Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

sowie

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

Vorgang: 2016-B-072 Crizotinib

Stand: Juli 2016

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Crizotinib **[zur Behandlung des ROS1-positiven nicht kleinzelligen Lungenkarzinoms]**	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	*Nicht angezeigt*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	**Nutzenbewertungen:** • Crizotinib: Beschluss vom 2. Mai 2013 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Afatinib: Beschluss vom 8. Mai 2014 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Nintedanib : Beschluss vom 18. Juni 2015 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Ceritinib: Beschluss vom 17. Dezember 2015 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Nivolumab : Beschluss vom 4. Februar 2016 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Crizotinib (neues AWG): Beschluss vom 16. Juni 2016 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Crizotinib **[zur Behandlung des ROS1-positiven nicht kleinzelligen Lungenkarzinoms]**	
Kriterien gemäß 5. Kapitel § 6 VerfO	
	Richtlinien: Carboplatin: Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie - Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten - (Stand: 26. Februar 2016): Arzneimittel, die unter Beachtung der dazu gegebenen Hinweise in nicht zugelassenen Anwendungsgebieten (Off-Label-Use) verordnungsfähig sind: • Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCL) – Kombinationstherapie Richtlinie Methoden Krankenhausbehandlung (Stand: 7. Mai 2016); Ausgeschlossene Methoden (§ 4): • Protonentherapie beim inoperablen nicht-kleinzelligen Lungenkarzinom des UICC Stadiums IV • Protonentherapie bei Hirnmetastasen • Protonentherapie bei Lebermetastasen
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Beratungsanforderung/Fachinformation)
Zu prüfendes Arzneimittel:	
Crizotinib L01XE16 Xalkori®	XALKORI wird angewendet bei Erwachsenen zur Behandlung des ROS1-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, NSCLC).
Chemotherapien:	
Carboplatin L01XA02 (generisch)	Off-Label-Indikation für Carboplatin: Kombinationstherapie des fortgeschrittenen NSCLC (palliativ)
Cisplatin L01XA01 (generisch)	Cisplatin wird angewendet zur Behandlung des: fortgeschrittenen oder metastasierten nichtkleinzelligen Bronchialkarzinoms. Cisplatin kann als Mono- oder Kombinationstherapie angewendet werden. (Cisplatin Teva® 1 mg / ml Konzentrat; März 2015)
Docetaxel L01CD02 (generisch)	Nicht-kleinzelliges Bronchialkarzinom: Docetaxel ist zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Bronchialkarzinom nach Versagen einer vorausgegangenen Chemotherapie angezeigt. Docetaxel ist in Kombination mit Cisplatin zur Behandlung von Patienten mit nicht resezierbarem, lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Bronchialkarzinom ohne vorausgegangene Chemotherapie angezeigt. (Docetaxel-ratiopharm® 20 mg/ml; Konzentrat Februar 2016)
Etoposid L01CB01 (generisch)	Etoposid ist in Kombination mit anderen antineoplastisch wirksamen Arzneimitteln bei der Behandlung folgender bösartiger Neubildungen angezeigt: Palliative Therapie des fortgeschrittenen nicht-kleinzelligen Bronchialkarzinoms bei Patienten in gutem Allgemeinzustand (Etopophos® 100 mg/1000 mg; September 2015)
Gemcitabin	Gemcitabin ist in Kombination mit Cisplatin als Erstlinientherapie von Patienten mit lokal fortgeschrittenem oder metastasiertem

L01BC05 (generisch)	nichtkleinzelligen Bronchialkarzinom (NSCLC) angezeigt. Eine Gemcitabin-Monotherapie kann bei älteren Patienten oder solchen mit einem Performance Status 2 in Betracht gezogen werden. (Gemcitabin Kabi 38 mg/ml Konzentrat; März 2015)
Ifosfamid L01AA06 (Holoxan®)	Nicht-kleinzellige Bronchialkarzinome: Zur Einzel- oder Kombinationschemotherapie von Patienten mit inoperablen oder metastasierten Tumoren. (Holoxan® Januar 2015)
Mitomycin L01DC03 (generisch)	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Bei intravenöser Gabe ist es in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei folgenden metastasierenden Tumoren wirksam: […] nicht-kleinzelliges Bronchialkarzinom […]. (Mitomycin Teva® 1 mg/ml; Februar 2016)
Paclitaxel L01CD01 (generisch)	Fortgeschrittenes nicht-kleinzelliges Bronchialkarzinom (NSCLC): Paclitaxel ist, in Kombination mit Cisplatin, zur Behandlung des nicht-kleinzelligen Bronchialkarzinoms bei Patienten angezeigt, für die potentiell kurative chirurgische Maßnahmen und/oder eine Strahlentherapie nicht in Frage kommen. (Paclitaxel-GRY® 6 mg/ml Konzentrat; März 2016)
Pemetrexed L01BA04 (Alimta®)	Alimta ist in Kombination mit Cisplatin angezeigt zur first-line Therapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie. Alimta in Monotherapie ist angezeigt für die Erhaltungstherapie bei lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie bei Patienten, deren Erkrankung nach einer platinbasierten Chemotherapie nicht unmittelbar fortgeschritten ist. Alimta in Monotherapie ist angezeigt zur Behandlung in Zweitlinientherapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie. (Alimta®; Februar 2016)
Vindesin L01CA03 (Eldesine®)	Kombinationschemotherapie: Lokal fortgeschrittenes oder metastasiertes nicht-kleinzelliges Bronchialkarzinom (Stadium IIIB, IV).
Vinorelbin L01CA04 (generisch)	Vinorelbin ist angezeigt zur Behandlung: des nicht kleinzelligen Bronchialkarzinoms (Stadium 3 oder 4). (Vinorelbin Hospira 10 mg/ml Konzentrat Juni 2014)
Proteinkinase-Inhibitoren:	

Afatinib L01XE13 (Giotrif®)	Giotrif® als Monotherapie wird angewendet zur Behandlung von: epidermaler Wachstumsfaktorrezeptor (EGFR)-Tyrosinkinaseinhibitor (TKI)-naiven erwachsenen Patienten mit lokal fortgeschrittenem und/oder metastasiertem nicht-kleinzelligen Lungenkarzinom (NSCLC, non small cell lung cancer) mit aktivierenden EGFR-Mutationen; lokal fortgeschrittenem oder metastasiertem NSCLC mit Plattenepithel-Histologie, das unter oder nach Platin-basierter Chemotherapie fortschreitet. (Giotrif®; März 2016)
Erlotinib L01XE03 (Tarceva®)	Nicht-kleinzelliges Lungenkarzinom (NSCLC): Tarceva ist zur First-Line-Behandlung bei Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit aktivierenden EGFR-Mutationen angezeigt. Tarceva ist auch für eine Wechsel-Erhaltungstherapie (switch maintenance treatment) bei Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC mit aktivierenden EGFR-Mutationen und unverändertem Krankheitszustand nach First-Line-Chemotherapie angezeigt. Tarceva ist auch zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC angezeigt, bei denen mindestens eine vorausgegangene Chemotherapie versagt hat. Beim Verschreiben von Tarceva sollten Faktoren, die im Zusammenhang mit einer verlängerten Überlebenszeit stehen, berücksichtigt werden. Bei Patienten mit epidermalen Wachstumsfaktor-Rezeptor-(EGFR)-IHC-negativen Tumoren konnten weder ein Überlebensvorteil noch andere klinisch relevante Wirkungen durch die Behandlung gezeigt werden. (Tarceva®; Januar 2016)
Gefitinib L01XE02 (Iressa®)	Iressa® ist angezeigt zur Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Lungenkarzinom (NSCLC) mit aktivierenden Mutationen der EGFR-TK. (Iressa® 250 mg; September 2014)
Osimertinib L01XE35 (Tagrisso®)	Tagrisso ist angezeigt zur Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem, nichtkleinzelligem Lungenkarzinom (NSCLC) und einer positiven T790M-Mutation des epidermalen Wachstumsfaktor-Rezeptors (Epidermal Growth Factor Receptor, EGFR). (Tagrisso®; März 2016)
Ceritinib L01XE28 (Zykadia®)	Zykadia wird angewendet bei erwachsenen Patienten zur Behandlung des fortgeschrittenen, Anaplastische-Lymphomkinase(ALK)-positiven, nicht-kleinzelligen Bronchialkarzinoms (NSCLC), die mit Crizotinib vorbehandelt wurden. (Zykadia®; August 2015)
Nintedanib L01XE31	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

(Vargatef®)	Erstlinienchemotherapie. (Vargatef®;Januar 2016)
Antikörper:	
Bevacizumab L01XC07 (Avastin®)	Bevacizumab wird zusätzlich zu einer platinhaltigen Chemotherapie zur First-Line-Behandlung von erwachsenen Patienten mit inoperablem fortgeschrittenem, metastasiertem oder rezidivierendem nicht-kleinzelligem Bronchialkarzinom, außer bei vorwiegender Plattenepithel-Histologie, angewendet. Bevacizumab wird in Kombination mit Erlotinib zur First-Line-Behandlung von erwachsenen Patienten mit inoperablem fortgeschrittenem, metastasiertem oder rezidivierendem nicht-kleinzelligem Nicht-Plattenepithel-Bronchialkarzinom mit Mutationen, die den epidermalen Wachstumsfaktorrezeptor (EGFR) aktivieren, angewendet. (Avastin®; Juni 2016)
Necitumumab L01XC22 (Portrazza®)	Portrazza ist in Kombination mit Gemcitabin- und Cisplatin-Chemotherapie indiziert zur Therapie von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem, den epidermalen Wachstumsfaktor-Rezeptor (EGFR) exprimierenden, plattenepithelialen, nicht-kleinzelligen Lungenkarzinom, wenn diese bislang keine Chemotherapie für dieses Stadium der Erkrankung erhalten haben. (Portrazza®; Februar 2016)
Nivolumab L01XC17 (Opdivo®)	Nicht-kleinzelliges Lungenkarzinom (NSCLC): Opdivo ist zur Behandlung des lokal fortgeschrittenen oder metastasierten nichtkleinzelligen Lungenkarzinoms (NSCLC) nach vorheriger Chemotherapie bei Erwachsenen indiziert. (Opdivo®; Mai 2016)
Ramucirumab L01XC21 Cyramza®	Cyramza ist in Kombination mit Docetaxel indiziert zur Behandlung von erwachsenen Patienten mit einem lokal fortgeschrittenen oder metastasierten nicht-kleinzelligen Lungenkarzinom mit Tumorprogress nach platinhaltiger Chemotherapie. (Cyramza®; Januar 2016)

Quellen: AMIS-Datenbank, Fachinformationen

Recherche und Synopse der Evidenz zur Bestimmung der zVT:

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation **„fortgeschrittenes nicht-kleinzelliges Lungenkarzinom“** durchgeführt. Der Suchzeitraum wurde insgesamt auf die letzten 6 Jahre eingeschränkt, eine Initialrecherche erfolgte am 05.06.2015 und eine Folgerecherche wurde am 13.06.2016 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, 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 1270 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 69 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation für die Recherche:

bei Erwachsenen zur Behandlung des fortgeschrittenen nicht kleinzelligen Lungenkarzinoms

Berücksichtigte Wirkstoffe/Therapien:

Siehe Übersicht „I. Zweckmäßige Vergleichstherapie“ und „II. Zugelassene Arzneimittel im Anwendungsgebiet.“

Ergänzungen/Hinweise zur Auswahl der Literatur:

- Die Leitlinien und Systematischen Reviews sind nach Erst- und Zweitlinie geordnet.
- Variationen in den Therapieregimen (z.B. Therapiedauern und zeitliche Abfolgen, Therapiezyklen, Therapiewechsel und ihre Bedingungen) wurden nicht berücksichtigt.
- Publikationen zur Radiochemotherapie wurden nicht eingeschlossen. Ebenso hier nicht berücksichtigt ist die Prothonentherapie ist (vgl. G-BA, 2011**:** Protonentherapie beim Nichtkleinzelligen Lungenkarzinom (NSCLC). Abschlussbericht. Beratungsverfahren nach § 137c SGB V (Krankenhausbehandlung 13. Januar 2011. Protokollnotiz: Beratungen hierzu sollen 2015 wieder aufgenommen werden).
- Studien zur Erhaltungstherapie wurden nicht eingeschlossen *(Hinweis: Eigene aktuelle Synopse zur Beratung: Durvalumab 2016-B-066)*

- Gelb markierte Literaturquellen stellen neue Evidenz, resultierend aus der Folgerecherche da bzw. beinhalten ergänzend extrahierte Inhalte die relevant für das zu beratende Anwendungsgebiet sind.

Abkürzungen

ACCP	American College of Chest Physicians
AE	unerwünschte Ereignisse (adverse events)
AIOT	Italian Associatlon of Thoracic Oncology
ALK	Anaplastic Lymphoma Kinase
AM	Arzneimittel
ASCO	American Society of Clinical Oncology
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
BSC	Best supportive care
CCO	Cancer Care Ontario
CECOG	Central European Cooperative Oncology Group
CI	Konfidenzintervall
CIS	Cisplatin
DAHTA	Deutsche Agentur für Health Technology Assessment
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
ESMO	European Society for Medical Oncology
FACT-L	Functional assessment of cancer-lung (questionnaire)
FEM	Fixed effects model
G-BA	Gemeinsamer Bundesausschuss
GEF/GFT	Gefintinib
GEM	Gemcitabin
GIN	Guidelines International Network
GoR	Grade of Recommendation
GP	Gemcitabin + Cisplatin
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	hazard ratio
ILD	interstitial lung disease
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
k.A.	keine Angabe
KRAS	Kirsten rat sarcoma viral oncogene homolog
LoE	Level of Evidence
M+	mutation positive (EGFR)
NCCN	National Comprehensive Cancer Network
NCI	U.S. National Cancer Institute
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NSCLC	non-small cell lung cancer (nichtkleinzelliges Bronchialkarzinom)
OR	Odds ratio
ORR	Gesamtansprechen (overall response)
OS	Gesamtüberleben (Overall survival)
PAX	Paclitaxel
PEM	Pemetrexed
PFS	Progressionsfreies Überleben (progression free survival)
PLAT	Platinhaltige Chemotherapeutika
PR	Partial response
PS	Performance status

QOL/ QoL	Quality of life
RCT	randomized controlled trial
RR	risk ratio
SACT	systemic anticancer therapy
SR	Systematisches Review
TA	Technology Assessment
TAX	Docetaxel
TKI	Tyrosinkinsaseinhibitor
TOI	Trial outcome index
TRIP	Turn Research into Practice Database
TTP	Time to Progression
UICC	Union for International Cancer Control
VEGF	vascular endothelial growth factor
VNB	Vinorelbin
vs.	versus
WHO	World Health Organisation
WT	wild type

IQWiG Berichte/G-BA Beschlüsse

G-BA, 2015 [23]. 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	**Zugelassenes Anwendungsgebiet:** Nintedanib (Vargatef®) wird angewendet in Kombination mit Docetaxel zur Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem, metastasiertem oder lokal rezidiviertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit Adenokarzinom-Histologie nach Erstlinienchemotherapie. **Zweckmäßige Vergleichstherapie:** - Eine Chemotherapie mit Docetaxel oder Pemetrexed *oder* - Gefitinib oder Erlotinib (nur für Patienten mit aktivierenden EGFR-Mutationen) *oder* - Crizotinib (nur für Patienten mit aktivierenden ALK-Mutationen) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber einer Chemotherapie mit Docetaxel: Hinweis für einen geringen Zusatznutzen
G-BA, 2014 [18]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage VI - Off-Label-Use Teil A Ziffer III. Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie, Zustimmung eines pharmazeutischen Unternehmers	Der Gemeinsame Bundesausschuss hat in seiner Sitzung am 17. Juli 2014 beschlossen, die Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (Arzneimittel-Richtlinie) in der Fassung vom 18. Dezember 2008 / 22. Januar 2009 (BAnz. Nr. 49a vom 31. März 2009), zuletzt geändert am 19. Juni 2014 (BAnz AT 09.09.2014 B2), wie folgt zu ändern: I. Die Ziffer III. der Anlage VI Teil A zur Arzneimittel-Richtlinie wird unter Nr. 1 Buchstabe j „Zustimmung des pharmazeutischen Unternehmers“ wie folgt geändert: Im zweiten Absatz wird nach der Angabe „Stada Arzneimittel AG“ die Angabe „Sun Pharmaceuticals Germany GmbH“ eingefügt. II. Die Änderungen treten am Tag nach ihrer Veröffentlichung im Bundesanzeiger in Kraft. Die Tragenden Gründe zu diesem Beschluss werden auf den Internetseiten des Gemeinsamen Bundesausschusses unter www.g-ba.de veröffentlicht. Eckpunkte der Entscheidung (Anmerkung: aus den Tragenden Gründen zum Beschluss) Die Firma Sun Pharmaceuticals Germany GmbH hat ... über die Umsetzung der Empfehlung der Expertengruppe Off-Label zu „Carboplatin-haltigen Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie“ die Anerkennung des bestimmungsgemäßen Gebrauchs nach § 84 AMG ihrer Carboplatin-haltigen Arzneimittel zur Anwendung bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie erklärt.
G-BA, 2013 [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 –	**Anwendungsgebiet:** Zur Behandlung des vorbehandelten Anaplastische-Lymphom-Kinase (ALK)-positiven, fortgeschrittenen nicht kleinzelligen Bronchialkarzinoms (non small cell lung cancer, NSCLC). **Zweckmäßige Vergleichstherapie:** a) Patienten, bei denen eine Chemotherapie angezeigt ist: Docetaxel oder PEM zur Behandlung von Patienten, bei denen eine Chemotherapie angezeigt ist (dies können insbesondere Patienten mit ECOG-PS 0, 1 und gegebenenfalls 2 sein). **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber der Chemotherapie mit Docetaxel oder PEM:

Crizotinib	Anhaltspunkt für einen *beträchtlichen* Zusatznutzen. **Zweckmäßige Vergleichstherapie:** b) Patienten, bei denen eine Chemotherapie nicht angezeigt ist: BSC zur Behandlung von Patienten, bei denen eine Chemotherapie nicht angezeigt ist (dies können insbesondere Patienten mit ECOG-PS 4, 3 und gegebenenfalls 2 sein). **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber BSC: Ein Zusatznutzen ist *nicht belegt.*
GBA, 2011 [24]. Protonentherapie beim Nichtkleinzelligen Lungenkarzinom (NSCLC) Abschlussbericht. Beratungsverfahren nach § 137c SGB V (Krankenhausbehandlung)	Der Gemeinsame Bundesausschuss hat in seiner Sitzung am 21. Oktober 2010 beschlossen, die Richt-linie zu Untersuchungs- und Behandlungsmethoden im Krankenhaus (Richtlinie Methoden Kranken-hausbehandlung) in der Fassung vom 21. März 2006 (BAnz. 2006, S. 4466), zuletzt geändert am 18. Februar 2010 (BAnz. 2010, S. 1784), wie folgt zu ändern: I. In § 4 („Ausgeschlossene Methoden“) werden nach Nummer 3.7 folgende Nummern angefügt: „3.8 Protonentherapie beim operablen nicht-kleinzelligen Lungenkarzinom 3.9 Protonentherapie beim inoperablen nicht-kleinzelligen Lungenkarzinom des UICC Stadiums IV“ II. In Anlage II „Methoden, deren Bewertungsverfahren ausgesetzt sind“ wird nach Nummer 2.2 folgende Nummer 2.3 angefügt: „2.3 Protonentherapie beim inoperablen nicht-kleinzelligen Lungenkarzinom der UICC Stadien I bis III Beschluss gültig bis 31. Dezember 2015“
G-BA, 2015 Afatanib [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 – Afatinib (Beschluss vom 05.11.2015)	**AWG:** GIOTRIF als Monotherapie wird angewendet zur Behandlung von EGFR-TKI-naiven er-wachsenen Patienten mit lokal fortgeschrittenem und/oder metastasiertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit aktivierenden EGFR-Mutationen. **Zusatznutzen** von Afatnib gegenüber der zVT

	1) Nicht vorbehandelte Patienten mit ECOG-Performance-Status 0 oder 1 **Zweckmäßige Vergleichstherapie:** – Gefitinib oder Erlotinib *oder* – Cisplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel oder Pemetrexed) unter Beachtung des Zulassungsstatus *oder* – Carboplatin in Kombination mit einem Drittgenerationszytostatikum (nur für Patienten mit erhöhtem Risiko für Cisplatin-induzierte Nebenwirkungen im Rahmen einer Kombinationstherapie; vgl. Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Cisplatin in Kombination mit Pemetrexed:** a) Patientengruppe mit EGFR-Mutation Del19: Hinweis auf einen erheblichen Zusatznutzen. b) Patientengruppe mit EGFR-Mutation L858R: Ein Zusatznutzen ist nicht belegt. c) Patientengruppe mit anderen EGFR-Mutationen: Ein Zusatznutzen ist nicht belegt. 2) Nicht vorbehandelte Patienten mit ECOG-Performance-Status 2 **Zweckmäßige Vergleichstherapie:** – Gefitinib oder Erlotinib *oder* – alternativ zu den unter 1) angegebenen platinbasierten Kombinationsbehandlungen: Monotherapie mit Gemcitabin oder Vinorelbin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt. 3) Patienten nach Vorbehandlung mit einer Platin-basierten Chemotherapie **Zweckmäßige Vergleichstherapie:** – Gefitinib oder Erlotinib *oder* – Docetaxel oder Pemetrexed **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt. **Studienergebnisse nach Endpunkten:** 1) Nicht vorbehandelte Patienten mit ECOG-Performance-Status 0 oder 1 Afatinib vs. Cisplatin in Kombination mit Pemetrexed (Studie Lux-Lung 3)[1]
G-BA, 2016 [20] Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII -	**Zugelassenes Anwendungsgebiet (laut Zulassung vom 20.07.2015):** OPDIVO ist zur Behandlung des lokal fortgeschrittenen oder metastasierten nichtkleinzelli-gen Lungenkarzinoms (NSCLC) mit plattenepithelialer Histologie nach vorheriger Chemothe-rapie bei Erwachsenen indiziert. 1) Patienten, für die eine Behandlung mit Docetaxel angezeigt ist: **Zweckmäßige Vergleichstherapie:** Docetaxel

Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Nivolumab (neues Anwendungsgebiet)	**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 **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care:** 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 – Crizotinib (neues Anwendungsgebiet)	**Zugelassenes Anwendungsgebiet (laut Zulassung vom 23.11.2015):** XALKORI wird angewendet bei Erwachsenen zur Erstlinienbehandlung des Anaplastische-Lymphom-Kinase(ALK)-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, NSCLC). **Zweckmäßige Vergleichstherapie:** Patienten mit ECOG-Performance-Status 0, 1 oder 2: − Cisplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel oder Pemetrexed) unter Beachtung des Zulassungsstatus *oder* − Carboplatin in Kombination mit einem Drittgenerationszytostatikum (nur für Patienten mit erhöhtem Risiko für Cisplatin-induzierte Nebenwirkungen im Rahmen einer Kombinationstherapie; vgl. Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie) Patienten mit ECOG-Performance-Status 2: − alternativ zur Platin-basierten Kombinationsbehandlung: eine Monotherapie mit Gemcitabin oder Vinorelbin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Cisplatin in Kombination mit Pemetrexed *oder* Carboplatin in Kombination mit Pemetrexed:** Anhaltspunkt für einen beträchtlichen Zusatznutzen.

de Castria TB, et al., 2013 [12]. Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer	**1. Fragestellung** To assess the efficacy and safety of carboplatin-based chemotherapy when compared with cisplatin-based chemotherapy, both in combination with a third-generation drug, in people with advanced NSCLC. To compare quality of life in people with advanced NSCLC receiving chemotherapy with cisplatin and carboplatin combined with a third-generation drug.
	2. Methodik ***Population:*** people with advanced NSCLC (first-line) ***Interventionen und Komparatoren:*** regimens with cisplatin or carboplatin in combination with a third-generation drug (i.e. docetaxel, paclitaxel, vinorelbine, gemcitabine or irinotecan) • Cisplatin plus gemcitabine versus carboplatin plus gemcitabine. • Cisplatin plus docetaxel versus carboplatin plus docetaxel. • Cisplatin plus paclitaxel versus carboplatin plus paclitaxel. • Cisplatin plus vinorelbine versus carboplatin plus vinorelbine. • Cisplatin plus irinotecan versus carboplatin plus irinotecan. We included trials comparing these compounds for any number of cycles or treatment schedules. ***Endpunkte*:** <u>Primär</u>: • Overall survival. • One-year survival rate. • QoL. • Drug toxicities (according to the National Cancer Institute Common Toxicity Criteria v2.0) <u>Sekundär</u>: Objective response rate, classified according to the Response Evaluation Criteria in Solid Tumors (RECIST) (Eisenhauer 2009). ***Suchzeitraum:*** 1966 bis 03/2013 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 10/5 017 ***Qualitätsbewertung der Studien:*** Risk of bias' tool created by The Cochrane Collaboration: mittlere bis gute Qualität (nur RCTs) ***Heterogenitätsuntersuchungen:*** *durchgeführt (siehe Punkt 3.): geringe Heterogenitäten*
	3. Ergebnisdarstellung

OS

There was no difference between carboplatin based and cisplatin-based chemotherapy in overall survival (hazard ratio (HR) 1.00; 95% confidence interval (CI) 0.51 to 1.97, I^2 =0%) and one-year survival rate (risk ratio (RR) 0.98; 95% CI 0.88 to 1.09, I^2 = 24%).

ORR

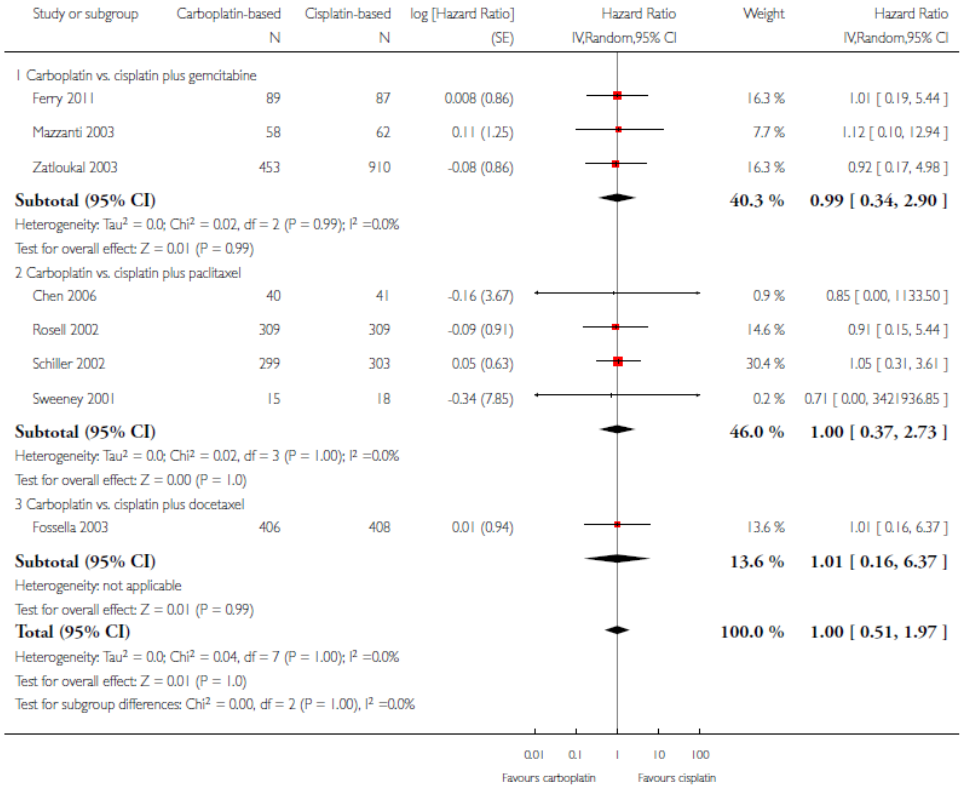
Cisplatin had higher response rates when we performed an overall analysis (RR 0.88; 95% CI 0.79 to 0.99, I^2 = 3%), but trials using paclitaxel or gemcitabine plus a platin in both arms had equivalent response rates (paclitaxel: RR 0.89; 95% CI 0.74 to 1.07, I^2 = 0%; gemcitabine: RR 0.92; 95% CI 0.73 to 1.16, I^2 = 34%).

Adverse events

Cisplatin caused more nausea or vomiting, or both (RR 0.46; 95% CI 0.32 to 0.67, I2 = 53%) and carboplatin caused more thrombocytopenia (RR 2.00; 95% CI 1.37 to 2.91, I2 = 21%) and neurotoxicity (RR 1.55; 95% CI 1.06 to 2.27, I^2 = 0%). There was no difference in the incidence of grade III/IV anaemia (RR 1.06; 95% CI 0.79 to 1.43, I2 = 20%), neutropenia (RR 0.96; 95% CI 0.85 to 1.08, I^2 = 49%), alopecia (RR 1.11; 95% CI 0.73 to 1.68, I2 = 0%) or renal toxicity (RR 0.52; 95% CI 0.19 to 1.45, I^2 = 3%).

QoL

Two trials performed a quality of life analysis; however, they used different methods of measurement so we could not perform a meta-analysis.



	4. Anmerkungen/Fazit der Autoren The initial treatment of people with advanced NSCLC is palliative, and carboplatin can be a treatment option. It has a similar effect on survival but a different toxicity profile when compared with cisplatin. Therefore, the choice of the platin compound should take into account the expected toxicity profile and the person's comorbidities. In addition, when used with either paclitaxel or gemcitabine, the drugs had an equivalent response rate.

Systematische Reviews (Erstlinientherapie)

Sheng Z, Zhang Y, 2015 [57]. EGFR-TKIs combined with chemotherapy versus EGFR-TKIs single agent as first-line treatment for molecularly selected patients with non-small cell lung cancer	**1. Fragestellung** EGFR-TKIs added to chemotherapy and EGFR-TKIs single agent have been used as first-line treatment for advanced non-small cell lung cancer patients with and without EGFR mutations. However, direct headto-head comparison between them is still lacking. We performed indirect comparisons to assess the treatment effects of EGFR-TKIs added to chemotherapy versus EGFR-TKIs alone via common comparator of standard chemotherapy in both subgroups.
	2. Methodik ***Population:*** patients with previously untreated advanced NSCLC, defined as inoperable locally advanced (stage IIIB) or metastatic or recurrent disease (stage IV) ***Interventionen und Komparatoren:*** first-generation EGFR-TKIs (erlotinib or gefitinib) vs. standard platinum doublet chemotherapy as firstline treatment ***Endpunkte*:** Primär: PFS (PFS was measured from the date of enrollment, randomization, or treatment start until disease progression, relapse, or death) Sekundär: OS (OS was measured from the date of enrollment, randomization, or treatment start until death from any cause.) ***Suchzeitraum:*** Bis 9/2014 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 12/2 160 ***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, outcome assessment, and (4) intention-to-treat (ITT) analyses. Each criterion was rated as yes, no, or unclear. ***Heterogenitätsuntersuchungen:*** Cochrane chi-Quadrat Test
	3. Ergebnisdarstellung We found that EGFR-TKIs combined with chemotherapy did confer an

additive PFS advantage over standard chemotherapy both for patients with mutant EGFR tumors (HR 0.54, 95 % CI [0.30, 0.95], P = 0.03) and for patients with wild-type EGFR tumors (HR 0.82, [0.68, 0.98], P = 0.03), but no survival difference between the treatments in both subgroups.

When using standard chemotherapy as common comparator, indirect comparison indicated that addition of chemotherapy to EGFR-TKIs did confer an additive PFS benefit (HR 0.38, [0.32, 0.46], p<0.001) and survival benefit (HR 0.75, [0.66, 0.85], P<0.001) over EGFR TKIs alone in patients with wild-type EGFR, but showed a PFS disadvantage (HR 1.35, [1.03, 1.77], p = 0.03) and a marginal trend toward survival disadvantage (HR 1.16, [0.99, 1.35], p = 0.06) compared with EGFR-TKIs alone in patients with mutant EGFR tumors.

Table 1 Demographic characteristics of patients

Study name (Ref)	No. of $EGFR^-$	No. of $EGFR^+$	Therapy regimen	EGFR assessment method
EGFR-TKIs versus Chemotherapy				
First-SIGNAL [3]	54	43	Gefitinib versus CisG	Direct sequencing
IPASS [4, 5]	176	261	Gefitinib versus CP	ARMS
WJTOG3405 [6, 7]	0	172	Gefitinib versus CisD	Direct sequencing, PCR clamp
NEJ002[b] [8, 9]	0	228	Gefitinib versus CP	PCR clamp
GTOWG[a] [10]	75	10	Erlotinib versus CV	Direct sequencing
TORCH [11]	236	39	Erlotinib versus CisG	Direct sequencing/fragment analysis/MS
EURTAC [12]	0	173	Erlotinib versus platinum-G or platinum-D	Direct sequencing
OPTIMAL [13, 14]	0	154	Erlotinib versus CG	Direct sequencing
EGFR-TKIs + Chemotherapy				
INTACT 1 [15, 16]	280	32	Gefitinib + CisG versus CisG	Direct sequencing
INTACT 2 [16, 17]			Gefitinib + CP versus CP	
TALENT [18, 19]	NA	NA	Erlotinib + CisG versus CisG	NA
TRIBUTE [20]	198	29	Erlotinib + CP versus CP	Direct sequencing

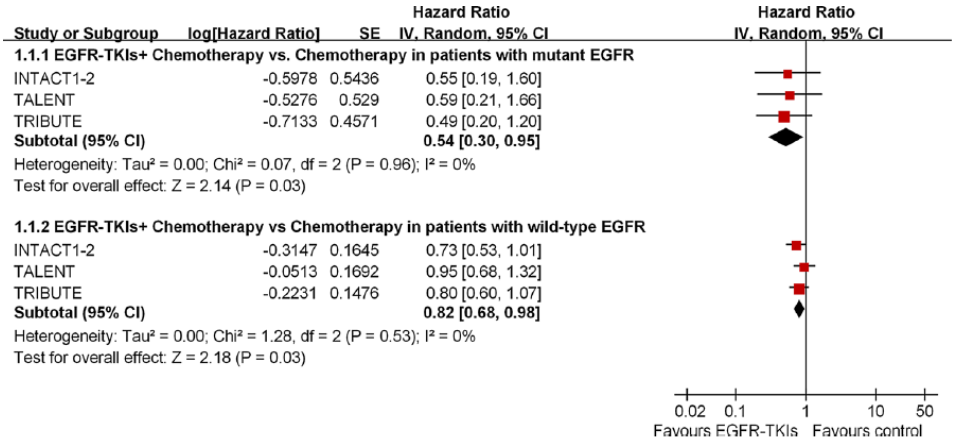
ARMS amplification refractory mutation system, *CisG* cisplatin–gemcitabine, *CP* carboplatin–paclitaxel, *CV* carboplatin–vinorelbine, *CisD* cisplatin–docetaxel, *CG* carboplatin–gemcitabine, *G* gemcitabine, *D* docetaxel, $EGFR^+$ presence of epidermal growth factor receptor mutation, $EGFR^-$ absence of epidermal growth factor receptor mutation, *NA* not available, *PCR* polymerase chain reaction. EGFR mutation based on exon 19 and exon 21 only

[a] Trials reported in abstract format

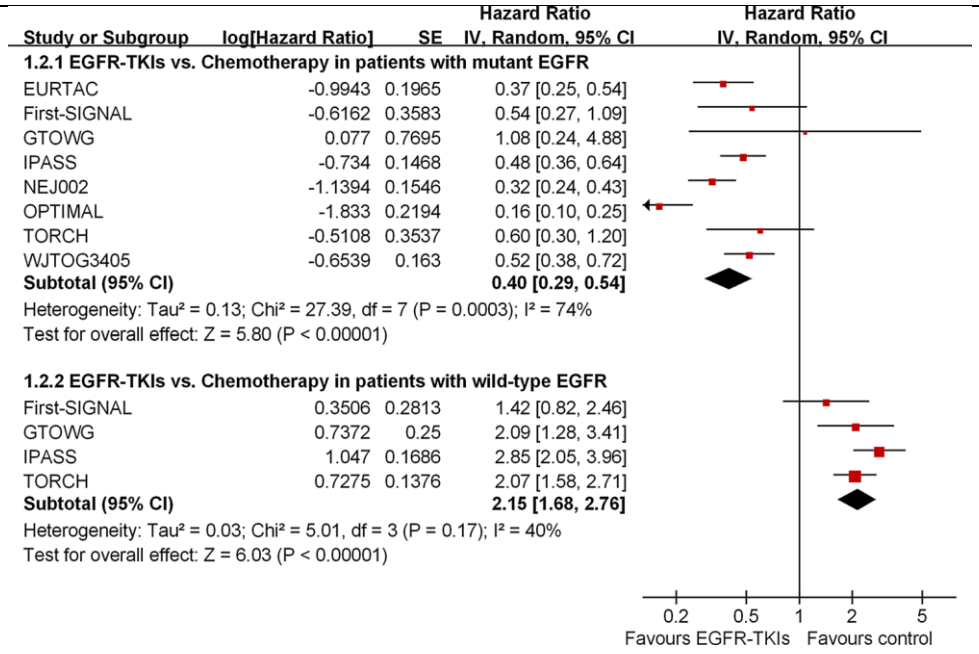
[b] Median age not available; mean age calculated instead

PFS: (random-effects model)

EGFR-TKIs added to chemotherapy versus chemotherapy alone)

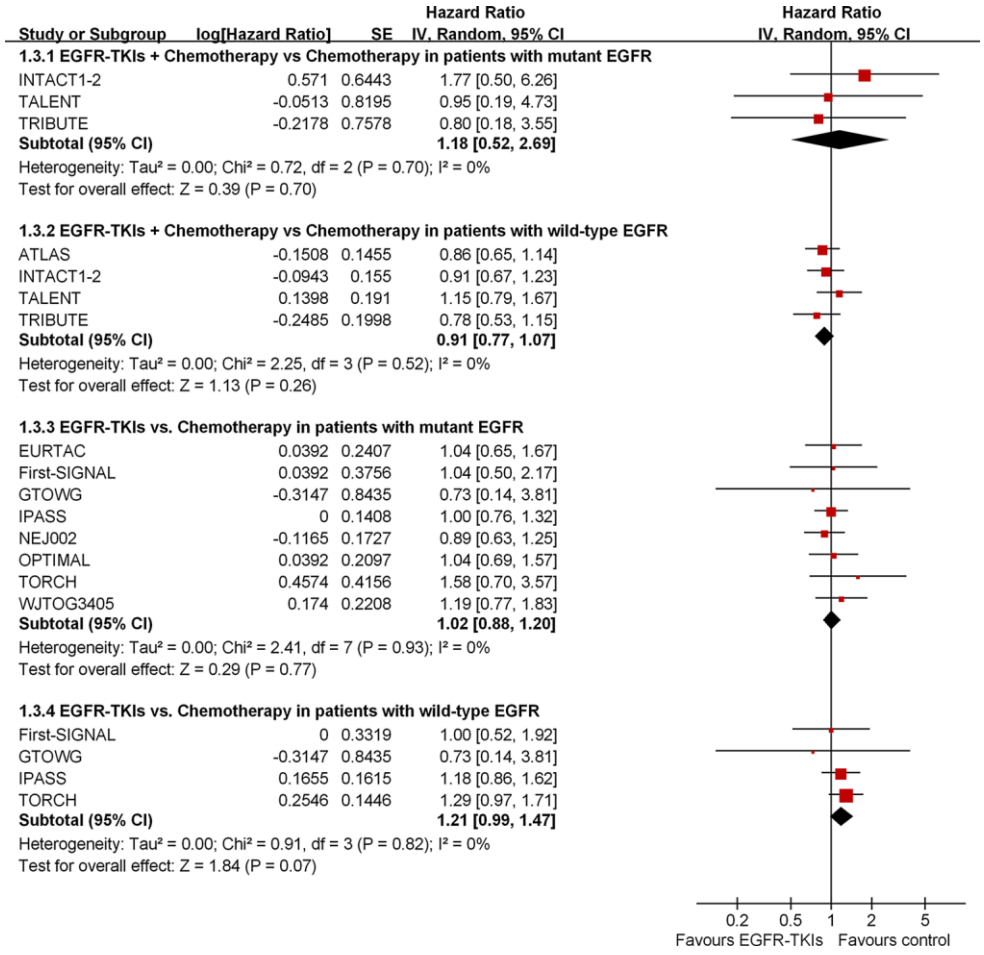


EGFR-TKIs single agent versus chemotherapy



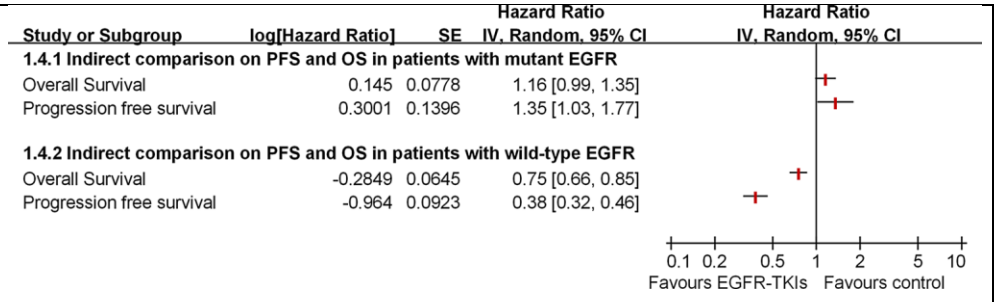
OS: (random-effects model)

EGFR-TKIs arms versus chemotherapy



Indirekter Vergleich:

chemotherapy added to EGFR-TKIs versus EGFR-TKIs single agent

	
	4. Anmerkungen/Fazit der Autoren In summary, addition of chemotherapy to EGFR-TKIs as first-line treatment did confer an additive benefit over EGFR-TKIs alone in patients with wild-type EGFR tumors, but was inferior to EGFR-TKIs alone in patients with mutant EGFR tumors. • limitation of the power of indirect comparison • not an individual patient data-based meta-analysis • effect of heterogeneity needs to be taken into account
Luo L et al., 2015 [35]. Comparing single-agent with doublet chemotherapy in first-line treatment of advanced non-small cell lung cancer with performance status 2: A meta-analysis	**1. Fragestellung** This systematic review and meta-analysis was performed to assess the efficacy and side effects between single-agent and doublet chemotherapy in first-line treatment of advanced non-small cell lung cancer with performance status 2 (PS2).
	2. Methodik ***Population:*** cytologically or pathologically confirmed with NSCLC and in clinical stages III–IV ***Interventionen und Komparatoren:*** efficacy or toxicity of single-agent chemotherapy with doublet chemotherapy in PS2 patients (when participants received prior chemotherapy or surgery, these studies were excluded; and (v) prior radiation therapy was permitted if it did not encompass the index lesion and it was completed 2 or more weeks before protocol enrollment) ***Endpunkte*:** efficacy and toxicity [nicht näher spezifiziert] ***Suchzeitraum:*** Bis 7/2013 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 6 (776); RCTs ***Qualitätsbewertung der Studien:***

Jadad scale

Heterogenitätsuntersuchungen: I^2

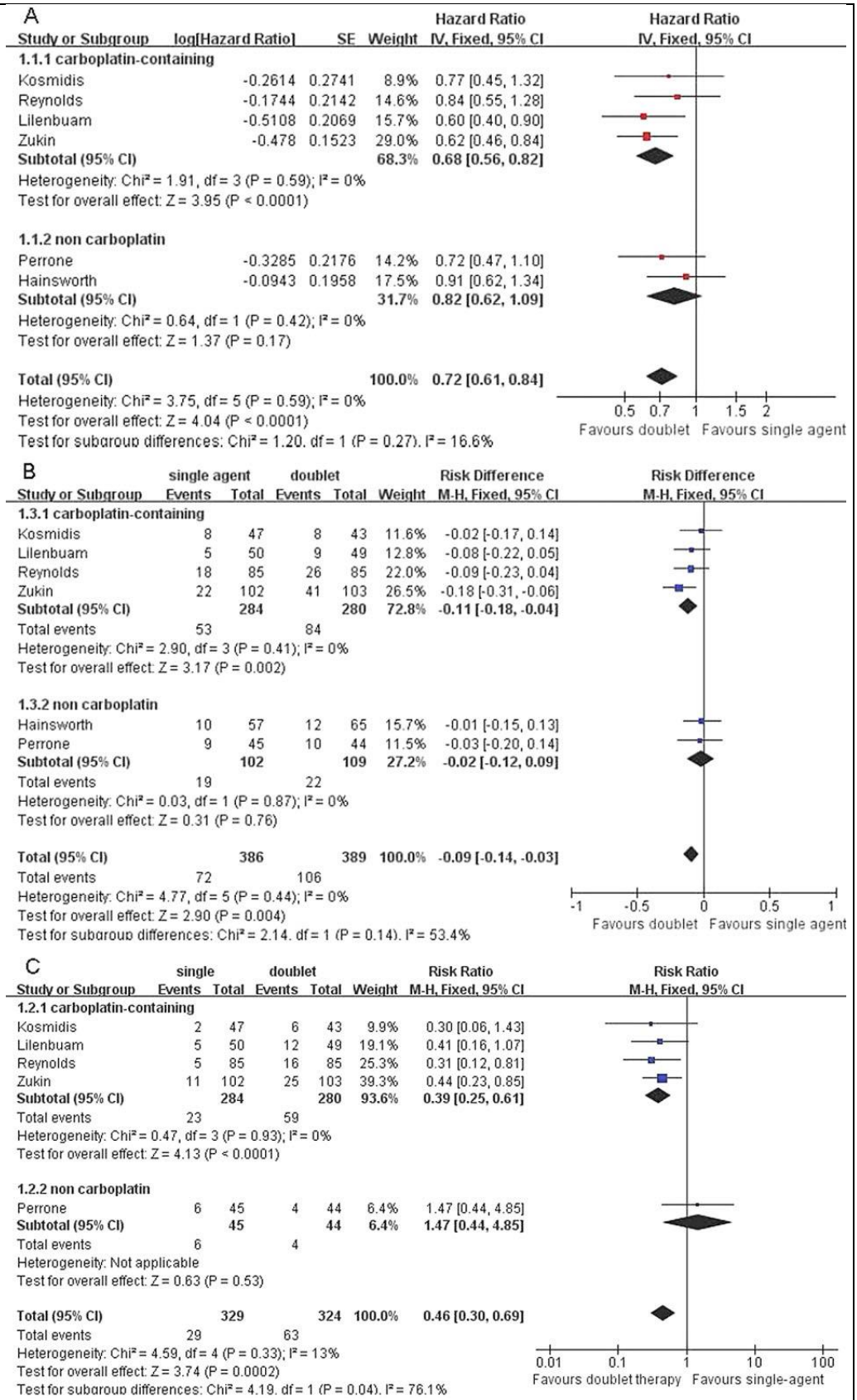
3. Ergebnisdarstellung

Table 1 Characteristics of included studies

Study	Journal	Jadad scale	Clinical trial phase	Treatment	Case	Median age (year)	Median survival (month)	Objective response rate (%)
Perrone *et al.* 2004[9]	Journal of Clinical Oncology	3	Phase III trial	GEM 1000 mg/m^2 NVB 25 mg/m^2	44	>70	5.8	9.1
				NVB 30 mg/m^2	45	>70	3.5	13.3
Lilenbaum 2005	Journal of Clinical Oncology	3	Phase III trial	TAX 225 mg/m^2 CBP AUC = 6	49	—	4.7	24
				TAX 225 mg/m^2	50	—	2.4	10
Kosmidis *et al.* 2007[11]	Journal of Thoracic Oncology	3	Phase II trial	GEM 1250 mg/m^2 d1,d14 CBP AUC = 3	43	70.5	6.7	14
				GEM 1250 mg/m^2 d1,d14	47	73	4.8	4
Hainsworth *et al.* 2007[12]	Cancer	3	Phase III trial	TXT 36 mg/m^2 d1,d8,d15 GEM 800 mg/m^2 d1,d8,d15	65	—	4.8	—
				TXT 36 mg/m^2 d1,d8,d15	57	—	3.9	—
Reynolds *et al.* 2009[13]	Journal of Clinical Oncology	3	Phase III trial	GEM 1000 mg/m^2 d1,d8 CBP AUC = 5 d1	85	72.9	6.7	43.9
				GEM 1250 mg/m^2 d1,d8	85	75.0	5.1	16.4
Zukin 2013	Journal of Clinical Oncology	2	Phase III trial	PEM 500 mg/m^2 CBP AUC = 5	103	65	9.3	24
				PEM 500 mg/m^2	102	65	5.3	10

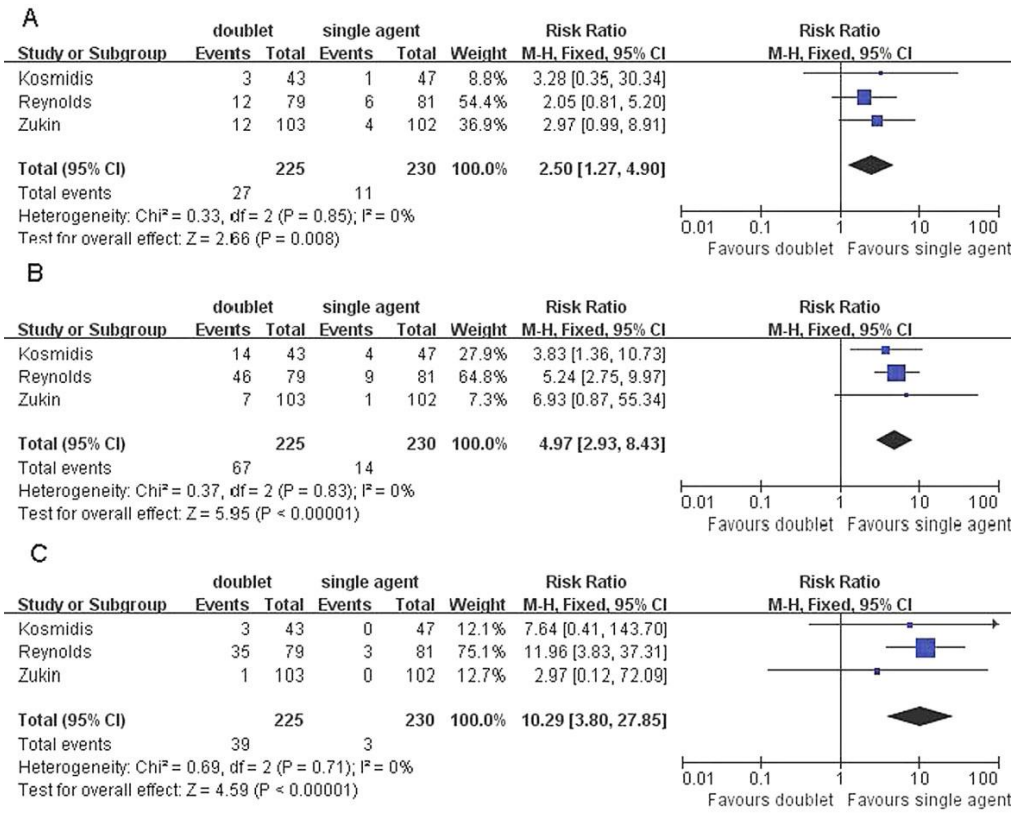
CBP, carboplatin; GEM, gemcitabine; NVB, vinorelbine; PEM, pemetrexed; TAX, paclitaxel; TXT, docetaxel.

Efficacy of single-agent with doublet chemotherapy efficacy in first-line treatment of advanced non-small cell lung cancer with PS2 (a: meta-analysis of OS; b: meta-analysis of 1-year survival rate; c: meta-analysis of ORR).

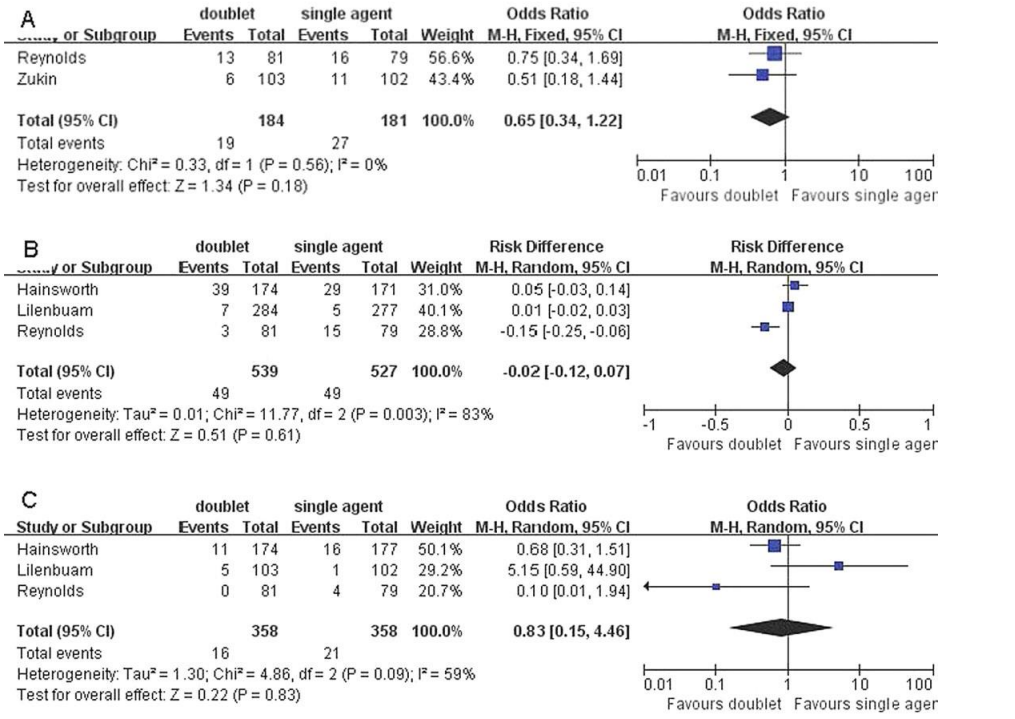


Side effect of single-agent with doublet chemotherapy efficacy in first-line treatment of advanced non-small cell lung

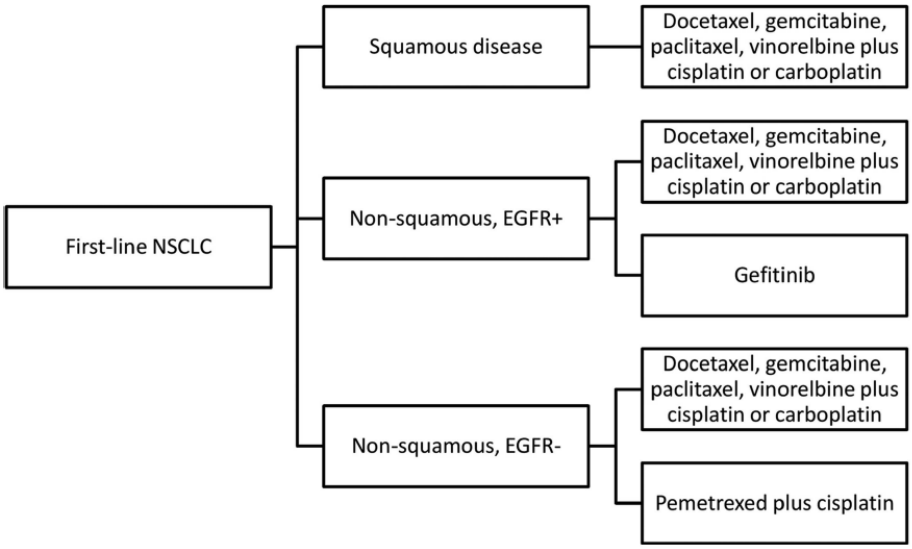
cancer with PS2 (a: meta-analysis of grade 3/4 anemia; b: meta-analysis of grade 3/4 neutropenia; c: meta-analysis of grade ¾ thrombocytopenia).



Side effect of single-agent with doublet chemotherapy efficacy in first-line treatment of advanced non-small cell lung cancer with PS2 (a: meta-analysis of grade 3/4 dyspnea; b: meta-analysis of grade 3/4 fatigue; c: meta-analysis of grade ¾ nausea/vomiting).



	4. Anmerkungen/Fazit der Autoren In conclusion, the results from our meta-analysis imply that carboplatin-containing doublet chemotherapy may well be superior to non-carboplatincontaining treatment. Additional prospective clinical trials are warranted to evaluate treatment combinations. **Limitierungen:** • Some of our selected studies are not blinded. • the number of trials is quite small and may not represent the real situation. • After a careful retrieval in the different database, we found that there was only one article that reported the quality of life (QOL) comparison of the single-agent with doublet chemotherapy in first-line treatment of advanced NSCLC with PS2. There was no evidence that showed the difference between single-agent and doublet chemotherapy in first-line treatment of advanced NSCLC with PS2. We could not expand the analysis of toxicity comparison about the QOL by a meta-analysis.
Pilkington G et al., 2015 [47]. A systematic review of the clinical effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer	**1. Fragestellung** Our aim was to evaluate the clinical effectiveness of chemotherapy treatments currently licensed in Europe and recommended by the National Institute for Health and Care Excellence (NICE) for the first-line treatment of adult patients with locally advanced or metastatic nonsmall cell lung cancer (NSCLC).
	2. Methodik ***Population:*** adult patients with locally advanced or metastatic NSCLC ***Interventionen und Komparatoren:*** treatments had to be currently licensed for use in Europe and recommended by NICE, 1. Linie To reflect current UK treatment pathways (see figure 1), analyses were undertaken and reported for three subpopulations on patients with NSCLC: patients with predominantly squamous disease, patients with predominantly non-squamous disease, and patients who were EGFR M+. In the main, all analyses were conducted on the total population according to randomisation; however, subpopulation data were included in our analyses if used previously for international or national decision making.



***Endpunkte*:** PFS, OS

Suchzeitraum: 2001 to August 2010

Anzahl eingeschlossene Studien/Patienten (Gesamt): 23 RCTs

Qualitätsbewertung der Studien: eigenes Bewertungssystem; Ergebnisse ausführlich berichtet

Heterogenitätsuntersuchungen:

Statistical heterogeneity was assessed by considering the chi-Quardat test for heterogeneity with a 10% level of significance, and the I^2 statistic with a value of 50% representing moderate heterogeneity.

3. Ergebnisdarstellung

Table 1 MA and MTC results, NSCLC population with squamous disease

Reference treatment vs comparator	Number of data points (trials with head-to-head comparison)	Number of patients in reference treatment/ comparator	Number of events (deaths) in reference treatment/comparator	MA HR (95% CI) N=18	MTC HR (95% CI) N=18
Overall survival					
GEM+PLAT vs VNB+PLAT[8 9 21 25–28 35]	8	1075/1077	842/860	1.08 (0.98 to 1.20)	1.09 (0.99 to 1.19)
GEM+PLAT vs PAX+PLAT[9 11 23 28 33 34]	6	1245/1344	1053/1186	1.03 (0.94 to 1.13)	1.05 (0.96 to 1.15)
GEM+PLAT vs DOC+PLAT[34]	1	301/304	262/271	1.06 (0.89 to 1.28)	1.00 (0.88 to 1.13)
VNB+PLAT vs PAX+PLAT[9 19 24 28]	4	625/630	496/481	0.98 (0.83 to 1.16)	0.96 (0.86 to 1.08)
VNB+PLAT vs DOC+PLAT[10 20 22 30]	4	766/1175	607/920	0.89 (0.78 to 1.00)	0.92 (0.81 to 1.03)
PAX+PLAT vs DOC+PLAT[34]	1	602/304	538/271	0.98 (0.76 to 1.27)	0.95 (0.82 to 1.10)
Progression-free survival					
GEM+PLAT vs VNB+PLAT[8 26]	2	269/269	312*	1.09 (0.87 to 1.38)	1.06 (0.81 to 1.39)
GEM+PLAT vs PAX+PLAT[23 34]	2	350/656	142/304†	1.17 (1.00 to 1.36)	1.23 (0.94 to 1.62)
GEM+PLAT vs DOC+PLAT[34]	1	301/304	105/114	1.15 (0.96 to 1.37)	1.08 (0.79 to 1.45)
VNB+PLAT vs PAX+PLAT[19]	1	70/70	7/14†	**1.52 (1.06 to 2.17)**	1.16 (0.87 to 1.61)
VNB+PLAT vs DOC+PLAT[20 22]	2	168/165	92/86	0.92 (0.74 to 1.16)	1.02 (0.78 to 1.36)
PAX+PLAT vs DOC+PLAT[34]	1	602/304	130/263†	0.97 (0.75 to 1.24)	0.88 (0.62 to 1.21)
Time to tumour progression					
GEM+PLAT vs VNB+PLAT[9 21 25 35]	4	433/436	91†/82†	1.03 (0.90 to 1.18)	1.02 (0.83 to 1.25)
GEM+PLAT vs PAX+PLAT[9 11 33]	3	744/742	417†/423†	1.01 (0.90 to 1.13)	1.21 (0.73 to 1.99)
GEM+PLAT vs DOC+PLAT	0	No trial data	No trial data	No trial data	0.98 (0.62 to 1.52)
VNB+PLAT vs PAX+PLAT[9]	1	203/204	34†/37†	0.90 (0.64 to 1.28)‡	0.99 (0.77 to 1.28)
VNB+PLAT vs DOC+PLAT[10]	1	404/406	86†/88†	0.96 (0.70 to 1.31)‡	0.96 (0.65 to 1.43)
PAX+PLAT vs DOC+PLAT	0	No trial data	No trial data	No trial data	0.98 (0.6 to 1.55)

*In one trial PFS events were reported for both arms.
†Includes progressive disease (PD) only as PFS/TTP event (PD or death) not reported.
‡Direct evidence.
Bold text indicates statistically significant results.
DOC, docetaxel; GEM, gemcitabine; MA, meta-analysis; MTC, mixed treatment comparison; NSCLC, non-small cell lung cancer; PAX, paclitaxel; PLAT, platinum; VNB, vinorelbine.

Table 2 MA and MTC results, NSCLC population with non-squamous disease

Reference treatment vs comparator	Number of data points (trials with head-to-head comparison)	Number of patients in reference treatment/ comparator	Number of deaths in reference treatment/ comparator	MA HR (95% CI) N=20	MTC HR (95% CI) N=20
Overall survival					
GEM+PLAT vs VNB+PLAT[8 9 25–28 35 21]	8	1075/1077	842/860	1.08 (0.98 to 1.20)	1.08 (0.99 to 1.18)
GEM+PLAT vs PAX+PLAT[9 11 23 28 33 34]	6	1245/1344	1053/1186	1.03 (0.94 to 1.13)	1.06 (0.97 to 1.16)
GEM+PLAT vs DOC+PLAT[34]	1	301/304	262/271	1.06 (0.89 to 1.28)	0.99 (0.87 to 1.13)
GEM+PLAT vs PEM+PLAT[4 29]	2	1084/1087	755/772	0.85 (0.73 to 1.00)	**0.85 (0.74 to 0.98)**
VNB+PLAT vs PAX+PLAT[9 19 24 28]	4	625/630	496/481	0.98 (0.83 to 1.16)	0.92 (0.68 to 1.24)
VNB+PLAT vs DOC+PLAT[10 20 22 30]	4	766/1175	607/920	0.89 (0.78 to 1.00)	0.98 (0.87 to 1.09)
VNB+PLAT vs PEM+PLAT	0	No trial data	No trial data	No trial data	0.92 (0.82 to 1.03)
PAX+PLAT vs DOC+PLAT[34]	1	602/304	538/271	0.98 (0.76 to 1.27)	**0.79 (0.66 to 0.93)**
PAX+PLAT vs PEM+PLAT	0	No trial data	No trial data	No trial data	0.85 (0.63 to 1.16)
DOC+PLAT vs PEM+PLAT	0	No trial data	No trial data	No trial data	0.94 (0.81 to 1.09)
Progression-free survival					
GEM+PLAT vs VNB+PLAT[8 26]	2	269/269	312*	1.09 (0.87 to 1.38)	1.06 (0.78 to 1.66)
GEM+PLAT vs PAX+PLAT[23 34]	2	350/651	142/304†	1.17 (1.00 to 1.36)	1.23 (0.77 to 1.65)
GEM+PLAT vs DOC+PLAT[34]	1	301/304	105/114	1.15 (0.96 to 1.37)	1.08 (0.7 to 1.61)
GEM+PLAT vs PEM+PLAT[4]	1	1084/1087	NR	0.90 (0.79 to 1.02)	0.90 (0.53 to 1.52)
VNB+PLAT vs PAX+PLAT[19]	1	70/70	7/14†	**1.52 (1.06 to 2.17)**	1.16 (0.6 to 1.65)
VNB+PLAT vs DOC+PLAT[20 22]	2	168/165	92/86	0.92 (0.74 to 1.16)	1.02 (0.61 to 1.44)
VNB+PLAT vs PEM+PLAT	No trial data	No trial data	No trial data	No trial data	0.85 (0.42 to 1.51)
PAX+PLAT vs DOC+PLAT[34]	1	602/304	130/263†	0.97 (0.75 to 1.24)	0.88 (0.59 to 1.52)
PAX+PLAT vs PEM+PLAT	No trial data	No trial data	No trial data	No trial data	0.73 (0.42 to 1.53)
DOC+PLAT vs PEM+PLAT	No trial data	No trial data	No trial data	No trial data	0.83 (0.43 to 1.65)

*Number of events are for both arms.
†Includes progressive disease (PD) only as PFS event (PD or death) not reported.
Bold text indicates statistically significant results.
DOC, docetaxel; GEM, gemcitabine; MA, meta-analysis; MTC, mixed treatment comparison; NSCLC, non-small cell lung cancer; PAX, paclitaxel; PFS, progression-free survival; PEM, pemetrexed; PLAT, platinum; VNB, vinorelbine.

Overall, the quality of the included RCTs was poor—few trials fully reported methods and the definitions of the health outcomes used often differed between trials.

OS, PFS

Table 3 MA and MTC results, NSCLC population with EGFR M+ status

Reference treatment vs comparator	Total deaths/patients in both arms	MA HR (95% CI) N=3	MTC HR (95% CI) N=3
Overall survival			
PAX+PLAT vs GEF[5 31 36]	199*/448	0.94 (0.74 to 1.18)	0.94 (0.67 to 1.3)
DOC+PLAT vs GEF[32]	NR/172	1.64 (0.75 to 3.58)†	1.64 (0.54 to 4.96)
PAX+PLAT vs DOC+PLAT	No trial data	No trial data	0.57 (0.18 to 1.81)
Progression-free survival			
PAX+PLAT vs GEF[5 31 36]	NR/488	**0.38 (0.24 to 0.60)**	**0.39 (0.29 to 0.52)**
DOC+PLAT vs GEF[32]	NR/172	**0.49 (0.33 to 0.73)†**	**0.49 (0.28 to 0.86)**
PAX+PLAT vs DOC+PLAT	No trial data	No trial data	0.79 (0.42 to 1.48)

*Overall survival events not reported by EGFR M+.
†Direct evidence.
Bold text indicates statistically significant results.
DOC, docetaxel; GEF, gefitinib; MA, meta-analysis; MTC, mixed treatment comparison; NR, not reported; NSCLC, non-small cell lung cancer; PAX, paclitaxel; PLAT, platinum.

Quality of Life

Only 12 trials reported outcomes relating to QoL, with QoL being the primary outcome in two trials. MA was not performed due to limited data and variability in the outcome assessment measures reported. …

Eight trials did not report any significant difference in QoL between treatment groups. Four trials reported some significant differences between treatment groups for QoL; in one trial results after two cycles of chemotherapy favoured the paclitaxel+carboplatin arm, whereas results after four cycles favoured the vinorelbine+cisplatin arm.

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	Table 4 Top 10 adverse events by chemotherapy regimen DOC+PLAT: Neutropenia 71.4%; Leucopenia 43.5%; Weakness 16.0%; Pneumonitis 11.5%; Anaemia 11.2%; Asthenia 10.2%; Nausea 9.9%; Vomiting 9.8%; Cancer pain 8.4%; Infection 7.5% GEM+PLAT: Granulocytopenia 48.8%; Asthenia 40.3%; Neutropenia 36.4%; Thrombocytopenia 34.6%; Anorexia 27.0%; Leucopenia 20.1%; Transfusion 18.5%; Alopecia 17.2%; Weakness 17.0%; Anaemia 16.5% PAX+PLAT: Neutropenia 62.5%; Leucopenia 31.9%; Weakness 14.5%; Cancer pain 13.2%; Nausea 10.3%; Anaemia 10.0%; Lethargy 9.4%; Thrombocytopenia 8.3%; Neuropathy 7.9%; Vomiting 7.4% PEM+PLAT: Granulocytopenia 37.9%; Blood transfusions 26.9%; Infection 16.4%; Neutropenia 15.1%; Alopecia 11.9%; Leucopenia 8.2%; Thrombocytopenia 8.1%; Anaemia 7.0%; Fatigue 6.7%; Nausea 6.2% VNB+PLAT: Neutropenia 68.3%; Leucopenia 47.2%; Oedema 24.0%; Anaemia 19.3%; Phlebitis 15.7%; Nausea/vomiting 11.5%; Vomiting 10.3%; Nausea 9.9%; Asthenia 9.4%; Pain 8.3% GEF: Aminotransferase elevation 33.8%; Appetite loss 5.3%; Rash/acne 3.3%; Toxic deaths 3.1%; Diarrhoea 3.1%; Neutropenia 2.8%; Pneumonitis 2.6%; Fatigue 2.5%; Infection 1.8%; Anaemia 1.6% DOC, docetaxel; GEF, gefitinib; GEM, gemcitabine; PAX, paclitaxel; PEM, pemetrexed; PLAT, platinum; VNB, vinorelbine. **4. Anmerkungen/Fazit der Autoren** There are no statistically significant differences in OS between any of the four thirdgeneration chemotherapy regimens. There is statistically significant evidence that pemetrexed+platinum increases OS compared with gemcitabine+platinum. There are no statistically significant differences in OS between gefitinib and docetaxel+platinum or between gefitinib and paclitaxel+platinum. There is a statistically significant improvement in PFS with gefitinib compared with docetaxel+platinum and gefitinib compared with paclitaxel+platinum. Due to reduced generic pricing, third-generation chemotherapy regimens (except vinorelbine) are still competitive options for most patients. **5. Anmerkungen der FBMed:** • Das Ende des Suchzeitraumes liegt relativ weit zurück. • 4 Studien waren nicht adäquat gepowert bei einer Studie war dies unklar. • Unterschiedlich lange Follow-Up-Zeiten: von 11 bis 36 Wochen
Mörth C et al., 2014 [37]. Single-agent versus combination chemotherapy as first-line treatment for patients with advanced non-small cell lung cancer and performance	**1. Fragestellung** The purpose of this study was to compare the efficacy and tolerability of first-line treatment with combination versus single agent chemotherapy in patients with advanced non-small cell lung cancer (NSCLC) and performance status (PS) 2. **2. Methodik** ***Population***: advanced NCSLC mit PS 2 ***Intervention***: combination chemotherapy **Komparator**: single agent chemotherapy ***Endpunkte***: Primär: OS; sekundär: PFS, ORR ***Suchzeitraum***: bis 07/213

status 2: a literature-based meta-analysis of randomized studies	***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 12/1 114 ***Qualitätsbewertung der Studien:*** Cochrane's risk of bias tool ***Heterogenitätsuntersuchungen:*** Durchgeführt (I^2)

3. Ergebnisdarstellung

OS (11 Studien, 1114 Patienten):

- significant improvement in OS in favor of combination treatment compared with single-agent chemotherapy (HR:0.79, 95% CI: 0.71–0.88, p-value < 0.001)
- both for studies dedicated to patients with PS 2 and those that performed subgroup analy-sis based on PS (HR: 0.73, 95% CI: 0.62–0.87 for studies dedicatedto PS 2 and HR: 0.83, 95% CI: 0.72–0.96 for studies with subgroupanalysis, p-value for subgroup difference = 0.30)
- improvement in OS was more pronounced in trials with platinum-based combination versus single-agent therapy (HR: 0.71, 95% CI: 0.61–0.81) while no difference was observed in studies with non-platinum based combination (HR: 0.96, 95% CI: 0.80–1.15) (p-value for subgroup difference = 0.009) (Fig. 2)
- no statistical heterogeneity was observed

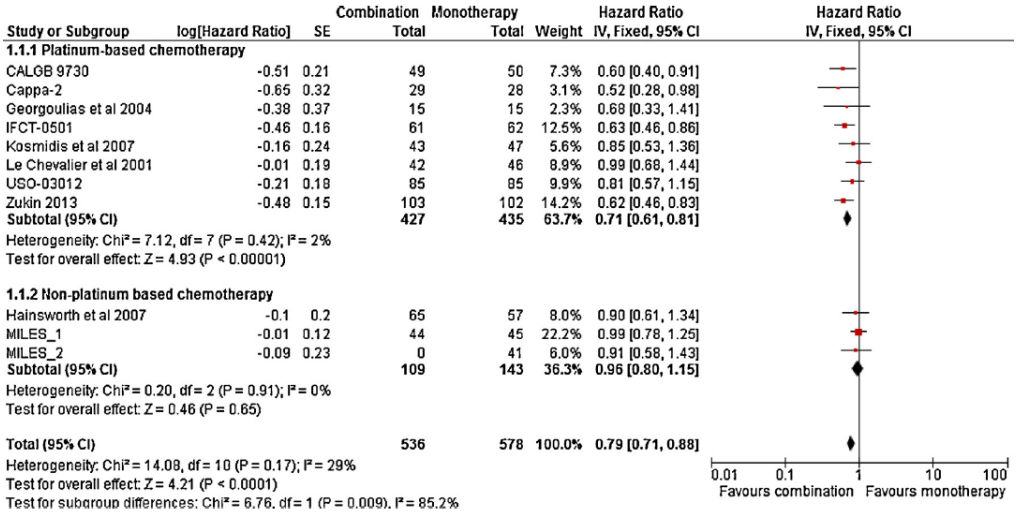


Fig. 2. Forest plot for overall survival (with subgroup analysis based on the administration of platinum-based or non-platinum based chemotherapy in combination arms).The size of the squares indicates the weight of the study. Error bars represent 95% confidence intervals (CIs). The diamond indicates the summary hazard ratio. Values lowerthan one indicate survival advantage of combination chemotherapy.

Table 2
Meta-analyses of grade III–IV adverse events.

Toxicity grade III–IV	No of studies	No of patients analyzed	Pooled OR (95% CI)	*p*-Value
Hematologic				
Anemia	4	519	3.12 (1.55–6.27)	0.001
Trombocytopenia	4	519	12.81 (4.65–33.10)	<0.001
Neutropenia	4	519	7.91 (3.97–15.78)	<0.001
Non-hematologic				
Febrile neutropenia	3	432	0.32 (0.05–2.06)	0.23
Fatigue	3	349	0.75 (0.40–1.40)	0.36
Nausea	3	432	1.21 (0.05–29.34)	0.91

***PFS** (5 Studien, 522 Patienten)*

	combination chemotherapy resulted in statisticallysignificant longer PFS compared with single agent chemotherapy(HR: 0.61, 95% CI: 0.45–0.84, p-value = 0.002) ***grades III and IV toxicity*** *(4 Studien)* Due to lack of adequate data, we could not perform meta-analysis on the incidence of other toxicities.
	4. Anmerkungen/Fazit der Autoren This meta-analysis provides evidence supporting the use of combination chemotherapy in patients with NSCLC and PS 2. However, the patients should be informed about the higher risk for toxicity with the combination chemotherapy and the final treatment strategy should be individualized **Einschränkungen:** unable to investigate whether the survival benefit with combination chemotherapy is similar on different histological subtypesof lung cancer *Anmerkungen FB Med:* • *eine Phase II Studie eingeschlossen* • *study funded by the Centre for Clinical ResearchSörmland, Uppsala University* • *authors have no conflict of interest to declare*
Brown T et al., 2013 [8]. Clinical effectiveness and cost-effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: a systematic review and economic evaluation	**1. Fragestellung** To evaluate the clinical effectiveness and cost-effectiveness of first-line chemotherapy currently licensed in Europe and recommended by NICE, for adult patients with locally advanced or metastatic nonsmall cell lung cancer (NSCLC).
	2. **Methodik** **Population**: locally advanced or metastatic NSCLC **Intervention**: chemotherapy drug regimens that are currently licensed in Europe and are recommended by NICE in a monotherapy or in combination, first line **Komparator**: platinum (PLAT) drug **Endpunkte**: Overall survival (OS), OS at 1 and 2 years, progression-free survival (PFS), time to progression (TTP), tumour overall response rate, quality of life (QoL) and adverse events (AEs). **Suchzeitraum**: 1990 bis 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 23/11 428 **Qualitätsbewertungen der Studien**: All included trials were assessed for methodological quality using criteria based on the Centre for Reviews and Dissemination (CRD) guidance.

	3. Ergebnisdarstellung ***Quality assessment*** Overall, the quality of the included RCTs was poorer than expected: there were few trials with fully reported methods and the definitions of the health outcomes used often differed between trials. • 23 trials involving > 11,000 patients in total met the inclusion criteria ***patients with squamous disease*** • no statistically significant differences in OS between treatment regimes ***patients with non-squamous disease (mixed-treatment comparison)*** • pemetrexed (Alimta®, Eli Lilly and Company; PEM) + platinum (PLAT) increases OS statistically significantly compared with gemcitabine (Gemzar®, Eli Lilly and Company; GEM) + PLAT [hazard ratio (HR) = 0.85; 95% confidence interval (CI) 0.74 to 0.98] • docetaxel (Taxotere®, Sanofi-aventis; DOC) + PLAT increases OS statistically significantly compared with paclitaxel (Abraxane®, Celgene Corporation; PAX) + PLAT (HR = 0.79, 95% CI 0.66 to 0.93) • It remains unknown whether or not the clinical effectiveness of PEM + PLAT is superior to that of GEF monotherapy for patients with non-squamous disease. ***patients with EGFR M+ status*** • none of the comparisons found any statistically significant differences in OS • direct metaanalysis: statistically significant improvement in PFS with gefitinib (Iressa®, AstraZeneca; GEF) compared with DOC + PLAT and PAX + PLAT (HR = 0.49; 95% CI 0.33 to 0.73; and HR = 0.38; 95% CI 0.24 to 0.60, respectively), with significant quantitative heterogeneity between the two trials ***QoL (insgesamt 12 Studien)*** Measuring QoL outcomes in patients with advanced NSCLC is difficult mainly because of the severity of symptoms, the side effects of chemotherapy and early deaths associated with NSCLC. However, the British Thoracic Oncology Group Trial 2 has shown that it is feasible to collect QoL data in patients with performance status (PS) 0–2, stage IIIB/IV NSCLC disease within a clinical trial setting. • employed instruments/tools: EORTC QLQ-C30 + lung cancer-specific module QLQ-LC13 (5 trials), LCSS (3 trials), FACT-L32 (3 trials) Four reported some significant differences between treatment groups for QoL; however, in one of these trials, results after two cycles of chemotherapy favoured the PAX + CARB arm over the VNB + CIS arm, and results after four cycles favoured the VNB + CIS arm. In one trial, significantly more patients in the GEF group than in the PAX + CARB group had a clinically relevant improvement in QoL, as assessed by scores on the FACT-L

	questionnaire (odds ratio = 1.34; 95% CI 1.06 to 1.69; p = 0.01) and by scores on the Trial Outcome Index (TOI) (which is the sum of the physical well-being, functional well-being and lung cancer subscale scores of FACT-L; odds ratio = 1.78; 95% CI 1.40 to 2.26; p < 0.001). Seven trials reported no significant difference in QoL between treatment groups. ***AEs*** Across all the chemotherapy arms of the included trials, the most common AEs were neutropenia, anaemia and leucopenia. Rates of haematological AEs were similar for all the chemotherapy drugs with the exception of GEF, which appears to be associated with a significantly lower evere AE rate than some of the other drugs. The trials often varied in the way that AEs were defined, measured and reported. ***Limitations*** Poor trial quality and a lack of evidence for all drug comparisons complicated and limited the data analysis. Outcomes and adverse effects are not consistently combined across the trials. Few trials reported quality-of-life data despite their relevance to patients and clinicians.
	4. Anmerkungen/ Fazit der Autoren The results of this comprehensive review are unique to NSCLC and will assist clinicians to make decisions regarding the treatment of patients with advanced NSCLC. The design of future lung cancer trials needs to reflect the influence of factors such as histology, genetics and the new prognostic biomarkers that are currently being identified. In addition, trials will need to be adequately powered so as to be able to test for statistically significant clinical effectiveness differences within patient populations. New initiatives are in place to record detailed information on the precise chemotherapy (and targeted chemotherapy) regimens being used, together with data on age, cell type, stage of disease and performance status, allowing for very detailed observational audits of management and outcomes at a population level. It would be useful if these initiatives could be expanded to include the collection of health economics data.
Zhang X et al., 2013 [65]. **Pemetrexed plus platinum or gemcitabine plus platinum for advanced non-small cell lung cancer: final survival analysis from a**	**1. Fragestellung** To systematically evaluate pemetrexed/platinum as firstline treatment for advanced NSCLC.
	2. Methodik **Population**: patients with stage IIIB or stage IV NSCLC. First-line **Intervention**: pemetrexed/platinum **Komparator**: gemcitabine/platinum **Endpunkte**: OS, toxicity **Qualitätsbewertung dre Primärstudien**: Jadad scale

multicentre randomized phase II trial in the East Asia region and a meta-analysis	**Suchzeitraum**: up to 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 3/2 412

3. Ergebnisdarstellung

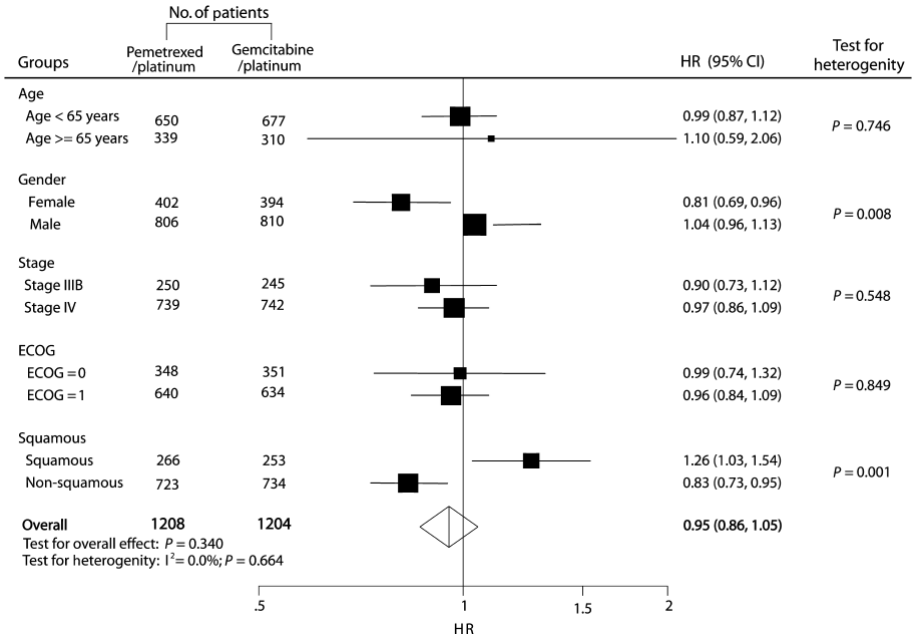
Table 4 Characteristics of the trials included in the meta-analysis

Study	Total accrual	Treatment dose and schedule	Stage IV (%)	ECOG PS = 2 (%)	Non-squamous (%)	Female (%)	Median OS (95% CI) (month)	1-year survival rate (%)	2-year survival rate (%)
Scagliotti *et al.* (2008)[7]	1725	Pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 on d1, every 3 weeks for up to six cycles	76.2	0	71.7	29.8	10.3 (9.8, 11.2)	43.5	18.9
		Gemcitabine 1,250 mg/m^2 on d1 and d8, plus cisplatin 75 mg/m^2 on d1, every 3 weeks for up to six cycles	75.7	0	73.5	29.9	10.3 (9.6, 10.9)	41.9	14.0
Grønberg *et al.* (2009)[8]	436	Pemetrexed 500 mg/m^2 plus carboplatin AUC5 on d1, every 3 weeks for up to four cycles	71	22	74	44	7.3 (6.1, 8.6)	34	NR
		Gemcitabine 1,000 mg/m^2 on d1 and d8, plus carboplatin AUC5 on d1, every 3 weeks for up to four cycles	72	23	77	41	7.0 (5.8, 8.2)	31	NR
Zhang *et al.* (current study)	251	Pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 on d1, every 3 weeks for up to six cycles	64.6	0	82.7	38.6	15.3 (12.2, 18.9)	59.6	27.3
		Gemcitabine 1,000 mg/m^2 on d1 and d8, plus cisplatin 75 mg/m^2 on d1, every 3 weeks for up to six cycles	71.8	0	80.6	37.9	16.9 (14.6, 20.3)	65.9	27.9

AUC, area under concentration/time curve; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; NR, not reported; OS, overall survival.

Overall survival:

- Overall population: no statistically significant difference
- Female population: statistically significant difference in favor of pemetrexed/platinum (HR 0.81; 95% CI 0.69–0.96, significant heterogeneity)
- Non squamous cell lung cancer: statistically significant difference in favor of pemetrexed/platinum (HR 0.83; 95% CI 0.73–0.95, significant heterogeneity)
- Squamous cell lung cancer:statistically significant difference in favor of gemcitabine/platinum (HR 1.26; 95% CI 1.03–1.54, significant heterogeneity)



Pooled treatment effect on overall survival within the major patient subgroups, as determined by meta-analysis. ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval.

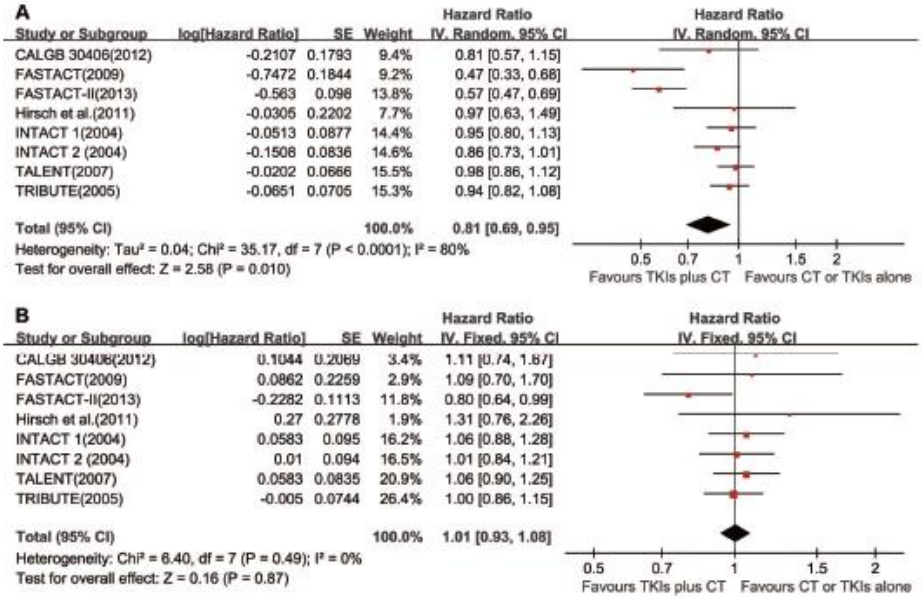
Toxicity: pemetrexed-platinum treatment was associated with significantly lower ORs for leukopenia (OR 0.43; 95% CI 0.29-0.65; p < 0.0001),

	thrombocytopenia (OR 0.28; 95% CI 0.21–0.37; p < 0.001) and neutropenia (OR 0.57; 95% CI 0.45–0.74; p < 0.001).
	4. Anmerkungen/Fazit der Autoren Meta-analysis supports the use of pemetrexed-platinum as first-line treatment for female patients and those with the non-squamous cell subtype of advanced NSCLC. ***Anmerkungen der FB Med:*** • *1 Phase II Studie mit chinesischen Patient*innen eingeschlossen* • *JH and JL received consulting fees from QILU Pharmaceutical Co. Ltd. JW and PM are employed by QILU Pharmaceutical Co. Ltd.*
Ou Yang PY et al., 2013 [44]. Combination of EGFR-TKIs and Chemotherapy as First-Line Therapy for Advanced NSCLC: A Meta-Analysis	**1. Fragestellung** Controversy continues regarding the role of the addition of EGFR–TKIs in patients receiving chemotherapy. Therefore, we conducted this meta-analysis to comprehensively estimate the treatment effect of the combined regimen on PFS and overall survival (OS) based on characteristics of patients.
	2. Methodik **Population**: chemotherapy-naive patients with advanced NSCLC **Intervention**: Chemotherapy, first-line treatment **Komparator**: EGFR–TKI monotherapy or the combined regimen of EGFR–TKI and chemotherapy **Endpunkte**: PFS, OS **Suchzeitraum**: k.A. **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 8/4 585 **Qualitätsbewertung der Studien:** examined the randomization procedure, estimation of sample size, blinding, loss to follow-up, dropout and if the intention-to-treat analysis (prospective randomized controlled trials (phase II or III) **Heterogenitätsuntersuchungen**: Chi-square test and I2 statistic **Publication bias**: Begg's test and Egger's test
	3. Ergebnisdarstellung • 3 Phase II Studien, 5 Phase III Studien eingeschlossen • all studies were of high quality – blinding, showing randomization procedure, conducting estimation of sample size, mostly reporting dropout and following the principle of intention to-treat analysis ***Unselected Patients (4 Studien)*** ***PFS:*** Significant PFS benefit was observed from the combined regimen of TKIs and chemotherapy (HR= 0.81, 95% CI 0.69–0.95, P = 0.01; Figure 2a) based on random-effects model, due to significant heterogeneity (Chi2 =

35.17, P<0.001; I^2 = 80%).

OS: no evidence of improvement in OS with the combined regimen (HR= 1.01, 95% CI 0.93–1.08, P = 0.87, fixed-effects model

Figure 2. Forest plots in unselected patients.

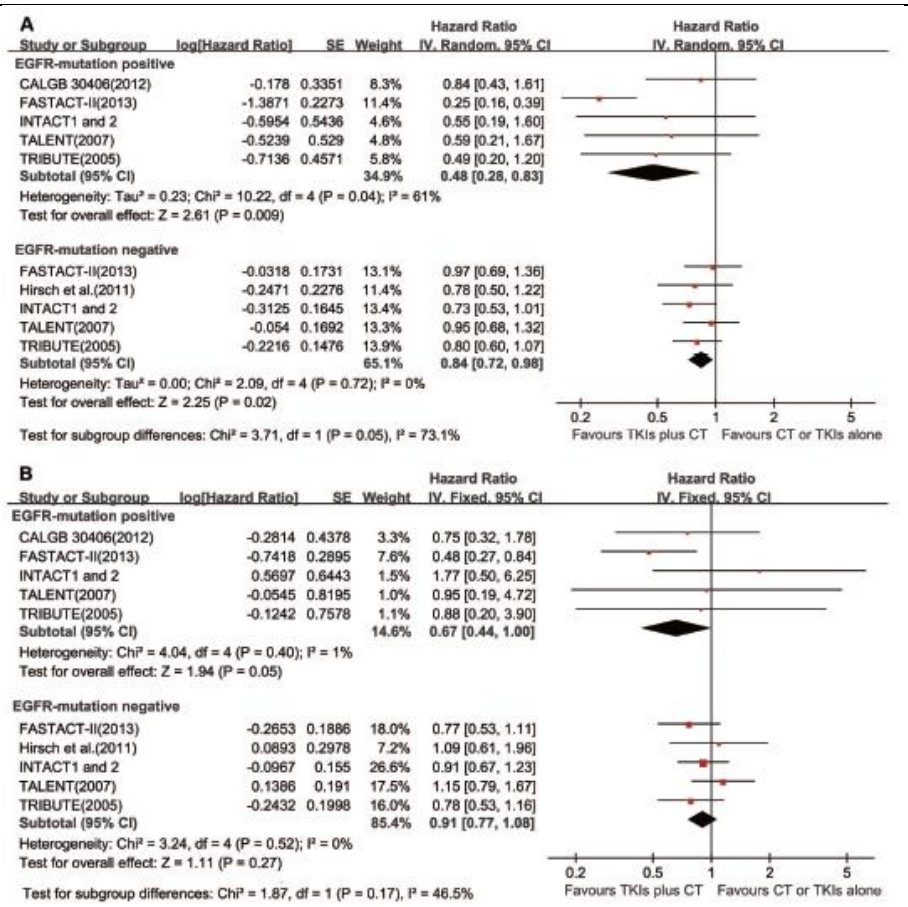


Selected Patients by EGFR-Mutation Status (4 Studien)

PFS: combined regimen was superior over chemotherapy or TKIs monotherapy with a significant improvement in PFS (HR= 0.48, 95% CI 0.28–0.83, P = 0.009); combined regimen also showed significant PFS benefit in the EGFR-mutation negative cohort, compared with chemotherapy or TKIs monotherapy (HR =0.84, 95% CI 0.72–0.98, p= 0.02, Figure 3a)

OS: combined regimen marginally enhanced OS of EGFR-mutation positive patients (HR =0.67, 95% CI 0.44–1.00, P = 0.05), but not EGFR-mutation negative patients (HR =0.91, 95% CI 0.77–1.08, p= 0.27, Figure 3b)

Figure 3. Forest plots in selected patients

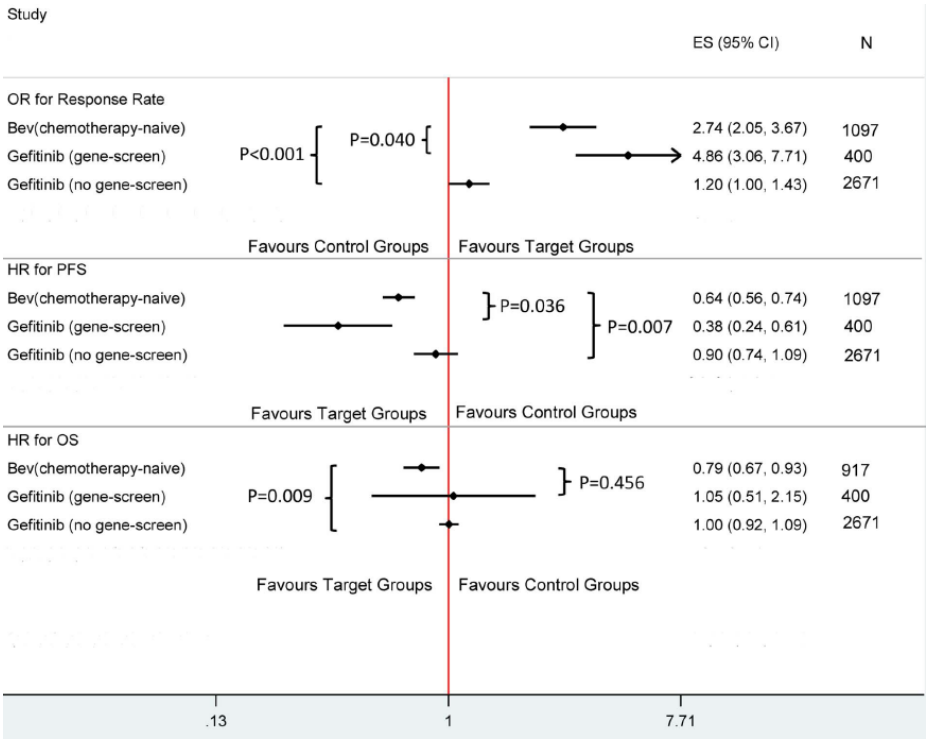
	 **4. Anmerkungen/Fazit der Autoren** In conclusion, on the basis of this meta-analysis, combination of EGFR–TKIs and chemotherapy leads to PFS benefit as first-line treatment for advanced NSCLC, regardless of EGFR-mutation status, but has no demonstrable impact on OS. And there is a larger magnitude of PFS benefit for Asian patients, with sequential administration of EGFR–TKIs and chemotherapy. EGFR-mutation status is still a predictive biomarker of benefit with the combined regimen, for a larger magnitude of improvement in EGFR-mutation positive patients. This strategy deserved to be considered in the future although it is not approved for advanced NSCLC at the moment. *Anmerkungen FB Med* • *Funding: The authors have no support or funding to report.* • *Competing Interests: The authors have declared that no competing interests exist.*
Jiang J et al., 2013 [30]. Non-platinum doublets were as effective as platinum-based	**1. Fragestellung** The aim was to compare the efficacy between doublets of third-generation agents (non-platinum) and doublets of platinum plus a third-generation agent (platinum-based) for chemotherapy-naı¨ve advanced non-smallcell lung cancer (NSCLC).
	2. Methodik

doublets for chemotherapy-naive advanced non-small-cell lung cancer in the era of third-generation agents	**Population**: cytologically or pathologically confirmed of NSCLC and in clinical III–IV stage and chemotherapy-naive **Intervention**: non-platinum doublets (two-thirdgeneration agents combination) **Komparator**: platinum-based doublets (cisplatin or carboplatin combined with a thirdgeneration agent) **Endpunkte**: Primär: OS, sekundär; PFS, RR; toxicity **Suchzeitraum**: 2000 bis 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 16/k.A. **Qualitätsbewertung der Studien**: assessed with the components recommended by the Cochrane Collaboration **Heterogenitätsuntersuchungen**: Cochran Q statistic
	3. Ergebnisdarstellung ***OS*** pooled HR f (HR = 1.03, 95 % CI = 0.98–1.08, p = 0.29) ***RR*** Pooled RR = 0.99, 95 % CI = 0.90–1.08, p = 0.24 ***PFS*** pooled HR : platinum-based doublets might have an advantage in PFS compared with non-platinum doublets (HR = 1.06, 95 % CI = 1.01–1.12, p = 0.03). ***Toxicity*** • The Grade 3–4 nausea or vomiting, anemia, neutropenia, thrombocytopenia, alopecia, and hearing loss of **vinorelbine plus gemcitabine** may be less frequent than platinum-based doublets, while grade 3–4 constipation of vinorelbine plus gemcitabine may be more frequent than platinum-based doublets. • The grade 3–4 toxicity of **vinorelbine plus paclitaxel** may be comparable with platinum-based doublets excepted for neutropenia and allergy, which might be more frequent in **vinorelbine plus paclitaxel** group. • **Gemcitabine plus paclitaxel** was more tolerable than platinum-based doublets on the whole according to anemia, neutropenia, thrombocytopenia except grade 3–4 peripheral neuropathy and alopecia. • **Gemcitabine plus carboplatin** caused especially more grade 3–4 anemia, neutropenia, thrombocytopenia and hemorrhage than gemcitabine plus paclitaxel. • **Gemcitabine plus docetaxel** caused less nausea or vomiting, diarrhea,

	anemia and neutropenia, but more lung toxicity than platinum-based doublets. • **Vinorelbine plus cisplatin** may cause more grade 3–4 peripheral neuropathy than gemcitabine plus docetaxel.
	4. Anmerkungen/Fazit der Autoren Non-platinum doublets were as effective as platinum-based doublets with different toxicity profile for chemotherapy-naı¨ve advanced NSCLC in the era of thirdgeneration agents. *Anmerkungen der FB Med:* • *Kein Hinweis auf Publikationsbias (Begg's funnel plot)* • *5 Phase II Studien eingeschlossen, „Sensitivity analyses were conducted when the low-quality studies were removed." – no significant differences* • *work supported by the National Natural Science Foundation of China (Grant number 81101551)* • *Conflict of interest: None*
Cui J et al., 2013 [11]. The Efficacy of Bevacizumab Compared with Other Targeted Drugs for Patients with Advanced NSCLC: A Meta-Analysis from 30 Randomized Controlled Clinical Trials	**1. Fragestellung** The extent of the benefit of bevacizumab combined with chemotherapy in the treatment of advanced nonsmall- cell lung cancer (NSCLC) is still unclear. We performed this meta-analysis to compare the efficacy of bevacizumab with other commonly used targeted drugs for different patients with advanced NSCLC.
	2. Methodik **Population:** patients with confirmed stage IIIB, stage IV or recurrent NSCLC based on historical or cytological evidence **Intervention**: bevacizumab (15 mg/kg) with chemotherapy **Komparator**: standard chemotherapy alone, 1. und 2. Linie **Endpunkt**: OS, ORR, PFS **Suchzeitraum**: 1999 to 2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 30/k.A. **Qualitätsbewertung der Primärstudien**: Jadad Score **Heterogenitätsuntersuchungen**: I2
	3. Ergebnisdarstellung 1. Linie (chemotherapy-naive patients) • the pooled OR of response rate was 2.741(95%CI: 2.046, 3.672), • the pooled HR for disease progression was 0.645 (95%CI: 0.561, 0.743), • the pooled HR for death was 0.790 (95%CI: 0.674, 0.926),

respectively

EGFR-Status



Response rate, PFS, OS of Bevacizumab versus Gefitinib in NSCLC patients with different EGFR status.

Table 2. Crude and risk-adjusted hazard ratio of BEV comparing to C/E/G.

patients	Response variable	Treatment group	Number of trials	Crude		Adjusted	
				HR_{Crude}	95%CI	$HR_{Adjusted}$	95%CI
Chemotherapy-naïve	HR_{PFS}	Bev	3	0.753	(0.570, 0.996)	0.847*	(0.687, 1.043)
		C/E/G	18	1	–	1	–
Previously-treated	HR_{PFS}	Bev	2	0.758	(0.482, 1.191)	0.680*	(0.492,0.942)
		C/E/G	6	1	–	1	–
Chemotherapy-naïve	HR_{OS}	Bev	2	0.774	(0.617, 0.972)	1.151**	(0.828, 1.600)
		C/E/G	18	1	–	1	–
Previously-treated	HR_{OS}	Bev	2	0.985	(0.658, 1.475)	1.262**	(0.927, 1.710)
		C/E/G	6	1	–	1	–

*$HR_{adjusted}$ was adjusted by $\ln(OR_{ORR})$.
**$HR_{adjusted}$ was adjusted by $\ln(HR_{PFS})$.

4. Fazit der Autoren

Bevacizumab accompanied by chemotherapy was found to significantly improve patients' response rate, progression free survival (PFS), and overall survival (OS) among chemotherapy-naive patients compared to other targeted drugs in the treatment of non-small cell lung carcinoma (NSCLC).

Limitierungen

- Our study included clinical trials with only slightly different enrollment criteria and patient demographics. However patient characteristics (age, gender, ECOG performance status) were found not to be balanced between groups in a small number of trials. Such patient level difference may lead to heterogeneity in the meta-analysis.
- Inconsistency of chemotherapies of the control group did exist in this analysis, which could not be eliminated due to the study background.

	• Finally, the clinical trials collected in this study show high heterogeneity. *Anmerkungen Fb Med:* • *Funding: The work is supported by the National Natural Science Foundation of China (30972551, 81273187); http://www.nsfc.gov.cn/. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.* • *Competing Interests: The authors have declared that no competing interests exist.*
Jiang J et al., 2013 [31]. Paclitaxel plus platinum or gemcitabine plus platinum in first-line treatment of advanced non-small-cell lung cancer: results from 6 randomized controlled trials	**1. Fragestellung** to compare the efficacy and toxicity of paclitaxel plus platinum (TP) with gemcitabine plus platinum (GP) in untreated advanced non-small-cell lung cancer by a meta-analysis.
	2. Methodik **Population:** patients must be cytologically or pathologically confirmed of NSCLC and in clinical III–IV stage, patients must be chemotherapy-naive **Intervention:** paclitaxel plus platinum (TP) **Komparator:** gemcitabine plus platinum (GP) **Endpunkt:** efficacy, toxicity **Suchzeitraum:** bis 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 6/ 2 793 **Qualitätsbewertung der Primärstudien:** Jadad score **Heterogenitätsuntersuchungen:** I^2
	3. Ergebnisdarstellung As there were no double-blind trials, the highest quality scores of the 6 trials according to Jadad's method were 3, and all 6 trials scored 3 **1-Jahres-Überleben (6 trials):** no statistically significant difference (RR = 0.99, 95% CI = 0.90–1.09, p = 0.87; I^2=6%) **Gesamtüberleben (6 trials)**: no statistically significant difference (RR = 1.06, 95% CI = 1.00–1.13, p = 0.07; I^2=16%) **Response (6 trials)**: no statistically significant difference (RR = 0.99, 95 % CI = 0.88–1.13, p = 0.92, I^2=9%) **Toxicity:** Grade 3–4 nausea or vomiting was less frequent in the TP than the GP group (10.5 vs. 17.4 %, RR = 0.53, 95 % CI = 0.35–0.78, p = 0.002). Grade 3–4 sensory neuropathy and fatigue were comparable between the TP and GP arms. Grade 3–4 anemia (8.8 vs. 22.4 %, RR = 0.37, 95 % CI = 0.30–0.45, p<0.00001) and thrombocytopenia (8.8 vs. 47.8 %, RR = 0.20, 95 % CI = 0.14–0.27, p<0.00001) were less frequent in the TP than the GP

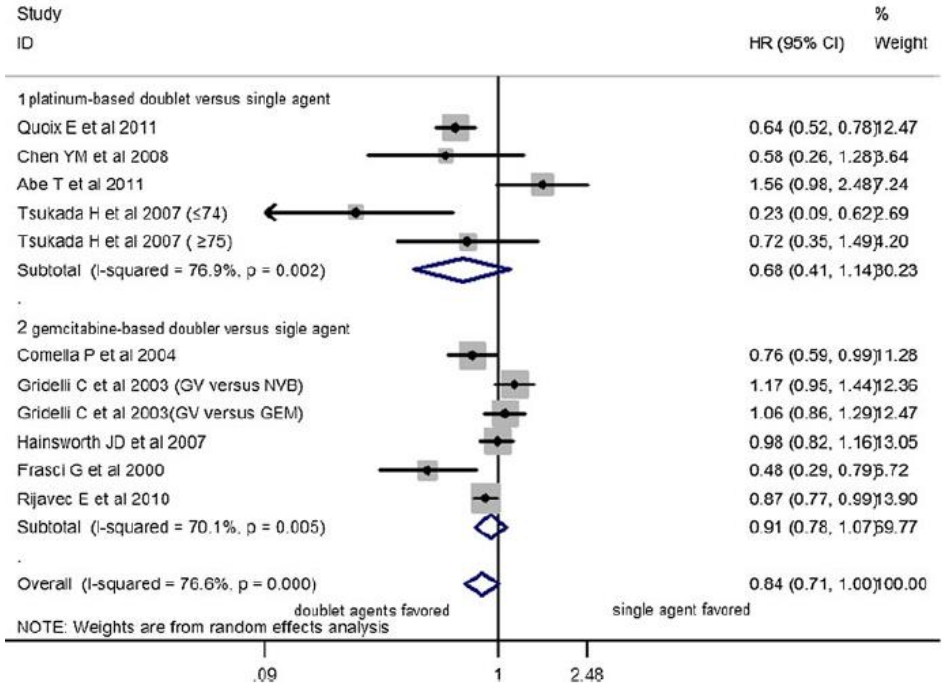
	group.
	4. Anmerkungen/Fazit der Autoren Our meta-analysis showed that paclitaxel plus platinum had similar efficacy and less toxicity compared with gemcitabine plus platinum in first-line treatment of advanced non-small-cell lung cancer. *Anmerkungen FB Med:* • *Acknowledgments This work was supported by grants from the National Natural Science Foundation of China (81101551).* • *Conflict of interest The authors indicated no potential conflicts of interest.* • *eine Phase II Studie eingeschlossen, in sensitivitätsanalysen keine Unterschiede*
Qi WX et al., 2012 [50]. **Doublet versus single cytotoxic agent as first-line treatment for elderly patients with advanced non-small-cell lung cancer: a systematic review and meta-analysis**	**1. Fragestellung** to perform a systematic review and meta-analysis of all randomized controlled trials that compared the efficacy of doublet versus single third-generation cytotoxic agent as first-line treatment for elderly patients with advanced non-small-cell lung cancer (NSCLC).
	2. Methodik **Population**: elderly (older than 65 years) patients with advanced non-small-cell lung cancer. First-line **Interventionen**: doublet cytotoxic agents **Komparator**: single third-generation cytotoxic agent **Endpunkte**: OS, TTP, ORR, Toxicity **Suchzeitraum**: 1980-2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 10/2 510 Qualitätsbewertung der Studien: Jadad Score Heterogenitätsanalysen: I^2
	3. Ergebnisdarstellung

Table 1 Baseline characteristics of the eight trials comparing doublet with single agent for elderly patients with advanced NSCLC

References	Years	Patient age	Chemotherapy regimens	No. of patients	Median TTP (months)	Median PFS (months)	Median OS (months)	1-year SR (%)	Jadad score
Quoix et al. [18] (IFCT-0501)	2011	≥70	CBP AUC = 6 d1 + PTX 90 mg/m², d1,8,15 iv q.4.w.	225	NA	6.0	10.3	44.5	3
			NVB 25 mg/m², d1,8 ivq.3.w. or GEM 1,150 mg/m², d1,8 iv q.3.w.	226	NA	2.8	6.2	25.4	
Chen et al. [19]	2008	≥70	NVB 22.5 mg/m² iv, d1,8 + DDP 50 mg/m² iv dl q.3.w.	34	5.2	NA	11.3	47.2	3
			NVB 25 mg/m², d1,8 iv q.3.w.	31	3.1	NA	12	50.9	
Comella et al. [20]	2004	≥70 or poor performance status	GEM 1,000 mg/m² iv, d1,8 + NVB 25 mg/m²,d1,8 iv q.3.w.	68	NA	NA	9.7	32 %	3
			GEM 1,000 mg/m² iv, d1,8 + PTX 80 mg/m² iv, d1,8 q.3.w.	65	NA	NA	9.4	44 %	
			GEM 1,200 mg/m²iv, d1,8,15 q.4.w.	68	NA	NA	5.1	29 %	
			PTX 100 mg/m² iv, d1,8,15 q.4.w.	63	NA	NA	6.4	25 %	
Gridelli et al. [7] (MILES)	2003	≥70	GEM 1,000 mg/m² iv, d1,8 + NVB 25 mg/m² iv, d1,8 q.3.w.	232	19 weeks	NA	30 weeks	30	3
			GEM 1,200 mg/m² iv, d1,8 q.3.w.	233	17 weeks	NA	28 weeks	28	
			GEM 1,000 mg/m² iv, d1,8 + NVB 25 mg/m² iv, d1,8 q.3.w.	232	19 weeks	NA	30 weeks	30	
			NVB 30 mg/m² iv, d1,8q.3.w.	233	18 weeks	NA	36 weeks	38	
Hainsworth et al. [21]	2007	>65 or poor performance status	GEM 800 mg/m² iv, d1,8,15 + TXT 30 mg/m² iv, d1,8,15 q.4.w.	174	4.8	NA	5.5	26 %	3
			TXT 36 mg/m² iv, d1,8,15 q.4.w.	171	2.9	NA	5.1	24 %	
Frasci et al. [22]	2000	≥70	GEM 1,200 mg/m² iv, d1,8 + NVB 30 mg/m² iv, d1,8 q.3.w.	60	NA	NA	29 weeks	30 %	3
			NVB 30 mg/m² iv, d1,8 q.3.w.	60	NA	NA	18 weeks	13 %	
Rijavec et al. [23]	2010	≥70	TXT 35 mg/m² iv, d1,8,15 + GEM 800 mg/m² iv, d1,8,15 q.4.w.	36	3.9	NA	7.2	NA	2
			TXT 35 mg/m² iv, d1,8,15q.4.w.	33	7.4	NA	7.9	NA	
Kampeanis et al. [24]	2010	≥70	TXT 30 mg/m² iv, d1,8 + GEM 900 mg/m² iv, d1,8 q.3.w.	49	3.17	NA	15.9	NA	2
			GEM 1,200 mg/m² iv, d1,8 q.3.w.	47	2.53	NA	12.2	NA	
Tsukada et al. [25]	2007	≥70	TXT 20 mg/m² iv, d1,8,15 + DDP 25 mg/m² iv, d1,8,15 q.4.w.	63	NA	NA	NA	NA	2
			TXT 25 mg/m² iv, d1,8,15 q.4.w.	63	NA	NA	NA	NA	
Abe et al. [26]	2011	≥70	TXT 20 mg/m² iv, d1,8,15 + DDP 25 mg/m² iv, d1,8,15 q.4.w.	139	NA	NA	13.3	NA	2
			TXT 60 mg/m² iv, d1 q.3.w.	137	NA	NA	17.3	NA	

CBP carboplatin, *NVB* vinorelbine, *PTX* paclitaxel, *DDP* cisplatin, *GEM* gemcitabine, *TXT* docetaxel, *PFS* progression-free survival, *TTP* time to progression, *OS* overall survival, *NA* not available

Overall survival (9 trials): no statistically significant difference, HR of 0.84 (95% CI = 0.71–1.00, p = 0.053, I^2=76.6%)



1-year survival (6 trials statistically significant difference in favor of doublet therapy (RR = 1.17, 95 % CI = 1.02–1.35, p = 0.03, I^2=47.1%)

TTP (3 trials):

statistically significant difference in favor of doublet therapy (HR = 0.76, 95 % CI = 0.60–0.96, p=0,022, I^2=72.2%).

ORR (10 trials):

statistically significant difference in favor of doublet therapy (RR = 1.54, 95 % CI = 1.36–1.73, p = 0.0001, I^2=0)

Toxicity:

	More incidences of grade 3 or 4 anemia, thrombocytopenia, and neurotoxicity were observed with doublet therapy. With respect to the risk of grade 3 or 4 neutropenia and nonhematologic toxicities such as diarrhea, fatigue, nausea, and vomiting, equivalent frequencies were found between the two groups
	4. Anmerkungen/Fazit der Autoren Our results indicated that doublet therapy was superior to a single third-generation cytotoxic agent for elderly patients with advanced NSCLC. The optimal dosage and schedule of platinum-based doublet should be investigated in future prospective clinical trials. Gemcitabine-based doublet could be considered for elderly patients who were not suitable for platinum-based chemotherapy. ***Anmerkungen der FB Med:*** • *2 Phase II Studien eingeshlossen, aber alle Studien qualitätsbewertet* • *supported by grants from the National Natural Science Foundation of China (81001191) and Science and Technology Commission of Shanghai (10PJ1408300).* • *Wei-Xiang Qi, Li-na Tang, Zan Shen, Ai-na He, Feng Lin, and Yao Yang have no conflicts of interest to disclose.*
Li M et al., 2012 [34]. Pemetrexed plus platinum as the first-line treatment option for advanced non-small cell lung cancer: a meta-analysis of randomized controlled trials	**1. Fragestellung** The objective of this metaanalysis was to compare the efficacy and toxicities of PPC with other platinum-based regimens (PBR) in the treatment of patients with previously untreated advanced NSCLC.
	2. Methodik ***Population:*** NSCLC patients were previously untreated ***Interventionen und Komparatoren:*** PPC (pemetrexed plus cisplatin or carboplatin chemotherapy) with other PBR (third-generation agents plus cisplatin or carboplatin regimens); treated patients had stage IIIB or IV NSCLC, regardless of the publication status (published, conference proceedings, or unpublished) ***Endpunkte*:** nicht päspezifiziert ***Suchzeitraum:*** 2008 - 2011 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 4 / 2518, RCTs ***Qualitätsbewertung der Studien:*** Jadad Score ***Heterogenitätsuntersuchungen:*** Statistical heterogeneity of the trial results was assessed with the Chi-Quadrat test for heterogeneity and the I^2 test for inconsisteny.
	3. Ergebnisdarstellung

OS

Table 1. Characteristics of Studies Included in the Meta-analysis.

Study	Quality (Scores)	Therapy	n	Age Median	Male (%)	Stage IIIB(%)	Stage IV(%)	Non-squ (%)	OS Median	PFS Median
Scagliotti et al. [7]	3	PEM- 500 mg/m2 d1+P-75 mg/m2 d1, q3w	862	61.1	70.2	23.8	76.2	71.7	10.3	4.8
		GEM-1,250 mg/m2 d1,8+P-75 mg/m2 d1, q3w	863	61.0	70.1	24.3	75.7	73.5	10.3	5.1
Gronberg et al. [9]	3	PEM- 500 mg/m2 d1+P#-AUC 5 d1, q3w	219	64	56	29	71	74	7.3	NA
		GEM-1,000 mg/m2 d1,8+P#-AUC 5 d1, q3w	217	66	59	28	72	77	7.0	NA
Socinski et al. [10]	2	PEM- 500 mg/m2 d1+P#-AUC 6 d1, q3w	74	66	55	7	93	70	12.7	NA
		Doc-75 mg/m2 d1+P#-AUC 6 d1, q3w	72	65	58	8	92	81	9.2	NA
Rodrigues-Pereira et al. [17]	3	PEM- 500 mg/m2 d1+P#-AUC 5 d1, q3w	106	60.1	60.4	16	84	100	14.9	5.8
		Doc-75 mg/m2 d1+P#-AUC 5 d1, q3w	105	58.9	47.6	21.9	78.1	100	14.7	6.0

Abbreviations: PEM, pemetrexed; GEM, gemcitabine; Doc, docetaxel; P, cisplatin; P#, carboplatin; Ade, adenocarcinoma; Non-squ, non-squamous cell carcinoma; AUC, area under the concentration/time curve. NA, not available; OS, overall survival; progression-free survival.

doi:10.1371/journal.pone.0037229.t001

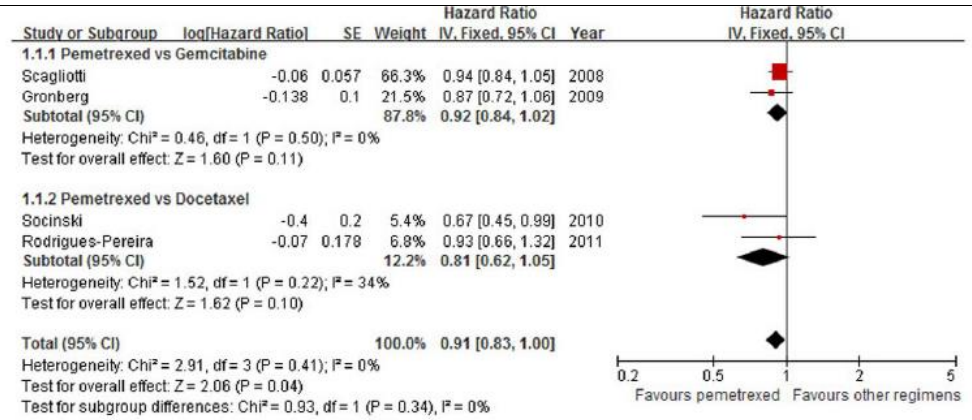


Figure 2. Comparison of overall survival between pemetrexed plus platinum chemotherapy and other platinum-based regimens. Abbreviations: SE, standard error; IV, inverse variance; CI, confidence interval.

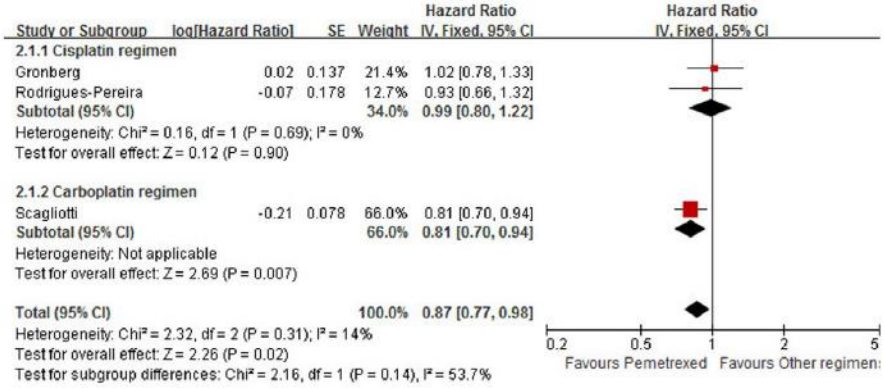


Figure 3. Comparison of overall survival in patients with nonsquamous histology between pemetrexed plus platinum chemotherapy and other platinum-based regimens. Abbreviations: SE, standard error; IV, inverse variance; CI, confidence interval.

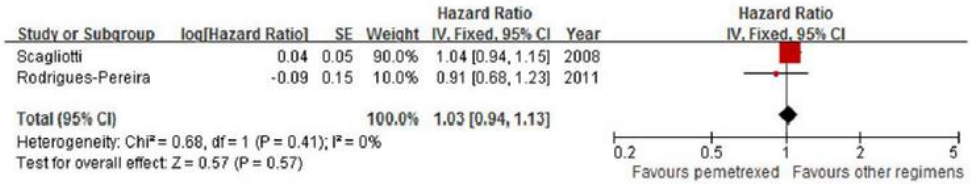


Figure 4. Comparison of progression-free survival between pemetrexed plus platinum chemotherapy and other platinum-based regimens. Abbreviations: SE, standard error; IV, inverse variance; CI, confidence interval.

UE

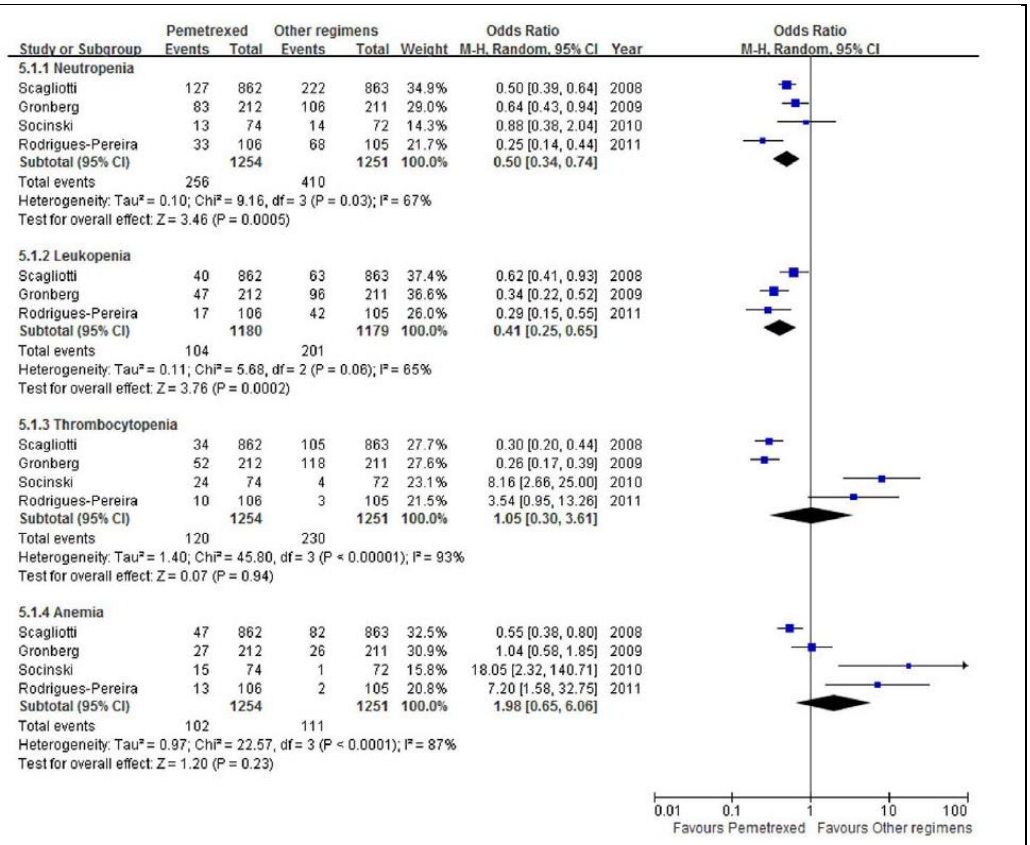


Figure 6. Summary of grade 3–4 hematological toxicity. Abbreviations: M-H, mantel-haenszel; CI, confidence interval.

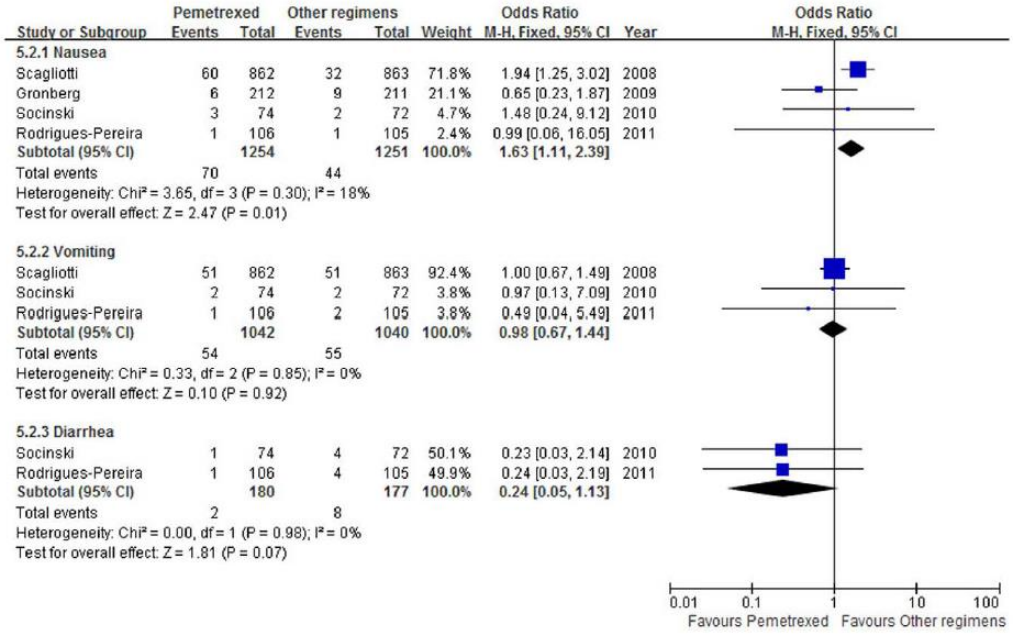


Figure 7. Summary of grade 3–4 nonhematological toxicity. Abbreviations: M-H, mantel-haenszel; CI, confidence interval.

4. Anmerkungen/Fazit der Autoren

Pemetrexed plus platinum chemotherapy (PPC) improved survival compared with other platinum-based regimens (PBR) in patients with advanced NSCLC (HR = 0.91, 95% CI: 0.83–1.00, p = 0.04), especially in those with non-

	squamous histology (HR = 0.87, 95% CI: 0.77–0.98, p = 0.02). No statistically significant improvement in either PFS or RR was found in PPC group as compared with PBR group (HR = 1.03, 95% CI: 0.94–1.13, p = 0.57; OR = 1.15, 95% CI: 0.95–1.39, p = 0.15, respectively). Compared with PBR, PPC led to less grade 3–4 neutropenia and leukopenia but more grade 3–4 nausea. However, hematological toxicity analysis revealed significant heterogeneities. Our results suggest that PPC in the first-line setting leads to a significant survival advantage with acceptable toxicities for advanced NSCLC patients, especially those with non-squamous histology, as compared with other PRB. PPC could be considered as the first-line treatment option for advanced NSCLC patients, especially those with non-squamous histology.
Wang F et al., 2011 [61]. Gefitinib Compared with Systemic Chemotherapy as First-line Treatment for Chemotherapy-naive Patients with Advanced Non-small Cell Lung Cancer: A Meta-analysis of Randomised Controlled Trials	**1. Fragestellung** To define the efficacy of gefitinib in chemotherapy-naive patients with advanced non-small cell lung cancer.
	2. Methodik **Population**: Chemotherapy-naive patients with NSCLC **Intervention**: Gefitinib therapy as first-line **Komparator**: Conventional therapy **Endpunkt**: PFS, OS **Qualitätsbewertung der Primärstudien**: (1) generation of allocation concealment, (2) description of drop-outs, (3) masking of randomisation, intervention, outcome assessment, (4) intention-to-treat analyses, (5) final analysis reported; each criterion rated as yes, no or unclear **Suchzeitraum**: up to 2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 8/4 656
	3. Ergebnisdarstellung <u>Gefitinib monotherapy</u> OS • Patients with lung adenocarcinoma: statistically significant difference in favor of gefitinib monotherapy compared to chemotherapy. HR 0.89 (0.81, 0.99); p = 0.03 • EGFR mutant treated with gefitinib monotherapy: no statistically significant difference Combination of conventional chemotherapy with gefitinib: no statistically significant difference PFS • EGFR mutant treated with gefitinib monotherapy: statistically significant difference in favor of gefitinib monotherapy compared to chemotherapy

	HR 0.43 (0.32, 0.58) (p < 0.001) • Patients with lung adenocarcinoma: statistically significant difference in favor of gefitinib monotherapy compared to chemotherapy HR 0.71 (0.60, 0.83) (p < 0.001) • Patients without EGFR mutant: statistically significant difference in favor of chemotherapy compared to gefitinib monotherapy. HR 2.16 (1.17, 3.99) p = 0.01 • Patients with lung non- adenocarcinoma: no statistically significant difference
	4. Anmerkungen/Fazit der Autoren First-line treatment with gefitinib conferred prolonged progression-free survival than treatment with systemic chemotherapy in a molecularly or histologically defined population of patients with non-small cell lung cancer, and improved survival in the subgroup of patients with lung adenocarcinoma. *Anmerkungen der FB Med:* • *keine Infos zu CoI und Finanzierung verfügbar*
Chen P et al., 2011 [10]. EGFR-targeted therapies combined with chemotherapy for treating advanced non-small-cell lung cancer: a meta-analysis	**1. Fragestellung** to systematically evaluate EGFR targeted therapies plus chemotherapy for advanced NSCLC
	2. Methodik **Population:** adults (aged 18 or older) with advanced NSCLC. Patients previously exposed to EGFR-directed agents or radiotherapy were excluded (alle first-line) **Intervention**: EGFR targeted therapies plus platinum-based doublet chemotherapy **Komparator**: platinum-based doublet chemotherapy **Endpunkt**: OS, PFS, ORR **Suchzeitraum**: up to 2010 **Qualitätsbewertung:** scoring system developed by Jadad **Heterogenitätsuntersuchung:** I^2 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 10/5 936
	3. Ergebnisdarstellung Niedermolekulare TKIs + Chemotherapie vs. Chemotherapie (basierend auf 6 Studien mit 3 918 Erkrankten: 3 trials mit Erlotinib, 2 trials mit Gefitinib, 1 trial mit Vandetanib):

Table 1 Characteristics of randomized clinical trials reviewed in the meta-analysis

Study	Number of patients	Mean age (years)	Year of study	Center	Median OS (month)	First-line treatment	EGFR-targeted therapies used	Chemotherapy used	Jadad score
Gatzemeier [12]	1,159	60/59.1	2007	multicenter	9.9/10.2	Yes	Erlotinib	Gemcitabine, Cisplatin	5
Herbst [9]	1,079	62.7/62..6	2005	multicenter	10.6/10.5	Yes	Erlotinib	Paclitaxel, Carboplatin	3
Mok [20]	154	57.5/57	2009	multicenter	6.8/5.1	Yes	Erlotinib	Gemcitabine, Cisplatin or Carboplatin	3
Roy S. Herbst [14]	690	61/63	2004	multicenter	9.8/9.9	Yes	Gefitinib	Paclitaxel, Carboplatin	5
Giaccone [13]	728	59/61	2004	multicenter	9.9/10.9	Yes	Gefitinib	Gemcitabine, Cisplatin	5
Heymach [15]	108	60/59	2008	unclear	10.2/12.6	Yes	vandetanib	Paclitaxel, Carboplatin	4
Pirker [17]	1,125	59/60	2009	multicenter	11.3/10.1	Yes	Cetuximab	Cisplatin, Vinorelbine	3
Butts [19]	131	66/64	2007	multicenter	11.9/9.26	Yes	Cetuximab	Gemcitabine, Cisplatin or Carboplatin	2
Rosell [18]	86	58/57	2008	multicenter	8.3/7.3	Yes	Cetuximab	Vinorelbine, Cisplatin	3
Lynch [16]	676	64/65	2010	multicenter	9.69/8.38	Yes	Cetuximab	Paclitaxel or Docetaxel, Carboplatin	4

Overall survival: Kein stat. signifikanter Unterschied zwischen den Gruppen

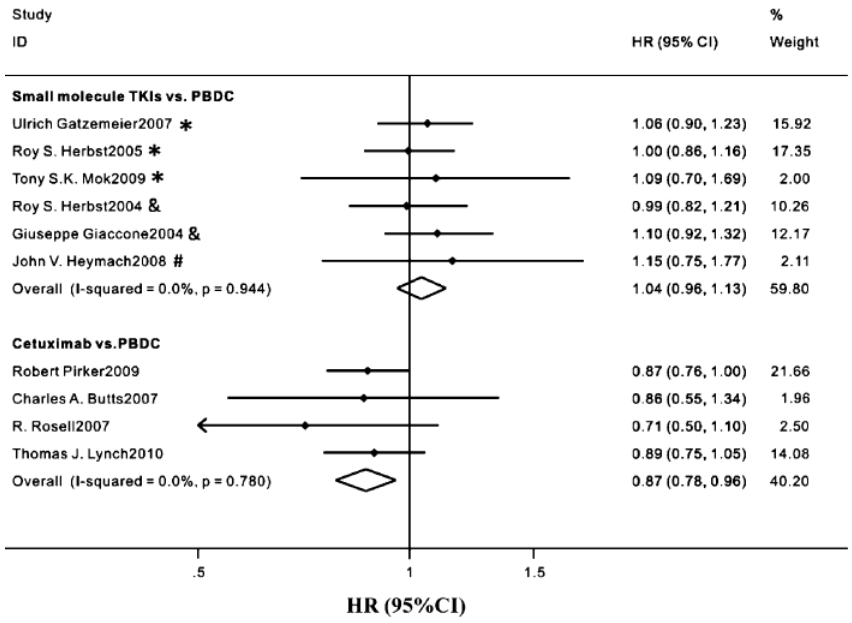


Fig. 2 Overall survival of epidermal growth factor receptor (EGFR)-targeted combination therapies vs. platinum-based doublet chemotherapy (PBDC). *Erlotinib administered, & gefitinib administered, # vandetanib administered, HR hazard ratio, 95% CI 95% confidence interval, HR<1 numerically longer survival than control chemotherapy group, HR>1 numerically shorter survival than control chemotherapy group, 95% CI not including the number 1 statistical difference between groups

PFS: stat. signifikanter Vorteil unter der Kombinationstherapie (HR=0.87, 95% KI: 0.76–0.99, p=0.030 bei gleichzeitig hoher Heterogenität I^2=68,2%)

ORR: stat. signifikanter Vorteil unter der Kombinationstherapie (RR 1.10 95% CI, 1.00–1.20).

4. Anmerkungen/Fazit der Autoren

… Small-molecule TKIs plus PBDC lead to a slightly additive efficacy compared with PBDC alone.

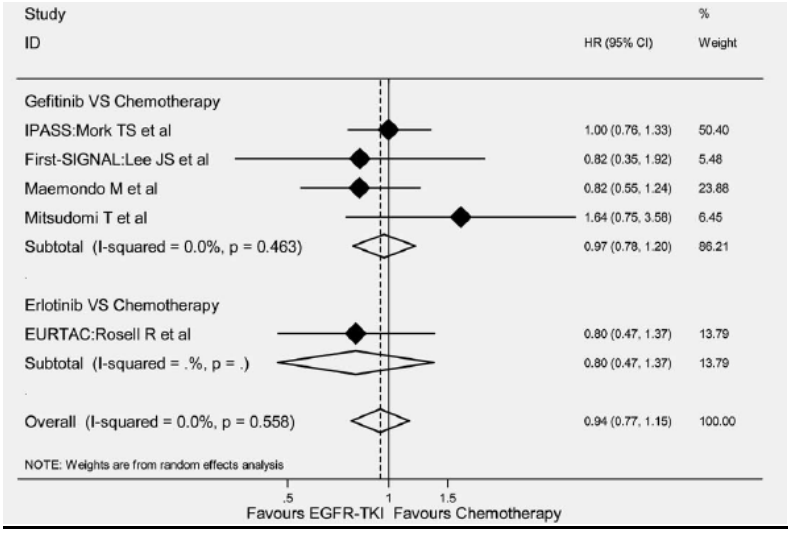
	Anmerkung FB Med: • *Vandetanib nicht zugelassen* • *All authors declare no potential conflict of interest.*
Gao G et al., 2011 [16]. Epidermal growth factor receptor-tyrosine kinase inhibitor therapy is effective as first-line treatment of advanced non-small-cell lung cancer with mutated EGFR: a meta-analysis from six phase III randomized controlled trials	**1. Fragestellung** The results of comparing the EGFR-TKI with standard platinum-based doublet chemotherapy as the first-line treatment in advanced NSCLC patients with activated EGFR mutation were still controversial. A meta-analysis was performed to derive a more precise estimation of these regimens.
	2. Methodik **Population**: patients >18 years, pathologically proven NSCLC with EGFR mutation-positive, clinical IIIB‑IV stage, previously untreated **Intervention**: EGFR-TKI, first-line **Komparator**: platinum-based doublet chemotherapy **Endpunkt**: PFS, OS, ORR **Suchzeitraum**: 1966 bis 06/2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 6/1 021 **Qualitätsbewertung der Primärstudien**: … with particular emphasis on randomization, masking of patients and clinicians, concealment of allocation, documentation of dropouts and withdrawals and intent-to-treat (ITT) analysis **Heterogenitätsuntersuchung:** Ist erfolgt (I2)
	3. Ergebnisdarstellung Table 1. Baseline characteristics of the 6 trials comparing Epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) with Chemotherapy for patients with previously untreated NSCLC with mutated EGFR

Study	Country	Group	Primary endpoint	Eligible for evaluation	Female (%)	Adenocarcinoma (%)	Never smokers (%)	Type of EGFR mutation (%)		CR+PR (%)	PFS (Months)	OS (Months)
								Exon 19 deletion	L858R			
IPASS: Mork TS et al	East Asia[1]	Gefitinib 250 mg/day	PFS	132	NR	NR	NR	50.0	48.5	71.2	9.5	21.6
		PTX 200 mg/m^2,d1,q3w + CBP (AUC = 5–6) d1,q3w × 6 cycles		139	NR	NR	NR	57.4	36.4	47.3	6.3	21.9
First-SIGNAL: Lee JS et al	Korea	Gefitinib 250 mg/day	OS	26	NR	100	100	NR	NR	84.6	8.4	30.6
		GEM 1,250 mg/m^2 d1,8,q3w + DDP 80 mg/m^2, d1,q3w × 9 cycles		16	NR	100	100	NR	NR	37.5	6.7	26.5
Maemondo M et al	Japan	Gefitinib 250 mg/day	PFS	114	63.2	90.4	65.8	50.9	43.0	73.7	10.8	30.5
		PTX 200 mg/m^2,d1,q3w + CBP (AUC = 6) d1,q3w × >3 cycles		114	64.0	96.5	57.9	51.8	42.1	30.7	5.4	23.6
Mitsudomi T et al	Japan	Gefitinib 250 mg/day	PFS	86	68.6	96.5	70.9	58.1	41.9	62.1	9.2	30.9
		DXT 60 mg/m^2,d1,q3w + DDP 80 mg/m^2,d1,q3w × 3–6 cycles		86	69.8	97.7	66.3	43.0	57.0	32.2	6.3	NR
OPTIMAL: Zhou CC et al	China	Erlotinib 150 mg/day	PFS	83	59.0	88.0	72.0	52.0	48.0	83.0	13.1	NR
		GEM 1,000 mg/m^2 d1,8,q3w + CBP(AUC = 5) d1,q3w × 4 cycles		82	60.0	86.0	69.0	54.0	46.0	36.0	4.6	NR
EURTAC: Rosell R et al	Europe[2]	Erlotinib 150 mg/	PFS	77	68.0	NR		70.0	64.0	55.0	9.4	18.9
		Standard platinum-based doublet chemotherapy[3]		76	79.0	NR		74.0	63.0	11.0	5.2	14.4

[1]East Asia: China, Hong Kong, Japan, Taiwan, Singapore, Malaysia, Philippines, Thailand. [2]Europe: Spain, France, Italy. [3]Standard platinum-based doublet chemotherapy options:GEM 1,250 mg/m^2 d1,8 + DDP 75 mg/m^2, d1 or DXT 75 mg/m^2,d1 + DDP 75 mg/m^2,d1 or DXT 75 mg/m^2,d1 + CBP(AUC = 6) d1 or GEM 1,000 mg/m^2 d1,8 + CBP(AUC = 5) d1.
Abbreviations: PTX: paclitaxel; CBP: carboplatin; DDP: cisplatin; GEM: gemcitabine; DXT: docetaxel; CR: complete response; PR: partial response; PFS: progression-free survival; OS: overall survival; NR: not Report.

PFS

The patients receiving EGFR-TKI as front-line therapy had a significantly longer progression-free survival (PFS) than patients treated with chemotherapy [median PFS was 9.5 versus 5.9 months; hazard ratio (HR) 5

	0.37; 95% confidence intervals (CI) 5 0.27–0.52; p < 0.001]. ***OS*** The overall survival (OS) was numerically longer in the patients received EGFR-TKI than patients treated by chemotherapy, although the difference did not reach a statistical significance (median OS was 30.5 vs. 23.6 months; HR= 0.94; 95% CI 5 0.77–1.15; p= 0.57).  Meta-analysis of overall survival (OS) among patients receiving EGFR-TKI or chemotherapy. The pooled HR for OS failed to display a difference between EGFR-TKI and chemotherapy in patients with previously untreated NSCLC with mutated EGFR (p ¼ 0.57). Subgroupanalysis and sensitivity analysis of Gefitinib vs. Chemotherapy also revealed the same conclusion (p = 0.78).
	4. Anmerkungen/Fazit der Autoren Comparing with first-line chemotherapy, treatment of EGFR-TKI achieved a statistical significantly longer PFS, higher ORR and numerically longer OS in the advanced NSCLC patients harboring activated EGFR mutations, thus, it should be the first choice in the previously untreated NSCLC patients with activated EGFR mutation. **Limitation**: • Nebenwirkungsprofile nicht untersucht *Anmerkungen der FB Med:* • *Grant sponsors: Scientific Research Foundation of Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China*
Guetz et al., 2016 [26]. Is There a Survival Benefit of First-Line Epidermal Growth Factor	1. Fragestellung Tyrosine-kinase inhibitors (TKIs) markedly improve progression-free survival (PFS) of patients with advanced non-small-cell lung cancer (NSCLC) mutated for epidermal growth factor receptor (EGFR). Results on overall survival (OS) are less clear-cut. We performed a publication based meta-analysis to address further this issue.
	2. Methodik

Receptor Tyrosine-Kinase Inhibitor Monotherapy Versus Chemotherapy in Patients with Advanced Non-Small-Cell Lung Cancer?: A Meta-Analysis	Population: patients with metastatic or advanced NSCLC (stage IIIB or IV) Intervention/Komparator: Firstline, exclusively among mutated patients → platinum-based doublet chemotherapy vs. EGFR TKI monotherapy Endpunkte: OS, PFS and toxicity Suchzeitraum (Aktualität der Recherche): Publications were identified by an electronic search using online using PubMed, updated on March 6, 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 studies included 2962 patients (780 males, 2182 females, mostly Asian, median age 60 years), 2909 adenocarcinomas (98 %), 1739 mutated tumors (897 exon 19 deletion, 699 L858 mutation), 448 stage IIIB, and 2222 stage IV (75 %) tumours and 2453 never smokers (83 %). Four studies assessed gefitinib, two studies assessed erlotinib, and two studies assessed afatinib. Chemotherapies were doublets including a platinum salt. All studies included patients with EGFR mutations, but six studies included only EGFR mutated patients *Hinweis*: Only Phase III studies included Qualitätsbewertung der Studien: We did not assess the quality of studies by Jadad score because there is no general agreement on the suitability of such scores.
	3. Ergebnisdarstellung • OS was similar among patients who first received TKI or chemotherapy. • Conversely, compared with chemotherapy, EGFR TKIs significantly improved PFS in patients with EGFR-mutated tumours (HR 0.37, 95 % CI 0.29-0.49, random effect model). • Concerning side effects, rash (RR 6.29, 95 % CI 4.05-9.77), diarrhoea (RR 3.51, 95 % CI 2.15-5.75), stomatitis (RR 3.57, 95 % CI 1.81-7.04), and interstitial lung disease (RR 6.07, 95 % CI 1.66-22.2) were significantly more frequent after TKIs. • As expected, fatigue (RR 0.38, 95 % CI 0.32-0.45), nausea/vomiting (RR 0.19, 95 % CI 0.11-0.32), and haematological disorders, including thrombocytopenia (RR 0.18, 95 % CI 0.09-0.35), anaemia (RR 0.22, 95 % CI 0.15-0.33), and grade 3-4 neutropenia (RR 0.06, 95 % CI 0.04-0.08), were significantly more frequent after chemotherapy.
	4. Fazit der Autoren: *The present MA shows no benefit on OS of first-line TKIs monotherapy compared with first-line chemotherapy in NSCL C. However, afatinib shows promising results in del19 patients. In EGFR-mutated patients, TKIs should be prescribed as first line therapy due to a better safety profile. Ongoing studies aim to compare the effects of various TKIs in order to determine the best therapeutic option. In wild-type patients or*

	patients with unknown mutational status, first-line treatment should be chemotherapy. 5. Hinweise durch FB Med • Fehlende Bewertung der eingeschlossenen Studien, lediglich Angaben, dass ausschließlich Phase III Studien berücksichtigt wurden.
Haspinger ER et al., 2015 [27]. Is there evidence for different effects among EGFR-TKIs? Systematicreview and meta-analysis of EGFR tyrosine kinase inhibitors (TKIs)versus chemotherapy as first-line treatment for patients harboring EGFRmutations	1. Fragestellung We performed a systematic review and meta-analysis using indirect comparisons to estimate the risk/benefit associated witheach drug.
	2. Methodik Population: patients of any age and race, with histologically proven NSCLC harboring an activating EGFR-mutation Intervention: First line EGFR-TKI Komparator: Standard chemotherapy (platinum-based doublet, at any dosage or number ofcycles), generally considered of similar clinical efficacy Endpunkte: • Primary: PFS → whenever possible only independently reviewed data were extracted • Secondary outcomes: PFS in exon 19 deletion, PFS in L858R mutation, OS, ORR (complete and/or partialand/or stable assessed using RECIST criteria) and treatment related toxic events assessed with the NCI CT Criteria. Suchzeitraum (Aktualität der Recherche): up to June 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): The remaining 9 RCTs, which involved globally 1.774 EGFR-mutated patients, met all the inclusion/exclusion criteria and were included in the meta-analysis Qualitätsbewertung der Studien: Cochrane Handbook for Systematic Reviews of Interventions
	3. Ergebnisdarstellung **Qualität der Studien:**

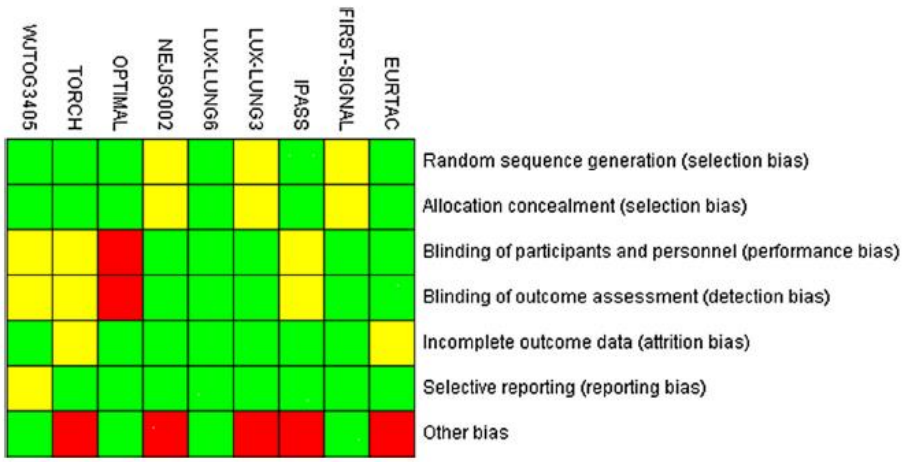


Fig. 6. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Direct comparisons

Gefitinib versus chemotherapy alone

- Four RCTs enrolling 699 EGFR-mutation-positivepatients compared the treatment effects of gefitinib versus chemotherapy on PFS. Pooled results showed a statistically significant difference for PFS and ORR. The combined HRs for PFS and ORR were 0.43 (95% CI0.32–0.56; I2= 54%) and 2.45 (95% CI 2.03–2.95; I2= 0%) respectively, favoring gefitinib versus chemotherapy.
- Analyzing PFS separately for exon 19 deletion and L858R mutations, the results were still in favor of gefitinib (HR:0.40; 95% CI 0.29–0.55; I2= 0% and HR: 0.53; 95% CI0.38–0.76; I2= 0%).
- There was a non-statistically significant difference for OS, treatment-related death
- Gefitinib was associated with a statistically significant risk for diarrhea (RR: 2.00; 95% CI 1.40–2.85; I2= 80%), rash (RR: 4.42; 95%CI 2.82–6.92; I2= 84%), hypertransaminasemia (RR: 2.54;95% CI 1.51–4.29; I2= 84%) compared with chemotherapy,but there was less risk of treatment discontinuation (RR: 0.51;95% CI 0.36–0.73).

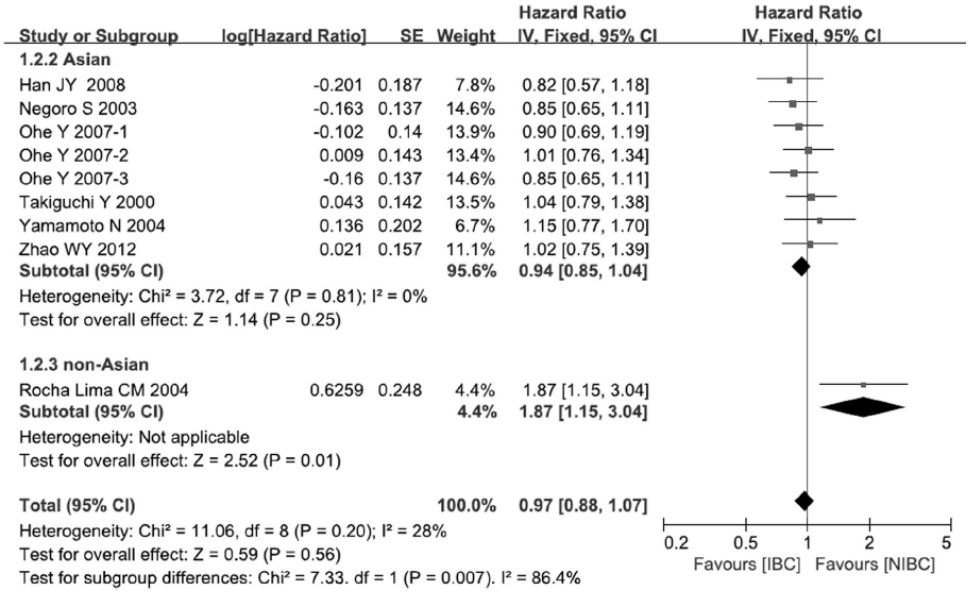
Erlotinib versus chemotherapy alone

- Three RCTs enrolling 366 EGFR-mutation-positive patients compared the treatment effects of erlotinib versus chemotherapy
- There was a statistically significantbenefit with erlotinib over chemotherapy for PFS (HR: 0.32;95% CI 0.16–0.65; I2= 84%), ORR (RR: 2.54, 95% CI1.80–3.59; I2= 28%). Analyzing PFS separately for exon19 deletion and L858R mutations, the results were still infavor of erlotinib (HR: 0.20; 95% CI 0.09–0.46; I2= 76% andHR: 0.38; 95% CI 0.18–0.79; I2= 64%).
- non-significant difference between erlotinib andchemotherapy for OS, treatment-related death, hypertransaminasemia
- Erlotinib was associated with significantly worsediarrhea (RR: 2.55, 95%

	CI 1.42–4.56; I2= 75%) and rash(RR: 4.42, 95% CI 1.57–12.44; I2= 93%) than chemotherapy, but the risk of treatment discontinuation was lower (RR:0.52, 95% CI 0.27–0.99; I2= 0%). *Afatinib versus chemotherapy alone* • Two RCTs enrolling 709 EGFR-mutation-positive patients compared the effects of afatinib versus chemotherapy • These two studies showed a statistically significant benefit in PFS for afatinib versus chemotherapy (HR: 0.41,95% CI 0.20–0.82; I2= 90%), confirmed for exon 19 mutation (HR: 0.24, 95% CI 0.17–0.33; I2= 4%), but not for L858R mutation. Analysis showed even an advantage in ORR (RR: 2.70, 95% CI 2.12–3.45, I^2= 0%). • Comparison for OS was based ondata not yet mature for both trials with a non statisticallysignificant result • There were a statistically significant differences in diar-rhea (RR: 6.98, 95% CI 4.97–9.81, I2= 0%), and rash (RR:10.90, 95% CI 6.89–17.24, I2= 0%). Afatinib did not seemto be associated with hypertransaminasemia, treatment dis-continuation and treatment-related deaths. **Indirect comparisons** *Gefitinib versus afatinib* • statistically non-significant difference between gefitinib and afatinib in PFS as a whole and PFS for patients with L858R mutation. • For patients with exon 19 deletion afatinib seemed to be associ-ated with better PFS. No differences were observed even in ORR. • Indirect comparison for OS gave a statistically non-significant result. • Gefitinib seemed less toxic than afatinib fordiarrhea (RR: 0.29, 95% CI 0.20–0.41) and rash (RR: 0.41,95% CI 0.25–0.65), but patients experienced more hypertransaminasemia (RR: 2.02, 95% CI 1.17–3.46). • There were no differences in treatment discontinuation and treatment-related deaths. *Erlotinib versus afatinib:* • The indirect comparison of erlotinib and afatinib showed a statistically non-significant difference in PFS as a whole and for exon 19 deletion andL858R mutation. • No differences were found in ORR and in OS). • Like gefitinib, erlotinib had a smalle rnumber of events than afatinib for diarrhea (RR: 0.36, 95%CI 0.25–0.54) and rash (RR: 0.41, 95% CI 0.25–0.66). • There were no differences in hypertransaminasemia, treatment dis-continuation and treatment-related deaths. *Gefitinib versus erlotinib:* • Gefitinib and erlotinib gave the same benefit and safetyprofiles for all the outcomes except hypertransaminasemia where erlotinib is likely to be the

	favored drug (RR: 2.29,95% CI 1.63–3.23).
	4. Fazit der Autoren: *In conclusion, also after this attempt we are unable toselect a drug up-front based on clinical evidence. Further-more, the real clinical unmet need on how to treat patientsafter disease progression and how to overcome acquired resis-tance remains still unsolved and without any approved drugs. For the 10% of EGFR-mutated patients, after nine phase3 trials we are unable to choose the best drug for first-linetreatment. In fact, due to a lack of direct comparisons madein the research carried out so far, prescriptive choice willnot presently be based on scientific evidence. Therefore, webelieve that "me too" drugs should be accepted by the regu-latory agencies only when there is the final proof of greaterefficacy or demonstrated less toxicity.*
Yang XQ et al., 2015 [64]. Comparison of first-line chemotherapy based on irinotecan or other drugs to treat non-small cell lung cancer in stage IIIB/IV: a systematic review and meta-analysis.	1. Fragestellung To compare the efficacy and toxicity of irinotecan-based chemotherapy (IBC) and non-irinotecan-based chemotherapy (NIBC) as first-line treatment for stage IIIB/IV non-small cell lung cancer (NSCLC).
	2. Methodik Population: patients locally advanced (stage IIIB) or metastatic (stage IV) NSCLC Intervention*:* IBC Komparator: NIBC Endpunkte: overall response rate (ORR), OS and frequencies of toxicity Suchzeitraum (Aktualität der Recherche): up to 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): Seven RCTs (6 RCTs from Asian population and 1 from non-Asian population) involving 1473 patients with previously untreated stage IIIB/IV NSCLC. In total, 590 patients with stage IIIB/IV NSCLC were randomized to receive IBC, and 883 patients to receive NIBC. The IBC regimen was irinotecan and platinum in five trials and irinotecan and docetaxel or gemcitabine in the remaining trials. Qualitätsbewertung der Studien: modified Jadad score
	3. Ergebnisdarstellung Qualität der Studien: The quality of the seven trials was assessed using the modified Jadad score. The full score was seven points. As none of the trials was double-blinded, no trials received the highest possible score.

- IBC and NIBC were associated with similar ORR, OS and PFS
- Subgroups between Asian and non-Asian patients differed significantly in OS (HR: 0.94 vs 1.87, p = 0.007).



- There was no significant difference for hematological toxicity and significant worse for non-hematological toxicity (RR: 2.28, 95 %CI: 1.60 to3.24, p < 0.001), when IBC compared to NIBC.

4. Fazit der Autoren: *As the available evidence suggests that IBC and NIBC are equivalent in terms of ORR, PFS, OS, at least in Asian patients, we recommend that IBC be considered as a first-line treatment in Asian patients with stage IIIB/IV NSCLC. However, the non-hematological toxicity of IBC must be considered.*

5. Hinweise der FBMed:

- meta-analysis aggregated patients with various histological types of advanced NSCLC

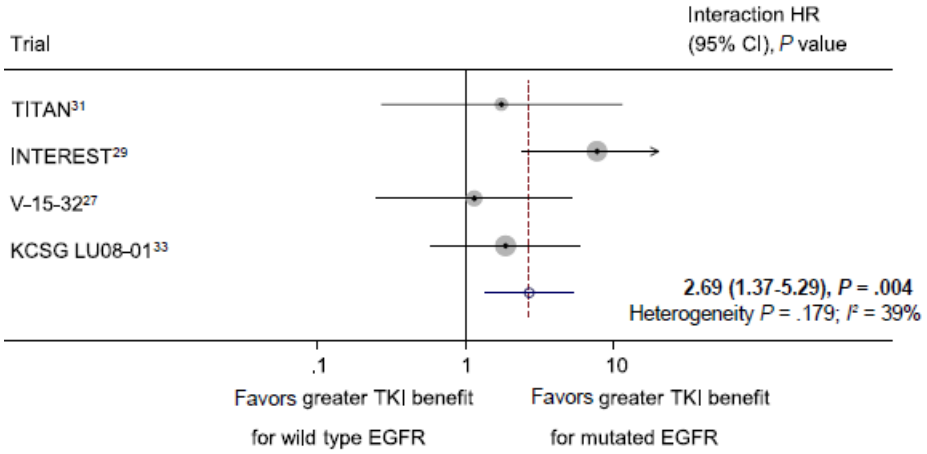
Systematische Reviews (Zweitlinientherapie)

Vale CL et al., 2015 [60]. 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 Studiencharakteristika: siehe *Anhang* **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

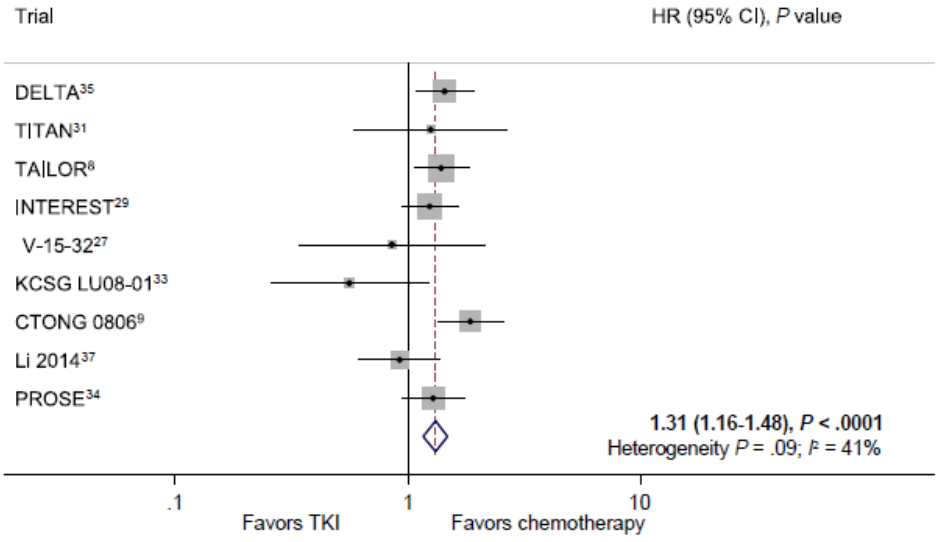
bias and 3 were judged as unclear risk. No trials were judged to be at high risk for any of the domains assessed.

PFS

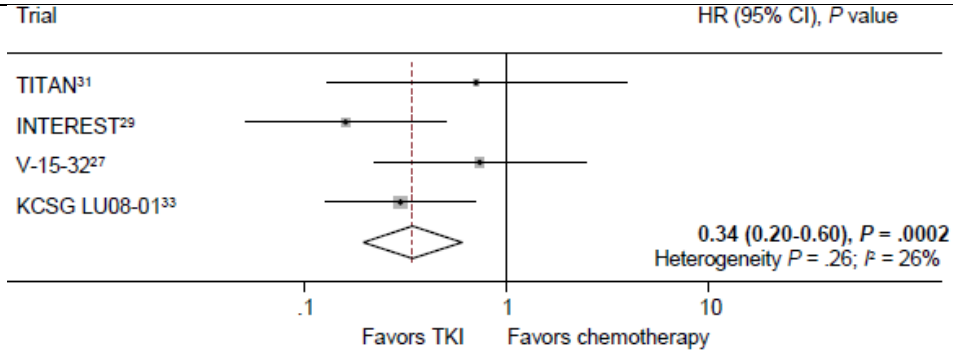
TKI vs. Chemotherapie



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			Random Effect			Interaction HR[a] (95% CI) P	Interaction Heterogeneity, P
			HR	95% CI	P	HR	95% CI	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 [66].

Efficacy of epidermal growth factor receptor inhibitors versus chemotherapy

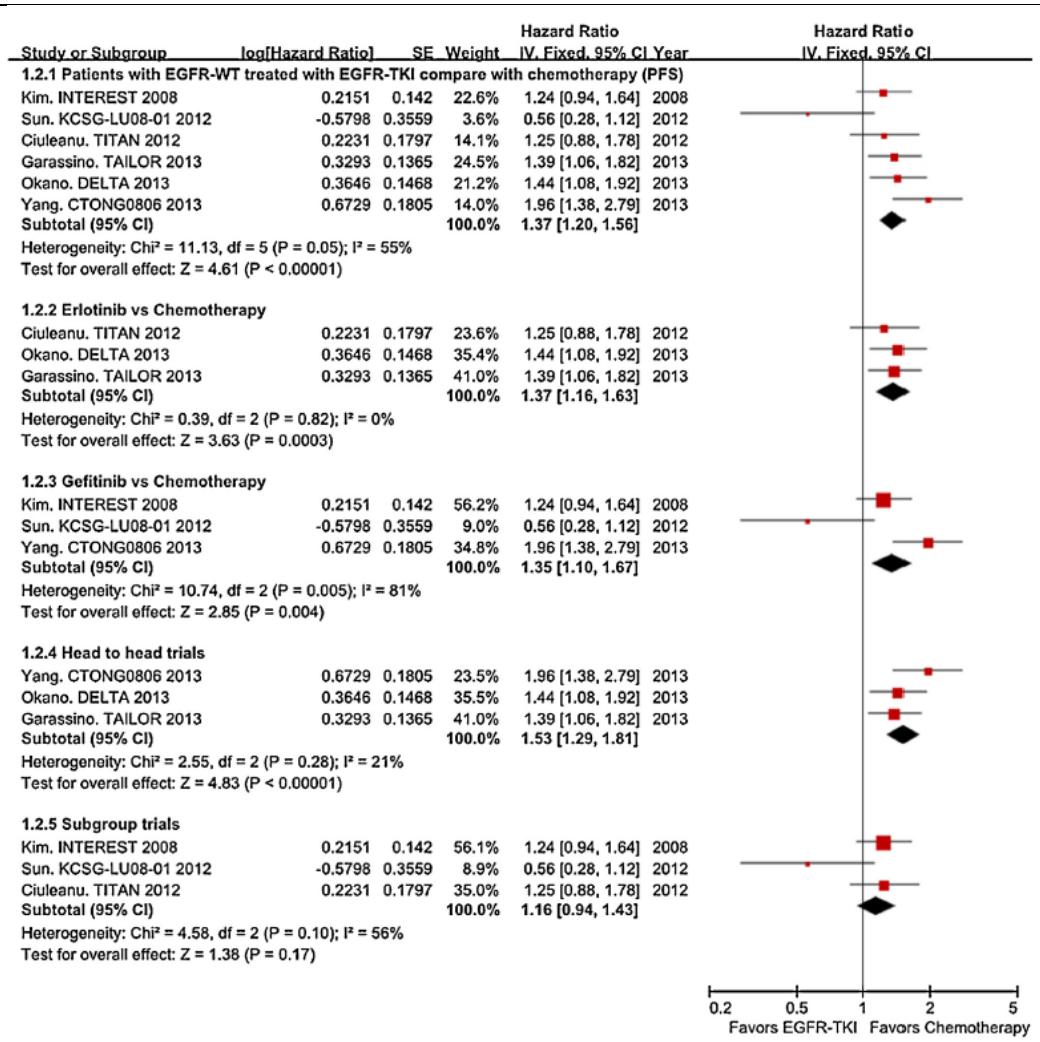
1. Fragestellung

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

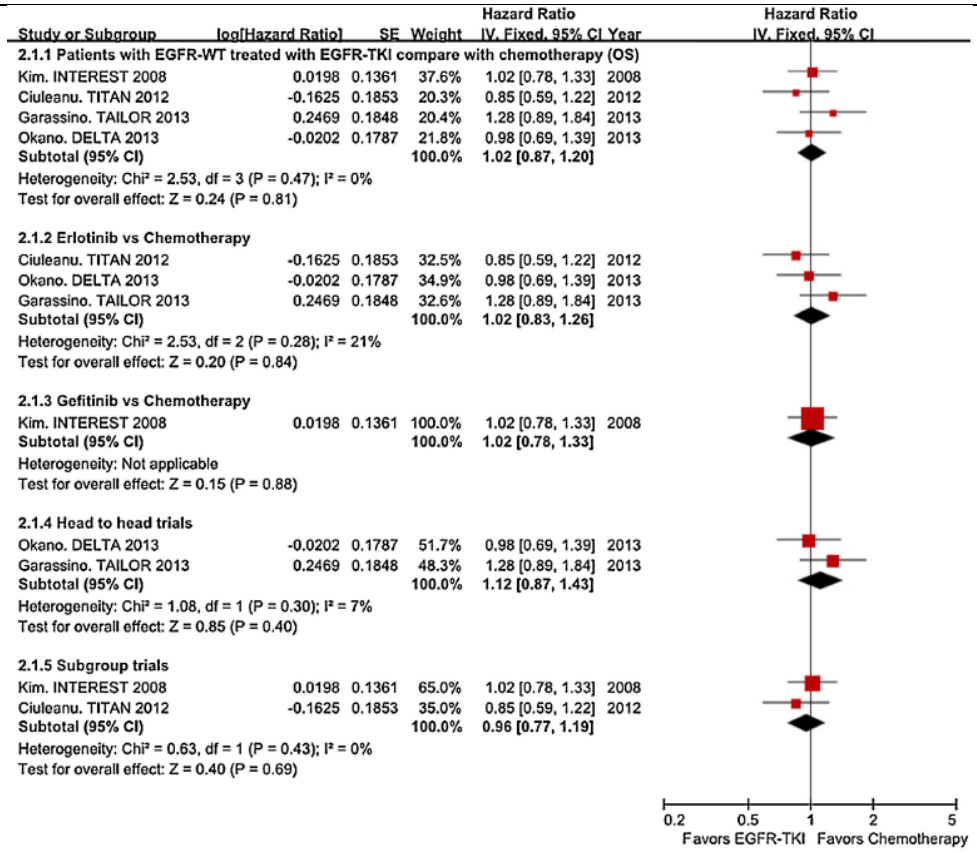
as second-line treatment in advanced non-small-cell lung cancer with wild-type EGFR: a meta-analysis of randomized controlled clinical trials	**Intervention:** EGFR TKIs ***Komparator:*** chemotherapy ***Endpunkte:*** progression-free survival (PFS), overall survival (OS), objective response rate (ORR) ***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
	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. <u>PFS (</u>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. *Hinweise durch FB Med:* • *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)*
Ganguli A et al., 2013 [15]. The impact of second-line agents on patients' health-related quality of life in the treatment for non-small cell lung	**1. Fragestellung** The purpose of this review is to systematically assess the available literature reporting QOL results in clinical trial studies of guideline-supported 2L chemotherapy with docetaxel, erlotinib, gefitinib, and pemetrexed for the treatment for advanced NSCLC.
	2. Methodik ***Population:*** advanced NSCLC

cancer: a systematic review	***Intervention:*** Patients were treated with docetaxel, pemetrexed, erlotinib, or gefitinib; Second-line (2L) ***Komparator:*** Nicht spezifiziert ***Endpunkte*:** quality of life (QOL) ***Suchzeitraum:*** 2000 bis 2010 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 28/Range: 31 – 1 692 ***Qualitätsbewertung der Studien:*** Checklist for Evaluating QOL Outcomes in Cancer Clinical Trials ***Heterogenitätsuntersuchungen:*** qualitativ berücksichtigt und berichtet
	3. Ergebnisdarstellung • Docetaxel: 8 trials; Erlotinib 4 trials; gefitinib: 11 trials; pemetrexed one trial • Function Assessment of Cancer Therapy-Lung (FACT-L): used in 12 studies; European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC-QLQ30/LC13): used in 9 studies;Lung Cancer Symptom Scale (LCSS): used in 4 studies • Median age of participants: 58 – 68 years; PS 0 – 1; **Table 2** Summary of QOL-related significant results stratified by therapeutic agent Domain/areas | Docetaxel | Gefitinib | Erlotinib Overall QOL | T | X | X Domain specific Social functioning | | X | Physical functioning | | X | X Emotional functioning | | X | X, T Role functioning | X | X | Symptoms Pain | X, T | X | X, T Appetite | X, T | X | Cough | X, T | X | X, T Dyspnea | X | X | X, T Fatigue | X | X | X Vomiting | X, T | | Sore mouth | | | X Constipation | | | X Analgesic use | X, T | | T Hair loss | T | | T Hemoptysis | X | | Diarrhea | T | | Trial outcome index | | T | No significant results were found for pemetrexed *QOL*, quality of life; *T*, significant effects on time to deterioration; *X*, significant results in QOL score Studienqualität sehr heterogen
	4. Anmerkungen/Fazit der Autoren Significant improvements in overall QOL with 2L chemotherapy for advanced NSCLC were infrequent. Single-arm studies and those with less toxic regimens more commonly provided statistically significant improvements in QOL outcomes.

	Methodological heterogeneity impedes cross-study QOL comparisons. *Anmerkungen FB Med:* • *auch Phase II und Beobachtungsstudien eingeschlossen* • *P.W., X.G., J.A.C., and M.F.B. are employees of Pharmerit International, which received funding support related to the development of this manuscript from Abbott Laboratories. A.G. and S.R. are employees of Abbott Laboratories.*
Jiang J et al., 2011 [29]. Gefitinib versus Docetaxel in previously treated advanced non-small-cell lung cancer: a meta-analysis of randomized controlled trials	**1. Fragestellung** A meta-analysis of randomized controlled trials was performed to compare the efficacy, quality of life (QOL), symptom improvement and toxicities of gefitinib with docetaxel in previously treated advanced non-small-cell lung cancer.
	2. Methodik: **Population**: Patienten mit einem NSCLC (Stadium IIIB oder IV), die mindestens ein vorheriges Chemotherapie-Regime erhalten haben, positiver Marker für EGFR-Mutation kein Einschlusskriterium **Vergleich**: Gefitinib vs. Docetaxel **Endpunkte**: OS, PFS, ORR, Lebensqualität und Symptomverbesserung, Nebenwirkungen **Suchzeitraum**: bis Mai 2009 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 4/2 257 **Qualitätsbewertung der Primärstudien**: Jadad score **Heterogenitätsuntersuchung**: I2
	3. Ergebnisse: • Jadad: für drei Studien nur 2 von 5 Punkten, eine Studie erreicht 5 Punkte • OS, PFS: keine statistisch signifikanten Unterschiede; keine statistische Heterogenität • ORR: statistisch signifikanter Vorteil unter Gefitinib gegenüber Docetaxel (RR: 1.58; 95%KI: 1.02-2.45, p = 0.04), bei signifikanter Heterogenität • Lebensqualität und Symptomverbesserung: statistisch signifikanter Vorteil unter Gefinitib hinsichtlich dem FACT-L und dem TOI Fragebogen (RR: 1.55; 95%KI: 1.27-1.88; p = 0.00 / RR: 1.86; 95%KI: 1.43-2.42; p = 0.00), kein Unterschied hinsichtlich einer Verbesserung der Symptomatik • Nebenwirkungen: Stat. signifikant mehr Risiko hinsichtlich Grad 3/4 Neutropenien und Fatigue unter Docetaxel, verglichen mit Gefinitib (OR: 0.02; 95%KI: 0.01-0.03; p=0.00 / OR: 0.47; 95%KI: 0.32-0.70; p=0.00). Gegensätzlich zeigte sich ein stat. signifikanter Nachteil unter Gefitinib gegenüber Docetaxel hinsichtlich Grad 3/4 Hautausschlägen (OR: 2.87; 95%KI: 1.24-6.63; p=0.01). Grad 3/4 Erbrechen, Übelkeit und Durchfälle

	waren vergleichbar zwischen den Gruppen.
	4. Fazit der Autoren: Although similar OS and PFS, gefitinib showed an advantage over docetaxel in terms of objective response rate, QoL and tolerability. Therefore, gefitinib is an important and valid treatment option for previously treated advanced non-small-cell lung cancer patients. *Hinweise FB Med:* • *Notwendigkeit der EGFR-Mutation nicht diskutiert* • *eine Phase II Studie eingeschlossen* • *Acknowledgements: analysis supported by a grant from the scientific research foundation of Huashan Hospital Fudan University* • *all authors indicated no potential conflicts of interest* • *publication bias was not found*
Greenhalgh J et al., 2015 [25]. Erlotinib and gefitinib for treating non-small cell lung cancer that has progressed follow ing prior chemotherapy (review of NICE technology appraisals 162 and 175): a systematic review and economic evaluation	**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.
	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								
[a]Bhatnagar et al. 2012[33]	RCT	Gefitinib 250 mg daily	Docetaxel 75 mg/m^2 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/m^2 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/m^2 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/m^2 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 2008[37]	Open-label Phase II RCT	Gefitinib 250 mg daily	Docetaxel 75 mg/m^2 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/m^2 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								
[a]DELTA 2013[40]	Open-label Phase III RCT	Erlotinib 150 mg daily	Docetaxel 60 mg/m^2 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/m^2	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								
BR21 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.

- 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).

- 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

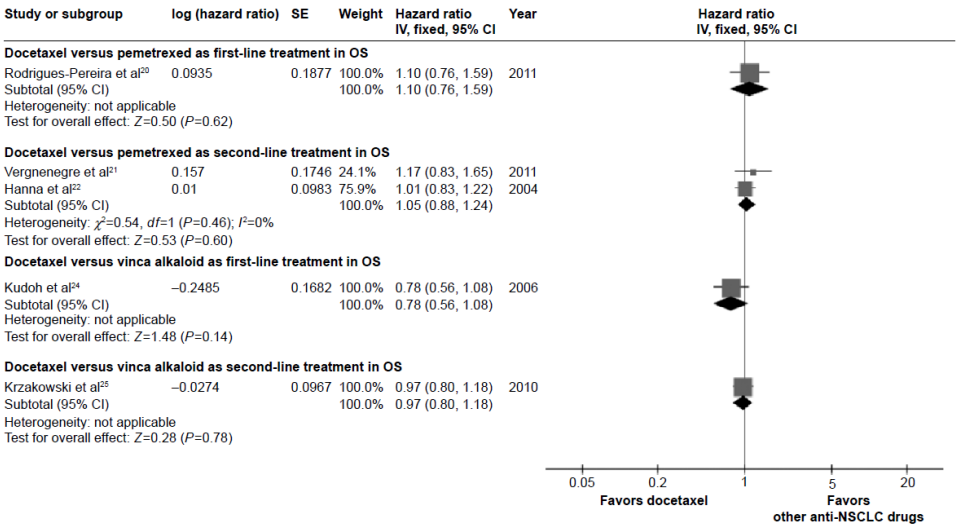
	analy9s comparing erlotinib with docetaxel in patients whose disease has progres:ed favour the use of docetaxel. Switching from an oral therapy (erlotinib) to an intravenous therapy (docetaxel) would have substantial implications for service provision for both patients and staff in the UK NHS Suggested 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. Hinweise der FBMed** Keine quantitative Zusammenfassung der Ergebnisse
He X, 2015 [25]. Efficacy and safety of docetaxel for advanced non-small-cell lung cancer: a meta-analysis of Phase IIIrandomized controlled trials	**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 ***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 syste*m* ***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

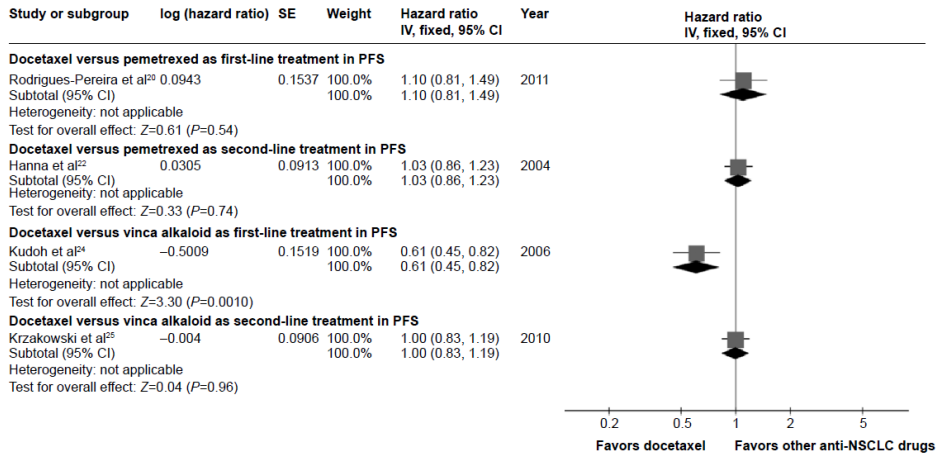
Study	Study region	Intervention	Number	Median age (years)	Male (%)	Stage	Outcome	Jadad score
Rodrigues-Pereira et al[20]	Argentina	Doc (75 mg/m^2) + Carb	105	58.9	47.6	Stage IIIB/IV	SWT, OS, PFS	3
		Pem (500 mg/m^2) + Carb	106	60.1	60.4			
Karampeazis et al[23]	Greece	Doc (38 mg/m^2)	66	75.5	92.4	Stage IIIB/IV	OS, ORR, TTP, Toxl	4
		Vin (25 mg/m^2)	64	77	93.8			
Vergnenegre et al[21]	France	Doc (75 mg/m^2)	75	64	85.3	Stage IIIB/IV	OS, PFS, ORR, Toxl	3
		Pem (500 mg/m^2)	75	62	82.7			
Krzakowski et al[25]	France	Doc (75 mg/m^2)	275	60	75.3	Stage III/IV	PFS, ORR, OS	4
		Vfl (320 mg/m^2)	262	61.9	75			
Kudoh et al[24]	Japan	Doc (60 mg/m^2)	88	76	77.5	Stage IIIB/IV	OS, PFS, ORR, Toxl	3
		Vin (25 mg/m^2)	91	76	74.7			
Hanna et al[22]	United States	Doc (75 mg/m^2)	288	57	75.3	Stage III/IV	OS, PFS, ORR, Toxl	3
		Pem (500 mg/m^2)	283	59	68.6			
Kubota et al[26]	Japan	Doc (60 mg/m^2) + Cis	151	63	64.2	Stage IV	OS, ORR, Toxl	3
		Vds (3 mg/m^2) + 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.

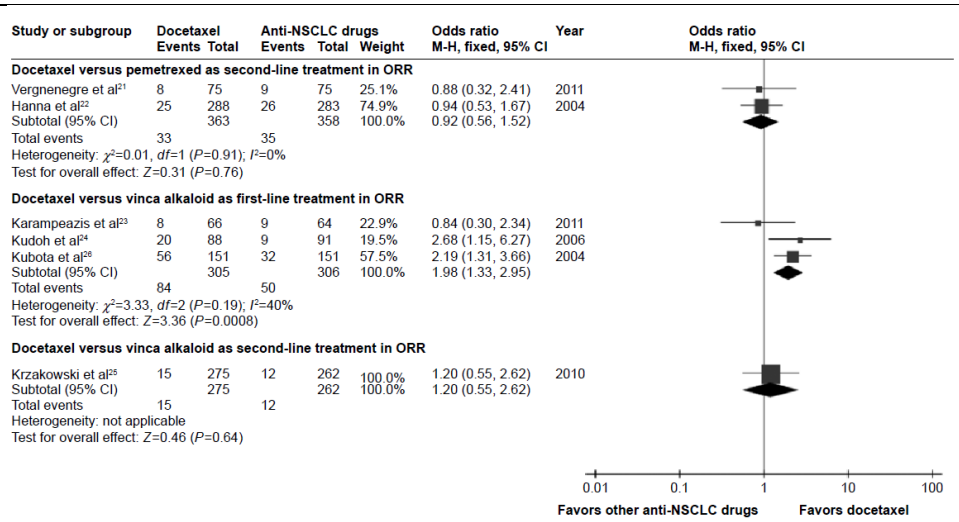
OS



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 [63].

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

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 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

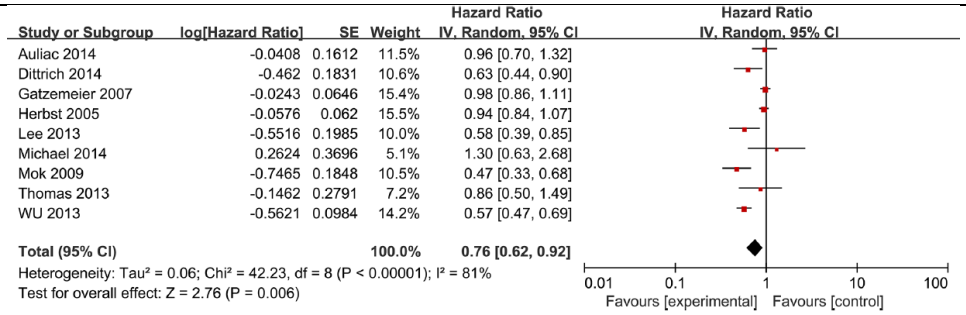


Fig 2. Forest Plot of Meta-analysis for PFS.

Subgruppenanalyse PFS

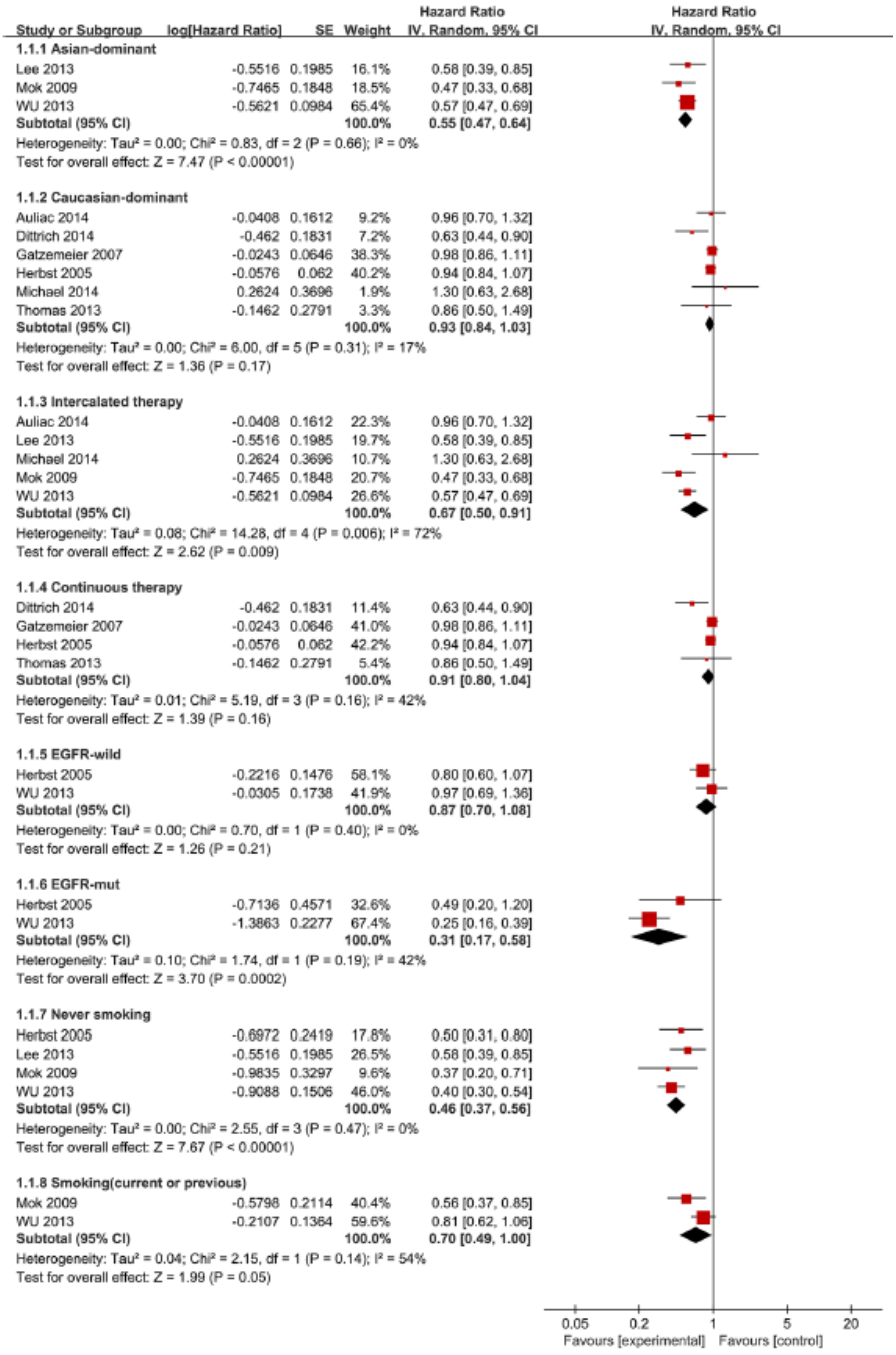


Fig 3. Forest Plot of Subgroup Analysis for PFS.

OS

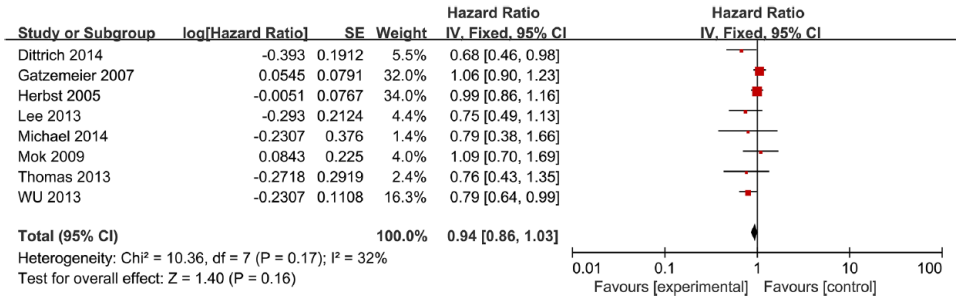
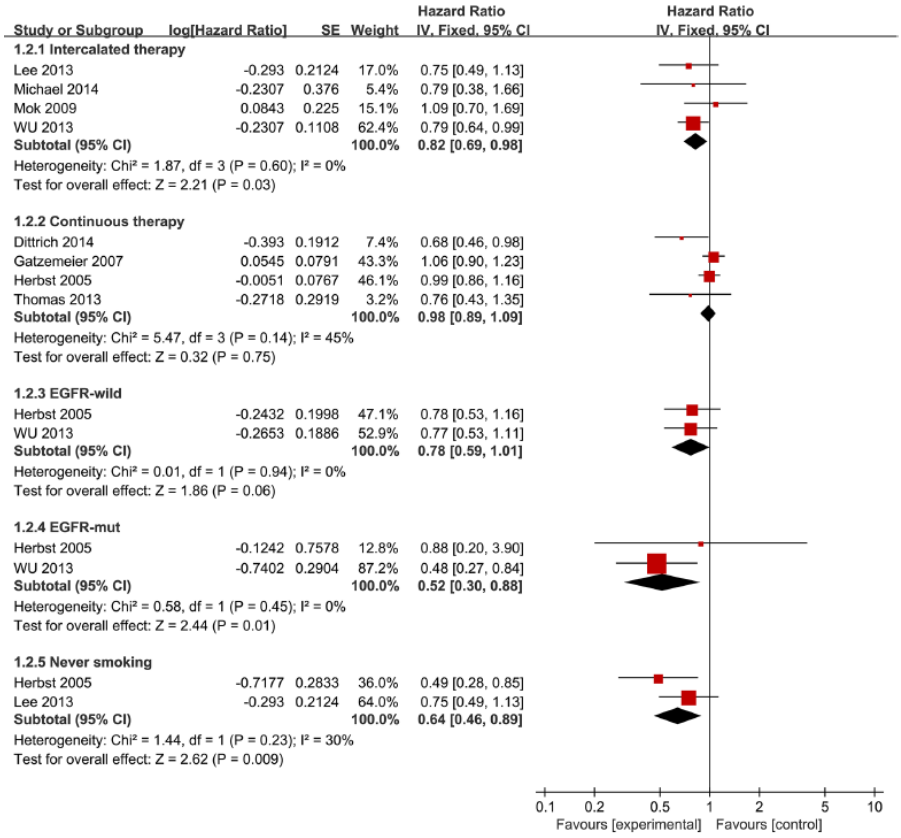


Fig 4. Forest Plot of Meta-analysis for OS.

Subgruppenanalyse OS



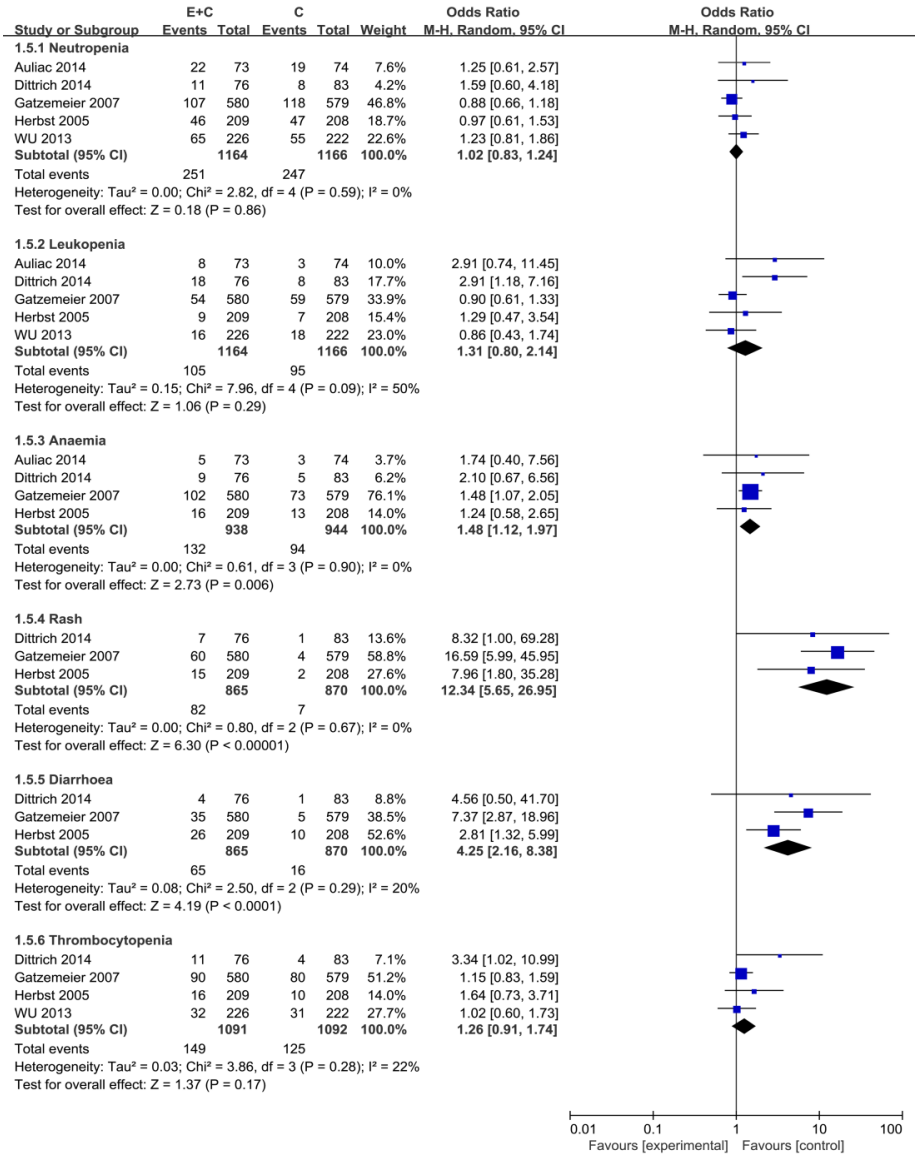
Adverse events

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



S1 - Figure

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 inpatients 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 [67]. 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

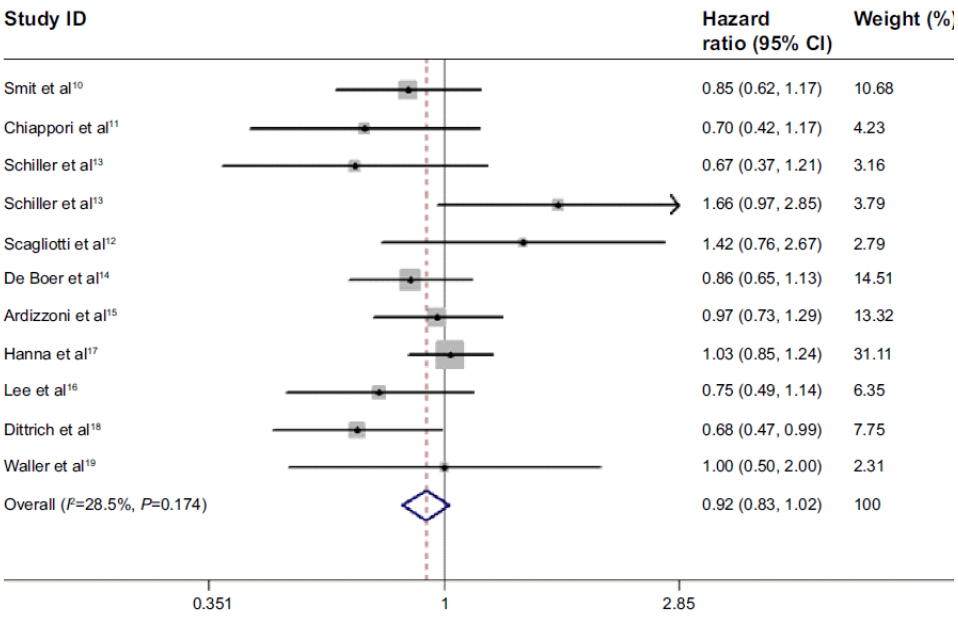
Authors	Phase	Regimes	No of patients analyzed	Patients per arm	Median age	Male (%)	Smoker (%)	Squamous histology (%)	ECOG PS 0 (%)	Jadad score
Smit et al[10]	Phase II	Pemetrexed plus carboplatin	240	119	59	62	NR	24	29	3
		Pemetrexed		121	59	64	NR	26	31	
Chiappori et al[11]	Phase II	Pemetrexed plus enzastaurin	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.

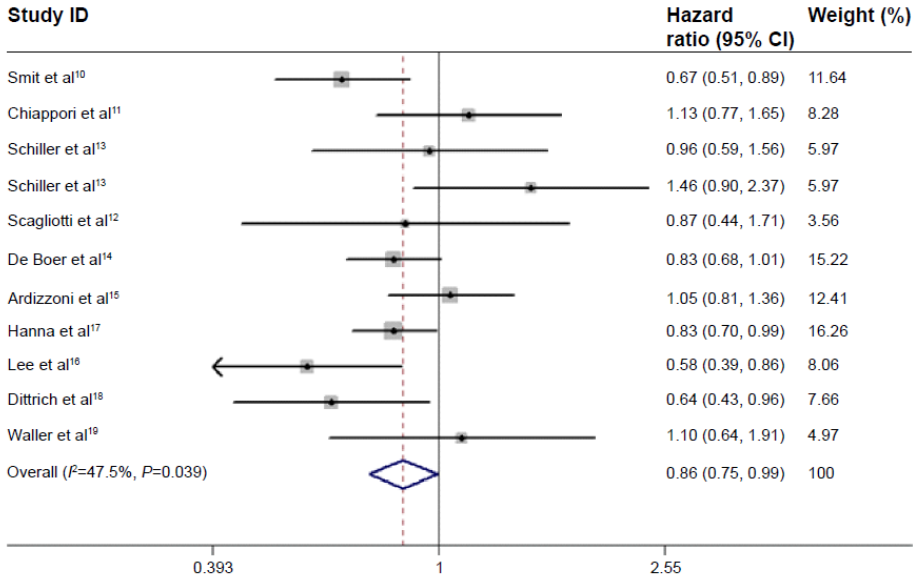


Figure 3 Forest plot of progression-free survival in patients treated with pemetrexed-based doublet therapy and pemetrexed alone.
Note: Weights are from random effects analysis.
Abbreviation: CI, confidence interval.

ORR

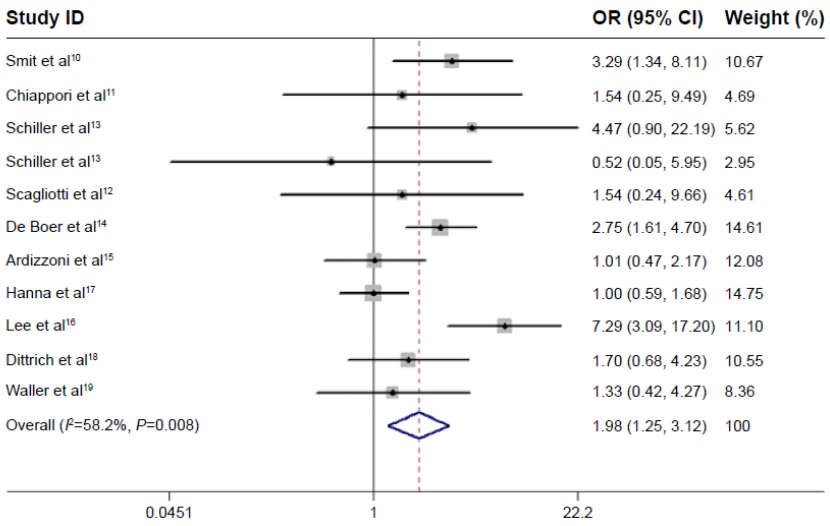


Figure 4 Forest plot of objective response rate in patients treated with pemetrexed-based doublet therapy and pemetrexed alone.
Note: Weights are from random effects analysis.
Abbreviations: OR, odds ratio; CI, confidence interval.

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.
Popat S et al., 2015 [48]. Nintedanib plus docetaxel as second-line therapy in patients with non-small-cell lung cancer: a network meta-analysis	1. Fragestellung NMA to evaluate the comparative efficacy of nintedanib plus docetaxel with docetaxel, pemetrexed, erlotinib and gefitinib for the second-line treatment of patients with advanced or metastatic NSCLC of adenocarcinoma histology.
	2. Methodik Population: relapsed or refractory NSCLC – histologically or cytologically confirmed, locally advanced and/or metastatic NSCLC of stage IIIB or IV (according to American Joint Committee on Cancers) or recurrent NSCLC (all histologies) Intervention*:* any second-line chemotherapy or targeted therapy used alone or in combination Komparator: chemotherapy, targeted therapy, placebo or best supportive care Endpunkte: OS and PFS Suchzeitraum (Aktualität der Recherche): bis März 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 9 Studien
	3. Ergebnisdarstellung *Hinweis*: The assumption of similarity of populations across these studies is necessary in order to allow for a NMA; however, clinical heterogeneity was evaluated to identify potential effect modifiers. This evaluation highlighted that some identified trials had a high percentage of patients with known EGF receptor (EGFR) mutation-positive NSCLC at baseline or used clinical criteria to include patients with a higher likelihood of EGFR mutation-positive NSCLC. **Base case NMA** • For analysis of OS, nintedanib plus docetaxel showed a statistically significant advantage in prolonging OS compared with docetaxel alone or erlotinib alone. The estimated HR for OS favored nintedanib plus docetaxel compared with pemetrexed, but this comparison did not reach statistical significance. ○ The estimated probability of nintedanib plus docetaxel being the best treatment with regard to overall survival was 70% (versus 16% for pemetrexed, 10% for docetaxel and 3% for erlotinib). • For analysis of **PFS**, nintedanib plus docetaxel showed a statistically

	significant advantage in prolonging PFS compared with docetaxel alone or erlotinib. As for OS, HRs indicated that nintedanib plus docetaxel prolonged PFS compared with pemetrexed but the difference was not statistically significant. ○ The estimated probability of nintedanib plus docetaxel being the best treatment with regard to PFS was 69.7% compared ith 18.5% for pemetrexed, 6.8% for erlotinib and 5.0% for docetaxel. *Sensititivätsanalysen base case NMA - including trials with a high likelihood of containing patients with EGFR mutation-positive NSCLC* • Inclusion of these additional trials (n = 4) resulted in the addition of two further treatments to the network: gefitinib and erlotinib plus pemetrexed. In the random-effects model, no comparisons were statistically significant owing to wide credible intervals. • For PFS, erlotinib plus pemetrexed had the greatest probability of being the best treatment (62.0%), with nintedanib plus docetaxel ranked second (25.0%), followed by gefitinib (12.2%). All other treatments were associated with extremely low probabilities of being the best treatment with regard to PFS (each <1% chance). **Scenario NMA- Scenario NMA** *Hinweis*: Assumption, that rhe estimated HRs for OS and PFS from the scenario NMA, in which equal efficacy of docetaxel and pemetrexed was assumed • In the random-effects model, no comparisons were statistically significant owing to the wide credible intervals. The estimated probability of nintedanib plus docetaxel being the best treatment with regard to OS was 79% compared with 14% for docetaxel/pemetrexed and 7% for erlotinib, while the estimated probability of nintedanib plus docetaxel being the best treatment with regard to PFS was 84% compared with 9% for docetaxel/ pemetrexed and 8% for erlotinib. • Results from the fixed-effects scenario analysis indicated that nintedanib plus docetaxel showed a statistically significant advantage in prolonging both OS and PFS compared with patients who received docetaxel/pemetrexed alone or erlotinib. *Sensititivätsanalysen scenario NMA - including trials with a high likelihood of containing patients with EGFR mutation-positive NSCLC* • As for other randomeffects model analyses, no comparisons were • statistically significant owing to the wide credibility intervals.
	4. Fazit der Autoren: *NMA provides a useful source of information on the comparative benefits of different treatments for healthcare decision makers when direct head to head trials have not been conducted. Results of this NMA support the conclusions of the LUME-Lung 1 trial, that nintedanib plus docetaxel offers clinical benefit compared with docetaxel alone for the second-line treatment of*

	patients with advanced NSCLC of adenocarcinoma histology, and suggest that this combination may also add clinical benefit compared with erlotinib when used in this patient group. 5. Hinweise der FBMed: • Umgang mit Heterogenität/Homogenitätsanahme in Analyse: *Differences in the percentage of patients with EGFR mutation-positive NSCLC were controlled by excluding studies with a high likelihood of containing these patients, or studies known to contain patients with EGFR mutation-positive NSCLC, from the base case analysis. → base case analysis is considered the most appropriate network for indirect treatment comparisons as the trials included in this network are likely to have the most comparable patient populations.* • Nur indirekte Evidenz →Allgemeine Limitationen von NMA beachten
Sheng J et al., 2015 [54]. 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 patients population by tumor histology is substantial for future studies and clinical application of antiangiogenic therapy.* 5. Hinweise der FBMed: • 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.
Zhou JG et al., 2015 [69]. Treatment on advanced NSCLC: platinum-based chemotherapy plus erlotinib or platinum-based chemotherapy alone? A systematic review and meta-analysis of randomised controlled trials	1. Fragestellung We undertake a systematic review and meta-analysis to evaluate the potential of erlotinib plus platinum-based chemotherapy compared with platinumbased chemotherapy alone in advanced NSCLC.
	2. Methodik Population: patients were diagnosed as advanced NSCLC Intervention: erlotinib plus platinum-based chemotherapy Komparator: platinum-based chemotherapy alone Endpunkte: OS, ORR, PFS Suchzeitraum (Aktualität der Recherche): Systematische Literaturrecherche von 2000 bis 2014 *Hinweis*: Nur RCTs eingeschlossen

	Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 studies, involving 3,363 patients who 1,680 and 1,683 patients were divided into erlotinib plus platinum-based chemotherapy and platinum-based chemotherapy alone, respectively, were included in the meta-analysis Qualitätsbewertung der Studien: Cochrane handbook for systematic reviews of interventions. The GRADE system identified the following four grades for rating the quality of evidence. I^2 für Heterogentität
	3. Ergebnisdarstellung Qualität der Studien: All 8 trials were open-label. The overall methodological quality of the included trials was generally good and fair. • For PFS measure, an HR of 0.73 (0.58–0.93) with statistical significance was estimated when erlotinib plus platinum-based chemotherapy compared with platinum-based chemotherapy alone. • Objective response rate of 32.86 versus 24.85 % was obtained for both groups, respectively. • HR of 0.93 (0.86–1.00) with P of 0.170 was calculated for OS. Sensitivitätsanalysen: • Sensitivity analysis Significant heterogeneity was observed among the included studies for PFS (I2 = 85.1 %). • After excluding one study, the results suggested that compared with platinumbased chemotherapy, erlotinib plus chemotherapy was associated with an increased PFS (HR 0.652, 95 % CI 0.546–0.759, P<0.0001). No evidence of high heterogeneity was observed among the remaining studies (I2 = 44.7 %).
	4. Fazit der Autoren: *In summary, the current available evidence suggests that erlotinib lacks the potential to improve OS. PFS and objective response rate could be improved by using erlotinib plus chemotherapy in patients with advanced NSCLC. Finally, smoking status and histological type are important evaluation factors that should be considered for evaluating clinical therapy and prognosis.*

Systematische Reviews (beide Therapielinien)

Sheng Z and Zhang Y, 2015 [56]. The Efficacy of Epidermal Growth Factor Receptor	**1. 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, we performed an indirect meta-analysis to assess the treatment effects of EGFR-TKIs in such patients.

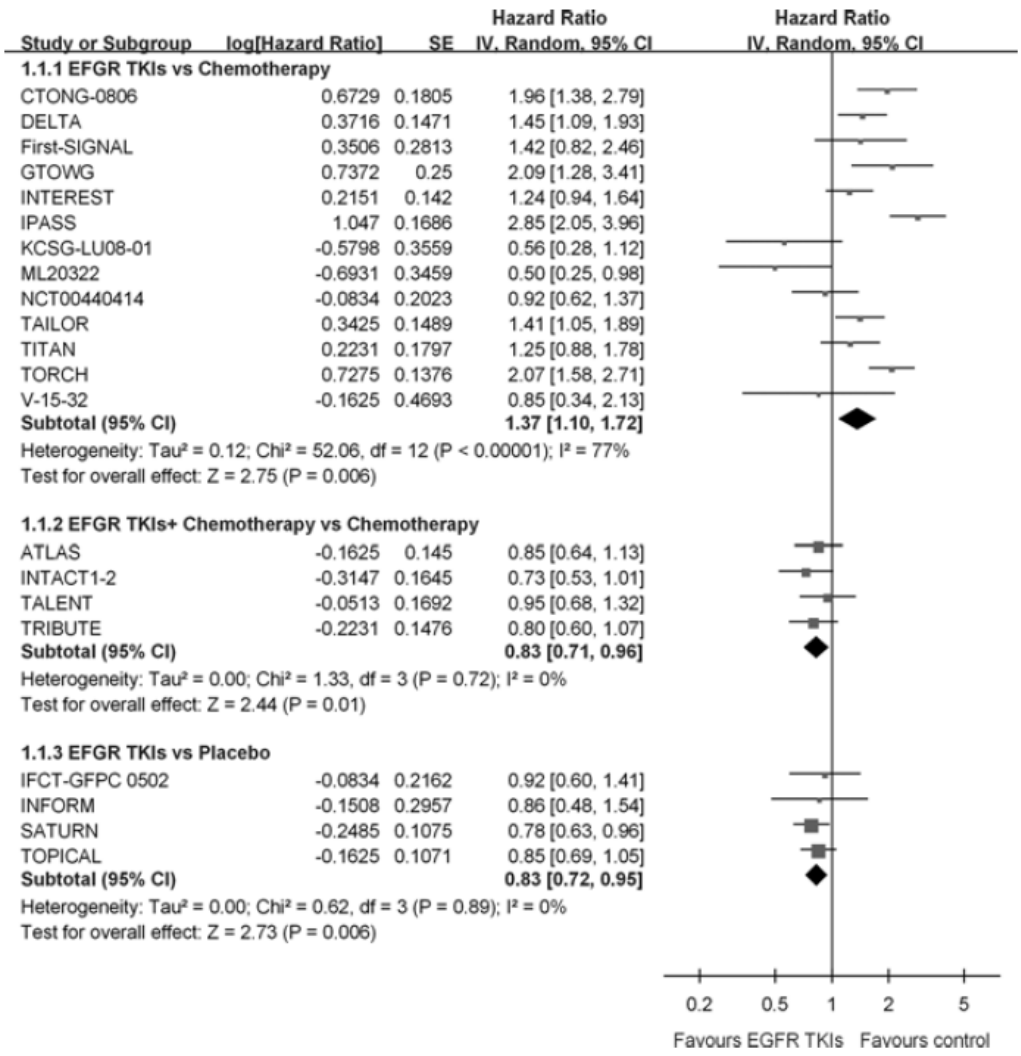
Tyrosine Kinase Inhibitors in Non-Small Cell Lung Cancer Harboring Wild-type Epidermal Growth Factor Receptor: A Meta-analysis of 25 RCTs	**2. Methodik** ***Population:*** advanced NSCLC, defined as inoperable locally advanced (stage IIIB) or metastatic or recurrent disease (stage IV), 1. Linie und 2./3. Linie sowie Erhaltungstherapie ***Interventionen und Komparatoren:*** first-generation EGFR-TKIs (erlotinib or gefitinib) vs. standard chemotherapy or placebo ***Endpunkte*:** PFS, OS ***Suchzeitraum:*** bis 09/2014 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 25 (4467); RCT ***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, outcome assessment, (4) intention-to-treat analyses. Each criterion was rated as yes, no or unclear. ***Heterogenitätsuntersuchungen:*** Chi-Quadrat, I^2

3. Ergebnisdarstellung

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

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

PFS

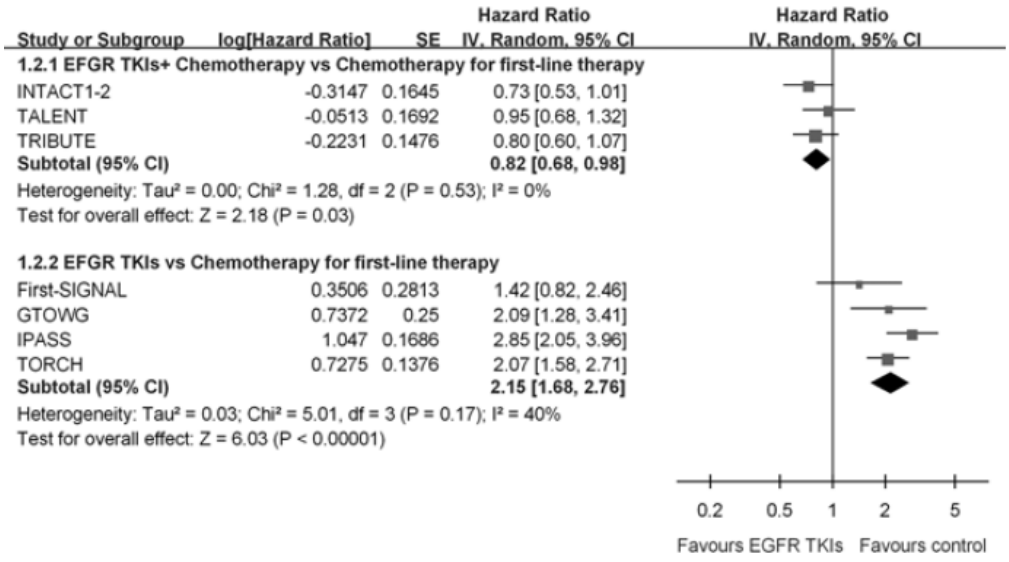


Meta-analysis of the treatment effects (epidermal growth factor receptor tyrosine kinase inhibitors [EGFR-TKIs] arms vs. control) on progression-free survival in patients with wild-type EGFR advanced non–small cell lung cancer. Random, random-effects model.

TABLE 2. Subgroup Analyses for EGFR-TKIs Versus Chemotherapy

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

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



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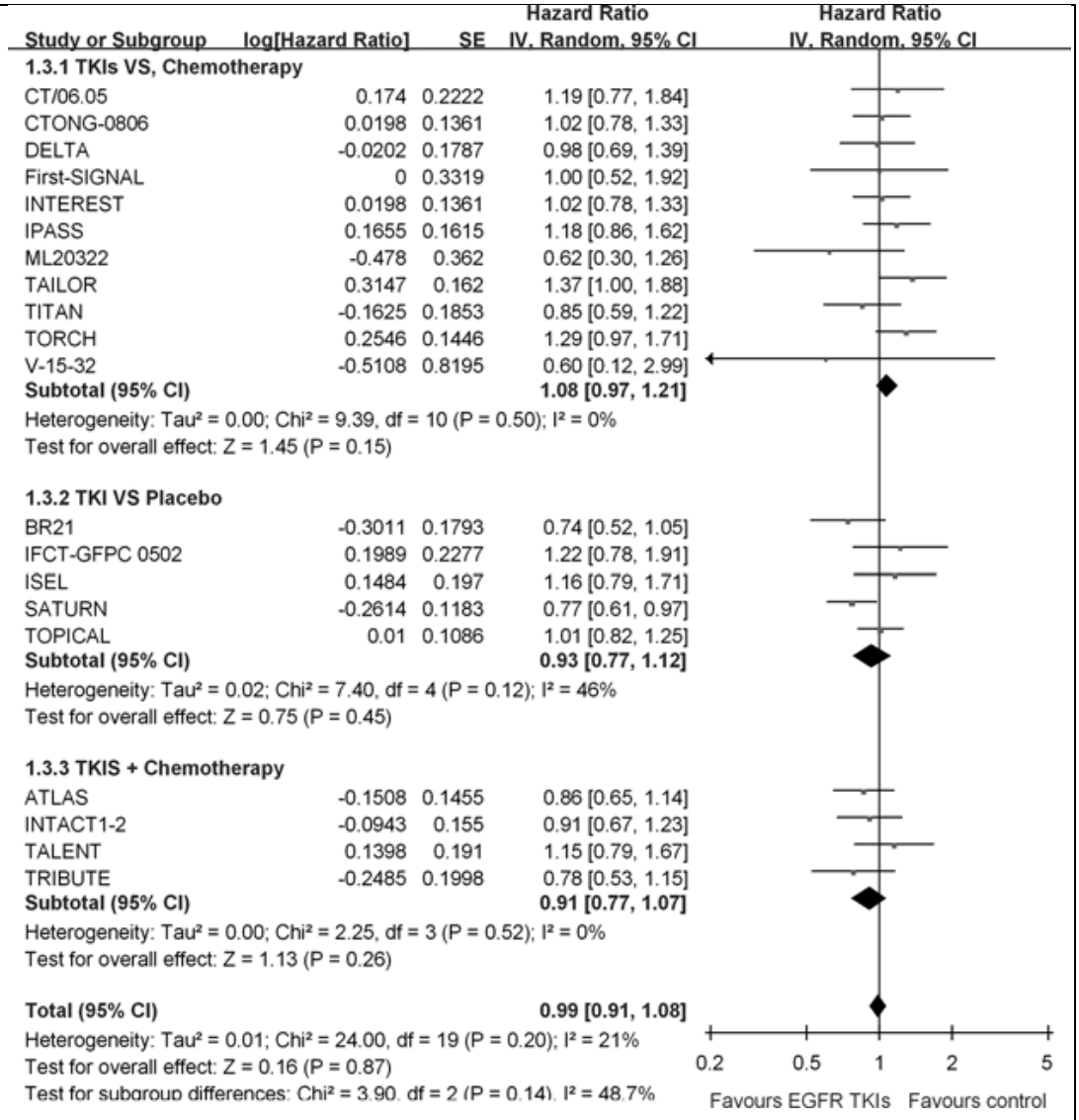
OS



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4. Anmerkungen/Fazit der Autoren

Among 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, but still superior to placebo in patients unfit for further chemotherapy. And, addition of EGFR-TKIs to chemotherapy could provide additive benefit over chemotherapy alone in such patients.

Qi WX et al., 2015 [49].

Anti-epidermal-growth-factor-receptor agents and complete responses

1. 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, we performed an indirect meta-analysis to assess the treatment effects of EGFR-TKIs in such patients.

2. Methodik

in the treatment of advanced non-small-cell lung cancer: a meta-analysis of 17 phase III randomized controlled trials	***Population:*** advanced NSCLC, defined as inoperable locally advanced (stage IIIB) or metastatic or recurrent disease (stage IV), 1. Linie und 2./3. Linie sowie Erhaltungstherapie ***Interventionen und Komparatoren:*** first-generation EGFR-TKIs (erlotinib or gefitinib) vs. standard chemotherapy or placebo ***Endpunkte*:** PFS, OS ***Suchzeitraum:*** bis 09/2014 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 25 (4467); RCT ***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, outcome assessment, (4) intention-to-treat analyses. Each criterion was rated as yes, no or unclear. ***Heterogenitätsuntersuchungen:*** Chi-Quadrat, I^2

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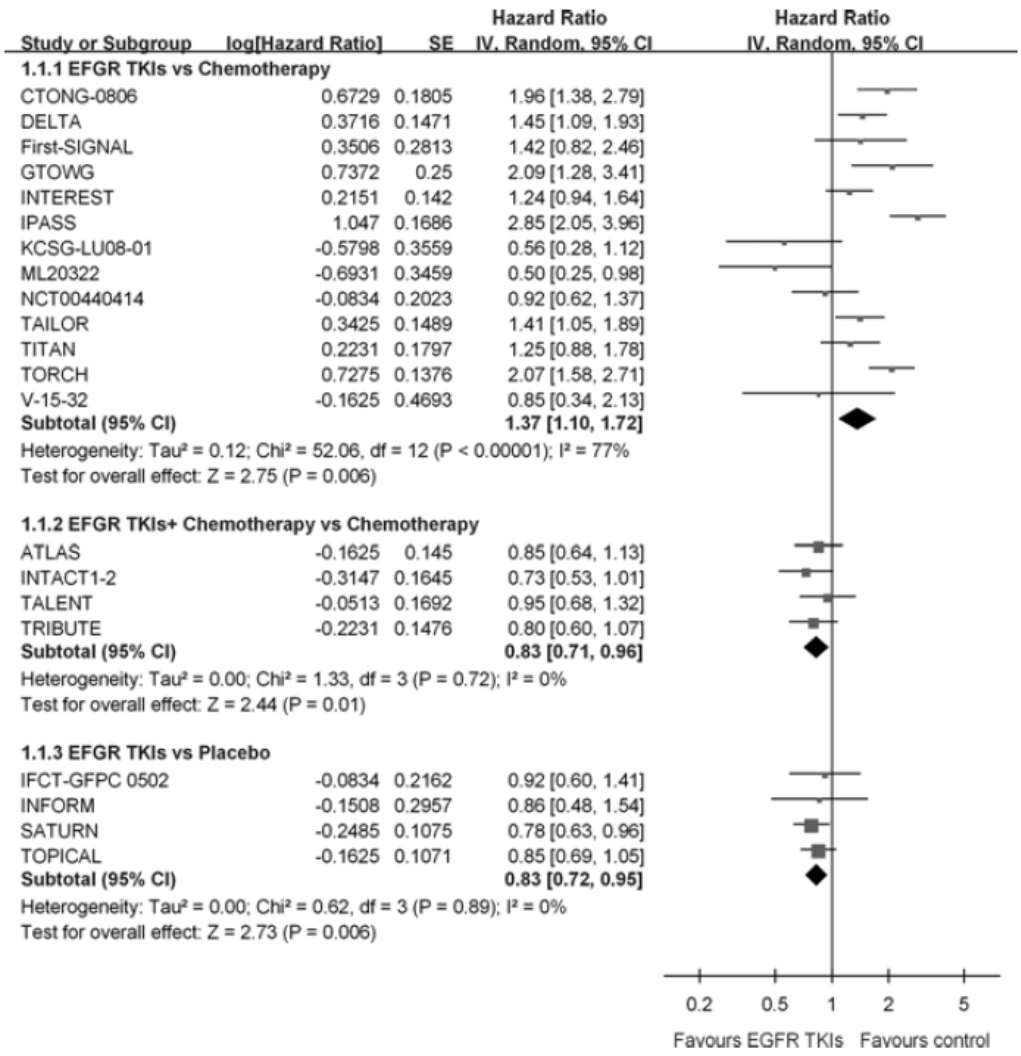
PFS



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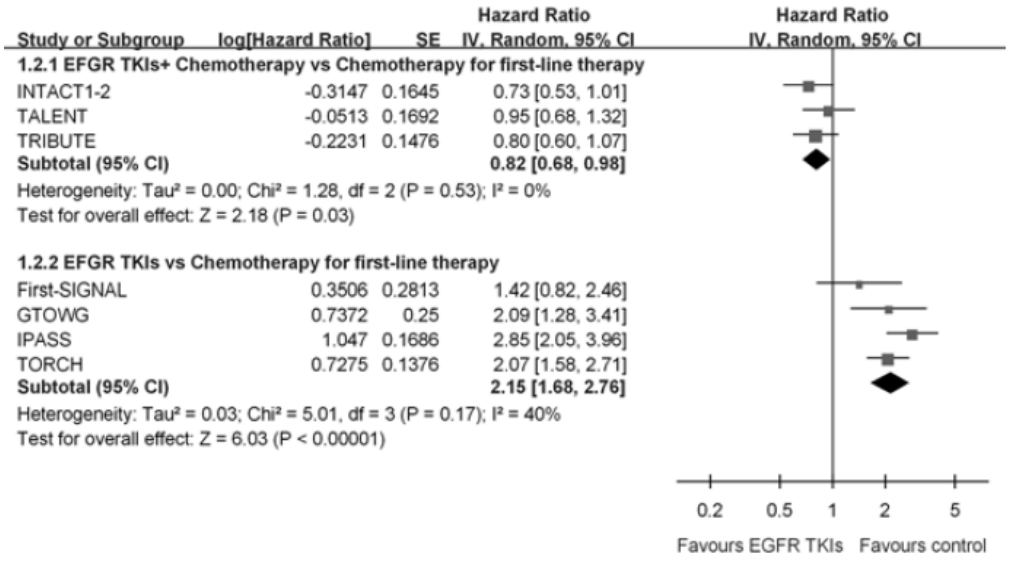
CI indicates confidence interval; HR, hazard ratio; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; WT, wild-type.



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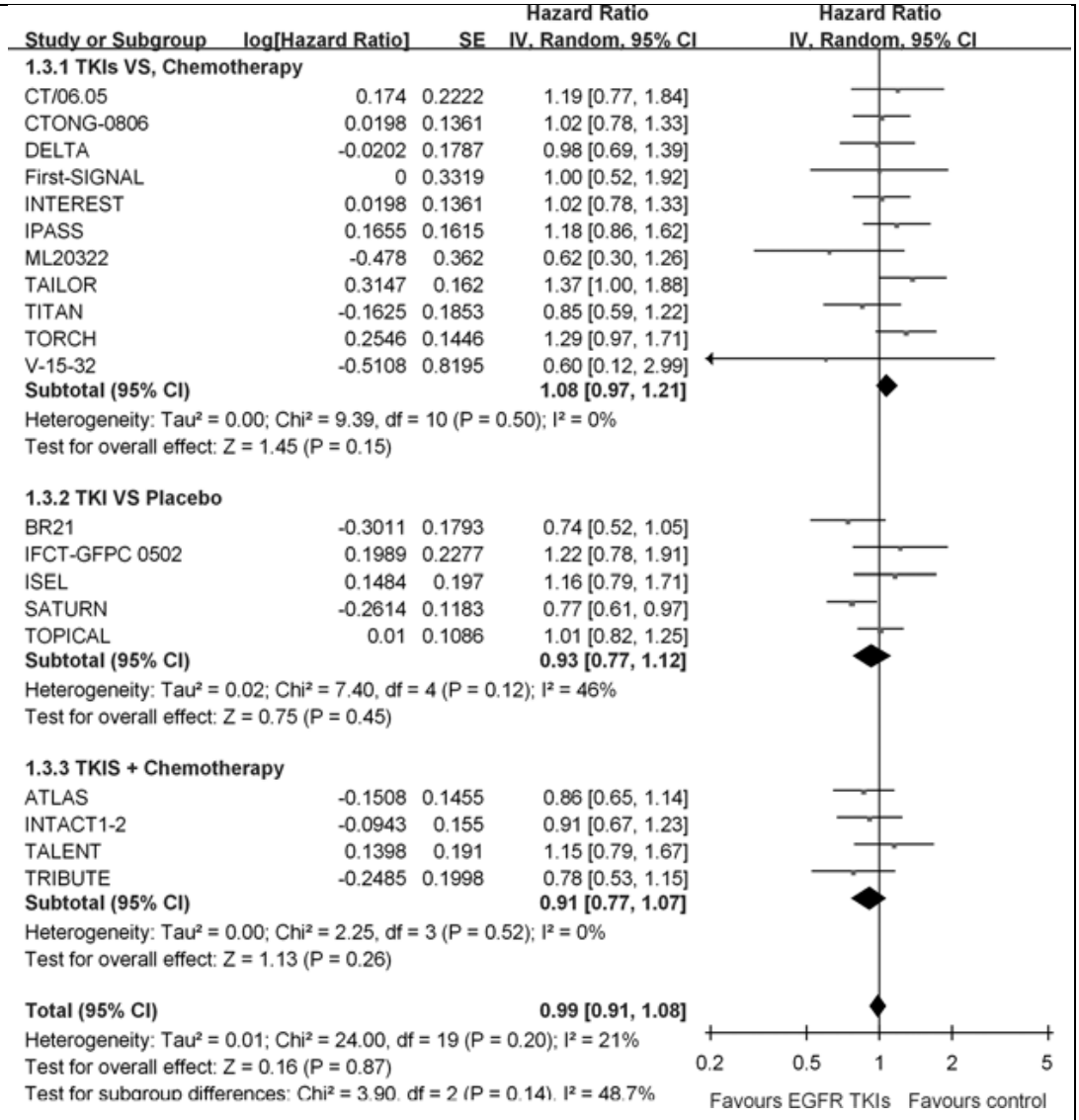
OS



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4. Anmerkungen/Fazit der Autoren

Among 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, but still superior to placebo in patients unfit for further chemotherapy. And, addition of EGFR-TKIs to chemotherapy could provide additive benefit over chemotherapy alone in such patients.

Anmerkungen der FB Med:

- *The authors declare no conflicts of interest.*

Burotto M, et al., 2015 [9].

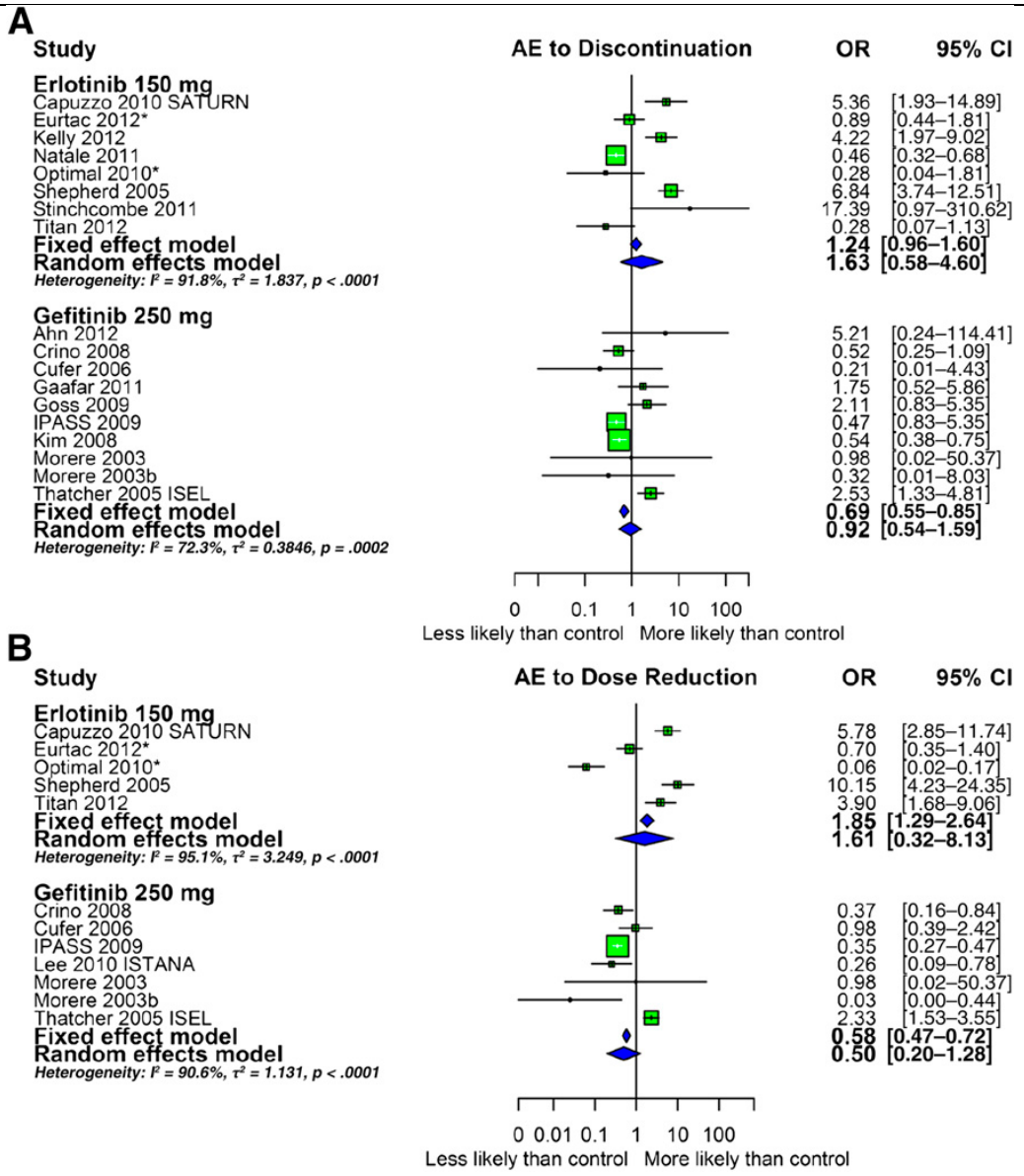
Gefitinib and Erlotinib in Metastatic Non-

1. Fragestellung

The objective of this study was to compare the efficacy and toxicity of erlotinib, gefitinib, and afatinib in NSCLC.

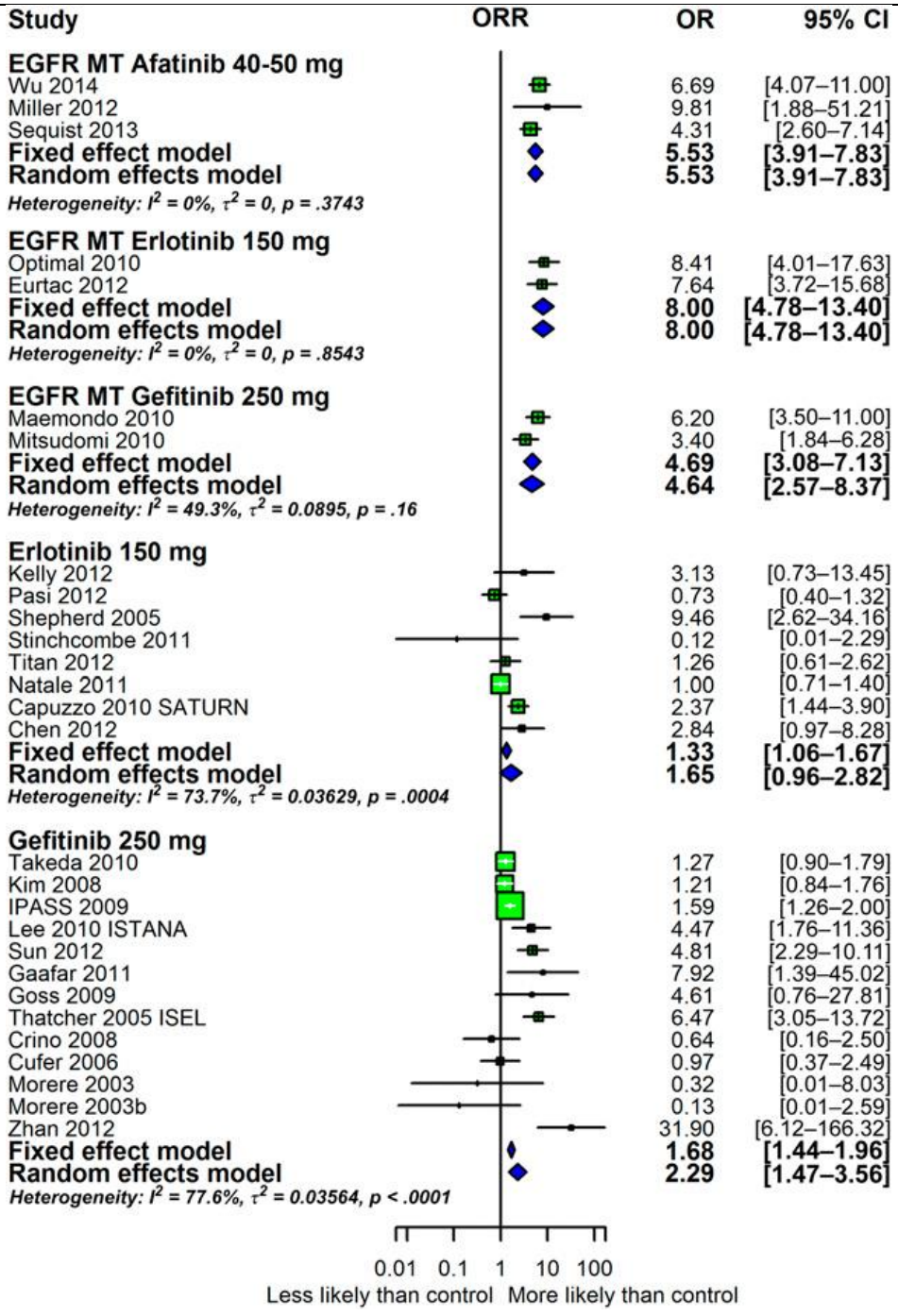
2. Methodik

Small Cell Lung Cancer: A Meta-Analysis of Toxicity and Efficacy of Randomized Clinical Trials	**Population**: advanced or metastatic stage IIIB or IV NSCLC according to the sixth American Joint Committee on Cancer classification **Intervention**: erlotinib or gefitinib **Komparatoren**: control arm did not receive erlotinib, gefitinib, or any other TKI **Endpunkte**: primär: PFS or OS; sekundär: nicht spezifiziert **Suchzeitraum**: 01/2003 – 12/2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** Erlotinib: 12/4 227, Gefitinib: 16/7 043 **Qualitätsbewertung der Studien:** Jadad-Score (phase II and phase III randomized studies; the treatment arm receiving the EGFR TKI had <40 patients) **Heterogenitätsuntersuchungen**: chi-square test
	3. Ergebnisdarstellung • trials had median/mean Jadad scores of 3/3.5 and 3/3 for gefitinib and erlotinib, respectively • 12 erlotinib reports included 7 phase III and 5 randomized phase II trials • 16 gefitinib studies were 11 phase III and 5 randomized phase II trials • for efficacy analyses comparing median OS and PFS distributions in the experimental arms of the erlotinib and gefitinib studies, we also analyzed trials according to the characteristics of the patients enrolled and the line of treatment, using the following groups: o monotherapy in second line, o monotherapy in first line (including the four trials in patient with mutated EGFR), o maintenance or consolidation in first line, o and monotherapy in the elderly population. **Toxitizität** • There is no direct comparison between erlotinib and gefitinib. • Clinical toxicities, including pruritus, rash, anorexia, diarrhea, nausea, fatigue, mucositis, paronychia, and anemia, were similar between erlotinib and gefitinib, although somestatistical differences were observed.



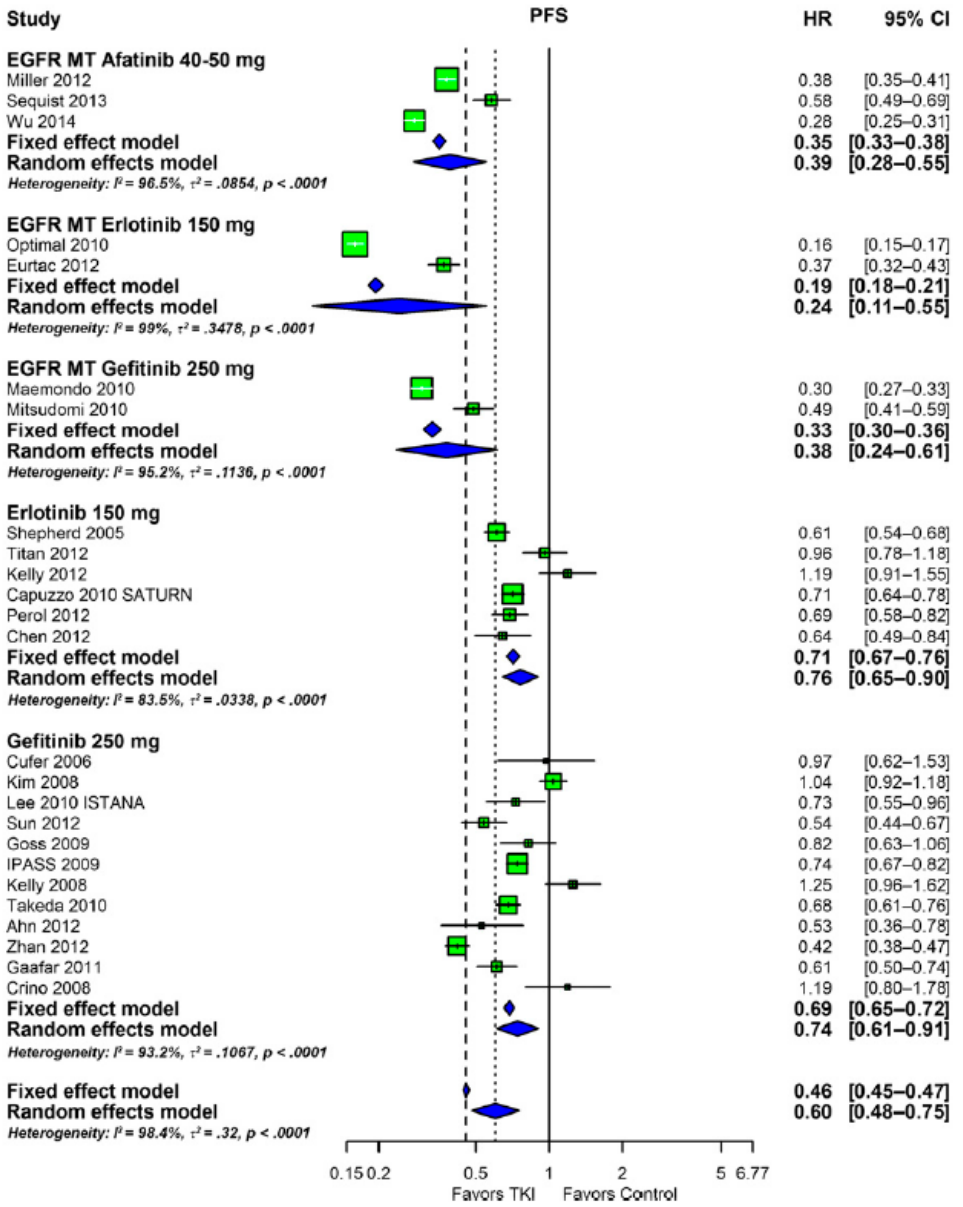
Forest plot depicting the meta-analysis using fixed-and random-effects models for drug discontinuation and dose reduction due to adverse events. An OR>1 indicates that the outcome was morelikely to occur in the arm receiving the tyrosine kinase inhibitor. (A): OR for drug discontinuation. (B): OR for dose reduction.

ORR



Forest plot depicting the efficacy of afatinib, erlotinib, and gefitinib in the studies evaluated as measured by ORR. An OR of > 1indicates that the arm with the tyrosine kinase inhibitor (TKI) performed better. An OR of <1 indicates that the arm with the TKI performed worse.The three groups at the top designated EGFRMT are studies that enrolled only patients with tumors harboring mutations in EGFR. The two groups at the bottom represent erlotinib and gefitinib studies conducted in all patients without prior determination of EGFR status.

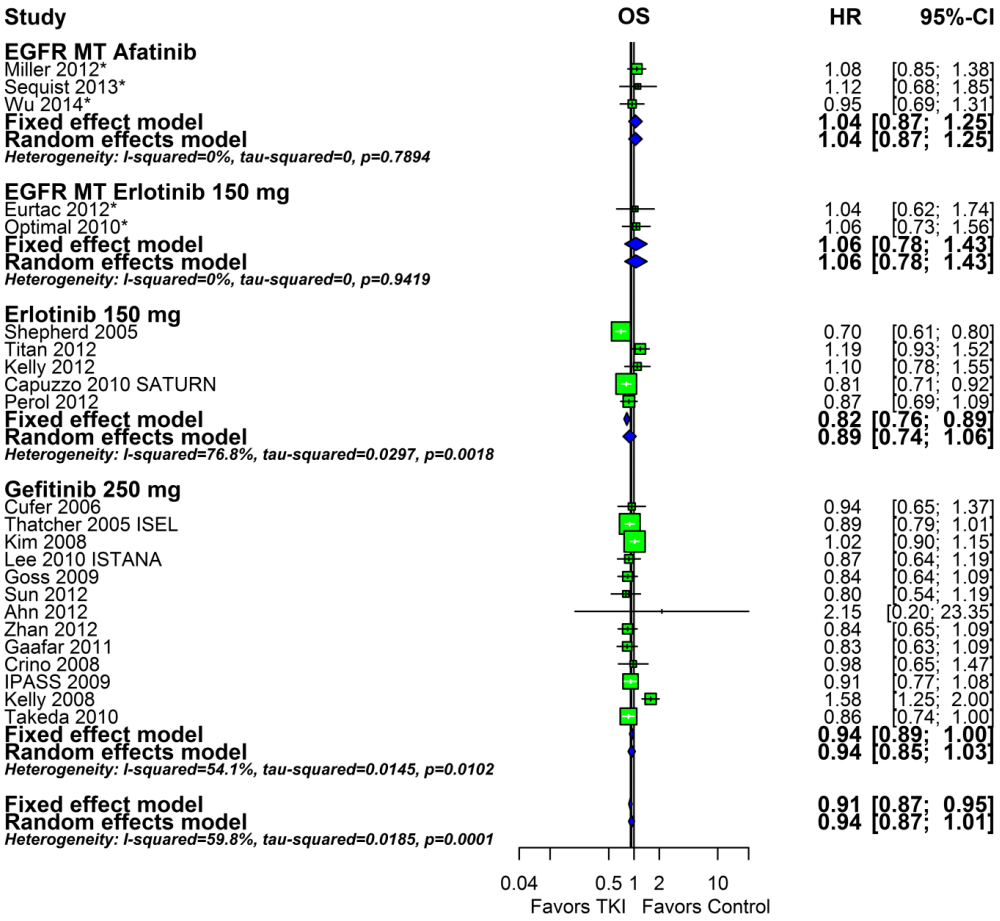
PFS



Forest plot depicting the meta-analysis of the PFS HR outcome. An odds ratio of <1 indicates that the arm with the tyrosine kinase inhibitor performed better than the control.

OS

- OS outcomes have poorer hazard ratios than those for PFS


Study
OS
HR
95%-CI
EGFR MT Afatinib
Miller 2012* 1.08 [0.85; 1.38]
Sequist 2013* 1.12 [0.68; 1.85]
Wu 2014* 0.95 [0.69; 1.31]
Fixed effect model 1.04 [0.87; 1.25]
Random effects model 1.04 [0.87; 1.25]
Heterogeneity: I-squared=0%, tau-squared=0, p=0.7894
EGFR MT Erlotinib 150 mg
Eurtac 2012* 1.04 [0.62; 1.74]
Optimal 2010* 1.06 [0.73; 1.56]
Fixed effect model 1.06 [0.78; 1.43]
Random effects model 1.06 [0.78; 1.43]
Heterogeneity: I-squared=0%, tau-squared=0, p=0.9419
Erlotinib 150 mg
Shepherd 2005 0.70 [0.61; 0.80]
Titan 2012 1.19 [0.93; 1.52]
Kelly 2012 1.10 [0.78; 1.55]
Capuzzo 2010 SATURN 0.81 [0.71; 0.92]
Perol 2012 0.87 [0.69; 1.09]
Fixed effect model 0.82 [0.76; 0.89]
Random effects model 0.89 [0.74; 1.06]
Heterogeneity: I-squared=76.8%, tau-squared=0.0297, p=0.0018
Gefitinib 250 mg
Cufer 2006 0.94 [0.65; 1.37]
Thatcher 2005 ISEL 0.89 [0.79; 1.01]
Kim 2008 1.02 [0.90; 1.15]
Lee 2010 ISTANA 0.87 [0.64; 1.19]
Goss 2009 0.84 [0.64; 1.09]
Sun 2012 0.80 [0.54; 1.19]
Ahn 2012 2.15 [0.20; 23.35]
Zhan 2012 0.84 [0.65; 1.09]
Gaafar 2011 0.83 [0.63; 1.09]
Crino 2008 0.98 [0.65; 1.47]
IPASS 2009 0.91 [0.77; 1.08]
Kelly 2008 1.58 [1.25; 2.00]
Takeda 2010 0.86 [0.74; 1.00]
Fixed effect model 0.94 [0.89; 1.00]
Random effects model 0.94 [0.85; 1.03]
Heterogeneity: I-squared=54.1%, tau-squared=0.0145, p=0.0102
Fixed effect model 0.91 [0.87; 0.95]
Random effects model 0.94 [0.87; 1.01]
Heterogeneity: I-squared=59.8%, tau-squared=0.0185, p=0.0001
0.04
0.5
1
2
10
Favors TKI
Favors Control

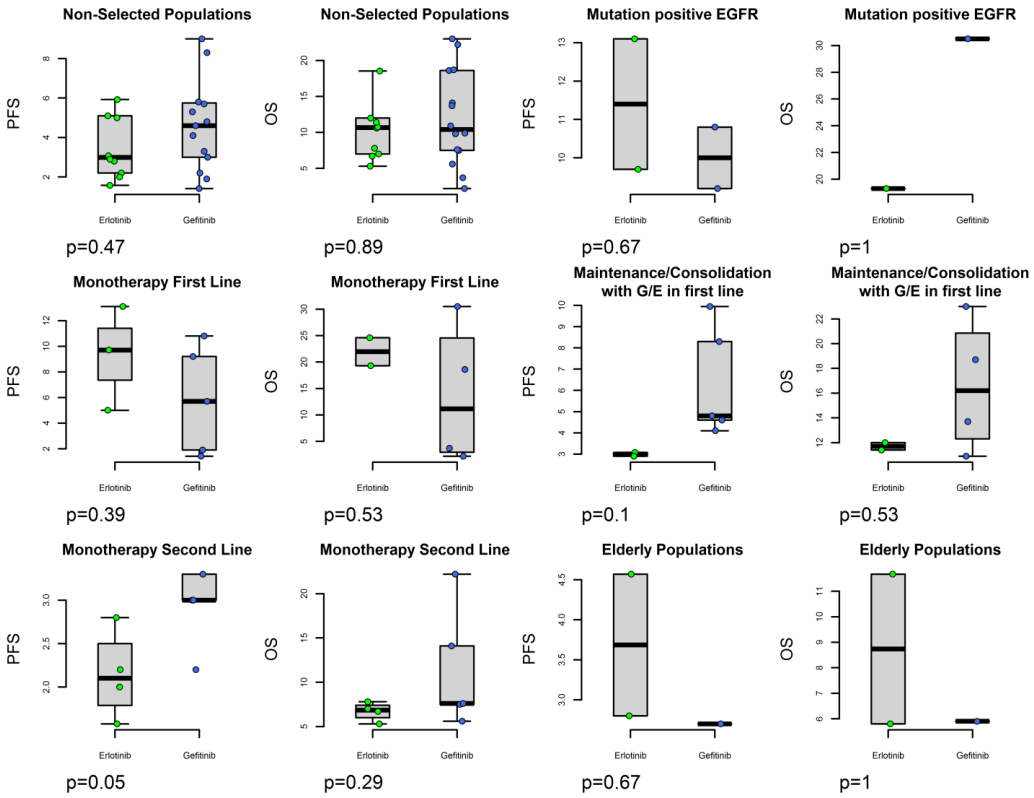


Figure S8: Efficacy analysis in all studies and in various subgroups comparing the efficacy of erlotinib and gefitinib. Results are presented for both reported median progression-free survival (PFS) and overall survival (OS) distributions. Boxplots depict the distributions, including the following attributes: the median (solid bar), interquartile range (IQR, box), the range as 1.5 times the IQR (dashed line, excluding any outliers), and the individual study data overlaid as scatterplots.

4. Anmerkungen/Fazit der Autoren

Gefitinib has similar activity and toxicity compared with erlotinib and offers a valuable alternative to patients with NSCLC. Afatinib has similar efficacy compared with erlotinib and gefitinib in first-line treatment of tumors harboring EGFR mutations but may be associated with more toxicity, although further studies are needed. Gefitinib deserves consideration for U.S. marketing as a primary treatment for EGFR-mutant NSCLC.

<u>Limitationen</u>:

- no head-to-head comparisons
- heterogeneity within subgroups for certain outcomes (i.e., variation between studies exists beyond that forwhich treatment group accounts)
- some might argue the 150-mg erlotinib dose is the maximum tolerated dose but that the 250-mg gefitinib dose is not, and this may “penalize” erlotinib; however, these are the approved doses and the doses for which data were available
- inclusion of patients with and without mutations makes analysis more difficult

Anmerkungen der FB Med:

- *Phase II Studien eingeschlossen, Jadad Score aber insgesamt gering*

	• *DISCLOSURES: The authors indicated no financial relationships.*
Perez-Moreno MA et al., 2014 [45]. Systematic review of efficacy and safety of pemetrexed in non-small-cell-lung cancer	**1. Fragestellung** to evaluate the efficacy and safety of pemetrexed therapy in adult patients with advanced stage NSCLC. And the specific objectives were to evaluate the efficacy of pemetrexed in NSCLC in each of the approved indications first-line induction, maintenance and second-line), according to histology (squamous/epidermoid adenocarcima or large cell) and to assess safety according to concomitant therapy administered.
	2. Methodik **Population**: NSCLC, Population: age 18 years or older patients **Intervention**: pemetrexed **Komparator**: Other available therapies **Endpunkte**: Nicht vorab spezifiziert **Suchzeitraum**: 04/ 2004 is 04/ 2012 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 5/ 3 541, nur RCTs **Qualitätsbewertung der Studien:** specific assessment scales, Critical Appraisal Skills Program (CASP) adapted for CASP Spain
	3. Ergebnisdarstellung Studienqualität moderate bis high <u>First line</u> • pemetrexed associated with a platinum was similar in terms of efficacy to other alternative chemotherapy regimens, • except in patients with non-squamous histology, in whom survival was higher in the experimental group <u>Second line</u> • no significant differences in terms of efficacy and safety for pemetrexed treatment versus other chemotherapy options <u>adverse reactions</u> • most frequent: hematological, gastrointestinal and neurological • all significantly less frequent with pemetrexed versus other alternative therapies, except for liver toxicity.
	4. Anmerkungen/Fazit der Autoren Due to the high degree of uncertainty as to its efficacy in certain subgroups of patients, including conflicting data; to its recent incorporation, and therefore lack of safety data in the medium and long term, and the high budgetary impact of its incorporation into health systems, it seems reasonable to optimize its use, identifying those patients who may benefit most.

	Anmerkungen der FB Med: • *supported by the Health Department of the Spanish Government. (Investigacio´n Cli´nica Independiente. Ministerio de Sanidad y Poli´tica Social).* • *The authors declare that they have no conflicts of interest.*
Shi L et al., 2014 [58]. 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. Anmerkungen/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 [32]. 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: TKI Group *EGFR* WT[a]	TKI Group Total[b]	Control Group *EGFR* WT[a]	Control Group Total[b]	Follow-up Duration, Median (Range), mo
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 sequencing + 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 sequencing + 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

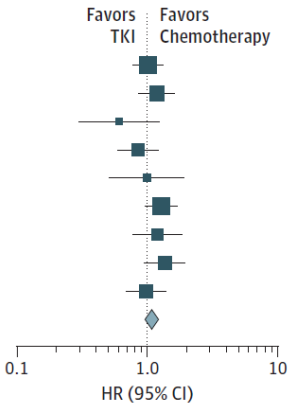
- significantly longer PFS with chemotherapy than with TKI in the patients with WT *EGFR* (HR, 1.41; 95% CI, 1.10-1.81); significant statistical heterogeneity noted (I^2 = 79.1%)

OS

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

B Overall survival

Source	No. of Patients With WT *EGFR*: TKI	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						

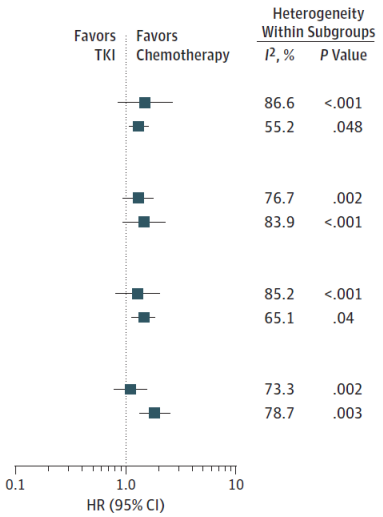


Figure 4. Subgroup Analyses for Progression-Free Survival According to the Line of Treatment (First vs Second or Later), EGFR TKI Agents, Ethnicity, and *EGFR* Mutation Analysis Methods for Patients WithWT *EGFR*

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.

Limitierungen:

- 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. Anmerkungen der FB Med

- 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.*

Qi WX et al., 2013 [51].

Incidence and risk of treatment-related mortality in cancer patients treated with EGFR-TKIs: a meta-

1. Fragestellung

Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) have become the cornerstone in the treatment of lung cancers that harbor EGFR mutations, but also play an important role in the treatment of other lung cancers and have been investigated among various types of solid tumors. However, these drugs have been associated with an increase in the risk of potentially life-threatening adverse event, such as arterial and venous thrombotic events. We

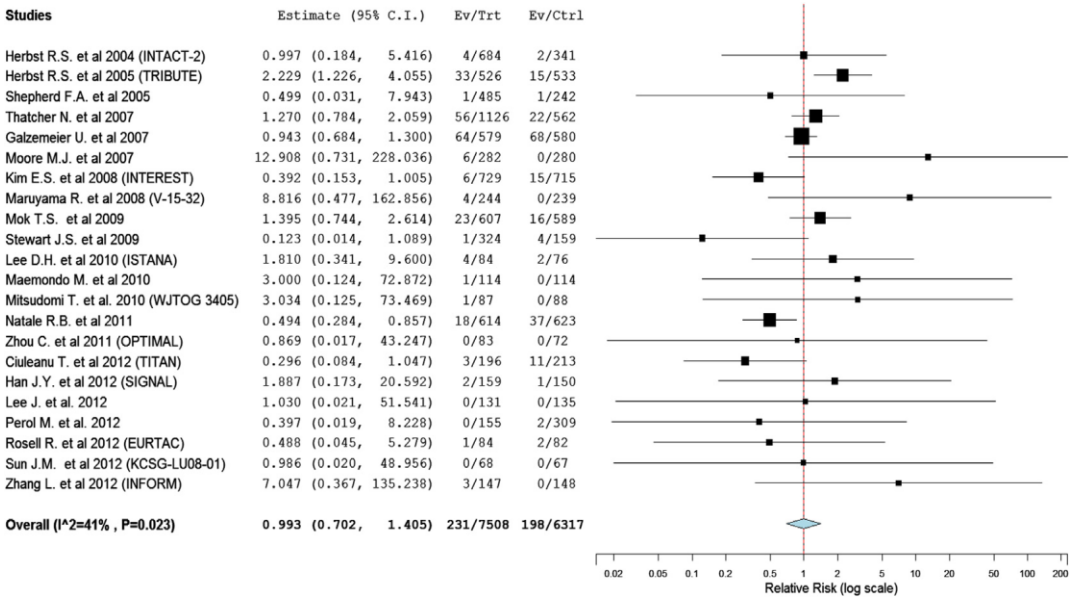
analysis of 22 phase III randomized controlled trials	performed a meta-analysis to determine the incidence and risk of fatal adverse events (FAEs) in cancer patients treated with EGFR-TKIs.
	2. Methodik ***Population:*** *Cancer patients* ***Interventionen und Komparatoren:*** EGFR-TKIs (erlotinib and gefitinib) vs. non-EGFRTKIs-containing therapy ***Endpunkte*:** incidence and risk of FAEs associated with the clinical use of EGFR-TKIs ***Suchzeitraum:*** 1/1990 – 12/2012 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 22 (13825), prospective phase III RCTs; (EGFR-TKIs: n = 7508; non-EGFR-TKIs: n = 6317) ***Qualitätsbewertung der Studien:*** Jadad-Scale ***Heterogenitätsuntersuchungen:*** Random effects models were used regardless of the actual inter-study heterogeneities, which were quantified using the chi-Quadrat-based Q statistic
	3. Ergebnisdarstellung Relative risk of fatal adverse events associated with EGFR-TKIs versus non-EGFR-TKIs therapy 

Table 1 Incidence and relative risk of FAEs with EGFR-TKIs according to prespecified subgroups.

Groups	Studies, *n*	Fatal adverse events, *n*/total, *n*		Incidence of fatal adverse events, % (95%CI)		RR (95%CI)	*p* Value
		EGFR-TKIs	Control	EGFR-TKIs	Control		
Tumor type							
NSCLC	19	224/6771	194/5743	2.1 (1.3–3.3)	2.1 (1.3–3.4)	1.00 (0.72–1.40)	0.98
Pancreatic cancer	1	6/282	0/280	2.1 (1.0–4.7)	0.2 (0–2.8)	12.91 (0.73–228.05)	0.08
Head and neck cancer	1	1/324	4/159	0.3 (0–2.2)	2.5 (0.9–6.5)	0.12 (0.01–1.09)	0.06
Biliary-tract cancer	1	0/135	0/131	0	0	–	–
EGFR-TKIs							
Erlotinib	10	105/4373	62/3248	1.7 (1.0–2.9)	1.9 (1.2–2.9)	1.13 (0.72–1.78)	0.60
Gefitinib	12	126/3135	136/3069	2.2 (1.1–4.3)	2.5 (1.3–4.9)	0.87 (0.50–1.51)	0.61
Country							
Asia	10	38/1724	19/1678	2.2 (1.4–3.5)	1.2 (0.6–2.4)	1.65 (0.98–2.78)	0.058
Non-Asia	12	193/5784	179/4639	1.9 (1.1–3.5)	2.6 (1.5–4.5)	0.80 (0.51–1.25)	0.32
EGFR-TKIs-based regimens							
Monotherapy	17	124/5306	113/4448	1.7 (1.1–2.7)	2.2 (1.5–3.3)	0.83 (0.54–1.29)	0.41
Combinations	5	107/2202	85/1869	2.9 (1.1–7.1)	1.6 (0.4–6.2)	1.48(0.75–2.92)	0.26
Treatment strategy							
First-line	12	191/4462	126/3526	2.7 (1.6–4.4)	1.8 (0.9–3.6)	1.22 (0.98–1.52)	0.08
Salvage treatment	8	37/2744	70/2334	1.4 (0.7–2.7)	2.6 (1.4–4.7)	0.51 (0.29–0.87)	0.013
Maintenance	2	3/302	2/457	1.3 (0.3–6.0)	0.6 (0.2–1.9)	1.71 (0.10–28.59)	0.71
Controlled therapy							
Placebo	3	60/1758	23/952	1.7 (0.4–7.2)	1.1 (0.2–7.0)	1.29 (0.81–2.07)	0.29
Active therapy	19	171/5750	175/5365	1.8 (1.1–3.0)	1.9 (1.2–3.3)	0.94 (0.63–1.41)	0.76
Overall	22	231/7508	198/6317	1.9 (1.2–2.9)	1.9 (1.2–3.0)	0.99 (0.70–1.41)	0.97

Abbreviations: NSCLC, non-small-cell lung cancer; EGFR-TKIs, epidermal growth factor receptor tyrosine kinase.

4. Anmerkungen/Fazit der Autoren

In conclusion, this analysis suggests that the use of EGFR-TKIs does not increase the risk of FAEs in patients with advanced solid tumors, and EGFR-TKIs are safety and tolerable for cancer patients, especially for those previously treated patients.

Hinweise der FBMed

- *3 von 22 Studien umfassen nicht NSCLC*
- *Vergleichstherapien (19 /22 Studien vergelichen gegen aktive Kontrolle) sind nicht spezifiziert bzw. näher ausgewertet*

Zhou H et al., 2013 [68].

Chemotherapy with or without gefitinib in patients with advanced non-small-cell lung cancer: a meta-analysis of 6,844 patients

1. Fragestellung

Gefitinib is wldely used in patlents with advanced non-small-cell lung cancer (NSCLC), in whom chemotherapy had failed. Previous triais reported inconsistent flndings regarding the efficacy of gefitinib on overall survival (OS) and progression free survival (PFS). This study was to evaluate the effects of chemotherapy plus gefitinib versus chemotherapy alone on survival of patients with NSCLC.

2. Methodik

Population: advanced NSCLC

Interventionen und Komparatoren: Gefitinib vs. [Kontrolle nicht präspezifiziert]

***Endpunkte*:** PFS, OS, ORR, UE

Suchzeitraum: bis 20.01.2012

Anzahl eingeschlossene Studien/Patienten (Gesamt): 12 (6844)

Qualitätsbewertung der Studien: Jadad Score

Heterogenitätsuntersuchungen: Chi square Test and I-squared statistic.

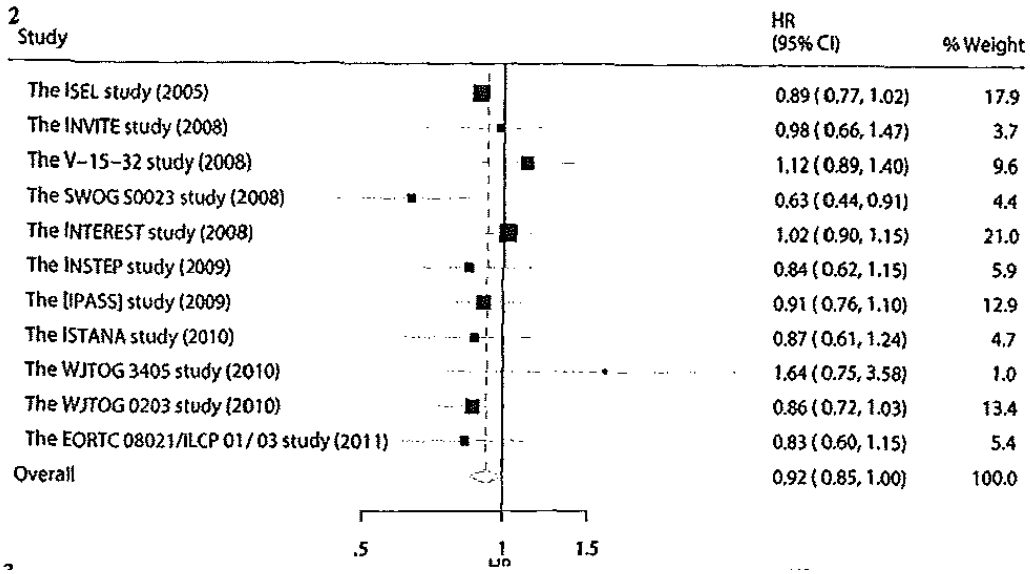
Statistical heterogeneity was considered significant when $P < 0.10$.

3. Ergebnisdarstellung

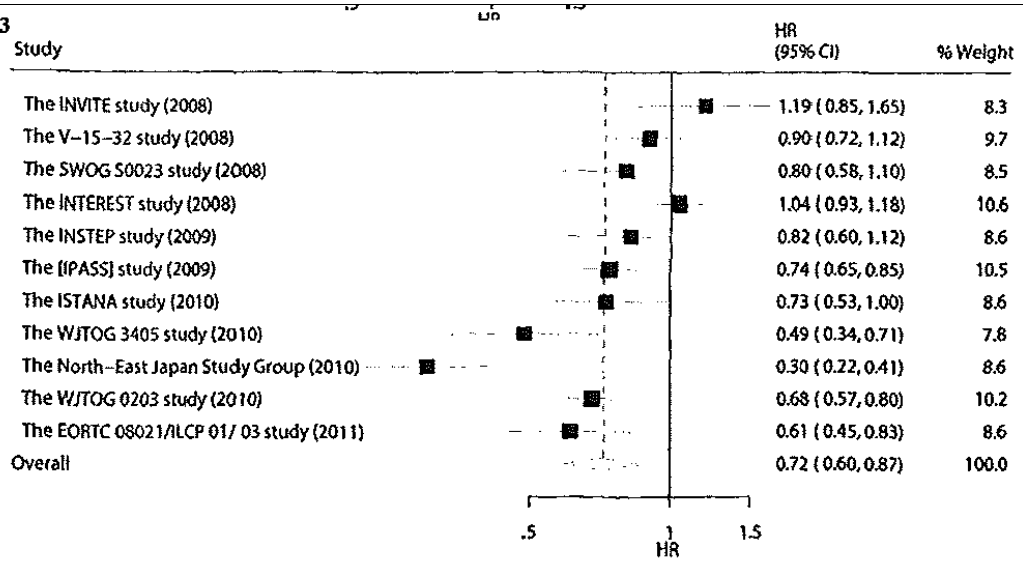
Table 1. Baseline characteristics for included trials

Trials	Number of Patients	Median age (years)	Sex, male (%)	Stage IIIB or IV (%)	Intervention	Treatment status	Follow-up (months)	Main endpoint	Jadad score
ISEL (2005)[14]	1692	62	67	81	Gefitinib; placebo	Second line	7.2	OS, ORR	4
INVITE (2008)[15]	196	74	76	100	Gefitinib; vinorelbine	First line	20	OS, PFS, ORR	3
V-15-32 (2008)[16]	489	20 years or older	62	83	Gefitinib; docetaxel	First line	36	OS, PFS, ORR	3
SWOG S0023 (2008)[17]	243	61	63	52	Gefitinib; placebo	Second line	60	OS, PFS	3
INTEREST (2008)[18]	1466	61	65	79	Gefitinib; docetaxel	Second line	7.6	OS, PFS, ORR	4
INSTEP (2009)[19]	201	75	61	NG	Gefitinib; placebo	Second line	24	OS, PFS, ORR	4
IPASS (2009)[8]	1217	57	21	100	Gefitinib; carboplatin plus paclitaxel	First line	24	OS, PFS, ORR	4
ISTANA (2010)[9]	161	57	61	100	Gefitinib; docetaxel	Second line	15	OS, PFS, ORR	3
WJTOG 3405 (2010)[10]	172	64	31	59	Gefitinib; cisplatin plus docetaxel	Second line	40	OS, PFS, ORR	3
North-East Japan (2010)[11]	230	63	36	91	Gefitinib; paclitaxel and carboplatin	First line	42	PFS, ORR	4
WJTOG 0203 (2010)[12]	604	62	64	100	Gefitinib; platinum-doublet chemotherapy	First line	60	OS, PFS, ORR	4
EORTC 08021/ILCP 01/03 (2011)[13]	173	62	77	100	Gefitinib; placebo	Second line	60	OS, PFS, ORR	4

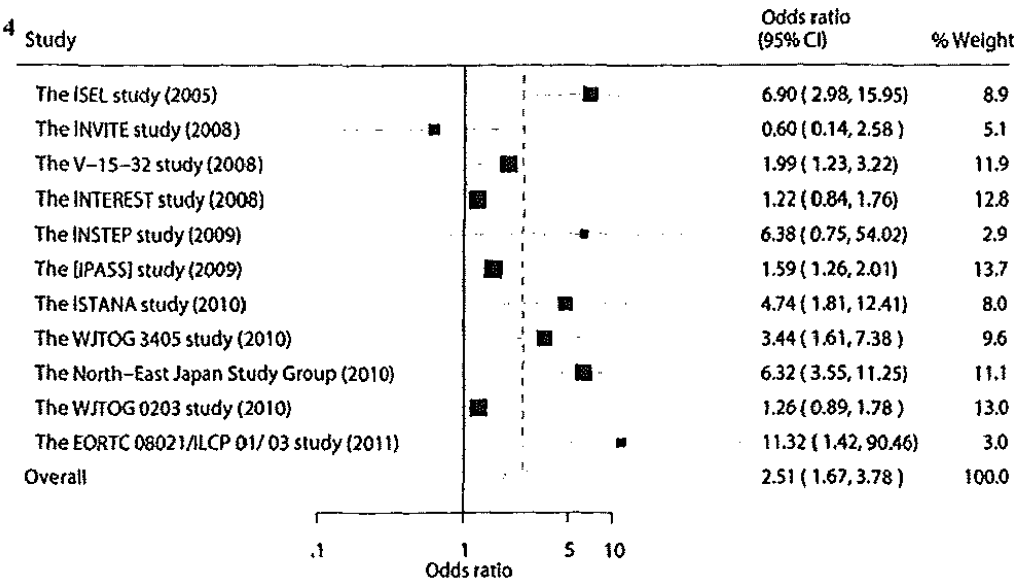
OS



PFS


3
Study
HR (95% CI)
% Weight
The INVITE study (2008) 1.19 (0.85, 1.65) 8.3
The V–15–32 study (2008) 0.90 (0.72, 1.12) 9.7
The SWOG S0023 study (2008) 0.80 (0.58, 1.10) 8.5
The INTEREST study (2008) 1.04 (0.93, 1.18) 10.6
The INSTEP study (2009) 0.82 (0.60, 1.12) 8.6
The [IPASS] study (2009) 0.74 (0.65, 0.85) 10.5
The ISTANA study (2010) 0.73 (0.53, 1.00) 8.6
The WJTOG 3405 study (2010) 0.49 (0.34, 0.71) 7.8
The North–East Japan Study Group (2010) 0.30 (0.22, 0.41) 8.6
The WJTOG 0203 study (2010) 0.68 (0.57, 0.80) 10.2
The EORTC 08021/ILCP 01/ 03 study (2011) 0.61 (0.45, 0.83) 8.6
Overall 0.72 (0.60, 0.87) 100.0
.5
1
1.5
HR

ORR


4
Study
Odds ratio (95% CI)
% Weight
The ISEL study (2005) 6.90 (2.98, 15.95) 8.9
The INVITE study (2008) 0.60 (0.14, 2.58) 5.1
The V–15–32 study (2008) 1.99 (1.23, 3.22) 11.9
The INTEREST study (2008) 1.22 (0.84, 1.76) 12.8
The INSTEP study (2009) 6.38 (0.75, 54.02) 2.9
The [IPASS] study (2009) 1.59 (1.26, 2.01) 13.7
The ISTANA study (2010) 4.74 (1.81, 12.41) 8.0
The WJTOG 3405 study (2010) 3.44 (1.61, 7.38) 9.6
The North–East Japan Study Group (2010) 6.32 (3.55, 11.25) 11.1
The WJTOG 0203 study (2010) 1.26 (0.89, 1.78) 13.0
The EORTC 08021/ILCP 01/ 03 study (2011) 11.32 (1.42, 90.46) 3.0
Overall 2.51 (1.67, 3.78) 100.0
.1
1
5
10
Odds ratio

UE

Table 2. Summary of the odds ratios of all toxicities outcomes assessed

Outcomes	Included studies	*OR* and 95% *CI*	*P* values	Heterogeneity (%)	*P* values for heterogeneity
Rash	8–16,18,19	8.73 (6.13, 12.45)	<0.001	77	<0.001
Diarrhoea	8–16,18,19	2.63 (1.96, 3.52)	<0.001	73	<0.001
Nausea	8–10,12,14–16,18,19	0.47 (0.28, 0.79)	0.004	93	<0.001
Anorexia	8,9,11,12,14–16,18,19	0.70 (0.47, 1.06)	0.09	87	<0.001
Vomiting	8,9,11,12,14–16,18,19	0.88 (0.54, 1.45)	0.62	87	<0.001
Dry skin	8,9,11,12,14–16,18,19	10.37 (5.98, 18.01)	<0.001	64	0.004
Constipation	8–10,12,14–16,18,19	0.56 (0.40, 0.78)	<0.001	76	<0.001
Pruritus	8,9,14,16,19	3.03 (1.67, 5.49)	<0.001	79	<0.001
Pyrexia	14–16,18	0.79 (0.41, 1.53)	0.48	85	<0.001
Asthenic condition	8,9,14,15,18	0.45 (0.25, 0.80)	0.006	91	<0.001
Cough	9,13,14,18	0.94 (0.76, 1.17)	0.59	0	0.61
Dyspnea	9,10,13–15,18,19	0.96 (0.79, 1.17)	0.68	0	0.79
Stomatitis	8–10,12,14,16,18,	1.24 (0.77, 2.00)	0.38	79	<0.001
Hemoptysis	9,14	1.34 (0.86, 2.11)	0.20	0	0.37
Pneumonia	11–14,18,19	0.97 (0.70, 1.34)	0.85	13	0.33
Cancer pain	9,13,14	0.69 (0.37, 1.28)	0.24	31	0.23
Edema peripheral	14–16,18,19	0.47 (0.33, 0.68)	<0.001	38	0.17
Paronychia	8–10,14,16	14.00 (1.14, 171.75)	0.04	87	<0.001
Fatigue	10–13,15,16,19	0.35 (0.19, 0.63)	<0.001	78	<0.001
Anemia	10–13,15,18,19	0.29 (0.14, 0.61)	0.001	84	<0.001
Hypokalemia	13,15	0.34 (0.09, 1.34)	0.12	0	0.38
Neutropenia	10–13,15,16,18	0.05 (0.01, 0.28)	<0.001	98	<0.001
Leukopenia	10,12,15,16	0.08 (0.01, 0.69)	0.02	97	<0.001
Febrile neutropenia	8,12,15,16,18	0.19 (0.05, 0.70)	0.01	88	<0.001
Upper abdominal pain	9,15,19	0.61 (0.20, 1.82)	0.37	53	0.12
Abnormal hepatic function	13,16	5.76 (3.15, 10.55)	<0.001	0	0.68
Insomnia	9,16,19	1.36 (0.60, 3.10)	0.46	66	0.05
Alopecia	8–10,16,18	0.06 (0.05, 0.09)	<0.001	38	0.17
Myalgia	8,9,16,18	0.18 (0.14, 0.24)	<0.001	4	0.37
Neurotoxicity	8,9,13,16	0.19 (0.05, 0.65)	0.008	95	<0.001
Arthralgia	8,9,13	0.15 (0.04, 0.55)	0.004	83	0.003
Dyspepsia	9,11,13	0.45 (0.05, 3.89)	0.47	88	<0.001
Dizziness	9,13	1.09 (0.40, 2.93)	0.87	0	0.45
Sensory disturbance	10–12	0.13 (0.02, 0.77)	0.02	86	<0.001
Thrombocytopenia	10–13	0.37 (0.20, 0.71)	0.003	51	0.11

Table 3. Subgroup analysis for the effect of Gefitinib therapy on OS and PFS

Variables	Hazard ratio (*HR*)	*P* values	Heterogeneity (%)	*P* values for heterogeneity
OS				
Number of patients				
≥1000	0.95 (0.87–1.04)	0.266	16.1	0.304
<1000	0.90 (0.78–1.03)	0.110	32.2	0.171
Median age				
<64	0.92 (0.84–1.00)	0.061	36.1	0.141
≥64	0.96 (0.73–1.26)	0.761	19.5	0.289
Gender (male, %)				
>65%	0.95 (0.88–1.04)	0.282	0	0.414
<65%	0.90 (0.79–1.03)	0.126	39.5	0.128
Control drug				
Traditional chemotherapy	0.97 (0.89–1.06)	0.517	7.7	0.369
Placebo	0.85 (0.76–0.95)	0.004	0	0.397
Treatment status				
First line	0.94 (0.84–1.06)	0.319	11.9	0.333
Second line	0.90 (0.79–1.02)	0.085	40.0	0.125
Follow-up				
≥36 months	0.90 (0.73–1.12)	0.345	59.6	0.042
<36 months	0.94 (0.87–1.02)	0.124	0	0.666
Smoker				
Never smoker	0.76 (0.59–0.98)	0.034	19.0	0.291
Current/former smoker	–	–	–	–
Racial				
Asian	0.91 (0.78–1.06)	0.216	48.5	0.084
Non-Asian	0.87 (0.78–0.97)	0.015	0	0.409
Disease status (IIIB or IV)				
≥90%	0.88 (0.79–0.98)	0.025	0	0.964
<90%	0.96 (0.81–1.13)	0.593	62.6	0.030
Pre-existent diseases				
Adenocarcinoma	0.85 (0.76–0.95)	0.005	0	0.599
Non-adenocarcinoma	–	–	–	–
EGFR FISH				
Positive	1.14 (0.18–7.16)	0.14	87.9	0.004
Negative	0.89 (0.59–1.33)	0.59	0	0.539
Jadad score				
4	0.93 (0.86–0.99)	0.031	0	0.505
<4	0.94 (0.73–1.21)	0.646	55.2	0.063

PFS				
Number of patients				
≥1000	0.88 (0.63–1.23)	0.447	92.8	<0.001
<1000	0.68 (0.54–0.86)	0.001	83.8	<0.001
Mean age				
<64	0.70 (0.56–0.87)	0.002	89.4	<0.001
≥64	0.79 (0.49–1.27)	0.329	83.6	0.002
Gender (male, %)				
>65%	0.92 (0.65–1.29)	0.623	82.5	0.003
<65%	0.66 (0.54–0.81)	<0.001	82.3	<0.001
Drug				
Traditional chemotherapy	0.71 (0.56–0.91)	0.006	90.7	<0.001
Placebo	0.73 (0.61–0.89)	0.001	7.7	0.339
Treatment status				
First line	0.70 (0.51–0.95)	0.024	90.9	<0.001
Second line	0.75 (0.58–0.95)	0.017	79.6	<0.001
Follow-up				
≥36 months	0.60 (0.45–0.81)	0.001	86.2	<0.001
<36 months	0.88 (0.72–1.08)	0.228	78.5	0.001
Smoker				
Never smoker	0.48 (0.33–0.70)	<0.001	0	0.832
Current/former smoker	–	–	–	–
Racial				
Asian	0.62 (0.48–0.79)	<0.001	86.6	<0.001
Non-Asian	0.83 (0.63–1.08)	0.161	64.5	0.037
Disease status (IIIB or IV)				
≥90%	0.66 (0.50–0.86)	0.002	87.4	<0.001
<90%	0.81 (0.62–1.06)	0.128	80.8	0.001
Pre-existent diseases				
Adenocarcinoma	0.63 (0.42–0.93)	0.021	76	0.041
Non-adenocarcinoma	–	–	–	–
EGFR FISH				
Positive	0.76 (0.22–2.65)	0.665	91.0	<0.001
Negative	1.29 (0.53–3.15)	0.579	90.9	<0.001
Jadad score				
4	0.67 (0.50–0.88)	0.005	92.2	<0.001
<4	0.80 (0.62–1.03)	0.080	70.2	0.009

4. Anmerkungen/Fazit der Autoren

Treatment wlth gefitinib had a clear effect on PFS and ORR, and it might contribute considerably to the OS. Furthermore, there was some evldence of benefit for gefitinib therapy among patlents with adenocarcinoma.

Hinweis der FBMed:

- *Komparatoren unklar beschrieben bzw. stark zusammengefasst*
- *Nicht alle Patienten waren sage IIIB oder IV (ca. 80%)*

Al-Saleh K, et al. 2012 [1].

Role of pemetrexed in advanced non-small-cell lung cancer: meta-analysis of randomized controlled trials, with histology subgroup analysis

1. Fragestellung

To compare the efficacy of pemetrexed with that of other treatments in advanced NSCLC

2. Methodik

Population: advanced NSCLC

Intervention: pemetrexed

Komparator: other treatments or plecebo

***Endpunkte*:** OS (survival outcome with a minimum follow up of 12 months

Suchzeitraum: completed in the fourth week of January 2010

Anzahl eingeschlossene Studien/Patienten (Gesamt): 5/Range 146 – 1725

Qualitätsbewertung der Studien: nur RCT, accordance with the Cochrane handbook guidelines and GRADE

Heterogenitätsuntersuchungen: Cochran Q and the I^2

3. Ergebnisdarstellung

TABLE 1 Studies included in the meta-analysis

Reference	*Pts (n)*	*Regimen*	*Remarks*	*Grade and quality*
Hanna *et al.*, 2004 [11]	288	Docetaxel 75 mg/m² every 21 days until disease progression (median number of cycles: 4)	Second line PS 0–2	Moderate No important study limitations Direct
	283	Pemetrexed 500 mg/m² every 21 days until disease progression (median number of cycles: 4)		No important imprecision Unlikely publication bias +++
Scagliotti *et al.*, 2008 [12]	863	Cisplatin 75 mg/m² on day 1 and gemcitabine 1250 mg/m² on days 1 and 8 for 6 cycles	First line PS 0–1	Moderate-high Few important study limitations No important inconsistencies
	862	Cisplatin 75 mg/m² and pemetrexed 500 mg/m² on day 1 for 6 cycles		Direct No important imprecision Unlikely publication bias ++++
Ciuleanu *et al.*, 2009 [14]	441	Pemetrexed 500 mg/m² on day 1 every 21 days till disease progression (median number of cycles: 5)	Maintenance therapy PS 0–1	Moderate-high No important study limitations No important inconsistency
	222	Placebo		Direct No important imprecision Possible publication bias (sponsor heavily involved) +++
Grønberg *et al.*, 2009 [13]	217	Gemcitabine 1000 mg/m² on days 1 and 8 plus carboplatin AUC 5 for 4 cycles	First line PS 0–2	Moderate-high Few important study limitations No important inconsistencies
	219	Pemetrexed 500 mg/m² plus carboplatin AUC 5 for 4 cycles		Direct No important imprecision Unlikely publication bias +++
Obasaju *et al.*, 2009 [15]	74	Pemetrexed 500 mg/m² and carboplatin AUC 6 every 3 weeks for 6 cycles	First line Abstract only 3-Arm trial	Low Serious study limitations No important inconsistency
	72	Docetaxel 75 mg/m² and carboplatin AUC 6 every 3 weeks for 6 cycles		Direct Imprecision Unlikely publication bias +

PS = Performance status.

<u>OS:</u>

- pemetrexed superior to other treatments: HR: 0.89; 95%; CI: 0.80 to 0.99
- <u>first- or second-line therapy: HR 0.89 vs. 0.88; Figure 2</u>
- non-squamous histology: HR 0.82; 95% CI: 0.73 to 0.91
- squamous histology: HR 1.19; 95% ci: 0.99 to 1.43

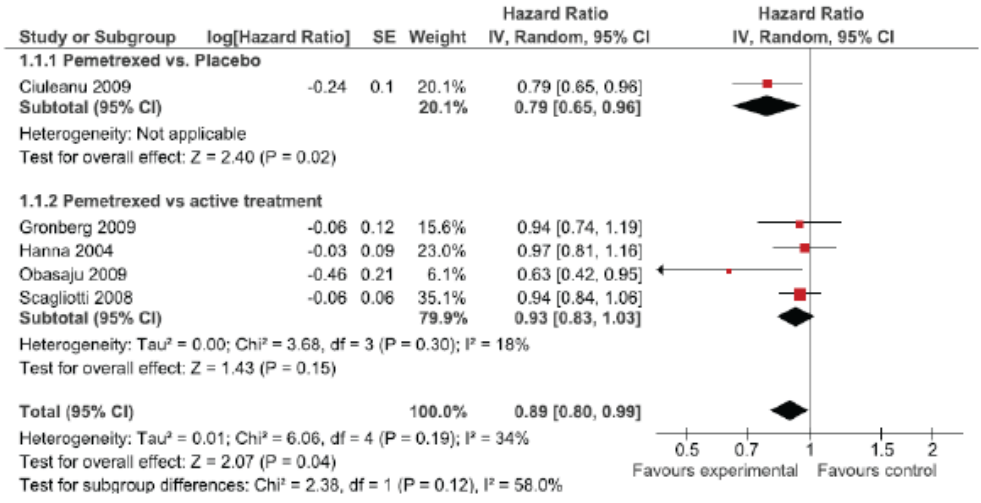


FIGURE 1 *Overall effect of pemetrexed treatment.*

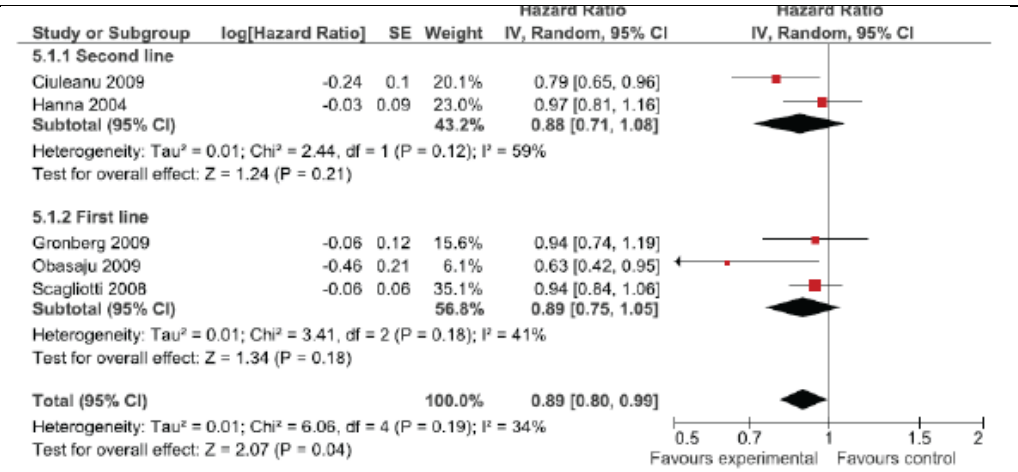


FIGURE 2 *First-line compared with second-line pemetrexed.*

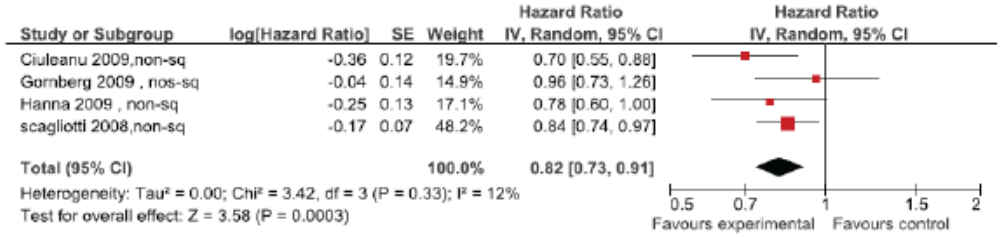


FIGURE 3 *Pemetrexed in non-squamous histology.*

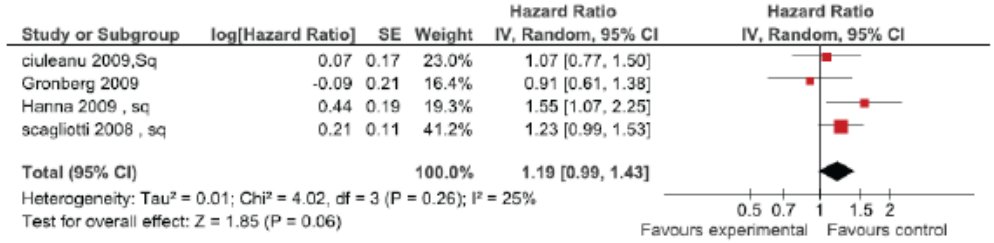


FIGURE 4 *Pemetrexed in squamous histology.*

Toxicity:

- fewer side effects for patients treated with pemetrexed: lower rate of hematologic toxicity, significantly less neutropenia observed [odds ratio (or): 0.41; 95% CI: 0.18 to 0.93], keeping in mind that all studies mandated vitamin B12 and folic acid supplementation for patients receiving pemetrexed
- more elevation of alanine aminotransferase (or: 11.68; 95 % CI: 0.64 to 212.19)
- no significant difference in the incidence of anemia for patients treated with pemetrexed (or: 1.36; 95% ci: 0.73 to 2.52)

4. Anmerkungen/Fazit der Autoren

Compared with other chemotherapy agents, pemetrexed is more effective for the treatment of NSCLC in patients with non-squamous histology.

Anmerkungen FB Med:

- *PE has received honoraria and research funding from Eli Lilly and Company. The remaining authors have no financial conflicts of interest to*

	declare.
Gao H et al., 2011 [17]. Efficacy of erlotinib in patients with advanced non-small cell lung cancer: a pooled analysis of randomized trials	**1. Fragestellung** to assess the efficacy and safety of erlotinib in patients with advanced NSCLC
	2. Methodik **Population**: advanced NSCLC **Intervention**: erlotinib alone or based combination therapy **Komparator**: other agent or based combination regimen **Endpunkt**: OS, PFS, ORR, toxicity **Qualitätsbewertung der Primärstudien**: nach Moher D, et al. Assessing the quality of randomized controlled trials: an annotated bibliography of scales and checklists. Control Clin Trials 1995; 16:62–73. **Suchzeitraum**: 1997 bis 2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 14/7 974
	3. Ergebnisdarstellung Validity assessment: no significant difference among the trials, results not considered in this pooled analysis

Table 1 **Characteristics of the fourteen trials included in this pooled analysis**

Author	Year	Publication form	Patients	Chemo/target therapy regimen	Sex (male, %)	PS 0–1 (%)	Age	Stage III/IV (%)	Adeno-carcinoma (%)	Smoking history (%)
Gatzemeier *et al.* [18]	2007	Full text	586	Erlotinib 150 mg/day, per oral + gemcitabine 1250 mg/m^2, days 1,8 + cisplatin 80 mg/m^2, day 1, 6 cycles	78.0	99.8	60.0	99.6	38.0	–
			586	Placebo + gemcitabine 1250 mg/m^2, days 1,8 + cisplatin 80 mg/m^2, day 1, 6 cycles	75.0	99.8	59.1	99.8	38.0	–
Herbst *et al.* [19]	2005	Full text	539	Erlotinib 150 mg/day, per oral + carboplatin AUC 6, day 1 + paclitaxel 200 mg/m^2, day 1, 6 cycles	61.6	100	62.7	100	59.9	86.6
			540	Placebo + carboplatin AUC 6, day 1 + paclitaxel 200 mg/m^2, day 1, 6 cycles	59.7	99.8	62.6	100	61.4	91.8
Lee *et al.* [20]	2010	Abstract	350	Erlotinib 150 mg/day, per oral	61.0	16	77.4	100	38	95.0
			320	Placebo	61.0	16	77.2	100	38	94.0
Lilenbaum *et al.* [21]	2008	Full text	52	Erlotinib 150 mg/day, per oral	44.0	0	51.0	100	50.0	88.0
			51	Carboplatin AUC 6, day 1 + paclitaxel 200 mg/m^2, day 1, 6 cycles	55.0	0	52.0	100	63.0	92.0
Reck *et al.* [22]	2010	Abstract	144	Erlotinib 150 mg/day, per oral	65.0	100	75.5	100	50.0	82.0
			140	Carboplatin AUC 5, day 1 + vinorelbine 25 mg/m^2, days 1,8, 6 cycles	71.0	100	76.1	99.0	49.0	86.0
Cappuzzo *et al.* [23]	2010	Full text	438	After CT, erlotinib 150 mg/day, per oral	73.0	31.0	60.0	100	47.0	82.0
			451	After CT, placebo	75.0	32.0	60.0	100	44.0	83.0
Miller *et al.* [11]	2009	Abstract	370	After CT, erlotinib 150 mg/day, per oral + bevacizumab 15 mg/kg, day 1, q3weeks	52.2	100	64.0	100	81.3	83.5
			373	After CT, placebo + bevacizumab 15 mg/kg, day 1, q3 weeks	52.3	99.7	64.0	100	82.5	82.3
Mok *et al.* [24]	2010	Full text	76	Erlotinib 150 mg/day, days 15–28 + gemcitabine 1250 mg /m^2, days 1, 8 + cisplatin 75 mg/m^2 (carboplatin AUC 5), day 1, 6 cycles	71.0	100	57.0	100	67.0	68.0
			78	Placebo + gemcitabine 1250 mg/m^2, days 1,8 + cisplatin 75 mg/m^2 (carboplatin AUC 5), day 1, 6 cycles	69.0	100	57.5	100	67.0	64.0
Perol *et al.* [25]	2010	Abstract	155	After CT, erlotinib 150 mg/day, per oral	73	100	56.4	100	63	–
			155	After CT, observation	73	100	59.8	100	67	–
Shepherd *et al.* [26]	2005	Full text	488	Erlotinib 150 mg/day, per oral	64.5	91.4	62.0	100	50.4	73.4
			243	Placebo	65.8	91.4	59.0	100	49.0	77.0
Herbst *et al.* [27]	2007	Full text	39	Erlotinib 150 mg/day, per oral + bevacizumab 15 mg/kg, day 1, q3 weeks	43.6	100	68.0	100	82.1	84.6
			40	Paclitaxel 75 mg/m^2, day 1/ pemetrexed 500 mg/m^2, day 1 + bevacizumab 15 mg/kg, day 1, q3 weeks	57.5	100	63.5	100	75.0	90.0
Vamvakas *et al.* [28]	2010	Abstract	166	Erlotinib 150 mg/day, per oral	81.3	79.2	65	100	53.6	–
			166	MTA 500 mg/m^2, d1, q3wks	82.5	81.3	66	100	56.6	–
Natale *et al.* [29]	2011	Full text	617	Erlotinib 150 mg/day, per oral	64.0	88.0	61.0	100	57.0	76.0
			623	Vandetanib 300 mg/day, per oral (a targeted drug)	61.0	99.0	60.0	100	63.0	79.0
Boyer *et al.* [30]	2010	Abstract	94	Erlotinib 150 mg/day, per oral	59.6	96.8	67.0	100	64.9	78.7
			94	PF299804 45 mg/day, per oral	58.5	81.9	69.0	100	66.0	79.8

All trials were randomized controlled phase III trials except for Lilenbaum *et al.* [21], Mok *et al.* [24], and Herbst *et al.* [27] trials, which were designed as randomized controlled phase II trials.
AUC, area under the serum concentration–time curve; CT, chemotherapy; PS, performance status.

First-line therapy

	Overall survival (4 trials): no statistically significant difference between erlotinib-based regimens and other regimens, Significant heterogeneity • The subgroup analysis showed a similar OS compared with placebo (HR: 1.02; 95% CI: 0.92–1.13; P=0.73) • a decreased OS compared with chemotherapy (HR: 1.39; 95% CI: 0.99–1.94; P=0.05) **PFS (3 trials)**: no statistically significant difference between erlotinib-based regimens and other regimens, significant heterogeneity • The pooled estimate showed a similar PFS when compared with placebo (HR: 0.93; 95% CI: 0.85–1.01; P=0.09) • a decreased PFS compared with chemotherapy (HR: 1.55; 95% CI: 1.24–1.93; P<0.01) • but a prolonged PFS compared with placebo as maintenance therapy (HR: 0.71; 95% CI: 0.60–0.83; P<0.01). ***Second/third-line therapy*** **Overall survival (3 trials)**: similar OS for erlotinib-based regimens, significant heterogeneity • subgroup analysis showed a prolonged OS compared with placebo (HR: 0.70; 95% CI: 0.58–0.84; P<0.01), similar OS compared with chemotherapy **PFS (3 trials):** pooled estimate showed a similar PFS for erlotinib-based regimens, significant heterogeneity • subgroup analysis showed a prolonged PFS compared with placebo (HR: 0.61; 95% CI: 0.51–0.73; P<0.01), similar PFS compared with chemotherapy ***Toxicity****:* • Grade 3/4 diarrhea (OR: 4.87; 95% CI: 3.19–7.44; P<0.01), • rash (OR: 28.94; 95% CI: 14.28–58.66; P<0.01), • anemia (OR: 1.39; 95% CI: 1.06–1.82; P=0.02) • all significantly prominent in the erlotinib-based regimens
	4. Anmerkungen/Fazit der Autoren Our findings demonstrate that erlotinib-based regimens significantly increase ORR and improve PFS as a first-line maintenance therapy or as a second/third-line therapy compared with placebo. Thus, the use of erlotinib may be a new effective therapy in treating advanced NSCLC as first-line maintenance therapy or second/third-line therapy compared with best supportive care. *Anmerkungen der FB Med:* • *Publicationbias untersucht und als unwahrscheinlich bewertet* • *3 Phase II Studien eingeschlossen* • *„There are no conflicts of interest"*

He X et al., 2015 [28]. Efficacy and safety of docetaxel for advanced non-small-cell lung cancer: a meta-analysis of Phase III randomized controlled trials	1. Fragestellung 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 Population: advanced NSCLC patients Intervention/Komparator*:* docetaxel vs. pemetrexed bzw. docetaxel vs. vinca alkaloid Endpunkte: overall survival, progression-free survival, and overall response rate with 95% confidence intervals and major grade 3/4 toxicity Suchzeitraum (Aktualität der Recherche): to January 24, 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 7 trials involving 2,080 patients There were 1,048 and 1,032 patients randomized to docetaxel and to other anti-NSCLC drug arms, respectively. Of the included studies, three studies compared docetaxel and pemetrexed, two studies compared docetaxel and vinorelbine and two studies compared docetaxel and vinorelbine analogs (vinflunine or vindesine). Qualitätsbewertung der Studien: Jadad scoring system was used. I^2 for heterogeneity.
	3. Ergebnisdarstellung Qualität der Studien: Overall, two trials scored 4, while the others scored 3. **Overall survival:** • We performed subgroup analysis in first-line and second-line, respectively, in order to distinguish the efficacy of the different lines of treatment. Five trials provided HR results of overall survival (OS) → No significant difference was found in the pooled HR for OS between docetaxel and pemetrexed as both first-line and second-line treatment. • Results were similar in the comparison of docetaxel with vinca alkaloid. **PFS:** • No statistically significant difference between docetaxel and pemetrexed as both first-line and second-line treatment. • In terms of docetaxel with vinca alkaloid as first-line treatment, there was a significant statistical difference in PFS (HR 0.63, 95% CI: 0.45–0.82, P=0.001), but not for second-line treatment.

	ORR: • There were no ORR data available for the comparison between docetaxel and pemetrexed as first-line treatment. • No significant statistical difference in ORR was detected in docetaxel versus pemetrexed as second-line treatment • In terms of first-line treatment, compared with vinca alkaloid, docetaxel was associated with significant improvement of ORR (OR 1.98, 95% CI: 1.33–2.95, P=0.0008). • In addition, there was a similar result for ORR between docetaxel and vinca alkaloid as second-line treatment **Grade 3/4 hematological and non-hematological toxicity** • Compared with pemetrexed, docetaxel led to higher neutropenia and febrile neutropenia (P=0.05), but there was no difference in non-hematological toxicity. • Docetaxel led to a lower rate of anemia as first-line treatment (P=0.05). • Moreover, docetaxel caused less grade 3/4 hematological and non-hematological toxicity compared with vinca alkaloid
	4. Fazit der Autoren: *In terms of the effectiveness and safety on patients with advanced NSCLC in first-line therapy, docetaxel leads to a better result than vinca alkaloid. Docetaxel also causes lower toxicity in second-line therapy compared with vinca alkaloid. However, the differences in efficacy and safety between docetaxel and pemetrexed are not obvious. Therefore, 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.*
Li G et al., 2016 [33]. 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 <u>Qualität der Studien:</u> 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.*

Petrelli Fet al., 2015 [46]. Efficacy of fourth-line chemotherapy in advanced non-small-cell lung cancer: a systematic review and pooled analysis of published studies	1. Fragestellung to provide a pooled analysis of published studies on the efficacy of treatments in patients who have had at least three unsuccessful lines of therapy.
	2. Methodik Population: patients with advanced/metastatic NSCLC Intervention/Komparator: fourth-line chemotherapy or biological agents Endpunkte: • Primäre Endpunkte: response rate (RR) and complete response rate (DCR) • Sekundäre Endpunkte: PFS, OS Suchzeitraum (Aktualität der Recherche): up to 11 January 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): Overall, 14 studies (673 patients), which were almost entirely published by Asian institutions, were eligible for this pooled analysis. Qualitätsbewertung der Studien: k.A → Hinweis FBMed: 3 Phase 2 Studien, der Rest der Studien (N=12) mit retrospektivem Design. I^2 für Heterogenität
	3. Ergebnisdarstellung *Hinweis*: Pooled analysis of a retrospective series of small unrandomized trials without a comparator arm; thus, a hypothetical survival benefit versus BSC cannot be shown **RR and DCR** • Thirteen trials were available for the RR analysis: The pooled overall RR was 13.6% (95% CI 10–18.3). Heterogeneity was moderate (I^2=42.6, P=0.058), and so a random-effect model was used. After excluding the study by Massarelli and colleagues, which used older agents (it included patients treated in European countries between 1993 and 2000), the final results were unchanged. • Thirteen trials were available for the DCR analysis. The pooled overall DCR was 47.3% (95% CI 38–56.9). Heterogeneity was high (I2 =77.7, P< 0.0001), and so a random-effect model was used. **Median PFS and OS** • Eight studies presented the median PFS rate with respective 95% CIs. The pooled median PFS for these studies was 3.34 months (95% CI 2.42–4.27). Heterogeneity was high (I^2= 72.2, P < 0.0001), and so a random-effect model was used.

	• Only seven trials reported a median OS rate that was useful for calculating pooled OS. The pooled median OS for these studies was 10.5 months (95% CI 9.57–11.52). Heterogeneity was low (I2 =0, P = 0.62), and so a fixed-effect model was used.
	4. Fazit der Autoren: *In conclusion, for NSCLC patients failing three or more lines of therapy, fourth-line treatment could be offered in select cases to good PS patients according to previous treatment exposure, patient wishes and physician choice. The present pooled analysis suggests that in this subgroup of patients, the activity of fourth-line agents is comparable with that of second-line and third-line trials. What the preferable agent is and whether these data can be generalized to Western countries cannot, however, be shown.* 5. Hinweise durch FBMed: • There are limited literature data on current treatment beyond first-line and second-line therapies for NSCLC • Almost totally Asian patients with intrinsically different outcomes and benefits from chemotherapy and biological agents.
Sheng J et al., 2015 [55]. The Efficacy of Combining EGFR Monoclonal Antibody With Chemotherapy for Patients With advanced Nonsmall Cell Lung Cancer	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.
	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.*

Leitlinien

<table>
<tr><td>NCCN 2016 [38].
Non-Small Cell Lung Cancer (Vers. 4.2016)</td><td>1. Fragestellung
Diagnose, Pathologie, Staging, Therapie des NSCLC</td></tr>
<tr><td></td><td>2. Methodik
Update der LL von 2014.
Literatursuche: in PubMed zwischen 06/2013 und 06/2014
Diskussion der Literatur und Empfehlungen im Expertenpanel.
GoR, LoE: Alle Empfehlungen entsprechen der Kategorie 2A, sofern nicht explizit anders spezifiziert.
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.</td></tr>
<tr><td></td><td>3. Empfehlungen (siehe Anhang)</td></tr>
<tr><td>Masters GA et al., 2015 [36].
Systemic Therapy for Stage IV Non–Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update</td><td>1. Fragestellung
To provide evidence-based recommendations to update the American Society of Clinical Oncology guideline on systemic therapy for stage IV non–small-cell lung cancer (NSCLC).</td></tr>
<tr><td></td><td>2. Methodik
Update der LL von 2009
An Update Committee of the American Society of Clinical Oncology NSCLC Expert Panel based recommendation on a systematic review of randomized controlled trials from January 2007 to February 2014.
LoE
<table><tr><th>Rating</th><th>Definition</th></tr><tr><td>High</td><td>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</td></tr><tr><td>Intermediate</td><td>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</td></tr></table></td></tr>
</table>

Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change the
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

GoR

Type of Recommendati	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	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
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)
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

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

3. Empfehlungen

First-Line Treatment for Patients:

- Without an EGFR-sensitizing mutation or ALK gene rearrangement and performance status (PS) 0 to 1 (or appropriate PS 2): a variety of combination cytotoxic chemotherapies are recommended. Platinum-based doublets are preferred, along with early concurrent palliative care and symptom management. Based on tumor histology (ie, squamous v nonsquamous), there are some variations *(evidence quality: high; strength of recommendation: strong).*

- Adding bevacizumab to carboplatin plus paclitaxel is recommended if there are no contraindications *(evidence quality: intermediate; strength of recommendation: moderate).*
- With PS 2: combination or single-agent chemotherapy or palliative care alone may be used *(chemotherapy: evidence quality: intermediate; strength of recommendation: weak; palliative care: evidence quality: intermediate; strength of recommendation: strong).*
- With sensitizing EGFR mutations: afatinib, erlotinib, or gefitinib is recommended *(evidence quality: high; strength of recommendation: strong for each).*
- With ALK gene rearrangements: crizotinib is recommended *(evidence quality: high; strength of recommendation).*
- With ROS1 rearrangement: crizotinib is recommended *(type: informal consensus; evidence quality: low; strength of recommendation: weak).* *Clinical interpretation:* Because no data were found in the systematic review to inform this clinical question, the Update Committee chose to make an informal consensus recommendation. The Update Committee relied on clinical experience, training, and judgment to formulate this recommendation, given that there were no conclusive data regarding this question. A study was published after the close of the date parameters for the systematic review that included 50 patients from a second-line crizotinib trial who had ROS1 rearrangements. The objective response rate was 72% (95% CI, 58 to 84), and there were three complete responses and 33 partial responses. Median duration of response was 17.6 months (95% CI, 14.5 to not reached). Median PFS was 19.2 months (95% CI, 14.4 to not reached). The authors state that "the safety profile of crizotinib was similar to that seen in patients with ALK-rearranged NSCLC."78(p1) Although these results are from an early trial, they are impressive. *(→ Quelle der Studie: 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*
- With large-cell neuroendocrine carcinoma: platinum plus etoposide or the same treatment as other patients with nonsquamous carcinoma may be administered *(type: informal consensus; evidence quality: low; strength of recommendation: weak).*
- First-line cytotoxic chemotherapy should be stopped at disease progression or after four cycles in patients with nonresponsive stable disease (no change).
- With stable disease or response after four cycles of a first-line pemetrexed-containing regimen: pemetrexed continuation maintenance may be used; if initial regimen does not contain pemetrexed, an alternative chemotherapy (switch) may be used, or a break from chemotherapy may be recommended until disease progression *(addition of pemetrexed: evidence quality: intermediate; strength of recommendation: moderate).*

Second-Line Treatment for Patients:

- With nonsquamous cell carcinoma (NSCC): docetaxel, erlotinib, gefitinib, or

	pemetrexed are acceptable *(evidence quality: high; strength of recommendation: strong).* • With SCC: docetaxel, erlotinib, or gefitinib are acceptable *(evidence quality: high; strength of recommendation: strong).* • With sensitizing EGFR mutations who did not respond to a first-line epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI): combination cytotoxic chemotherapy is recommended for those with NSCC, as listed in under first-line treatment *(type: informal consensus; evidence quality: intermediate; strength of recommendation: strong).* • With sensitizing EGFR mutations who received a first-line EGFR TKI and experienced disease progression after an initial response: may be switched to chemotherapy or another EGFR TKI as second-line therapy *(type: informal consensus; evidence quality: low; strength of recommendation: weak).* • With ALK rearrangement and progression after first-line crizotinib: chemotherapy or ceritinib may be offered *(chemotherapy: evidence quality: high; strength of recommendation: strong; ceritinib: evidence quality: intermediate; strength of recommendation: moderate).* **Third-Line Treatment for Patients:** • Who have not received erlotinib or gefitinib and have PS 0 to 3: erlotinib may be recommended. • Data are insufficient to recommend routine third-line cytotoxic drugs.
Australian Government, Cancer Council Australia. 2015 [4]. Clinical practice guidelines for the treatment of lung cancer	**Fragestellung** What is the optimal first-line chemotherapy regimen in patients with stage IV inoperable NSCLC? Is carboplatin based chemotherapy as effective as cisplatin based chemotherapy for treatment of stage IV inoperable NSCLC? Which new agent or platinum combination regimen is best for treatment of stage IV inoperable NSCLC? Is monotherapy with new third generation (3G) agents as effective as platinum combination therapy for treatment of stage IV inoperable NSCLC? Are three chemotherapy agents better than two chemotherapy agents for treatment of stage IV inoperable NSCLC? Are non-platinum doublet chemotherapy regimens as effective as platinum doublet regimens for treatment of stage IV inoperable NSCLC? Is chemotherapy with a biologic or targeted therapy superior to chemotherapy alone in unselected patients for treatment of stage IV inoperable NSCLC? What is the optimal chemotherapy regimen for overall quality of life for patients in the treatment of stage IV inoperable NSCLC? What is the optimal second-line therapy in patients with stage IV inoperable NSCLC?

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

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

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

Methodik

Grundlage der Leitlinie: Systematischer Review und Konsensusprozess über Empfehlungen. Alle Aussagen sind mit Literaturstellen (Meta-Analysen oder RCTs) belegt.

Suchzeitraum: bis 2012

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

Stage IV inoperable

Chemotherapy

Evidence summary	LoE
Platinum-based chemotherapy improves survival in stage IV NSCLC compared with best supportive care. Note that this evidence is based on clinical trials conducted in fit patients, with predominant performance status 0-1, no unstable co-morbidities, adequate organ function and without uncontrolled brain metastases.	I
Recommendation	**Grade**
Platinum-based chemotherapy can be used to extend survival in newly diagnosed patients with stage IV NSCLC.	A
Practice piont(s)	
The decision to undertake empirical platinum-based chemotherapy in a given patient should consider factors such as patient performance status (0,1 versus 2 or more) and co-morbidities, their disease extent and symptoms, proposed treatment toxicity and their individual preferences for benefit from specific treatment(s) and toxicities.	

Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 1995;311(7010):899-909

Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung cancer. Cochrane Database Syst Rev 2010 May 12;(5):CD007309

Evidence summary	LoE
First-line chemotherapy involving cisplatin results in a slightly higher likelihood of tumour response than the same chemotherapy with carboplatin.	I
There is no definite overall survival difference between cisplatin or carboplatin based first-line chemotherapy.	I
Cisplatin-based chemotherapy is associated with more severe nausea and vomiting and nephrotoxicity; severe thrombocytopaenia is more frequent during carboplatin-based chemotherapy.	I
Recommendation	Grade
In patients with high tumour burden and symptoms from stage IV NSCLC cisplatin based chemotherapy may be used in preference to carboplatin for the purpose of inducing a response, however, this benefit may be offset by its greater risk of toxicity.	B
Practice piont(s)	
The choice of cisplatin versus carboplatin in a given patient may consider the balance between perceived benefit (in tumour response) versus known toxicity, whilst considering patient preferences.	

Hotta K, Matsuo K, Ueoka H, Kiura K, Tabata M, Tanimoto M. Role of adjuvant chemotherapy in patients with resected non-small-cell lung cancer: reappraisal with a meta-analysis of randomized controlled trials. J Clin Oncol 2004 Oct 1;22(19):3860-7

Ardizzoni A, Boni L, Tiseo M, Fossella FV, Schiller JH, Paesmans M, et al. Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. J Natl Cancer Inst 2007 Jun 6;99(11):847-57

Jiang J, Liang X, Zhou X, Huang R, Chu Z. A meta-analysis of randomized controlled trials comparing carboplatin-based to cisplatin-based chemotherapy in advanced non-small cell lung cancer. Lung Cancer 2007 Sep;57(3):348-58

Evidence summary	LoE
3G platinum-based chemotherapy (vinorelbine, paclitaxel, docetaxel or gemcitabine) is associated with higher response ratio than older 2G platinum-based chemotherapy.	I
No 3G platinum-based chemotherapy regimen (vinorelbine, paclitaxel, docetaxel or gemcitabine) has been shown to be superior to another.	I
In first-line empirical treatment of advanced NSCLC, chemotherapy with cisplatin and pemetrexed is superior to cisplatin/gemcitabine in patients with non-squamous cell carcinoma histology.	II
In first-line empirical treatment of advanced NSCLC, chemotherapy with cisplatin and pemetrexed is inferior to cisplatin/gemcitabine in patients with SCC histology.	II
Recommendation	Grade
In the first-line setting, chemotherapy with cisplatin and gemcitabine is recommended in preference to cisplatin and pemetrexed in patients with squamous cell carcinoma histology.	B
3G platinum-based chemotherapy (with vinorelbine, paclitaxel, docetaxel or gemcitabine) is a standard of care as first-line chemotherapy in fit patients with stage IV NSCLC.	A
In the first-line setting, chemotherapy with cisplatin and pemetrexed is recommended in preference to cisplatin and gemcitabine in patients with non-squamous cell carcinoma histology.	B
Practice piont(s)	

The choice of first-line platinum combination chemotherapy in a given patient mayconsider patient performance status and co-morbidities, the proposed treatment toxicity, treatment scheduling and individual patient preferences.

Baggstrom MQ, Stinchcombe TE, Fried DB, Poole C, Hensing TA, Socinski MA. Third-generation chemotherapy agents in the treatment of advanced non-small cell lung cancer: a meta-analysis. J Thorac Oncol 2007 Sep;2(9):845-53

Gao G, Jiang J, Liang X, Zhou X, Huang R, Chu Z, et al. A meta-analysis of platinum plus gemcitabine or vinorelbine in the treatment of advanced non-small-cell lung cancer. Lung Cancer 2009 Sep;65(3):339-44

Grossi F, Aita M, Defferrari C, Rosetti F, Brianti A, Fasola G, et al. Impact of third-generation drugs on the activity of first-line chemotherapy in advanced non-small cell lung cancer: a meta-analytical approach. Oncologist 2009 May;14(5):497-510

Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008 Jul 20;26(21):3543-51

Evidence summary	LoE
3G platinum-based combination chemotherapy (vinorelbine, paclitaxel, docetaxel, irinotecan or gemcitabine) is superior to 3G agent monotherapy.	I
3G platinum-based monotherapy (vinorelbine, paclitaxel, docetaxel, or gemcitabine) improves survival compared with best supportive care.	I
Recommendation	**Grade**
Patients fit for chemotherapy should be offered 3G platinum-based combination chemotherapy (vinorelbine, paclitaxel, docetaxel, irinotecan or gemcitabine) in preference to 3G agent monotherapy, as it is more effective.	A
Patients unfit for combination chemotherapy could be considered for 3G monotherapy with vinorelbine, paclitaxel, docetaxel or gemcitabine.	A

Hotta K, et al. 2004

Baggstrom MQ, et al. 2007

Delbaldo C, Michiels S, Rolland E, Syz N, Soria JC, Le Chevalier T, et al. Second or third additional chemotherapy drug for non-small cell lung cancer in patients with advanced disease. Cochrane Database Syst Rev 2007 Oct 17;(4):CD004569

Evidence summary	LoE
Triplet chemotherapy regimens are associated with higher response rate, but no improvement in survival.	I
Triplet chemotherapy regimens are associated with greater grade 3 /4 toxicities.	I
Recommendation	**Grade**
Triplet chemotherapy regimens are not recommended, as benefit in responserate does not outweigh extra toxicity.	A

Delbaldo C, et al. 2007

Baggstrom MQ, et al. 2007

Evidence summary	LoE
Platinum-based doublet 3G chemotherapy is associated with a higher response rate and slightly higher one-year survival than non-platinum doublet chemotherapy.	I
Platinum-based doublet 3G chemotherapy is associated with greater risk of anaemia and thrombocytopaenia than non-platinum combination therapy.	I
Gemcitabine and paclitaxel improves response ratio without added	I

toxicity, compared with gemcitabine or paclitexel and carboplatin combinations.

Recommendation	Grade
Non-platinum 3G doublet chemotherapy is an effective alternative option for patients unsuitable for platinum-based therapy.	A

D'Addario G, Pintilie M, Leighl NB, Feld R, Cerny T, Shepherd FA. Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. J Clin Oncol 2005 May 1;23(13):2926-36

Rajeswaran A, Trojan A, Burnand B, Giannelli M. Efficacy and side effects of cisplatin- and carboplatin-based doublet chemotherapeutic regimens versus non-platinum-based doublet chemotherapeutic regimens as first line treatment of metastatic non-small cell lung carcinoma: a systematic review of randomized controlled trials. Lung Cancer 2008 Jan;59(1):1-11

Li C, Sun Y, Pan Y, Wang Q, Yang S, Chen H. Gemcitabine plus paclitaxel versus carboplatin plus either gemcitabine or paclitaxel in advanced non-small-cell lung cancer: a literature-based meta-analysis. Lung 2010 Oct;188(5):359-64

Evidence summary	LoE
In carefully selected** patients with advanced NSCLC, high dose bevacizumab improves tumour response rate and progression free survival.	I
**Patients with the following criteria were excluded from the trials: SCC histologic type, brain metastases, clinically significant haemoptysis,inadequate organ function, ECOG PS of 1, therapeutic anticoagulation, clinically significant cardiovascular disease, or medically uncontrolled hypertension.	
In carefully selected** patients with advanced NSCLC, treatment with high dose bevacizumab is associated with an increase in treatment related deaths.	I

Recommendation	Grade
High dose bevacizumab (15 mg/kg three-weekly) may be considered in addition to chemotherapy (carboplatin/paclitaxel or cisplatin/gemcitabine) in carefully selected** patients with non-squamous cell carcinoma.	B

Yang K, Wang YJ, Chen XR, Chen HN. Effectiveness and safety of bevacizumab for unresectable non-small-cell lung cancer: a meta-analysis. Clin Drug Investig 2010;30(4):229-41

Botrel TE, Clark O, Clark L, Paladini L, Faleiros E, Pegoretti B. 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 meta-analysis. Lung Cancer 2011 Oct;74(1):89-97

Evidence summary	LoE
The addition of the EGFR TKIs gefitinib or erlotinib to a standard chemotherapy regimen does not improve outcomes (OS, RR or time to progression (TTP)) compared with chemotherapy alone.	II

Recommendation	Grade
The first generation EGFR TKIs gefitinib or erlotinib should not be used in unselected patients in combination with standard chemotherapy.	A

Giaccone G, Herbst RS, Manegold C, Scagliotti G, Rosell R, Miller V, et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial--INTACT 1. J Clin Oncol 2004 Mar 1;22(5):777-84

Herbst RS, Giaccone G, Schiller JH, Natale RB, Miller V, Manegold C, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial--INTACT 2. J Clin Oncol 2004 Mar 1;22(5):785-94

Herbst RS, Prager D, Hermann R, Fehrenbacher L, Johnson BE, Sandler A, et al. TRIBUTE: a phase III trial of

erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2005 Sep 1;23(25):5892-9

Gatzemeier U, Pluzanska A, Szczesna A, Kaukel E, Roubec J, De Rosa F, et al. Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: the Tarceva Lung Cancer Investigation Trial. J Clin Oncol 2007 Apr 20;25(12):1545-52

Evidence summary	LoE
In patients with advanced NSCLC (selected by the presence of EGFR-positive tumour as measured by immunohistochemistry), the addition of cetuximab to chemotherapy increases response rate and improves overall survival. This overall benefit was modest and observed only in the phase III trial using cisplatin/vinorelbine .	I
Recommendation	**Grade**
In patients with advanced NSCLC whose tumours have been shown to express EGFR by immunohistochemistry, cetuximab may be considered in addition to cisplatin/vinorelbine chemotherapy to improve response rate and overall survival.	B

Lin H, Jiang J, Liang X, Zhou X, Huang R. Chemotherapy with cetuximab or chemotherapy alone for untreated advanced non-small-cell lung cancer: a systematic review and meta-analysis. Lung Cancer 2010 Oct;70(1):57-62

Ibrahim EM, Abouelkhair KM, Al-Masri OA, Chaudry NC, Kazkaz GA. Cetuximab-based therapy is effective in chemotherapy-naïve patients with advanced and metastatic non-small-cell lung cancer: a meta-analysis of randomized controlled trials. Lung 2011 Jun;189(3):193-8

Practice point(s)

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

Evidence summary	LoE
In <u>previously treated patients</u> with advanced NSCLC, single agent docetaxel 75 mg/m2 improves survival compared with best supportive care or vinorelbine and ifosfamide.	II
In previously treated patients with advanced NSCLC, single agent pemetrexed has similar efficacy but fewer side effects than three-weekly docetaxel.	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.	
Recommendation	**Grade**
In unselected patients previously treated for advanced NSCLC, 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.	B

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

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

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

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

Evidence summary	LoE
In unselected previously treated patients with advanced NSCLC single agent erlotinib150 mg per day orally as second-line therapy improves survival compared with placebo.	II
In unselected previously treated patients with advanced NSCLC, single agent gefitinib 250 mg per day orally does not improve survival compared with placebo.	II
In unselected previously treated patients with advanced NSCLC, gefitinib 250 mg per day orally is equivalent to three-weekly docetaxel chemotherapy.	II
In unselected patients with advanced NSCLC, progressing after first-line platinum-based chemotherapy, there is no difference in survival between erlotinib 150 mg daily or chemotherapy (either pemetrexed or docetaxel).	II
Recommendation	**Grade**
In unselected patients previously treated for advanced NSCLC, erlotinib 150 mg per day orally can be used as second-line therapy, instead of chemotherapy.	B

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

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 Jul 14;353(2):123-32

Kim ES, Hirsh V, Mok T, Socinski MA, Gervais R, Wu YL, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. Lancet 2008 Nov 22;372(9652):1809-18

Ciuleanu T, Stelmakh L, Cicenas S, Miliauskas S, Grigorescu AC, Hillenbach C, et al. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. Lancet Oncol 2012 Mar;13(3):300-8

Evidence summary	LoE
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.	I
Recommendation	**Grade**
Doublet therapy is not recommended as second-line treatment of advanced NSCLC .	B

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

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

Evidence summary		LoE
In unselected previously treated patients with advanced NSCLC who have received two lines of therapy, single agent erlotinib 150 mg per day orally as third-line therapy improves survival compared with placebo.		II
Recommendation		Grade
In unselected patients having previously received two lines of treatment for advanced NSCLC, erlotinib 150 mg per day orally can be used as third-line therapy.		B

Shepherd FA, et al. 2005

Evidence summary	LoE
In patients with poor performance status (PS 2), first-line monotherapy with 3G chemotherapy (vinorelbine, gemcitabine, paclitaxel or docetaxel) may improve survival and/or quality of life.	I, II
Recommendation	Grade
First-line monotherapy with 3G chemotherapy could be offered to selected patients with PS2 for symptom improvement and possible survival gain, who are willing to accept treatment toxicity.	B

Baggstrom MQ, et al. 2007

Crawford J, O'Rourke M, Schiller JH, Spiridonidis CH, Yanovich S, Ozer H, et al. Randomized trial of vinorelbine compared with fluorouracil plus leucovorin in patients with stage IV non-small-cell lung cancer. J Clin Oncol 1996 Oct;14(10):2774-84

Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. The Elderly Lung Cancer Vinorelbine Italian Study Group. J Natl Cancer Inst 1999 Jan 6;91(1):66-72

Anderson H, Hopwood P, Stephens RJ, Thatcher N, Cottier B, Nicholson M, et al. Gemcitabine plus best supportive care (BSC) vs BSC in inoperable non-small cell lung cancer--a randomized trial with quality of life as the primary outcome. UK NSCLC Gemcitabine Group. Non-Small Cell Lung Cancer. Br J Cancer 2000 Aug;83(4):447-53

Anderson H, Hopwood P, Stephens RJ, Thatcher N, Cottier B, Nicholson M, et al. Gemcitabine plus best supportive care (BSC) vs BSC in inoperable non-small cell lung cancer--a randomized trial with quality of life as the primary outcome. UK NSCLC Gemcitabine Group. Non-Small Cell Lung Cancer. Br J Cancer 2000 Aug;83(4):447-53

Roszkowski K, Pluzanska A, Krzakowski M, Smith AP, Saigi E, Aasebo U, et al. A multicenter, randomized, phase III study of docetaxel plus best supportive care versus best supportive care in chemotherapy-naive patients with metastatic or non-resectable localized non-small cell lung cancer (NSCLC). Lung Cancer 2000 Mar;27(3):145-57

Evidence summary	LoE
There is evidence for benefit with erlotinib 150 mg daily as second or third-line therapy in unselected poor performance status patients (PS2 or 3) .	II
Recommendation	Grade
Poor performance status patients having received 1 or 2 lines of prior therapy, may be offered erlotinib 150 mg daily.	B

Practice point(s)

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

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 Jul 14;353(2):123-32

Evidence summary	LoE
First-line single agent vinorelbine (30 mg/m2 on days one and eight, Q3 weekly) in patients over 70 years of age improves survival and reduces disease related symptoms.	II
In patients over 70 years of age, first line single agent docetaxel 60 mg/m2 (day one) compared to vinorelbine 25 mg/m2 (days one and eight) every 21 days, improves response rate, progression free survival and disease related symptoms, but not overall survival and is associated with more G3/4 neutropaenia.	II
In patients over 65 years of age, gemcitabine doublet chemotherapy improves response rate compared with single agent 3G chemotherapy, but does not improve survival and is associated with greater thrombocytopaenia.	I
In patients over 70 years of age, first-line carboplatin/weekly paclitaxel combination improves survival compared with 3G monotherapy (weekly vinorelbine or gemcitabine) but, is associated with more neutropaenia.	II
Recommendation	**Grade**
Suitably fit patients over 65 years of age, can be offered first-line mono-chemotherapy with a 3G single agent (vinorelbine (25-30 mg/ m2 day one, eight Q3 weekly), docetaxel (60 mg/m2 day one, Q3 weekly) or gemcitabine (1150 mg/m2 days one and eight, Q3 weekly).	B
In elderly patients, first-line gemcitabine doublet chemotherapy is not recommended.	B
In fit elderly patients, first-line carboplatin/weekly paclitaxel may be offered instead of 3G monotherapy, but at the expense of greater neutropaenia.	B

Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. The Elderly Lung Cancer Vinorelbine Italian Study Group. J Natl Cancer Inst 1999 Jan 6;91(1):66-72

Kudoh S, Takeda K, Nakagawa K, Takada M, Katakami N, Matsui K, et al. Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). J Clin Oncol 2006 Aug 1;24(22):3657-63

Russo A, Rizzo S, Fulfaro F, Adamo V, Santini D, Vincenzi B, et al. Gemcitabine-based doublets versus single-agent therapy for elderly patients with advanced nonsmall cell lung cancer: a Literature-based Meta-analysis. Cancer 2009 May 1;115(9):1924-31

Quoix E, Zalcman G, Oster JP, Westeel V, Pichon E, Lavolé A, et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet 2011 Sep 17;378(9796):1079-88

Evidence summary	LoE
Histology (non-squamous cell carcinoma versus squamous cell carcinoma) is associated with a significant treatment modifying effect for patients treated with pemetrexed based chemotherapy, with superior survival effect of pemetrexed observed in non-squamous cell carcinoma histology and inferior survival effect observed in squamous cell carcinoma histology, compared with other standard regimens when pemetrexed is used first-line, as switch maintenance or as second-line treatment.	I
Recommendation	**Grade**
Due to the therapeutic implications, it is important to classify the histologic subtype of NSCLC on diagnostic specimens as accurately as possible, particularly to enable accurate distinction between the key histologic subtypes: adenocarcinoma and squamous cell carcinoma.	A
Practice point(s)	

	Given the importance of accurate histologic diagnosis and the potential need to have sufficient tissue for subsequent molecular testing, it is important to obtain as much tissue as possible at initial diagnosis in patients suspected to have NSCLC. A multidisciplinary team discussion may be required in order to decide on the most appropriate diagnostic method to obtain adequate tissue. Standfield L, et al. 2011 Evidence summary — LoE In caucasian patients with advanced NSCLC and known activating EGFR GMs (exon-19 deletions or exon-21 point mutations), first-line therapy with erlotinib significantly prolongs progression free survival and increases overall response rate, compared with standard platinum based chemotherapy. — II Recommendation — Grade Patients with known activating gene mutations (exon-19 deletions or exon-21 point mutations) to EGFR should be treated with an EGFR TKI. — A on behalf of the Spanish Lung Cancer Group in collaboration with the Groupe Français de Pneumo-Cancérologie and the Associazione Italiana Oncologia Toracica, Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012 Mar;13(3):239-246 Evidence summary — LoE Progression free survival is significantly longer among patients treated with initial chemotherapy, than those treated with gefitinib in patients known not to have EGFR mutations. — II Recommendation — Grade Where EGFR mutation status is negative or unknown, patients should be treated with standard chemotherapy. — B Practice point(s) The evidence in support of large treatment benefits with first-line EGFR TKIs in response rate and progression free survival argues for consideration of obtaining adequate tumour tissue where possible, to enable molecular testing for the presence of activating EGFR gene mutations. This will enable clinicians to offer patients initial EGFR TKIs versus empirical therapy, bearing in mind that overall survival for EGFT GMT + patients does not appear to be compromised, as long they go on to receive EGFR TKIs after chemotherapy. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009 Sep 3;361(10):947-57
Scottish Intercollegiate Guidelines Network (SIGN) 2014 [52]. Management of lung	**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

cancer	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

Erstlinientherapie

<u>First line therapy for patients with stage IIIB and IV NSCLC</u>

Results from a meta-analysis and systematic review demonstrate the benefit of SACT for patients with advanced non-small cell lung cancer (absolute improvement in survival of 9% at 12 months versus control). **(LoE 1++)**

220. Burdett S, et al. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: A systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. J Clin Oncol 2008;26(28):4617-25.

Four randomised trials of single agent SACT (gemcitabine, paclitaxel, docetaxel and vinorelbine) versus best supportive care (including radiotherapy) in patients with advanced NSCLC reveal a trend to improved quality of life with increased survival in three of the four studies. **(LoE 1+)**

221. Anderson H, et al. Gemcitabine plus best supportive care (BSC) vs BSC in inoperable non-small cell lung cancer - a randomised trial with quality of life as the primary outcome. UK NSCLC Gemcitabine Group. Non-Small Cell Lung Cancer. . Br J Cancer 2000;83(4):447-53.

222. Ranson M, et al. Randomized trial of paclitaxel plus supportive care versus supportive care for patients

with advanced non-small-cell lung cancer. J Natl Cancer Inst 2000;92(13):1074-80.

223. Roszkowski K, et al. A multicenter, randomized, phase III study of docetaxel plus best supportive care versus best supportive care in chemotherapynaive patients with metastatic or non-resectable localized non-small cell lung cancer (NSCLC). Lung Cancer 2000;27(3):145-57.

224. Gridelli C. The ELVIS trial: a phase III study of single-agent vinorelbine as first-line treatment in elderly patients with advanced non-small cell lung cancer. Elderly Lung Cancer Vinorelbine Italian Study. Oncologist 2001;6(Suppl 1):4-7.

No particular combination of these agents in regimens with platinum has been shown to be more effective. **(LoE 1+)**

225. Schiller JH, et al. Comparison of four chemotherapy regimens for advanced nonsmall- cell lung cancer. N Engl J Med 2002;346(2):92-8.

Standard treatment is in four cycles, and exceptionally six cycles. Continuing beyond four cycles may increase progression-free survival but at the expense of an increase in toxicity and worse quality of life without any significant gain in survival. **(LoE 1+/1++)**

226. Goffin J, et al. First-line systemic chemotherapy in the treatment of advanced non-small cell lung cancer: A systematic review. J Thorac Oncol 2010;5(2):260-74.

227. Lima JP, et al. Optimal duration of first-line chemotherapy for advanced non-small cell lung cancer: a systematic review with meta-analysis. Eur J Cancer 2009;45(4):601-7.

In patients who have advanced disease and a performance status <2 at the time of diagnosis of NSCLC, first line treatment should be offered according to histology. Patients with non-squamous histology demonstrated a superior survival when treated with cisplatin and pemetrexed compared with cisplatin and gemcitabine (hazard ratio (HR) 0.84, 95% CI 0.74 to 0.96, p=0.011). Patients with squamous histology do not benefit from pemetrexed/platinum combination. **(LoE 1+)**

228. Scagliotti GV, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapynaive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26(21):3541-51.

229. Scagliotti GV, et al. Survival without toxicity for cisplatin plus pemetrexed versus cisplatin plus gemcitabine in chemonaïve patients with advanced non-small cell lung cancer: a risk-benefit analysis of a large phase III study. Eur J Cancer 2009;45(13):2298-303.

In patients with adenocarcinoma, overall survival was statistically superior for cisplatin/pemetrexed versus cisplatin/gemcitabine (n=847; 12.6 *v* 10.9 months). **(LoE 1+)**

Siehe 228

EGFR tyrosine kinase inhibitors (TKIs) are effective as first line treatment of advanced NSCLC in patients with sensitising EGFR mutations. The optimum treatment is orally delivered single agent therapy. TKIs significantly increased progression-free survival (PFS) (HR 0.45, 95% CI 0.36 to 0.58, P<0.0001) over SACT. In a European trial, the median PFS was 9.4 months in the erlotinib (TKI) group and 5.2 months in the doublet SACT group, (HR 0.42, 95% CI 0.27 to 0.64), p<0.0001. **(LoE 1+)**

230. Bria E, et al. Outcome of advanced NSCLC patients harboring sensitizing EGFR mutations randomized to EGFR tyrosine kinase inhibitors or chemotherapy as first-line treatment: a meta-analysis. Ann Oncol 2011;22(10):2277-85.

231. Rosell R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13(3):239-46.

Randomised evidence does not support the use of sACT in combination with a TKI in any patient group. **(LoE 1++)**

Siehe 231

232. Feld R, et al. Use of the epidermal growth factor receptor inhibitors gefitinib and erlotinib in the treatment of non-small cell lung cancer: A systematic review. J Thorac Oncol 2006;1(4):367-76.

Recommendations

- First line single agent tyrosine kinase inhibitors should be offered to patients with advanced NSCLC who have a sensitising *EGFR* mutation. Adding combination systemic anticancer therapy to a TKI confers no benefit and should not be used. (A)
- Patients who have advanced disease, are performance status 0-1, have predominantly nonsquamous NSCLC and are *EGFR* mutation negative should be offered combination systemic anticancer therapy with cisplatin and pemetrexed. (A)
- All other patients with NSCLC should be offered combination systemic anticancer therapy with cisplatin/carboplatin and a third generation agent (docetaxel, gemcitabine, paclitaxel or vinorelbine). (A)
- Platinum doublet systemic anticancer therapy should be given in four cycles; it is not recommended that treatment extends beyond six cycles. (A)

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.

[Anmerkung FB-Med: Review bezieht sich EGRF Inhibitoren aus folgenden Quellen: 1) Zulassungsstudie von Erlotinib vs. Placebo Shepherd 2005 und 2) Thatcher 2005; in der Gefitinib vs. Placebo verglichen wird]

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.

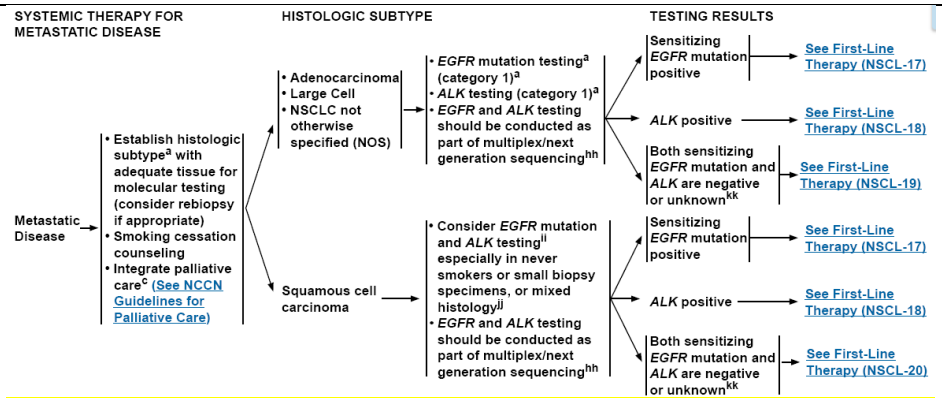
Compared with single agent docetaxel, treatment with PEM resulted in clinically equivalent efficacy outcomes, but with significantly fewer side effects in the second-line treatment of patients with advanced predominantly non-squamous cell NSCLC.

Recommendations

- 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 [14].

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 (Cancer Care Ontario; CCO)

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>Erstlinientherapie</u>** **Recommendation 1a** First-line therapy with an EGFR tyrosine kinase inhibitor (TKI) is not recommended in unselected (patients who have not undergone mutation testing) or clinically selected populations of patients. Available data would suggest that first-line EGFR TKI is inferior to platinum-based chemotherapy in this group of NSCLC patients. The use of clinical characteristics such as Asian ethnicity, female sex, adenocarcinoma histology and light/never smoking status is not recommended to select patients for first-line EGFR TKI therapy, as this strategy does not reliably select patients who have mutations. *Key Evidence* Twenty-six randomized first-line studies in unselected and clinically selected populations were used to formulate this recommendation. The results of these trials showed no benefit for the use of an EGFR inhibitor in unselected and clinically selected patients (1-26). 26 Quellen zitiert **Recommendation 1b** In patients with EGFR mutation-positive NSCLC, first-line therapy with an EGFR TKI such as gefitinib, erlotinib or afatinib is the preferred treatment compared to platinum-based therapies. There is no evidence to support one EGFR TKI over another, so the decision about which EGFR TKI to use should take into consideration the expected toxicity of the drug as well as the cost. EGFR TKI therapy is associated with higher response rates, longer PFS and improved quality of life. *Qualifying Statement* There is no clear difference in overall survival. Many patients in these trials randomized to platinum-doublet chemotherapy, crossed over to an EGFR TKI as subsequent therapy. The likely effect of this cross-over is to dilute any survival difference between the groups, making comparison of overall survival less informative. *Key Evidence* Seven randomized trials and two meta-analyses comprised the evidence base.

The trials and meta-analyses based on data from these trials showed that PFS was prolonged in molecularly selected patients when an EGFR was used as first-line treatment (27-33).

- Six trials were included in the initial meta-analysis that showed a hazard ratio (HR) of 0.35 (95% confidence interval (CI), 0.28-0.45; p<0.00001) (27-30,32,33).
- A second meta-analysis done on PFS that included subsets of EGFR-positive patients from first-line trials had similar results with an HR of 0.38 (95% CI, 0.31-0.44; p<0.00001) (20,21,28-30,32-34).
- All seven trials showed a decrease in adverse effects with an EGFR inhibitor compared to chemotherapy (28-34).

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Zweitlinientherapie

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)

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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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study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. J Clin Oncol. 2008 Sep 10;26(26):4244-52.

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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).

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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, 2012 [2]. Non-small cell lung cancer - stage III. Alberta Health Services und **Alberta Provincial Thoracic Tumour Team, 2013 [3].** 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 recommended first-line therapy for patients with stage IV non-small cell lung cancer (NSCLC)? What is the role for EGFR tyrosine kinase inhibitors in first-line treatment of patients with stage IV NSCLC? What is the optimal second-line therapy for patients with stage IV NSCLC?
	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

Palliative Treatment for Inoperable Disease

Recommendations

12. In patients where lung reserve precludes radical radiotherapy, palliative chemotherapy and/or palliative radiotherapy are recommended.

13. Palliative chemotherapy options include:

- 1st line: platinum-based doublets
- 2nd line: docetaxel, erlotinib or pemetrexed (For more information, please see the Non-Small Cell Lung Cancer, Stage IV Guideline.)

14. For symptomatic patients with poor performance status (ECOG>2) and/or significant weight loss (usually defined as >10% in previous 3 months), radiotherapy for symptom palliation is recommended. Dose-fractionation schedule options include:

- 20Gy in 5 fractions or 30Gy in 10 fractions
- Single fractions of radiotherapy less than 10Gy may be appropriate in some clinical circumstances such as poor performance status or patient travel distance.
- Split course radiation can also be used in select cases.

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33.Fairchild A, Harris K, Barnes E, Wong R, Lutz S, Bezjak A, et al. Palliative thoracic radiotherapy for lung cancer: a systematic review. J Clin Oncol 2008 Aug 20; 26(24):4001-4011.

Non-Small Cell Lung Cancer, Stage IV Guideline

Recommendations

…

3. Combination chemotherapy consisting of a platinum-based doublet is the standard of care for first-line treatment of advanced NSCLC (except for EGFR-positive patients; see recommendation 6 below). The combination of three chemotherapeutic agents for the first-line treatment of advanced NSCLC is not routinely recommended based on current evidence.

7. Delbaldo C, Michiels S, Rolland E, et al. Second or third additional chemotherapy drug for non-small cell lung cancer in patients with advanced disease. Cochrane Database Syst Rev. 2007;4(CD004569).

8. Paccagnella A, Oniga F, Bearz A, et al. Adding gemcitabine to paclitaxel/carboplatin combination increases survival in advanced non-small-cell lung cancer: results of a phase II-III study. J Clin Oncol. Feb 1 2006;24(4):681-687.

9. Comella P, Filippelli G, De Cataldis G, et al. Efficacy of the combination of cisplatin with either gemcitabine and vinorelbine or gemcitabine and paclitaxel in the treatment of locally advanced or metastatic non-small-cell lung cancer: a phase III randomised trial of the Southern Italy Cooperative

	Oncology Group (SICOG 0101). Ann Oncol. Feb 2007;18(2):324-330. 4. Therapy should be continued for four cycles in most patients, and not more than six cycles in responding patients. 5. Acceptable alternatives to combination chemotherapy include non-platinum doublets or monotherapy: • For patients with a borderline performance status (PS=2), single-agent chemotherapy with vinorelbine, gemcitabine, paclitaxel, docetaxel or pemetrexed (for non-squamous cell carcinoma patients only) is recommended over best supportive care alone. • For elderly patients who cannot tolerate a platinum-based combination, single-agent chemotherapy with vinorelbine, gemcitabine, docetaxel, or pemetrexed (for non-squamous cell carcinoma patients only) is associated with improved survival and quality of life when compared to best supportive care alone. However, elderly patients with a good performance status (PS=0-1) should receive combination chemotherapy with a platinum-based doublet. etwa 30 Quellen zitiert 6. First-line monotherapy with the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib is recommended for patients with EGFR mutation-positive NSCLC. 7. Testing for EGFR mutations should take place for all eligible patients with advanced NSCLC and adenocarcinoma (including adenosquamous) histology who are being considered for first-line therapy with gefitinib, irrespective of their gender, ethnicity, and smoking status. etwa 20 Quellen zitiert 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. **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 [62]. **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

Treatment of metastatic (stage cIV) and recurrent NSCLC

5.3.2. What is the most effective first-line chemotherapy? - Other considerations:

The guideline development group decided not to make a recommendation on bevacizumab as it is neither registered nor reimbursed in Belgium for this indication.

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

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
DELTA	0.3646	0.1468	25.6%	1.44 [1.08, 1.92]
INTEREST	0.2151	0.1413	27.7%	1.24 [0.94, 1.64]
TAILOR	0.3577	0.1369	29.5%	1.43 [1.09, 1.87]
TITAN	0.2231	0.1791	17.2%	1.25 [0.88, 1.78]
Total (95% CI)			100.0%	1.35 [1.16, 1.56]

Heterogeneity: Chi² = 0.91, df = 3 (P = 0.82); I² = 0%
Test for overall effect: Z = 3.99 (P < 0.0001)

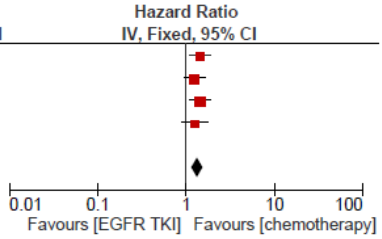
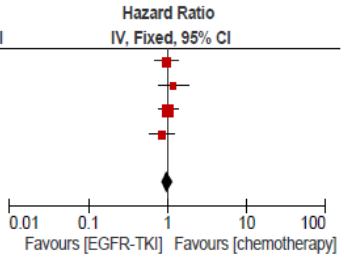


Figure 4 – Pooled (subgroup) effect on overall survival EGFR wildtype patients

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
DELTA	-0.0202	0.179	24.2%	0.98 [0.69, 1.39]
HORG	0.174	0.2221	15.7%	1.19 [0.77, 1.84]
INTEREST	0.0198	0.1435	37.7%	1.02 [0.77, 1.35]
TITAN	-0.1625	0.1863	22.4%	0.85 [0.59, 1.22]
Total (95% CI)			**100.0%**	**0.99 [0.84, 1.18]**

Heterogeneity: Chi² = 1.40, df = 3 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.94)



Conclusion

Chemotherapy extends overall survival in patients with stage IV NSCLC with ECOG/Zubrod PS of 0 or 1; the effect in patients with a PS 2 is less clear.

Platinum combinations are preferred over non-platinum combinations because they are superior in response rate, and marginally superior in OS.

Compared to Cisplatin, carboplatin associated with 12% higher relative hazard of death (HR 1,12; 95%CI: 1,01-1,23) in the subgroup of non squamous NSCLC although HR is comparable (HR 1,07; 95%CI: 0,99- 1,15) in the overall group.

Third generation cytostatica are superior to second generation.

Bevacizumab increases survival and progression free survival when added to carboplatin/paclitaxel but only increases progression free survival when added to cisplatin/gemcitabine.

Adding a EGFR TKI to doublet chemotherapy does not increase overall survival and has only a marginal effect on progression free survival.

Receptor tyrosine kinase inhibitors (EGFR TKI) as first-line treatment of patients with advanced EGFR-mutation positive NSCLC increases progression free survival and has less side effects, there is no evidence of an effect on overall survival, probably due to the cross over design used in the RCTs.

There is preliminary evidence from 1 phase III trial that crizotinib as second line treatment improves progression free survival but not overall survival in ALK-mutation positive NSCLC.

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* • The use of chemotherapy in patients with stage IV NSCLC with WHO/ECOG/Zubrod performance status (PS) of 0 or 1 and (based on clinical judgement) in some cases PS 2 is recommended. (SoE: strong / LoE: high) • Maximal efforts should be made to determine the epidermal growth factor receptor (EGFR) mutation status, using a sensitive and validated method, in all non-squamous NSCLC or in never/very light smokers with mixed squamous/non-squamous NSCLC. It is recommended to use EGFR - tyrosine kinase inhibitors (EGFR TKI) as first-line treatment of patients with advanced EGFR mutation positive non-squamous NSCLC because of the better tolerance. (SoE: strong / LoE: moderate) • If no EGFR TKI is given as first-line treatment in EGFR mutation positive NSCLC, a EGFR TKI should be offered thereafter, either as switch maintenance or at progression as second-line treatment. (SoE: strong / LoE: moderate) • In the presence of the equipoise in efficacy for proven wild-type EGFR carriers, issues as residual and expected toxicity, patient preference and societal drug cost are of importance in the decision to administer second line treatment. Pending the publication of further data, the use of TKI's in second or third line should be restricted to either those patients in whom an activating EGFR mutation is present but was not yet treated with a TKI, or those patients who are not considered for further chemotherapy and whose EGFR mutational status could not be determined despite maximal efforts. (SoE: strong / LoE: very low) • In patients with a WHO performance status of 0 or 1, evidence supports the use of a combination of two cytotoxic drugs for first-line therapy. Platinum combinations are preferred over non-platinum combinations because they are superior in response rate, and marginally superior in overall survival. Non-platinum therapy combinations are reasonable in patients who have contraindications to platinum therapy. (SoE: strong / LoE: high) • In these patients, the choice of either cisplatin or carboplatin is acceptable. Drugs that can be combined with platinum include the third generation cytotoxic drugs docetaxel, gemcitabine, irinotecan, paclitaxel, pemetrexed, and vinorelbine. (SoE: weak / LoE: low) • Pemetrexed is preferred to gemcitabine in patients with non-squamous NSCLC. Pemetrexed use should be restricted to non-squamous NSCLC in any line of treatment. (SoE: strong / LoE: low) • It is recommended to offer second-line chemotherapy for patients with advanced NSCLC with adequate performance status when the disease has

	progressed during or after first-line therapy. (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-cell lung cancer: a systematic review and meta-analysis. J Cancer Res Clin Oncol. 2012;138(5):745-51. 127. Jiang J, Huang L, Liang X, Zhou X, Huang R, Chu Z, et al. Gefitinib versus docetaxel in previously treated advanced non small-cell lung cancer: a meta-analysis of randomized controlled trials. Acta Oncol. 2011;50(4):582-8. 128. Ciuleanu T, Stelmakh L, Cicenas S, Miliauskas S, Grigorescu AC, Hillenbach C, et al. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. Lancet Oncol. 2012;13(3):300-8. Kawaguchi, et al. 2014 (DELTA) Garassino MC, et al. (TAILOR) 2013 131. Karampeazis A, Voutsina A, Souglakos J, Kentepozidis N, Giassas S, Christofillakis C, et al. Pemetrexed versus erlotinib in pretreated patients with advanced non-small cell lung cancer: A Hellenic Oncology Research Group (HORG) randomized phase 3 study. Cancer. 2013.
Socinski MA et al., 2013 [59]. Treatment of Stage IV Non-small	**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 –

Cell Lung Cancer	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 (siehe Anhang)** 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)** **First Line Treatment** 3.1.1.1. In patients receiving palliative chemotherapy for stage IV NSCLC, it is recommended that the choice of chemotherapy is guided by the histologic type of NSCLC **(Grade 1B).** Remark: The use of pemetrexed (either alone or in combination) should be limited to patients with nonsquamous NSCLC. Remark: Squamous histology has not been identified as predictive of better response to any particular chemotherapy agent.

	3.3.1.1. Bevacizumab improves survival combined with carboplatin and paclitaxel in a clinically selected subset of patients with stage IV NSCLC and good PS (nonsquamous histology, lack of brain metastases, and no hemoptysis). In these patients, addition of bevacizumab to carboplatin and paclitaxel is recommended **(Grade 1A)** . 3.3.1.2. In patients with stage IV non-squamous NSCLC and treated, stable brain metastases, who are otherwise candidates for bevacizumab therapy, the addition of bevacizumab to firstline, platinum-based chemotherapy is a safe therapeutic option **(Grade 2B)** . Remark: No recommendation can be given about the use of bevacizumab in patients receiving therapeutic anticoagulation or with an ECOG PS of 2. **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)** .
Brodowicz T et al., 2012 [7].	**1. Fragestellung** It is the aim of the present consensus to summarize minimal quality-oriented requirements for individual patients with NSCLC in its various stages based upon levels of evidence in the light of a rapidly expanding array of individual

Third CECOG consensus on the systemic treatment of non-small-cell lung cancer.	therapeutic options.
	2. Methodik ***Grundlage der Leitlinie:*** evidence-based consensus from experts from Europe and the United States based on systematic literature search ***Suchzeitraum:*** bis 12/2009 ***LoE/GoR:*** Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology *Sonstige methodische Hinweise* • *Kein formaler Konsensusprozess beschrieben* • *Bewertung der Literatur nicht beschrieben* • *14 author disclosures given, remaining authors have declared no conflicts of interest*
	Freitext/Empfehlungen *systemic therapy for advanced disease* <u>first-line therapy</u> 1 Platin-based doublets containing a third-generation cytotoxic drug is the treatment of choice in patients with advanced NSCLC, unless platinum is contraindicated [I,A]. 2 Cisplatin might be preferred in patients with good PS. 3 Nonsquamous histology is a prerequisite for pemetrexed efficacy [I,B]. 4 Cisplatin doses of <75–80 mg/m2 every 3–4 weeks are recommended [I,B]. 5 Chemotherapy should be given for four to six cycles but stopped at disease progression [II,B]. 15. Azzoli CG, Baker S Jr., Temin S et al. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol 2009; 27(36): 6251–6266. 16. Ardizzoni A, Boni L, Tiseo M et al. Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. J Natl Cancer Inst 2007; 99(11): 847–857. 17. Gandara DR, Crowley J, Livingston RB et al. Evaluation of cisplatin intensity in metastatic non-small-cell lung cancer: a phase III study of the Southwest Oncology Group. J Clin Oncol 1993; 11(5): 873–878. 18. Scagliotti GV, Parikh P, von Pawel J et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008; 26(21): 3543–3551. 21. Mok TS, Wu YL, Thongprasert S et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009; 361(10): 947–957. The addition of bevacizumab to first-line chemotherapy (either carboplatin–paclitaxel or cisplatin–gemcitabine) of advanced nonsquamous NSCLC provides

	benefit in patients with good PS and age < 70 [I,B]. The dose of bevacizumab may be either 7.5 or 15 mg/kg every 3 weeks depending on the chemotherapeutic backbone. 19. Reck M, von Pawel J, Zatloukal P et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAiL. J Clin Oncol 2009; 27(8): 1227–1234. 20. Sandler A, Gray R, Perry MC et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006; 355(24): 2542–2550. 23. Johnson DH, Fehrenbacher L, Novotny WF et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-smallcell lung cancer. J Clin Oncol 2004; 22(11): 2184–2191. Despite these results, the US Food and Drug Administration label for cetuximab does not yet include NSCLC, and the EMA did not grant its use in this indication owing to modest benefits and associated toxicity. Nevertheless, addition of cetuximab to a platinum-based chemotherapy regimen is a treatment option in advanced NSCLC [I,B]. 22. Pirker R, Pereira JR, Szczesna A et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomized phase III trial. Lancet 2009; 373(9674): 1525–1531. 24. Gatzemeier U, von Pawel J, Vynnychenko I et al. FLEX: cetuximab in combination with platinum-based chemotherapy (CT) improves survival versus CT alone in the 1st-line treatment of patients with advanced non-small cell lung cancer (NSCLC). J Thorac Oncol 2008; 3(11): 4. 25. O'Byrne KJ, BI, Barrios C et al. Molecular and clinical predictors of outcome for cetuximab in non-small cell lung cancer (NSCLC): data from the FLEX study. J Clin Oncol 2009; 27: 15s (suppl abstract 8007). 26. Lynch TJ, Patel T, Dreisbach L et al. Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non-small-cell lung cancer: results of the randomized multicenter phase III trial BMS099. J Clin Oncol 2010; 28(6): 911–917. 27. Pujol JL, LT, Rosell R et al. A meta-analysis of four randomized phase II/III trials adding cetuximab to platinum-based chemotherapy as 1st-line treatment in patients with non-small cell lung cancer (NSCLC). Eur J Cancer Suppl 2009; 7: S508; 9009. 1 It is strongly recommended to test for EGFR-activating mutations [I,A]. 2 In the absence of EGFR-activating mutations, chemotherapy remains the treatment of choice [I,A]. 3 In patients with EGFR-activating mutations, treatment with gefitinib is the preferred treatment option [I,A]. 28. Gatzemeier U, Pluzanska A, Szczesna A et al. Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: the Tarceva Lung Cancer Investigation Trial. J Clin Oncol 2007; 25(12): 1545–1552. 29. Giaccone G, Herbst RS, Manegold C et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 1. J Clin Oncol 2004; 22(5): 777–784. 30. Herbst RS, Giaccone G, Schiller JH et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 2. J Clin Oncol 2004; 22(5): 785–794. 31. Herbst RS, Prager D, Hermann R et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2005; 23(25): 5892–5899. Single-agent therapy remains a reasonable option for unfit elderly patients [I,B], although clinical evidence does not support selection of a specific firstline chemotherapy drug or combination based on age alone. However, the need for enhanced supportive care should be emphasized in this patient population.

26. Lynch TJ, Patel T, Dreisbach L et al. Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non-small-cell lung cancer: results of the randomized multicenter phase III trial BMS099. J Clin Oncol 2010; 28(6): 911–917.

36. Gridelli C, Maione P, Colantuoni G, Rossi A. Chemotherapy of non-small cell lung cancer in elderly patients. Curr Med Chem 2002; 9(16): 1487–1495.

37. The Elderly Lung Cancer Viborelbine Italian Study Group. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. The Elderly Lung Cancer Vinorelbine Italian Study Group. J Natl Cancer Inst 1999; 91: 66–72.

<u>second-line systemic therapy</u>

1 The data from RCTs on second-line therapy are sufficient to recommend either a cytotoxic agent (docetaxel for squamous NSCLC [II,B] or PEM for nonsquamous NSCLC [II,B]) or the EGFR TKI erlotinib [I,B].

Shepherd FA, Dancey J, Ramlau R 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): 2095–2103.

Fossella FV, DeVore R, Kerr RN 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; 18(12): 2354–2362.

Hanna N, Shepherd FA, Fossella FV 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; 22(9): 1589–1597.

2 An EGFR TKI should be strongly considered in patients with EGFR-activating mutations in their tumors who have not received it as first-line treatment [II,B]. Sequencing of chemotherapy after EGFR TKIs has not been defined and remains an important open issue.

Barlesi F, Jacot W, Astoul P, Pujol JL. Second-line treatment for advanced nonsmall cell lung cancer: a systematic review. Lung Cancer 2006;51(2): 159–172.

Weiss GJ, Rosell R, Fossella F et al. The impact of induction chemotherapy on the outcome of second-line therapy with pemetrexed or docetaxel in patients with advanced non-small-cell lung cancer. Ann Oncol 2007; 18(3): 453–460.

Shepherd FA, Dancey J, Ramlau R 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): 2095–2103.

Fossella FV, DeVore R, Kerr RN 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; 18(12): 2354–2362.

Hanna N, Shepherd FA, Fossella FV 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; 22(9): 1589–1597.

Kim ES, Hirsh V, Mok T et al. Gefitinib versus docetaxel in previously treated nonsmall-cell lung cancer (INTEREST): a randomised phase III trial. Lancet 2008;372(9652): 1809–1818.

Shepherd FA, Rodrigues Pereira J, Ciuleanu T et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005; 353(2): 123–132.

Thatcher N, Chang A, Parikh P 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): 1527–1537.

Zhu CQ, da Cunha Santos G, Ding K et al. Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol 2008; 26(26): 4268–4275.

Hirsch FR, Varella-Garcia M, Bunn PA Jr., et al. Epidermal growth factor receptor in non-small-cell lung carcinomas: correlation between gene copy number and protein expression and impact on

	prognosis. J Clin Oncol 2003; 21(20): 3798–3807.
National Institute for Health and Care Excellence (NICE). 2011 [41]. The diagnosis and treatment of lung cancer (CG121)	**1. Fragestellung** It offers evidence-based advice on the care and treatment of people with lung cancer.
	2. Methodik Grundlage der Leitlinie: evidenz- und konsensbasierte Aktualisierung, Entwicklergruppe: „team of health professionals, lay representatives and technical experts“, systematische Literatursuche und –bewertung, formaler Konsensprozess, Expertenreview Update: erste Version von 2005, **“**This guideline will shortly be checked to see if it needs updating, Next review date: December 2015” Suchzeitraum: July 2010 LoE/GoR: In den ‘qualifying statements’ beschrieben: „covering the strength of evidence, the degree of consensus”. Bei niedriger Evidenzqualität bzw. fehlender Evidenz informale Konsentierung. “To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations.“ *Sonstige Hinweise:* • *At the start of the guideline development process all GDG members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared new, arising conflicts of interest which were always recorded*
	3. Freitext/Empfehlungen/Hinweise 6 Chemotherapy for NSCLC *Recommendations* • Chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status (WHO 0, 1 or a Karnofsky score of 80–100), to improve survival, disease control and quality of life. [2005] • Chemotherapy for advanced NSCLC should be a combination of a single third generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Either carboplatin or cisplatin may be administered, taking account of their toxicities, efficacy and convenience. [2005] • Patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation drug. [2005] • Docetaxel monotherapy should be considered if second-line treatment is appropriate for patients with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy. [2005] *Gefitinib*

	• Refer to 'Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer' (NICE technology appraisal guidance 192 [2010]), available at www.nice.org.uk/guidance/TA192 *Pemetrexed* • Refer to 'Pemetrexed for the first-line treatment of non-small-cell lung cancer' (NICE technology appraisal guidance 181 [2010]), available at www.nice.org.uk/guidance/TA181 *Erlotinib* • Refer to 'Erlotinib for the treatment of non-small-cell lung cancer' (NICE technology appraisal guidance 162 [2008]), available at www.nice.org.uk/guidance/TA162
de Marinis F et al., 2011 [13]. **AIOT (Italian Associatlon of Thoracic Oncology)** Treatment of advanced non-small-cell-lung cancer: Italian Association of Thoracic Oncology (AIOT) clinical practice guidelines.	**1. Fragestellung** Which first-line treatment for fit patients? Cisplatin or carboplatin for first-line treatment? What ls the role for EGFR tyrosine-klnase Inhibitors in first-line treatment? Which first-line treatment for elderly patients? Which first-line treatment for PS 2 patients? Which second-line chemotherapy? Chemotherapy or EGFR lnhibitors for second-line treatment?
	2. Methodik Systematische Literatursuche und formaler Konsensusprozess, up-to-date, cllnlcal practice guidellnes, subsequently updated for this manuscrlpt on December 2010 ***Suchzeitraum:*** 2004 bis 2009 ***LoE, GoR*** *(siehe Anhang)* *Sonstige methodische Hinweise* • *Methodische Schritte entsprechen Agency for Healthcare Policy Research (AHCPR) System US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research.*
	3. Empfehlungen *3.1.1. Recommendations* Platinum-based (cisplatin orcarboplatin) chemotherapy for4-6 cycles is the standard treatment for patients wlth advanced non-small-celllung cancer (NSCLC) and performance status (PS)0-1. Patients wlth squamous tumour are ellgible For first-llne platlnum-based doublets with a thlrd-generatlon drug, with the exception ofpemetrexed. Patlents wlth advanced non-squamous NSCLC are ellgible for tirst-llne platinum-based doublets wlth a third-generation drug, includlng pemetrexed. Bevacizumab in comblnatlon with carboplatin plus paclltaxel or clsplatin plus gemcltablne is a further option for patlents considered

	ellgible to thls therapy, however carboplatln plus paclitaxel should be consldered the chemotherapybackbone for bevacizumab. A. Treatment options[or patients with squamous tumour Patients with advanced squamous NSCLC are eligib/e [or firstline platinum-based doublets with a third-generation drug, with the exception ojpemetrexed. B. Treatment options[or patients with non-squamous tumours Patients with advanced non-squamous NSCLC are e/igib/e [or first-line platinum-based doubiets with a third-generation drug, inc/uding pemetrexed. Bevac/zumab in combination with carboplatin plus paclitaxe/ orcisp/atin p/usgemdtabine is a[ilrtheroption [or patients considered eligible to this therapy. Carboplatin plus pac/itaxel should be considered the chemotherapy backhone [or bevac/zumab. **LoE lA/GoR A** 20 Quellen zitiert *3.2.1. Recommendations* Third-generation cisplatin-based reglmens are recommended for the treatment of advanced NSCLC patients, with PS 0-1 and without major co-morbldities. Where the use of cisplatin is contra-indicated third-generation carboplatin-based regimens are a valid therapeutic option. **LoE lA/GoR A** 11 Quellen zitiert *3.3.1. Recommendations* Gefitinib is recommended as first-line therapy of patients with EGFR mutat!on positive NSCLC EGFR analysis is recommended, if adequate tumour sampie is available, especially in patients selected on the basis of clinical and/or pathological characteristics known to be assodated w!th higher frequency of EGFR mutation (never or former smokers, adenocardnoma). **LoE lB/GoR A** (32(Mok 1'5, Wu YL. Thongprasert 5, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxelln pulmonary adenocarcinoma. N Eng! J Med 2009;361:947-57. (33)- Lee JS. Park· K. Kim SW, Lee DH, Kim HT, Han JY, et al. A randomized phase 111 study of gefitinlb (JRESSA) versus standard chemotherapy (gemcltablne plus cisplatin) as a first-llne treatment for never.smokers with advanced or metastaUe adenocardnoma of the Jung. J TI10rac Oncol 2009;4 (Suppl. 1):5283-4(abstrPRS.4]. [34) Maemondo M,lnoue A. Kobayashl K, Sugawara 5, Oizumi S,lsobe H,et i.Gefitinib or chemotherapy for non-small-celllung cancer with mutated EGFR. N Englj Med 2010;362:2380-8. (35) Mitsudami T, Morita s. Yatabe Y, Negoro s, Okamoto I, Tsurutani J, et al. Gefitinibversus clsplatin plus docetaxel in patients wlth non-small-celllungcancer harbouring mutations ofthe epldennal growth factor receptor(WJfOG3405): an open label, randomlsed phase 3 trial. Lancet Oncol2010;1 1:121-8. (36) Rosell R. Moran T, Queralt C. Porta R. Cardenal F, Camps C, et al. Screening for epidennal growth factor receptor mutations in Jung cancer. N Eng! J Med 2009;361:958-67. [371 Zhou c. wung VI, Chen G, feng J, Uu X, Wang c, et al. Efficacy results from the randomlsed phase 111 OPTIMAL (O"ONG 0802) study comparing first-line erletinib versus carboplatin plus

gemcitabine, in Chinese advanced non-smallcell Jung cancer patients wlth EGFR actlvatlng mutations. ln; Presented at European Soclety of Medical Oncology meeting. 2010 (abstr LBA 13),

[38) Gridelll c, Ciardlello F, Feld R, Butts CA. Gebbia V, Genestretl G, et al.International multlcenter randomlzed phase 111 studyoffirst-llneerlotinib (E)followed by second-llne clsplatln plusgemcltablne (CG) versus first-Hne CG fol/owed by second-line Ein advanced nen-small celllung cancer (aNSCLC); The TORCH trlal,j Clln Dncoi2010;28(15S):540s (abstr 7508).

3.5.1. Recommendations

• In elderly patients (older than 70 years) with advanced NSCLC, single-ogent treatment with a third-generation drug ls the recommended option for clinlcal practice. **(LoE lA/GoR A)**

• In elderly patients (older than 70 years) with advanced NSCLC and PS 0-1, without major co-morbldities and with adequate organ function, platinum-based chemotherapy wlth attenuated doses of clsplatin or carboplatln can be considered. **(LoE IB/GoR A)**

• In elderly patients(older than 70years), with EGFR mutation positive advanced NSCLC, gefitlnib ls the recommended treatment. **(LoE lA/GoR A)**

[42) Elderly Lung Cancer Vlnerelbine ltalfan Study Group. Effects ofvinorelblne on quallty of life and survlval of elderly patlents wlth advanced non-smalt-eeil Jung cancer.J Natl Cancer lnst 1991:91:66-72.

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(48) Quoix EA, Oster J, Westeel V, Pichon E, Zalcman G, Baudrin L. et al. Weekiy paclitaxel combined wlth monthlycarboplatln versus slngle--agent therapy in patlents age 70 to 89: IFCf-0501 randomized phase 111 study in advanced nonsmall celllung cancer(NSCI.C).J Clln oncol 2010;28(15S):5s (abstr 2).

3.6.1. Recommendations

• Flrst-line chemotherapy is recommended in patients wlth advanced NSCLC and ECOG PS 2 because lt ls assodated with a significant benefit in overall survival and quality of life, compared to BSC alone. **(LoE lA/GoR A)**

• Single-agent thlrd-generation drug ls a reasonable option. Comblnation chemotherapy with carboplatin or low doses of dsplatln ls a reasonable alternative. **(LoE IB/GoR B)**

• ln PS 2 patients, with EGFR mutationpositive advanced NSCLC, gefitlnib ls the recommended treatment. **(LoE IB/GoR A)**

10 Quellen zitiert

	3.7.1. Recommendations In patients with advanced NSCLC, after failure of first-line treatment, • Single-agent treatment with docetaxel or pemetrexed (the latter limlted to non-squamous tumours) is recommended. **LoE lB, GoR A** • In patients wlth advanced NSCLC, progressing after first-line treatment, combination chemotherapy is not recommended. **LoE lA, GoR A** 17 Quellen zitiert *3.8.1. Recommendations* • In patients wlth advanced NSCLC and EGFR mutation negative or unknown status, with progressive disease after first-line treatment chemotherapy (docetaxel or pemetrexed in non-squamous histology) or erlotinlb should be offered. There are no concluslve data to help the choice between chemotherapy and erlotinib. (**LoE IB, GoR A)** • In patients with advanced NSCLC, with progressive disease after second-line treatment erlotinib is the drug of cholce, lf not administered prevlously, because is the only approved for use ln clinical practice as third-line treatment (**LoE IB, GoR A)** 78. Shepherd FA, Rodrtgues Perelra J, Cluleanu T, Tan EH, Hlrsh V, Thongprasert s, et al. Erlotlnlb in previously treated non·small-celllungcancer. N Engl J Med 2005;353:123-32. 87. Vamvakas L, Agelaki S, Kentepozidis NK, Karampeazls A, Pallls AG, Christophyllakls c, et al. Pemetrexed (MTA) compared with erlotinlb (ERL) in pretreated patients with advanced non~small cell Jung cancer (NSClC): Results of a randomized phase III Hellenie Oncology Research Group trial. J Clln Oncol 2010;28(15S):543s (abstr7519). 88. Ci uleanu T, Stelma kh L, Cice nass, Esteban E. Erlotinlb versus docetaxe I o r pemetrexed as second~line therapy in patients with advanced non-small-celllung cancer(NSCLC)and poorprognosis: efficacy and safety results from the phase III TITAN study.ln: Presented at Chicago Thoraeie Multidisclplinary Symposium. 2010 fabstr LBOA5).
Azzoli CG, et al., 2010 [5]. **American Society of Clinical Oncology (ASCO)** Clinical Practice Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer.	**1. Fragestellung** To update its recommendations on the use of chemotherapy for advanced stage non–small-cell lung cancer (NSCLC), ASCO convened an Update Committee of its Treatment of Unresectable NSCLC Guideline Expert Panel. ASCO first published a guideline on this topic in 19971 and updated it in 2003.2 The current version covers treatment with chemotherapy and biologic agents and molecular markers for stage IV NSCLC and reviews literature published from 2002 through May 2009.
	2. Methodik ***Grundlage der Leitlinie:*** regelmäßig aktualisierte, evidenz- und konsensbasierte Leitlinie, „NSCLC update committee“ hat sich nach Sichtung aktueller relevanter Literatur für systematische Aktualisierung von Empfehlung 6 entschieden und die Aktualität der restlichen Empfehlungen bestätigt. ***Suchzeitraum:*** 2002 bis 07/2008, bis 2010 für Empfehlung A6 ***GoR, LoE***

	Keine Angabe in der zusammenfassenden Darstellung (vgl. Anhang) *Sonstige methodische Hinweise* • *Kein formaler Konsensusprozess beschrieben* • *The recommendations in this guideline were developed primarily on the basis of statistically significant improvements in overall survival (OS) documented in prospective RCTs. Treatment strategies demonstrated to improve only progression-free survival (PFS) prompted greater scrutiny regarding issues such as toxicity and quality of life.* • *CoI dargelegt*
	3. Empfehlungen (9 Erstlinienempfehlungen im Anhang) ***Second-Line Chemotherapy*** **Recommendation:** Docetaxel, erlotinib, gefitinib, or pemetrexed is acceptable as second-line therapy for patients with advanced NSCLC with adequate PS when the disease has progressed during or after first-line, platinum-based therapy. **Comment.** In addition to considering optimal regimen, the guideline evaluated data on schedules of administration for second- line therapy, which were available only for docetaxel. These data do not show any differences in efficacy of docetaxel based on schedule. A weekly schedule appears less toxic than a schedule of every 3 weeks, especially for hematologic toxicities. The data on combination biologic therapy as second-line therapy are limited to the combination of bevacizumab and erlotinib. At publication time, there were no published RCTs with positive results for OS using this combination. There are no data available on the optimal duration of second-line therapy. Phase III clinical trials of docetaxel, erlotinib, gefitinib, and pemetrexed allowed patients to continue chemotherapy, as tolerated, until disease progression. **Recommendation:** The evidence does not support the selection of a specific second-line chemotherapy drug or combination based on age alone. **Comment.** There is a paucity of research on people considered elderly who are receiving second-line therapy. The available evidence shows that benefits and toxicity do not differ by age. ***Third-Line Chemotherapy*** **Recommendation:** When disease progresses on or after second-line chemotherapy, treatment with erlotinib may be recommended as third-line therapy for patients with PS of 0 to 3 who have not received prior erlotinib or gefitinib. **Comment.** This recommendation is based on the registration trial for erlotinib (Recommendation B1). This trial included participants who had received one or two prior regimens, and an analysis of survival showed no significant difference between prior numbers of regimens. **Recommendation:** The data are not sufficient to make a recommendation for or against using a cytotoxic drug as thirdline therapy. These patients should

	consider experimental treatment, clinical trials, and best supportive care. **Comment.** Only a retrospective analysis was available on this issue. It found survival and response rates decreased with each subsequent regimen. Patients receiving third- and fourth fourthline cytotoxic therapy have infrequent responses, the responses are of short duration, and the toxicities are considerable.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

NICE, 2014 [39]. Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer (TA 310)	1 Guidance 1.1 Afatinib is recommended as an option, within its marketing authorisation, for treating adults with locally advanced or metastatic non-small-cell lung cancer only if: • the tumour tests positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation **and** • the person has not previously had an EGFR-TK inhibitor **and** • the manufacturer provides afatinib with the discount agreed in the patient access scheme.
Breuer J, et al., 2013 [6]. Afatinib (Giotrif®) for the treatment of EGFR TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s) **Institute for Health Technology Assessment Ludwig Boltzmann Gesellschaft**	Afatinib (Giotrif®) as monotherapy is indicated for the treatment of EGFR TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutations. **Current treatment** Modalities for the treatment of NSCLC which are generally used are surgery, radiation therapy, chemotherapy and targeted therapy. Depending on disease status, Eastern Cooperative Oncology Group (ECOG) performance status and prognostic factors, these treatments can be used either alone or in combination [12]. First-line therapy of advanced NSCLC depends on a number of factors, such as tumour stage, histo-pathological subtype and performance status. Current treatment options for the first-line therapy of patients with advanced or metastatic lung cancer are: double-agent chemotherapy regimen based on a platinum compound (cisplatin, carboplatin) in addition to one out of numerous other substances (paclitaxel, gemcitabine, vinorelbine or docetaxel and pemetrexed) ・ other chemotherapy regimens: due to the toxicity of platinum-based regimens, other drug combinations can be used (gemcitabine + docetaxel/paclitaxel/vinorelbine/pemtrexed, paclitaxel + vinorelbine) ・ single-agent chemotherapy as first-line treatment may be used for elderly patients ・ targeted therapies: EGFR inhibitors (erlotinib, gefitinib), monoclonal antibodies (bevacizumab) ・ a combined modality approach [10, 12, 15]. If patients are EGFR mutational status positive, EGFR-TK inhibitors (e.g. erlotinib, gefitinib) are increasingly used as standard first-line therapy, whereas patients with either unknown EGFR status or without EGFR mutation receive chemotherapy doublets, either alone or in combination with a monoclonal antibody (bevacizumab). If patients with driver mutations have initially been treated with chemotherapy, targeted

	therapy with a specific inhibitor is indicated after progression on the initial chemotherapy regimen either alone or in combination with chemotherapy [15, 16]. [10] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer (V 2.2013). 2013 [24.09.2013]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. [12] Lilenbaum R. Overview of the treatment of advanced non-small cell lung cancer. 2013 [26.09.2013]; Available from: http://www.uptodate.com/contents/overview-of-the-treatment-of-advanced-non-small-cell-lung-cancer?detectedLanguage=en&source=search_result&search=therapy+nsclc&selectedTitle=3~150&provider=noProvider. [15] Lilenbaum R. Systemic therapy for advanced non-small cell lung cancer with an activating mutation in the epidermal growth factor receptor. 2013 [26.09.2013]; Available from: http://www.uptodate.com/contents/systemic-therapy-for-advanced-non-small-cell-lung-cancer-with-an-activating-mutation-in-the-epidermal-growth-factor-receptor?detectedLanguage=en&source=search_result&search=first+line+therapy+nsclc&selectedTitle=8~150&provider=noProvider. [17] Wu YL, Zhou C, Hu CP, Feng JF, Lu S, Huang Y, et al. LUX-Lung 6: A randomized, open-label, phase III study of afatinib (A) versus gemcitabine/cisplatin (GC) as first-line treatment for Asian patients (pts) with EGFR mutation-positive (EGFR M+) advanced adenocarcinoma of the lung. Journal of Clinical Oncology. 2013;31(15).
Semlitsch T et al., 2013 [53]. Crizotinib (Xalkori®) for the treatment of anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) **Institute for Health Technology Assessment Ludwig Boltzmann Gesellschaft**	**Current treatment** As second line therapy the following treatments are recommended: • single agent chemotherapy (docetaxel or PEM) • targeted agent therapy (e.g. erlotinib) • a platinum based combination therapy for patients with EGFR mutation and progressive disease after tyrosine kinase inhibitor treat-ment (e.g. erlotinib) For ALK-positive NSCLC patients the targeted agent crizotinib is the currently recommended treatment option as first or second line therapy. Chemotherapy is an appropriate option for these patients with disease progression on crizotinib. As patients with the ALK fusion oncogene do not appear to respond to EGFR tyrosine kinase inhibitors, erlotinib therapy is not recommended.
NICE, 2013 [40]. Crizotinib for previously treated non- small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (TA 296)	1 Guidance 1.1 Crizotinib is not recommended within its marketing authorisation, that is, for treating adults with previously treated anaplastic-lymphoma-kinase-positive advanced non-small-cell lung cancer. 1.2 People currently receiving crizotinib that is not recommended according to 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.
NICE, 2012 [42]. Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer (TA 258)	1 Guidance 1.1 Erlotinib is recommended as an option for the first-line treatment of people with locally advanced or metastatic non-small-cell lung cancer (NSCLC) if: • they test positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation **and** • the manufacturer provides erlotinib at the discounted price agreed under the patient access scheme (as revised in 2012).
NICE, 2010 [43]. Gefitinib for the first-line treatment of locally advanced or	1 Guidance 1.1 Gefitinib is recommended as an option for the first-line treatment of people with locally advanced or metastatic non-small-cell lung cancer (NSCLC) if:

metastatic non-small-cell lung cancer (TA 192)	• they test positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation **and** • the manufacturer provides gefitinib at the fixed price agreed under the patient access scheme.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 05.06.2015 und 09.09.2016**

#	Suchfrage
1	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees
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 2010 to 2016

SR, HTAs in Medline (PubMed) am 05.06.2015 und am 13.06.2016

#	Suchfrage
1	Carcinoma, Non-Small-Cell Lung[MesH]
2	(((non[Title/Abstract]) AND small[Title/Abstract]) AND cell[Title/Abstract]) AND lung[Title/Abstract]
3	((((((tumor*[Title/Abstract]) OR tumour*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract]) OR neoplasm*[Title/Abstract]) OR sarcoma*[Title/Abstract]) OR cancer*[Title/Abstract]
4	#2 AND #3
5	#1 OR #4
29	Receptor Protein-Tyrosine Kinases[MesH] OR Antineoplastic Agents[MesH] OR Antineoplastic Agents[Supplementary Concept]OR ROS1[Title/Abstract]
30	#5 AND #29
31	(#30) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))))
32	(#31) AND ("2010/06/01"[PDAT] : "2016/06/13"[PDAT])
35	(#5) AND ((((((drug[Title/Abstract]) OR (drug therap*)[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR treat[Title/Abstract]) OR treatment*[Title/Abstract])
36	(#35) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract])

	OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
37	(#36) AND ("2010/06/01"[PDAT] : "2016/06/13"[PDAT])
40	#39 NOT #34
41	#39 OR #34

Leitlinien in Medline (PubMed) am 05.06.2015 und am 13.06.2016

#	Suchfrage
1	Carcinoma, Non-Small-Cell Lung[MeSH]
2	(((non[Title/Abstract]) AND small[Title/Abstract]) AND cell[Title/Abstract]) AND lung[Title/Abstract]
3	((((((tumor*[Title/Abstract]) OR tumour*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract]) OR neoplasm*[Title/Abstract]) OR sarcoma*[Title/Abstract]) OR cancer*[Title/Abstract]
4	#2 AND #3
5	#1 OR #4
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title] OR Consensus Development Conference[ptyp] OR recommendation*[Title/Abstract])
7	(#6) AND ("2010/06/01"[PDAT] : "2016/06/13"[PDAT])

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Anhang:

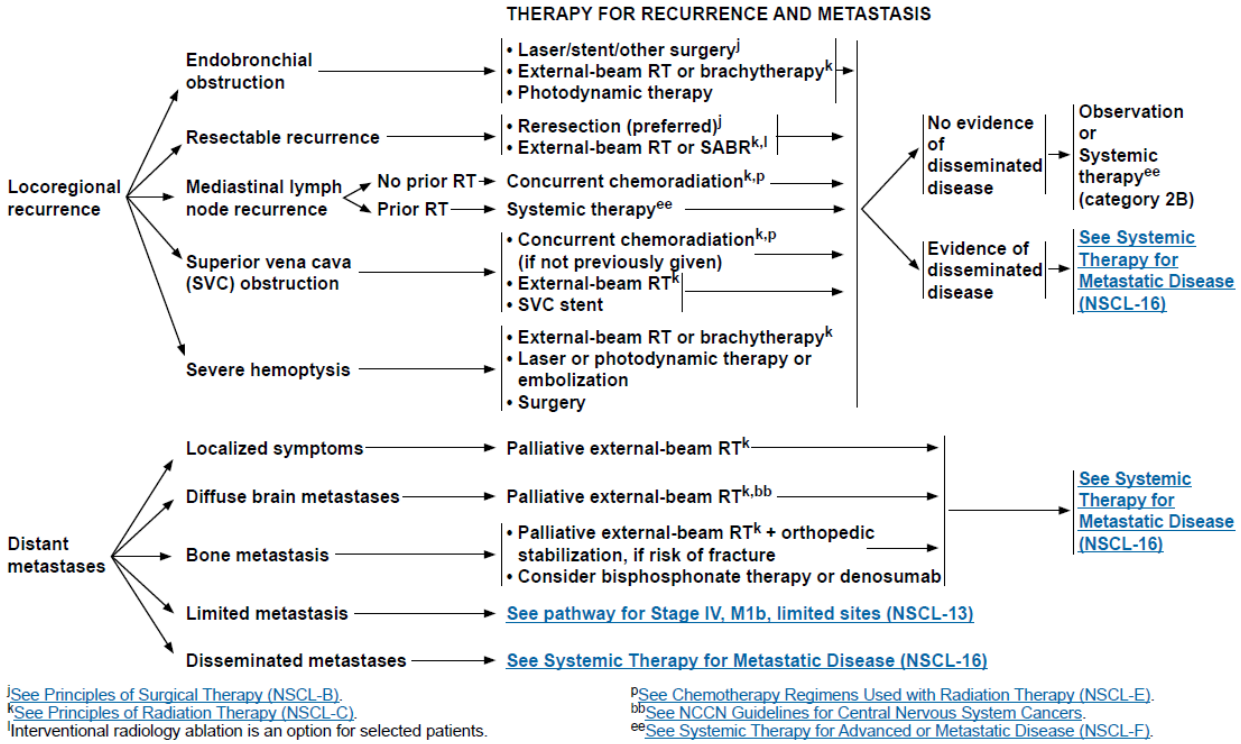

Abbildung 1: aus NCCN 2015

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (1 OF 3)

ADVANCED DISEASE:

- The drug regimen with the highest likelihood of benefit with toxicity deemed acceptable to both the physician and the patient should be given as initial therapy for advanced lung cancer.
- Stage, weight loss, performance status, and gender predict survival.
- Platinum-based chemotherapy prolongs survival, improves symptom control, and yields superior quality of life compared to best supportive care.
- Histology of NSCLC is important in the selection of systemic therapy.
- New agent/platinum combinations have generated a plateau in overall response rate (≈ 25%–35%), time to progression (4–6 mo), median survival (8–10 mo), 1-year survival rate (30%–40%), and 2-year survival rate (10%–15%) in fit patients.
- Unfit patients of any age (performance status 3–4) do not benefit from cytotoxic treatment, except erlotinib for *EGFR* mutation-positive patients.

First-line Therapy

- Bevacizumab + chemotherapy or chemotherapy alone is indicated in PS 0-1 patients with advanced or recurrent NSCLC. Bevacizumab should be given until disease progression.
- Erlotinib is recommended as a first-line therapy in patients with sensitizing *EGFR* mutations and should not be given as first-line therapy to patients negative for these *EGFR* mutations or with unknown *EGFR* status.
- Afatinib is indicated for patients with sensitizing *EGFR* mutations.
- Crizotinib is indicated for patients with *ALK* rearrangements.
- There is superior efficacy and reduced toxicity for cisplatin/pemetrexed in patients with nonsquamous histology, in comparison to cisplatin/gemcitabine.
- There is superior efficacy for cisplatin/gemcitabine in patients with squamous histology, in comparison to cisplatin/pemetrexed.
- Two drug regimens are preferred; a third cytotoxic drug increases response rate but not survival. Single-agent therapy may be appropriate in select patients.
- Cisplatin or carboplatin have been proven effective in combination with any of the following agents: paclitaxel, docetaxel, gemcitabine, etoposide, vinblastine, vinorelbine, pemetrexed, or albumin-bound paclitaxel.
- New agent/non-platinum combinations are reasonable alternatives if available data show activity and tolerable toxicity (eg, gemcitabine/docetaxel, gemcitabine/vinorelbine).
- Response assessment after 1-2 cycles, then every 2-4 cycles.

Abbildung 2: aus NCCN 2015

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (2 OF 3)

Maintenance Therapy

Continuation maintenance refers to the use of at least one of the agents given in first line, beyond 4–6 cycles, in the absence of disease progression. Switch maintenance refers to the initiation of a different agent, not included as part of the first-line regimen, in the absence of disease progression, after 4–6 cycles of initial therapy.

- Continuation Maintenance: Bevacizumab given in combination with chemotherapy should be continued until evidence of disease progression or unacceptable toxicity, as per the design of the clinical trials supporting their use.
  - Continuation of bevacizumab after 4–6 cycles of platinum-doublet chemotherapy and bevacizumab (category 1).
  - Continuation of pemetrexed after 4–6 cycles of cisplatin and pemetrexed chemotherapy, for patients with histologies other than squamous cell carcinoma (category 1).
  - Continuation of bevacizumab + pemetrexed after 4 to 6 cycles of bevacizumab, pemetrexed, cisplatin/carboplatin, for patients with histologies other than squamous cell carcinoma.
  - Continuation of gemcitabine after 4–6 cycles of platinum-doublet chemotherapy (category 2B).
- Switch Maintenance: Two studies have shown a benefit in progression-free and overall survival with the initiation of pemetrexed or erlotinib after first-line chemotherapy, in patients without disease progression after 4–6 cycles of therapy.
  - Initiation of pemetrexed after 4–6 cycles of first-line platinum-doublet chemotherapy, for patients with histologies other than squamous cell carcinoma (category 2B).
  - Initiation of erlotinib after 4–6 cycles of first-line platinum-doublet chemotherapy (category 2B).
  - Initiation of docetaxel after 4–6 cycles of first-line platinum-doublet chemotherapy in patients with squamous cell carcinoma (category 2B).
- Close surveillance of patients without therapy is a reasonable alternative to maintenance.

Subsequent Therapy

- In patients who have experienced disease progression either during or after first-line therapy, the following are established second-line agents.
  - Nivolumab improves survival when compared with docetaxel.
  - Docetaxel is superior to vinorelbine or ifosfamide.
  - Pemetrexed is considered equivalent to docetaxel with less toxicity in patients with adenocarcinoma and large cell carcinoma.
  - Ramucirumab + docetaxel improves survival when compared to docetaxel alone.
  - Erlotinib is superior to best supportive care.
  - Afatinib is indicated for patients with sensitizing *EGFR* mutations.
  - Ceritinib is indicated for patients with *ALK* rearrangements who have disease progression on or are intolerant to crizotinib.

Continuation After Disease Progression

- With the exception of targeted agents (erlotinib, gefitinib, afatinib, crizotinib, ceritinib) in patients with *EGFR*-sensitizing mutations or *ALK* rearrangements who have experienced objective regressions with targeted therapy, no agent should be continued after disease progression has been documented except in selected situations. (refer to discussion section)

Abbildung 3: aus NCCN 2015

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (3 OF 3)

Agents listed below are used in the treatment of patients with NSCLC. Most are used in combination, while others are used as monotherapy (eg, maintenance or second-line/subsequent therapy).

- **Cisplatin**[1-9]
- **Carboplatin**[4,6-11]
- **Paclitaxel**[1,4,6,8-11]
- **Docetaxel**[5,7,8,12,13]
- **Vinorelbine**[7,9,10]
- **Gemcitabine**[3,5,6,8,9,13]
- **Etoposide**[4]
- **Irinotecan**[9]
- **Vinblastine**
- **Mitomycin**
- **Ifosfamide**[12]
- **Pemetrexed**[14,15]
- **Erlotinib**[16]
- **Bevacizumab**[17]
- **Albumin-bound paclitaxel**[18-20] †
- **Crizotinib**[21]
- **Afatinib**[22]
- **Ceritinib**[23]
- **Ramucirumab**[24]
- **Nivolumab**[25,26]

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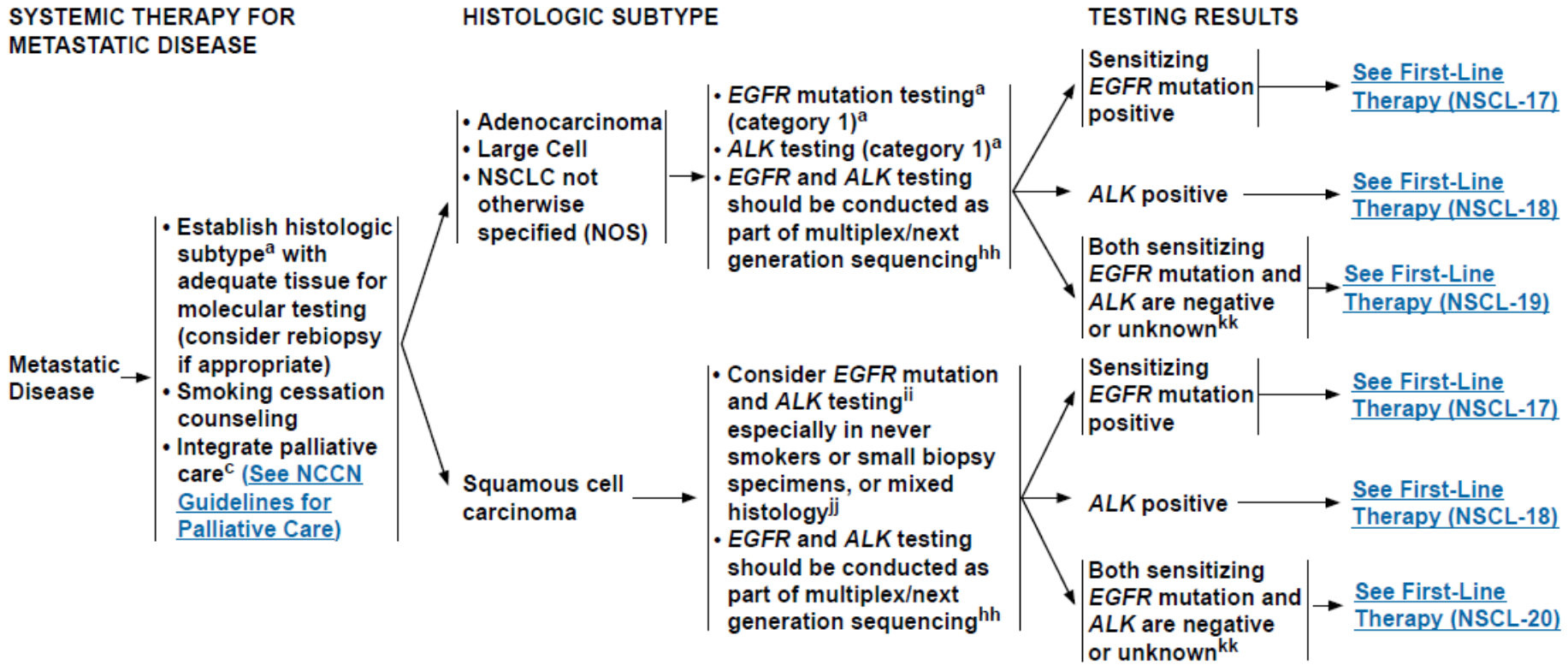
†Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or for patients where the standard premedications (ie, dexamethasone, H2 blockers, H1 blockers) are contraindicated.

Abbildung 4: aus NCCN 2015



[a] See Principles of Pathologic Review (NSCL-A).

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[ii] In patients with squamous cell carcinoma, the observed incidence of *EGFR* mutations is 2.7% with a confidence that the true incidence of mutations is less than 3.6%. This frequency of *EGFR* mutations does not justify routine testing of all tumor specimens. Forbes SA, Bharma G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). Curr Protoc Hum Genet 2008;chapter 10:unit 10.11.

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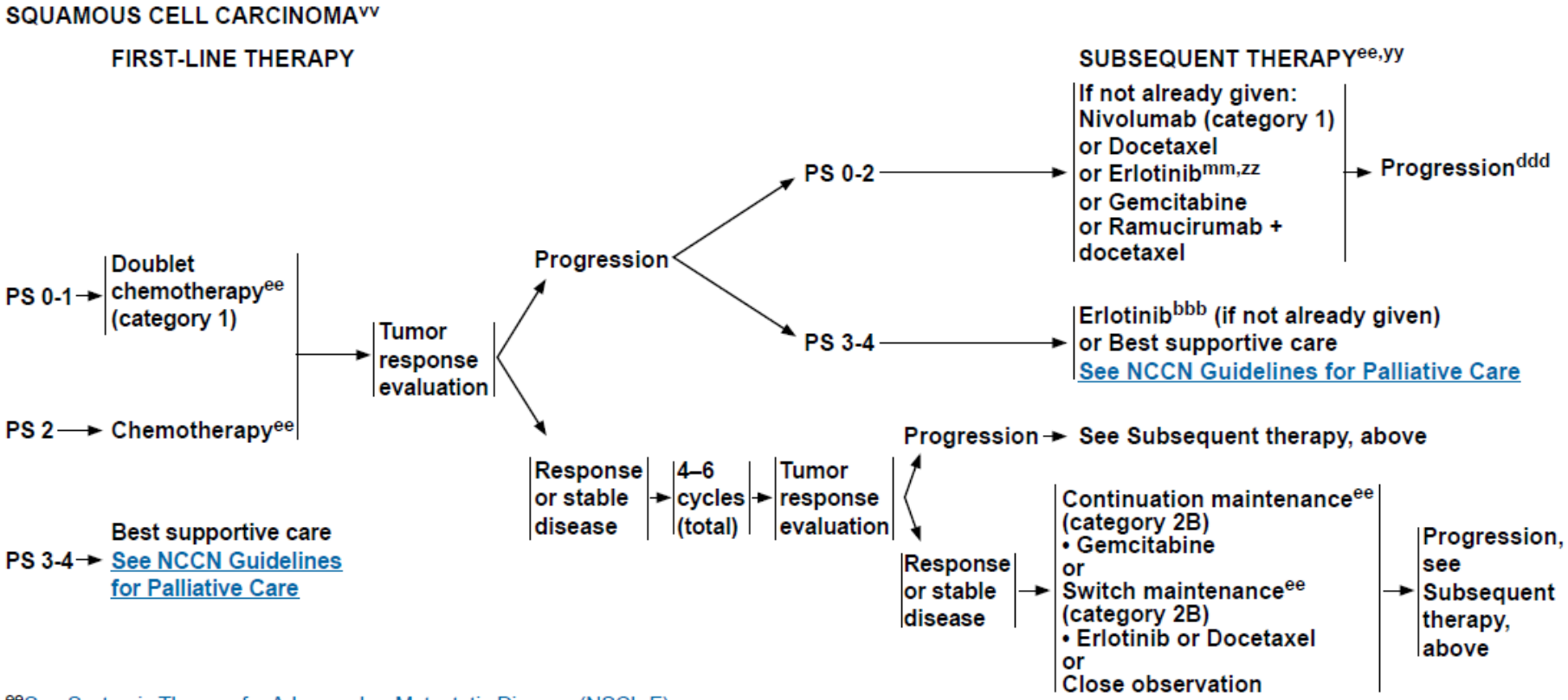
Abbildung 5: aus NCCN 2015 (Anmerkung FB Med: NSCL-17, -18, -19 verweisen wieder auf die Abbildungen 2 bis 4)



[ee] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[mm] In areas of the world where gefitinib is available, it may be used in place of erlotinib.
[vv] Consider additional mutational testing if only EGFR and ALK were performed. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).
[yy] Chemotherapy preferred in this setting. Grassino M, Martelli O, Broggini M, et al. Erlotinib versus docetaxel as second lin-line treatment of patients with advanced NSCLC and widl type EGFR tumors (TAILOR): a randomized trial. Lancet Oncol 2013; 14:981-988.
[zz] Recommend proteomic testing for patients with NSCLC and wild-type EGFR or with unknown EGFR status. A patient with a "poor" classification should not be offered erlotinib in the second-line setting. Gregorc V, Novello S, Lazzari C, et al. Predictive value of a proteomic signature in patients with non-small-cell lung cancer treated with second-line erlotinib or chemotherapy (PROSE): a biomarker stratified, randomised phase 3 trial. Lancet Oncol 2014; 15:713-21.
[bbb] Erlotinib may be considered for PS 3 and 4 patients with sensitizing EGFR mutations.
[ddd] If not already given, options for PS 0-2 include erlotinib, nivolumab, docetaxel (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include erlotinib or best supportive care. Options for further progression are best supportive care or clinical trial.

Abbildung 6: aus NCCN 2015 (Anmerkung FB Med: Seite NSCL-20 der Leitlinie)

Gemeinsamer Bundesausschuss

Table 1—*Strength of the Recommendations Grading System*

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

Abbildung 7: aus Socinski MA et al., 2013.

Table 1
Level of evidence and strength of recommendation.

Level of evidence		Strength of recommendation
Ia	Evidence from systematic reviews and meta-analysis of randomized controlled trials	A
Ib	Evidence from at least one randomized controlled trial	
IIa	Evidence from at least one controlled study without randomization	B
IIb	Evidence from at least one other type of quasi-experimental study	
III	Evidence from observational studies	
IV	Evidence from expert committee reports or experts	C

Abbildung 8: aus de Marinis F et al., 2011

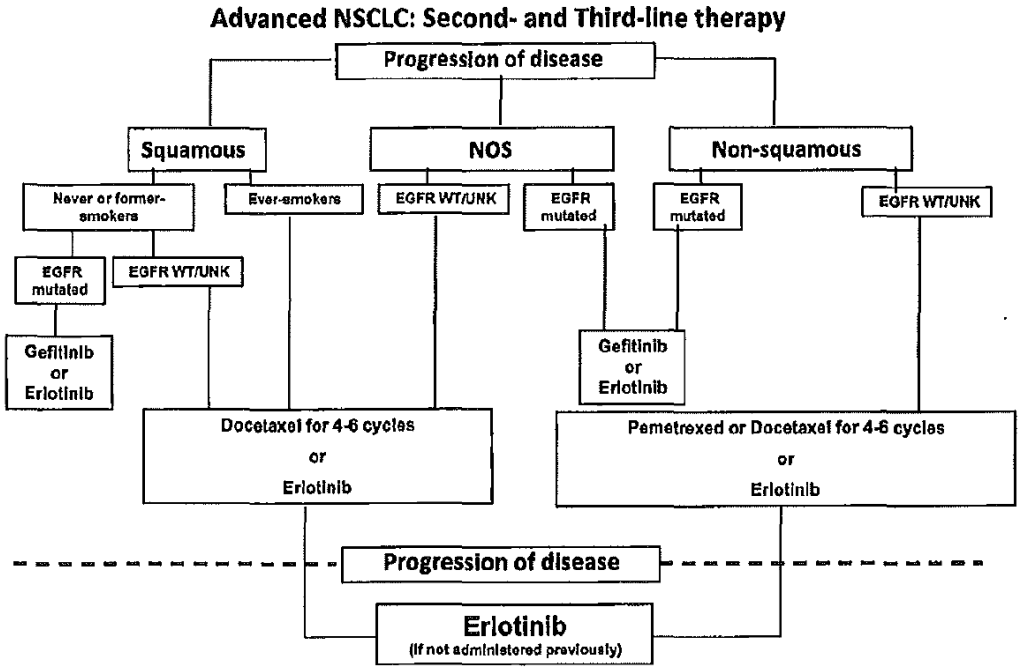


Fig. 3. Suggested algorithm for second- and third-line treatment of advanced non-small-cell lung cancer (NOS: not otherwise specified; EGFR: epidermal growth factor receptor; WT: wild type; and UNK: unknown).

Abbildung 9: aus de Marinis F et al., 2011.

Table 1. Summary of Recommendations

Recommendation	Summary
A. First-line chemotherapy	
A1	Evidence supports use of chemotherapy in patients with stage IV* NSCLC with ECOG/Zubrod performance status of 0, 1, possibly 2
A2	In patients with performance status of 0 or 1, evidence supports using combination of two cytotoxic drugs for first-line therapy; platinum combinations are preferred over nonplatinum combinations because they are superior in response rate and marginally superior in OS; nonplatinum therapy combinations are reasonable in patients who have contraindications to platinum therapy; recommendations A8 and A9 address whether to add bevacizumab or cetuximab to first-line cytotoxic therapy
A3	Available data support use of single-agent chemotherapy in patients with performance status of 2; data are insufficient to make recommendation for or against using combination of two cytotoxic drugs in patients with performance status of 2
A4	Evidence does not support selection of specific first-line chemotherapy drug or combination based on age alone
A5	Choice of either cisplatin or carboplatin is acceptable; drugs that may be combined with platinum include third-generation cytotoxic drugs docetaxel, gemcitabine, irinotecan, paclitaxel, pemetrexed, and vinorelbine; evidence suggests cisplatin combinations result in higher response rates than carboplatin and may improve survival when combined with third-generation agents; carboplatin is less likely to cause nausea, nephrotoxicity, and neurotoxicity than cisplatin but more likely to cause thrombocytopenia
A6	In patients with stage IV NSCLC, first-line cytotoxic chemotherapy should be stopped at disease progression or after four cycles in patients whose disease is **stable but** not responding to treatment; two-drug cytotoxic combinations should be administered for no more than six cycles; **for patients with stable disease or response after four cycles, immediate treatment with alternative, single-agent chemotherapy such as pemetrexed in patients with nonsquamous histology, docetaxel in unselected patients, or erlotinib in unselected patients may be considered; limitations of this data are such that break from cytotoxic chemotherapy after fixed course is also acceptable, with initiation of second-line chemotherapy at disease progression**
A7	In unselected patients, erlotinib or gefitinib should not be used in combination with cytotoxic chemotherapy as first-line therapy; in unselected patients, evidence is insufficient to recommend single-agent erlotinib or gefitinib as first-line therapy; first-line use of gefitinib may be recommended for patients with activating *EGFR* mutations; if *EGFR* mutation status is negative or unknown, cytotoxic chemotherapy is preferred (see A2)
A8	On basis of results of one large phase III RCT, update committee recommends addition of bevacizumab (15 mg/kg every 3 weeks) to carboplatin/paclitaxel, except for patients with squamous cell carcinoma histologic type, brain metastases, clinically significant hemoptysis, inadequate organ function, ECOG performance status > 1, therapeutic anticoagulation, clinically significant cardiovascular disease, or medically uncontrolled hypertension; bevacizumab may be continued as tolerated until disease progression
A9	On basis of results of one large phase III RCT, clinicians may consider addition of cetuximab to cisplatin/vinorelbine in first-line therapy in patients with EGFR-positive tumor as measured by immunohistochemistry; cetuximab may be continued as tolerated until disease progression
B. Second-line chemotherapy	
B1	Docetaxel, erlotinib, gefitinib, or pemetrexed is acceptable as second-line therapy for patients with advanced NSCLC with adequate performance status when disease has progressed during or after first-line platinum-based therapy
B2	Evidence does not support selection of specific second-line chemotherapy drug or combination based on age alone
C. Third-line chemotherapy	
C1	When disease progresses on or after second-line chemotherapy, treatment with erlotinib may be recommended as third-line therapy for patients with performance status of 0 to 3 who have not received prior erlotinib or gefitinib
C2	Data are not sufficient to make recommendation for or against using cytotoxic drug as third-line therapy; these patients should consider experimental treatment, clinical trials, and best supportive care
D. Molecular analysis	
D1	Evidence is insufficient to recommend routine use of molecular markers† to select systemic treatment in patients with metastatic NSCLC
D2	To obtain tissue for more accurate histologic classification or investigational purposes, update committee supports reasonable efforts to obtain more tissue than that contained in routine cytology specimen

NOTE. Bold font indicates 2011 focused update changes.

Abbreviations: ASCO, American Society of Clinical Oncology; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NSCLC, non–small-cell lung cancer; OS, overall survival; RCT, randomized clinical trial; TKI, tyrosine kinase inhibitor.

*As defined by the International Association for the Study of Lung Cancer Staging Project, for the 7th edition of the TNM Classification of Malignant tumors.[10a]

†In April 2011, ASCO issued a Provisional Clinical Opinion regarding EGFR testing; it will be incorporated into future updates of NSCLC guideline: On the basis of the results of five phase III RCTs, patients with NSCLC who are being considered for first-line therapy with an EGFR TKI (patients who have not previously received chemotherapy or an EGFR TKI) should have their tumor tested for *EGFR* mutations to determine whether an EGFR TKI or chemotherapy is appropriate first-line therapy (http://www.asco.org/pco/egfr).

Abbildung 10: aus Azzoli CG et al., 2010.

Table 1 Trial and Patient Characteristics (Based on All Randomized Patients)

Trial	Accrual Period	Patient n	TKI	Control	Median Age (Range)	Sex (% Female)	PS (% 0/1)	Ethnicity	Smoking History (% Never)	Histology (% Adenocarcinoma)	Patients With Known EGFR Status (% of Total Randomized)	EGFR Mutation, n (% of Total With Known Status)	EGFR Wild Type, n (% of Total With Known Status)
Trials of Second-Line Treatment													
SIGN[26]	2003-2004	141	Gefitinib	Docetaxel	61 (29-85)	30	67	Western	25	Unknown	NR	NR	NR
V-15-32[27]	2003-2006	489 (387[a])	Gefitinib	Docetaxel	Unknown	38	96	Asian	32	78	57 (12)	31 (55)	26 (45)
Herbst et al[28]	2004-2005	79	Erlotinib	Docetaxel or pemetrexed with bevacizumab	65.5 (40-88)	49	100	Western	13	78	30 (38)	1 (3)	29 (97)
INTEREST[29]	2004-2006	1466 (1316[a])	Gefitinib	Docetaxel	60.5 (20-84)	35	88	Western	20	54	267 (18)	38 (14)	229 (86)
ISTANA[30]	2005-2006	161	Gefitinib	Docetaxel	57.5 (20-74)	38	93	Asian	41	68	NR	NR	NR
Li et al[36]	2006-2008	98	Gefitinib	Docetaxel	Unknown	Unknown	Unknown	Asian	Unknown	Unknown	NR	NR	NR
TITAN[31]	2006-2010	424	Erlotinib	Docetaxel or pemetrexed	59 (22-79)	24	80	Western	17	50	160 (38)	11 (7)	149 (93)
HORG[32]	2006-2010	332	Erlotinib	Pemetrexed	65.5 (37-86)	18	85	Western	16	77 (non-sq)	NR	NR	NR
CTONG 0806[9,b]	2009-2012	157	Gefitinib	Pemetrexed	56.5 (24-78)	36	100	Asian	49	96	157 (100)	Only WT patients	157 (100)
TAILOR[9,b]	2007-2012	219	Erlotinib	Docetaxel	66.5 (35-83)	31	91	Western	22	68 (greater % in TKI arm)	219 (100)	Only WT patients	219 (100)
KCSG-LU08-01[33]	2008-2010	135	Gefitinib	Pemetrexed	61 (30-78) (younger in TKI arm)	85	91	Western	100	100	71 (53)	33 (46)	38 (54)
PROSE[34]	2008-2012	263	Erlotinib	Docetaxel or pemetrexed	65 (33-85)	27	94	Western	14	88 (non-sq)	177 (67)	14 (8)	163 (92)
DELTA[35]	2009-2012	301	Erlotinib	Docetaxel	67.5 (31-85)	29	96	Asian	25	69	255	51 (20)	199 (78)
Li et al[37,b]	2008-2014	123	Erlotinib	Pemetrexed	54.5 (30-75)	36	94	Asian	26	100	123 (100)	Only WT patients	123 (100)
Total		4388 (4136)									1516 (35)	179 (12)	1332 (88)
Trials of Maintenance Treatment													
SATURN[38]	2005-2008	889	Erlotinib	Placebo	60 (30-83)	26	100%	Western	17	45	368 (41)	40 (11)	328 (89)
IFCT-GFPC 0502 (NCT00300586)[39]	2006-2009	310[c]	Erlotinib	Observation	58 (36-72)	27	100%	Western	9	65	114 (37)	8 (7)	106 (93)
EORTC 08021[40]	2004-2009	173	Gefitinib	Placebo	61 (28-80)	23	94%	Western	22	51	NR	NR	NR

Abbildung 11: Studiencharakteristika nach Vale CL, et al. 2015

Table 1 Continued

Trial	Accrual Period	Patient n	TKI	Control	Median Age (Range)	Sex (% Female)	PS (% 0/1)	Ethnicity	Smoking History (% Never)	Histology (% Adenocarcinoma)	Patients With Known EGFR Status (% of Total Randomized)	EGFR Mutation, n (% of Total With Known Status)	EGFR Wild Type, n (% of Total With Known Status)
INFORM[41]	2008-2009	296	Gefitinib	Placebo	55 (20-75)	41	98%	Asian	54	71	79 (27)	30 (38)	49 (62)
SWOG S0023[42]	2001-2005	261	Gefitinib	Placebo	61 (24-81)	37	96%	Western	Unknown	31	NR	NR	NR
ATLAS[43,d]	2005-2008	768	Erlotinib	Placebo	64 (range unknown)	48	100%	Western	16	81	347 (45)[e]	52 (15)	295 (85)
Total		2697									908 (34)	130 (14)	778 (86)

Abbreviations: ATLAS = Avastin Tarceva Lung Adenocarcinoma Study; CTONG = Chinese Thoracic Oncology Group; DELTA = Docetaxel and Erlotinib Lung Cancer Trial; EGFR = epidermal growth factor receptor; EORTC = European Organisation for Research and Treatment of Cancer; HORG = Hellenic Oncology Research Group; IFCT-GFPC = Partenariat Intergroupe Francophone de Cancérologie Thoracique-Groupe Français de Pneumo-Cancérologie; INFORM = Iressa in NSCLC FOR Maintenance; INTEREST = IRESSA Non-small-cell lung cancer Trial Evaluating REsponse and Survival against Taxotere; ISTANA = Iressa as Second-line Therapy in Advanced NSCLC; KCSG = Korean Cancer Study Group; non-sq = Non-Squamous; PROSE = Predicting Response to Second-Line Therapy Using Erlotinib; PS = performance status; SATURN = Sequential Tarceva in Unresectable NSCLC; SIGN = Second-line Indication of Gefitinib in NSCLC; SWOG = South West Oncology Group; TAILOR = Tarceva Italian Lung Optimization Trial; TITAN = Tarceva In Treatment of Advanced NSCLC; TKI = tyrosine kinase inhibitor; WT = wild type.

[a]Progression-free survival analyses for patient number in parentheses, but patient characteristics reported for all patients.

[b]Only randomized patients with wild type EGFR.

[c]Three-arm trial including 464 randomized patients but only 2 arms included here.

[d]Includes bevacizumab in both arms.

[e]Total for progression-free survival, total for overall survival is 345.

Abbildung 12: Studiencharakteristika nach Vale CL, et al. 2015