Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2018-B-085 (Brigatinib)

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

Abkürzungsverzeichnis

ALK	Anaplastic Lymphoma Kinase
ASCO	American Society of Clinical Oncology
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BSC	Best supportive care
CIS	Cisplatin
DAHTA	DAHTA Datenbank
DOC	Docetaxel
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for QLQ Research and Treatment of Cancer Quality of Life Questionnaire
EGFR	Epidermal Growth Factor Receptor
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
OR	Odds Ratio
OS	Overall Survival
PAX	Paclitaxel
PEM	Pemetrexed
PFS	Progression Free Survival

QoL	Quality of Life
RCT	Randomized Controlled Trial
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TKI	Tyrosinkinsaseinhibitor
TRIP	Turn Research into Practice Database
TTP	Time to Progression
WHO	World Health Organization
WT	Wild Type

1 Indikation

Vorbehandelte erwachsene Patienten mit fortgeschrittenem nicht-kleinzelligem Lungenkarzinom (non-small cell lung cancer, NSCLC)

Anmerkung: Neu hinzugefügte Literatur, die nicht in der Evidenzsynopse 2017-B-188 zu finden ist, wurde rot markiert sowie blau markiert Literatur zu ALK-positiven 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 1324s 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 88 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 [20].

Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Osimertinib (Ablauf der Befristung)

Siehe auch IQWiG, 2017 [52].

Anwendungsgebiet

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

„Hinweis: Der Beschluss vom 19. Oktober 2017 bezieht sich ausschließlich auf die Bewertung des Zusatznutzens von Osimertinib in der Teilpopulation: Patienten nach Vorbehandlung mit einem EGFR-Tyrosinkinase-Inhibitor, für die eine zytotoxische Chemotherapie infrage kommt. Über die Nutzenbewertung von Osimertinib im gesamten Anwendungsgebiet laut Zulassung vom 2. Februar 2016 hat der G-BA bereits mit Beschluss vom 15. September 2016 beschlossen. Dabei wurden die Feststellungen zum Zusatznutzen für die oben genannte Teilpopulation (Teilpopulation „1a“ im Beschluss vom 15. September 2016) in ihrer Geltungsdauer zeitlich befristet.“

Patienten nach Vorbehandlung mit einem EGFR-Tyrosinkinase-Inhibitor:

Vergleichstherapie

„a) für Patienten, für die eine zytotoxische Chemotherapie infrage kommt:

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

oder gegebenenfalls

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

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 [32].

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

Siehe auch IQWiG, 2018 [41,44].

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 [30].

Beschlüsse über die Nutzen-bewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Trametinib

Siehe auch IQWiG, 2017 [55].

Anwendungsgebiet

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

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.

Studienergebnisse nach Endpunkten:

2) Patienten mit Vorbehandlung:
a) Für die eine Therapie mit Docetaxel oder Pemetrexed angezeigt ist:
Es liegen keine validen Daten vor.
b) Für die eine Therapie mit Docetaxel und Pemetrexed nicht angezeigt ist:
Es liegen keine validen Daten vor.

G-BA, 2017 [27].

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

Siehe auch IQWiG, 2017 [48].

Anwendungsgebiet

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

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.

Studienergebnisse nach Endpunkten:

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

Es liegen keine validen Daten vor.

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

Es liegen keine validen Daten vor.

G-BA, 2017 [31].

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

Siehe auch IQWiG, 2017 [40,43].

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, 2017 [25].

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

Siehe auch IQWiG, 2016 [45].

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 [26].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Crizotinib (neues Anwendungsgebiet: ROS1-positives, fortgeschrittenes nicht kleinzelliges Lungenkarzinom)

Siehe auch IQWiG, 2017 [46].

Anwendungsgebiet

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

(…)

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.

Studienergebnisse nach Endpunkten

(…)

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

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

Es liegen keine validen Daten vor.

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

Es liegen keine Daten vor.

G-BA, 2017 [29].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Pembrolizumab (neues Anwendungsgebiet: nicht-kleinzelliges Lungenkarzinom nach vorheriger Chemotherapie)

Siehe auch IQWiG, 2016 [53].

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 [21].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Crizotinib (neues Anwendungsgebiet) vom 16.06.2016

Siehe auch IQWiG, Jahr [47].

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).

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) Anhaltspunkt für einen beträchtlichen Zusatznutzen.

b) Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [33].

Beschluss über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Ramucirumab (neues Anwendungsgebiet Lungenkarzinom) vom 01.09.2016

Siehe auch IQWiG, 2016 [54].

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 [19].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Nivolumab (neues Anwendungsgebiet) vom 04.02.2016

Siehe auch IQWiG, 2015 [39,50].

Anwendungsgebiet

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

<u>1) Patienten, für die eine Behandlung mit Docetaxel angezeigt ist</u>

Zweckmäßige Vergleichstherapie

Docetaxel

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Docetaxel:

Hinweis auf einen beträchtlichen Zusatznutzen.

2) Patienten, für die eine Behandlung mit Docetaxel 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 belegt.

G-BA, 2016 [23].

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

Siehe auch IQWiG, 2016 [51].

Anwendungsgebiet

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

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

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 Gefitinib oder Erlotinib vorbehandelt wurden)

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

Best-Supportive-Care

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [22].

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

Siehe auch IQWiG, 2015 [39,50].

Anwendungsgebiet

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

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

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 [28].

Beschluss über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Nintedanib (nicht-kleinzelliges Lungenkarzinom) vom 18.06.2015

Siehe auch IQWiG, Jahr [49].

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, 2015 [24].

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

Siehe auch IQWiG, 2015 [42].

Anwendungsgebiet

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

(…)

3) Patienten nach Vorbehandlung mit einer Platin-basierten Chemotherapie

Vergleichstherapie

- Gefitinib oder Erlotinib

oder

- Docetaxel oder Pemetrexed

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

3.2 Cochrane Reviews

Sim EHA et al., 2018 [74].

Gefitinib for advanced non-small cell lung cancer

Fragestellung

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

Methodik

Population:

- advanced NSCLC (stage IIIB/IV) not curable with surgery

Intervention:

- Gefitinib as first – or second line therapy

Komparator:

- Placebo, chemotherapy, best supportive care, Gefitinib in combination with chemotherapy

Endpunkt:

- OS, PFS, time to treatment failure (TTS), QoL, response, disease control rate

Recherche/Suchzeitraum:

- The Cochrane Central Register of Controlled Trials (CENTRAL 2017, Issue 2) (Appendix 1); MEDLINE via PubMed (1966 to 17 February 2017) (Appendix 2); Embase via OVID (1980 to Week 08, 2017)

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 35 studies (first- and second line); a total of 12089 patients

Qualität der Studien:

- Overall, the risk of bias in the 35 included studies was moderate.

Studienergebnisse:

Gefitinib versus chemotherapy

Survival

- The SIGN and INTEREST studies compared gefitinib with docetaxel as second-line therapy (Cufer 2006 SIGN; Kim 2008 INTEREST). Only Kim 2008 INTEREST reported survival outcomes

- overall survival (HR 1.02, 95% CI 0.91 to 1.15, P = 0.74, moderate quality of evidence)
- progression-free survival (HR 1.04, 95% CI 0.92 to 1.17, P = 0.51, moderate quality of evidence)

Subgroup analysis: EGFR mutation positive population

- Gefitinib with second-line chemotherapy, data were available from two studies (Kim2008 INTEREST; Sun 2012 KCSG-LU08-01).
- Overall survival: HR 0.83, 95% CI 0.41 to 1.66, P = 0.60).
- Progression free survival: HR 0.24, 95% CI 0.12 to 0.47, P < 0.0001, I2 = 0%)

Gefitinib plus chemotherapy versus chemotherapy

Survival

- A single phase III trial recruited only EGFR mutation positive patients who had failed prior first-line gefitinib
- the addition of gefitinib to chemotherapy did not improve progression-free survival (HR 0.86, 95% CI 0.65 to 1.13, P = 0.28) (Soria 2015 IMPRESS).
- Overall survival appeared to be better in the chemotherapy alone group (HR 1.62, 95% CI 1.05 to 2.50, P = 0.03).

Overall response rate

- RR 0.93, 95% CI 0.66 to 1.31, P = 0.66, I2 = 0%), and the overall response rate was 32% in the gefitinib plus chemotherapy group and 34% in the chemotherapy alone group

Toxicity

- Side effects such as skin rash, diarrhoea and increased alanine aminotransferase (ALT) and aspartate transaminase (AST) are more common with gefitinib. Side effects such as nausea, vomiting, anorexia, fatigue, arthralgia, asthenia, neurotoxicity, neutropenia, leukopenia, thrombocytopaenia and anaemia are more common with chemotherapy.

Anmerkung/Fazit der Autoren

- Second-line gefitinib plus chemotherapy is probably more effective in improving progression-free survival than gefitinib alone.
- One second-line study selected EGFR mutation positive patients and showed that chemotherapy is more effective in improving survival than gefitinib plus chemotherapy in patients who have failed first-line gefitinib.

3.3 Systematische Reviews

Neu dazu gekommene systematische Reviews seit der Evidenzsynopse zu 2017-B-188

Su Q et al., 2017 [76].

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 [56].** Anti-PD-1/PD-L1 antibodies versus docetaxel in patients with previously treated non-small-cell lung cancer
- **Huang, G., 2018 [38].** 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. [88].** 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. [67].** 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 [17].** Immune Checkpoint Inhibitors for Patients With Advanced Non-Small-Cell Lung Cancer: A Systematic Review
- **Zhou G-W., 2016 [87].** 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:

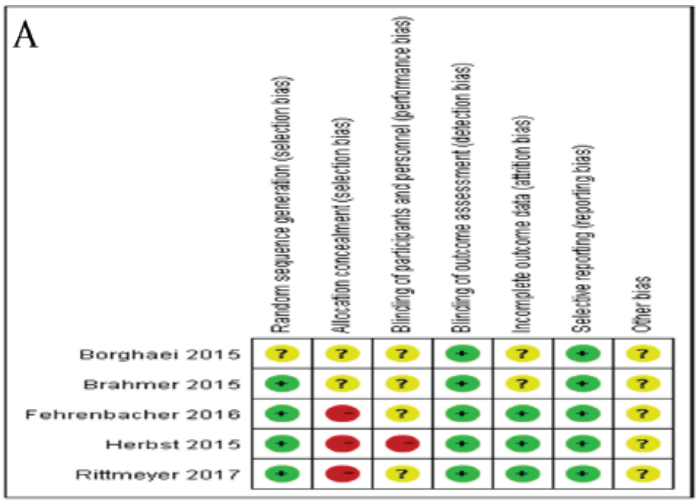
- one had data from SQ-NSCLC patients [15], while another one had data from NSQ-NSCLC patients [16], and the remaining three studies [17, 18, 19] had data from both SQ and NSQ NSCLC patients.

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.

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Anmerkung/Fazit der Autoren

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

Peng TR et al., 2017 [65].

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:

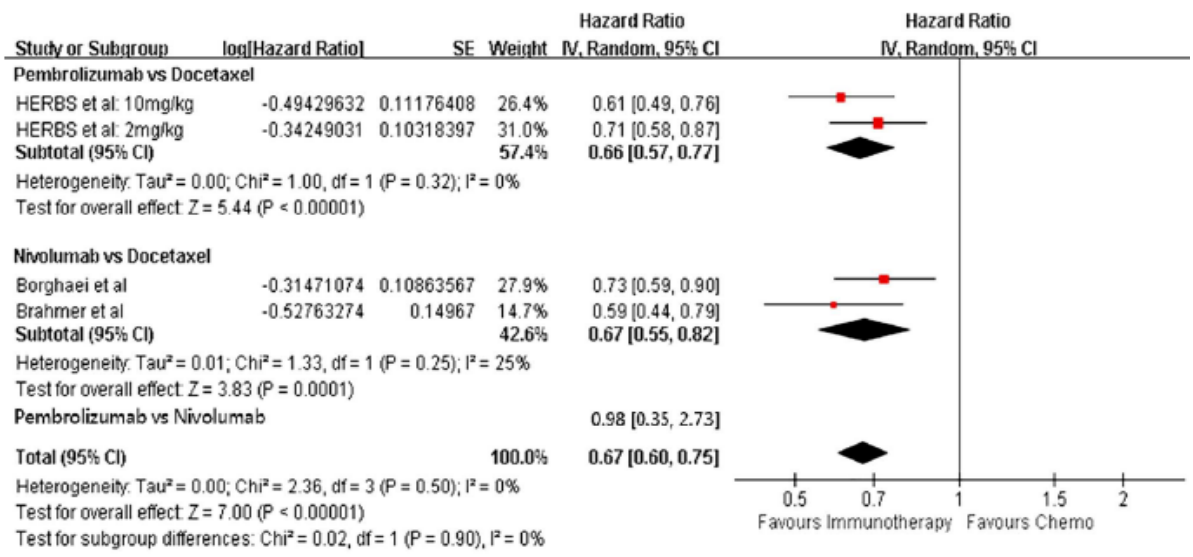
Table 2
The quality assessment of three randomized controlled trials included.

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

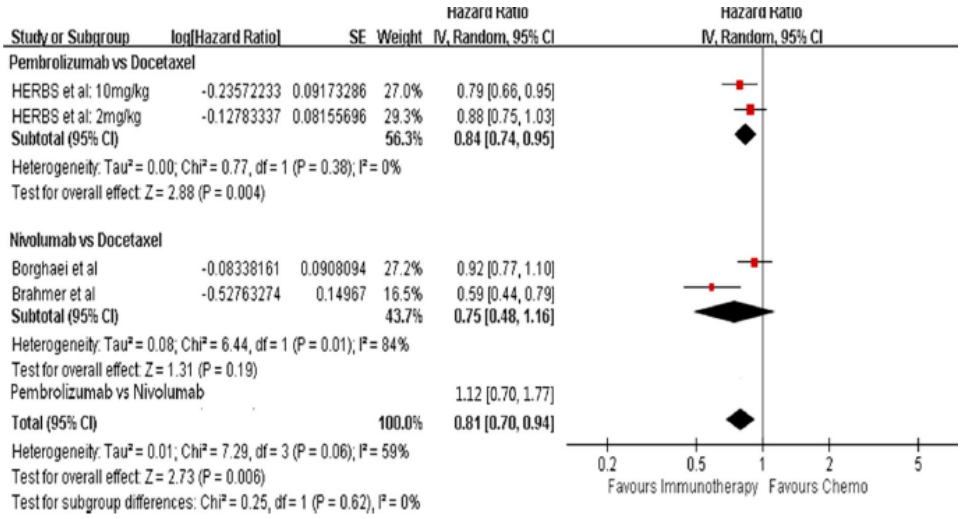


Fig. 3. Meta-analysis results of (A) OS and (B) PFS.

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)

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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.

Wu Di et al., 2017 [80].

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 [17-19, 24-33]. 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 [24, 25, 27], 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 [12, 13]) 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 [17, 19, 30, 32, 33], and three were second- or third-line setting [18, 28, 29, 31].
- Five trials majorly comprised of white patients [17, 28-31, 33], while the other three majorly included Asian patients [18, 19, 32].

Qualität der Studien:

- The included trials were overall low risk (Table 2).
- Sequence was adequately generated in all trials.
- Allocation concealment was adequately performed in nine trials, not detailed in one trials [32] and undone in two trials [25, 27].
- Though all trials were designed as open-labeled, six of them blinded assessment of outcome by independent, central radiologic reviews [24-27, 31] or independent review committee [19].
- 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 [30], two had biased baseline characteristics [19], and the other one had imbalanced number of patients underwent crossover [32].

Studienergebnisse:

Overall survival

- no evidence of significant inter-study heterogeneity for OS or PFS was identified (I2 = 0% and 27%, respectively).
- The pooled fixed-effect models showed that treatment of PD-1/PDL1 antibody was more effective in improving OS and PFS than chemotherapy in WT EGFR patients, with an estimated HR of 0.67 (95% CI 0.60-0.75, p < 0.001)
- no significant difference for OS was identified between chemotherapy and EGFR-TKI.

Progression-free survival

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

Subgroup analysis

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

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Anmerkung/Fazit der Autoren

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

Sheng Z et al., 2017 [72].

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:

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

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.

Créquit P et al., 2017 [15].

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.

Ma H et al., 2016 [61].

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.

Qualität der Studien:

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

Studienergebnisse:

PFS

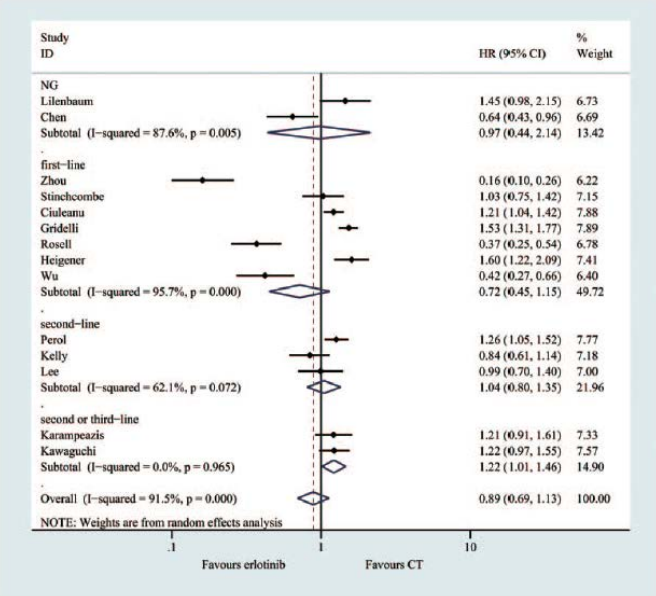
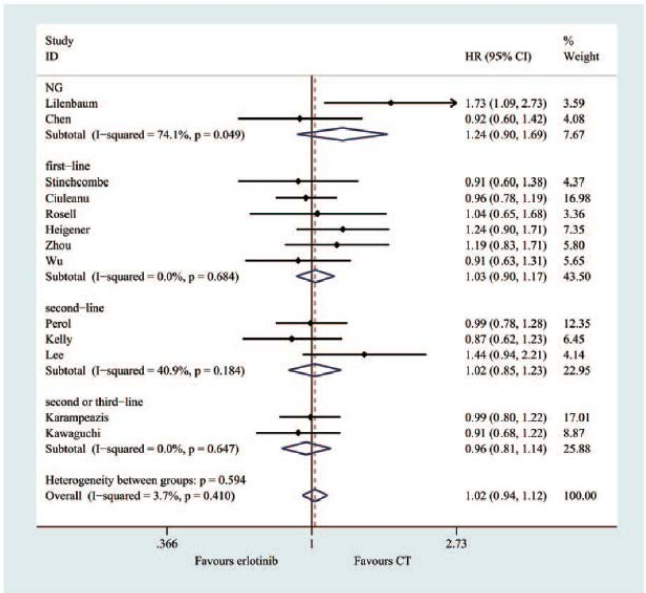


FIGURE 4. Meta-analysis results of the progression-free survival.

OS



- IGURE 5. Meta-analysis results of the overall survival.

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. […]

Hong et al. 2015, [37].

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:

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

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

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Sheng J et al., 2015 [70].

Efficacy of Addition of Antiangiogenic Agents to Taxanes-Containing Chemotherapy in Advanced Nonsmall-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:

Subgroup analyses → the practice in second-line application was associated with the significant prolonged OS

TABLE 2. Summary of the Subgroup Results: Pooled HRs and 95% CIs for OS

	No. of Articles	Pooled HR (95% CI)	*P*	Heterogeneity I^2	Analysis Model
First-line	8	0.96 (0.87–1.06)	0.39	0%	Fixed
Second-line	6	0.91 (0.85–0.96)	0.002	25%	Fixed
Angiokinase inhibitors	8	0.95 (0.88–1.01)	0.11	2%	Fixed
Monoclonal antibodies	6	0.89 (0.82–0.96)	0.004	17%	Fixed
Nonsquamous cancer	8	0.90 (0.84–0.96)	0.002	10%	Fixed
Squamous cancer	5	1.09 (0.87–1.35)	0.45	58%	Random
Nonsmoker	6	0.81 (0.70–0.94)	0.0005	0%	Fixed
Past or present smoker	6	0.99 (0.88–1.11)	0.85	89%	Random
Female	6	0.87 (0.77–0.98)	0.02	0%	Fixed
Male	6	0.96 (0.89–1.03)	0.28	33%	Fixed
IIIB	3	0.93 (0.71–1.23)	0.63	0%	Fixed
IV	4	0.93 (0.82–1.06)	0.29	60%	Random
ECOG=0	4	0.93 (0.82–1.06)	0.28	1%	Fixed
ECOG=1	4	0.92 (0.85–1.00)	0.06	49%	Fixed
≥65	3	0.98 (0.85–1.14)	0.83	0%	Fixed
<65	3	0.96 (0.81–1.15)	0.68	62%	Random

CI = confidence intervals, ECOG = Eastern Cooperative Oncology Group, HRs = harzard ratios, OS = overall survival.

Anmerkung/Fazit der Autoren

Subgroup analyses indicated that nonsquamous, nonsmoker, and female lung cancer patients as well as patients in second-line might be the potential target population.

Kommentare zum Review

Keine Subgruppenanalysen zur Zweitlinie für die weiteren Endpunkte vorhanden!

Li N et al., 2014 [60].

Meta-Analysis of EGFR Tyrosine Kinase Inhibitors Compared with Chemotherapy as Second-Line Treatment in Pretreated Advanced Non-Small Cell Lung Cancer

Fragestellung

To further investigate the optimal treatment and the role of EGFR mutation status in second-line setting, we performed this meta-analysis to compare the efficacy and safety of EGFR-TKIs versus chemotherapy as second-line treatment for pretreated advanced NSCLC

Methodik

Population:

- patients were previously treated with platinum compounds

Intervention:

- EGFR-TKI

Komparator:

- Standard second-line chemotherapy (docetaxel or pemetrexed)

Endpunkt:

- PFS and OS, grade 3-4 adverse events

Recherche/Suchzeitraum:

- PubMed, the Embase database, the Cochrane Central Register of Controlled Trials database (CENTRAL), the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO) and the World Conference of Lung Cancer (WCLC) was performed in July 2013

Qualitätsbewertung der Studien:

- Jadad Score

Ergebnisse

Anzahl eingeschlossener Studien:

- 10 publications (n=3825)

Charakteristika der Population:

- The total number of randomized patients of each trial ranged from 135 to 1466.

- Eight [7,11,12,22,23,24,25,26] of the 10 trials were phase III RCTs, and the other 2 trials [13,21] were phase II trials.
- Four trials [21,22,23,24] compared gefitinib and docetaxel, 2 [11,12] compared erlotinib and docetaxel, 2 [13,25] compared gefitinib and pemetrexed, 1 [26] compared erlotinib and pemetrexed, and 1 [7] compared erlotinib and docetaxel/ pemetrexed.

Qualität der Studien:

- None of the 10 included trials were placebo-controlled double-blinded trials and therefore none of them scored Jadad score 4 or above.

Studienergebnisse:

PFS:

- no significant difference between an EGFR-TKI and second-line chemotherapy (n=10; HR, 1.03; 95%CI, 0.87–1.21; P =0.73, random-effect model, I2=78,7%, p<0,001)

OS

- no significant difference between an EGFR-TKI and second-line chemotherapy (n=8; HR, 1.00; 95%CI, 0.92–1.08; P= 0.90, fixed effect model, I2=0,0%, P=0,88).

Subgroup Analysis Based on EGFR Mutation Status

- EGFR M- (n=6):
  - The pooled HR for PFS showed that there was a significant improvement in PFS for second-line chemotherapy compared with EGFR-TKI therapy for EGFR M2 patients (HR, 1.35; 95%CI, 1.09–1.66; P= 0.01)
  - whereas the OS between them was not significantly different (HR, 0.96; 95%CI, 0.77–1.19; P= 0.69).
- EGFR M+ :
  - 3 studies for PFS and 2 studies for OS. Totally, the reported number of EGFR M+ patients was 150
  - PFS: a significant improvement in PFS for EGFR-TKI therapy compared with second-line chemotherapy (HR, 0.28; 95%CI, 0.15–0.53; P,0.001
  - OS: not significantly different (HR, 0.86; 95%CI, 0.44–1.68; P =0.65)

Toxicity

- Compared with chemotherapy, EGFRTKIs led to more grade 3–4 rash (OR, 7.55; 95%CI: 3.97–14.37; P,0.001).
- compared with chemotherapy, a statistically significant decrease in fatigue/asthenia disorder, leukopenia and thrombocytopenia was observed (OR, 0.45; 95%CI: 0.32–0.64; P,0.001; OR, 0.04; 95%CI: 0.01–0.10; P,0.001; OR, 0.25; 95%CI: 0.08–0.83; P= 0.02, respectively).
- With regard to the risk of grade 3–4 diarrhea, nausea, vomiting, and anemia, equivalent frequencies were found between the EGFR-TKI arm and the chemotherapy arm.

Anmerkung/Fazit der Autoren

In conclusion, based on this meta-analysis, treatment with chemotherapy can prolong PFS in EGFR M2 patients, whereas has no impact on OS. EGFR-TKIs seem superior over

chemotherapy as second-line therapy for EGFR M + patients. It is worthwhile to obtain information on EGFR mutational status before initiation of second-line treatment. These results, combined with the toxicities, should be taken into consideration in the second-line treatment.

Sun L et al., 2015 [77]. 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	**1. 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.
	2. 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 Suchzeitraum (Aktualität der Recherche): bis 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): Nine studies with 1,779 cases in the bevacizumab group and 1,768 cases in the control group were included in the metaanalysis → two second-line studies including 756 cases Qualitätsbewertung der Studien: Cochrane Collaboration tool
	3. Ergebnisdarstellung Qualität der Studien: Only two studies were high quality **Zweitlinie:** 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)
	4. **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.*
	1. Fragestellung

Xiao B et al., 2015 [81]. 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	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.
	2. Methodik Population 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 Suchzeitraum (Aktualität der Recherche): bis 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 7 Studien (N = 1,168 patients) Qualitätsbewertung der Studien: Jadad score
	3. Ergebnisdarstellung Qualität der Studien: Overall, six studies scored 3, one scored 5. • 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.
	4. **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.*
Yu S et al., 2016 [83]. Erlotinib-based	**1. 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).

targeted dual agent versus erlotinib alone in previously treated advanced non-small-cell lung cancer: a meta-analysis of 13 randomized controlled trials	**2. 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 Suchzeitraum (Aktualität der Recherche): bis 2016 Anzahl eingeschlossene Studien/Patienten (Gesamt): 13 trials comprising 8 phase II trials and 5 phase III trials met the inclusion criteria of this meta-analysis, and 4509 patients were included in the assessment. Qualitätsbewertung der Studien: Jadad scale
	3. Ergebnisdarstellung Qualität der Studien: The quality was high in all the studies (Jadad score >3). • 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).
	4. **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.* **5. Kommentar zum Review** • This study had limitations about heterogeneities among the included trials, and the analysis was not based on individual patient data.
Zhang TT et al., 2016 [84]. Dual inhibiting EGFR and VEGF	**1. 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

pathways versus EGFR-TKIs alone in the treatment of advanced non-small-cell lung cancer: a meta-analysis of randomized controlled trials	meta-analysis to assess the efficacy and safety of this regimen versus EGFRTKIs alone in those patients.

2. Methodik

Population: patients with pathologically confirmed NSCLC

Intervention/Komparator: comparing dual inhibition of VEGF and EGFR pathways versus EGFR-TKIs alone

Endpunkte: siehe Ergebnisse

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

Anzahl eingeschlossene Studien/Patienten (Gesamt): 4 Studien; davon ist eine Studie mit 154 eingeschlossenen Patienten relevant

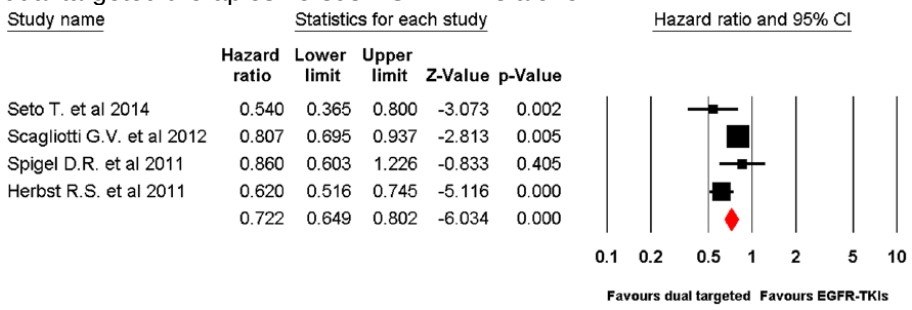
Qualitätsbewertung der Studien: Jadad scale

3. Ergebnisdarstellung

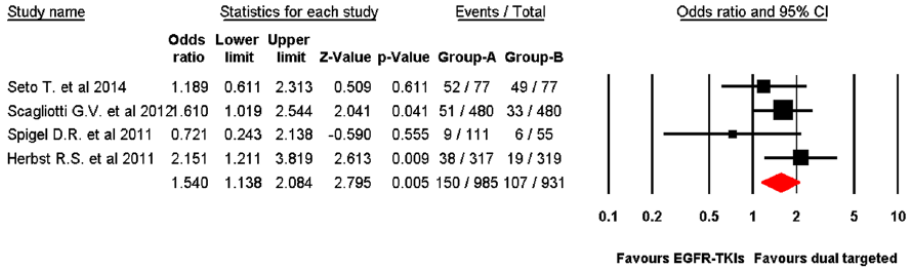
Study characteristics and critical appraisal

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	

Random-effects model of hazard ratio (95 % confidence interval) of PFS associated with dual targeted therapies versus EGFR-TKIs alone

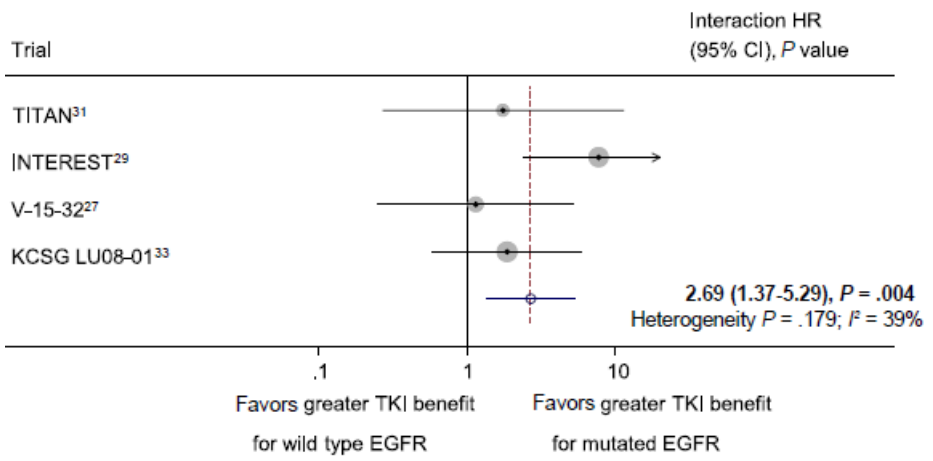


Fixed-effects model of odds ratio (95 % confidence interval) of ORR associated with dual targeted therapies versus EGFR-TKIs alone

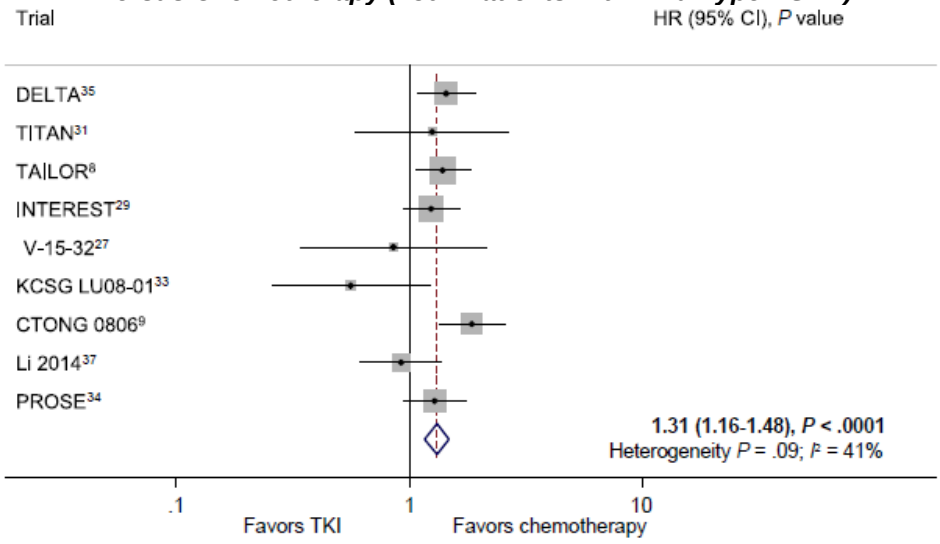


4. **Fazit der Autoren:** Our study suggests that dual inhibition of EGFR and VEGF pathways significantly improves PFS and ORR, but it does not translate into survival

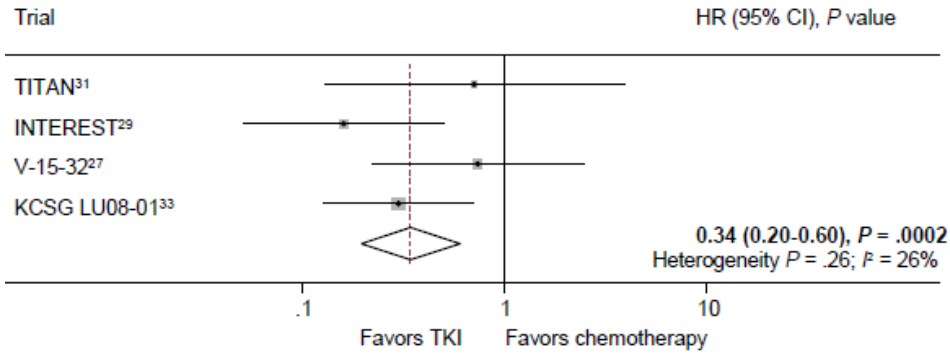
	benefit in unselected NSCLC patients. Prospective clinical trials investigating the role of this regimen in EGFR mutation-positive NSCLC are still warranted.
Vale CL et al., 2015 [78]. Should Tyrosine Kinase Inhibitors Be Considered for Advanced Non-Small-Cell Lung Cancer Patients with Wild Type EGFR? Two Systematic Reviews and Meta-Analyses of Randomized Trials	**1. Fragestellung** We assessed the effect of TKIs as second-line therapy and maintenance therapy after first-line chemotherapy in two systematic reviews and meta-analyses, focusing on patients without EGFR mutations.
	2. Methodik ***Population:*** advanced NSCLC irrespective of sex, age, histology, ethnicity, smoking history, or EGFR mutational status. Patients should not have received previous TKIs ***Interventionen und Komparatoren:*** TKI (erlotinib or gefitinib) vs. chemotherapy ***Endpunkte*:** PFS, OS ***Suchzeitraum:*** bis 2012 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** Second line: 14 (4388) Maintenance: 6 (2697) ***Qualitätsbewertung der Studien:*** The risk of bias of individual trials was assessed with a low risk of bias being desirable for sequence generation, allocation concealment, and completeness of outcome data reporting. Trials in the maintenance setting should have also been at low risk of bias for blinding. ***Heterogenitätsuntersuchungen:*** I^2
	3. Ergebnisdarstellung **Zweitlinienbehandlung** Trials compared TKIs with either docetaxel or pemetrexed chemotherapy and were conducted between 2003 and 2012. Six trials were carried out in predominantly Asian populations. Randomized patients had good performance status (0-2) and median age ranged from 54.5 to 67.5 years (range, 20-88 years). Most were men and either current or former smokers. One tria included considerably more women (85%) and only neversmokers. Three trials randomized patients with wild type EGFR exclusively. Five trials evaluated EGFR mutation status using a range of methods (including DAKO EGFR Pharma DX and Eppendorf Piezo-electric microdissector). Mutation status was not evaluated in 5 trials. Twelve trials (3963 patients, 90% of total) reported PFS and 14 trials (4355 patients, 99% of total) reported OS. One trial, published in Chinese language, was judged to be unclear for all domains. The remaining 13 trials were all at low risk of bias regarding incomplete outcome data. Missing data on EGFR mutational status largely resulted from unavailable tumor samples or because the trials were conducted before widespread testing. All were judged to be at low risk of bias for sequence generation. For allocation concealment, 10 trials were judged to be at low risk of bias and 3 were judged as unclear risk. No trials were judged to be at high risk for any of the domains assessed. **PFS** ***TKI vs. Chemotherapie***



TKI Versus Chemotherapy (1302 Patients with Wild Type EGFR)



TKI Versus Chemotherapy (113 Patients with Mutated EGFR)



OS

	Table 2 Results for Overall Survival

	Trial, n	Patient, n	Fixed Effect HR	Fixed Effect 95% CI	Fixed Effect P	Random Effect HR	Random Effect 95% CI	Random Effect P	Interaction HR[a] (95% CI) P	Interaction Heterogeneity, P
Second-Line Treatment										
EGFR wild type	9	1400	1.06	0.93-1.22	.37	1.06	0.93-1.20	.37	1.15 (0.60-2.18) .68	.37
EGFR mutations	4	97	0.90	0.49-1.64	.72	0.90	0.49-1.64	.72		
Maintenance Treatment										
EGFR wild type	3	707	0.85	0.72-1.02	.06	0.87	0.70-1.07	.70	1.40 (0.76-2.57) .28	.49
EGFR mutations	3	120	0.59	0.33-1.05	.07	0.59	0.33-1.05	.07		

Abbreviations: EGFR = epidermal growth factor receptor; HR = hazard ratio; TKI = tyrosine kinase inhibitor.
[a]Interaction HR > 1 shows greater TKI benefit for mutated EGFR.

4. Anmerkungen/Fazit der Autoren

For patients with wild type EGFR, TKIs seem to be an ineffective second-line treatment compared with chemotherapy, but might be effective as maintenance treatment, compared with no active treatment. In both settings, TKIs offer **PFS benefits** to patients with mutated EGFR.

- Results showed the effect of TKIs on progression-free survival (PFS) depended on EGFR status (interaction hazard ratio [HR], 2.69; P = .004). Chemotherapy benefited patients with wild type EGFR (HR, 1.31; P < .0001), TKIs benefited patients with mutations (HR, 0.34; P = .0002). Based on 12 trials (85% of randomized patients) the benefits of TKIs on PFS decreased with increasing proportions of patients with wild type EGFR (P = .014).
- Six trials of maintenance therapy (2697 patients) were included. Results showed that although the effect of TKIs on PFS depended on EGFR status (interaction HR= 3.58; P < .0001), all benefited from TKIs (wild type EGFR: HR, 0.82; P = .01; mutated EGFR: HR= 0.24; P < .0001).There was a suggestion that benefits of TKIs on PFS decreased with increasing proportions of patients with wild type EGFR (P = .11).

Zhao N et al., 2014 [85]. Efficacy of epidermal growth factor receptor inhibitors versus chemotherapy as second-line treatment in advanced non-small-cell lung cancer with wild-type EGFR: a meta-

1. Fragestellung

We sought to evaluate the effectiveness of EGFR-TKI as second-line treatment in EGFR wild-type NSCLC.

2. Methodik

Population: previously treated advanced NSCLC with wild-type EGFR
Intervention: EGFR TKIs
Komparator: chemotherapy
Endpunkte: progression-free survival (PFS), overall survival (OS), objective response rate (ORR)
Suchzeitraum: bis 07/ 2013
Anzahl eingeschlossene Studien/Patienten (Gesamt): 6/990 (5 phase III)
Qualitätsbewertung der Studien: Jadad scale
Heterogenitätsuntersuchungen: x^2-based Q test; p > 0,05 indicates low heterogeneity; p ≤ 0,05 reflects high heterogeneity, if significant random-effects model used, if not significant FEM used
„Publication bias“: tested by funnel plot

analysis of randomized controlled clinical trials

3. Ergebnisdarstellung

Characteristics of the randomized trials included in the meta-analysis.

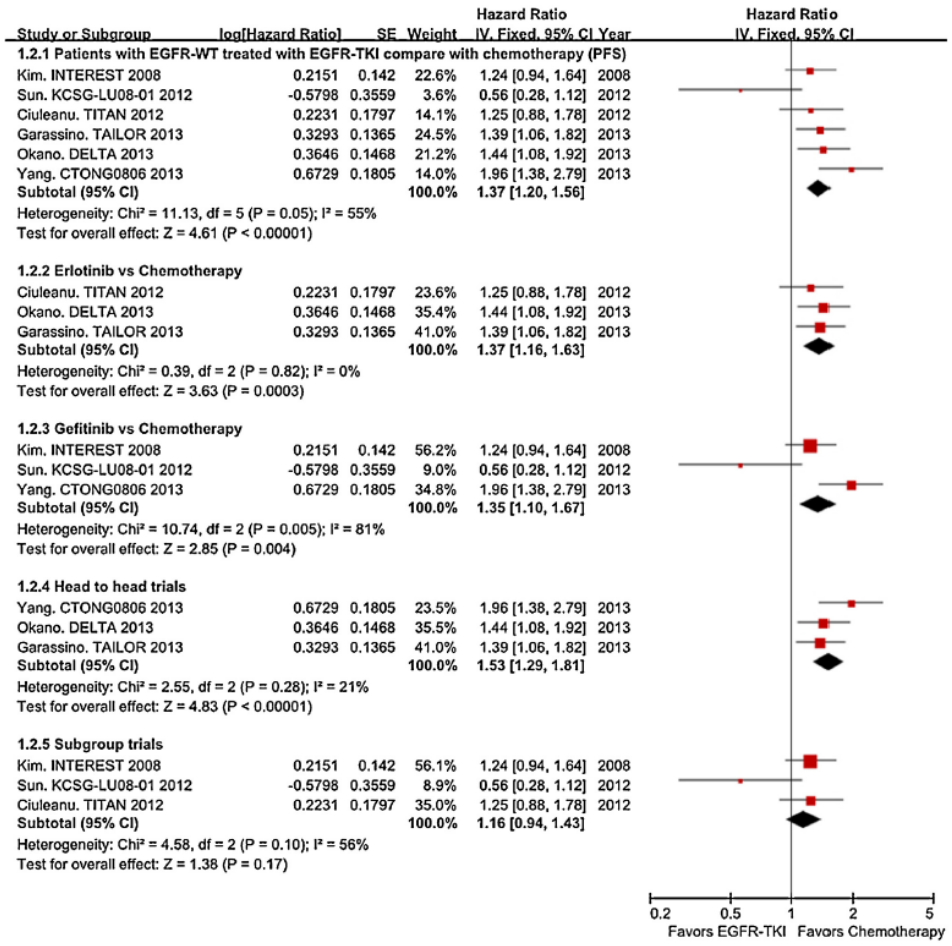
Author, study	Year	Experimental and control	Detection method	Primary endpoint	Method of assessment	EGFR-WT patients	PR/CR patients	ORR (%)	Median-PFS (Mon)	HR (95%CI, P)	Median-OS (Mon)	HR (95% CI, P)	Jadad score
Kim E.S. INTEREST [20] (Douillard J.Y. [25])	2008	Gefitinib Docetaxel	Direct sequencing	OS	Subgroup analysis	106 123	7 12	6.6 9.8	1.7 2.6	HR = 1.24 (0.94–1.64, P = 0.14)	6.4 6.0	HR = 1.02 (0.78–1.33, P = 0.91)	3
Ciuleanu T. TITAN [21]	2012	Erlotinib Doc/Pem	Direct sequencing	OS	Subgroup analysis	75 74	6 5	7.9 6.3	1.4 2.0	HR = 1.25 (0.88–1.78, P = 0.20)	6.6 4.4	HR = 0.85 (0.59–1.22, P = 0.37)	3
Sun J.M. KCSG-LU08-01 [22]	2012	Gefitinib Pemetrexed	Direct sequencing	PFS	Subgroup analysis	18 20	NA		5.9 2.7	HR = 0.56 (0.28–1.13, P = 0.099)	NA		3
Garassino M.C. TAILOR [18]	2013	Erlotinib Docetaxel	Sanger's sequencing and RFLP	OS	Head-to-head trial	110 109	3 15	3 15.5	2.4 2.9	HR = 0.72 (0.55–0.94, P = 0.01)	5.4 8.2	HR = 078 (0.51–1.05, P = 0.10)	3
Yang J.J. CTONG0806 [16]	2013	Gefitinib Pemetrexed	Direct sequencing	PFS	Head-to-head trial	81 76	11 10	14.7 13.3	1.6 4.8	HR = 0.51 (0.36–0.73, P < 0.001)	NA		3
Okano Y. DELTA [17]	2013	Erlotinib Docetaxel	NA	PFS	Head-to-head trial	109 89	6 17	5.6 20	1.3 2.9	HR = 1.44 (1.08–1.92, P = 0.013)	9.0 9.2	HR = 0.98 (0.69–1.39, P = 0.914)	3

Abbreviations: EGFR-WT, epidermal growth factor receptor wild type; Doc, docetaxel; Pem, pemetrexed; NA, not available.

PFS (EGFR-TKIs vs. chemotherapy)

- HR 1,37; 95 % KI 1,20 – 1,56; p < 0,00001 – in the second-/third-line treatment of EGFR wild-type NSCLC, PFS significantly inferior in EGFR-TKI group compared with chemotherapy group
- gefitinib and erlotinib significantly inferior to chemotherapy
- erlotinib vs. chemotherapy: HR 1,37; 95 % KI 1,16 – 1,63, p = 0,0003
- gefitinib vs. chemotherapy: HR 1,35; 95 % KI 1,10 – 1,67, p = 0,004
- head-to-head trials: results favored chemotherapy more obviously (HR 1,53; 95 % KI 1,29 – 1,81; p < 0.00001
- subgroup trials, which had only subgroup analyses for EGFR wild-type patients: PFS not significantly different (HR 1,16; 95 % KI 0,94 – 1,43; p = 0,17)

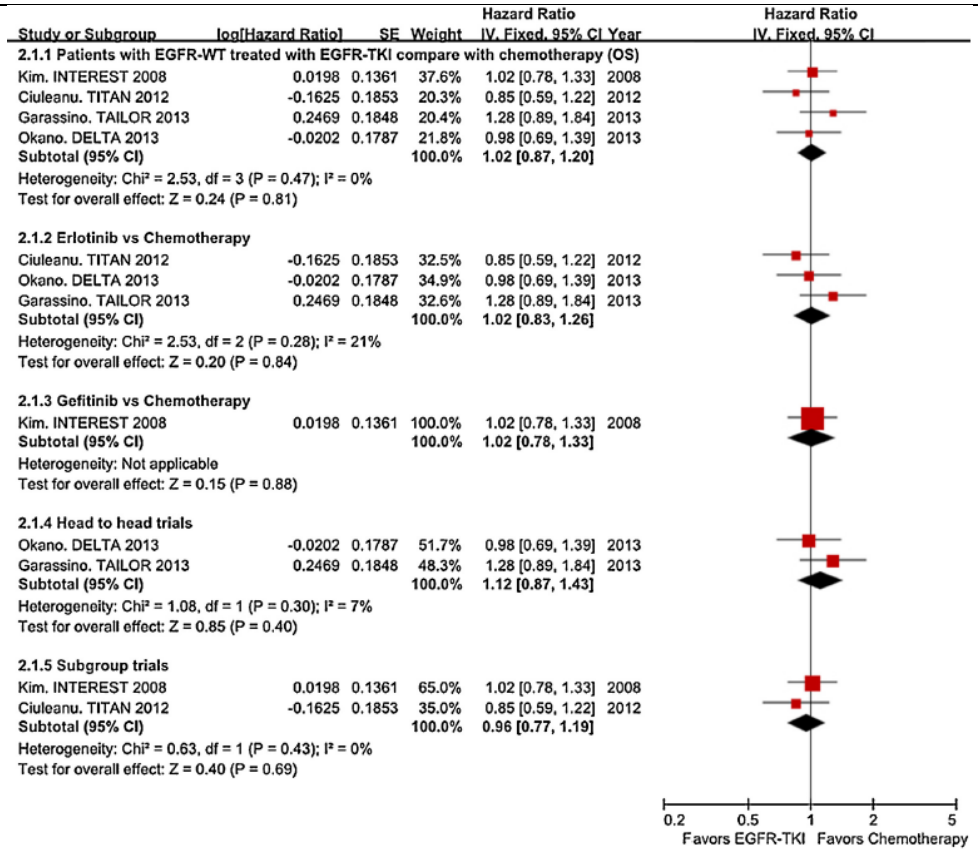
PFS bei EGFR wild type:



<u>OS and ORR</u>

- equal results

OS bei EGFR wild type:



4. Anmerkungen/Fazit der Autoren

Chemotherapy improves PFS significantly but not OS, compared with EGFR-TKIs as a second-line treatment in advanced NSCLC with wild-type EGFR. Whether EGFR-TKIs should be used in EGFR wild-type patients should be considered carefully.

5. Kommentare zum Review:

- study quality not further discussed
- eine Phase II Studie enthalten
- no evidence of publication bias
- authors declared no potential conflicts of interest
- work supported by Key Technologies R&D Programof Guangzhou (2011Y2-00014) and Key Laboratory Program ofGuangdong (2012A061400006) (Y.L. Wu)

Greenhalgh J et al., 2015 [34]. Erlotinib and gefitinib for treating non-small cell lung cancer that has progressed follow ing prior

1. Fragestellung

To appraise the clinical effediveness and co&-effediveness of erlotinib [Tarceva, Roche (UK) Ltd] and gefitinib (IRESSA®, AstraZeneca) compared with each other, docetaxel or best srupportive care (BSC) for the treatment of NOCLC after disease progression following prior chemotherapy. The effectiveness of treatment with gefitinib was considered only for patients with epidermal growth factor mutation-positive (EGFR M +) disease.

The remit of this appraisal is to review and update (if necessary) the dinical effectiveness and cost-effectiveness evidence base described in NICE TA 162 and NICE TA 175.

chemotherapy (review of NICE technology appraisals 162 and 175): a systematic review and economic evaluation	**2. Methodik** ***Population:*** Adults with locally advanced or metastatic NSCLC that has progressed following prior chemotherapy ***Interventionen und Komparatoren:*** Gefitinib oder Erlotinib Erlotinib and gefitinib to be oompared with each other and with: • docetaxel • best supportive care ***Endpunkte*:** PFS, OS, Response Rate, AE, HRQoL ***Suchzeitraum:*** bis 04 /2013 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** *12 / k.A.* davon: 7 Gefitinib vs. Chemotherapie oder BSC, 4 Erlotinib vs. Chemotherapie oder BSC, 1 Gefitinib vs. Erlotinib ***Qualitätsbewertung der Studien:*** Centre for Reviews and Dissemination at York University's suggested criteria ***Heterogenitätsuntersuchungen:*** Funding: The National Institute for Health Feseach Health Tedlnology Assesrnent programme
	3. Ergebnisdarstellung

TABLE 8 Summary of included trials

Trial	Design	Intervention	Comparator	Patient population (EGFR M+, EGFR M– or EGFR unknown)	Retrospective EGFR subgroup data available
Gefitinib vs. erlotinib					
Kim et al.[32]	Open-label, non-comparative randomised Phase II trial	Gefitinib	Erlotinib	EGFR M+ and two out of three factors associated with EGFR mutations	Yes
Gefitinib vs. docetaxel					
Bhatnagar et al.[33]	RCT	Gefitinib	Docetaxel	EGFR unknown	No
INTEREST[34]	Open-label Phase III RCT	Gefitinib	Docetaxel	EGFR unknown	Yes
ISTANA[35]	Open-label Phase III RCT	Gefitinib	Docetaxel	EGFR unknown	No
Li et al.[36]	RCT	Gefitinib	Docetaxel	EGFR unknown	No
SIGN[37]	Open-label Phase II RCT	Gefitinib	Docetaxel	EGFR unknown	No
V-15-32[38]	Open-label Phase III RCT	Gefitinib	Docetaxel	EGFR unknown	Yes
Gefitinib vs. placebo					
ISEL[39]	Placebo-controlled Phase III RCT	Gefitinib + BSC	Placebo + BSC	EGFR unknown	Yes
Erlotinib vs. docetaxel					
DELTA[40]	Open-label Phase III RCT	Erlotinib	Docetaxel	EGFR M+ and EGFR M–	Yes
TAILOR[41]	Open-label Phase III RCT	Erlotinib	Docetaxel	EGFR M– only	Yes
Erlotinib vs. docetaxel/pemetrexed					
TITAN[42]	Open-label Phase III RCT	Erlotinib	Docetaxel or pemetrexed	EGFR unknown	Yes
Erlotinib vs. placebo					
BR.21[31]	Placebo-controlled Phase III RCT	Erlotinib	Placebo	EGFR unknown	Yes

DELTA, Docetaxel and Erlotinib Lung Cancer Trial; INTEREST, IRESSA NSCLC Trial Evaluating REsponse and Survival versus Taxotere; ISTANA, IRESSA as Second-line Therapy in Advanced NSCLC – KoreA; ISEL, IRESSA Survival Evaluation in Lung cancer; SIGN, Second-line Indication of Gefitinib in NSCLC; TAILOR, TArceva Italian Lung Optimization tRial; TITAN, Tarceva In Treatment of Advanced NSCLC.

Epidermal growth factor mutation positive: No trials were identified that were conducted in a population of oolely EGFR M + patients.

Trial	Type of trial	Intervention	Comparator	Number patients	Location	Median follow-up	Trial support	Treatment crossover
Gefitinib vs. erlotinib								
Kim et al. 2012[32]	Open-label, non-comparative randomised Phase II	Gefitinib 250 mg daily	Erlotinib 150 mg daily	N = 96; gefitinib, n = 48; erlotinib n = 48	South Korea	16.3 months	IN-SUMG Foundation for Medical Research	At the discretion of each physician
Gefitinib vs. docetaxel								
*Bhatnagar et al. 2012[33]	RCT	Gefitinib 250 mg daily	Docetaxel 75 mg/m² every 3 weeks	N = 30	India	2 years	NS	NS
INTEREST 2008[34]	Open-label Phase III non-inferiority RCT	Gefitinib 250 mg daily	Docetaxel 75 mg/m² every 3 weeks	N = 1466; gefitinib, n = 733; docetaxel, n = 733	Europe, Asia and the Americas	7.6 months	AstraZeneca	Gefitinib arm: n = 28 (4%) EGFR-TKI; n = 225 (31%) docetaxel; n = 112 (15%) other chemotherapy Docetaxel arm: n = 4 (1%) docetaxel; n = 268 (37%) EGFR-TKI; n = 74 (10%) other chemotherapy
ISTANA 2010[35]	Open-label Phase III RCT	Gefitinib 250 mg daily	Docetaxel 75 mg/m² every 3 weeks	N = 161; gefitinib, n = 82; docetaxel, n = 79	Korea	13 months	AstraZeneca	Gefitinib arm: 24.7% received no further systemic chemotherapy apart from further EGFR-TKIs (2.5% gefitinib/erlotinib), 22.2% received no treatment, 29.6% received docetaxel and 44.4% received other chemotherapy Docetaxel arm: 67.1% received an EGFR-TKI and 6.6% received other chemotherapy
Li et al. 2010[36]	RCT	Gefitinib 250 mg daily	Docetaxel 75 mg/m² every 3 weeks	N = 98; gefitinib, n = 50; docetaxel, n = 48	People's Republic of China	NS	NS	NS

Trial	Type of trial	Intervention	Comparator	Number patients	Location	Median follow-up	Trial support	Treatment crossover
SIGN 2006[37]	Open-label Phase II RCT	Gefitinib 250 mg daily	Docetaxel 75 mg/m² every 3 weeks	N = 141; gefitinib, n = 68; docetaxel, n = 73	Europe, South America and the Middle East	9.2 months (gefitinib), 9.4 months (docetaxel)	AstraZeneca	NS
V-15-32 2008[38]	Open-label Phase III non-inferiority RCT	Gefitinib 250 mg daily	Docetaxel 60 mg/m² every 3 weeks	N = 490; gefitinib, n = 245; docetaxel, n = 244[b]	Japan	21 months	AstraZeneca	Crossover was greater than initially expected, and differences in the number and types of patients who received these post-study treatments complicated interpretation of survival results
Gefitinib vs. placebo								
ISEL 2005[39]	Placebo-controlled double-blind Phase III RCT	Gefitinib 250 mg daily	Placebo + BSC	N = 1692; gefitinib, n = 1129; placebo, n = 563	Europe, Asia, Central and South America, Australia and Canada	7.2 months	AstraZeneca	Placebo arm: 3% received gefitinib. All subsequent treatments for NSCLC were well balanced between the treatment groups. The protocol allowed for up to 15% crossover to gefitinib
Erlotinib vs. docetaxel								
*DELTA 2013[40]	Open-label Phase III RCT	Erlotinib 150 mg daily	Docetaxel 60 mg/m² every 3 weeks	N = 301; erlotinib, n = 150; docetaxel, n = 151	Japan	NS	Japanese National Hospital Organization	NS
TAILOR 2013[41]	Open-label Phase III RCT	Erlotinib 150 mg daily	Docetaxel 75 mg/m²	N = 222; erlotinib, n = 112; docetaxel, n = 110	Italy	33 months	Italian Agency for Drug Administration	No crossover allowed Erlotinib arm: seven participants crossed over Docetaxel arm: four participants crossed over. Third-line treatment with pemetrexed/GEM/VIN

Trial	Type of trial	Intervention	Comparator	Number patients	Location	Median follow-up	Trial support	Treatment crossover
Erlotinib vs. docetaxel/pemetrexed								
TITAN 2012[42]	Open-label Phase III RCT	Erlotinib 150 mg daily	Docetaxel or pemetrexed dosing at discretion of the investigator	N = 424; erlotinib, n = 203; chemotherapy, n = 221	International	Erlotinib: 27.9 months, docetaxel/ pemetrexed: 24.8 months	Hoffmann F–La Roche, Basel, Switzerland	Erlotinib arm: 25% antimetabolites, 23% docetaxel or PAX Chemotherapy arm: 12% antimetabolites, 23% TKIs, 5% switch to docetaxel, 7% switch to pemetrexed
Erlotinib vs. placebo								
BR.21 2005[31]	Placebo-controlled Phase III RCT	Erlotinib 150 mg daily	Placebo	N = 731; erlotinib, n = 488; placebo, n = 243	International	NS	Supported in part by a grant from OSI Pharmaceuticals	Erlotinib arm: 8 (1.6%) Placebo arm: 18 (7.4%) received other EGFR inhibitors after study medication discontinued

GEM, gemcitabine; NS, not stated; PAX, paclitaxel; VIN, vinorelbine.
a Abstract only.
b One person was excluded from the docetaxel group after randomisation for a good clinical practice violation.

Summary of clinical results

Epidermal growth factor mutation-positive population

- No trials were identified that were conducted in a population of solely EGFR M+ patients. Limited EGFR mutation status data were retrospectively derived from relatively small subgroup analyses of RCTs that included patients of unknown EGFR mutation status at the time of randomisation.
- Four studies reported OS outcomes,[31,34,39,42] none of which was statistically significantly different for any of the comparisons described.
- Five studies reported PFS,[31,32,34,39,42] but only one trial[36] found a statistically significant improvement for any comparison considered, and the results favoured gefitinib over docetaxel.

Epidermal growth factor mutation-negative population

- Key data were derived from results of TAILOR[41] and DELTA[40] trials.
- EGFR mutation status data were retrospectively derived from subgroup analyses in BR.21,[31,43] Kim et al.,[32] TITAN,[42] INTEREST,[34,45] and ISEL.[39,44]
- OS outcome: no statistically significant differences were noted for OS for either erlotinib or gefitinib compared with any treatment.
- PFS outcome: TAILOR[41] and DELTA[40] reported a statistically significant benefit of docetaxel compared with erlotinib. No statistically significant PFS benefit was reported from subgroup data.
- RR: patients in the docetaxel arm of TAILOR[41] had statistically significantly higher RRs than patients in the erlotinib arm.

Epidermal growth factor mutation unknown: overall population

- Data were available from 11 trials[31–41] carried out in populations in which EGFR mutation status was not a factor in the recruitment process (or in which overall trial results were presented).
- OS outcome: the only statistically significant OS benefit for any treatment was reported in BR.21[31] (erlotinib vs. placebo). However, this finding was based on an adjusted rather than an unadjusted analysis of the data.

	l PFS outcome: ¢ Gefitinib versus docetaxel – only one of the four trials (ISTANA[35]) reported a statistically significant benefit of gefitinib. ¢ Gefitinib versus BSC – gefitinib was reported to have a statistically significant benefit.[39] ¢ Erlotinib versus placebo (BR.21[31]) – a statistically significant PFS benefit of erlotinib was reported (in an adjusted analysis). l RR of the trials reporting RRs,[31,32,34–39,41] two noted significant differences in favour of gefitinib when compared with docetaxel[38] and BSC.[39] Meta-analysis and network meta-analysis For clinical and methodological reasons, no meta-analysis or network meta-analysis was conducted by the AG. Quality of life Where reported, the QoL data were derived from the EGFR unknown patients (overall population, i.e. the data are not specific to the EGFR mutation status of patients). All of the 12 trials included in this review measured QoL. However, the QoL outcomes from TAILOR[41] and DELTA[40] are not yet available. Adverse events Adverse events were reported for the overall population, that is the data are not specific to the EGFR mutation status of patients, with the exception of TAILOR[41] Details of the AEs reported in Bhatnagar et al.,[33] Li et al.[36] and DELTA[40] were limited. The AG considers that the AEs reported, despite inconsistencies across trials, appear to be consistent with the information available for erlotinib, gefitinib and docetaxel in the SPCs.[24]
	4. Fazit der Autoren **Conclusions** Implications for service provision The largest group of patients to whom the results of this appraisal apply is the EGFR M- patient population. The results of the AG's cos-effectiveness analy9s comparing erlotinib with docetaxel in patients whose disease has progresed favour the use of docetaxel. Switching from an oral therapy (erlotinib) to an intravenous therapy (docetaxel) would have substantial implications for service provision for both patients and staff in the UK NHS Suggested research priorities: It is suggested that any future trials in this area should distinguish between patients who have EGFR M + and EGFR M- disease. To date, the evidence base supporting the use of post-progression treatments following prior chemotherapy for patients with activating EGFR mutations is weak and is not sufficiatly robust to inform decision-making. **5. Kommentar zum Review** Keine quantitative Zusammenfassung der Ergebnisse
He X, 2015 [36]. Efficacy and safety of docetaxel for advanced non-small-cell lung	**1. Fragestellung** Several clinical trials have performed risk–benefit analyses comparing docetaxel and pemetrexed or docetaxel and vinca alkaloid, but the efficacy and safety remain uncertain. The aim was 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.
	2. Methodik

cancer: a meta-analysis of Phase III randomized controlled trials	***Population:*** advanced NSCLC **Intervention:** docetaxel ***Komparator:*** pemetrexed or vinca alkaloid ***Endpunkte:*** overall response rate (ORR), median survival time, progression-free survival (PFS), disease control rate, and toxicities ***Suchzeitraum:*** bis 01/ 2015 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 7 / 2080 (RCT, phase III) ***Qualitätsbewertung der Studien:*** Jadad scoring system ***Heterogenitätsuntersuchungen:*** chi-square test and expressed by the I^2 index

3. Ergebnisdarstellung

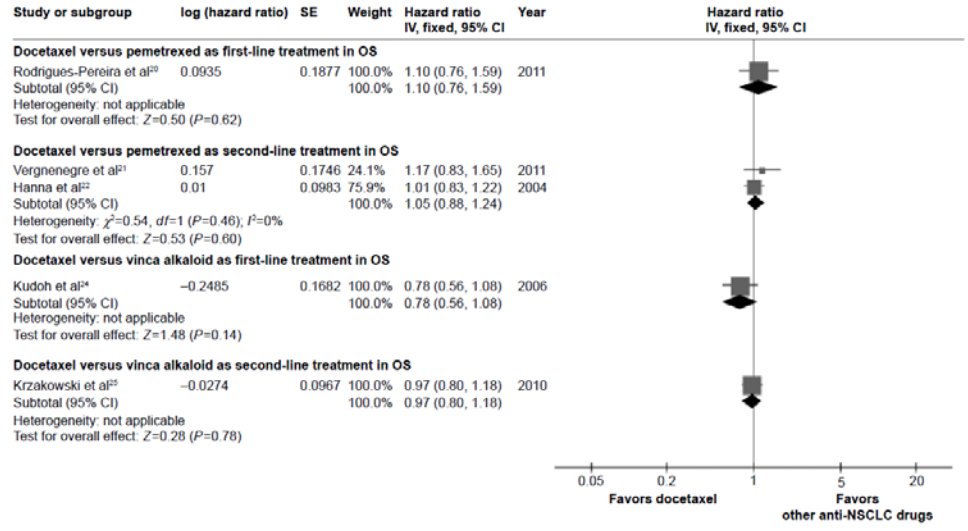
The Jadad score was used to assess the quality of the included trials. Overall, two trials scored 4, while the others scored 3.

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

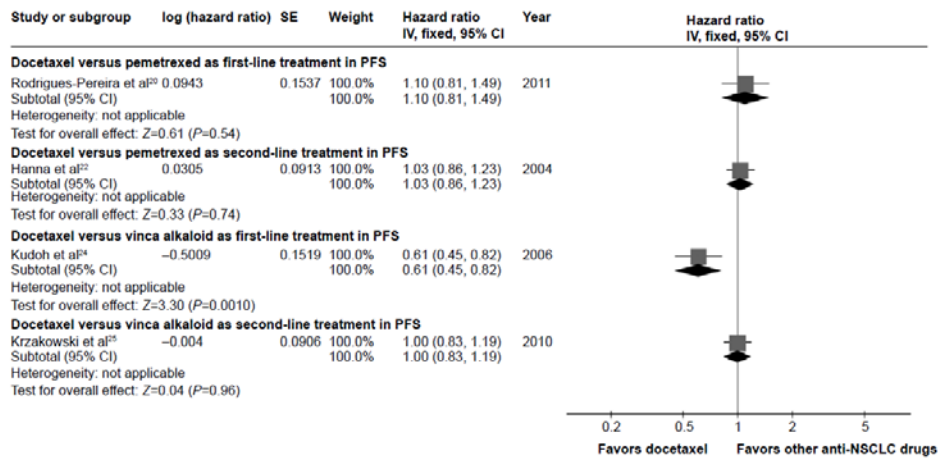
Study	Study region	Intervention	Number	Median age (years)	Male (%)	Stage	Outcome	Jadad score
Rodrigues-Pereira et al[20]	Argentina	Doc (75 mg/m²) + Carb	105	58.9	47.6	Stage IIIB/IV	SWT, OS, PFS	3
		Pem (500 mg/m²) + Carb	106	60.1	60.4			
Karampeazis et al[23]	Greece	Doc (38 mg/m²)	66	75.5	92.4	Stage 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.

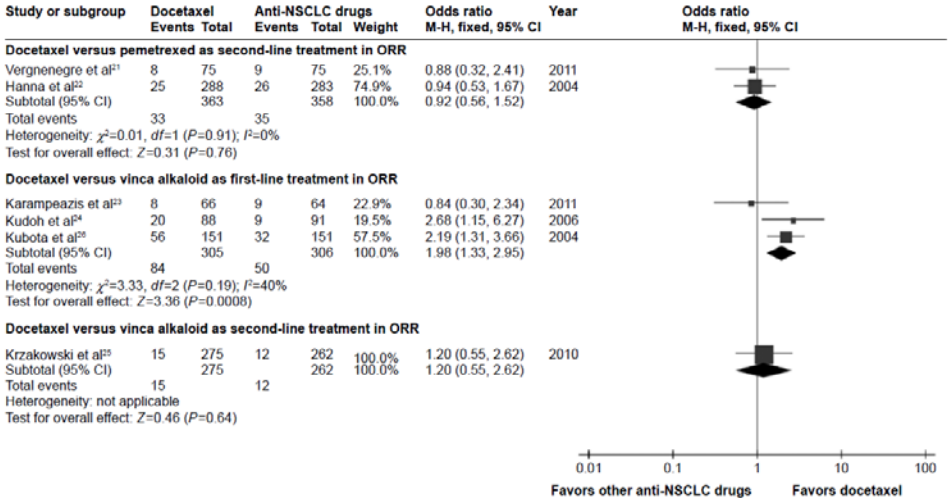
OS



PFS



ORR



AE

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

Abbreviations: CI, confidence interval; OR, odds ratio.

4. 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.

Xu JL et al, 2015 [82]. Chemotherapy	**1. 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

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

currently available evidence and compare the efficacy and safety of chemotherapy plus erlotinib versus chemotherapy alone for treating advanced NSCLC.

2. Methodik

Population: patients with NSCLC, keine Erhaltungstherapie
Intervention: erlotinib plus standard chemotherapy
Komparator: standard chemotherapy alone
Endpunkte: OS, PFS
Suchzeitraum: bis 10 / 2014
Anzahl eingeschlossene Studien/Patienten (Gesamt): *9 / 3599 (RCT)*
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.
Heterogenitätsuntersuchungen: I^2 statistic
„Publication bias“: subjective funnel plots and objective Begg's and Egger's tests

3. Ergebnisdarstellung

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

doi:10.1371/journal.pone.0131278.t001

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. No significant publication bias was detected for any of the measured outcomes by funnel plots.

PFS

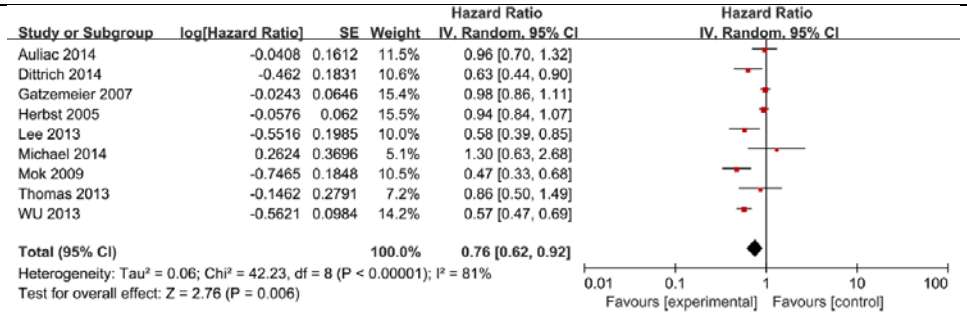


Fig 2. Forest Plot of Meta-analysis for PFS.

OS

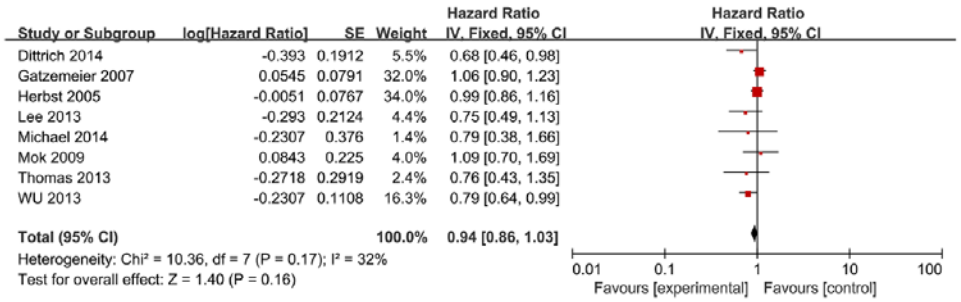


Fig 4. Forest Plot of Meta-analysis for OS.

Adverse events

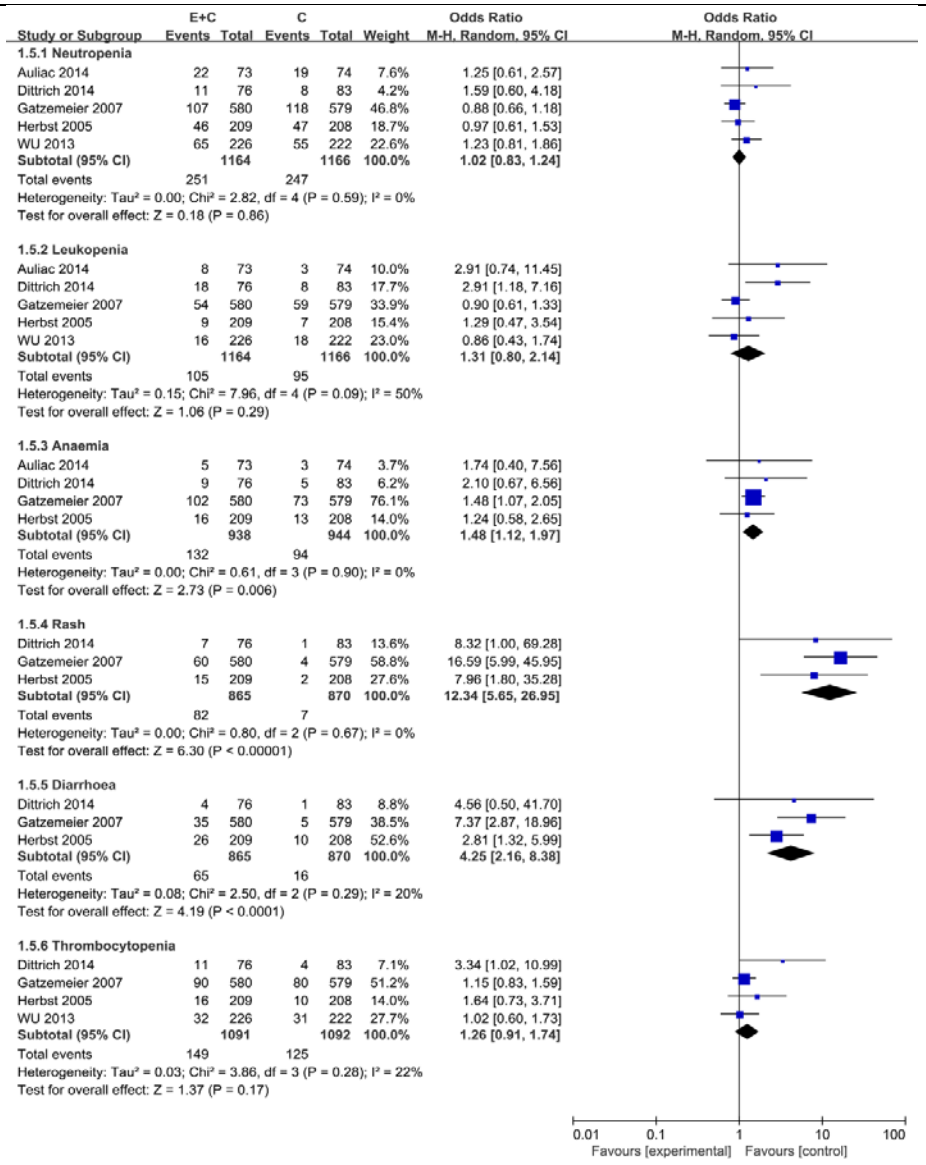
Data for the grade 3 or 4 adverse events were available in five studies [9–11, 15, 16]. There were more incidences of grade 3 or 4 anemia (OR = 1.48 [95% CI 1.12, 1.97], P = 0.006), rash Fig 2. Forest Plot of Meta-analysis for PFS.

Chemotherapy plus Erlotinib for Advanced Non Small Cell Lung Cancer (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 (OR = 1.02 [95% CI 0.83, 1.24]], P = 0.86), leucopoenia (OR = 1.31 [95% CI 0.80, 2.14], P = 0.29), or thrombocytopenia (OR = 1.26 [95% CI 0.91, 1.74], P = 0.17). Forest plots are shown in S1 Fig. The complete results are presented in S1 Table.

CTCAE Grade 3/4 Toxicity	Trials	E+Chem	Chem	OR[95%CI]	*P* value	Heterogeneity I^2	
						P value	I^2
Neutropenia	5	251/1164	247/1166	1.02 [0.83, 1.24]	0.86	0.59	0%
Anaemia	4	132/938	94/944	1.48 [1.12, 1.97]	0.006	0.90	0%
Leucopaenia	5	105/1164	95/1166	1.31 [0.80, 2.14]	0.29	0.09	50%
Rash	3	82/865	7/870	12.34 [5.65, 26.95]	<0.00001	0.67	0%
Diarrhoea	3	65/865	16/870	4.25 [2.16, 8.38]	<0.0001	0.29	20%
Thrombocytopenia	4	149/1091	125/1092	1.26 [0.91, 1.74]	0.17	0.28	22%

Abbreviations: CTCAE = common terminology criteria for adverse events, AE = Adverse event, E: Erlotinib, Chem: Chemotherapy

S1 Table. Comparison of Grade 3/4 AEs between Erlotinib plus Chemotherapy and Chemotherapy Alone



4. **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.
Zhong A et al., 2015 [86]. 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	**1. 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.
	2. Methodik ***Population:*** patients diagnosed pathologically with NSCLC and treated previously **Intervention:** single-agent pemetrexed ***Komparator:*** *pemetrexed-based doublet* ***Endpunkte:*** progression-free survival (PFS), overall survival (OS), objective response rate (ORR) ***Suchzeitraum:*** bis 03/ 2015 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 10/ 2519 (randomized Phase II and III RCTs) ***Qualitätsbewertung der Studien:*** Cochrane Collaboration's tool for assessing risk of bias; Jadad Score ***Heterogenitätsuntersuchungen:*** Interstudy heterogeneity was assessed using Cochran's test (P,0.1). The I2 statistic was also calculated, and an I2.50% indicated significant heterogeneity across studies ***„Publication bias":*** subjective funnel plots and objective Begg's and Egger's tests
	3. Ergebnisdarstellung

Table 1 Baseline characteristics of the included studies

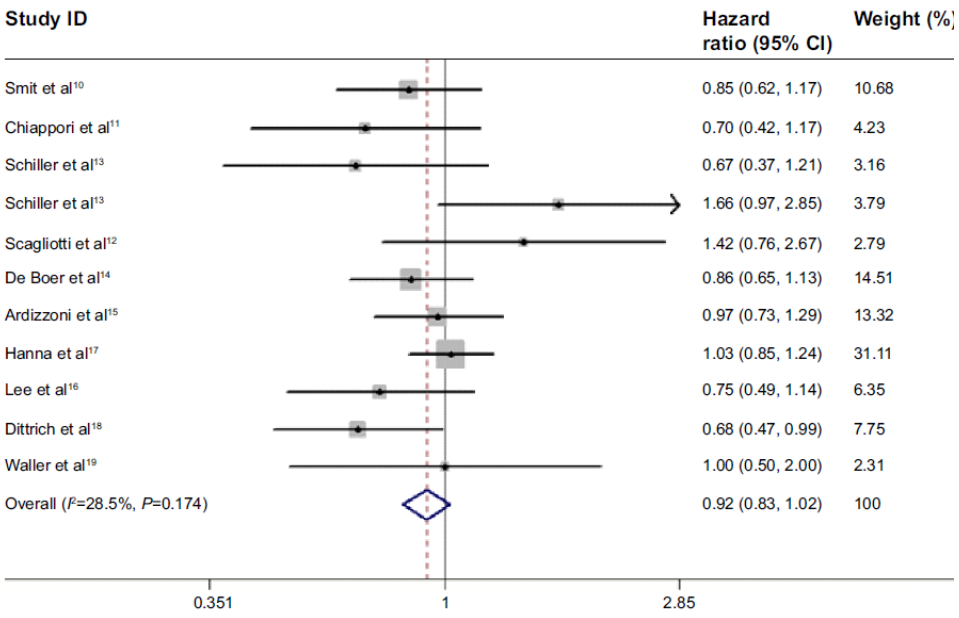
Authors	Phase	Regimes	No of patients analyzed	Patients per arm	Median age	Male (%)	Smoker (%)	Squamous histology (%)	ECOG PS 0 (%)	Jadad score
Smit et al[10]	Phase II	Pemetrexed plus carboplatin	240	119	59	62	NR	24	29	3
		Pemetrexed		121	59	64	NR	26	31	
Chiappori et al[11]	Phase II	Pemetrexed plus enzastaurin	160	80	62.1	67.5	85.9	34	NR	5
		Pemetrexed plus placebo		80	60.7	67.5	85.9	23	NR	
Scagliotti et al[12]	Phase II	Pemetrexed plus bortezomib	90	45	60	65	79	44	25	3
		Pemetrexed		45	58	71	88	39	20	
Schiller et al[13]	Phase II	Pemetrexed plus matuzumab (800 mg/wk)	148	51	62	69	NR	22	NR	3
		Pemetrexed plus matuzumab (1,600 mg/3 wk)		47	63	57	NR	36	NR	
		Pemetrexed		50	61	66	NR	36	NR	
De Boer et al[14]	Phase III	Pemetrexed plus vandetanib	534	256	60	62	78	21	41	5
		Pemetrexed plus placebo		278	60	62	81	22	41	
Ardizzoni et al[15]	Phase II	Pemetrexed plus carboplatin	239	119	64	72.3	NR	14.3	58	4
		Pemetrexed		120	64	75.8	NR	10	63.3	
Lee et al[16]	Phase II	Pemetrexed plus erlotinib	156	76	55.8	25.6	0	0	NR	4
		Pemetrexed		80	55.9	43.8	0	0	NR	
Hanna et al[17]	Phase III	Pemetrexed plus nintedanib	683	353	59	45	NR	0	NR	2
		Pemetrexed plus placebo		330	59	42	NR	0	NR	
Dittrich et al[18]	Phase II	Pemetrexed plus erlotinib	159	76	64	60.5	86.8	0	44	5
		Pemetrexed		83	61	59	83.1	0	39.8	
Waller et al[19]	Phase II	Pemetrexed plus eribulin	80	41	59	61	NR	NR	24	3
		Pemetrexed		39	60	67	NR	NR	8	

Abbreviations: ECOG PS 0, Eastern Cooperative Oncology Group performance status (normal activity); NR, no report; wk, week.

OS and PFS

The pooled HR for OS revealed that there were no significant differences between pemetrexed-based doublet therapy and pemetrexed alone (HR, 0.92; 95% CI, 0.83–1.02; *P*=0.137). In addition, no significant interstudy heterogeneity was found (*I*2=28.5%, *P*=0.174; Figure 2). 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 (*I*2=47.5%, *P*=0.039; Figure 3).



igure 2 Forest plot of overall survival in patients treated with pemetrexed-based doublet therapy and pemetrexed alone.
bbreviation: CI, confidence interval.

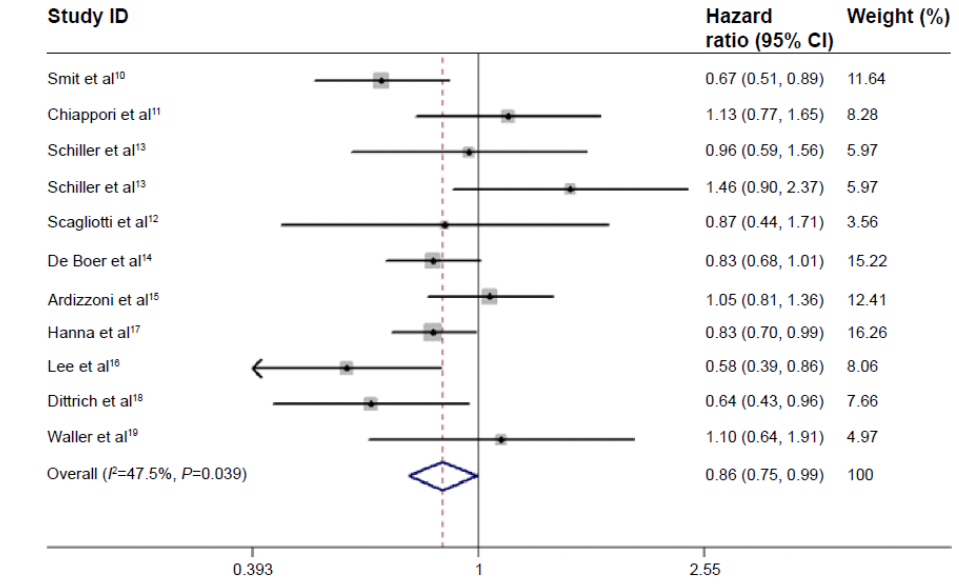


Figure 3 Forest plot of progression-free survival in patients treated with pemetrexed-based doublet therapy and pemetrexed alone.
Note: Weights are from random effects analysis.
Abbreviation: CI, confidence interval.

ORR

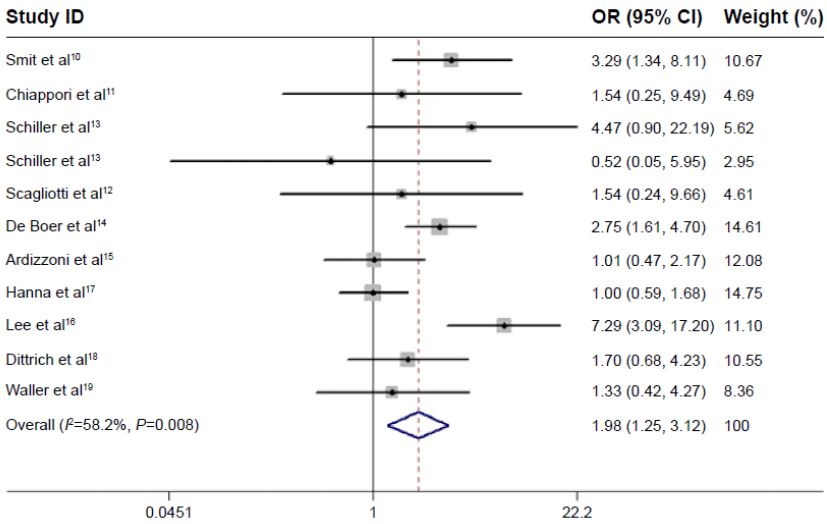


Figure 4 Forest plot of objective response rate in patients treated with pemetrexed-based doublet therapy and pemetrexed alone.
Note: Weights are from random effects analysis.
Abbreviations: OR, odds ratio; CI, confidence interval.

UE

Table 3 Outcome of grade 3 or 4 toxicities in a meta-analysis comparing pemetrexed-based doublet therapy with pemetrexed alone

Toxicity	Trials	Pemetrexed-based doublet therapy	Pemetrexed alone therapy	Heterogeneity		OR (95% CI)	*P*-value
				P	I^2		
Grade 3–4 anemia	7	43/719	52/737	0.076	47.5	0.85 (0.56–1.28)	0.43
Grade 3–4 neutropenia	8	122/528	61/547	0.56	0	2.01 (1.45–2.78)	0.00
Grade 3–4 thrombocytopenia	6	57/479	16/476	0.44	0	3.77 (2.16–6.59)	0.00
Grade 3–4 fatigue	7	55/706	54/677	0.59	0	1.04 (0.70–1.55)	0.59
Grade 3–4 leukopenia	7	65/536	41/515	0.125	38.3	1.66 (0.90–3.05)	0.10

Abbreviations: OR, odds ratio; CI, confidence interval.

Subgruppen

Table 2 Pooled and subgroup analysis of OS and PFS

Subgroup	Number of trials	OS, HR (95% CI)	PFS, HR (95% CI)
All	10	0.92 (0.83–1.02)	**0.86 (0.75–0.99)**
Phase			
II	8	0.89 (0.74–1.07)	0.89 (0.72–1.09)
III	2	0.97 (0.83–1.14)	**0.83 (0.73–0.95)**
Combined agent			
Erlotinib[a]	2	**0.71 (0.54–0.94)**	**0.61 (0.46–0.81)**
Target drug	8	0.93 (0.82–1.05)	**0.85 (0.77–0.94)**
Carboplatin	2	0.92 (0.74–1.13)	0.84 (0.54–1.31)
Histology			
Squamous	3	0.62 (0.31–1.21)	0.94 (0.64–1.40)
Nonsquamous	6	0.98 (0.94–1.02)	**0.80 (0.71–0.91)**

Notes: [a]Patients all had a nonsquamous histology. The figures in bold indicate the pooled HR was significantly different between pemetrexed-based doublet therapy and pemetrexed alone.
Abbreviations: OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

Kein Publikationsbias identifiziert

4. **Fazit:** *A total of 2,519 patients from ten randomized controlled trials were included. Compared to pemetrexed alone, PFS and ORR significantly improved in the pemetrexed-based doublet group (HR, 0.86; 95% CI [confidence interval], 0.75–0.99; P=0.038; and OR, 1.98; 95% CI, 1.25–3.12; P=0.003, respectively). However, no statistically significant differences in OS were observed between groups (HR, 0.92; 95% CI, 0.83–1.02; P=0.132). In addition, subgroup analyses indicated that improved OS was only observed in nonsquamous NSCLC patients who received the combination of pemetrexed and erlotinib. An increasing incidence of grade $3 neutropenia and thrombocytopenia was observed in the pemetrexed-based doublet group. Among patients with advanced NSCLC, pemetrexed-based doublet treatment tended to be associated with improved PFS, ORR, and increased toxicity, but not OS.*

Sheng J et al., 2015 [69]. 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	**1. 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.
	2. 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 leat reported→ PFS, OS, ORR and DCR Suchzeitraum (Aktualität der Recherche): In October 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 13 phase II/III RCTs which involved a total of 8358 participants were included. Qualitätsbewertung der Studien: The data collection and assessment of methodological quality followed the QUORUM and the Cochrane Collaboration guidelines. I^2 for heterogenity
	3. Ergebnisdarstellung 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. • 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).
	4. 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.* **5. Kommentar 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.
Qi WX et al., 2015 [66]. Anti-epidermal-growth-factor-receptor agents and complete responses in the treatment of advanced non-small-cell lung cancer: a meta-analysis of 17 phase III randomized controlled trials	**1. Fragestellung** We meta-analyze the incidence of complete response (CR) in advanced NSCLC patients treated with anti-EGFR agents and controls in randomized controlled trials (RCTs)..
	2. Methodik ***Population:*** advanced NSCLC ***Interventionen und Komparatoren:*** anti-EGFR agents (erlotinib, gefitinib, and cetuximab) vs. other treatments (k.A.; siehe Ergebnisteil) ***Endpunkte*:** CR ***Suchzeitraum:*** bis 2013 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 25 (4467); RCT ***Qualitätsbewertung der Studien:*** Jadad Score ***Heterogenitätsuntersuchungen:*** Chi-Quadrat, I^2
	3 Ergebnisdarstellung Qualität der Studien: Jadad's score was three for nine studies and five for eight studies Table 2. Incidence and odds ratio of CR with anti-EGFR agents based on prespecified subgroups.

Groups	Studies, *n*	No. of CR/total patients, *n*		Incidence of CR, % (95% CI)		OR (95% CI)	*p* Value	*P* value for group difference
		EGFR-targeted agents	Control	EGFR-targeted agents	Control			
Overall	17	66/6803	18/5365	1.1 (0.7–1.7)	0.6 (0.4–0.9)	2.12 (1.28–3.49)	0.003	NA
Anti-EGFR agents								
Gefitinib	6	40/3227	9/2031	1.9 (1.4–2.6)	0.7 (0.4–1.3)	2.18 (1.07–4.47)	0.033	0.32
Erlotinib	9	17/2694	2/2446	0.9 (0.6–1.5)	0.3 (0.1–0.6)	4.09 (1.38–12.14)	0.011	
Cetuximab	2	9/882	7/888	1.4 (0.8–2.7)	0.9 (0.4–1.8)	1.33 (0.49–3.57)	0.58	
Treatment line								
First line	12	58/4432	17/3678	1.5 (1.0–2.3)	0.7 (0.5–1.1)	2.11 (1.22–3.63)	0.007	0.65
Second line	5	8/2371	1/1687	0.5 (0.3–0.9)	0.2 (0.1–0.6)	3.06 (0.65–14.36)	0.15	
Rate of female in arms[a]								
<50%	11	52/5558	16/4126	0.9 (0.6–1.6)	0.6 (0.4–1.0)	1.97 (1.12–3.45)	0.019	0.45
≥50%	5	14/1049	2/1026	1.8 (0.8–4.2)	0.4 (0.1–1.2)	3.77 (1.09–13.08)	0.036	
Rate of adenocarcinoma in arms								
<50%	5	24/2782	10/1936	1.0 (0.5–1.9)	0.7 (0.3–1.5)	1.60 (0.77–3.30)	0.21	0.23
≥50%	12	42/4021	8/3429	1.2 (0.7–2.1)	0.4 (0.2–0.8)	3.00 (1.46–6.18)	0.003	
Rate of Asian patients in arms								
<50%	12	51/5612	15/4196	0.9 (0.5–1.6)	0.6 (0.4–1.0)	1.98 (1.12–3.49)	0.019	0.41
≥50%	5	15/1191	3/1169	1.6 (0.7–3.6)	0.4 (0.2–1.1)	3.41 (1.06–10.97)	0.04	
Rate of non-smokers in arms[b]								
<50%	9	20/4142	8/3435	0.6 (0.3–1.1)	0.4 (0.2–0.8)	1.87 (0.84–4.16)	0.13	0.61
≥50%	6	17/1275	3/1251	1.7 (0.9–3.4)	0.4 (0.2–1.1)	3.58 (1.20–10.66)	0.022	
Rate of EGFR mutation in arms								
100%	3	9/281	0/268	3.3 (1.7–6.3)	0	6.47 (1.14–36.62)	0.035	0.20
<50% or unknown	14	57/6522	18/5097	0.9 (0.6–1.4)	0.6 (0.4–0.9)	1.98 (1.16–3.38)	0.013	

CR, complete response; OR, odds ratio.
[a]One RCT did not reported the percentage of female patients in groups.
[b]Two RCTs did not reported the percentage of non-smoking patients in groups.

	4. Fazit der Autoren Although CR is a rare event in advanced NSCLC, the use of EGFR-targeted agents significantly increase the odds ratio of obtaining a complete response when compared to controls, especially for patients with EGFR mutations. Further studies are needed to investigate whether the increase of CR with anti-EGFR therapy would be translated into survival benefits.

Shi L et al., 2014 [73]. Risk of interstitial lung disease with gefitinib and erlotinib in advanced non-small cell lung cancer: A systematic review and meta-analysis of clinical trials	**1. Fragestellung** We performed a systematic review and meta-analysis to determine the incidence and the relative risk (RR) associated with the use of gefitinib and erlotinib.
	2. Methodik **Population**: Patients with advanced NSCLC, assigned to treatment with gefitinib or erlotinib **Intervention**: Gefitinib oder Erlotinib **Komparator**: Platinbasierte Chemotherapie, Pemetrexed, Docetaxel, Paclitaxel, Vinorelbin oder Placebo **Endpunkte**: Overall incidence of interstitial lung disease (ILD) **Suchzeitraum**: Januar 2000 bis Oktober 2012 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 29 RCTs/15 618 **Qualitätsbewertung der Studien:** Jadad Score **Heterogenitätsuntersuchungen:** wurden durchgeführt
	3. Ergebnisdarstellung The overall incidence for all-grade ILD events was 1.2% (95% CI, 0.9–1.6%) among patients receiving gefitinib and erlotinib, with a mortality of 22.8% (95% CI, 14.6–31.0%). Compared with controls, the RR of all-grade ILD events associated with gefitinib and erlotinib was 1.53 (95% CI, 1.13–2.08; P = 0.006) using a fixed effects model. The RR of fatal ILD events associated with EGFR TKIs treatment was 1.96 (95% CI, 1.03–3.72, P = 0.041) compared with control patients. The analysis was also stratified for drug type, study location, treatment arm, and treatment line, but no significant differences in RRs were observed.
	4. Fazit der Autoren Treatment with EGFR TKIs gefitinib and erlotinib is associated with a significant increase in the risk of developing both all-grade and fatal ILD events in advanced NSCLC. **Limits:** The National Cancer Institute's common toxicity criteria grading system for ILD has its own limitations. No term specific for ILD is listed in NCI CTCAE v2.0 or v3.0. Also, the majority of trials included in this analysis reported ILD events in combined grades (all-grade, or high-grade), we cannot distinguish cases in each grade. ILD is not a single disease, but encompasses many different pathological diseases. There were no uniform diagnostic criteria of ILD in various studies, also, the trials included in the analysis were performed at various centers, and the ability to detect ILD events might vary among these institutions, which could result in a bias of reported incidence rates. The incidence of ILD events showed significant heterogeneity among the included studies. This might reflect differences in trial designs, sample sizes, concomitant chemotherapy, and many other factors among these studies. Despite these differences, the RRs reported by all of these studies showed remarkable homogeneity. In addition, calculation using the random-effects model for overall incidence estimation might minimize the problem. The study might have a potential observation time bias because EGFR TKIs groups might have longer follow-up time than controls owing to the prolonged PFS that is often associated with the use of EGFR TKIs. However, most ILD events did not occur evenly over time, but in the early phase (first 4 weeks) of EGFR TKIs treatment.

	This is a meta-analysis at the study level, data were abstracted from published clinical trial results, and individual patient information was not available. Therefore, subgroup analyses according to possible risk factors for the development of ILD, including preexisting pulmonary fibrosis, age, performance status, gender, smoking history, lung cancer histology, and the mutational status of EGFR, are not possible in this analysis.
Lee JK, et al. 2014 [57]. Epidermal growth factor receptor tyrosine kinase inhibitors vs conventional chemotherapy in non-small cell lung cancer harboring wild-type epidermal growth factor receptor: a meta-analysis	**1. Fragestellung** Current guidelines recommend both epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and cytotoxic chemotherapy drugs as standard treatment options for patients with wild-type (WT) EGFR who were previously treated for non–small cell lung cancer (NSCLC). However, it is not clear that EGFR TKIs are as efficacious as chemotherapy in patients with WT EGFR.
	2. Methodik **Population**: Patients with advanced NSCLC, defined as inoperable locally advanced (stage IIIB) or metastatic or recurrentdisease (stage IV) **Intervention**: first-generation EGFR TKI (erlotinib and gefitinib), alle Therapielinien **Komparator**: chemotherapy **Endpunkte**: OS, OR, PFS **Suchzeitraum**: bis 12/2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 11/1 605 **Qualitätsbewertung der Studien**: Risk of bias assessment **Heterogenitätsuntersuchungen**: I^2
	3. Ergebnisdarstellung • 4 trials in first-line settings, 4 in second-line, 3 in second- or later-line settings • all 11 trials open-labeled

Source	Line of Treatment	Experimental Drugs	Dominant Ethnicity, No. (%)	Age, Median (Range), y	Adeno-carcinoma, No. (%)	*EGFR* Mutation Analysis	No. of Patients				Follow-up Duration, Median (Range), mo
							TKI Group		Control Group		
							EGFR WT[a]	Total[b]	*EGFR* WT[a]	Total[b]	
INTEREST,[12,27] 2008 and 2010	Second or later	Gefitinib vs Docetaxel	White 1090 (74.4)	61 (20-84)	830 (56.6)	Direct sequencing	106	733	123	733	7.6 (NR)
IPASS,[5,28] 2009 and 2011	First	Gefitinib vs paclitaxel + carboplatin	Asian 1214 (99.8)	57 (24-84)	1214 (99.8)	ARMS	91	609	85	608	17.0 (NR)
ML20322,[29] 2012	First	Erlotinib vs vinorelbine (oral)	Asian (100)	77 (70-90)	73 (64.6)	Direct sequencing	21	57	15	56	13.0 (NR)
TITAN,[13] 2012	Second	Erlotinib vs docetaxel or pemetrexed	White 362 (85.4)	59 (22-80)	210 (49.5)	Direct sequencing	75	203	74	221	27.9 vs 24.8[c] (0.0-50.3)
First-SIGNAL,[30] 2012	First	Gefitinib vs gemcitabine + cisplatin	Asian (100)	57 (19-74)	313 (100)	Direct sequencing	27	159	27	154	35.0 (19.3-49.4)
TORCH,[14] 2012	First	Erlotinib vs gemcitabine + cisplatin	Non-Asian 736 (96.8)	62 (27-81)	422 (55.5)	Direct sequenc-ing + fragment analysis + MS	119	380	117	380	24.3 (NR)
KCSG-LU08-01,[31] 2012	Second	Gefitinib vs pemetrexed	Asian (NR)	NR (30-78)	141 (100)	Direct sequencing	18	71	20	70	15.9 (NR)
CT/06.05,[32] 2013	Second or third	Erlotinib vs pemetrexed	White (NR)	66 (37-86)	257[d] (77.4)	Direct sequencing	55[e]	179	57[e]	178	29.0 vs 27.3[c] (NR)
TAILOR,[15] 2013	Second	Erlotinib vs docetaxel	White 217 (99.1)	67 (35-83)	155 (70.8)	Direct sequenc-ing + fragment analysis	109	112	110	110	33.0 (NR)
DELTA,[33] 2013	Second or third	Erlotinib vs docetaxel	Asian (NR)	67 (31-85)	207 (68.8)	Highly sensitive PCR-based method[43]	109	150	90	151	(NR)
CTONG-0806,[34] 2013	Second	Gefitinib vs pemetrexed	Asian (NR)	57 (24-78)	151 (96.2)	Direct sequencing	81	81	76	76	(NR)

Abbreviations: ARMS, amplification-refractory mutation system; *EGFR*, epidermal growth factor receptor; MS, mass spectrometry; NR, not reported; PCR, polymerase chain reaction; TKI, tyrosine kinase inhibitors; WT, wild type.

[a] Numbers used in the analyses of progression-free survival.

[b] Numbers of randomized patients.

[c] TKI group vs chemotherapy group.

[d] Number of nonsquamous histology (number of adenocarcinoma was not available).

[e] Numbers used in the analyses of time to progression.

PFS

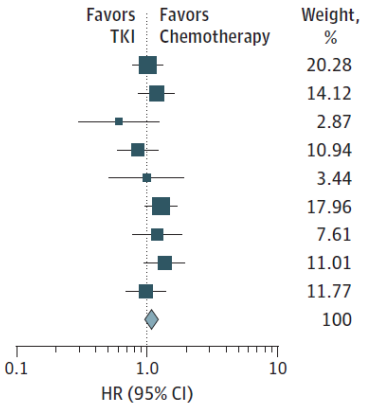
- significantly longer PFS with chemotherapy than with TKI in the patients with WT *EGFR* (HR, 1.41; 95% CI, 1.10-1.81); significant statistical heterogeneity noted (I^2 = 79.1%)

OS

HR for TKI (1.08; 95% CI, 0.96-1.22)

B Overall survival

Source	No. of Patients With WT *EGFR* TKI	No. of Patients With WT *EGFR* Chemotherapy	HR (95% CI)	Weight, %
INTEREST,[12,27] 2008 and 2010	119	134	1.02 (0.78-1.33)	20.28
IPASS,[5,28] 2009 and 2011	91	85	1.18 (0.86-1.63)	14.12
ML20322,[29] 2012	21	15	0.62 (0.30-1.24)	2.87
TITAN,[13] 2012	75	74	0.85 (0.59-1.22)	10.94
First-SIGNAL,[30] 2012	27	27	1.00 (0.52-1.91)	3.44
TORCH,[14] 2012	119	117	1.29 (0.97-1.71)	17.96
CT/06.05,[32] 2013	55	57	1.19 (0.77-1.84)	7.61
TAILOR,[15] 2013	109	110	1.28 (0.95-1.96)	11.01
DELTA,[33] 2013	109	90	0.98 (0.69-1.39)	11.77
Overall: I^2 = 0%; P = .496	725	709	1.08 (0.96-1.22)	100



Subgruppen

Subgroup	No. of Trials	No. of Patients With WT *EGFR* TKI	No. of Patients With WT *EGFR* Chemotherapy	Progression-Free Survival, HR (95% CI)	Heterogeneity Within Subgroups I^2, %	Heterogeneity Within Subgroups *P* Value
Line of treatment						
First[5,14,28-30]	4	258	244	1.53 (0.87-2.69)	86.6	<.001
Second or later[12,13,15,27,31-34]	6	498	493	1.34 (1.09-1.65)	55.2	.048
Subgroup difference: P = .58						
Experimental drug						
Erlotinib[13-15,29,32,33]	5	433	406	1.33 (0.97-1.81)	76.7	.002
Gefitinib[5,12,27,28,30,31,34]	5	323	331	1.49 (0.95-2.33)	83.9	<.001
Subgroup difference: P = .67						
Ethnicity						
Asian-dominant[5,28-31,33,34]	6	347	313	1.30 (0.82-2.06)	85.2	<.001
White-dominant[12-15,27,32]	4	409	424	1.47 (1.15-1.87)	65.1	.04
Subgroup difference: P = .78						
EGFR mutation analysis method						
Direct sequencing-only[12,13,27,29-32,34]	6	328	335	1.12 (0.79-1.58)	73.3	.002
More sensitive platform[5,14,15,28,33]	4	428	402	1.84 (1.35-2.52)	78.7	.003
Subgroup difference: P = .11						

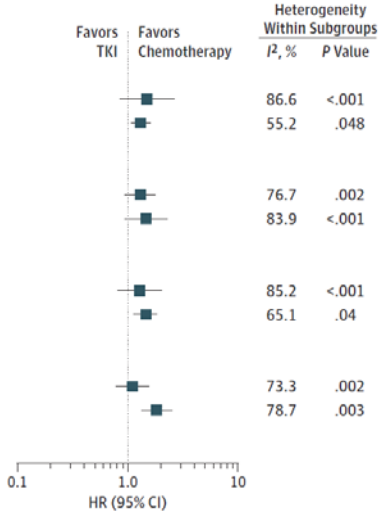


Figure 4. Subgroup Analyses for Progression-Free Survival According to the Line of Treatment (First vs Second or Later), EGFR TKI Agents, Ethnicity, and *EGFR* Mutation Analysis Methods for Patients WithWT *EGFR*

4. Anmerkungen/Fazit der Autoren

Among patients with advanced NSCLC harboring WT *EGFR*, conventional chemotherapy, compared with first-generation EGFR TKI, was associated with improvement in PFS but not overall survival.

Limiatationen:

- a large number of trials had available data on the *EGFR* mutation status in only a small portion of the enrolled patients
- toxitity: not possible to perform an analysis to dealwith such a concern because reports of adverse events from each subgroup were not available

5. Kommentar zum Review

	• Auswertungen nach Wirkstoff und Therapielinie (und EGFR-Mutationsstatus) erfolgte nicht • supported in part by National Research Foundation of Korea (NRF) grants funded by the Korean government (2010-0009563, 2012-0000994). • Dr D.-W. Kim reports having received grants from the Korean government and personal fees from Pfizer, Lilly, and Novartis. Dr S.-H. Lee reports having received personal fees from Pfizer, Novartis, Bayer, and GlaxoSmithKline. No *other disclosures were reported.*
Li G et al., 2016 [59]. The Efficacy of Single-Agent Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy in Biologically Selected Patients with Non-Small-Cell Lung Cancer: A Meta-Analysis of 19 Randomized Controlled Trials	**1. Fragestellung** To determine the efficacy of first-generation single-agent epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy in advanced non-small-cell lung cancer patients with known EGFR mutation status
	2. Methodik Population: advanced non-small-cell lung cancer patients with known EGFR mutation status (defined as inoperable locally advanced (stage IIIB) or metastatic or recurrent disease (stage IV) Intervention*:* firstgeneration single-agent EGFR-TKI therapy (erlotinib or gefitinib) Komparator: standard chemotherapy Endpunkte: PFS (primary endpoint) and/or overall survival (OS) Suchzeitraum (Aktualität der Recherche): to April 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 19 RCTs enrolling 2,016 patients with wild-type EGFR tumors and 1,034 patients with mutant EGFR tumors. Qualitätsbewertung der Studien: Two reviewers independently assessed the quality of selected studies using the following criteria: (1) generation of allocation concealment, (2) description of dropouts, (3) masking of randomization, intervention, and outcome assessment, and (4) intention-to-treat analysis. Each criterion was rated as ‘yes’, ‘no’, or ‘unclear’.

	3. Ergebnisdarstellung 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. • For EGFR mutant patients, single-agent EGFR-TKI therapy improved progression-free survival (PFS) over chemotherapy: the summary hazard ratios (HRs) were 0.41 ($p < 0.001$) for the first-line setting and 0.46 ($p = 0.02$) for the second-/thirdline setting. • For those EGFR wild-type patients, single-agent EGFR-TKI therapy did not do as well as chemotherapy in the first-line setting (HR = 1.65, $p = 0.03$) and in the second-/third-line setting (HR = 1.27, $p = 0.006$). • No statistically significant difference was observed in terms of overall survival (OS). • Using platinum-based doublet chemotherapy as a common comparator, indirect comparison showed the superior efficacy of single-agent EGFR-TKI therapy over EGFR-TKIs added to chemotherapy in PFS [HR = 1.35 (1.03, 1.77), p= 0.03]. • A marginal trend towards the same direction was found in the OS analysis [HR = 1.16 (0.99, 1.35), p = 0.06]. • For those EGFR wild-type tumors, single-agent EGFR-TKI therapy was inferior to EGFRTKIs added to chemotherapy in PFS [HR = 0.38 (0.33, 0.44), $p < 0.001$] and OS [HR = 0.83 (0.71, 0.97), p= 0.02].
	4. Fazit der Autoren: *Despite these limitations, our pooled analysis contributes to a better understanding of the efficacy of singleagent EGFR-TKI therapy in patients with known EGFR mutation status. We found that for these EGFR mutant patients, single-agent EGFR-TKI therapy prolonged PFS over chemotherapy. However, single-agent EGFR-TKI therapy was inferior to chemotherapy in PFS for those EGFR wild-type patients. Single-agent EGFR-TKI therapy could improve PFS over the combination of EGFR-TKIs and chemotherapy in these EGFR mutant patients. However, EGFR-TKIs combined with chemotherapy could provide additive PFS and OS benefit over single-agent EGFR-TKI therapy in those EGFR wild-type patients.*
Sheng J et al., 2015 [71].	**1. Fragestellung** The purpose of this meta-analysis was to assess the advantage and toxicity profile of chemotherapy plus EGFR-mAbs versus chemotherapy alone for patients with NSCLC.

The Efficacy of Combining EGFR Monoclonal Antibody With Chemotherapy for Patients With advanced Nonsmall Cell Lung Cancer	**2. Methodik** Population: patients with advanced NSCLC Intervention: standard chemotherapy plus EGFR-mAbs, Komparator: chemotherapy alone Endpunkte: OS, progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), or toxicity Suchzeitraum (Aktualität der Recherche): bis Januar 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 13 phase II/III RCTs which involved a total of 8358 participants Qualitätsbewertung der Studien: Cochrane Collaboration guidelines. I^2 for hetergeneity

	3. Ergebnisdarstellung Qualität der Studien: In general, no high risk of bias was detected **OS:** • In general, the median OS of patients treated with EGFRmAbs plus chemotherapy was superior to those treated with chemotherapy alone (HR was 0.91, 95% confidence interval [CI]: 0.86–0.97, P=0.006). • Seven studies provided the detailed analysis in chemotherapy-naive patients. The median OS were 8.3 to 12.0 months for the combination group, compared with 7.3 to 11.5 months among the chemotherapy alone group in first-line setting. The pooled HR for OS was 0.88 (95% CI: 0.82–0.95, P=0.0006) in favor of the addition of EGFR-mAbs to the first-line standard chemotherapy. However, it failed to provided additional survival benefit in second-line setting. • the addition of EGFR-mAbs to chemotherapy produced a significant OS improvement for patients with squamous cancer (HR¼0.83, 95% CI: 0.74– 0.93, P=0.001). The risk of death was decreased 17% by combination with EGFR-mAbs. Similarly, there were 3 studies provided the result of the adenocarcinoma subgroup. However, this group population only got slightly survival improvement from the addition of EGFR-mAbs and the pooled HR → no statistically significant difference **PFS, ORR, DCR, and Serious Adverse Effects:** • the risk of disease progression was slightly but significantly decreased by 7% compared with the control group (pooled HR was 0.93, 95% CI: 0.87–0.98, P=0.01). Meanwhile, the addition of EGFR-mAbs to chemotherapy also significantly improved the ORR (pooled OR was 1.28, 95% CI: 1.12–1.47, P=0.0003) and DCR (pooled OR was 1.17, 95% CI: 1.01–1.36, P=0.04). • Serious adverse effects for patients receiving chemotherapy plus EGFRmAbs were mainly acne-like rash (weighted rate: 10.39% vs 0.18%; OR 41.00, 95% CI: 18.25–92.08, P<0.0001), infusion related reactions (weighted rate: 4.56% vs 0.81%; OR 4.83, 95% CI: 1.94–12.01, P=0.0007) and diarrhea (weighted rate: 4.03% vs 1.86%; OR 2.17, 95% CI: 1.33–3.52, P=0.002). • Besides, the risk for some Grade 3 toxicities, such as leukopenia, febrile neutropenia, and thromboembolic events also slightly increased by the addition of EGFR-mAbs, compared with chemotherapy alone. • The combination regimens did not significantly increased the incidence of neutropenia, anemia, or fatigue.
	4. Fazit der Autoren: *The addition of EGFR-mAbs to chemotherapy could provide superior clinical benefit to patients with advanced NSCLC, especially those harboring squamous cancer and in first-line setting. Further validation in front-line investigation, proper selection of the potential benefit population by tumor histology, and development of prognostic biomarkers are warranted for future research and clinical application of EGFR-mAbs.*

3.4 Leitlinien

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft (DKG) et al. 2018 [58].

AWMF, DKG

S3-Leitlinie Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms Version 1.0

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

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

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 %	

In der ASCEND-5 Phase-III-Studie wurden 231 ALK-positive Patienten, die eine Progression nach Vorbehandlung mit Chemotherapie und Crizotinib erlitten hatten, randomisiert einer Behandlung mit Ceritinib (n=115) oder Chemotherapie (n=116, davon n=113 tat-sächlich behandelt) mit Pemetrexed oder Docetaxel zugeführt.

Der primäre Zielparameter PFS betrug 5,4 Monate unter Ceritinib gegenüber 1,6 Monaten unter Chemotherapie (HR 0,49, p<0,001). Das OS zeigte zum Zeitpunkt der Analyse keinen signifikanten Unterschied zwischen beiden Gruppen (18,1 gegenüber 20,1 Monate). Es muss allerdings berücksichtigt werden, dass 75 der 113 Patienten in der Chemotherapiegruppe nach Progress in den Ceritinib Arm wechselten.

Die häufigsten Nebenwirkungen waren Übelkeit (58 %), Diarrhö (68 %), Erbrechen (44 %), Fatigue (22 %) und erhöhte Transaminasen (22-23 %) sowie Gewichtsabnahme (27 %) allerdings im Wesentlichen nicht schwerer Graduierung. Schwere Nebenwirkungen (Grad 3,4) beinhalteten Transaminasenerhöhung (1-3 %) und Dyspnoe (2 %) [877].

Weitere ALK-Inhibitoren der nächsten Generation, deren Nutzen derzeit geprüft wird, sind: Alectinib [878], Brigatinib [879].

875. Shaw, A.T., et al., Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med, 2013. 368(25): p. 2385-94.
876. Shaw, A.T., et al., Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med, 2014. 370(13): p. 1189-97.
877. Shaw, A.T., et al., Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol, 2017. 18(7): p. 874-886.
878. Shaw, A.T., et al., Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. Lancet Oncol, 2016. 17(2): p. 234-42.

879. Gettinger, S.N., et al., Activity and safety of brigatinib in ALK-rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial. Lancet Oncol, 2016. 17(12): p. 1683-1696.

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 %	

Ist eine Studienteilnahme nicht möglich, werden diese Patienten in Abhängigkeit von ihrem Allgemeinzustand entweder mit einer platinbasierten Chemotherapie oder einer Monochemotherapie behandelt. Die platinbasierte Chemotherapie sollte als Kombinationspartner Pemetrexed enthalten, die erste Wahl einer Monochemotherapie sollte ebenfalls Pemetrexed sein, da in der Zweitlinienstudie zum Einsatz von Crizotinib vs. Zweitlinienchemotherapie [875] die Ansprechrate und das PFS in den ALK+ Patienten mit Pemetrexed höher lagen als mit Docetaxel.

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

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 %	

Von den mit Crizotinib in der Expansionskohorte behandelte Patienten hatten 44% be-reits mehr als eine Chemotherapie erhalten. Formelle Daten zur Behandlung nach Crizotinib liegen für ROS 1 positive Patienten nicht vor, allerdings ist es plausibel dass die Daten von anderen molekularen Subgruppen übertragbar sind.

Zweitlinientherapie bei Patienten mit Plattenepithelkarzinom und ohne Mutationsnachweis

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

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

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

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

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

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

Zweitlinientherapie bei Patienten mit nicht-Plattenepithelkarzinom ohne Mutationsnachweis

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

8.86.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad A	Bei Patienten (ECOG 0-1) mit Nicht-Plattenepithelkarzinom und PDL1-Negativität soll eine 2. Linientherapie angeboten werden. Therapieoption sind: - Docetaxel-Nintedanib, - Docetaxel-Ramucirumab, - Pemetrexed, - Docetaxel, - Erlotinib - Nivolumab.[1]	
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 %	

8.6.5.2. Resistenzmechanismen und Zweitlinientherapie bei EGFR mutierten Patienten

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

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

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

National Comprehensive Cancer Network, 2018 [64].

NCCN

Non-Small Cell Lung Cancer, Vers. 03.2018

Leitlinienorganisation/Fragestellung

Diagnose, Pathologie, Staging, Therapie des NSCLC

Methodik

Grundlage der Leitlinie

- Update von 01.2018
- Allgemeiner NCCN-Methodenreport beschreibt systematische Evidenzaufbereitung mit Konsensusprozessen
- Suche in Pubmed seit 2017

LoE, GoR: Diskussion der Literatur und Empfehlungen im Expertenpanel

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Sonstige methodische Hinweise

- Repräsentativität der Gremien unklar
- ob formalisierte Konsensusverfahren angewendet werden ist unklar
- industriefinanziert
- Bewertung der Studien unklar

Empfehlung

Subsequent Therapy
- Response assessment with CT of known sites of disease with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.

Sensitizing *EGFR* Mutation
- First-line therapy
  - Afatinib[1]
  - Erlotinib[2]
  - Gefitinib[3,4]
  - Osimertinib[5]
- Subsequent therapy
  - Osimertinib[6]

ALK Rearrangement
- First-line therapy
  - Alectinib[7,8]
  - Ceritinib[9]
  - Crizotinib[10,11]
- Subsequent therapy
  - Alectinib[12,13]
  - Brigatinib[14]
  - Ceritinib[15]

ROS1 Rearrangement
- First-line therapy
  - Ceritinib[16]
  - Crizotinib[17]

BRAF V600E Mutation
- First-line therapy
  - Dabrafenib/trametinib[18]
- Subsequent therapy
  - Dabrafenib/trametinib[19,20]

PD-L1 Expression
- First-line therapy
  - Pembrolizumab[21,22]
- Subsequent therapy
  - Atezolizumab[23]
  - Nivolumab[24,25]
  - Pembrolizumab[26]

Government Cancer Council Australia, 2017 [2].

Cancer Australia

Clinical practice guidelines for the treatment of lung cancer

Leitlinienorganisation/Fragestellung

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

Methodik

Grundlage der Leitlinie

Systematischer Review und Konsensusprozess über Empfehlungen.

Alle Aussagen sind mit Literaturstellen (Meta-Analysen oder RCTs) belegt.

Recherche/Suchzeitraum:

- u.a. Pubmed bis 2018, Embase bis 2017

LoE (nur die hier benötigten)

- I: A systematic review of level II studies
- II: A randomised controlled trial

GoR

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP (practice point)	Where no good-quality evidence is available but there is consensus among Guideline committee members, consensus-based guidance points are given, these are called "Practice points"

Empfehlungen

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

Empfehlung 1 (Empfehlungsgrad B)

In unselected patients previously treated for advanced NSCLC not suitable for immunotherapy, chemotherapy with docetaxel or pemetrexed may be used as second-line therapy. Pemetrexed is preferred in non-squamous cell carcinoma histology, and docetaxel is preferred in squamous cell carcinoma.

In previously treated patients with advanced NSCLC, single agent docetaxel 75 mg/m2 improves survival compared with best supportive care or vinorelbine and ifosfamide. (LoE: II)

In previously treated patients with advanced NSCLC not suitable for immunotherapy, single agent pemetrexed has similar efficacy but fewer side effects than three-weekly docetaxel. (LoE: II

In previously treated patients with advanced NSCLC, compared with docetaxel, pemetrexed appears to have greater efficacy in non-squamous cell carcinoma histology, and inferior efficacy in squamous cell carcinoma. (LoE: I)

Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000 May;18(10):2095-103 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/10811675.
Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000 Jun;18(12):2354-62 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/10856094.
Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004 May 1;22(9):1589-97 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/15117980.
Standfield L, Weston AR, Barraclough H, Van Kooten M, Pavlakis N. Histology as a treatment effect modifier in advanced non-small cell lung cancer: a systematic review of the evidence. Respirology 2011 Nov;16(8):1210-20 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/21801275.

Empfehlung 2 (Empfehlungsgrad A)

Doublet therapy is not recommended as second-line treatment of advanced NSCLC.

Doublet therapy as second-line treatment of advanced NSCLC increases response rate and progression free survival, but is more toxic and does not improve overall survival compared with single agent chemotherapy. (LoE: I)

Di Maio M, Chiodini P, Georgoulias V, Hatzidaki D, Takeda K, Wachters FM, et al. Meta-analysis of single-agent chemotherapy compared with combination chemotherapy as second-line treatment of advanced non-small-cell lung cancer. J Clin Oncol 2009 Apr 10;27(11):1836-43 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/19273711.
Qi WX, Tang LN, He AN, Shen Z, Yao Y. Effectiveness and safety of pemetrexed-based doublet versus pemetrexed alone as second-line treatment for advanced non-small-cell lung cancer: a systematic review and meta-analysis. J Cancer Res Clin Oncol 2012 Jan 19 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/22258853.

Empfehlung 3 (Empfehlungsgrad B)

Erlotinib is not effective in WT EGFR patients.

Erlotinib is inferior to docetaxel as 2nd line therapy in patients without EGFR activating mutations.8, 9 LoE: II

Garassino MC, Martelli O, Broggini M, Farina G, Veronese S, Rulli E, 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 Sep;14(10):981-8 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/23883922.

Kawaguchi T, Ando M, Asami K, Okano Y, Fukuda M, Nakagawa H, 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 Jun 20;32(18):1902-8 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/24841974.

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

Empfehlung 3 (Empfehlungsgrad B)

In fit, previously treated patients with advanced NSCLC who have received two lines of therapy, single agent docetaxel administered 3 weekly can be considered.

Kawaguchi T, Ando M, Asami K, Okano Y, Fukuda M, Nakagawa H, 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 Jun 20;32(18):1902-8 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/24841974.

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

Empfehlung 3 (Empfehlungsgrad B)

Poor performance status patients having received 1 or 2 lines of prior therapy, may be offered erlotinib 150 mg daily.

Thatcher N, Chang A, Parikh P, Rodrigues Pereira J, Ciuleanu T, von Pawel J, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet 2005 Oct;366(9496):1527-37 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/16257339.

Nasser H et al., 2017 [35].

ASCO

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

Leitlinienorganisation/Fragestellung

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

Weitere Informationen zur Leitlinienmethodik: http://www.instituteforquality.org/guideline-development-process

Empfehlungen

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).

ALK gene rearrangement (no change from 2015). The Panel notes that in May 2017, while this guideline was in development, the FDA approved an ALK inhibitor (that was not a prespecified agent included in the ASCO systematic literature search) based on a 137-patient, phase I/II, single-arm study with five cohorts in the second-line or greater setting that was presented at the 2016 ASCO Annual Meeting. It was published in The Lancet Oncology in December 2016 (PubMed had not indexed the publication as of May 9, 2017, and therefore, it was outside the parameters of the systematic review for the guidelines).33

With sensitizing EGFR mutations:

- In patients with disease progression after first-line therapy with an EGFR tyrosine kinase inhibitor (TKI) and the presence of the T790M resistance mutation, osimertinib is recommended (Evidence quality: high; Strength of recommendation: strong).
- If T790M mutation is not present, a platinum doublet is recommended (Type: informal consensus; Evidence quality: low; Strength of recommendation: strong).
- In patients who received an EGFR-TKI in the first-line setting, had an initial response, and subsequently experienced slow or minimal disease progression at isolated sites, EGFR-TKI with local therapy to the isolated sites is an option (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: weak).

With ROS1 rearrangement:

- In patients who have not received prior crizotinib, crizotinib is recommended (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- In patients who have received prior crizotinib, platinum-based therapy in the second line with or without bevacizumab is recommended (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

With BRAF mutations:

- In patients without prior immune checkpoint therapy and high PD-L1 expression (TPS . 1%), atezolizumab, nivolumab, or pembrolizumab is recommended (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: weak).

- In patients who have received prior immune checkpoint therapy, dabrafenib alone or in combination with trametinib in third line is an option (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

Third-Line Treatment for Patients

- In patients without a tumor EGFR-sensitizing mutation or ALK or ROS1 gene rearrangement and with non–squamous cell carcinoma and PS of 0 or 1 (and appropriate PS of 2), who received chemotherapy with or without bevacizumab an 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.

Ältere Leitlinien aus Evidenzsynopse zu 2017-B-188

Ellis PM, Vella ET, Ung YT and the Lung Cancer Disease Site Group, 2016 [18]. **ASCO** Systemic Treatment for Patients with Advanced Non-Small Cell Lung Cancer	Fragestellung/Zielsetzung • 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 Sonstige methodische Hinweise – Further information: PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook* – The following recommendations were endorsed with no modifications: A1.a, A1.b, A2.a.2, A2.b, A3, A3.a, A4, A5, A6, A7, and do not appear in Table 3-2 (siehe Anhang). – Systematisches Review: MEDLINE (1946 to February 16, 2016), EMBASE (1996 to February 16, 2016), and PubMed (February 16, 2016) databases were searched for RCTs. – Inclusion Criteria o Phase II or III RCTs comparing treatment with immune checkpoint inhibitors with chemotherapy; and o Stage IIIB or IV NSCLC; and o Fully published papers or published abstracts of trials that reported at least one of the following outcomes by treatment group: OS, PFS, response rate, or adverse events. – Exclusion Criteria o Pilot trials, dose-escalation trials, or case series (including expanded access programs) studies. o Letters and editorials that reported clinical trial outcomes. o Conference abstracts published before 2013. – Empfehlungen sind mit Literaturstellen verknüpft
	Freitext/Empfehlungen/Hinweise • 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? For patients with advanced NSCLC, NSCC, negative or unknown EGFR/ALK status, and adequate PS, when disease has progressed during or after first-line platinum-based therapy, nivolumab (in all patients with NSCLC) or pembrolizumab (in patients with PD-L1-positive tumours) is preferred, if either is available, over docetaxel, erlotinib, gefitinib, or pemetrexed as second-line therapy. • 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? For patients with advanced NSCLC, SCC, negative or unknown EGFR/ALK status, and adequate PS, when disease has progressed during or after first-line platinum-based therapy, nivolumab (in all patients with NSCLC) or

	pembrolizumab (in patients with PD-L1-positive tumours) is preferred, if either is available, over docetaxel, erlotinib, or gefitinib as second-line therapy. • 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? For patients with a sensitizing *EGFR* mutation who did not respond to a first-line EGFR TKI, combination cytotoxic chemotherapy (Recommendation A2) or *a third-generation EGFR TKI such as osimertinib in patients shown to have a T790M mutation* is recommended, following the first-line recommendations for patients with NSCC. • 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? Patients who received an EGFR TKI in the first-line setting, had an initial response, and subsequently experienced disease progression may be switched to chemotherapy or a third-generation EGFR TKI such as osimertinib in patients shown to have a T790M mutation as second-line therapy. There is insufficient evidence to recommend the use of other EGFR TKIs, such as afatinib, in previously treated patients, as available data do not demonstrate any improvement in overall survival. • 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? Patients whose tumours have ALK rearrangements and who received crizotinib in the first-line setting may be offered the option of chemotherapy (after first-line recommendations for patients with NSCC [see Recommendation A2]) or ceritinib in the second-line setting. • Clinical Question B5: What is the optimal second-line treatment for elderly patients with stage IIIB/IV NSCLC? The evidence does not support the selection of a specific second-line chemotherapy drug or combination based on age alone. As stated in Recommendation A8, age alone is not a contraindication to chemotherapy for NSCLC.
Scottish Intercollegiate Guidelines Network (SIGN), 2014 [68]. Management of lung cancer	**1. Fragestellung** In patients with NSCLC (locally advanced or metastatic disease), what is the most effective first/second line systemic anticancer therapy (chemotherapy, targeted therapy, EGFR Inhibitors)? Outcomes: Overall survival, progression-free survival, toxicity, quality of life
	***2.* Methodik** **Grundlage der Leitlinie:** systematische Recherche und Bewertung der Literatur, Entwicklung durch multidisziplinäre Gruppe von praktizierenden klinischen ExpertInnen, Expertenreview, öffentliche Konsultation

Suchzeitraum:

2005 - 2012

LoE/GoR:

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS	
LEVELS OF EVIDENCE	
1^{++}	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well conducted meta-analyses, systematic reviews, *or* RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion
GRADES OF RECOMMENDATION	
Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.	
A	At least one meta-analysis, systematic review, or RCT rated as 1^{++}, and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2^{+}
GOOD PRACTICE POINTS	
✓	Recommended best practice based on the clinical experience of the guideline development group

3. Empfehlungen

Zweitlinientherapie

In patients who are PS ≤ 2 at the time of progression of their advanced NSCLC, second line treatment with single agent docetaxel, erlotinib or PEM improve survival rates compared to BSC. **(LoE 1+)**

Tassinari D, Scarpi E, Sartori S, Tamburini E, Santelmo C, Tombesi P, et al. Second-line treatments in non-small cell lung cancer. A systematic review of literature and metaanalysis of randomized clinical trials. Chest 2009;135(6):1596-609.

Second line docetaxel improved time to progression, survival and quality of life. Patient's opioid requirements and weight loss were reduced with docetaxel compared to BSC only. This was clearest in the patients who received 100 mg/m2 rather than 75 mg/m2 every three weeks, however the higher dose was associated with more overall toxicity, and is not recommended as standard. **(LoE 1+)**

Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18(10):2095-103.

	Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, et al. Randomised phase III trial of docetaxel versus vinorelbine or ifosfamide inpatients with advanced non-small cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000;18(12):2354-62. Weekly docetaxel is not recommended over three-weekly due to increased toxicity. **(LoE 1+)** Tassinari D, Carloni F, Santelmo C, Tamburini E, Agli LL, Tombesi P, et al. Second line treatments in advanced platinum-resistant non small cell lung cancer: A critical review of literature. Rev Recent Clin Trials 2009;4(1):27-33. Randomised evidence does not support the use of combination SACT as second line treatment for patients with advanced NSCLC based on an increase in toxicity without any gain in survival. **(LoE 1++)** Di Maio M, Chiodini P, Georgoulias V, Hatzidaki D, Takeda K, Wachters FM, et al. Meta-analysis of single-agent chemotherapy compared with combination chemotherapy as second-line treatment of advanced non-small-cell lung cancer. J Clin Oncol 2009;27(11):1836-43. Second line erlotinib improves overall survival compared to BSC in patients with NSCLC. Median survival was improved with moderate toxicity. The response rate was 8.9% in the erlotinib group and less than 1% in the placebo group (p<0.001); the median duration of the response was 7.9 months and 3.7 months, respectively. Progression-free survival was 2.2 months and 1.8 months, respectively (HR 0.61, adjusted for stratification categories; p<0.001). Overall survival was 6.7 months and 4.7 months, respectively (HR 0.70; p<0.001) in favour of erlotinib. **(LoE 1++)** Noble J, Ellis PM, Mackay JA, Evans WK. Second-line or subsequent systemic therapy for recurrent or progressive non-small cell lung cancer: A systematic review and practice guideline. J Thorac Oncol 2006;1(9):1042-58. Compared with single agent docetaxel, treatment with PEM resulted in clinically equivalent efficacy outcomes, but with significantly fewer side effects in the second-line treatment of patients with advanced predominantly non-squamous cell NSCLC. <u>Recommendations</u> • Second line systemic anticancer therapy with single agent docetaxel or erlotinib should be considered for patients with performance status 0-2 recurrent NSCLC who have been previously treated with first line SACT for advanced disease. **(A)** • Second line systemic anticancer therapy with pemetrexed should be considered for patients with advanced non-squamous cell NSCLC who have been previously treated with first line SACT for advanced disease. **(A)** **ROS1** […] Other gene rearrangements (ie, gene fusions) have recently been identified (such as ROS1, RET) that are susceptible to targeted therapies.

	[kk:] Consider ROS1 testing, if positive, may treat with crizotinib (Quelle: *Shaw AT, Ou SH, Bang YJ, et al: Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med 371:1963-1971, 2014*)
Ellis PM et al., 2014 [16]. Use of the Epidermal Growth Factor Receptor Inhibitors Gefitinib (Iressa®), Erlotinib (Tarceva®), Afatinib, Dacomitinib or Icotinib in the Treatment of Non-Small-Cell Lung Cancer: A Clinical Practice Guideline	**1. Fragestellung** **QUESTIONS** 1. In patients with advanced non–small-cell lung cancer (NSCLC) who have not received any chemotherapy (chemo-naive), is first-line therapy with the epidermal growth factor receptor (EGFR) inhibitors gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib superior to platinum-based chemotherapy for clinical meaningful outcomes (overall survival, progression-free survival (PFS), response rate and quality of life)? 2. In patients with advanced NSCLC who have progressed on platinum-based chemotherapy, does subsequent therapy with EGFR inhibitors gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib improve overall survival or PFS? Is there a preferred sequence for second-line therapy with an EGFR inhibitor or chemotherapy? 3. In patients with advanced stage IIIB or IV NSCLC who have received initial first-line platinum-based chemotherapy, does maintenance therapy with erlotinib, gefitinib, afatinib, dacomitinib or icotinib improve overall survival or PFS? 4. What are the toxicities associated with gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib? **TARGET POPULATION** This practice guideline applies to adult patients with advanced (stage IIIB or IV) non–small-cell lung cancer.
	2. Methodik **Grundlage der Leitlinie:** The PEBC is using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (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. **Suchzeitraum**: bis 2014 **LoE und GoR:** Studienqualität geprüft und detailliert in Evidenztabellen dargestellt, Empfehlungsstärken über die Formulierung dargestellt
	3. Empfehlungen **<u>Zweitlinientherapie</u>** ***Recommendation 2***

	In patients well enough to consider second-line chemotherapy, an EGFR TKI can be recommended as second- or third-line therapy. There is insufficient evidence to recommend the use of a second EGFR TKI, such as afatinib, in patients whose disease has progressed following chemotherapy and gefitinib or erlotinib, as available data does not demonstrate any improvement in overall survival. *Qualifying Statements:* There are data to support the use of an EGFR TKI in patients who have progressed on platinum-based chemotherapy. Erlotinib is known to improve overall survival and quality of life when used as second- or third-line therapy, in comparison to best supportive care. However, available data would suggest that second-line therapy with either chemotherapy or an EGFR TKI results in similar PFS and overall survival. Available evidence would support the use of either erlotinib or gefitinib in this situation. • Data from a randomized phase II trial suggests improved PFS for dacomitinib versus (vs) erlotinib, but these data require confirmation in a phase III trial. • The Lux Lung 1 study failed to meet its primary outcome of improved overall survival. However, the study showed improved PFS for patients randomized to afatinib and was associated with improvements in lung cancer symptoms. ***Key Evidence*** Three studies examined an EGFR inhibitor as a second-line treatment against a placebo and best supportive care. One study reported on the use of erlotinib and showed a significant improvement in PFS (p=0.001) and overall survival (p=0.001). The other two studies evaluated gefitinib, with one study finding significant results for response rate (p<0.0001) and the other for PFS (p=0.002). • A meta-analysis done on seven second-line studies showed no improvement with EGFR TKIs vs chemotherapy for progression-free survival (HR, 0.99; 95% CI 0.86-1.12, p=0.67) and overall survival (HR, 1.02; 95% CI, 0.95-1.09, p=0.56) • One phase II study that compared erlotinib to dacomitinib showed significant results for dacomitinib for response rate (p=0.011) and for PFS (p=0.012). • The Lung Lux 1 study examined the use of afatinib in the third- and fourth-line setting against a placebo. This study showed improved PFS (HR, 0.38; 95% CI, 0.31-0.48, p<0.0001) but no difference in overall survival (HR, 1.08; 95% CI, 0.86-1.35, p=0.74) 35. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. 2005;353(2):123-32. 36. Gaafar RM, Surmont VF, Scagliotti GV, Van Klaveren RJ, Papamichael D, Welch JJ, et al. A double-blind, randomised, placebo-controlled phase III intergroup study of gefitinib in patients with advanced NSCLC, non-progressing after first line platinum-based chemotherapy (EORTC 08021/ILCP 01/03). Eur J Cancer. 2011;47 (15):2331-40. 37. Thatcher N, Chang A, Parikh P, Rodrigues Pereira J, Ciuleanu T, von Pawel J, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet. 2005;366(9496):1527-37.

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Recommendation 3

An EGFR TKI is recommended as an option for maintenance therapy in patients who have not progressed after four cycles of a platinum-doublet chemotherapy. No recommendation can be made with respect to the choice of gefitinib or erlotinib.

Qualifying Statements

Trials have evaluated both erlotinib and gefitinib, but no trials directly compare these two agents as maintenance therapy. However, the strongest data would support the use of erlotinib in this setting, although the overall survival advantage is modest for both agents.

There are competing strategies of maintenance chemotherapy without an EGFR TKI, such as pemetrexed, that are not addressed in this guideline. The recommendation for TKI above should not be taken as excluding these other strategies as reasonable options; as this evidence was not reviewed, no statement can be made for or against these other strategies. The Lung Disease Site Group (DSG) plans to develop a separate guideline on maintenance therapy as soon as possible.

This recommendation applies to both EGFR mutation positive and wild-type patients.

	Key Evidence Six studies evaluated the use of an EGFR inhibitor in the maintenance setting. • Two of the trials reported a statistically significant survival benefit with erlotinib: one for response rate (p=0.0006) when compared to placebo (47) and one for progression-free survival when combined with bevacizumab against bevacizumab alone (p<0.001). • One study comparing erlotinib and gemcitabine did not report significance but found a higher response rate with erlotinib (15% vs 7%) and 9.1 months vs 8.3 months for overall survival. • Two trials evaluating gefitinib found a statistically significant benefit for PFS in the maintenance setting, p<0.001 when combined with chemotherapy and against chemotherapy (48) and p<0.0001 compared to a placebo. • Another trial evaluated gefitinib and showed a higher response rate, but this was not significant (p=0.369). 47. Cappuzzo F, Ciuleanu T, Stelmakh L, Cicenas S, Szczesna A, Juhasz E, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol. 2010;11(6):521-9. 48. Takeda K, Hida T, Sato T, Ando M, Seto T, Satouchi M, et al. Randomized phase III trial of platinum-doublet chemotherapy followed by gefitinib compared with continued platinum-doublet chemotherapy in Japanese patients with advanced non-small-cell lung cancer: results of a west Japan thoracic oncology group trial (WJTOG0203). J Clin Oncol. 2010;28(5):753-60. 49. Zhang L, Ma S, Song X, Han B, Cheng Y, Huang C, et al. Gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804): A multicentre, double-blind randomised phase 3 trial. Lancet Oncol. 2012;13(5):466-75. 50. Bylicki O, Ferlay C, Chouaid C, Lavole A, Barlesi F, Dubos C, et al. Efficacy of pemetrexed as second-line therapy in advanced NSCLC after either treatment-free interval or maintenance therapy with gemcitabine or erlotinib in IFCT-GFPC 05-02 phase III study. Journal of Thoracic Oncology. 2013;8(7):906-14. 51. Johnson BE, Kabbinavar F, Fehrenbacher L, Hainsworth J, Kasubhai S, Kressel B, et al. ATLAS: randomized, double-blind, placebo-controlled, phase IIIB trial comparing bevacizumab therapy with or without erlotinib, after completion of chemotherapy, with bevacizumab for first-line treatment of advanced non-small-cell lung cancer. J Clin Oncol. 2013;31(31):3926-34. 52. Ahn MJ, Yang JCH, Liang J, Kang JH, Xiu Q, Chen YM, et al. Randomized phase II trial of first-line treatment with pemetrexed-cisplatin, followed sequentially by gefitinib or pemetrexed, in East Asian, never-smoker patients with advanced non-small cell lung cancer. Lung Cancer. 2012;77(2):346-52. **Recommendation 4** The most common toxicities from EGFR inhibitors were diarrhea and rash. Fatigue was also noted to be more prevalent with EGFR inhibitors. Rarer adverse events include interstitial lung disease (ILD). The newer TKIs (icotinib, dacomitinib and afatinib) were noted to have greater incidence of diarrhea, dermatitis and hepatotoxicity. ***Key Evidence*** Two randomized phase II trials, each involving more than 200 patients randomized to either 250 mg or 500 mg of gefitinib daily, identified that grade 3 or 4 toxicity was higher with the higher dose gefitinib. Interstitial lung disease-type events

	occurred in only one of the two trials, and only with 500 mg/day gefitinib (1% of patients). • One study comparing dacomitinib to erlotinib identified a greater predilection to diarrhea, dermatitis and paronychia with dacomitinib. • One study comparing icotinib to gefitinib identified a greater incidence of elevated liver transaminases with gefitinib (12.6% vs 8%). 53. Fukuoka M, Yano S, Giaccone G, Tamura T, Nakagawa K, Douillard J-Y, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial) [corrected].[Erratum appears in J Clin Oncol. 2004 Dec 1;22(23):4863]. J Clin Oncol. 2003;21(12):2237-46. 54. Shi Y, Zhang L, Liu X, Zhou C, Zhang L, Zhang S, et al. Icotinib versus gefitinib in previously treated advanced non-small-cell lung cancer (ICOGEN): a randomised, double-blind phase 3 non-inferiority trial. Lancet Oncol. 2013;14(10):953-61.
Alberta Provincial Thoracic Tumour Team, 2013 [1]. Non-small cell lung cancer - stage IV. Alberta Health Services	**Fragestellung** When is palliation recommended, and what are the recommended palliative treatment options for patients with inoperable stage III non-small cell lung cancer? What is the optimal second-line therapy for 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 **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.*
	Freitext/Empfehlungen **Non-Small Cell Lung Cancer, Stage IV Guideline** Recommendations

	… 8. 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. **65.** Kowalski DM, Krzakowski M, Ramlau R, Jaskiewicz P, Janowicz-Zebrowska A. Erlotinib in salvage treatment of patients with advanced non-small cell lung cancer: results of an expanded access programme in Poland. Wspolczesna Onkol. 2012;16(2):170-175. →squamous-cell (n = 23), adenocarcinoma (n = 20), or broncho-alveolar carcinoma (n = 2), keine Infos zu EGFR **100.** Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. Jul 14 2005;353(2):123-132. →= Zulassungsstudie **101.** Florescu M, Hasan B, Seymour L, Ding K, Shepherd FA. A clinical prognostic index for patients treated with erlotinib in National Cancer Institute of Canada Clinical Trials Group study BR.21. J Thorac Oncol. Jun 2008;3(6):590-598. → (gehört zu Sherperd) **102.** Ciuleanu T, Stelmakh L, Cicenas S, Esteban E. Erlotinib versus docetaxel or pemetrexed as second-line therapy in patients with advanced non-small-cell lung cancer (NSCLC) and poor prognosis: efficacy and safety results from the phase III TITAN study. . In: Oncol JT, ed. Vol 52010. → EGFR-Expressionsstatus erfasst, keine signifikanten Unterschiede beim OS beobachtet (Gesamtpopulation als auch Subgruppe zum EGFR-Expressionstatus) **103.** LeCaer H, Greillier L, Corre R, et al. A multicenter phase II randomized trial of gemcitabine followed by erlotinib at progression, versus the reverse sequence, in vulnerable elderly patients with advanced non small-cell lung cancer selected with a comprehensive geriatric assessment (the GFPC 0505 study). *Lung Cancer.* Jul 2012;77(1):97-103. →elderly patients with NSCLC not selected for EGFR expression 9. 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. 10. 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. <u>Quellen:</u> **112**. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature. Aug 2 2007;448(7153):561-566. **113**. Kim DW, Ahn MJ, Shi Y, et al. Results of a global phase II study with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC). Paper presented at: 2012 Annual Meeting of the American Society of Clinical Oncology2012. **114**. Ramalingam SS, Owonikoko TK, Khuri FR. Lung cancer: New biological insights and recent therapeutic advances. CA Cancer J Clin. Mar-Apr 2011;61(2):91-112. **115**. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med. Oct 28 2010;363(18):1693-1703. **116**. Lee JK, Park HS, Kim DW, et al. Comparative analyses of overall survival in patients with anaplastic lymphoma kinase-positive and matched wild-type advanced nonsmall cell lung cancer. Cancer. Jul 15 2012;118(14):3579-3586. **117**. Shaw AT, Kim DW, Nakagawa K, et al. Phase III study of crizotinib versus pemetrexed or docetaxel chemotherapy in patients with advanced ALK-positive non-small cell lung cancer (NSCLC) (PROFILE 1007). Paper presented at: Congress of the European Society for Medical Oncology 20122012.

	118. Camidge DR, Bang YJ, Kwak EL, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol. Oct 2012;13(10):1011-1019. **119**. Kimura H, Nakajima T, Takeuchi K, et al. ALK fusion gene positive lung cancer and 3 cases treated with an inhibitor for ALK kinase activity. Lung Cancer. 2012;75(1):66-72. …
Wauters I et al., 2013 [79]. **Belgian Health Care Knowledge Centre** Non-small cell and small cell lung cancer: diagnosis, treatment and follow-up	**Fragestellung** 4. What are the best treatment options for patients with metastatic and recurrent NSCLC?
	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. ***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			

Empfehlungen

5.3.3. Second and third line chemotherapy - Other Considerations:

A preliminary meta-analysis shows a pooled effect on progression free survival favoring chemotherapy and no effect on overall survival. This subgroup analysis should be treated with extreme caution, as in most studies only in a minority of patients EGFR status could be determined. However, the claims of the investigators that the effect is similar in EGFR mutated and non mutated patients is not supported by the facts, because the test for interaction used could not possibly have the power to detect this difference.

Figure 3 – Pooled (subgroup) effect on progression free survival in EGFR wildtype patients

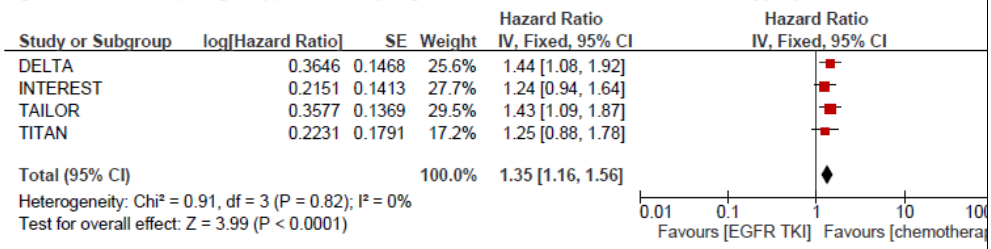
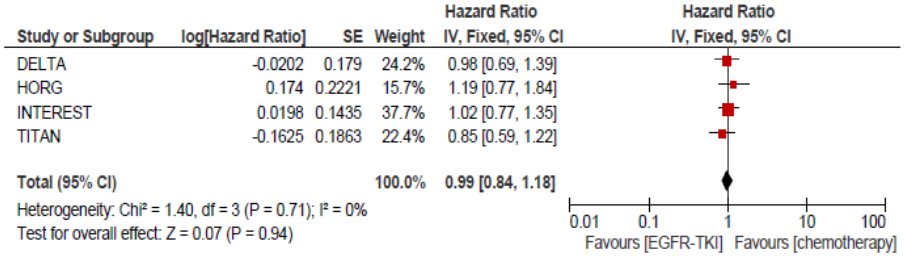


Figure 4 – Pooled (subgroup) effect on overall survival EGFR wildtype patients



Conclusion

	Second line chemotherapy has a statistically significant effect on overall survival in patients with advanced NSCLC and an adequate PS when the disease has progressed during or after first-line, platinum-based therapy. Docetaxel or pemetrexed (only in non-squamous NSCLC) are acceptable as second-line therapy for patients with advanced NSCLC with adequate PS when the disease has progressed during or after first-line, platinumbased therapy as there is no evidence that one is superior to another. Erlotinib and gefitinib only have a proven effect in EGFR mutation positive NSCLC. Combination second line therapies have a marginal effect on progression free survival compared to monotherapy but no proven effect on overall survival. *Recommendation* • 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. (SoE: strong / LoE: moderate) • Crizotinib is recommended as second-line therapy in ALK mutation-positive patients. (SoE: strong / LoE: 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. (SoE: weak / LoE: very low) *Good clinical practice* It is recommended to offer radiotherapy for palliation of local symptoms to patients with NSCLC. 4. Azzoli CG, Temin S, Giaccone G. 2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer. J Oncol Pract. 2012;8(1):63-6. 7. Landelijke werkgroep longtumoren IKNL. Niet-kleincellig longcarcinoom - Landelijke richtlijn, Versie 2.0. In. 2.0 ed; 2011. 74. Group NM-aC, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet. 2010;375(9722):1267-77. 121. Botrel TE, et al. Efficacy of bevacizumab (Bev) plus chemotherapy (CT) compared to CT alone in previously untreated locally advanced or metastatic non-small cell lung cancer (NSCLC): systematic review and metaanalysis. Lung Cancer. 2011;74(1):89-97. 122. Lima AB, Macedo LT, Sasse AD. Addition of bevacizumab to chemotherapy in advanced non-small cell lung cancer: a systematic review and meta-analysis. PLoS ONE. 2011;6(8):e22681. 123. Reck M, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol. 2010;21(9):1804-9. 124. Niho S, et al. Randomized phase II study of first-line carboplatin-paclitaxel with or without bevacizumab in Japanese patients with advanced nonsquamous non-small-cell lung cancer. Lung Cancer. 2012;76(3):362-7. 125. Qi WX, Shen Z, Yao Y. Meta-analysis of docetaxel-based doublet versus docetaxel alone as second-line treatment for advanced non-small-cell lung cancer. Cancer Chemotherapy and Pharmacology. 2012;69(1):99-106. 126. Qi W-X, Tang L-N, He A-N, Shen Z, Yao Y. Effectiveness and safety of pemetrexed-based doublet versus pemetrexed alone as second-line treatment for advanced non-small-

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Socinski MA et al., 2013 [75]. Treatment of Stage IV Non-small Cell Lung Cancer	**1. Fragestellung** Therapie des NSCLC Stage IV
	2. 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 **Literatursuche:** 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. **Suchzeitraum:** bis 12/2011 **LoE und GoR** 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 . ***Sonstige methodische Hinweise*** • *direkte Verknüpfung von Literatur mit Empfehlung nicht durchgängig gegeben*
	3. Empfehlungen **General Approach** (Recommendations adapted from First and Second Editions) 2.1.1. 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)

	2.2.2. 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)** . **Second and Third Line Treatment** 4.1.1. 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)**. 4.1.2. 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. **Special Patient Populations and Considerations** 5.1.1. In elderly patients (age > 69–79 years) with stage IV NSCLC who have good PS and limited co-morbidities, treatment with the two drug combination of monthly carboplatin and weekly paclitaxel is recommended **(Grade 1A)** . *Remark:* In patients with stage IV NSCLC who are 80 years or over, the benefi t of chemotherapy is unclear and should be decided based on individual circumstances. 6.2.1.For patients with stage IV NSCLC with a PS of 2 in whom the PS is caused by the cancer itself, double agent chemotherapy is suggested over single agent chemotherapy **(Grade 2B)** . 6.2.2. In patients with stage IV NSCLC who are an ECOG PS of 2 or greater, it is suggested not to add bevacizumab to chemotherapy outside of a clinical trial **(Grade 2B)** . 7.1.1. In patients with stage IV NSCLC early initiation of palliative care is suggested to improve both QOL and duration of survival **(Grade 2B)** .

3.5 Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

CADTH, 2017 [5].

pCODR: Final Recommendation: Alectinib

siehe auch: **CADTH, 2017 [4].** Alectinib (Alecensaro) NSCLC; Final Clinical Guidance Report

pERC RECOMMENDATION	pERC does not recommend reimbursement of alectinib (Alecensaro) as monotherapy for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib and have central nervous system (CNS) metastases. The Committee made this recommendation as it was not confident of the net clinical benefit of alectinib because of limitations in the evidence from available clinical trials. While pERC was confident that alectinib produces a CNS tumour response, the Committee was unable to determine how alectinib compares with other treatments with respect to outcomes important to decision-making, including overall survival (OS), progression-free survival (PFS), and quality of life. pERC noted that alectinib aligned with patient values as there is a need for more effective treatment options, other than chemotherapy and whole-brain radiation therapy (WBRT), that have tolerable side effects for patients with ALK-positive NSCLC who have progressed on or are intolerant to crizotinib and have CNS metastases. pERC concluded that, at the submitted price, alectinib was not cost-effective compared with chemotherapy (pemetrexed with or without cisplatin); however, there was considerable uncertainty in the cost-effectiveness estimates because of a lack of direct comparative effectiveness data in the submitted economic evaluation.

CADTH, 2017 [7].

Ceritinib (Zykadia) for Non-Small Cell Lung Cancer; Final recommendation

Siehe auch: **CADTH, 2017 [6].** Ceritinib (Zykadia) for Non-Small Cell Lung Cancer; Final Clinical Guidance Report

pERC RECOMMENDATION	pERC recommends reimbursement of ceritinib (Zykadia) monotherapy for patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cance (NSCLC) who have disease progression on or intolerance to crizotinib conditional on the cost-effectiveness being improved to an acceptable level. pERC made this recommendation because the Committee was confident of the net clinical benefit of ceritinib, based on statistically significant and clinically meaningful improvements in progression-free survival (PFS) compared to chemotherapy. The Committee acknowledged that quality of life with ceritinib was similar to chemotherapy; however, ceritinib is associated with manageable but not insignificant toxicity compared with chemotherapy. pERC agreed that ceritinib aligned with patient values, as there is a clear unmet need for more effective treatment options. However, the increased toxicity profile compared with chemotherapy tempered pERC's conclusions with respect to alignment with patient values. The Committee also concluded that, at the submitted price, ceritinib was not cost-effective compared with chemotherapy and would require a substantial price reduction.

CADTH, 2017 [11].
Osimtertinib (Tagrisso) for Non-Small Cell Lung Cancer; Final recommendation

Siehe auch: **CADTH, 2017 [12].** Osimtertinib(Tagrisso) for Non-Small Cell Lung Cancer; Final Clinical Guidance Report

pERC RECOMMENDATION	pERC recommends reimbursement of osimertinib (Tagrisso) in patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) who have progressed on EGFR tyrosine kinase inhibitor (TKI) therapy conditional on the cost-effectiveness being improved to an acceptable level. pERC made this recommendation because the Committee was confident of the net clinical benefit of osimertinib based on a substantial improvement in progression-free survival (PFS) that was statistically significant and clinically meaningful. Osimertinib also had a manageable toxicity profile and, based on the available data, treatment did not result in a decrement or an improvement in patients' quality of life. Osimertinib also aligned with patient values. The Committee concluded that, at the submitted price, osimertinib was not cost-effective compared with chemotherapy and would require a substantial price reduction.

CADTH, 2016 [14].
Pembrolizumab (Keytruda) NSCLC; Final Recommendation

Siehe auch: **CADTH, 2016 [13].** Pembrolizumab (Keytruda) NSCLC; Final Clinical Guidance Report

pERC RECOMMENDATION	pERC recommends reimbursement of pembrolizumab (Keytruda) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours express PD-L1 (as determined by a validated test) and who have disease progression on or after cytotoxic chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumour aberrations should have disease progression on authorized therapy for these aberrations and cytotoxic chemotherapy prior to receiving pembrolizumab. Patients could receive up to 12 months of pembrolizumab if they experienced an investigator-determined confirmed radiographic disease progression, according to immune-related response criteria after stopping their initial treatment with pembrolizumab due to achievement of a confirmed complete response or having experienced 35 administrations of pembrolizumab. Funding should be for patients with a Tumour Proportion Score (TPS) of PD-L1 ≥ 1% and who have good performance status. Treatment should continue until confirmed disease progression or unacceptable toxicity, or to a maximum

CADTH, 2016 [10].
Nivolumab (Opdivo) Non-Small Cell Lung Cancer; Final Recommendation

Siehe auch: **CADTH, 2016 [9].** Nivolumab (Opdivo) Non-Small Cell Lung Cancer; Final Clinical Guidance Report

pERC RECOMMENDATION	pERC recommends funding nivolumab (Opdivo) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for the treatment of adult patients with advanced or metastatic non-small cell lung cancer (NSCLC) with disease progression on or after cytotoxic chemotherapy for advanced disease and have a good performance status. Treatment should continue until confirmed disease progression or unacceptable toxicity. pERC made this recommendation because it was satisfied that there is a net overall clinical benefit with nivolumab, based on the statistically significant and clinically meaningful improvements in overall survival and objective response rate, a meaningful improvement in the toxicity profile, and at least stable quality of life compared with docetaxel. The Committee was satisfied that nivolumab also aligned with patient values. pERC concluded that nivolumab compared with docetaxel could not be considered cost-effective in patients with advanced or metastatic NSCLC with disease progression on or after cytotoxic chemotherapy.

CADTH, 2014 [8]. Crizotinib (Xalkori) Resub Advanced NSCLC; Final Clinical Guidance Report

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall benefit to crizotinib in treatment of patients with ALK-positive advanced or metastatic NSCLC as second-line systemic therapy. Crizotinib has demonstrated a clear clinically and statistically significant benefit in terms of progression-free survival compared to standard second-line chemotherapy in one Phase III randomised study.

Baumann et al., 2016 [3].

Pembrolizumab (Keytruda®) in previously treated advanced non-small cell lung cancer (NSCLC)

KEYNOTE-010 reports superior efficacy (OS, PFS and RR) with fewer side effects for PD-L1 positive patients, defined as an expression of ≥50% by means of an FDA-specified test compared to docetaxel. Besides the challenge of defining a PD-L1 expression cut-off value or other predictive biomarkers for response, and technical issues in regard to PD-L1 testing, generalizability is unclear as only relatively young patients with an ECOG of 0 or 1 have been included in the KEYNOTE-010 trial. Additionally, the benefit for patients with an EGFR mutation has to be further examined. Patient-relevant outcomes (such as QoL) are still missing but shall be measured in an ongoing trial. Also, the evaluation of safety and efficacy of combination therapies is ongoing.

McGahan L et al., 2017 [62].

Atezolizumab (Tecentriq®) in previously treated non-small cell lung cancer (NSCLC)

Overall, with the exception of those with EGFR mutations, atezolizumab in-creases OS and DOR in previously treated NSCLC patients regardless of PD-L1 expression or histology, with a favourable safety profile compared to docetaxel. There is no evidence regarding quality of life, patient reported outcome measures or patient reported experience measures to determine whether atezolizumab provides clinically significant improvement in the symptoms or severity of NSCLC. Results from OAK hold limited external validity as participants are not entirely generalizable to clinical practice. Longer trials are needed that directly compare the safety and efficacy of ate-zolizumab versus other immunotherapies such as nivolumab or pembroli-zumab, or docetaxel in combination with nintedanib or ramucirumab.

Nachtnebel et al., 2015 [63].

Nivolumab (Nivolumab BMS®) for the second-line therapy of metastatic squamous non-small cell lung cancer

Overall, improved outcomes in all assessed endpoints were demonstrated in the CheckMate 017 trial, with fewer AEs in comparison to standard secondline chemotherapy. It is likely that the drug will become the new standard for the treatment of non-squamous NSCLC. Nonetheless, high costs are incurred, data for patient-reported outcomes have not been published yet and long-term adverse effects of immune therapies are unknown.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 13.03.2018

#	Suchfrage
1	[mh “Carcinoma, Non-Small-Cell Lung”]
2	(((non next small) or nonsmall) next cell next lung):ti,ab,kw
3	(tumor* or tumour* or carcinoma* or adenocarcinoma* or neoplasm* or sarcoma* or cancer*):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 from 2013 to 2018

SR, HTAs in Medline (PubMed) am 13.03.2018

#	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 ("2013/03/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 13.03.2018

#	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 ("2013/03/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT ((Humans[mh] AND animals[MeSH:noexp]) NOT ("The Cochrane database of systematic reviews"[Journal])))

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[Zugriff: 13.03.2018]. (pan-Canadian Oncology Drug Review (pCODR)). URL: https://www.cadth.ca/sites/default/files/pcodr/nivolumab_opdivo_nsclc_fn_rec.pdf.

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