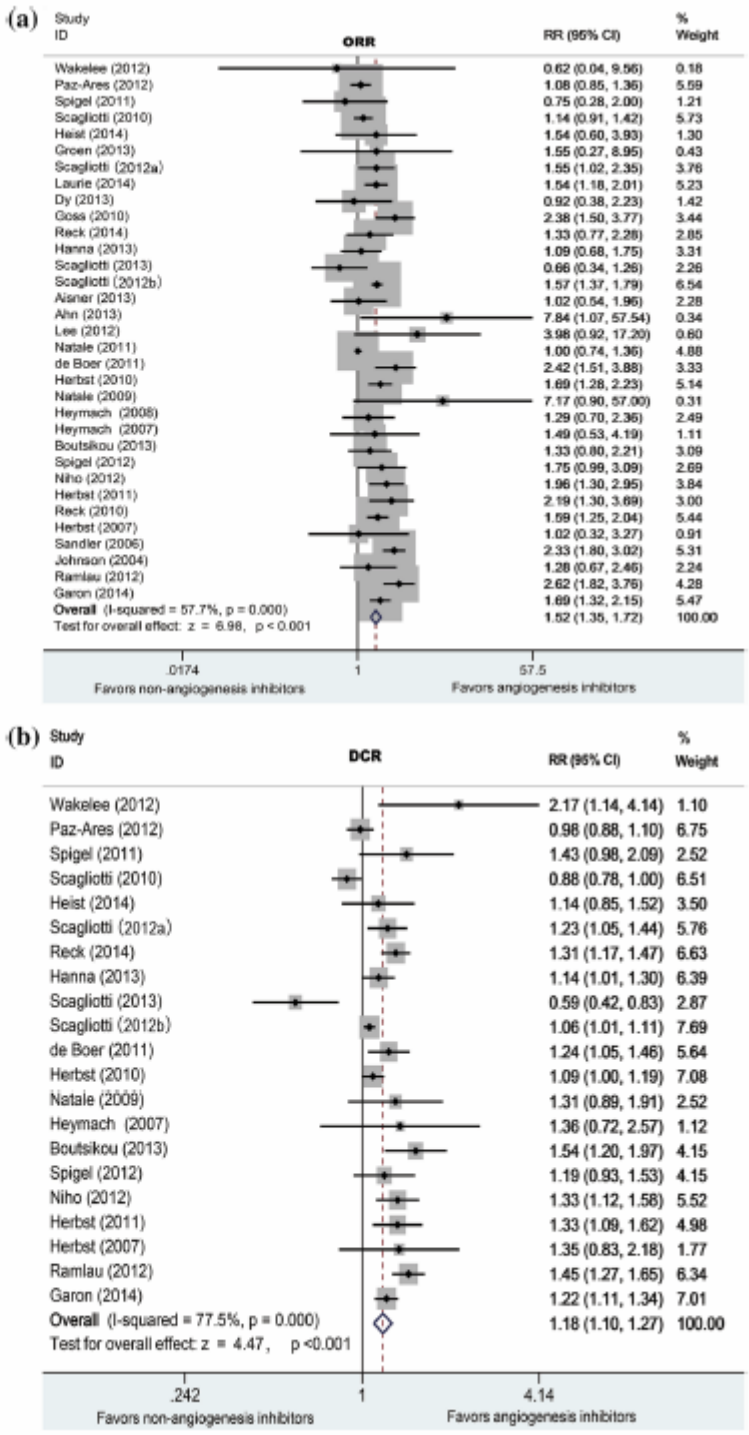


Fig. 3 Relative efficacy of angiogenesis inhibitors in advanced non-small cell lung cancer patients in terms of **a** objective response rate (ORR) and **b** disease control rate (DCR). *CI* confidence interval, *RR* relative risk

Table 2 Subgroup analysis according to individual angiogenesis inhibitor for non-small cell lung cancer

Outcomes	Drug	No. of studies	OR/HR (LL, UL)	Effect size		Heterogeneity[a]	
				Z	*p* value	*p* value	I^2
PFS	Sorafenib	4	0.85 (0.71, 1.02)	1.75	0.08	0.084	54.80 %
	Sunitinib	3	0.92 (0.73, 1.16)	0.71	0.48	0.112	54.40 %
	Cediranib	3	**0.83 (0.69, 0.99)**	2.02	**0.043**	0.52	0.00 %
	Nintedanib	2	**0.84 (0.76, 0.93)**	3.32	**0.001**	0.826	0.00 %
	Pazopanib	1	0.75 (0.43, 1.29)	1.03	0.301	–	–
	Motesanib	1	**0.79 (0.71, 0.87)**	4.55	**<0.001**	–	–
	Vandetanib	9	**0.79 (0.70, 0.89)**	3.90	**<0.001**	0.032	52.60 %
	Bevacizumab	7	**0.69 (0.61, 0.79)**	5.41	**<0.001**	0.109	42.30 %
	Aflibercept	1	**0.82 (0.72, 0.94)**	2.92	**0.004**	–	–
	Ramucirumab	1	**0.76 (0.68, 0.85)**	4.58	**<0.001**	–	–
OS	Sorafenib	4	1.01 (0.89, 1.13)	0.11	0.916	0.208	34.00 %
	Sunitinib	3	0.99 (0.87, 1.13)	0.17	0.865	0.011	77.80 %
	Cediranib	3	0.82 (0.67, 1.00)	1.96	0.05	0.453	0.00 %
	Nintedanib	2	0.96 (0.87, 1.07)	0.71	0.476	0.42	0.00 %
	Pazopanib	1	1.22 (0.64, 2.33)	0.60	0.546	–	–
	Motesanib	1	**0.89 (0.80, 0.99)**	2.14	**0.032**	–	–
	Vandetanib	8	0.98 (0.92, 1.05)	0.46	0.647	0.651	0.00 %
	Bevacizumab	8	**0.91 (0.83, 1.00)**	2.06	**0.039**	0.466	0.00 %
	Aflibercept	1	1.01 (0.87, 1.17)	0.13	0.895	–	–
	Ramucirumab	1	**0.86 (0.75, 0.98)**	2.21	**0.027**	–	–
ORR	Sorafenib	4	1.10 (0.94, 1.28)	1.14	0.256	0.829	0.00 %
	Sunitinib	3	**1.54 (1.06, 2.24)**	2.28	**0.023**	1	0.00 %
	Cediranib	3	**1.65 (1.10, 2.49)**	2.4	**0.016**	0.109	54.80 %
	Nintedanib	2	1.19 (0.83, 1.70)	0.93	0.352	0.591	0.00 %
	Pazopanib	1	0.66 (0.34, 1.26)	1.26	0.208	–	–
	Motesanib	1	**1.57 (1.37, 1.79)**	6.55	**<0.001**	–	–
	Vandetanib	9	**1.61 (1.16, 2.24)**	2.82	**0.005**	0.011	59.60 %
	Bevacizumab	8	**1.80 (1.52, 2.13)**	6.80	**<0.001**	0.267	20.50 %
	Aflibercept	1	**2.62 (1.82, 3.76)**	5.21	**<0.001**	–	–
	Ramucirumab	1	**1.69 (1.32, 2.15)**	4.19	**<0.001**	–	–
DCR	Sorafenib	4	1.08 (0.88, 1.33)	0.73	0.468	0.006	75.70 %
	Sunitinib	2	**1.21 (1.05, 1.39)**	2.61	**0.009**	0.652	0.00 %
	Nintedanib	2	**1.23 (1.07, 1.40)**	2.97	**0.003**	0.117	59.30 %
	Pazopanib	1	**0.59 (0.42, 0.83)**	3.04	**0.002**	–	–
	Motesanib	1	**1.06 (1.01, 1.11)**	2.41	**0.016**	–	–
	Vandetanib	4	**1.13 (1.05, 1.22)**	3.17	**0.002**	0.448	0.00 %
	Bevacizumab	5	**1.34 (1.21, 1.48)**	5.60	**<0.001**	0.731	0.00 %
	Aflibercept	1	**1.45 (1.27, 1.65)**	5.60	**<0.001**	–	–
	Ramucirumab	1	**1.22 (1.11, 1.34)**	4.05	**<0.001**	–	–

HR for PFS and OS. RR for ORR and DCR. Bold fonts indicate significant difference between the effects of angiogenesis inhibitors and non-angiogenesis inhibitors

RR relative risk, *HR* hazard ratio, *LL* lower limit, *UL* upper limit, *PFS* progression-free survival, *OS* overall survival, *ORR* objective response rate, *DCR* disease control rate, *TKIs* tyrosine kinase inhibitors, *Abs* antibodies

[a] Heterogeneity tests are available only when more than one studies are included

Table 3 Subgroup analyses according to drug class, treatment line and drug regimens of angiogenesis inhibitors for non-small cell lung cancer

Outcomes	Subgroups	No. of studies	RR/HR (LL, UL)	Effect size		Heterogeneity[a]	
				Z	*p* value	*p* value	I^2
PFS	Class						
	TKIs	23	**0.83 (0.79, 0.88)**	6.54	**<0.001**	0.082	30.70 %
	Abs	9	**0.73 (0.66, 0.80)**	6.56	**<0.001**	0.075	44.00 %
	Line						
	1st	12	**0.82 (0.77, 0.88)**	5.39	**<0.001**	0.332	11.50 %
	≥2nd	17	**0.80 (0.74, 0.86)**	6.10	**<0.001**	0.001	58.80 %
	Maintenance	3	**0.64 (0.50, 0.80)**	3.78	**<0.001**	0.664	0.00 %
	Regimen						
	Monotherapy	6	**0.71 (0.56, 0.89)**	2.92	**0.004**	0.002	73.80 %
	Combination	26	**0.80 (0.76, 0.84)**	8.88	**<0.001**	0.073	30.40 %
OS	Class						
	TKIs	22	0.96 (0.92, 1.00)	1.82	0.069	0.167	22.60 %
	Abs	10	**0.91 (0.85, 0.98)**	2.57	**0.010**	0.417	2.40 %
	Line						
	1st	13	0.95 (0.89, 1.02)	1.47	0.142	0.502	0.00 %
	≥2nd	17	**0.95 (0.91, 0.99)**	2.36	**0.018**	0.074	35.30 %
	Maintenance	2	0.82 (0.60, 1.13)	1.23	0.218	0.325	0.00 %
	Regimen						
	Monotherapy	5	0.99 (0.92, 1.07)	0.20	0.839	0.428	0.00 %
	Combination	27	**0.94 (0.90, 0.98)**	3.16	**0.002**	0.182	19.60 %
ORR	Class						
	TKIs	23	**1.37 (1.19, 1.58)**	4.38	**<0.001**	0.002	51.90 %
	Abs	10	**1.85 (1.59, 2.15)**	8.09	**<0.001**	0.164	30.60 %
	Line						
	1st	13	**1.41 (1.22, 1.63)**	4.61	**<0.001**	0.008	55.20 %
	≥2nd	17	**1.68 (1.39, 2.02)**	5.40	**<0.001**	0.002	56.80 %
	Maintenance	3	1.64 (0.39, 6.91)	0.68	0.499	0.112	54.30 %
	Regimen						
	Monotherapy	6	1.64 (0.86, 3.13)	1.49	0.135	0.052	54.40 %
	Combination	27	**1.55 (1.38, 1.75)**	7.35	**<0.001**	<0.001	56.40 %
DCR	Class						
	TKIs	14	**1.11 (1.02, 1.20)**	2.42	**0.016**	<0.001	74.80 %
	Abs	7	**1.32 (1.23, 1.41)**	7.72	**<0.001**	0.325	13.80 %
	Line						
	1st	7	1.06 (0.92, 1.21)	0.82	0.415	<0.001	84.50 %
	≥2nd	13	**1.24 (1.17, 1.31)**	7.44	**<0.001**	0.139	30.60 %
	Maintenance	1	**2.17 (1.14, 4.14)**	2.35	**0.019**	–	–
	Regimen						
	Monotherapy	2	1.57 (0.97, 2.54)	1.84	0.066	0.182	44.00 %
	Combination	19	**1.17 (1.09, 1.26)**	4.18	**<0.001**	<0.001	78.60 %

HR for PFS and OS. RR for ORR and DCR. Bold fonts indicate significant difference between the effects of angiogenesis inhibitors and non-angiogenesis inhibitors

RR relative risk, *HR* hazard ratio, *LL* lower limit, *UL* upper limit, *PFS* progression-free survival, *OS* overall survival, *ORR* objective response rate, *DCR* disease control rate, *TKIs* tyrosine kinase inhibitors, *Abs* antibodies

[a] Heterogeneity tests are available only when more than one studies are included

Table 4 Relative risk (RR) of developing common adverse events in advanced non-small cell lung cancer patients treated angiogenesis inhibitors

Adverse events	All grades				Grade ≥ 3			
	Number of trials	RR	95 % CI	*p*	Number of trials	RR	95 % CI	*p*
Hypertension	18	3.23	1.93–5.41	<0.001	23	5.42	4.06–7.22	<0.001
Hemorrhage	11	1.68	0.98–2.86	0.058	15	1.71	1.24–2.35	0.001
Thromboembolism	7	0.80	0.58–1.10	0.174	12	1.01	0.77–1.31	0.956
Anemia	15	0.83	0.71–0.97	0.021	17	0.76	0.57–1.01	0.055
Neutropenia	16	1.31	1.09–1.58	0.005	19	1.24	1.08–1.42	0.002
Thrombocytopenia	15	1.69	1.22–2.34	0.002	17	1.90	1.34–2.69	<0.001

Anmerkung/Fazit der Autoren

Angiogenesis inhibitors were superior to non-angiogenesis inhibitors in terms of ORR, DCR, PFS and OS in advanced NSCLC patients. The advantages of anti-angiogenesis therapy were

mostly highlighted with antibody-based agents and in ≥second-line settings. Further studies are warranted to explore the predictive biomarkers to pick up those patients who may benefit from angiogenesis inhibition.

Kommentare zum Review

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

Sheng J et al., 2015 [44].

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

Fragestellung

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

Methodik

Population:

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

Intervention + Komparator:

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

Endpunkt:

- OS, PFS, ORR, DCR, Toxizität

Recherche/Suchzeitraum:

- bis 2015

Qualitätsbewertung der Studien:

- Cochrane Collaboration /Jadad Score

Ergebnisse

Anzahl eingeschlossener Studien:

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

Qualität der Studien:

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

Studienergebnisse:

OS:

- According to the original data, 2 trials reported statistically significant improvement on OS. The pooled result showed that the combination with AA was associated with the significant improved OS (HR 0.92, 95% CI 0.87–0.97, P=0.002) compared with standard TCC. No apparent heterogeneity was detected among the recruited studies (P=0.34, I2=11%).
- Subgroup analyses indicated that slightly OS improvement was observed in first-line application (HR 0.96, 95% CI 0.87–1.06, P= 0.39). However, the practice in second-line application was associated with the significant prolonged OS (HR 0.91, 95% CI 0.85–0.96, P=0.002). Other clinical factors directing significant OS improvement by the combination strategy included histologically nonsquamous cancer (HR 0.90, 95% CI 0.84–0.96, P=0.002), nonsmokers (HR 0.81, 95% CI 0.70–0.94, P=0.0005), or female (HR 0.87, 95% CI 0.77–0.98, P=0.02). Only monoclonal antibodies (HR 0.89, 95% CI 0.82–0.96, P=0.004) were proved efficient in combination with TCC. However, indirect analyses failed to validate the superiority of monoclonal antibodies (HR 0.94, 95% CI 0.84–1.04, P¼0.22).

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

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

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

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

Sun et al., 2015 [49].

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

Siehe auch: Siehe auch: Sheng M et al., 2016 [45]

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

Xiao B et al., 2015 [54].

Meta-analysis of Seven Randomized Control Trials to Assess the Efficacy and Toxicity of Combining EGFR-TKI with Chemotherapy for Patients with Advanced NSCLC who Failed First-Line Treatment

Fragestellung

to systematically study the efficacy and toxicity of combination of EGFR-TKI and chemotherapy for patients with advanced NSCLC who failed first-line treatment. Subgroup analysis was performed according to different first-line treatment and different chemotherapeutic agents in combination with EGFR-TKI to discuss their potential clinical applications and the better combination strategy.

Methodik

Population:

- patients with NSCLC after failure of first-line treatment

Intervention/Komparator:

- combined regimen of EGFR-TKI and chemotherapy was compared with chemotherapy or EGFR-TKI monotherapy in patients with NSCLC after failure of first-line treatment.

Endpunkte:

- OS, PFS, ORR, Toxizität

Recherche/Suchzeitraum:

- Bis 2014

Qualitätsbewertung der Studien:

- Jadad Score

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 Studien (N = 1,168 patients)

Qualität der Studien:

- Overall, six studies scored 3, one scored 5.

Studienergebnisse:

- combined regimen arm had a significant higher ORR (RR 1.76 [1.16, 2.66], p=0.007) and longer PFS (HR 0.75 [0.66-0.85], p<0.00001), but failed to show effects on OS (HR 0.88 [0.68- 1.15], p=0.36).
- Subgroup results: continuation of EGFR-TKI in addition to chemotherapy after first-line EGFR-TKI resistance confered no improvement in ORR and PFS, and OS was even shorter (HR1.52 [1.05- 2.21], p=0.03). However, combination therapy with EGFR-TKI and chemotherapy after failure of first-line chemotherapy significantly improved the ORR (RR 2.06 [1.42, 2.99], p=0.0002), PFS (HR 0.71 [0.61, 0.82], p<0.00001) and OS (HR 0.74 [0.62-0.88], p=0.0008), clinical benefit being restricted to combining EGFR-TKI with pemetrexed, but not docetaxel.
- Grade 3-4 toxicity was found at significantly higher incidence in the combined regimen arm.

Anmerkung/Fazit der Autoren

In conclusion, our meta-analysis showed that different first-line therapy resulted in different clinical effect of combination of EGFR-TKI and chemotherapy as second-line therapy. Continuation of EGFR-TKI in addition to chemotherapy at the time of EGFR-TKI resistance should be avoided. Combination therapy with EGFR-TKI and pemetrexed for advanced NSCLC showed better activity and should be further investigated prognostic and predictive factors to find the group with the highest benefit of the combination.

Kommentare zum Review

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

Yu S et al., 2016 [57].

Erlotinib-based targeted dual agent versus erlotinib alone in previously treated advanced non-small-cell lung cancer: a meta-analysis of 13 randomized controlled trials

Fragestellung

To compare the effects of an erlotinib-based targeted dual agent with erlotinib alone in previously treated patients with advanced non-small lung cancer (NSCLC).

Methodik

Population:

- previously treated patients with NSCLC

Intervention:

- erlotinib with another targeted agent in previously advanced NSCLC

Komparator:

- k.A. (siehe Ergebnisteil)

Endpunkte:

- partial response, complete response, stable disease, PFS and OS, Toxizität

Recherche/Suchzeitraum:

- bis 2016

Qualitätsbewertung der Studien:

- Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 trials comprising 8 phase II trials and 5 phase III trials met the inclusion criteria of this meta-analysis, and 4509 patients

Charakteristika der Population:

Table 2. Characteristics of studies in the meta-analysis.

Author Year, Phase	Group	No. of patients	Median age, years	Female sex (%)	Ever smokers (%)	Non-squamous (%)	ECOG PS 0 (%)	Stage IV (%)
Lynch[17] 2009, II	Experiment	25	62	56	84	72	29	84
	Control	25	64	48	80	72	28	88
Herbst[18] 2011, III	Experiment	301	64.8	46	89	97	41	—
	Control	306	65	46	90	95	38	—
Spigel[19] 2011, II	Experiment	111	65	44	85	69	29	—
	Control	55	65	53	83	70	29	—
Sequist[20] 2011, II	Experiment	84	64	39	80	69	27	91
	Control	83	62	41	78	71	20	87
Ramalingam[21] 2011, II	Experiment	63	32	86	26	74	88	63
	Experiment	62	33	91	28	72	88	62
	Control	62	35	84	21	79	81	62
Scagliotti[22] 2012, III	Experiment	480	61	38.1	80	72	38.3	91.3
	Control	480	61	40.8	81.3	72	36.5	93.3
Witta[23] 2012, II	Experiment	67	66	42	84	73	43	—
	Control	65	67	34	83	68	34	—
Spigel[24] 2013, II	Experiment	69	64	42	86	71	32	—
	Control	68	63	38	88	71	31	—
Groen[25] 2013, II	Experiment	65	59	40	88	77	32	97
	Control	67	61	33	85	72	31	100
Spigel[16] 2014, III	Experiment	250	62	—	—	86	33	—
	Control	249	62	—	—	86	33	—
Besse[26] 2014, II	Experiment	66	60	45.5	80.3	85	—	97
	Control	67	60.5	49.3	80.6	85	—	94
Yoshioka[27] 2015, III	Experiment	154	63	30	74	100	43	96.1
	Control	153	63	33	75	100	33	93.5
Scagliotti[28] 2015, III	Experiment	526	62	41.1	80.8	100	31.9	94.9
	Control	522	61	40.8	81.2	100	32.2	96

Qualität der Studien:

- The quality was high in all the studies (Jadad score >3).

Studienergebnisse:

- Compared with erlotinib alone, combination therapy showed no improvement in OS though significantly prolonged PFS (HR: 0.82; 95% CI, 0.75–0.90; P<.001).

- Combination therapy significantly increased ORR (RR: 1.32; 95% CI, 1.09–1.60; P=.005) and DCR (RR=1.26; 95% CI, 1.17–1.36, P<.001).
- Sub-analysis assessment failed to identify any sub-groups whichcould benefit from combination therapy in terms of OS.
- Combination therapy was associated with more grade 3 or higher toxic effects (RR=1.54; 95% CI, 1.22–1.95; P<.001). Patients treated with combination therapy had more grade 3 or greater fatigue (RR=1.49; 95% CI, 1.16–1.91; P=.002), but did not develop more diarrhea (RR=2.02; 95% CI, 0.86–4.77; P=.107) or rash (RR=1.29, 95% CI, 0.90–1.85; P=.172).

Anmerkung/Fazit der Autoren

In conclusion, erlotinib-based combination therapy increased ORR and DCR, but showed little efficacy in PFS and OS in previously treated NSCLC. Currently it is strongly recommended not to apply such a combination as second- or third-line treatment.

Kommentare zum Review

- This study had limitations about heterogeneities among the included trials, and the analysis was not based on individual patient data.
- Keine seperaten Analysen/Angaben zum Stadium oder EGFR-Status.

Zhang TT et al., 2016 [58].

Dual inhibiting EGFR and VEGF pathways versus EGFR-TKIs alone in the treatment of advanced non-small-cell lung cancer: a meta-analysis of randomized controlled trials

Fragestellung

The strategy of dual inhibiting epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) pathways has been extensively investigated in advanced non-small-cell lung cancer (NSCLC), but the benefit-to-risk ratio of dual-targeted regimen versus EGFR-tyrosine kinase inhibitors (TKIs) alone is still unclear. We thus perform this meta-analysis to assess the efficacy and safety of this regimen versus EGFRTKIs alone in those patients.

Methodik

Population:

- patients with pathologically confirmed NSCLC

Intervention/Komparator:

- comparing dual inhibition of VEGF and EGFR pathways versus EGFR-TKIs alone

Endpunkte:

- siehe Ergebnisse

Recherche/Suchzeitraum:

- Pubmed (data from Jan 2000 to March 2015), Embase (data from Jan 2000 to March 2014) and the Cochrane Library electronic databases

Qualitätsbewertung der Studien:

- Jadad Scale

Ergebnisse

Anzahl eingeschlossener Studien:

- Four published RCTs with 1918 NSCLC patients were included in the meta-analysis

Qualität der Studien:

References	Total patients	Therapy line	Treatment regimens	Median age, years	Median PFS, months	Median OS	Jadad score
Seto et al. [21]	154	First line	Bevacizumab 5 mg/kg/week + erlotinib 150 mg/day	67	16	NR	5
			Placebo + erlotinib 150 mg/day	67	9.7	NR	
Scagliotti et al. [22]	960	Second-line	Sunitinib 37.5 mg/day + erlotinib 150 mg/day	61	3.6	9	5
			Placebo + erlotinib 150 mg/day	61	2	8.5	
Spigel et al. [23]	168	Second-line	Sorafenib 400 mg bid + erlotinib 150 mg/day	65	3.38	8	5
			Placebo + erlotinib 150 mg/day	65	1.94	4.5	
Herbst et al. [24]	636	Second-line	Bevacizumab 5 mg/kg/ week + erlotinib	65	3.4	9.3	3
			Placebo + erlotinib 150 mg/day	64.8	1.7	9.2	

Studienergebnisse:

- Overall survival
  - Three of the four trials reported OS data. The pooled results demonstrated that combined targeted regimens did not significantly improve OS in comparison with EGFRTKIs alone (I2 = 0 %).
- Progression-free survival
  - All of four trials reported PFS data. The pooled hazard ratio for PFS demonstrated that dual targeted regimens significantly improve PFS by giving HR 0.71 (95 % CI 0.58–0.86, p<0.001), compared with EGFR-TKIs alone. There was significant heterogeneity between trials (I2 = 61.6 %, p = 0.05), and the pooled HR for PFS was performed by using random-effects model.

Anmerkung/Fazit der Autoren

Our study suggests that dual inhibition of EGFR and VEGF pathways significantly improves PFS and ORR, but it does not translate into survival benefit in unselected NSCLC patients. Prospective clinical trials investigating the role of this regimen in EGFR mutation-positive NSCLC are still warranted.

Kommentare zum Review

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

He et al., 2015 [27].

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.

Xu et al., 2015 [56].

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

Fragestellung

Whether a combination of chemotherapy and erlotinib is beneficial for advanced non-small cell lung cancer (NSCLC) remains controversial. This study aimed to summarize the currently available evidence and compare the efficacy and safety of chemotherapy plus erlotinib versus chemotherapy alone for treating advanced NSCLC.

Methodik

Population:

- patients with NSCLC, keine Erhaltungstherapie

Intervention:

- erlotinib plus standard chemotherapy

Komparator:

- standard chemotherapy alone

Endpunkte:

- OS, PFS

Recherche/Suchzeitraum:

- bis 10 / 2014

Qualitätsbewertung der Studien:

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

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 / 3599 (RCT)

Charakteristika der Population:

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

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

Qualität der Studien:

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

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

Studienergebnisse:

- Progression free survival
  - This meta-analysis showed a longer PFS in patients who received a combination of erlotinib and chemotherapy treatment (HR = 0.76 [95% CI 0.62, 0.92], P = 0.006). The heterogeneity between studies was significant [$\chi 2$ = 14.28, df = 4 (P = 0.006); I2 = 72%]. The pooled HR meta-analysis for intercalated erlotinib plus chemotherapy showed an improvement in PFS (HR = 0.67 [95% CI 0.50, 0.91], P = 0.009). Meanwhile, continuous erlotinib plus chemotherapy treatment failed to show an improvement in PFS.
  - Subgroup analysis demonstrated improvements in PFS in never smoking patients (HR = 0.46 [95% CI 0.37, 0.56], P<0.00001) and patients with EGFR mutant tumors (HR = 0.31 [95% CI 0.17, 0.58], P = 0.0002). No significant difference was shown in PFS between the chemotherapy plus erlotinib group and the chemotherapy group in patients with EGFR wild-type tumors.
- Overall survival
  - HRs for OS data were available from8 trials. No statistically significant improvement was shown in OS, and there was no significant heterogeneity [$\chi 2$ = 10.36, df = 7 (P = 0.17); I2 = 32%].
  - Intercalated erlotinib plus chemotherapy treatment showed a modest but statistically significant improvement in OS (HR = 0.82 [95% CI 0.69, 0.98], P = 0.03).
  - Continuous erlotinib plus chemotherapy treatment failed to show an improvement in OS. (…) Additionally, a statistically significant improvement in OS was observed in patients with EGFR mutant tumors (HR = 0.52 [95% CI 0.30, 0.88], P = 0.01).
  - No significant difference in OS was noted in patients with EGFR wild-type tumors.
- Adverse events
  - Data for the grade 3 or 4 adverse events were available in five studies. There were more incidences of grade 3 or 4 anemia (OR = 1.48 [95% CI 1.12, 1.97], P = 0.006), rash (OR = 12.34 [95% CI 5.65, 26.95], P<0.00001), and diarrhea (OR = 4.25 [95% CI 2.16, 8.38], P<0.0001) in the erlotinib and chemotherapy combination treatment.
  - However, there was no difference in incidences of grade 3 or 4 neutropenia, leucopoenia, or thrombocytopenia.

Anmerkung/Fazit der Autoren

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

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

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

Kommentare zum Review

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

Zhong et al., 2015 [61].

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.

Sheng et al., 2015 [43].

The efficacy of combining antiangiogenic agents with chemotherapy for patients with advanced non-small cell lung cancer who failed first-line chemotherapy: a systematic review and meta-analysis

Fragestellung

The purpose of this study was to assess the advantage of antiangiogenic therapy plus standard treatment versus standard treatment alone for this population of patients.

Methodik

Population:

- Adult (18 years) patients with histologically or cytologically confirmed stage IIIB/IV NSCLC (all histologies)

Intervention:

- angiogenesis inhibitors plus a present standard single agent chemotherapy (pemetrexed, doctaxel or erlotinib) as salvage cure for patients progressing after first-line treatment (defined as agent blocking angiogenic pathways mediated by vascular endothelial growth factor receptor (VEGFR). Oral small-molecule TKIs or monoclonal antibodies were classified as two types of angiogenesis inhibitors)

Komparator:

- the corresponding cytotoxic agent

Endpunkte:

- at least reported→ PFS, OS, ORR and DCR

Recherche/Suchzeitraum:

- In October 2014

Qualitätsbewertung der Studien:

- The data collection and assessment of methodological quality followed the QUORUM and the Cochrane Collaboration guidelines. I^2 for heterogenity

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 phase II/III RCTs which involved a total of 8358 participants were included.

Qualität der Studien:

- For most studies included in this meta-analyses, low risk of bias existed for all key domains, including sequence generation, allocation concealment, blinding of participants or outcome assessment, incomplete outcome data, selective outcome reporting and other sources of bias. No high risk of bias was detected among the thirteen RCTs.

Studienergebnisse:

- Overall, there was significant improvement in OS (HR 0.94, 95%CI: 0.89-0.99, p=0.03), PFS (HR 0.80, 95%CI: 0.76-0.84, p<0.00001), ORR (RR 1.75, 95%CI: 1.55-1.98, p<0.00001) and DCR (RR 1.23, 95%CI: 1.18-1.28, p<0.00001) in the group with antiangiogenic therapy plus standard treatment versus the group with standard treatment alone.
- Subgroup analysis showed that OS benefit was presented only in patients treated with docetaxel plus antiangiogenic agents (HR 0.92, 95%CI: 0.86-0.99, p=0.02) and patients with nonsquamous NSCLC (HR for OS 0.92, 95%CI: 0.86-0.99, p=0.02).

Table 3. Summary of the subgroup results: Pooled HR & 95%CI for OS.

	No. of articles	Pooled HR with 95%CI	P-value	Heterogeneity (I^2)	Analysis model
AT*	9	0.95 (0.89–1.02)	0.16	30%	Fixed
AA[&]	4	0.93 (0.85–1.01)	0.08	18%	Fixed
Pemetrexed	3	1.14 (0.80–1.64)	0.47	78%	Random
Doctaxel	5	0.92 (0.86–0.99)	0.02	0%	Fixed
Non-Doctaxel	7	0.98 (0.90–1.07)	0.66	43%	Fixed
EGFR-TKI	4	0.95 (0.85–1.06)	0.34	0%	Fixed
Chemotherapy	9	0.94 (0.88–1.00)	0.05	46%	Fixed
Double TKI [¶]	3	0.94 (0.82–1.07)	0.34	0%	Fixed
Non-Squamous cancer	9	0.92 (0.86–0.99)	0.02	10%	Fixed
Squamous cancer	6	0.96 (0.87–1.07)	0.50	0%	Fixed
Non-squamous cancer+AT	5	0.91 (0.83–1.00)	0.05	0%	Fixed
Adenocarcinoma	4	0.90 (0.81–1.00)	0.06	9%	Fixed

* AT for antiangiogenic-TKI;
[&] AA refers to antiangiogenic antibody;
[¶] Double TKI means antiangiogenic-TKI plus EGFR-TKI.

Anmerkung/Fazit der Autoren

In conclusion, our study revealed that adding antiangiogenic agents to standard treatments could provide clinical benefits to NSCLC patient who failed their first-line therapy. Furthermore, proper selection of the standard treatment regimens and patient population by tumor histology is substantial for future studies and clinical application of antiangiogenic therapy.

Kommentare zum Review

- clinical heterogeneity due to the involvement of various standard treatment regimens and antiangiogenic agents.
- for certain subgroup analysis, publication bias existed due to unclear reasons.
- Gemischte Population. Keine seperaten Analysen/Ergebnisse hinsichtlich Stadium.

Shan et al., 2018 [42].

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

Fragestellung

to evaluate combination maintenance therapy with bevacizumab plus pemetrexed.

Methodik

Population:

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

Intervention:

- combination maintenance with pemetrexed plus bevacizumab

Komparator:

- any other maintenance therapy or no maintenance therapy

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

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

Ergebnisse

Anzahl eingeschlossener Studien:

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

Qualität der Studien:

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

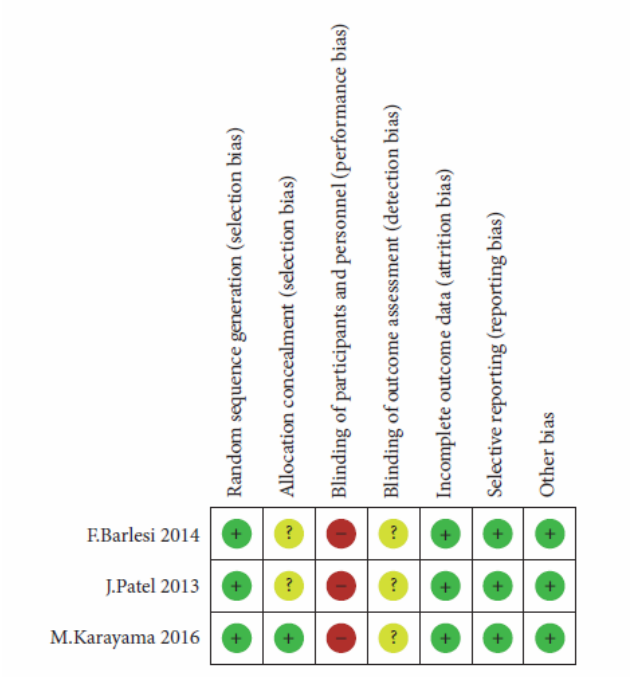


FIGURE 2: Risk of bias assessment in each item. -: high risk of bias; ?: unclear risk of bias; +: low risk of bias.

Studienergebnisse:

- An evident PFS improvement (HR = 0.73, 95% CI = 0.63–0.83, <0.01) was observed in patients with pemetrexed and bevacizumab combination maintenance therapy compared

with single-agent maintenance therapy, yet it did not subsequently lead to a significant improvement in OS (HR = 0.97, 95% CI = 0.84–1.10, P = 0.66).

- statistically increased risks for provoking grade 3-4 adverse events in patients managed using pemetrexed plus bevacizumab combination (RR = 1.59, 95% CI = 1.07–2.36, P = 0.022).
- Subgroupanalyses
  - Patients managed using the combination strategy appeared to be at an advantage with regard to PFS compared with patients receiving other maintenance regimens when based on subset factors of age, ECOG score, and smoking history. And, remarkably, lower hazard ratios were observed in patients with younger age (< 65, HR = 0.64, 95% CI =0.39–0.90, P < 0.01), better physical status (ECOG score =0, HR = 0.60, 95% CI = 0.32–0.87, P < 0.01), and no smoking history (never smoked, HR = 0.45, 95% CI = 0.27–0.63, P <0.01).
  - As for overall survival, a clear trend for longer OS was observed in patients with age < 65 years, ECOG score = 0, or never smoked. However, no statistically significant improvement was detected in all three subsets.

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

- heterogeneity across included trials

Wang et al., 2016 [51].

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

Fragestellung

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

Methodik

Population:

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

Intervention/Komparator:

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

Endpunkte:

- OS, PFS, averse events

Recherche/Suchzeitraum:

- from inception to November 09, 2015

Qualitätsbewertung der Studien:

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

Ergebnisse

Anzahl eingeschlossener Studien:

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

Charakteristika der Population:

-

Qualität der Studien:

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

Studienergebnisse:

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

- In total, 24 trials were included in the OS analysis: Based on assessment of model fit, results calculated by random effects models are presented in this section.
- Several maintenance therapy regimens yielded longer OS than no-maintenance, although differences were not statistically significant in some regimens. Switch-docetaxel, continue-paclitaxel, switch-sunitinib, switch-vandetanib, switch-carboxyaminoimidazole (CAI), and switch-vinorelbine did not improve OS. Switch-maintenance therapy with racotumomab-alum vaccine showed excellent efficacy compared to no-maintenance with a HR D 0.64 [95% credible intervals (CrI), 0.45-0.92]
- In PFS analysis, we included 23 trials: Continue-paclitaxel, switch-belagenpumatucel-L, or switch-CAI did not yield longer PFS than no-maintenance. Switch-pemetrexed and switch-gefitinib showed excellent efficacy compared to no-maintenance with HRs D 0.54 (95% CI [0.26-1.04]) and 0.60 (95% CI [0.40-0.90]).
- Ranking which indicated the probability of the best regimen in descending order, among all treatments

- Based on OS): switch-racotumomab-alum vaccine had the greatest probability as the best regimen (52%), with switch-pazopanib ranked second (32%), and switch-pemetrexed ranked third (6%).
- Based on PFS, switch-pemetrexed ranked first (34%), followed by switch-sunitinib (19%), with switch-pazopanib ranked third (12%).

- Adverse events:
  - Maintenance chemotherapy (including pemetrexed, gemcitabine, docetaxel, paclitaxel, and vinorelbine) was commonly associated with hematologic events such as neutropenia, thrombocytopenia, and anemia. Maintenance tyrosine kinase inhibitor (TKI) (including EGFR-TKI and other TKIs) commonly caused more skin and gastrointestinal AEs, such as rash, nausea, and vomiting. Maintenance vaccine (including belagenpumatucel-L, racotumomab-alum, and L-BLP25) was commonly associated with injection site reaction and flu-like symptoms. The main AE of CAI was nausea.

Anmerkung/Fazit der Autoren

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

Tan P et al., 2015 [50].

Bayesian network meta-comparison of maintenance treatments for stage IIIb/IV non-small-cell lung cancer (NSCLC) patients with good performance status not progressing after first-line induction chemotherapy: results by performance status, EGFR mutation, histology and response to previous induction

Fragestellung

systematic review and network meta-analysis of maintenance treatments in subgroups determined by performance status (PS), epidermal growth factor receptor (EGFR) mutation, histology and response to induction.

Methodik

Population:

- stage IIIb/IV NSCLC patients not progressing after first-line chemotherapy

Intervention/Komparator:

- Maintenance treatments (siehe Ergebnisteil)

Endpunkte:

- OS, PFS and AEs (all grades and grade 3 or worse)

Recherche/Suchzeitraum:

- 1st December 2003 to 14th October 2014

Qualitätsbewertung der Studien:

- K.A.

Ergebnisse

Anzahl eingeschlossener Studien:

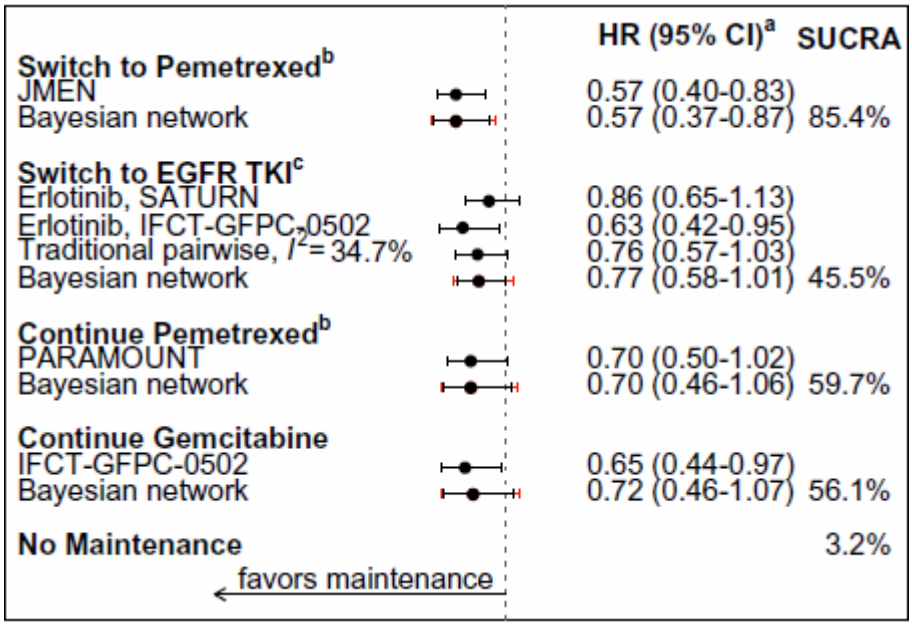
- Twelve trials evaluating eight maintenance treatments in 3850 patients

Qualität der Studien:

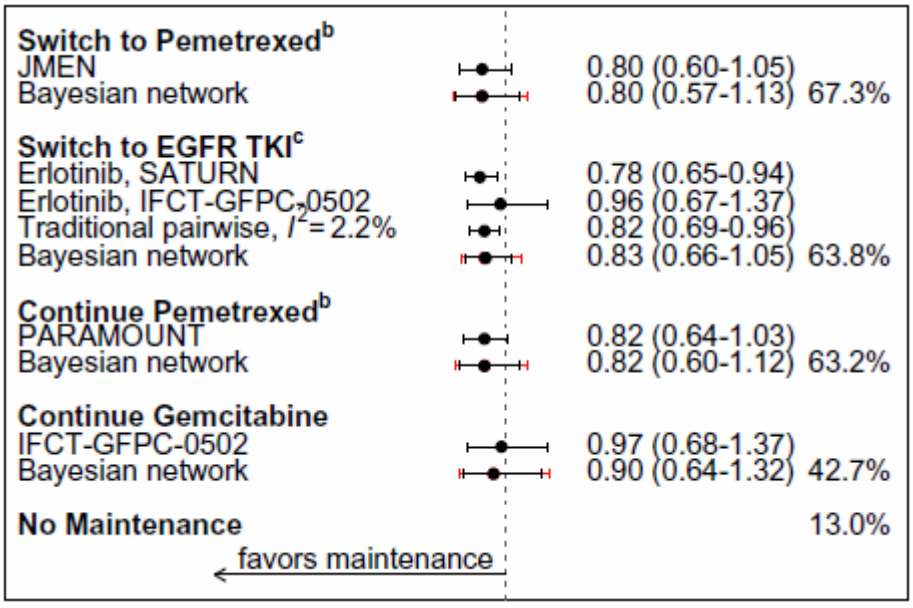
- K.A.

Studienergebnisse:

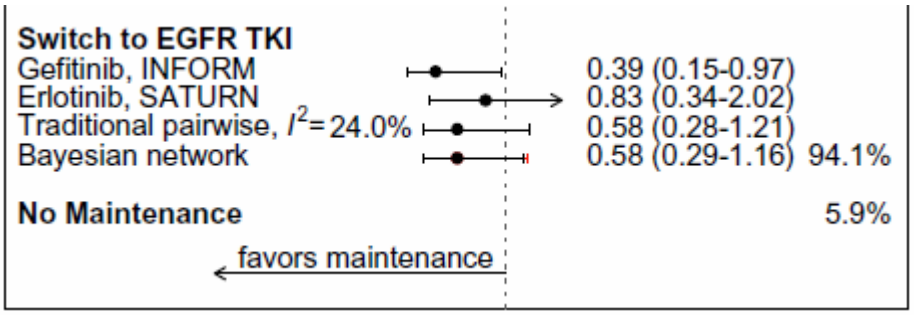
- Selected maintenance treatments showed clinically meaningful benefits of ≥20% reduction in hazards of death with ≥90% probability of outperforming no maintenance in terms of OS:
  - (i) switch to or continue pemetrexed (nonsquamous), continue gemcitabine, or switch to EGFR tyrosine kinase inhibitors (TKIs) for PS 0 patients



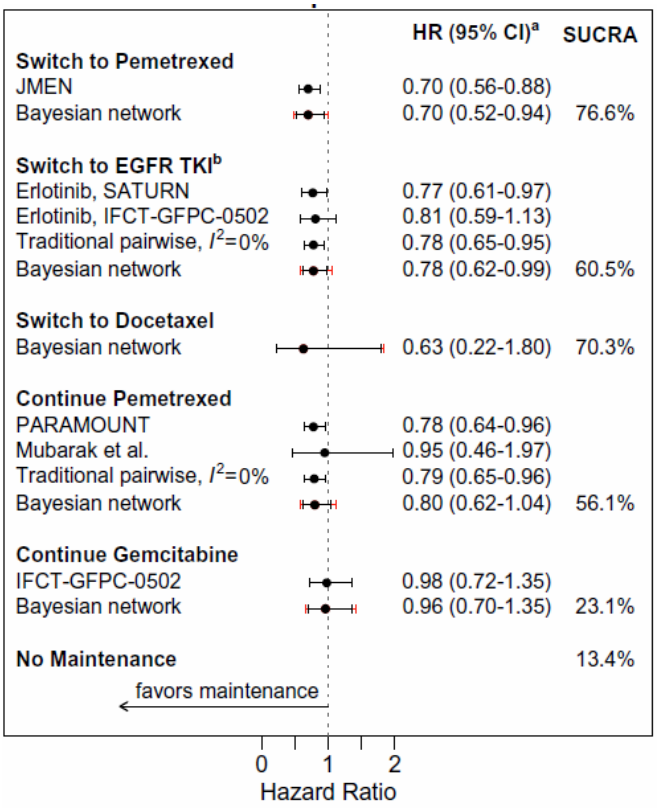
  - (ii) switch to pemetrexed (nonsquamous) for PS 1 patients



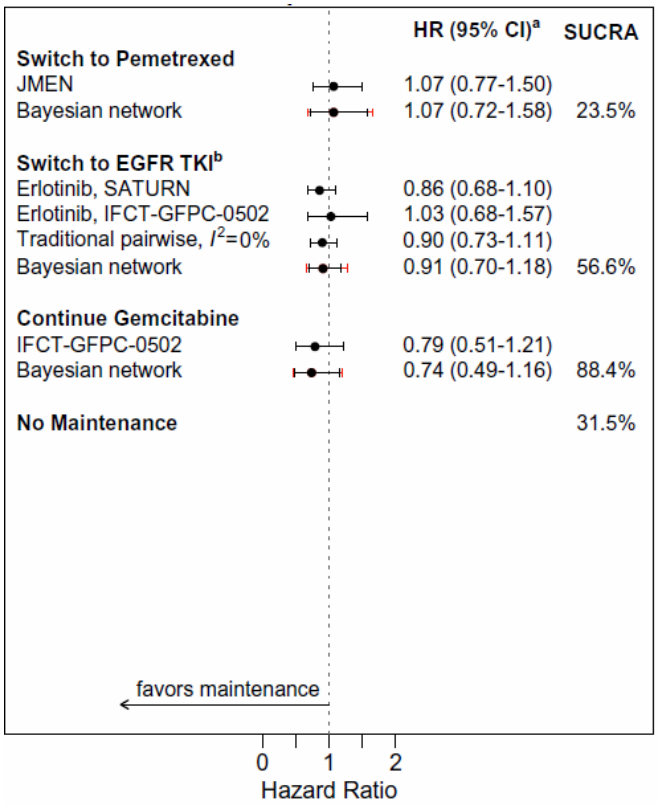
- (iii) switch to EGFR TKI for EGFR mutation positive patients



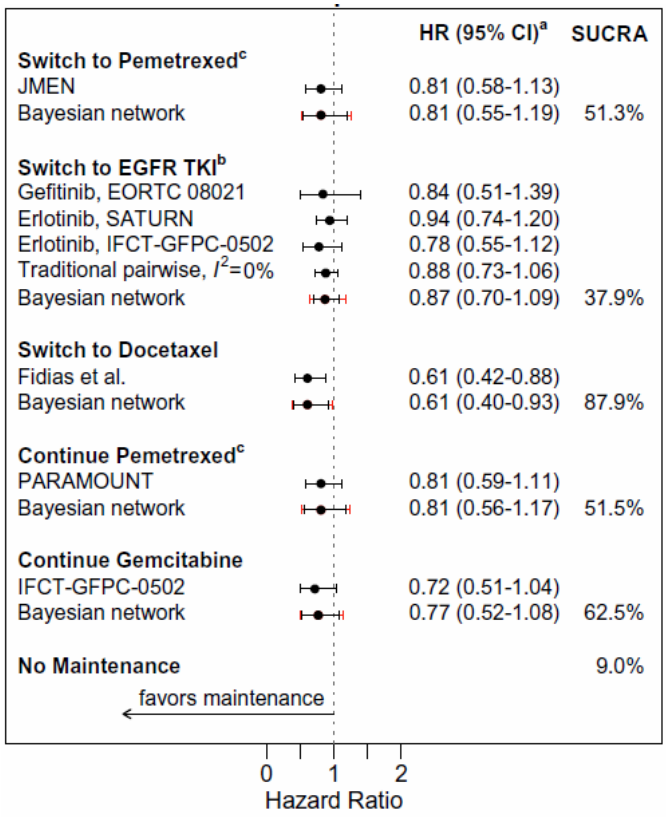
- (iv) switch to or continue pemetrexed or switch to EGFR TKI for <u>nonsquamous</u> patients



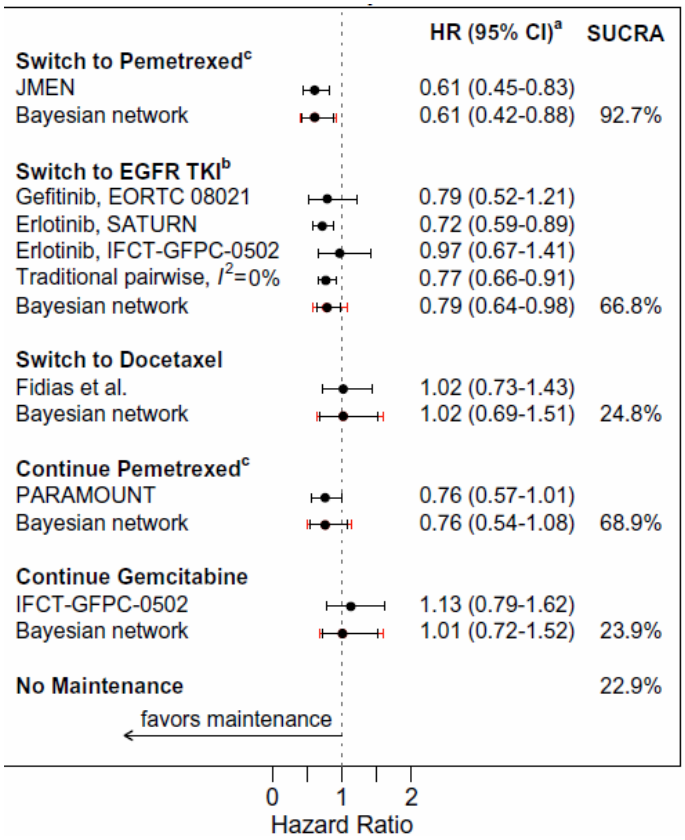
- (v) continue gemcitabine for <u>squamous</u> patients



- (vi) switch to docetaxel or continue gemcitabine for responders (CR/PR) to induction



- (vii) switch to or continue pemetrexed (nonsquamous→ siehe (v) squamous patients) or switch to EGFR TKI for patients with stable disease post-induction.



- Adverse events
  - Maintenance chemotherapy was commonly associated with haematologic events, with neutropenia frequently seen with docetaxel (76%) and gemcitabine (42%), and less common with pemetrexed (6–12%). Maintenance EGFR TKI was commonly associated with skin and gastrointestinal adverse events, maintenance MKI was associated with hypertension and maintenance bevacizumab was associated with hypertension and haemorrhagic events.
- Combination maintenance therapy with bevacizumab
  - Combination maintenance with bevacizumab/pemetrexed in AVAPERL and bevacizumab/erlotinib in ATLAS versus bevacizumab suggested a trend for OS benefits with significant PFS benefits.
  - Similar to other EGFR TKI maintenance trials, ATLAS] demonstrated the possibility of substantial OS benefit in the EGFR mutation positive population (OS HR 0.46, 95% CI 0.21–1.02) versus wild-type (OS HR 0.86, 95% CI 0.65–1.15).

Anmerkung/Fazit der Autoren

In conclusion, selected maintenance treatments administered to good performance status patients with non-progressing stage IIIb/IV NSCLC after first-line chemotherapy show clinically meaningful survival benefits. Benefits are optimised by targeting specific maintenance to individual patients, guided by performance status, EGFR mutation status, histology and response to previous induction. Tolerability of maintenance and patient preferences should also be considered in treatment decisions.

Kommentare zum Review

- Inability to evaluate combination bevacizumab maintenance in the efficacy analysis.

Hu et al., 2016 [29].

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

Fragestellung

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

Methodik

Population:

- patients were pathologically diagnosed with advanced chemotherapy-naïve NSCLC

Intervention:

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

Komparator:

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

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- GRADE system / Cochrane risk of bias tool

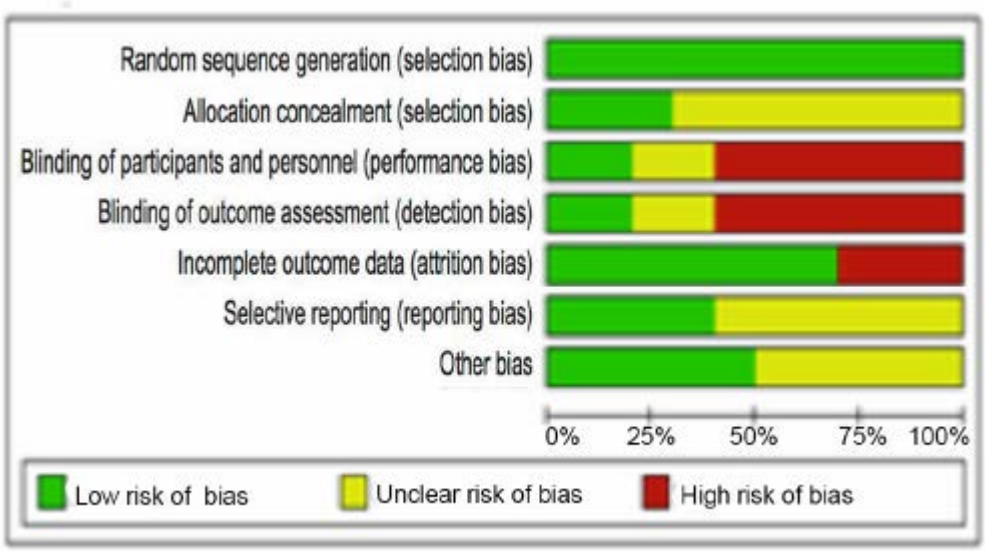
Ergebnisse

Anzahl eingeschlossener Studien:

- Eleven randomized controlled trial (RCT) studies

Qualität der Studien:

- Risk of bias:



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

Studienergebnisse:

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

    Adverse events: Thus, in the gemcitabine vs. BSC/observation group, the pooled HR was 4.70 (2.87–7.69, p = 0.000; I2 = 14.6%, p = 0.279). In the pemetrexed vs. BSC ± placebo group, the pooled HR was 3.27 (1.56–6.83, p = 0.002; I2 = 63.8%, p = 0.063). In the pemetrexed + bevacizumab vs. bevacizumab group, the HR was 1.25 (1.08–1.45, p = 0.002; I2 = 62.1%, p = 0.104). In the pemetrexed vs. bevacizumab group, the HR was 0.79 (0.49–1.29, p = 0.343; I2 = 65.7, p = 0.088).

Anmerkung/Fazit der Autoren

In our article, we confirmed that gemcitabine significantly improved PFS compared with BSC, pemetrexed significantly improved PFS and OS compared with BSC ± placebo, and pemetrexed + bevacizumab approached a significantly improved PFS compared with bevacizumab alone. The incidence of grade 3–4 AEs was significantly increased in the maintenance therapy arm compared with the control arm. Additional trials are required to confirm the impact of pemetrexed + bevacizumab vs. bevacizumab and pemetrexed vs. bevacizumab. In particular, randomized, controlled double-blind trials are required. Randomized, controlled double-blind trials are also

needed for gemcitabine vs. BSC studies. In pemetrexed + bevacizumab vs. bevacizumab or pemetrexed vs. bevacizumab studies, the contribution of maintenance therapy to the outcomes should be separately evaluated. Finally, regarding the socioeconomic impact, the problems of maintenance therapy must identify new solutions.

Kulkarni et al., 2016 [33].

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

Fragestellung

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

Methodik

Population:

- Patients with stage IIIB or IV NSCLC

Intervention/Komparator:

- maintenance systemic treatment against another systemic treatment or placebo

Endpunkte:

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

Recherche/Suchzeitraum:

- To 2014

Qualitätsbewertung der Studien:

- GRADE system

Ergebnisse

Anzahl eingeschlossener Studien:

- Fourteen randomized controlled trials with 22 publications were included

Qualität der Studien:

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

Studienergebnisse:

- OS:
  - The overall survival benefit was strongest for maintenance therapy with pemetrexed for patients with nonsquamous NSCLC (HR= 0.74, 95% CI: 0.64–0.86) but not significant for patients with squamous NSCLC.
  - There was also an overall survival benefit with maintenance therapy with epidermal growth factor receptor tyrosine kinase inhibitors, but the magnitude of the benefit was smaller than with pemetrexed HR = 0.84, 95% CI: 0.75–0.94).

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

Anmerkung/Fazit der Autoren

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

3.4 Leitlinien

Leitlinienprogramm Onkologie, 2018 [35].
Deutsche Krebsgesellschaft (DKG), Deutsche Krebshilfe, Arbeitsgemeischaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
S3-Leitlinie Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms .

Leitlinienorganisation/Fragestellung

Die Leitlinie adressiert die Versorgung aller Patienten mit einem Lungenkarzinom sowie darüber hinaus die Versorgung bzgl. Früherkennung von Bürgern mit einem erhöhten Risiko für ein Lungenkarzinom.

Methodik

Grundlage der Leitlinie

- Diese S3-Leitlinie ist maximal bis 2022 oder bis zur nächsten Aktualisierung gültig.
- Neuerungen in der aktuellen LL: u.a. Therapien des Stadium IV (ohne Indikation zur definitiven Lokaltherapie, palliativmedizinische Behandlung beim Lungenkarzinom
- formalen Konsensusverfahrens.: durch die AWMF moderierte, nominale Gruppenprozesse bzw. strukturierte Konsensuskonferenzen.
- Interdisziplinäre LL-Entwicklungsgruppe
- Interessenskonflikte dargelegt und Umgang beschrieben

Recherche/Suchzeitraum:

- Molekular stratifizierte Therapie (05.06.2014); Molekular stratifizierte Therapie (05.06.2014); Anti VEGF (22.07.2014)

LoE

- Cochrane Risk of Bias Tool

GoR

Tabelle 6: Schema der Empfehlungsgraduierung für Empfehlungen 2018

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll
B	Empfehlung	sollte
0	Empfehlung offen	kann

Tabelle 7: Konsensusstärke

Konsenstärke	Prozentuale Zustimmung
Starker Konsens	> 95 % der Stimmberechtigten
Konsens	> 75 – 95 % der Stimmberechtigten
Mehrheitliche Zustimmung	50 – 75 % der Stimmberechtigten
Dissens	< 50 % der Stimmberechtigten

Empfehlungen

Stadium IV (ohne Indikation zur definitiven Lokaltherapie)

- Systemtherapie (Erstlinie) bei Patienten ohne Mutationsnachweis

8.6.2.1. Patienten mit PD-L1-Expression von ≥50 %

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

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

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

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

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

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

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

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

- Stellenwert von Erhaltungstherapien

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

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

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

- 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)

8.6.6.1. Erstlinientherapie bei Chemotherapie-naiven Patienten

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

8.6.6.2. Zweitlinientherapie nach Versagen einer platinbasierten Standardchemotherapie

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

8.6.6.3. Therapie nach Crizotinib-Versagen

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

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

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

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

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

8.6.7.1. Erstlinientherapie

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

8.6.7.2. Zweitlinientherapie (bei Crizotinib-Versagen)

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

8.6.8. Systemtherapie bei Patienten mit BRAF-V600-Mutation

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

- Therapie bei sonstigen Treibermutationen beim NSCLC

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

- 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 %	

- Erhaltungstherapie

Chemotherapie

9.31.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad A	Insgesamt kann der Stellenwert einer Erhaltungschemotherapie trotz einer positiven Metaanalyse als nicht gesichert betrachtet und damit ihr routinemäßiger Einsatz nicht empfohlen werden (Evidenzgrad 1b)	

Biologische Substanzen

9.32.	Evidenzbasierte Empfehlung	2010
Empfehlungsgrad A	Eine Erhaltungstherapie mit biologischen oder molekular-gezielten Substanzen kann zum jetzigen Zeitpunkt nicht empfohlen werden (Evidenzgrad 1b).	

Hanna N et al., 2017 [26].

Siehe auch: Masters GA et al. 2016 [38].

American Society of Clinical Oncology (ASCO)

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

Leitlinienorganisation/Fragestellung

What systemic therapy treatment options should be offered to patients with stage IV NSCLC, depending on the subtype of the patient's cancer?

Methodik

Grundlage der Leitlinie

- Update der LL von 2015
- An Update Committee of the American Society of Clinical Oncology NSCLC Expert Panel based recommendation on a systematic review of randomized controlled trials from February 2014 to February 2016.
- The guideline recommendations were crafted, in part, using the GuideLines Into DEcision
- Support (GLIDES) methodology and accompanying BRIDGE-Wiz softwareTM. The process incorporates distilling the actions involved, identifying who will carry them out, to whom, under what circumstances, and clarifying if and how end users can carry out the actions consistently. This process helps the Expert Panel focus the discussion, avoid using unnecessary and/or ambiguous language, and clearly state its intentions.
- The methodological review is completed by a member of the CPGC'S Methodology Subcommittee and/or by ASCO guidelines staff using AGREE II instrument.

LoE

Rating	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (e.g., balance of benefits versus harms) and further research is very unlikely to change either the magnitude or direction of this net
Intermediate	Intermediate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect, however it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change the magnitude and/or
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. Reliance on consensus opinion of experts may be reasonable to provide guidance on the topic until better

GoR

Type of Recommendation	Definition
Evidence-based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.

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

Rating for Strength of Recommendation	**Definition**
Strong	There is high confidence that the recommendation reflects best practice. This is based on: a) strong evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with no or minor exceptions; c) minor or no concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: a) good evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with minor and/or few exceptions; c) minor and/or few concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: a) limited evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, but with important exceptions; c) concerns about study quality; and/or d) the extent of panelists' agreement. Other considerations (discussed in the

Empfehlungen

<u>First-Line Treatment for Patients</u>

- 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]).
- With ALK gene rearrangements, crizotinib is recommended (Evidence quality: intermediate; Strength of recommendation: moderate).
- With ROS1 rearrangement, crizotinib is recommended (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

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).
  - s 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.

Ellis PM et al., 2016 [7].

Cancer Care Ontario (CCO)

Systemic Treatment for Patients with Advanced Non-Small Cell Lung Cancer

Leitlinienorganisation/Fragestellung

- Clinical Question B1: What is the most effective second-line therapy for patients with stage IIIB/IV NSCLC with negative or unknown EGFR/ALK status and NSCC?
- Clinical Question B2: What is the most effective second-line therapy for patients with stage IIIB/IV NSCLC with negative or unknown EGFR/ALK status and SCC?
- Clinical Question B3.a: What is the most effective second-line therapy for patients with stage IIIB/IV NSCLC with a sensitizing EGFR mutation who received a first-line EGFR TKI and experienced disease progression?
- Clinical Question B3.b: What is the most effective second-line therapy for patients with stage IIIB/IV NSCLC with a sensitizing EGFR mutation who received a first-line EGFR TKI and experienced disease progression after an initial response?
- Clinical Question B4: What is the most effective second-line therapy for patients with stage IIIB/IV NSCLC with ALK rearrangement with progression after first-line crizotinib?
- Clinical Question B5: What is the optimal second-line treatment for elderly patients with stage IIIB/IV NSCLC?

Methodik

Grundlage der Leitlinie

- update von 2009 und 2010, in 2016 Adaptation der aktuellen Leitlinie der American Society of Clinical Oncology (ASCO) mit ergänzenden systematischen Übersichten zu den klinischen Fragestellungen (siehe oben), methodisches Vorgehen orientiert an AGREE II, internes formales Abstimmungsverfahren, externes Review, COI z.T. vorhanden
- LoE und GoR: Studienqualität geprüft und detailliert dargestellt, Empfehlungsstärken über die Formulierung abgebildet

- Systematisches Review: MEDLINE (1946 to February 16, 2016), EMBASE (1996 to February 16, 2016), and PubMed (February 16, 2016) databases were searched for RCTs.
- Empfehlungen sind mit Literaturstellen verknüpft

Recommendations

First-Line Treatment for Patients:

- Without an epidermal growth factor receptor (EGFR)-sensitizing mutation or ALK gene rearrangement, and Eastern Cooperative Oncology Group performance status (PS) 0 to 1 (or appropriate PS 2), a variety of combination cytotoxic chemotherapies are recommended. Platinum-based doublets are preferred, along with early concurrent palliative care and symptom management. Based on tumour histology (ie, squamous vs. non-squamous), there are some variations.
- Adding bevacizumab to carboplatin plus paclitaxel is recommended if there are no contraindications. An alternative treatment strategy for patients who are eligible for carboplatin, paclitaxel, and bevacizumab would include cisplatin or carboplatin plus pemetrexed and maintenance pemetrexed.
- With PS 2: combination or single-agent chemotherapy or palliative care alone may be used.
- With ALK gene rearrangements: crizotinib is recommended.
- With ROS1 rearrangement: crizotinib is recommended.

Second-Line Treatment for Patients:

- With NSCC: nivolumab (in all patients with NSCLC) or pembrolizumab (in patients with programmed cell death ligand 1 [PD-L1]-positive tumours) is preferred over docetaxel, erlotinib, gefitinib, or pemetrexed.
- With ALK rearrangement and progression after first-line crizotinib: chemotherapy or ceritinib may be offered.

Third-Line Treatment for Patients:

- Who have not received erlotinib or gefitinib and have PS 0 to 3: erlotinib may be recommended.
- With NSCC and progression on nivolumab or pembrolizumab: docetaxel, erlotinib, gefitinib, or pemetrexed may be recommended.

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

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 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 overall survival advantage was modest for both agents.
- The recommendation for EGFR TKIs applies to both EGFR mutation-positive and wild-type patients. Since the cut-off date of the review of the literature, a notification has been released by Health Canada based on the results of the IUNO trial [3,4]. While the results are not available in the public domain, Health Canada has recommended that EGFR TKI maintenance therapy should not be used in patients with EGFR wild-type advanced NSCLC.
- In patients receiving maintenenance bevacizumab, it is unclear whether the addition of maintenance pemetrexed improves overall survival.

Alberta Health Services (AHS), 2013 [1].

Alberta Provincial Thoracic Tumour Team

Non-small cell lung cancer - stage IV

Leitlinienorganisation/Fragestellung

- What is the recommended first-line therapy for patients with stage IV non-small cell lung cancer (NSCLC)?
- What is the role for EGFR tyrosine kinase inhibitors in first-line treatment of patients with stage IV NSCLC?
- What is the optimal second-line therapy for patients with stage IV NSCLC?
- What is the role of palliative radiotherapy in the management of patients with stage IV NSCLC?

Methodik

Grundlage der Leitlinie

systematic literature search, evidence tables, AGREE used for retrieved guidelines, working group reviewed currency and acceptability of all relevant literature, then circulated a draft of the updated guideline to entire provincial tumour team for final feedback and approval

Recherche/Suchzeitraum:

- bis 2013

LoE/GoR

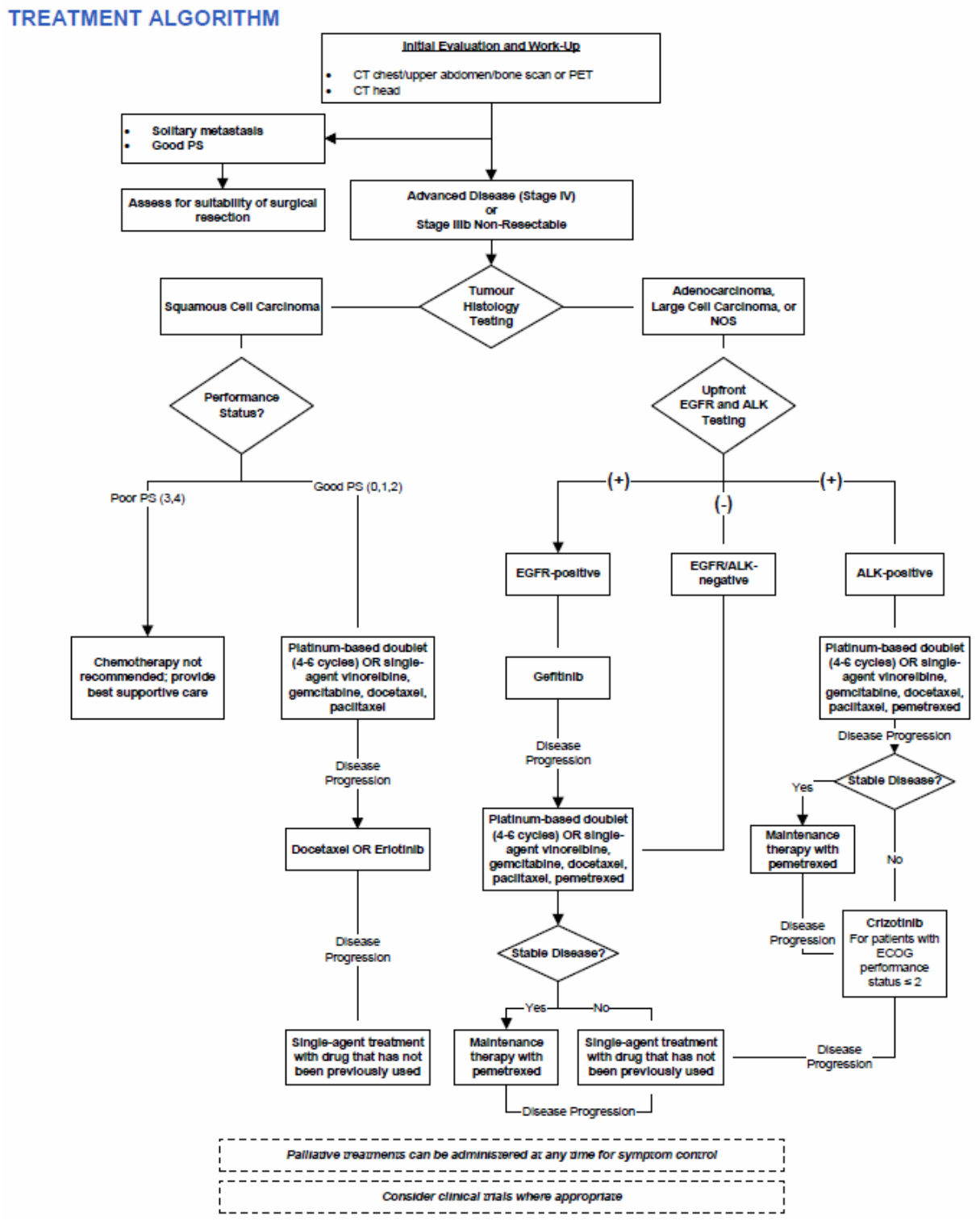
- no use of formal rating schemes for describing the strength of the recommendations, rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations

Sonstige methodische Hinweise

- direkte Verknüpfung von Literatur mit Empfehlung nicht durchgängig gegeben
- kein formaler Konsensusprozess beschrieben
- no direct industry involvement in the development or dissemination of this guideline
- authors have not been remunerated for their contributions
- Some members of the Alberta Provincial Thoracic Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

Recommendations

- Patients with a solitary metastasis as the basis for stage IV disease with good performance status and otherwise resectable and limited thoracic disease may benefit from more aggressive management, including surgical intervention and/or stereotactic radiotherapy.
- Combination chemotherapy consisting of a platinum-based doublet is the standard of care for first-line treatment of advanced NSCLC (except for EGFR-positive patients). The combination of three chemotherapeutic agents for the first-line treatment of advanced NSCLC is not routinely recommended based on current evidence.
- Therapy should be continued for four cycles in most patients, and not more than six cycles in responding patients.
- Acceptable alternatives to combination chemotherapy include non-platinum doublets or monotherapy:
  - For patients with a borderline performance status (PS=2), single-agent chemotherapy with vinorelbine, gemcitabine, paclitaxel, docetaxel or pemetrexed (for non-squamous cell carcinoma patients only) is recommended over best supportive care alone.
  - For elderly patients who cannot tolerate a platinum-based combination, single-agent chemotherapy with vinorelbine, gemcitabine, docetaxel, or pemetrexed (for non-squamous cell carcinoma patients only) is associated with improved survival and quality of life when compared to best supportive care alone. However, elderly patients with a good performance status (PS=0-1) should receive combination chemotherapy with a platinum-based doublet.
- Second-line or subsequent chemotherapy options for advanced NSCLC include single-agent docetaxel or erlotinib for patients with squamous cell carcinoma histology, or single agent treatment with a drug that has not been previously used.
- Crizotinib has been approved for second-line treatment of patients who are positive for ALK-rearrangements from the pan-Canadian Oncology Drug Review (pCODR) and has also been approved for provincial coverage in Alberta.
- Testing for ALK mutations should take place for all eligible patients with advanced NSCLC and adenocarcinoma (including adenosquamous) histology who are being considered for second line therapy with crizotinib.
- Palliative radiotherapy is recommended for relief of specific symptoms and prophylactic prevention of symptom development.



Maintenance chemotherapy: Recent phase III clinical trials have reported a survival benefit associated with maintenance therapy in select patients with stage IIIB or IV NSCLC who have responded to initial chemotherapy and/or who have not progressed after four cycles of platinum-based chemotherapy. In one randomized double-blind study, Ciuleanu and colleagues compared 441 patients treated with maintenance pemetrexed plus BSC to 222 patients who

received BSC alone; all patients had stage IIIB or IV disease and had not progressed after four cycles of platinum-based chemotherapy. Pemetrexed was associated with improved progression-free survival (4.3 vs. 2.6 months; HR=0.50; 95% CI 0.42–0.61, p<0.0001) and overall survival (13.4 vs. 10.6 months; HR=0.79; 95% CI 0.65–0.95, p=0.012) compared with placebo. The improvements in progression-free and overall survival were recorded mainly in patients with non-squamous histology; more specifically, in a post hoc intention-to-treat analysis, median progression-free survival for the 328 patients with adenocarcinoma histology was significantly better for those treated with pemetrexed versus placebo (4.7 vs. 2.6 months; HR=0.45, 95% CI 0.35-0.59; p<0.0001). Similarly, in the SATURN trial, patients were randomized to receive maintenance therapy with either erlotinib (n=438) or placebo (n=451) if they did not have progressive disease following four cycles of platinum-based chemotherapy.82 The median progression-free survival was significantly longer for patients treated with erlotinib versus placebo (12.3 vs. 11.1 months; HR=0.71; 95% CI 0.62–0.82, p<0.0001). For patients with EGFR-positive immunohistochemistry, those who were treated with erlotinib had a significantly longer progression-free survival compared to those treated with placebo. Fidias et al. reported the results of a phase III randomized trial involving patients with stage IIIB or IV disease who were treated with first-line gemcitabine and carboplatin.83 After four cycles, patients who had not progressed were randomly assigned to immediately receive six cycles of docetaxel or to follow the standard of care, which was defined as no additional therapy until disease progression, at which point they received docetaxel. Treatment with immediate docetaxel was associated with a significantly longer progression-free survival than treatment with delayed docetaxel (5.7 vs. 2.7 months, p=0.0001); there was also a non-significant trend toward improved survival with immediate docetaxel compared with delayed docetaxel (12.3 vs. 9.7 months, p=0.0853). Notably, while 95 percent of patients in the immediate treatment arm received at least one cycle of docetaxel, only 63 percent of patients in the delayed arm actually went on to receive docetaxel at progression. Median survival for the patients in the delayed arm who actually received docetaxel was equivalent to the 12.5 month survival of the patients in the immediate arm, suggesting that the patients in the immediate docetaxel arm trended toward improved overall survival because more patients were able to receive an active drug. A 2012 phase III RCT by Perol et al compared gemcitabine or erlotinib maintenance versus observation in 464 patients. All patients had previously received first-line cisplatin and gemcitabine. Upon completion of first-line treatment patients were randomly assigned to observation, gemcitabine on days 1 and 8 of a 3 week cycle at a dosage of 1250mg/m2 or daily erlotinib at a dosage of 150mg/day. The authors found that although there were no differences in OS between the three groups the PFS rates were significantly greater for gemcitabine versus observation (3.8 months vs 1.9 months) and erlotinib versus observation (2.9 months vs 1.9 months). They concluded that gemcitabine continuation maintenance or erlotinib switch maintenance significant reduced disease progression and were well tolerated.

Wauters et al., 2013 [52].

Belgian Health Care Knowledge Centre (KCE)

Non-small cell and small cell lung cancer: diagnosis, treatment and follow-up.

Leitlinienorganisation/Fragestellung

Methodik

Grundlage der Leitlinie

- developed using a standard methodology based on a systematic review of the evidence (further details: https://kce.fgov.be/content/kce-processes)
- developed by adapting (inter)national CPGs to the Belgian context (formal methodology of the ADAPTE group: www.adapte.org)
- in general, and whenever necessary, included guidelines updated with more recent evidence
- AGREE II instrument used to evaluate the methodological quality of the identified CPGs (www.agreetrust.org)
- quality of systematic reviews assessed by using the Dutch Cochrane checklist (www.cochrane.nl)
- critical appraisal of randomized controlled trials: Cochrane Collaboration's Risk of Bias Tool used
- When new RCTs were found in addition to an existing meta-analysis, or in case subgroup analysis was needed for certain topics, meta-analysis was performed using Review Manager Version 5

Recherche/Suchzeitraum:

- searches for guidelines: 20 February 2012 (23 guidelines retained for full-text evaluation),
- update searches: between April, 2012 and January, 2013

LoE/GoR

- GRADE

Table 1 – Levels of evidence according to the GRADE system

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias	1. Large effect 2. Dose-response 3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	High (⊕⊕⊕⊕) Moderate (⊕⊕⊕⊖) Low (⊕⊕⊖⊖) Very low (⊕⊖⊖⊖)
Observational studies	Low			

Recommendations

Treatment of metastatic (stage cIV) and recurrent NSCLC

Recommendation	Strength of recommendation	Level of evidence
The use of chemotherapy in patients with stage IV NSCLC with WHO/ECOG/Zubrod performance status (PS) of 0 or 1 and (based on clinical judgement) in some cases PS 2 is recommended.	strong	high
Maximal efforts should be made to determine the epidermal growth factor receptor (EGFR) mutation status, using a sensitive and validated method, in all non-squamous NSCLC or in never/very light smokers with mixed squamous/non-squamous NSCLC. It is recommended to use EGFR - tyrosine kinase inhibitors (EGFR TKI) as first-line treatment of patients with advanced EGFR mutation positive non-squamous NSCLC because of the better tolerance.	strong	moderate
If no EGFR TKI is given as first-line treatment in EGFR mutation positive NSCLC, a EGFR TKI should be offered thereafter, either as switch maintenance or at progression as second-line treatment.	strong	moderate
In the presence of the equipoise in efficacy for proven wild-type EGFR carriers, issues as residual and expected toxicity, patient preference and societal drug cost are of importance in the decision to administer second line treatment. Pending the publication of further data, the use of TKI's in second or third line should be restricted to either those patients in whom an activating EGFR mutation is present but was not yet treated with a TKI, or those patients who are not considered for further chemotherapy and whose EGFR mutational status could not be determined despite maximal efforts.	strong	very low
In patients with a WHO performance status of 0 or 1, evidence supports the use of a combination of two cytotoxic drugs for first-line therapy. Platinum combinations are preferred over non-platinum combinations	strong	high
because they are superior in response rate, and marginally superior in overall survival. Non-platinum therapy combinations are reasonable in patients who have contraindications to platinum therapy.		
In these patients, the choice of either cisplatin or carboplatin is acceptable. Drugs that can be combined with platinum include the third generation cytotoxic drugs docetaxel, gemcitabine, irinotecan, paclitaxel, pemetrexed, and vinorelbine.	weak	low
Pemetrexed is preferred to gemcitabine in patients with non-squamous NSCLC. Pemetrexed use should be restricted to non-squamous NSCLC in any line of treatment.	strong	low
It is recommended to offer second-line chemotherapy for patients with advanced NSCLC with adequate performance status when the disease has progressed during or after first-line therapy.	strong	moderate
Crizotinib is recommended as second-line therapy in ALK mutation-positive patients.	strong	low
The use of pemetrexed (only in non-squamous NSCLC) or docetaxel is acceptable as second-line therapy for patients with advanced NSCLC with adequate performance status when the disease has progressed during or after first-line, platinum-based therapy.	weak	very low
Maintenance therapy with pemetrexed can be considered after 4 cycles of chemotherapy in patients without disease progression.	weak	very low
Good clinical practice		
It is recommended to offer radiotherapy for palliation of local symptoms to patients with NSCLC.		

Socinski et al., 2013 [47] & Lewis SZ et al., 2013 [36].

American College of Chest Physicians

Treatment of stage IV non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines.

Leitlinienorganisation/Fragestellung

Therapie des NSCLC Stage IV

Methodik

Grundlage der Leitlinie

A writing committee was assembled and approved according to ACCP policies as described in the methodology article of the lung cancer guidelines – systematische Suche und Bewertung der Literatur – Formulierung und Konsentierung der Empfehlung nach standardisierten Verfahren - Update der Versionen aus 2003 und 2007.

Recherche/Suchzeitraum:

- bis 12/2011
- focused primarily on randomized trials, selected metaanalyses, practice guidelines, and reviews. In addition, phase 2 controlled studies that provided relevant information (eg, for toxicity or particular patient subgroups) were included.

LoE/GoR

Grade of Recommendation	Benefit vs Risk and Burdens	Methodologic Strength of Supporting Evidence	Implications
Strong recommendation, high-quality evidence (1A)	Benefits clearly outweigh risk and burdens or vice versa	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence (1B)	Benefits clearly outweigh risk and burdens or vice versa	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation, low-quality evidence (1C)	Benefits clearly outweigh risk and burdens or vice versa	Evidence for at least one critical outcome from observational studies, case series, or from randomized controlled trials with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Weak recommendation, high-quality evidence (2A)	Benefits closely balanced with risks and burden	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on circumstances or patients' or societal values. Further research is very unlikely to change our confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence (2B)	Benefits closely balanced with risks and burden	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Best action may differ depending on circumstances or patients' or societal values. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak recommendation, low-quality evidence (2C)	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk and burden may be closely balanced	Evidence for at least one critical outcome from observational studies, case series, or from randomized controlled trials with serious flaws or indirect evidence	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.

Sonstige methodische Hinweise

- direkte Verknüpfung von Literatur mit Empfehlung nicht durchgängig gegeben.

Recommendations

- In patients with a good performance status (PS) (ie, Eastern Cooperative Oncology Group [ECOG] level 0 or 1) and stage IV non-small cell lung cancer (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). (Grade 1A)
  - Remark: Patients may be treated with several chemotherapy regimens (carboplatin and cisplatin are acceptable, and can be combined with paclitaxel, docetaxel, gemcitabine, pemetrexed or vinorelbine)
- In patients with stage IV NSCLC and a good PS, 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. (Grade 1A)

First Line Treatment

- In patients receiving palliative chemotherapy for stage IV NSCLC, it is recommended that the choice of chemotherapy is guided by the histologic type of NSCLC (Grade 1B)
  - Remark: The use of pemetrexed (either alone or in combination) should be limited to patients with nonsquamous NSCLC.
  - Remark: Squamous histology has not been identified as predictive of better response to any particular chemotherapy agent.
- Bevacizumab improves survival combined with carboplatin and paclitaxel in a clinically selected subset of patients with stage IV NSCLC and good PS (nonsquamous histology, lack of brain metastases, and no hemoptysis). In these patients, addition of bevacizumab to carboplatin and paclitaxel is recommended (Grade 1A)
- In patients with stage IV non-squamous NSCLC and treated, stable brain metastases, who are otherwise candidates for bevacizumab therapy, the addition of bevacizumab to firstline, platinum-based chemotherapy is a safe therapeutic option (Grade 2B)
  - Remark: No recommendation can be given about the use of bevacizumab in patients receiving therapeutic anticoagulation or with an ECOG PS of 2.

Maintenance Therapy

- NSCLC who do not experience disease progression after 4 cycles of platinum-based therapy (which does not include pemetrexed), treatment with switch maintenance pemetrexed is suggested (Grade 2B).
- In patients with stage IV NSCLC, switch maintenance therapy with chemotherapy agents other than pemetrexed has not demonstrated an improvement in overall survival and is not recommended (Grade 1B).
- In patients with stage IV non-squamous NSCLC who do not experience disease progression after 4 cycles of platinum-pemetrexed ther apy, continuation pemetrexed maintenance therapy is suggested (Grade 2B).
- In patients with stage IV NSCLC who do not experience disease progression after 4 cycles of platinum-based double agent chemotherapy, maintenance therapy with erlotinib is suggested (Grade 2B).
- In patients with stage IV NSCLC the addition of cetuximab in combination with chemotherapy is suggested not to be used outside of a clinical trial (Grade 2B).

Second and Third Line Treatment

- In patients with stage IV NSCLC who have good PS (ECOG 0-2), second-line treatment with erlotinib or docetaxel (or equivalent single-agent such as pemetrexed) is recommended (Grade 1A)
- In patients with stage IV NSCLC who have good PS (ECOG 0-2), third-line treatment with erlotinib improves survival compared with BSC and is recommended (Grade 1B)
  - Remark: No recommendation can be given about the optimal chemotherapeutic strategy in patients with stage IV NSCLC who have received three prior regimens for advanced disease.

CCO, 2015 [3].

Cancer Care Ontario (CCO)

The Use of Systemic Treatment in the Maintenance of Patients with Non-small Cell Lung Cancer

Leitlinienorganisation/Fragestellung

To make recommendations in the maintenance setting regarding the use of systemic treatment in the care of patients with non-small cell lung cancer (NSCLC).

Methodik

Grundlage der Leitlinie

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) [18]. The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [18]. PEBC guidelines include an evidence review (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The PEBC uses the AGREE II as its organizational methodological framework. Beginning with a project plan, systematic methods of evidence synthesis (see section 4) and/or adaptation, consensus of interpretation of evidence, drafting and contextualization of recommendations, and internal and external review (see section 5) of the draft guideline define key steps in the process. The PEBC's processes and methods are described in more detail in the PEBC Handbook.

A search for existing guidelines for adaptation or endorsement was conducted and no comprehensive guidelines that covered all types of systemic treatments for maintenance were found.

Recherche/Suchzeitraum:

- To 2014

LoE/GoR

- GRADE method

Recommendations

- 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 epidermal growth factor receptor (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. Please refer to the Program in Evidence-Based Care guidelines on the use of second-line therapies in NSCLC [1,2].

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 overall survival advantage was modest for both agents.
- The recommendation for EGFR TKIs applies to both EGFR mutation-positive and wild-type patients.
- In patients receiving maintenenance bevacizumab, it is unclear whether the addition of maintenance pemetrexed improves overall survival (OS).

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Database of Systematic Reviews (Issue 10 of 12, October 2018) am 15.10.2018

#	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:ti,ab,kw or metastat*:ti,ab,kw or metastas*:ti,ab,kw or recurren*:ti,ab,kw or relaps*:ti,ab,kw
5	#2 and #3 and #4
6	nsclc*:ti,ab,kw
7	#1 or #5 or #6
8	#7 with Cochrane Library publication date from Oct 2013 to Oct 2018, in Cochrane Reviews and Cochrane Protocols

Systematic Reviews in Medline (PubMed) am 15.10.2018

#	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]
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 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 ("2013/10/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 15.10.2018

#	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*[Title])
10	((#9) AND ("2013/10/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT ((Humans[mh] AND animals[MeSH:noexp]) NOT ("The Cochrane database of systematic reviews"[Journal])))

Referenzen

1. **Alberta Provincial Thoracic Tumour Team.** Non-small cell lung cancer stage IV [online]. Edmonton (CAN): Alberta Health Services (AHS); 2013. [Zugriff: 16.10.2018]. (Clinical practice guideline; Band LU-004, vers. 06). URL: http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-lu004-nsclc-stage4.pdf.

2. **Armoiry X, Tsertsvadze A, Connock M, Royle P, Melendez-Torres GJ, Souquet PJ, et al.** Comparative efficacy and safety of licensed treatments for previously treated non-small cell lung cancer: a systematic review and network meta-analysis. PLoS One 2018;13(7):e0199575.

3. **Cancer Care Ontario (CCO).** The Use of Systemic Treatment in the Maintenance of Patients with Non-small Cell Lung Cancer [online]. 01.2016. Toronto (CAN): CCO: 2015. [Zugriff: 16.10.2018]. (Evidence-Based Series; Band 7-22). URL: https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=345527.

4. **Chen JH, Yang JL, Chou CY, Wang JY, Hung CC.** Indirect comparison of efficacy and safety between immune checkpoint inhibitors and antiangiogenic therapy in advanced non-small-cell lung cancer. Sci Rep 2018;8(1):9686.

5. **Crequit P, Chaimani A, Yavchitz A, Attiche N, Cadranel J, Trinquart L, et al.** Comparative efficacy and safety of second-line treatments for advanced non-small cell lung cancer with wild-type or unknown status for epidermal growth factor receptor: a systematic review and network meta-analysis. BMC Med 2017;15(1):193.

6. **Ellis PM, Vella ET, Ung YC.** Immune checkpoint inhibitors for patients with advanced non-small-cell lung cancer: a systematic review. Clin Lung Cancer 2017;18(5):444-459.

7. **Ellis PM, Vella ET, Ung YT, and the Lung Cancer Disease Site Group.** Systemic treatment for patients with advanced non-small cell lung cancer [online]. 11.2016. Toronto (CAN): Cancer Care Ontario (CCO); 2016. [Zugriff: 16.10.2018]. (Evidence-Based Series; Band 7-10, Vers. 3). URL: https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=366077.

8. **Fan J, Xia Z, Zhang X, Chen Y, Qian R, Liu S, et al.** The efficacy and safety of alectinib in the treatment of ALK+ NSCLC: a systematic review and meta-analysis. Onco Targets Ther 2018;11:1105-1115.

9. **Gemeinsamer Bundesausschuss (G-BA).** Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage VI - Off-Label-Use, Teil A, Ziffer III: Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) - Kombinationstherapie, Zustimmung eines pharmazeutischen Unternehmers vom 17. Juli 2014 [online]. Berlin (GER): G-BA; 2014. [Zugriff: 16.10.2018]. URL: https://www.g-ba.de/downloads/39-261-2035/2014-07-17_AM-RL-VI_Carboplatin-haltige%20AM_BAnz.pdf.

10. **Gemeinsamer Bundesausschuss (G-BA).** 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 [online]. Berlin (GER): GBA; 2018. [Zugriff: 16.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-304/2018-02-01_Geltende-Fassung_Ceritinib_nAWG_D-296.pdf.

11. **Gemeinsamer Bundesausschuss (G-BA).** 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 [online]. Berlin (GER): GBA; 2016. [Zugriff: 16.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-222/2016-09-01_Geltende-Fassung_Ramucirumab_nAWG_D-217.pdf

12. **Gemeinsamer Bundesausschuss (G-BA).** 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 [online]. Berlin (GER): GBA; 2017. [Zugriff: 16.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-259/2017-02-02_Geltende-Fassung_Pembrolizumab_nAWG_D-251.pdf

13. **Gemeinsamer Bundesausschuss (G-BA).** 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 [online]. Berlin (GER): GBA; 2017. [Zugriff: 16.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-278/2017-08-03_Geltende-Fassung_Pembrolizumab_nAWG_D-274.pdf.

14. **Gemeinsamer Bundesausschuss (G-BA).** 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 [online]. Berlin (GER): GBA; 2016. [Zugriff: 16.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-248/2016-12-15_Geltende-Fassung_Crizotinib_A-Bfr_D-240.pdf

15. **Gemeinsamer Bundesausschuss (G-BA).** 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) [online]. Berlin (GER): GBA; 2016. [Zugriff: 16.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-209/2016-06-16_Geltende-Fassung_Crizotinib_nAWG_D-205.pdf

16. **Gemeinsamer Bundesausschuss (G-BA).** 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) [online]. Berlin (GER): GBA; 2017. [Zugriff: 16.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-262/2017-03-16_Geltende-Fassung_Crizotinib_nAWG_D-261.pdf

17. **Gemeinsamer Bundesausschuss (G-BA).** 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 [online]. Berlin (GER): GBA; 2017. [Zugriff: 16.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-264/2017-03-16_Geltende-Fassung_Ceritinib_D-259.pdf

18. **Gemeinsamer Bundesausschuss (G-BA).** 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 [online]. Berlin (GER): GBA; 2018. [Zugriff: 16.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-314/2018-03-16_Geltende-Fassung_Atezolizumab_D-313.pdf.

19. **Gemeinsamer Bundesausschuss (G-BA).** 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 [online]. Berlin (GER): GBA; 2015. [Zugriff: 16.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-155/2015-06-18_Geltende-Fassung_Nintedanib_D-147.pdf

20. **Gemeinsamer Bundesausschuss (G-BA).** 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) [online]. Berlin (GER): GBA; 2017. [Zugriff: 16.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-289/2017-10-19_Geltende-Fassung_Dabrafenib_nAWG_D-285.pdf

21. **Gemeinsamer Bundesausschuss (G-BA).** 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 [online]. Berlin (GER): GBA; 2017. [Zugriff: 16.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-288/2017-10-19_Geltende-Fassung_Trametinib_nAWG_D-284.pdf

22. **Gemeinsamer Bundesausschuss (G-BA).** 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 2018 - Alectinib [online]. Berlin (GER): GBA; 2017. [Zugriff: 16.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-285/2017-10-19_Geltende-Fassung_Alectinib_D-281.pdf.

23. **Gemeinsamer Bundesausschuss (G-BA).** 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 [online]. Berlin (GER): GBA; 2016. [Zugriff: 16.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-232/2016-10-20_Geltende-Fassung_Nivolumab_nAWG_D-231.pdf.

24. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 21. Juni 2018 - Alectinib (neues Anwendungsgebiet: Erstlinienbehandlung nicht-kleinzelliges Lungenkarzinom) [online]. Berlin (GER): GBA; 2018. [Zugriff: 16.10.2018]. URL: https://www.g-ba.de/downloads/91-1385-339/2018-06-21_Geltende-Fassung_Alectinib-nAWG_D-326.pdf.

25. **Han S, Hong Y, Liu T, Wu N, Ye Z.** 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. Oncotarget 2018;9(18):14619-14629.

26. **Hanna N, Johnson D, Temin S, Baker S, Brahmer J, Ellis PM, et al.** Systemic therapy for stage IV non-small-cell lung cancer: american society of clinical oncology clinical practice guideline update. J Clin Oncol 2017;35(30):3484-3515.

27. **He X, Wang J, Li Y.** Efficacy and safety of docetaxel for advanced non-small-cell lung cancer: a meta-analysis of Phase III randomized controlled trials. Onco Targets Ther 2015;8:2023-2031.

28. **Hong S, Tan M, Wang S, Luo S, Chen Y, Zhang L.** Efficacy and safety of angiogenesis inhibitors in advanced non-small cell lung cancer: a systematic review and meta-analysis. J Cancer Res Clin Oncol 2015;141(5):909-921.

29. **Hu X, Pu K, Feng X, Wen S, Fu X, Guo C, et al.** Role of Gemcitabine and Pemetrexed as Maintenance Therapy in Advanced NSCLC: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. PLoS One 2016;11(3):e0149247.

30. **Huang G, Sun X, Liu D, Zhang Y, Zhang B, Xiao G, et al.** The efficacy and safety of anti-PD-1/PD-L1 antibody therapy versus docetaxel for pretreated advanced NSCLC: a meta-analysis. Oncotarget 2018;9(3):4239-4248.

31. **Jiang Q, Xie M, He M, Yan F, Zhang X, Yu S.** Anti-PD-1/PD-L1 antibodies versus docetaxel in patients with previously treated non-small-cell lung cancer. Oncotarget 2018;9(7):7672-7683.

32. **Khan M, Lin J, Liao G, Tian Y, Liang Y, Li R, et al.** 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. Medicine (Baltimore) 2018;97(33):e11936.

33. **Kulkarni S, Vella ET, Coakley N, Cheng S, Gregg R, Ung YC, et al.** The Use of Systemic Treatment in the Maintenance of Patients with Non-Small Cell Lung Cancer: A Systematic Review. J Thorac Oncol 2016;11(7):989-1002.

34. **Lai XX, Xu RA, Yu-Ping L, Yang H.** Risk of adverse events with bevacizumab addition to therapy in advanced non-small-cell lung cancer: a meta-analysis of randomized controlled trials. Onco Targets Ther 2016;9:2421-2428.

35. **Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft (DKG), Deutsche Krebshilfe, Arbeitsgemeischaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)).** Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms. S3-Leitlinie; Langversion [online]. AWMF-Registernr. 020-007. Berlin (GER): 2018. [Zugriff: 16.10.2018]. URL: http://www.leitlinienprogramm-onkologie.de/leitlinien/lungenkarzinom/.

36. **Lewis SZ, Diekemper R, Addrizzo-Harris DJ.** Methodology for development of guidelines for lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl):41S-50S.

37. **Ma H, Tian X, Zeng XT, Zhang Y, Wang Y, Wang F, et al.** The efficacy of erlotinib versus conventional chemotherapy for advanced nonsmall-cell lung cancer: A PRISMA-compliant systematic review with meta-regression and meta-analysis. Medicine (Baltimore) 2016;95(2):e2495.

38. **Masters GA, Johnson DH, Temin S.** Systemic therapy for stage IV non-small-cell lung cancer: american society of clinical oncology clinical practice guideline update. J Oncol Pract 2016;12(1):90-93.

39. **Peng TR, Tsai FP, Wu TW.** Indirect comparison between pembrolizumab and nivolumab for the treatment of non-small cell lung cancer: a meta-analysis of randomized clinical trials. Int Immunopharmacol 2017;49:85-94.

40. **Ramos-Esquivel A, van der Laat A, Rojas-Vigott R, Juarez M, Corrales-Rodriguez L.** 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. ESMO Open 2017;2(3):e000236.

41. **Santos FN, de Castria Tiago B, Cruz MR, Riera R.** Chemotherapy for advanced non-small cell lung cancer in the elderly population. Cochrane Database of Systematic Reviews [online]. 2015(10):Cd010463. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010463.pub2/abstract.

42. **Shan F, Zhang B, Sun L, Xie L, Shen M, Ruan S.** The Role of Combination Maintenance with Pemetrexed and Bevacizumab for Advanced Stage Nonsquamous Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. Biomed Res Int 2018;2018:5839081.

43. **Sheng J, Yang Y, Ma Y, Yang B, Zhang Y, Kang S, et al.** The efficacy of combining antiangiogenic agents with chemotherapy for patients with advanced non-small cell lung

cancer who failed first-line chemotherapy: a systematic review and meta-analysis. PLoS One 2015;10(6):e0127306.

44. **Sheng J, Yang YP, Yang BJ, Zhao YY, Ma YX, Hong SD, et al.** Efficacy of addition of antiangiogenic agents to taxanes-containing chemotherapy in advanced nonsmall-cell lung cancer: a meta-analysis and systemic review. Medicine (Baltimore) 2015;94(31):e1282.

45. **Sheng M, Zhao Y, Wang F, Li S, Wang X, Shou T, et al.** Targeted drugs for unselected patients with advanced non-small-cell lung cancer: a network meta-analysis. J Thorac Dis 2016;8(1):98-115.

46. **Sheng Z, Zhang Y.** The Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer harboring wild-type epidermal growth factor receptor: a ,eta-analysis of 25 RCTs. Am J Clin Oncol 2017;40(4):362-369.

47. **Socinski MA, Evans T, Gettinger S, Hensing TA, VanDam Sequist L, Ireland B, et al.** Treatment of stage IV non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl):e341S-e368S.

48. **Su Q, Sun Z, Zhang C, Hou Y, Cao B.** PD-1/PD-L1 antibodies efficacy and safety versus docetaxel monotherapy in advanced NSCLC patients after first-line treatment option: systems assessment. Oncotarget 2017;8(35):59677-59689.

49. **Sun L, Ma JT, Zhang SL, Zou HW, Han CB.** 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. Med Oncol 2015;32(2):473.

50. **Tan PS, Lopes G, Acharyya S, Bilger M, Haaland B.** Bayesian network meta-comparison of maintenance treatments for stage IIIb/IV non-small-cell lung cancer (NSCLC) patients with good performance status not progressing after first-line induction chemotherapy: results by performance status, EGFR mutation, histology and response to previous induction. Eur J Cancer 2015;51(16):2330-2344.

51. **Wang Q, Huang H, Zeng X, Ma Y, Zhao X, Huang M.** Single-agent maintenance therapy for advanced non-small cell lung cancer (NSCLC): a systematic review and Bayesian network meta-analysis of 26 randomized controlled trials. PeerJ 2016;4:e2550.

52. **Wauters I, Robays J, Verleye L, Holdt Henningsen K, Hulstaert F, Berghmans T, et al.** Non-small cell and small cell lung cancer: diagnosis, treatment and follow-up [online]. Brüssel (BEL): Belgian Health Care Knowledge Centre; 2013. [Zugriff: 16.10.2018]. (KCE Report; Band 206). URL: https://kce.fgov.be/sites/default/files/page_documents/KCE_206_lung_cancer.pdf.

53. **Wu D, Duan C, Wu F, Chen L, Chen S.** 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. Oncotarget 2017;8(39):66491-66503.

54. **Xiao BK, Yang JY, Dong JX, Ji ZS, Si HY, Wang WL, et al.** Meta-analysis of seven randomized control trials to assess the efficacy and toxicity of combining EGFR-TKI with chemotherapy for patients with advanced NSCLC who failed first-line treatment. Asian Pac J Cancer Prev 2015;16(7):2915-2921.

55. **Xiao HQ, Tian RH, Zhang ZH, Du KQ, Ni YM.** 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. Onco Targets Ther 2016;9:1471-1476.

56. **Xu JL, Jin B, Ren ZH, Lou YQ, Zhou ZR, Yang QZ, et al.** Chemotherapy plus erlotinib versus chemotherapy alone for treating advanced non-small cell lung cancer: a meta-analysis. PLoS One 2015;10(7):e0131278.

57. **Yu S, Xu Q, Yuan Y, Li X, Cai H.** Erlotinib-based targeted dual agent versus erlotinib alone in previously treated advanced non-small-cell lung cancer: a meta-analysis of 13 randomized controlled trials. Curr Med Res Opin 2016;32(12):1927-1934.

58. **Zhang TT, Wang RM, Yang Z, Chen GB.** Dual inhibiting EGFR and VEGF pathways versus EGFR-TKIs alone in the treatment of advanced non-small-cell lung cancer: a meta-analysis of randomized controlled trials. Clin Transl Oncol 2016;18(6):576-581.

59. **Zhao S, Gao F, Zhang Y, Zhang Z, Zhang L.** 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. Int J Cancer 2018;142(8):1676-1688.

60. **Zhao X, Feng Z, Wang G, Pang H, Wang M.** Ceritinib Alone for Crizotinib-naive Versus Crizotinib-pretreated for Management of Anaplastic Lymphoma Kinase-rearrangement Non-Small-cell Lung Cancer: A Systematic Review. Clin Lung Cancer 2018;19(6):e945-e956.

61. **Zhong A, Xiong X, Shi M, Xu H.** 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. Drug Des Devel Ther 2015;9:3685-3693.

62. **Zhou GW, Xiong Y, Chen S, Xia F, Li Q, Hu J.** Anti-PD-1/PD-L1 antibody therapy for pretreated advanced nonsmall-cell lung cancer: A meta-analysis of randomized clinical trials. Medicine (Baltimore) 2016;95(35):e4611.

63. **Zhuansun Y, Huang F, Du Y, Lin L, Chen R, Li J.** 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. J Thorac Dis 2017;9(3):655-665.