Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2015-B-188 Osimertinib

Stand: Januar 2016

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Osimertinib **zur Behandlung des lokal fortgeschrittenen oder metastasierten, nicht-kleinzelligem Lungenkarzinom (NSCLC) mit T790M-Mutation des EGFR**	
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	• Afatinib: Beschluss vom 5. November 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 • Crizotinib: Beschluss vom 2. Mai 2013 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 • Nivolumab (nicht-kleinzelliges Lungenkarzinom): Beschluss vom 4. Februar 2016 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Carboplatin: Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie - Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten - (Stand: 30. Juni 2014): 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
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:	
Osimertinib L01XE35 TAGRISSO™	Osimertinib ist angezeigt zur Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Lungenkarzinom (NSCLC) und einer positiven T790M-Mutation des epidermalen Wachstumsfaktor-Rezeptors (Epidermal Growth Factor Receptor, EGFR).
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.
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.
Etoposid L01CB01 (generisch)	Kombinationstherapie folgender Malignome: Palliative Therapie des fortgeschrittenen NSCLC bei Patienten mit gutem Allgemeinzustand (Karnofsky-Index >80%).
Gemcitabin L01BC05 (generisch)	Gemcitabin ist in Kombination mit Cisplatin als Erstlinientherapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nichtkleinzelligen Bronchialkarzinom (NSCLC) angezeigt. Eine Gemcitabin-Monotherapie kann bei älteren Patienten oder solchen mit einem Performance Status 2 in Betracht gezogen werden.
Ifosfamid L01AA06 Holoxan®	Nicht-kleinzellige Bronchialkarzinome: Zur Einzel- oder Kombinationschemotherapie von Patienten mit inoperablen oder metastasierten Tumoren.
Mitomycin L01DC03 (generisch)	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Bei intravenöser Gabe ist es in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei folgenden metastasierenden Tumoren wirksam: […] nicht-kleinzelliges Bronchialkarzinom […].
Paclitaxel 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 L01CD01 Abraxane®	Abraxane ist in Kombination mit Carboplatin indiziert für die Erstlinienbehandlung des nicht-kleinzelligen Bronchialkarzinoms bei erwachsenen Patienten, bei denen keine potentiell kurative Operation und/oder Strahlentherapie möglich ist.
Pemetrexed L01BA04 Alimta®	ALIMTA ist in Kombination mit Cisplatin angezeigt zur first-line Therapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie. ALIMTA in Monotherapie ist angezeigt für die Erhaltungstherapie bei lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie bei Patienten, deren Erkrankung nach einer platinbasierten Chemotherapie nicht unmittelbar fortgeschritten ist. ALIMTA in Monotherapie ist angezeigt zur Behandlung in Zweitlinientherapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie.
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).
Proteinkinase-Inhibitoren:	
Afatinib L01XE13 Giotrif®	Giotrif® als Monotherapie wird angewendet zur Behandlung von EGFR-TKI-naiven erwachsenen Patienten mit lokal fortgeschrittenem und/oder metastasiertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit aktivierenden EGFR-Mutationen.
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.
Crizotinib L01XE16 Xalkori®	XALKORI wird angewendet bei Erwachsenen zur Erstlinienbehandlung des Anaplastische-Lymphom-Kinase(ALK)-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, NSCLC). XALKORI wird angewendet bei Erwachsenen zur Behandlung des vorbehandelten Anaplastische-Lymphom-Kinase(ALK)-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, NSCLC).
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 als Monotherapie zur Erhaltungsbehandlung bei Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC angezeigt, deren Krankheitszustand nach 4 Behandlungszyklen einer platinbasierten First-Line-Standardchemotherapie unverändert ist. 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 (siehe Abschnitt 5.1).
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. (FI Iressa®, 04-2014)
Nintedanib L01XE31 Vargatef®	Vargatef wird angewendet in Kombination mit Docetaxel zur Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem, metastasiertem oder lokal rezidiviertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit Adenokarzinom-Histologie nach Erstlinienchemotherapie.
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. (FI Avastin®, 07-2014)
Nivolumab L01XC17 Opdivo®	OPDIVO ist zur Behandlung des lokal fortgeschrittenen oder metastasierten nichtkleinzelligen Lungenkarzinoms (NSCLC) mit plattenepithelialer Histologie nach vorheriger Chemotherapie bei Erwachsenen indiziert.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2015-B-188 Osimertinib

Datum: 26.01.2016

Recherche und Synopse der Evidenz zur Bestimmung der zVT:

Indikation für die Recherche:

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

Berücksichtigte Wirkstoffe/Therapien:

Für das Anwendungsgebiet zugelassenen Arzneimittel siehe Tabelle „II. Zugelassene Arzneimittel im Anwendungsgebiet“

- Es wurden nur Publikationen eingeschlossen, die eine Aussage zu Patienten mit EGFR M+ Status beinhalten.

- Systematische Reviews wurden nur dann berücksichtigt, wenn die Ergebnisse mindestens einer quantitativen Subgruppenanalyse für EGFR M+ Patienten dargelegt sind.
- Es wurden – abweichend vom üblichen Vorgehen – besonders aktuelle Systematische Reviews (Publikationsjahr 2015 und 2014) auch dann aufgenommen, wennn in ihnen keine Qualitätsbewertung der Primärstudien ausgewiesen ist. Dies jeweils verwemerkt.
- 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 Protonentherapie 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).

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation **„**Nichtkleinzelligen Lungenkarzinom (NSCLC)“ durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 05.01.2016 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, DAHTA, G-BA, GIN, IQWiG, NGC, TRIP, WHO. Aufgrund der onkologischen Indikation wurde zusätzlich in folgenden Datenbanken bzw. Internetseiten folgende Organisationen gesucht: CCO, DGHO, ESMO, NCCN, NCI. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien (z.B. NICE, SIGN). Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab **731** 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 **41** Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

ACCP	American College of Chest Physicians
ADK	adenocarcinoma
AE	Unerwünschte Ereignisse (adverse events)
Afl	aflibercept
AIOT	Italian Associatlon of Thoracic Oncology
ALK	Anaplastic Lymphoma Kinase
AM	Arzneimittel
ANITA	Adjuvant Navelbine International Trialist Association
AP	pemetrexed + cisplatin
ASCI	Antigen Specific Cancer Immunotherapeutic
ASCO	American Society of Clinical Oncology
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
Bev	Bevacizumab
BSC	Best supportive care
CARB	Carboplatin
CBDCA	carboplatin
CCT	controlled clinical trial
CDDP	cisplatin
CECOG	Central European Cooperative Oncology Group
Cet	cetuximab
CG	clinical gudeline
CI	Konfidenzintervall
CIS	Cisplatin
CR	Complete response
CT	Chemotherapie
CTX	Chemoradiation
DAHTA	Deutsche Agentur für Health Technology Assessment
DART	Documentation and Appraisal Review Tool
DCR	disease control rate
DGHO-Onkopedia	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie
DGP	Gesellschaft für Pneumologie und Beatmungsmedizin
DKG	Deutsche Kresgesellschaft
DC	Docetaxel
DOC	Docetaxel
DP	docetaxel + cisplatin
DSG	Disease Site Group
fNECOG	Eastern cooperative oncology group
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
EGFR M+	EGFR-positiv (Vorliegen einer Mutatation)
Enz	enzastaurin
Erl / ERL	erlotinib
ESMO	European Society for Medical Oncology
FACT-L	Functional assessment of cancer-lung (questionnaire)
FEM	Fixed effects model
Gan	ganetespib
G-BA	Gemeinsamer Bundesausschuss
GEF/GFT	Gefintinib
GEM	Gemcitabin
GIN	Guidelines International Network

GN	gemcitabine + vinorelbine
GoR	Grade of Recommendation
GP	gemcitabine + cisplatin
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard ratio
HRQoL	Gesundheitsbezogene Lebensqualität (health related quality of life)
HSP	heat shock protein
ILD	interstitial lung disease
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
k.A.	keine Angabe
KPS	Karnofsky Performance Status scale
KRAS	Kirsten rat sarcoma viral oncogene homolog
LACE	Lung Adjuvant Cisplatinum Evaluation
LoE	Level of Evidence
Mat	matuzumab
mut	Mutation
M+	mutation positive (EGFR)
n	number
N.A	not available
NCCN	National Comprehensive Cancer Network
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NIHR HSC	National Institute for Health Research Horizon Scanning Centre
Nin	nintedanib
NNT	Number needed to treat
NP	vinorelbine + cisplatin
NR	not reported
NSCLC	non-small cell lung cancer (nichtkleinzelliges Bronchialkarzinom)
OR	Odds ratio
ORR	Gesamtansprechen (overall response)
OS	Gesamtüberleben (Overall survival)
PAX	Paclitaxel
PBC	platinum-based doublet chemotherapy
PD	Progressive disease
PD-L1	Programmed death-ligand 1
PDGFR	platelet-derived growth factor receptor
PEM	Pemetrexed
Pem	pemetrexed
PFS	Progressionsfreies Überleben (progression free survival)
PKB	protein kinase B
PKC	protein kinase C
Pla	placebo
PLAT	Platinhaltige Chemotherapeutika
PORT	Post-operative Radiotherapie
PR	Partial response
PS	Performance status
PSA	probabilistic sensitivity analysis
Pts.	patients
QOL	Quality of life
QoL	Lebensqualität (quality of life)
QUADAS	Quality assessment tool for diagnostic studies
RCT	Randomized controlled trial
Ref.	reference
REM	Random effects model
RET	rearranged during transfection
RR	Risk ratio

RR	Relatives Risiko
RT	Radiotherapie
SACT	systemic anticancer therapy
SD	Stable disease; oder: standard deviation
Sel	selumetinib
SR	Systematisches Review
TA	Technology Assessment
TAX	Docetaxel
TC	paclitaxel + carboplatin
TKI	Tyrosinkinsaseinhibitor
TNM	Tumor-Node-Metastasis (Klassifikationssystem)
TOI	Trial outcome index
TRIP	Turn Research into Practice Database
TTP	Time to Progression
UFT	Tegafur/Uracil
UICC	Union for International Cancer Control
Van	vandetanib
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VNB	Vinorelbin
vs.	versus
w	weeks
WJTOG	Western Japan Thoracic Oncology Group
WHO	World Health Organisation
WT	Wild type

IQWiG Berichte/G-BA Beschlüsse

G-BA, 2015 [14]. 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 Vom 5.11.2015	**1. Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie** 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 Kom-bination 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. <u>2) Nicht vorbehandelte Patienten mit ECOG-Performance-Status 2</u> **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. <u>3) Patienten nach Vorbehandlung mit einer Platin-basierten Chemotherapie</u> **Zweckmäßige Vergleichstherapie:** − Gefitinib oder Erlotinib *oder*

<table>
<tr><td></td><td>− Docetaxel oder Pemetrexed

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:
Ein Zusatznutzen ist nicht belegt.</td></tr>
<tr><td>IQWiG, 2015 [17].

Afatinib –

Nutzenbewertung gemäß § 35a SGB V

IQWiG-Berichte Nr. 206</td><td>Patientengruppen, zweckmäßige Vergleichstherapien und Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Afatinib für TKI-naive erwachsene Patienten mit lokal fortgeschrittenem und / oder metastasiertem nichtkleinzelligem Lungenkarzinom mit aktivierenden EGFR-Mutationen

<table>
<tr><th>Therapielinie</th><th>Patientengruppe</th><th>Zweckmäßige Vergleichstherapie[a]</th><th>Subgruppe</th><th>Ausmaß und Wahrscheinlichkeit des Zusatznutzens</th></tr>
<tr><td rowspan="4">nicht vorbehandelte Patienten</td><td rowspan="3">ECOG-PS 0-1</td><td rowspan="3">Gefitinib oder Erlotinib
oder
Cisplatin + (Vinorelbin, Gemcitabin, Docetaxel, Paclitaxel oder Pemetrexed)</td><td>EGFR-Mutation Del19</td><td>Hinweis auf erheblichen Zusatznutzen</td></tr>
<tr><td>EGFR-Mutation L858R,
Alter < 65
Alter ≥ 65</td><td>Anhaltspunkt für geringen Zusatznutzen
Zusatznutzen nicht belegt</td></tr>
<tr><td>andere[b] EGFR-Mutationen</td><td>Hinweis auf geringeren Nutzen</td></tr>
<tr><td>ECOG-PS 2</td><td>Gefitinib oder Erlotinib
oder
Gemcitabin</td><td colspan="2">Zusatznutzen nicht belegt</td></tr>
<tr><td colspan="2">mit einer oder mehreren Chemotherapie(n) vorbehandelte Patienten</td><td>Erlotinib oder Gefitinib</td><td colspan="2">Zusatznutzen nicht belegt</td></tr>
<tr><td colspan="5">a: Dargestellt ist jeweils die vom G-BA festgelegte zweckmäßige Vergleichstherapie. In den Fällen, in denen der pU aufgrund der Festlegung der zweckmäßigen Vergleichstherapie durch den G-BA aus mehreren Alternativen eine Vergleichstherapie auswählen kann, ist die entsprechende Auswahl des pU fett markiert.
b: nicht L858R, nicht Del19-Mutation
ECOG-PS: Eastern Cooperative Oncology Group Performance Status</td></tr>
</table>

Für Patienten mit Del19-Mutation gibt es einen Hinweis auf einen erheblichen Zusatznutzen für den Endpunkt Gesamtüberleben; eine Altersabhängigkeit wurde nicht gezeigt. Hin-sichtlich der Symptomatik und der gesundheitsbezogenen Lebensqualität zeigen sich für diese Subgruppe mehrheitlich Anhaltspunkte für positive Effekte von Afatinib. Diese sind teilweise altersabhängig. Negative Effekte von Afatinib treten nur vereinzelt auf. In der Zusammen-schau der Effekte ergibt sich für die Subgruppe der Patienten mit einer Del19-Mutation ein Hinweis auf einen erheblichen Zusatznutzen von Afatinib gegenüber Cisplatin + Pemetrexed.

In der Subgruppe der Patienten mit L858R-Mutation finden sich hinsichtlich der Sympto-matik und gesundheitsbezogenen Lebensqualität Anhaltspunkte für positive und negative Effekte von Afatinib, wobei positive Effekte überwiegen. Diese Effekte sind teilweise alters-abhängig. In der Gesamtschau ergibt sich für Patienten < 65 Jahren ein Anhaltspunkt für einen geringen Zusatznutzen von Afatinib. Für Patienten ≥ 65 Jahren gibt es keinen Beleg für einen Zusatznutzen.</td></tr>
</table>

	Für Patienten mit anderen EGFR-Mutationen als Del19 oder L858R gibt es einen Hinweis auf einen geringeren Nutzen von Afatinib für den Endpunkt Gesamtüberleben. Dieser Effekt ist nicht altersabhängig. Hinsichtlich der Symptomatik und der gesundheitsbezogenen Lebens-qualität zeigen sich Anhaltspunkte für positive und negative Effekte von Afatinib. Diese sind teilweise altersabhängig, ohne eindeutige Vorteile von Afatinib gegenüber der zweckmäßigen Vergleichstherapie zu zeigen. Die altersabhängigen Effekte beeinflussen in diesem Fall die Gesamtaussage nicht wesentlich, und führen somit nicht zu einer unterschiedlichen Ein-schätzung des Zusatznutzens für die betrachteten Altersgruppen. Insgesamt ergibt sich für die Subgruppe der Patienten mit anderen EGFR-Mutationen als Del19 oder L828R ein Hinweis auf einen geringeren Nutzen von Afatinib gegenüber Cisplatin in Kombination mit Pemetrexed.

Cochrane Reviews

a) TKI-nicht-vorbehandelte Patienten

Es wurden keine Cochrane-Reviews gefunden.

b) TKI-vorbehandelte Patienten

Es wurden keine Cochrane-Reviews gefunden.

Systematische Reviews

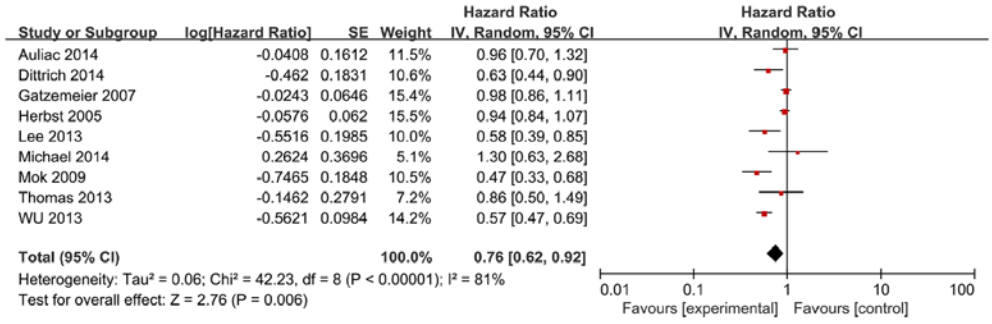
a) TKI-nicht-vorbehandelte Patienten

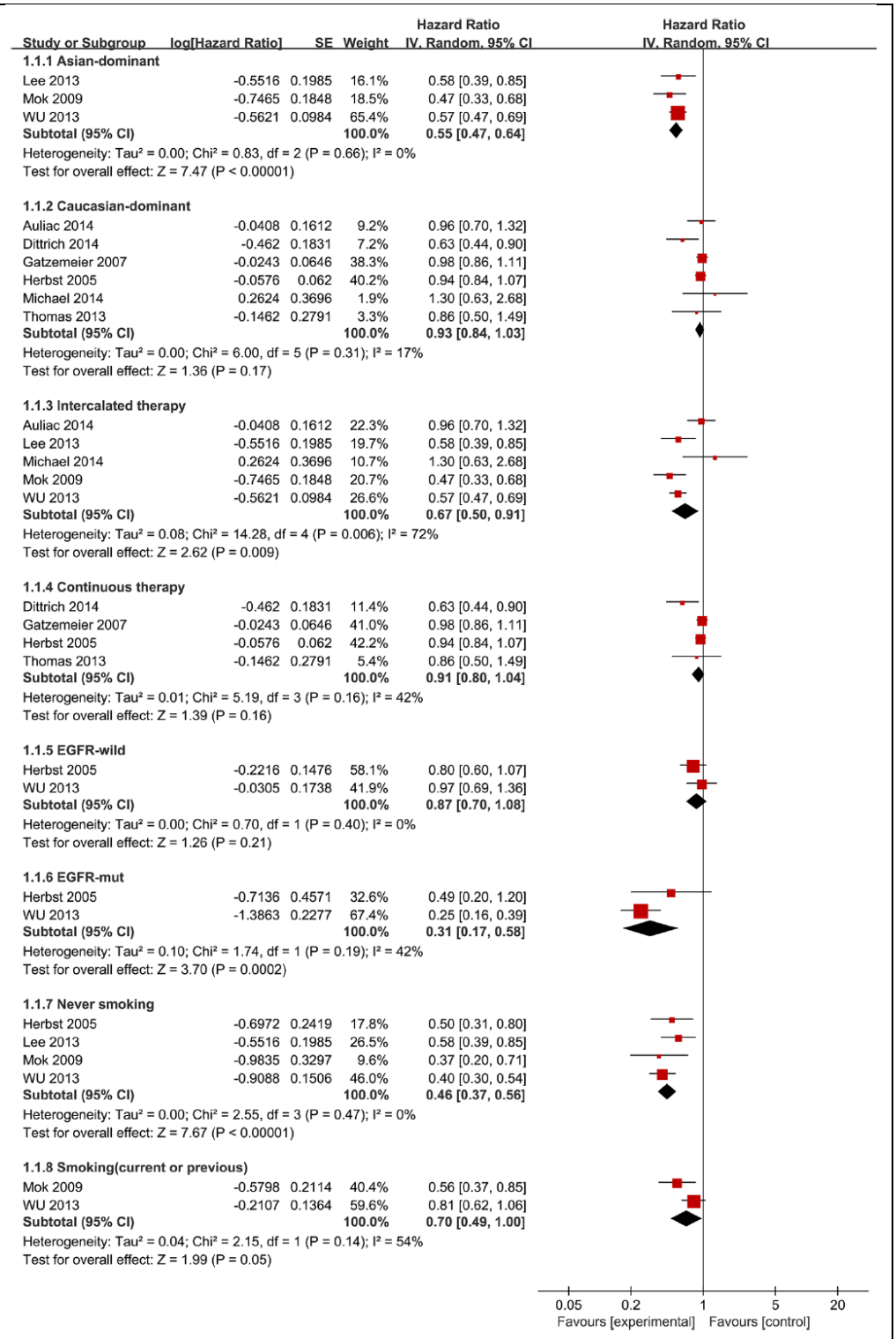
Xu JG et al., 2015 [39]. Chemotherapy plus Erlotinib versus Chemotherapy Alone for Treating Advanced Non-Small Cell Lung Cancer: A Meta-Analysis	**1. Fragestellung** Whether a combination of chemotherapy and erlotinib is beneficial for advanced non-small cell lung cancer (NSCLC) remains controversial. 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:** advanced NSCLC, **Intervention:** erlotinib plus standard chemotherapy **Komparator:** standard chemotherapy alone **Endpunkte:** PFS, OS, AE **Suchzeitraum:** bis 10/2014 **Anzahl eingeschlossene Studien/Ptienten (Gesamt):** 9 (3599) **Qualitätsbewertung der Studien:** Cochrane Handbook for Systematic Reviews of Interventions **Heterogenitätsuntersuchungen:** **3. Ergebnisdarstellung** 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; and one trial missed three patients who were still in treatment. 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 .

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

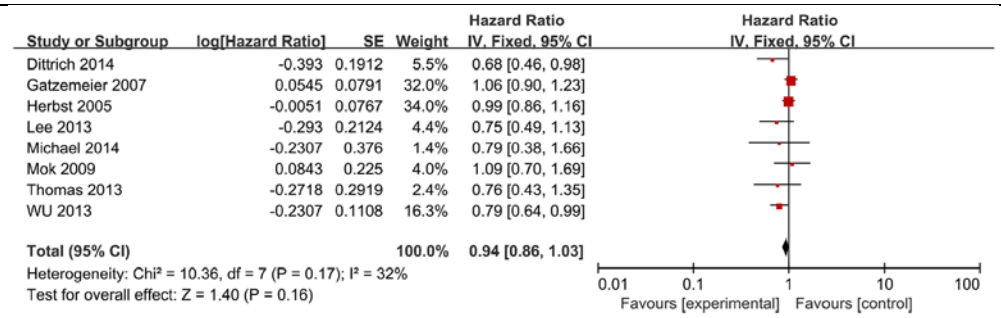
Study	Number of points	Dominant ethnicity	Female	Age (range)	Drug delivery	Treatment comparison	Non-smoker	EGFR-mutant	EGFR-wild-type
Herbst, 2005	1079	Caucasian/934	424	24–84	Continuous	E+Carb+Pac vs. Carb+Pac +Placebo	116	29	198
Gatzemeier, 2007	1159	Caucasian/1064	267	26–84	Continuous	E+Gem+Cisp vs. 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

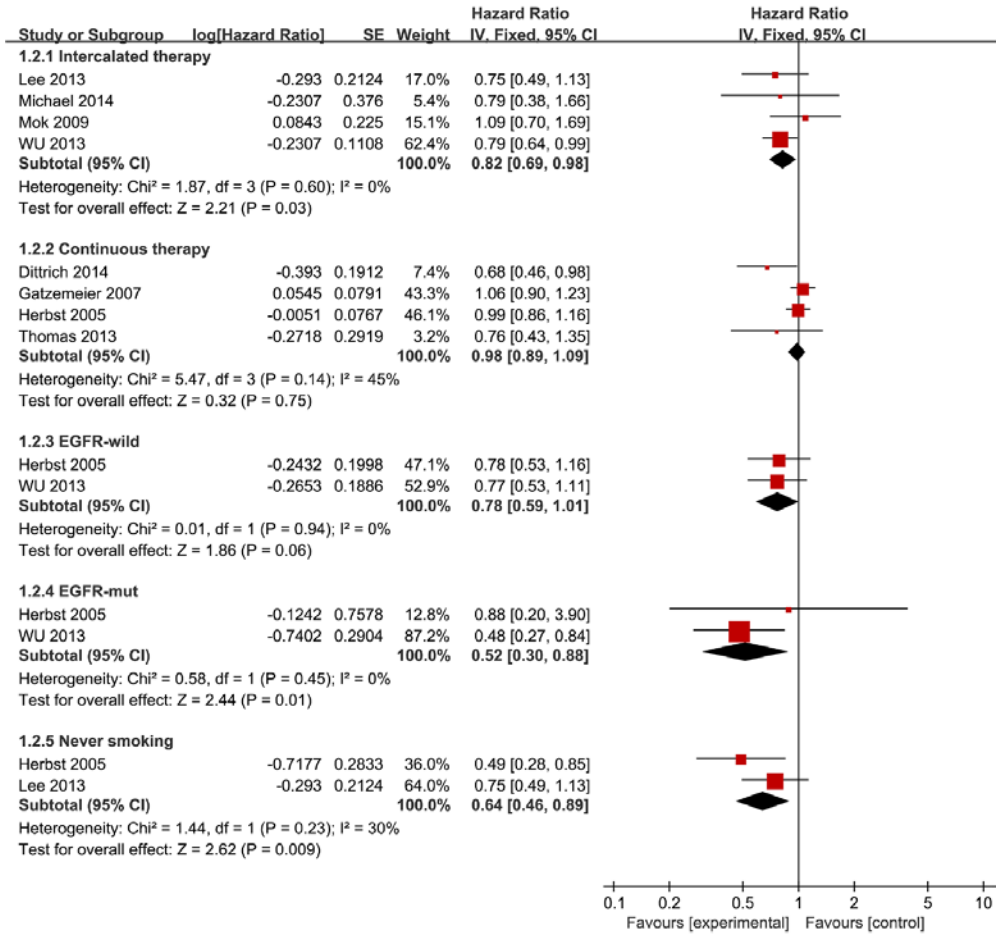
PFS




Study or Subgroup log[Hazard Ratio] SE Weight Hazard Ratio IV, Random, 95% CI
Hazard Ratio IV, Random, 95% CI
1.1.1 Asian-dominant
Lee 2013 -0.5516 0.1985 16.1% 0.58 [0.39, 0.85]
Mok 2009 -0.7465 0.1848 18.5% 0.47 [0.33, 0.68]
WU 2013 -0.5621 0.0984 65.4% 0.57 [0.47, 0.69]
Subtotal (95% CI) 100.0% 0.55 [0.47, 0.64]
Heterogeneity: Tau² = 0.00; Chi² = 0.83, df = 2 (P = 0.66); I² = 0%
Test for overall effect: Z = 7.47 (P < 0.00001)
1.1.2 Caucasian-dominant
Auliac 2014 -0.0408 0.1612 9.2% 0.96 [0.70, 1.32]
Dittrich 2014 -0.462 0.1831 7.2% 0.63 [0.44, 0.90]
Gatzemeier 2007 -0.0243 0.0646 38.3% 0.98 [0.86, 1.11]
Herbst 2005 -0.0576 0.062 40.2% 0.94 [0.84, 1.07]
Michael 2014 0.2624 0.3696 1.9% 1.30 [0.63, 2.68]
Thomas 2013 -0.1462 0.2791 3.3% 0.86 [0.50, 1.49]
Subtotal (95% CI) 100.0% 0.93 [0.84, 1.03]
Heterogeneity: Tau² = 0.00; Chi² = 6.00, df = 5 (P = 0.31); I² = 17%
Test for overall effect: Z = 1.36 (P = 0.17)
1.1.3 Intercalated therapy
Auliac 2014 -0.0408 0.1612 22.3% 0.96 [0.70, 1.32]
Lee 2013 -0.5516 0.1985 19.7% 0.58 [0.39, 0.85]
Michael 2014 0.2624 0.3696 10.7% 1.30 [0.63, 2.68]
Mok 2009 -0.7465 0.1848 20.7% 0.47 [0.33, 0.68]
WU 2013 -0.5621 0.0984 26.6% 0.57 [0.47, 0.69]
Subtotal (95% CI) 100.0% 0.67 [0.50, 0.91]
Heterogeneity: Tau² = 0.08; Chi² = 14.28, df = 4 (P = 0.006); I² = 72%
Test for overall effect: Z = 2.62 (P = 0.009)
1.1.4 Continuous therapy
Dittrich 2014 -0.462 0.1831 11.4% 0.63 [0.44, 0.90]
Gatzemeier 2007 -0.0243 0.0646 41.0% 0.98 [0.86, 1.11]
Herbst 2005 -0.0576 0.062 42.2% 0.94 [0.84, 1.07]
Thomas 2013 -0.1462 0.2791 5.4% 0.86 [0.50, 1.49]
Subtotal (95% CI) 100.0% 0.91 [0.80, 1.04]
Heterogeneity: Tau² = 0.01; Chi² = 5.19, df = 3 (P = 0.16); I² = 42%
Test for overall effect: Z = 1.39 (P = 0.16)
1.1.5 EGFR-wild
Herbst 2005 -0.2216 0.1476 58.1% 0.80 [0.60, 1.07]
WU 2013 -0.0305 0.1738 41.9% 0.97 [0.69, 1.36]
Subtotal (95% CI) 100.0% 0.87 [0.70, 1.08]
Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.26 (P = 0.21)
1.1.6 EGFR-mut
Herbst 2005 -0.7136 0.4571 32.6% 0.49 [0.20, 1.20]
WU 2013 -1.3863 0.2277 67.4% 0.25 [0.16, 0.39]
Subtotal (95% CI) 100.0% 0.31 [0.17, 0.58]
Heterogeneity: Tau² = 0.10; Chi² = 1.74, df = 1 (P = 0.19); I² = 42%
Test for overall effect: Z = 3.70 (P = 0.0002)
1.1.7 Never smoking
Herbst 2005 -0.6972 0.2419 17.8% 0.50 [0.31, 0.80]
Lee 2013 -0.5516 0.1985 26.5% 0.58 [0.39, 0.85]
Mok 2009 -0.9835 0.3297 9.6% 0.37 [0.20, 0.71]
WU 2013 -0.9088 0.1506 46.0% 0.40 [0.30, 0.54]
Subtotal (95% CI) 100.0% 0.46 [0.37, 0.56]
Heterogeneity: Tau² = 0.00; Chi² = 2.55, df = 3 (P = 0.47); I² = 0%
Test for overall effect: Z = 7.67 (P < 0.00001)
1.1.8 Smoking(current or previous)
Mok 2009 -0.5798 0.2114 40.4% 0.56 [0.37, 0.85]
WU 2013 -0.2107 0.1364 59.6% 0.81 [0.62, 1.06]
Subtotal (95% CI) 100.0% 0.70 [0.49, 1.00]
Heterogeneity: Tau² = 0.04; Chi² = 2.15, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 1.99 (P = 0.05)
0.05 0.2 1 5 20
Favours [experimental] Favours [control]

OS





AE

Keine Darstellung nach Mutationsstatus

4. Anmerkungen/Fazit der Autoren

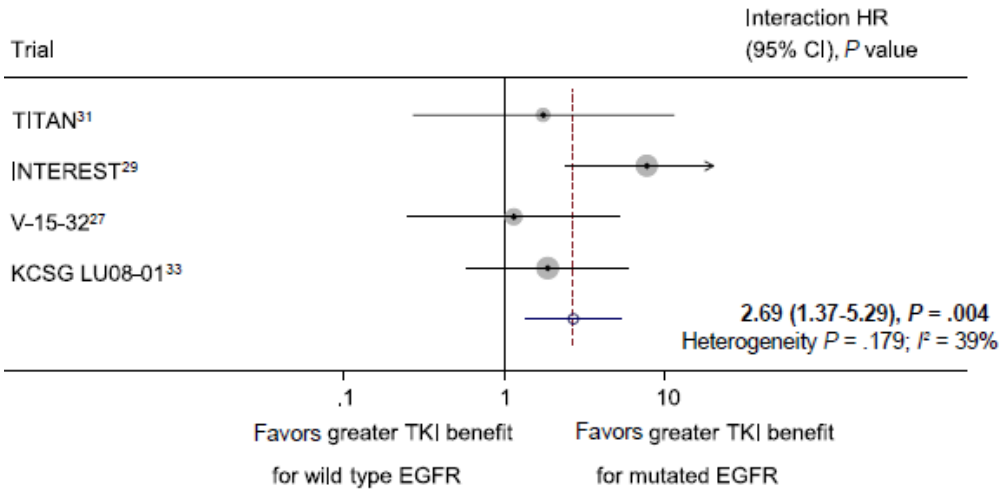
Combination of chemotherapy and erlotinib is a viable treatment option for patients with NSCLC, especially for patients who never smoked and patients with EGFR mutation-positive disease. In addition, intercalated administration is an effective combinatorial strategy.

Vale CL et al., 2015 [37]. Should	**1. Fragestellung** We assessed the effect of TKIs as second-line therapy and maintenance therapy after first-line chemotherapy in two systematic reviews and

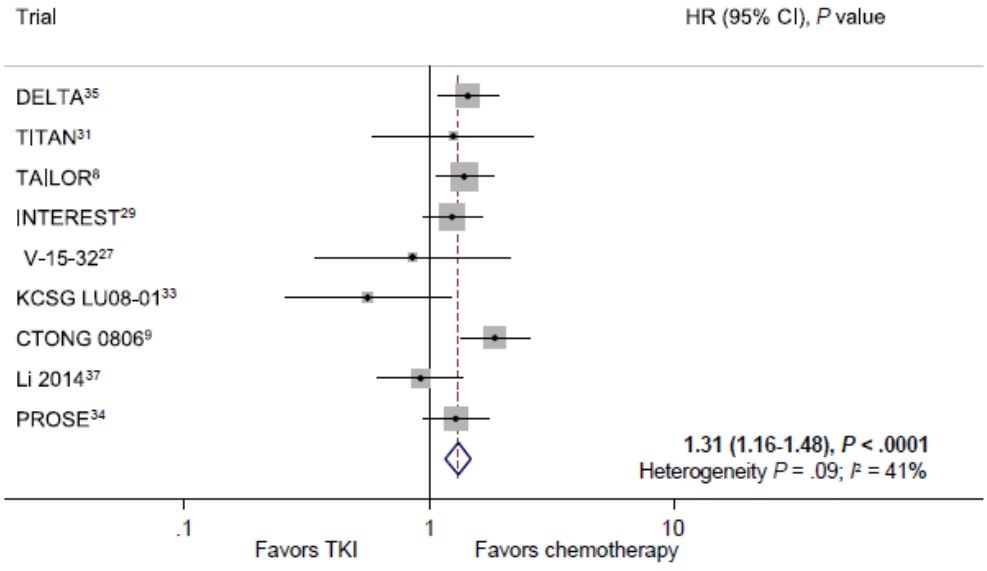
Tyrosine Kinase Inhibitors Be Considered for Advanced Non-Small-Cell Lung Cancer Patients With Wild Type EGFR? Two Systematic Reviews and Meta-Analyses of Randomized Trials	meta-analyses, focusing on patients without EGFR mutations.
	2. Methodik ***Population:*** advanced NSCLC irrespective of sex, age, 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

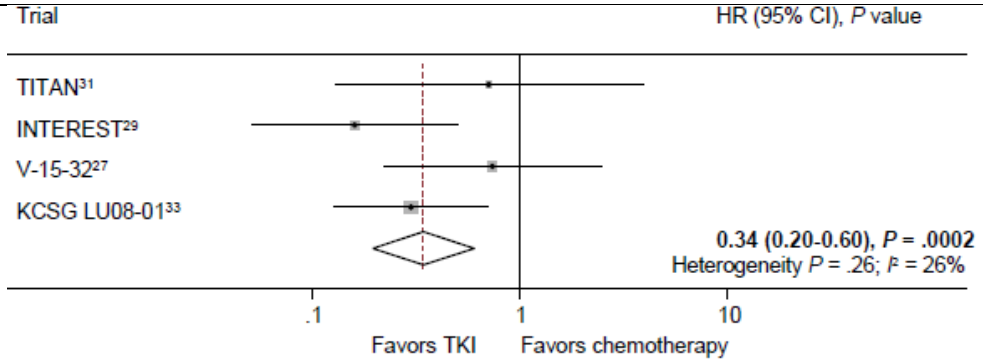
TKI vs. Chemotherapie



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).

Tan PS et al 2015 [36].

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

1. Fragestellung

Recent trials have suggested that maintenance treatments improve outcomes for patients not progressing after first-line therapy for advanced non-small-cell lung cancer (NSCLC). However, physicians have little guidance on selecting which patients benefit the most and what drug or regimen is optimal. Here, we report a systematic review and network meta-analysis of maintenance treatments in subgroups determined by performance status (PS), epidermal growth factor receptor (EGFR) mutation, histology and response to induction.

2. Methodik

Population: advanced NSCLC,
had at least 80% subjects with good PS: Eastern Cooperative Oncology Group (ECOG) PS 0-1, World Health Organisation (WHO) PS 0-1, or Karnofsky PS >80,
Intervention: nicht präspezifiziert
Komparator: nicht präspezifiziert
Maintenance treatment was defined as treatment administered to non-progressing patients after first-line induction chemotherapy
Endpunkte: OS, PFS, AE
Suchzeitraum: 12/2003- 10/2014
Anzahl eingeschlossene Studien/Patienten (Gesamt): 12 (3850)
Qualitätsbewertung der Studien: nicht erfolgt
Heterogenitätsuntersuchungen: I^2

3. Ergebnisdarstellung

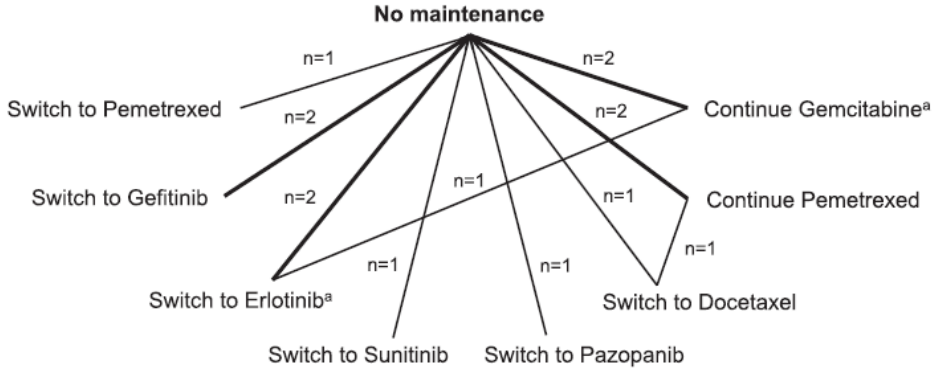
Characteristics of included studies comparing maintenance treatments in good performance status stage IIIb/IV NSCLC patients not progressing after first-line chemotherapy.[a]

Study	Population	Induction	Maintenance	*N*	Median follow-up (months)
Switch to pemetrexed versus no maintenance					
JMEN [8,39,40]	Treatment-naïve (systemic) stage IIIb/IV NSCLC with ECOG PS 0-1 not progressing after induction	Carboplatin or cisplatin/gemcitabine, paclitaxel, or docetaxel (4 cycles)	Switch to pemetrexed 500 mg/m^2 day 1 of 21-day cycles plus BSC	441	11.2
			Placebo plus BSC	222	10.1
Switch to gefitinib versus no maintenance					
INFORM; C-TONG 0804 [15,19]	Treatment-naïve stage IIIb/IV NSCLC with WHO PS 0-2 not progressing after induction	Platinum-doublet chemotherapy (4 cycles)	Switch to gefitinib 250 mg daily	148	17.8
			Placebo	148	
EORTC 08021/ILCP 01/03 [14]	Treatment-naïve stage IIIb/IV NSCLC with WHO PS 0-2 not progressing after induction	Platinum-containing chemotherapy (median 4 cycles, range 2–6 cycles)	Switch to gefitinib 250 mg daily	86	41
			Placebo	87	
Switch to erlotinib versus no maintenance					
SATURN [16,41,42]	Treatment-naïve recurrent or stage IIIb/IV NSCLC with ECOG PS 0-1 not progressing after induction	Platinum-doublet chemotherapy (4 cycles)	Switch to erlotinib 150 mg daily	438	11.4
			Placebo	451	11.5
IFCT-GFPC 0502 [17]	Treatment-naïve stage IIIb/IV NSCLC with ECOG PS 0-1 not progressing after induction	Cisplatin/gemcitabine (4 cycles)	Switch to erlotinib 150 mg daily	155	25.6
			Observation	155	
Switch to sunitinib versus no maintenance					
CALGB 30607 [43]	Treatment-naïve stage IIIb/IV NSCLC with ECOG PS 0-1 not progressing after induction	Platinum containing chemotherapy (4 cycles)	Switch to sunitinib 37.5 mg qd	106	–
			Placebo	104	–
Switch to pazopanib versus no maintenance					
EORTC 08092 [44]	Treatment-naïve advanced NSCLC with ECOG PS 0-2 not progressing after induction	Platinum containing chemotherapy (4–6 cycles)	Switch to pazopanib 800 mg daily	50	–
			Placebo	52	–
Switch to docetaxel versus no maintenance					
Fidias et al. [10,25]	Chemo-naive stage IIIb/IV NSCLC with ECOG PS 0-2 not progressing after induction	Carboplatin/gemcitabine (4 cycles)	Switch to immediate docetaxel 75 mg/m^2 day 1 every 21-day cycle (maximum 6 cycles)	153	–
			Delayed docetaxel 75 mg/m^2 day 1 every 21-day cycle (maximum 6 cycles) at progression	156	–

Study	Population	Induction	Maintenance	*N*	Median follow-up (months)
Switch to docetaxel versus continue pemetrexed					
Karayama et al. [45]	Chemo-naïve nonsquamous stage IIIb/IV NSCLC with ECOG PS 0-1 not progressing after induction	Carboplatin/pemetrexed (4 cycles)	Switch to docetaxel 60 mg/m^2 day 1 every 21-day cycle	25	16.8
			Continue pemetrexed 500 mg/m^2 day 1 every 21-day cycle	26	
Continue pemetrexed versus no maintenance					
PARAMOUNT [9,46,47]	Chemo-naïve nonsquamous stage IIIb/IV NSCLC with ECOG PS 0-1 not progressing after induction[b]	Cisplatin/pemetrexed (4 cycles)	Continue pemetrexed 500 mg/m2 day 1 every 21-day cycle plus BSC	359	12.5
			Placebo plus BSC	180	
Mubarak et al. [48]	Treatment-naïve (systemic) nonsquamous stage IIIb/IV NSCLC with ECOG PS 0-1 not progressing after induction	Cisplatin/pemetrexed (4 cycles)	Continue pemetrexed 500 mg/m^2 every 21 days plus BSC	28	–
			BSC	27	
Continue gemcitabine versus no maintenance					
IFCT-GFPC 0502 [17]	Treatment-naïve stage IIIb/IV NSCLC with ECOG PS 0-1 not progressing after induction[f]	Cisplatin/gemcitabine (4 cycles)	Continue gemcitabine 1250 mg/m^2 days 1 and 8 every 21-days cycle	154	25.6
			Observation	155	
Brodowicz et al. [18]	Chemo-naïve stage IIIb/IV NSCLC with Karnofsky PS >80 not progressing after induction[e]	Cisplatin/gemcitabine (4 cycles)	Continue gemcitabine 1250 mg/m^2 days 1 and 8 every 21-days cycle plus BSC	66	20.5
			BSC	33	17
Pemetrexed/bevacizumab versus bevacizumab alone					
AVAPERL [35,36]	Treatment-naïve nonsquamous recurrent or stage IIIb/IV NSCLC with ECOG PS 0-1	Cisplatin/pemetrexed/bevacizumab 7.5 mg/kg (4 cycles)	Bevacizumab 7.5 mg/kg/pemetrexed 500 mg/m^2 on day 1 of 21-days cycle	128	14.8
			Bevacizumab 7.5 mg/kg on day 1 of 21-days cycle	125	
Erlotinib/bevacizumab versus bevacizumab alone					
ATLAS [37,38]	Treatment-naïve recurrent or stage IIIb/IV NSCLC with ECOG PS 0-2	Chemotherapy/bevacizumab 15 mg/kg (4 cycles)	Bevacizumab 15 mg/kg on day 1 of 21-days cycle/erlotinib 150 mg daily	370	8.5
			Bevacizumab 15 mg/kg on day 1 of 21-days cycle /placebo	373	8.3

[a] Maintenance treatments were continued in patients with complete response, partial response, or stable disease after induction until disease progression, unacceptable toxicity, and/or physician's decision to terminate, unless otherwise stated. Outcomes were measured from randomisation. Where multiple publications are available, most mature results were used.
[b] Included 3/539 patients with ECOG PS >1.
[c] Subgroup results of subjects with KPS >80 were used. *N*, sample size; BSC, best supportive care; PS, performance status; NSCLC, non-small-cell lung cancer; ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organisation.

Trials included in network meta-analysis evaluating maintenance treatments in good performance status stage IIIb/IV non-small-cell lung cancer (NSCLC) patients not progressing after first-line induction. Thicknesses of lines are proportional to the number of trials included in analyses.



OS

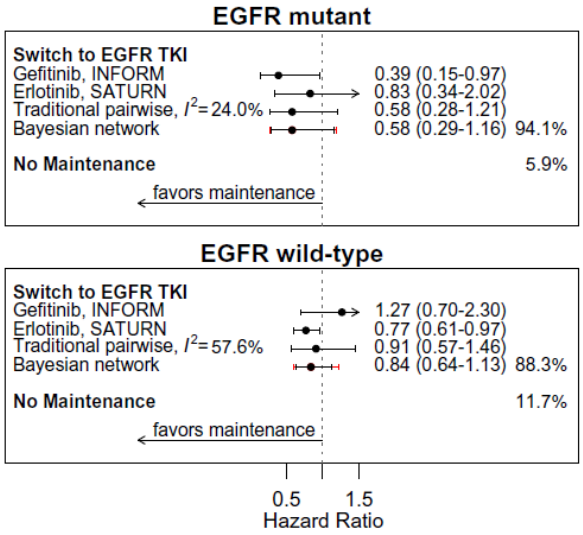
In the EGFR mutation positive population, SUCRA, probability of being the best, and probability of outperforming no maintenance for switch to EGFR TKI was 94.1%, as these measures are equivalent for the comparison of only two treatments, EGFR TKI and no maintenance. In the EGFR wild-type population, SUCRA, probability of being the best, and probability of outperforming no maintenance for switch to EGFR TKI was 88.3% (Fig. 3, Table 2). Examination of treatment by EGFR mutation interaction showed that switch to EGFR TKI had 84% posterior probability of performing better relative to no maintenance in the EGFR mutation positive versus EGFR wild-type population (Table 2). There was no evidence of a difference between switch erlotinib and switch gefitinib in either the EGFR mutant or wild-type subpopulations (Appendix Table A3). At the time of SATURN

analysis, OS for EGFR mutation positive subjects was not mature with median survival not reached, and authors reported extensive cross-over of subjects receiving erlotinib upon progression (67%) [

Table 2
Overall survival surface under the cumulative ranking curves (SUCRAs), posterior probabilities best, posterior probabilities of outperforming no maintenance, and hazard ratios by Eastern Cooperative Oncology Group (ECOG) performance status (PS), epidermal growth factor receptor (EGFR) mutation status, histology, and induction response for maintenance treatments in good performance status stage IIIb/IV non-small-cell lung cancer (NSCLC) patients not progressing after first-line induction. Predictive probability estimates represent expected treatment efficacies in a new study or setting. Treatments by covariate interactions examine posterior probability of treatment efficacies relative to no maintenance by patient subgroups.

Maintenance	SUCRA, % (predictive)[c]	Probability best (predictive)[c]	Probability outperforming no maintenance (predictive)[c]	Overall survival, HR (95% CrI)	Treatment by covariate interaction[d]
ECOG PS 0					Probability better in PS 0 versus PS 1
Switch to pemetrexed[a]	85.4 (83.7)	0.63 (0.60)	1.00 (0.99)	0.57 (0.37–0.87)	0.89 (0.87); $p = 0.149$
Continue pemetrexed[a]	59.7 (59.3)	0.18 (0.19)	0.96 (0.94)	0.70 (0.46–1.06)	0.73 (0.71); $p = 0.469$
Continue gemcitabine	56.1 (55.9)	0.15 (0.16)	0.95 (0.93)	0.72 (0.46–1.07)	0.80 (0.77); $p = 0.137$
Switch to EGFR TKI[b]	45.5 (46.0)	0.04 (0.05)	0.97 (0.94)	0.77 (0.58–1.01)	0.65 (0.62); $p = 0.707$
No maintenance	3.2 (5.1)	0.00 (0.00)	–	1.00	–
ECOG PS 1					
Switch to pemetrexed[a]	67.3 (65.9)	0.38 (0.36)	0.90 (0.88)	0.80 (0.57–1.13)	–
Switch to EGFR TKI[b]	63.8 (62.3)	0.20 (0.21)	0.95 (0.90)	0.83 (0.66–1.05)	–
Continue pemetrexed[a]	63.2 (62.0)	0.29 (0.28)	0.90 (0.87)	0.82 (0.60–1.12)	–
Continue gemcitabine	42.7 (43.8)	0.13 (0.14)	0.73 (0.71)	0.90 (0.64–1.32)	–
No maintenance	13.0 (16.0)	0.00 (0.00)	–	1.00	–
EGFR mutant					Probability better in EGFR mutant versus wild-type
Switch to EGFR TKI	94.1 (93.3)	0.94 (0.93)	0.94 (0.93)	0.58 (0.29–1.16)	0.84 (0.83); $p = 0.301$
No maintenance	5.9 (6.7)	0.06 (0.07)	–	1.00	–
EGFR wild-type					
Switch to EGFR TKI	88.3 (84.4)	0.88 (0.84)	0.88 (0.84)	0.84 (0.64–1.13)	
No maintenance	11.7 (15.6)	0.12 (0.16)	–	1.00	
Nonsquamous					Probability better in nonsquamous versus squamous
Switch to pemetrexed	76.6 (74.7)	0.30 (0.29)	0.99 (0.98)	0.70 (0.52–0.94)	0.96 (0.94); $p = 0.039$
Switch to docetaxel	70.3 (69.9)	0.54 (0.53)	0.81 (0.81)	0.63 (0.22–1.80)	–
Switch to EGFR TKI[b]	60.5 (59.4)	0.09 (0.10)	0.98 (0.95)	0.78 (0.62–0.99)	0.80 (0.75); $p = 0.335$
Continue pemetrexed	56.1 (55.7)	0.05 (0.07)	0.96 (0.93)	0.80 (0.62–1.04)	–
Continue gemcitabine	23.1 (25.1)	0.01 (0.02)	0.59 (0.58)	0.96 (0.70–1.35)	0.16 (0.19); $p = 0.429$
No maintenance	13.4 (15.2)	0.00 (0.00)	–	1.00	–
Squamous					
Continue gemcitabine	88.4 (86.0)	0.79 (0.74)	0.92 (0.90)	0.74 (0.49–1.16)	–
Switch to EGFR TKI[b]	56.6 (55.9)	0.13 (0.15)	0.78 (0.74)	0.91 (0.70–1.18)	–
No maintenance	31.5 (32.8)	0.02 (0.02)	–	1.00	–
Switch to pemetrexed	23.5 (25.3)	0.07 (0.08)	0.36 (0.37)	1.07 (0.72–1.58)	–
Induction response CR/PR					Probability better in CR/PR versus SD
Switch to docetaxel	87.9 (86.2)	0.66 (0.62)	0.99 (0.98)	0.61 (0.40–0.93)	0.96 (0.95); $p = 0.044$
Continue gemcitabine	62.5 (61.1)	0.15 (0.15)	0.94 (0.91)	0.77 (0.52–1.08)	0.87 (0.84); $p = 0.081$
Continue pemetrexed[a]	51.5 (51.3)	0.09 (0.10)	0.87 (0.85)	0.81 (0.56–1.17)	0.40 (0.41); $p = 0.770$
Switch to pemetrexed[a]	51.3 (51.1)	0.10 (0.11)	0.86 (0.84)	0.81 (0.55–1.19)	0.14 (0.17); $p = 0.219$
Switch to EGFR TKI[b]	37.9 (38.8)	0.01 (0.02)	0.89 (0.84)	0.87 (0.70–1.09)	0.25 (0.30); $p = 0.317$
No maintenance	9.0 (11.5)	0.00 (0.00)	–	1.00	–

Overall survival by Eastern Cooperative Oncology Group (ECOG) performance status (PS) and epidermal growth factor receptor (EGFR) mutation status for maintenance treatments in good performance status stage IIIb/IV non-small-cell lung cancer (NSCLC) patients not progressing after first-line induction. Treatments were compared to no maintenance. aBayesian network estimates reported as hazard ratio (95% credible intervals in black and 95% predictive intervals in red). bSwitch pemetrexed [39] and continue pemetrexed estimates were estimated from trials results within the nonsquamous population. cTKI estimates by PS were in a predominantly Caucasian population. TKI, tyrosine kinase inhibitors; HR, hazard ratio.



PFS

PFS benefit was broadly consistent with OS benefit although more pronounced, with selected maintenance treatments showing remarkable ≥99% probability of outperforming no maintenance.

4. Anmerkungen/Fazit der Autoren

Für alle Patienten (unabhängig vom Mutationsstatus):

Selected maintenance treatments showed clinically meaningful benefits of P20% reduction in hazards of death with P90% probability of outperforming no maintenance in terms of OS: (i) switch to or continue pemetrexed (nonsquamous), continue gemcitabine, or switch to EGFR tyrosine kinase inhibitors (TKIs) for PS 0 patients, (ii) switch to pemetrexed (nonsquamous) for PS 1 patients, (iii) switch to EGFR TKI for EGFR mutation positive patients, (iv) switch to or continue pemetrexed or switch to EGFR TKI for nonsquamous patients, (v) continue gemcitabine for squamous patients, (vi) switch to docetaxel or continue gemcitabine for responders to induction, or (vii) switch to or continue pemetrexed (nonsquamous) or switch to EGFR TKI for patients with stable disease post-induction.

Maintenance treatments show clinically meaningful survival benefits in good performance status patients with advanced NSCLC not progressing after first-line chemotherapy. Benefits are optimised by targeting specific maintenance to individual patients guided by PS, EGFR mutation status, histology and response to induction.

Hinweis der FBMed:

Es erfolgte keine Qualitätsbewertung der Primärstudien.

Sheng Z , Zhang Y, 2015 [34].

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: advanced NSCLC, defined as inoperable locally advanced (stage IIIB) or metastatic or recurrent disease (stage IV)
Intervention: first-generation EGFR-TKIs (erlotinib or gefitinib)
Komparator: control: standard platinum doublet chemotherapy as firstline treatment
Endpunkte: PFS, OS
Suchzeitraum: bis 09/2014
Anzahl eingeschlossene Studien/Ptienten (Gesamt): 12 (2031)
Qualitätsbewertung der Studien: Two reviewers (Z.X.S. and Y.X.Z.) 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: I^2

3. Ergebnisdarstellung

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

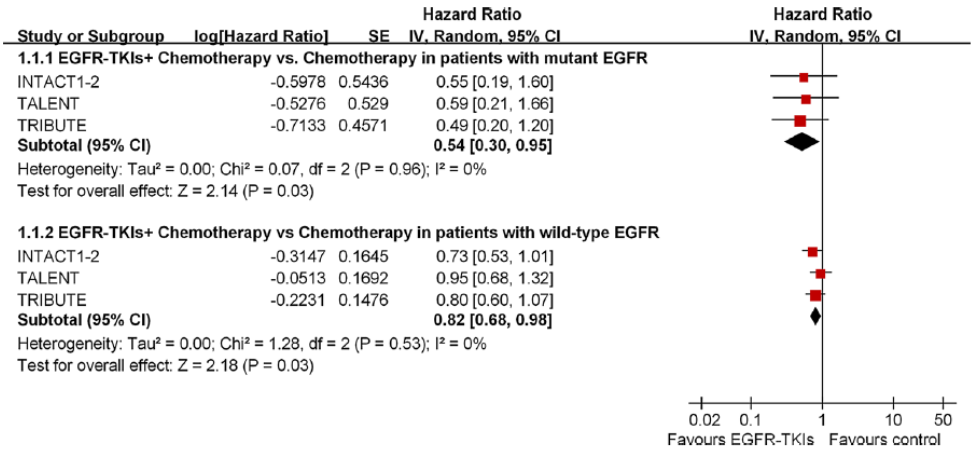
ARMS amplification refractory mutation system, *CisG* cisplatin–gemcitabine, *CP* carboplatin–paclitaxel, *CV* carboplatin–vinorelbine, *CisD* cisplatin–docetaxel, *CG* carboplatin–gemcitabine, *G* gemcitabine, *D* docetaxel, *EGFR*$^+$ presence of epidermal growth factor receptor mutation, *EGFR*$^-$ 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

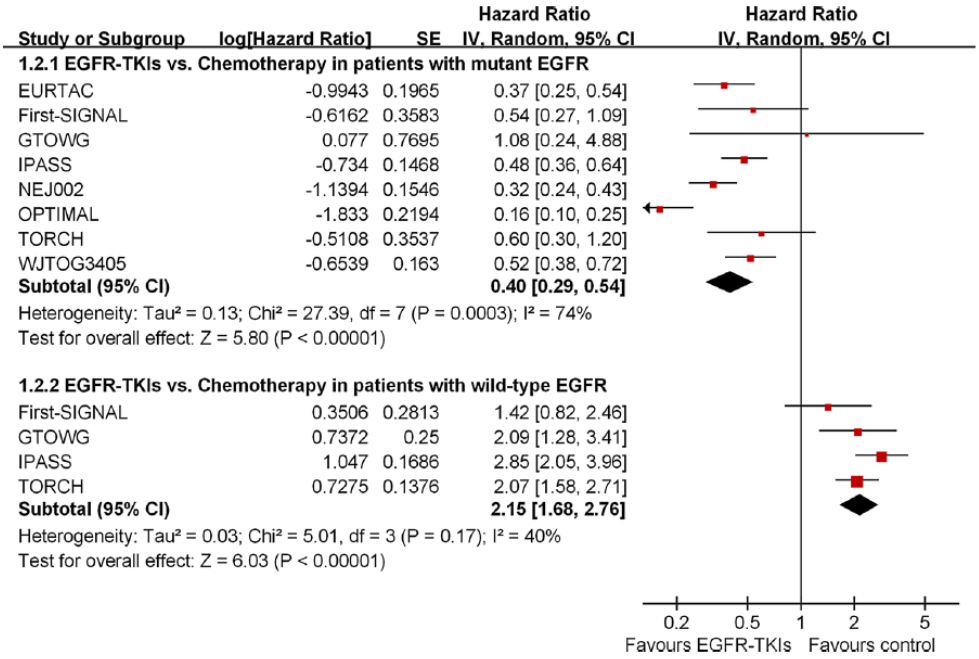
[b] Median age not available; mean age calculated instead

PFS

Meta-analysis of the treatment effects (**EGFR-TKIs added to chemotherapy versus chemotherapy alone**) on progression-free survival (PFS) in previously untreated advanced NSCLC patients with and without EGFR mutations. HR hazard ratio, CI 95 % confidence interval. Random, random-effects model

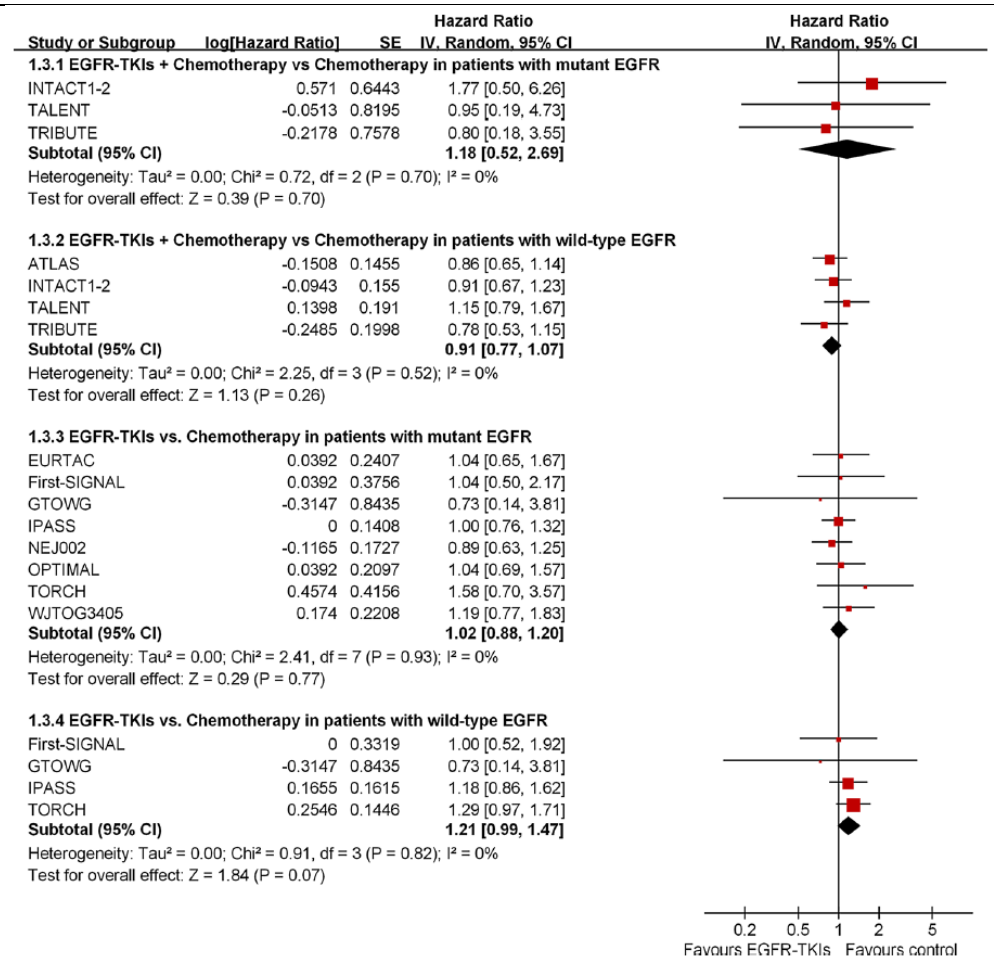


Meta-analysis of the treatment effects (**EGFR-TKIs single agent versus chemotherapy**) on progressionfree survival (PFS) in previously untreated advanced NSCLC patients with and without EGFR mutations. HR hazard ratio, CI 95 % confidence interval. Random, random-effects model

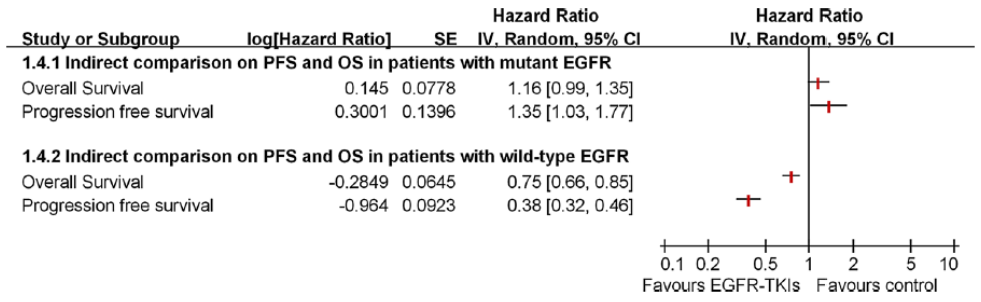


OS

Meta-analysis of the treatment effects (EGFR-TKIs arms versus chemotherapy) on overall survival (OS) in previously untreated advanced NSCLC patients with and without EGFR mutations. HR hazard ratio, CI 95 % confidence interval. Random, random-effects model



Indirect comparison of chemotherapy added to EGFR-TKIs versus EGFR-TKIs single agent on progression-free survival (PFS) and overall survival (OS) in previously untreated advanced NSCLC patients with and without EGFR mutations. HR hazard ratio, CI 95 % confidence interval. Random, random-effects model



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.

Pilkington G et al, 2015 [31]. 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:** advanced NSCLC, patients with known EGFRmutation status **Intervention:** first-line chemotherapy treatments; treatments had to be currently licensed for use in Europe and recommended by NICE **Komparator:** - **Endpunkte:** OS, median PFS/TTP, overall response rate, 1- and 2-year survival, adverse events (AEs) and QoL data **Suchzeitraum:** 2001 – 8/2010 **Anzahl eingeschlossene Studien/Ptienten (Gesamt):** 23 **Qualitätsbewertung der Studien:** **Heterogenitätsuntersuchungen:** **3. Ergebnisdarstellung** 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. All trials reported the number of patients randomised, however only six RCTs were assessed as adequately randomised with adequate concealment of allocation. All trials reported eligibility criteria; 20 trials reported detailed information about baseline comparability and three trials partially reported information about baseline comparability, but only five trials achieved baseline comparability. Although the majority of trials reported second-line chemotherapy, only one trial20 was designed to consider second-line therapy. Seven trials were reported as ‘open’ and it was assumed that assessors, administrators and patients were not blinded to treatment except for one trial where the radiologist was stated to be blinded. Blinding of participants, investigators or outcome assessors was not reported in 16 studies. The outcomes of over 80% of patients were assessed in all studies and all studies reported reasons for dropout; 10 trials used an intention to treat approach to assess OS. Five of the trials appeared to report fewer outcomes than initially stated, thus indicating the possibility of selective reporting. **OS/ PFS für EGFR M+**

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.

4. Anmerkungen/Fazit der Autoren

NSCLC population with EGFR+ status Evidence was found that EGFR M+ patients have a better prognosis than other NSCLC patients; this means that gefitinib could only be compared with two standard treatments through evidence from three small trials which recruited from this specific patient subgroup. As there is currently no evidence of OS advantage, at the current price paid by the UK NHS, gefitinib does not appear to be cost effective compared to docetaxel or paclitaxel doublets.

The evidence relating to patients with EGFR M+ status is based on the results from three trials conducted in East Asian countries.

Mok TS, Wu Y-L, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947–57.

Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380–8.

Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010;11:121–8.

Fukuoka M, Wu Y-L, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non–small-cell lung cancer in Asia (IPASS). J Clin Oncol 2011;29:2866–74.

It is questionable whether the results of these trials are generalisable to UK clinical practice as evidence suggests that East Asian populations with NSCLC have a more favourable prognosis compared with non-East Asian populations. EGFR mutation rates are likely to differ between countries (in Europe and the UK estimated EGFR M+ rates are low compared to Asian countries), although the actual response to chemotherapy may not differ in patients with the same mutation status. Evidence from our review shows that patients who are EGFR M+ have improved OS outcomes compared to all other patients. As yet there are no relevant UK-based trial data for patients with EGFR M+ status; this is not surprising as only a small proportion of UK patients participate in international RCTs. In trials where ethnicity is not a risk factor for disease, this is less of a problem when considering the generalisability

	of results. **5. Hinweis der FBMed** Das Ende des Suchzeitraumes lag 5 Jahre vor dem Veröffentlichungsjahr dieses SR.
Liu J et al., 2015 [21]. The Efficacy of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors forMolecularly Selected Patients with Non-Small Cell Lung Cancer: AMeta-Analysis of 30 Randomized Controlled Trials	**Fragestellung** To determine the efficacy of first-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) in molecularly selected patients with advanced non-small cell lung cancer (NSCLC), we performed this pooled analysis. **Methodik** **Population:** advanced NSCLC, patients with known EGFRmutation status **Intervention:** first-generation EGFR-TKIs (erlotinib or gefitinib) **Komparator:** standard chemotherapy or placebo. **Endpunkte:** PFS, OS **Suchzeitraum:** bis 09/2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 30 (4053) **Qualitätsbewertung der Studien:** Two reviewers (Z.X.S. and Y.X.Z.) independently assessed the quality of selected studies using the following criteria: (1) generation of allocation concealment, (2) description of drop-outs, (3) masking of randomization, intervention, outcome assessment, (4) intention-to-treat (ITT) analysis. Each criterion was rated as yes, no, or unclear. **Heterogenitätsuntersuchungen:** Cochrane $\chi 2$ test, I^2 **Ergebnisdarstellung** All included trials were open-labeled. Random sequence generation and allocation concealment were performed adequately in most of the trials. None were blinded. Only two trials that exclusively designed for wild-type EGFR patients and four trials that designed for mutant EGFR patients reported intention-to-treat analyses, and description of dropouts for molecularly selected patients.

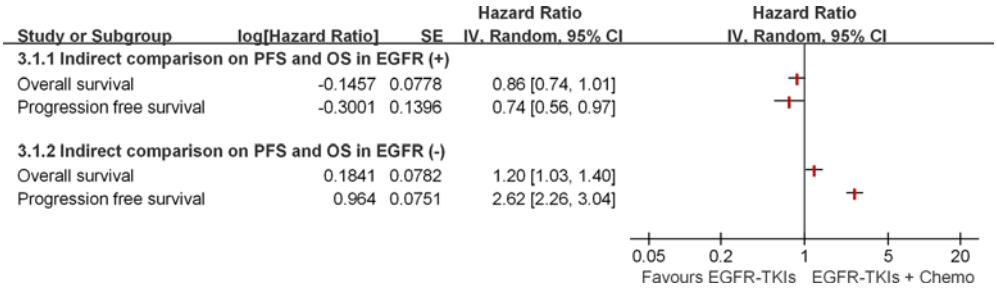
Table 1 Main characteristics of the studies included in the meta-analysis

Study name (year)	No. of patients		Therapy Regimen	EGFR Assessment Method
	$EGFR^-$	$EGFR^+$		
EGFR TKIs vs. Chemotherapy				
First-Line Therapy				
First-SIGNAL 2012 [15]	54	43	Gefitinib vs. CisG	Direct sequencing
IPASS 2009 [16, 17]	176	261	Gefitinib vs. CP	ARMS
GTOWG 2010 [18]	75	10	Erlotinib vs. CV	Direct sequencing
TORCH 2012 [19]	236	39	Erlotinib vs. CisG	Direct sequencing/Fragment analysis/MS
ML 20322, 2012 [20]	36	24	Erlotinib vs. vinorelbine	Direct sequencing
WJTOG3405 [21, 22]	0	172	Gefitinib vs. CisD	Direct sequencing, PCR clamp
NEJ002 23, [24]	0	228	Gefitinib vs. CP	PCR clamp
EURTAC [25]	0	173	Erlotinib vs. platinum-G or platinum-D	Direct sequencing
OPTIMAL [26, 27]	0	154	Erlotinib vs. CG	Direct sequencing
Second/Third-Line Therapy				
V-15-32 2008 [28]	26	31	Gefitinib vs. D	Direct sequencing
INTEREST 2008 [29, 30]	253	44	Gefitinib vs. D	Direct sequencing
KCSG-LU08-01 2012 [31]	38	33	Gefitinib vs. Pem	Direct sequencing
CTONG-0806 2013 [32]	157	0	Gefitinib vs. Pem	Direct sequencing
TAILOR 2013 [33]	219	0	Erlotinib vs. D	Direct sequencing + fragment analysis
DELTA 2014 [34]	199	56	Erlotinib vs. Docetaxel	PCR-based method
TITAN 2012 [35]	149	11	Erlotinib vs. pem or D	Direct sequencing
NCT01565538 2014 [36]	123	0	Erlotinib vs. pem	ARMS
CT/06.05, 2013 [37]	112	11	Erlotinib vs. pem	Direct sequencing
PROSE [38]	163	14	Erlotinib vs. pem or D	NA
EGFR TKIs vs. Placebo				
First-line Therapy				
TOPICAL 2010 [39, 40]	362	28	Erlotinib vs. placebo	SequenomOncoCarta Panel
Second/Third-Line Therapy				
ISEL 2005 [41]	189	26	Gefitinib vs. Placebo	Direct sequencing, ARMS
BR21 2005 [42, 43]	170	34	Erlotinb vs. Placebo	Direct sequencing, ARMS
Maintenance Therapy				
IFCT-GFPC 0502 2010 [44]	106	8	Erlotinib vs. Placebo	NA
INFORM 2011 [45]	49	30	Gefitinib vs. Placebo	NA
SATURN 2010 [46]	388	49	Erlotinib vs. Placebo	Direct sequencing
EGFR TKIs + Chemotherapy vs. Chemotherapy alone				
First-Line Therapy				
INTACT 1▲ 2004 [47, 48]	280	32	Gefitinib + CisG vs. CisG	Direct sequencing
INTACT 2▲ 2004 [48, 49]			Gefitinib + CP vs. CP	
TALENT 2007 [50, 51]	NA	NA	Erlotinib + CisG vs. CisG	NA
TRIBUTE 2005 [52]	198	29	Erlotinib + CP vs. CP	Direct sequencing
Maintenance Therapy				
ATLAS 2013 [53]	295	52	Erlotinib + B vs. B	NA

* *No.* number, *ARMS* Amplifcation refractory mutation system, *MS* MassARRAY, *CG* Carboplatin-gemcitabine, *CisD* Cisplatin-docetaxel, *CisG* Cisplatin-gemcitabine, *CisPem* Cisplatin-pemetrexed, *CP* Carboplatin-paclitaxel, *CV* Carboplatin-venorelbine, *D* Docetaxel, *PEM* Pemetrexed, *B* Bevacizumab, *$EGFR^+$* Presence of epidermal growth factor receptor mutation, *$EGFR^-$* Absence of epidermal growth factor receptor mutation, *G* Gemcitabine, *NA* Not available, *PCR* Polymerasechain reaction;.* EGFR mutation based on exon 19 and exon 21 only. ▲ INTACT 2 and INTACT 1 did not report the No. of patients with known EGFR status separately, but reported it together. Also, they both used direct sequencing as the EGFR assessment method

PFS Twenty-eight trials provided available data on PFS except ISEL and BR21 in molecularly selected patients. The treatment effect of EGFR-TKIs in different subgroups is indicated in Fig. 2. *Siehe Anlage 1* - In those patients with mutant EGFR, EGFR-TKIs treatment produced a prominent reduction of the risk of progression over chemotherapy in the first-line setting (HR=0.41 [0.31, 0.55], p<0.00001) and second/third-line treatment (HR=0.46 [0.24, 0.89], p=0.02), as shown in Fig. 2a. However, using a random-effects model, the pooled analysis showed a significantly longer PFS with chemotherapy than with TKIs in the patients with wild-type EGFR (HR, 1.38 [1.12, 1.70], p=0.002) (Fig. 2b), and EGFR-TKIs have fared worse than chemotherapy in the first-line setting (HR=1.65 [1.06, 2.58], p=0.03) and in the second/third-line treatment (1.27 [1.08, 1.51], p=0.005) (Fig. 2b). Also, there were three outlying small trials (ML 20322, V-15-32, KCSG-LU08-01) [20, 28, 31] of less than 50 patients with wild-type EGFR. To strengthen the results of this subgroup analysis, the three small trials

	including less than 50 patients with wild-type EGFR were excluded; the same trend favoring chemotherapy over EGFR-TKIs was also found for first-line setting (HR=2.15 [1.68, 2.76], p<0.00001) for second/third-line setting (HR= 1.35 [1.17, 1.56], p<0.00001). The heterogeneity within each subgroup decreased prominently, but the difference between the first-line and second/third-line subgroup was significant (p=0.001). The pooled results of four trials showed that patients treated with EGFR-TKIs had a more pronounced PFS benefit compared with placebo among patients with (HR, 0.26 [0.09, 0.79], p=0.02) (Fig. 2c) and without (HR, 0.83 [0.72, 0.95], p=0.006) (Fig. 2d) EGFR mutant tumors. The heterogeneity between the EGFR mutant subpopulation and EGFR wildtype one is significant (p=0.04), suggesting these patients harboring EGFR mutation had a greater improvement in PFS. This benefit was consistent across those trials within the subgroup of patients with EGFR wild-type tumors, but the heterogeneity within the subgroup of EGFR mutant patients was significant because of the TOPICAL trial [39, 40], which was the only trial of first-line treatment. The other three trials were conducted compared EGFR-TKIs versus placebo for maintenance treatment. When pooling them, the same trend favoring EGFR-TKIs over placebo was also found among patients with (HR, 0.14 [0.08, 0.26], p<0.00001) (Fig. 2c) and without (HR, 0.81 [0.68, 0.97], p=0.02) (Fig. 2d) EGFR mutant tumors. The pooled results of five trials showed that patients treated with EGFR-TKIs added to chemotherapy had a more pronounced PFS benefit over chemotherapy alone among patients with (HR, 0.49 [0.32, 0.77], p=0.002) (Fig. 2e) and without (HR, 0.83 [0.71, 0.96], p=0.01) (Fig. 2f) EGFRmutant tumors. The heterogeneity between the two subpopulation is significant (p=0.03), suggesting that these patients harboring EGFR mutation had a greater improvement. Four of the five trialswere conducted using EGFR-TKIs in combination with standard platinum doublet chemotherapy for previously untreated patients. When pooling them, the therapeutic advantage for the concurrent addition of EGFR-TKIs to standard first-line platinum doublet chemotherapy was similar: the summary HRs were 0.54 [0.30, 0.95] (p=0.03) (Fig. 2e) for patients with EGFR mutant tumors, 0.82 [0.68 0.98] (p=0.03) (Fig. 2f) for patients with EGFR wild-type tumors, respectively. **OS** In OS analysis, only single-agent EGFR-TKIs was inferior to chemotherapy in EGFR wild-type patients in both the first-line and second/third-line therapy settings: the summary HR was 1.13, [1.02, 1.26] (p=0.02) for EGFR-TKIs vs. Chemotherapy (Fig. 3b). Vgl. Anlage 1 - No statistically significant difference in terms of overall survival was observed in any other subgroup analysis (Fig. 3): for these patients with mutant EGFR, the summary HRs were 1.01, [0.87, 1.17] (p=0.94) for EGFR-TKIs vs. Chemotherapy, 0.72, [0.45, 1.15] (p=0.17) for EGFR-TKIs vs. placebo, 0.74, [0.40, 1.38] (p=0.35) for EGFR-TKIs added to chemotherapy vs. Chemotherapy alone, respectively. For these patients with wild-type EGFR, the summary HRs were 0.93, [0.77, 1.12] (p=0.45) for EGFR-TKIs vs. placebo, 0.91, [0.77, 1.07] (p=0.26) for EGFR-TKIs added to chemotherapy vs. Chemotherapy alone, respectively.

	Indirect Comparison of EGFR-TKIs Versus EGFR-TKIs Added to Chemotherapy Indirect comparison of EGFR-TKIs versus EGFR-TKIs added to chemotherapy when using standard platinum doublet chemotherapy as common comparator was shown in Fig. 4. For patients with mutant EGFR, EGFR-TKIs was superior to the combination of EGFR-TKIs and chemotherapy in terms of PFS (HR, 0.74 [0.56, 0.97], p=0.03) (Fig. 4a). A marginal trend towards the same direction was also found in the survival analysis (HR, 0.86 [0.74, 1.01], p=0.06) (Fig. 4c). In contrast, EGFR-TKIs was inferior to the combination of EGFRTKIs and chemotherapy in the EGFR wild-type subpopulation in terms of PFS (HR, 2.62 [2.26, 3.04], p<0.001) (Fig. 4b) and OS (HR, 1.20 [1.03, 1.40], p=0.02) (Fig. 4d).  **Anmerkungen/Fazit der Autoren** For EGFR mutant patients, EGFR-TKIs therapy produced a prominent PFS benefit in all settings. Among EGFR wild-type patients, EGFR-TKIs were inferior to chemotherapy both for first-line treatment and for second/thirdline treatment. However, EGFR-TKIs maintenance and addition of EGFR-TKIs to chemotherapy could provide additive benefit over chemotherapy alone in such EGFR wild-type patients.
Lee CK et al., 2015 [19]. Impact of Specific Epidermal Growth Factor Receptor (EGFR) Mutations and Clinical Characteristics on Outcomes After Treatment With EGFR Tyrosine Kinase Inhibitors	**Fragestellung** We examined the impact of different epidermal growth factor receptor (EGFR) mutations and clinical characteristics on progression-free survival (PFS) in patients with advanced EGFR-mutated non–small-cell lung cancer treated with EGFR tyrosine kinase inhibitors (TKIs) as first-line therapy. **Methodik Population:** advanced NSCLC, EGFR M+ **Intervention:** EGFR TKIs **Komparator:** chemotherapy **Endpunkte:** PFS **Suchzeitraum:** 2004 – 02/2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 7 (1649) **Qualitätsbewertung der Studien:** keine Angaben **Heterogenitätsuntersuchungen:** chi Quadrat Cochran Q test

Versus Chemotherapy in EGFR-Mutant Lung Cancer: A Meta-Analysis

Ergebnisdarstellung

Table 1. Characteristics of Patients in Constituent Trials

Study Name, Year	Treatment Comparison	Median PFS (months)	No. of Patients	Exon 19 Deletion (%)	Exon 21 L858R Substitution (%)	Age < 65 Years (%)	ECOG PS 0 and 1 (%)	Asian (%)	Women (%)	Never-Smoker (%)	Adenocarcinoma (%)
NEJ002, 2010, 2013[2,15*]	Gefitinib *v* CP	10.8 *v* 5.4	224†	51	43	49	99	100	63	62	93
WJTOG 3405, 2010, 2012[3,16]	Gefitinib *v* CisD	9.6 *v* 6.5	172	51	49	53	100	100	69	69	97
OPTIMAL, 2011, 2012[4,18]	Erlotinib *v* CG	13.1 *v* 4.6	154	53	47	75	94	100	59	71	87
EURTAC, 2012[5]	Erlotinib *v* platinum-G or platinum-D	9.7 *v* 5.2	173	66	34	49	86	0	73	69	92
LUX-Lung 3, 2013[6*]	Afatinib *v* CisPem	11.1 *v* 6.9	345	49	40	61	100	72	65	68	100
LUX-Lung 6, 2014[7*]	Afatinib *v* CisG	11.0 *v* 5.6	364	51	38	76	100	100	65	77	100
ENSURE, 2014[8‡]	Erlotinib *v* CisG	11.0 *v* 5.5	217	54	45	79	94	100	61	71	94

Abbreviations: CG, carboplatin-gemcitabine; CisD, cisplatin-docetaxel; CisG, cisplatin-gemcitabine; CisPem, cisplatin-pemetrexed; CP, carboplatin-paclitaxel; ECOG, Eastern Cooperative Oncology Group; EURTAC, European Tarceva Versus Chemotherapy; NEJ002, North East Japan 002; PFS, progression-free survival; PS, performance status; WJTOG, West Japan Thoracic Oncology Group.
*Includes patients with uncommon mutations of the *EGFR* gene.
†NEJ002 recruited a total of 228 patients; PFS outcome was only reported for 224 patients.
‡Reported in abstract only.

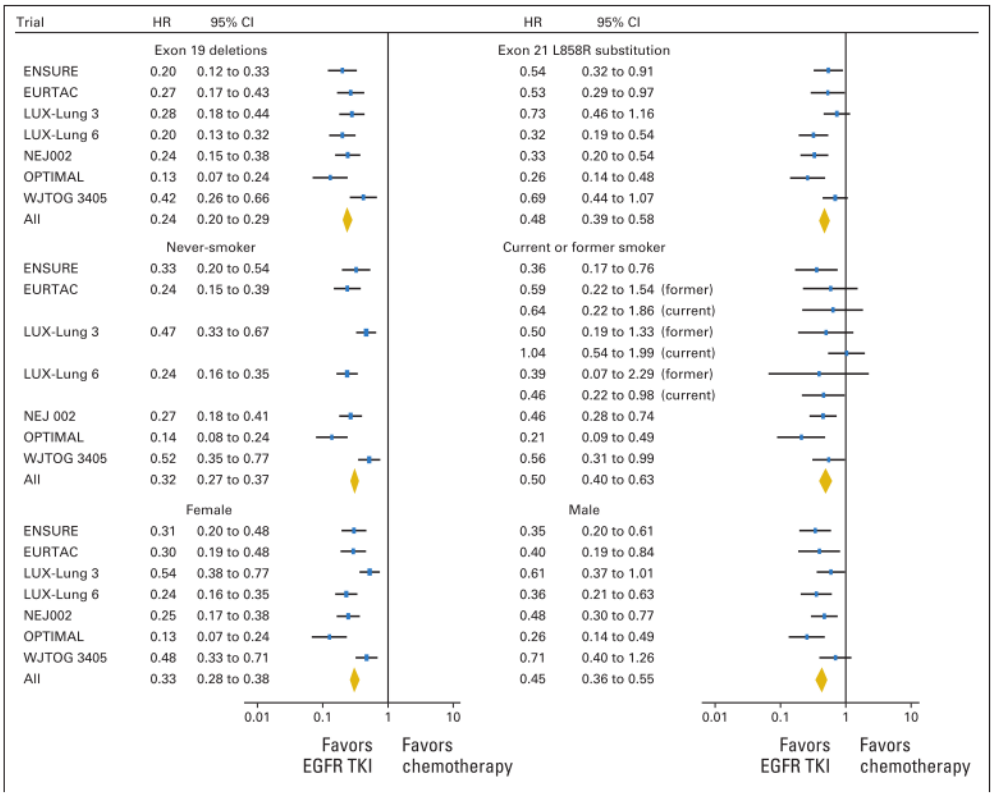


Fig 2. Forest plot of the effect of treatment on progression-free survival in subgroups of patients according to mutations of the epidermal growth factor receptor (*EGFR*) gene, smoking status, and sex. Hazard ratios (HRs) for each trial are represented by the squares, and the horizontal line crossing the square represents the 95% CI. The diamonds represent the estimated overall effect based on the meta-analysis fixed effect. All statistical tests were two sided. EURTAC, European Tarceva Versus Chemotherapy; NEJ002, North East Japan 002; TKI, tyrosine kinase inhibitor; WJTOG, West Japan Thoracic Oncology Group.

Table 2. Unadjusted and Adjusted Treatment Effect of EGFR TKIs Versus Chemotherapy in Four Clinical Trials

Subgroup	Unadjusted Analysis HR	Unadjusted Analysis 95% CI	Adjusted Analysis HR	Adjusted Analysis 95% CI
Exon 19 deletions				
EURTAC	0.27	0.17 to 0.43	0.25*	0.15 to 0.41
NEJ002	0.24	0.15 to 0.38	0.24*	0.15 to 0.38
OPTIMAL	0.13	0.07 to 0.25	0.12*	0.06 to 0.22
WJTOG 3405	0.42	0.26 to 0.68	0.46*	0.28 to 0.76
Pooled result	0.26	0.20 to 0.34	0.26	0.20 to 0.33
Exon 21 L858R substitution				
EURTAC	0.53	0.29 to 0.97	0.51*	0.28 to 0.94
NEJ002	0.33	0.20 to 0.54	0.33*	0.20 to 0.55
OPTIMAL	0.26	0.14 to 0.49	0.23*	0.12 to 0.45
WJTOG 3405	0.69	0.44 to 1.07	0.69*	0.44 to 1.08
Pooled result	0.45	0.34 to 0.58	0.44	0.34 to 0.58
Treatment-*EGFR* mutation interaction		$P = .004$		$P = .004$
Never-smoker				
EURTAC	0.24	0.15 to 0.39	0.23†	0.14 to 0.38
NEJ002	0.27	0.18 to 0.41	0.24†	0.16 to 0.37
OPTIMAL	0.14	0.08 to 0.25	0.14†	0.08 to 0.25
WJTOG 3405	0.52	0.35 to 0.77	0.52†	0.34 to 0.79
Pooled result	0.29	0.24 to 0.37	0.28	0.22 to 0.35
Current or former smoker				
EURTAC (former)	0.59	0.22 to 1.54	0.67†	0.25 to 1.78
EURTAC (current)	0.64	0.22 to 1.86	0.56†	0.19 to 1.71
NEJ002	0.46	0.28 to 0.74	0.45†	0.28 to 0.73
OPTIMAL	0.21	0.09 to 0.49	0.20†	0.08 to 0.47
WJTOG 3405	0.56	0.31 to 0.99	0.57†	0.32 to 1.02
Pooled result	0.46	0.34 to 0.62	0.46†	0.34 to 0.62
Treatment-smoking interaction		$P = .02$		$P = .01$
Women				
EURTAC	0.30	0.19 to 0.48	0.29‡	0.18 to 0.47
NEJ002	0.25	0.17 to 0.38	0.21‡	0.14 to 0.33
OPTIMAL	0.13	0.07 to 0.24	0.13‡	0.07 to 0.24
WJTOG 3405	0.48	0.33 to 0.71	0.50‡	0.33 to 0.76
Pooled result	0.30	0.24 to 0.38	0.28	0.22 to 0.36
Men				
EURTAC	0.40	0.19 to 0.84	0.37‡	0.17 to 0.81
NEJ002	0.48	0.30 to 0.77	0.45‡	0.28 to 0.74
OPTIMAL	0.26	0.14 to 0.50	0.23‡	0.12 to 0.45
WJTOG 3405	0.71	0.40 to 1.26	0.69‡	0.39 to 1.22
Pooled result	0.46	0.34 to 0.61	0.43	0.32 to 0.58
Treatment-sex interaction		$P = .02$		$P = .03$

Abbreviations: EGFR, epidermal growth factor receptor; EURTAC, European Tarceva Versus Chemotherapy; HR, hazard ratio; NEJ002, North East Japan 002; TKI, tyrosine kinase inhibitor; WJTOG, West Japan Thoracic Oncology Group.

*HR (EGFR TKI *v* chemotherapy) adjusted for smoking status and sex.

†HR (EGFR TKI *v* chemotherapy) adjusted for sex and type of *EGFR* mutation.

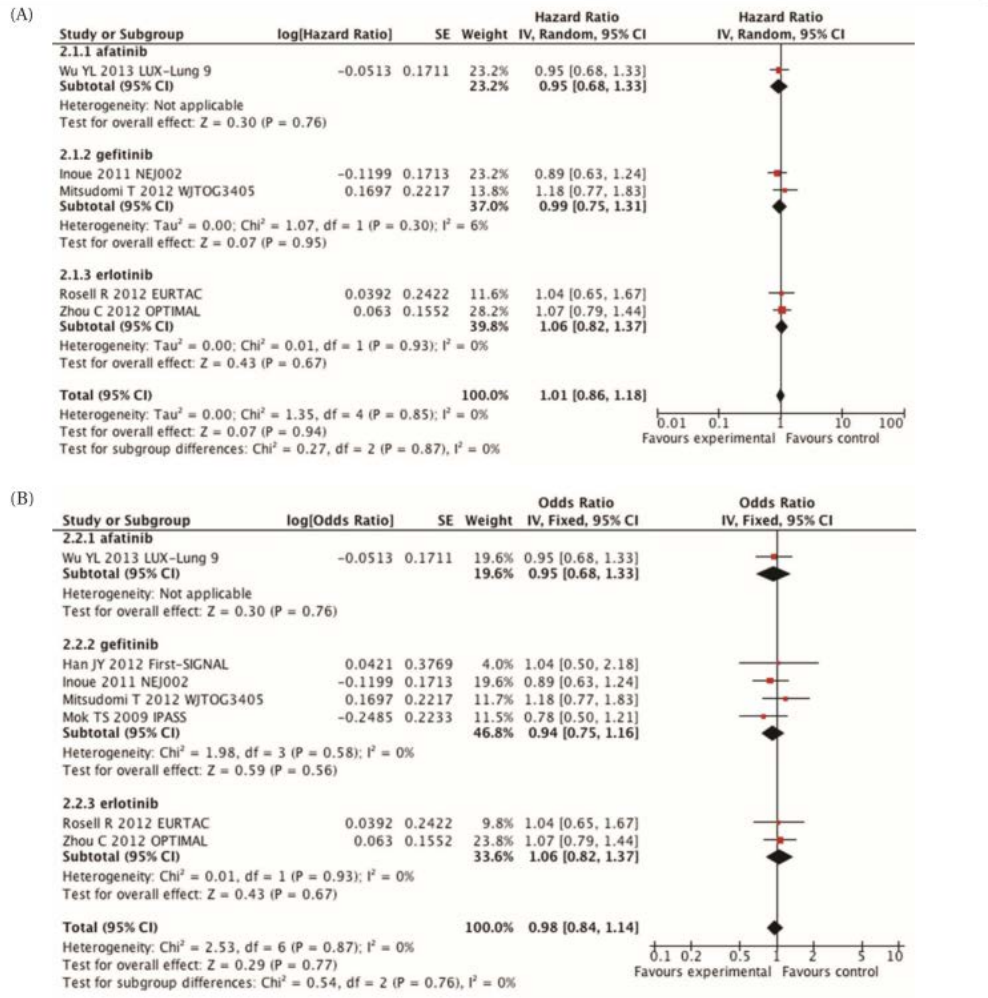
‡HR (EGFR TKI *v* chemotherapy) adjusted for smoking status and type of *EGFR* mutation.

In four trials there were no significant correlations between EGFR mutation type and age, performance status, sex, histology, or smoking status

	Table 3. Association Between Baseline Characteristics and Exon 19 Deletion or Exon 21 L858R Substitution: Pooled Data From Four Clinical Trials Exon 19 Deletion (n = 401) / Exon 21 L858R Substitution (n = 313) Characteristic — No. — % — No. — % — P Age, years — .20 < 65 — 233 — 58 — 166 — 53 ≥ 65 — 168 — 42 — 147 — 47 ECOG PS — .32 0 — 186 — 46 — 136 — 44 1 — 191 — 48 — 164 — 52 2 — 24 — 6 — 13 — 4 Sex — .81 Female — 268 — 67 — 206 — 66 Male — 133 — 33 — 107 — 34 Smoking — .81 Never — 268 — 67 — 212 — 68 Ever — 133 — 33 — 101 — 32 Histologic subtype — .11 Adenocarcinoma — 377 — 94 — 284 — 91 Other — 24 — 6 — 29 — 9 Abbreviations: EGOG, Eastern Cooperative Oncology Group; PS, performance status. **Anmerkungen/Fazit der Autoren** Although EGFR TKIs significantly prolonged PFS overall and in all subgroups, compared with chemotherapy, greater benefits were observed in those with exon 19 deletions, never-smokers, and women. These findings should enhance drug development and economic analyses, as well as the design and interpretation of clinical trials. **Hinweis der FBMed** Es ist keine Qualitätsbewertung der Primärstudien dargelegt.
Ellis PM et al. 2015 [12]. Use of the epidermal growth factor receptor inhibitors gefitinib, erlotinib, afatinib, dacomitinib, and icotinib in the treatment of non-small-cell lung cancer: a systematic review	**Fragestellung** This systematic review addresses the use of epidermal growth factor receptor (egfr) inhibitors in three populations of advanced non-small-cell lung cancer (nsclc) patients—unselected, selected, and molecularly selected—in three treatment settings: first line, second line, and maintenance. **Methodik** **Population:** NSCLC; patients—unselected, selected, and molecularly selected In the unselected group, any nsclc patient was allowed to participate in the trial as long as the other trial eligibility criteria were met in the absence of molecular testing. In the clinically selected group, patients were selected based on clinical characteristics predictive of an EGFR mutation such as Asian ethnicity, adenocarcinoma histology, female sex, smoking status, or age. In the mo lecularly selected group, patients were included if their tumours tested positive for an EGFR mutation. **Intervention:** EGFR-TKI (first line, second line, and maintenance) **Komparator:** nicht präspezifiziert **Endpunkte:** nicht präspezifiziert **Suchzeitraum:** 2006 - 3/2014

	Anzahl eingeschlossene Studien/Patienten (Gesamt): 96, nur RCT **Qualitätsbewertung der Studien:** nicht durchgeführt **Heterogenitätsuntersuchungen:** chi-Quadrat , I^2 **Ergebnisdarstellung** Überwiegend qualitatives Review 1. **Linie** Molecularly Selected Populations: Seven trials used an egfr inhibitor in molecularly selected patients with stage iiib/iv nsclc. One trial selected patients on the basis of egfr protein overexpression (assessed by immunohis- tochemistry) or increased gene copy number (assessed by fluorescence in situ hybridization, Table iii). Six tri- als selected patients with tumours harbouring an EGFR mutation. A meta-analysis of this group of patients was performed because the patients were homogenous, and the treatment comparators were platinum-based chemo- therapy regimens. All six trials observed higher response rates favouring the egfr inhibitor group. Three of the trials (Mitsudomi et al.46, Zhou et al.48 and Yang et al.51) found the results to be statistically significant ($p < 0.0001$). In every trial, PFS was also statistically significant and favoured the EGFR inhibitor. A meta-analysis [Figure 1(A)] demonstrated a statistically significant im- provement in pfs (hr: 0.35; 95% ci: 0.28 to 0.45; $p < 0.00001$). However, the I2 is high at 80%, which shows considerable statistical heterogeneity. In each of the subgroup analyses (different egfr inhibitors), the I2 also remains high. The cause of the heterogeneity remains unknown at this time. The addition of the subgroup analyses from both the ipass and First-signal trials in patients with a known EGFR mutation status36,38 resulted in similar findings [hr: 0.38; 95% ci: 0.31 to 0.46; $p < 0.00001$; Figure 1(B)]. Evidence of statistical heterogeneity remains, with an I2 of 76%. Six trials reported os. The data are difficult to interpret, because many patients are likely to have crossed over to the other treatment arm, but the actual percentages are not reported. Meta-analysis of those trials demonstrates no difference in survival between the two groups [hr: 1.01; 95% ci: 0.86 to 1.18; $p = 0.94$; Figure 2(A)]. Inclusion of data from the ipass and First-signal trials did not change that result [hr: 0.98; 95% ci: 0.84 to 1.14; $p = 0.77$; Figure 2(B)]. One additional study compared an egfr inhibitor plus chemotherapy with an egfr inhibitor alone in patients with egfr protein overexpression or increased gene copy num-ber53. No clear recommendation can be made from that trial. Response rate and pfs were higher in the egfr plus chemotherapy group, but os favoured the egfr-inhibitor- alone group The most significant toxicity was skin rash, which occurred in slightly higher numbers in the egfr-inhibitor-alone group 53. Symptom control and quality of life were discussed in the Yang et al. and Wu et al. studies. A significant delay in time to deterioration of the cancer-related symptoms of cough (hr: 0.60; $p = 0.0072$) and dyspnea (hr: 0.68; $p = 0.0145$) was seen with the egfr inhibitor afatinib. A higher proportion of patients in the afatinib group experienced a

significantly longer time to deterioration (hr: 0.56; 95% ci: 0.41 to 0.77; p = 0.0002)52. The adverse effects were consistent with those found with EGR inhibitors and chemotherapy.



GURE 2 (A) Meta-analysis of overall survival, comparing epidermal growth factor receptor inhibitors with chemotherapy in molecularly selected tients. (B) Meta-analysis of overall survival, comparing epidermal growth factor receptor inhibitors with chemotherapy in molecularly selected tients, including those in the IPASS and First-SIGNAL trials. SE = standard error; IV = inverse variance; CI = confidence interval.

2. Linie

Molecularly Selected Populations: EGFR Inhibitor Compared with Chemotherapy: One study compared the use of an egfr inhibitor with the use of chemotherapy in pa tients known to be EGFR wild-type. The trial specifically excluded crossover to the other treatment at the time of progression. Compared with erlotinib, docetaxel was associated with an improved pfs (hr: 0.71; 95% ci: 0.53 to 0.95; p = 0.02). The primary outcome in the trial was os, which was also significant for docetaxel at 8.2 months compared with 5.4 months for erlotinib (hr: 0.73; 95% ci: 0.53 to 1.00; p = 0.05; Table VIII).

TABLE VIII Second-line epidermal growth factor receptor (EGFR) inhibitor trials in molecularly selected populations

Reference (study details)	Patients (*n*)		Treatment (CR+PR)	Response rate	Median survival	
	Enrolled	Analyzed			Progression-free	Overall
Second-line EGFR inhibitor compared with chemotherapy in molecularly selected patients						
Garassino *et al.*, 2013[100] (TAILOR, phase III)	112		Erlotinib 150 mg daily	Not reported	2.4 Months	5.4 Months
	110		Docetaxel 75 mg/m^2		2.9 Months HR: 0.71; 95% CI: 0.53 to 0.95 (p=0.02)	8.2 Months HR: 0.73; 95% CI: 0.53 to 1.00 (p=0.05)
Second-line EGFR inhibitor plus another agent compared with EGFR inhibitor in molecularly selected patients						
Gitlitz *et al.*, 2011[101] (APRICOT-L, phase II, abstract)	120		Erlotinib 150 mg daily plus apricoxib 400 mg daily	Not reported	TTP: 2.1 months	5.6 Months
	176		Placebo plus erlotinib 150 mg daily		TTP: 1.8 months HR: 0.5 (p=0.018)	5.9 Months HR: 0.4 (p=0.025)
Belani *et al.*, 2013[102] (phase II)	18		PF-3512676 (0.20 mg/kg) plus erlotinib 150 mg daily	Not reported	1.6 Months	6.4 Months
	21		Erlotinib 150 mg daily		1.7 Months HR: 1.00; 95% CI: 0.5 to 2.0 (p=0.9335)	4.7 Months HR: 1.3; 95% CI: 0.6 to 2.8 (p=0.4925)
Second-line EGFR inhibitor compared with EGFR inhibitor in molecularly selected patients						
Kim *et al.*, 2012[103] (phase II)	48		Gefitinib 250 mg daily	47.9%	4.9 Months	Not reached
	48		Erlotinib 150 mg daily	39.6%	3.1 Months (p=0.336)	

CR = complete response; PR = partial response; HR = hazard ratio; CI = confidence interval; TTP = time to progression.

Erhaltungstherapie Keine Studien mit EGFR M+ Patienten -

Anmerkungen/Fazit der Autoren In the first-line setting, data about the efficacy of egfr tyrosine kinase inhibitors (tkis) compared with platinum-based chemotherapy are inconsistent. Results from studies that selected patients based on clinical characteristics are also mixed. There is high-quality evidence that an egfr tki is preferred over a platinum doublet as initial therapy for patients with an activating mutation of the EGFR gene. The egfr tkis are associated with a higher likelihood of response, longer progression-free survival, and improved quality of life. Multiple trials of second-line therapy have compared an egfr tki with chemotherapy. Meta-analysis of those data demonstrates similar progression- free and overall survival. There is consequently no preferred sequence for second-line egfr tki or second-line chemotherapy. The egfr tkis have also been evaluated as switch-maintenance therapy. No molecular marker could identify patients in whom a survival benefit was not observed; however, the magnitude of the benefit was modest. Determination of EGFR mutation status is essential to making appropriate treatment decisions in patients with nsclc. Patients who are EGFR mutation–positive should be treated with an egfr tki as first-line therapy. An egfr tki is still appropriate therapy in patients who are EGFR wild-type, but the selected agent should be administered as second- or third-line therapy.

Hinweis der FBMed

Es ist keine Qualitätsbewertung der Primärstudien dargelegt.

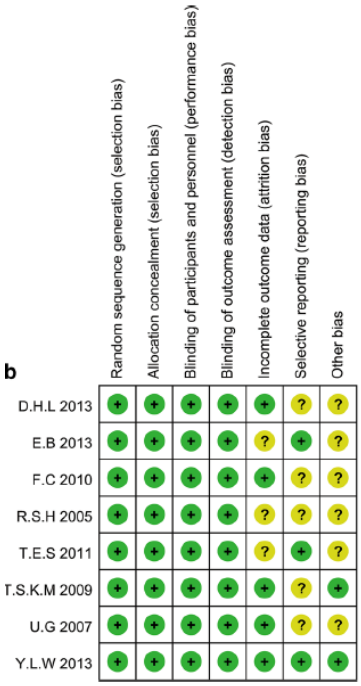
Zhou JG et al. 2015 [41]. Treatment on advanced	**Fragestellung** to assess the potential of erlotinib plus platinum based chemotherapy relative to platinum-based chemotherapy alone for advanced non-small-cell

NSCLC: platinum-based chemotherapy plus erlotinib or platinum-based chemotherapy alone? A systematic review and meta-analysis of randomised controlled trials	lung cancer (NSCLC). **Methodik Population**: advanced NSCLC **Intervention**: erlotinib plus platinum-based chemotherapy **Komparator**: platinum-based chemotherapy alone **Endpunkte**: OS, ORR, PFS **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: 2000-2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 8 **Qualitätsbewertung der Studien:** Cochrane risk of bias. Mittlere bis gute Qualität. **Ergebnisdarstellung**

Table 1 Main characteristics of the studies

References	Phase	Line of treat	Intervention regimen	Control regimen	Participants	Median age (years)	Stage IIIB (n, %)	PFS HR (95 % CI)	OS HR (95 % CI)
Herbst et al. [26]	III	1	Erl 150 mg/day plus Car AUC = 6 D1 and Pac 200 mg/m^2 D1	Car AUC = 6 D1 and Pac 200 mg/m^2 D1, 6 cycle	180/164	62.6/62.7	84 (46.7)/96 (58.5)	NG	0.99 (0.86–1.16)
Gatzemeier et al. [25]	III	NG	Erl 150 mg/day plus (Gem 1,250 mg/m^2 D1,8 and Cis 80 mg/m^2 D1)*6 cycles	Gem 1,250 mg/m^2 D1,8 and Cis 80 mg/m^2 D1)*6 cycles	579/580	61/60	242 (41.8)/225 (38.8)	0.98 (0.86–1.11)	1.06 (0.90–1.23)
Mok et al. [24]	II	1	Erl 150 mg/day plus (Gem 1,250 mg/m^2 D1,8 and either Cis75 mg/m^2 D1 or Car AUC = 5, D1)	Gem 1,250 mg/m^2 D1,8 and either	57.5/57	76/78	13 (17.1)/16 (20.5)	0.71 (0.62–0.82)	1.09 (0.70–1.69)
Cappuzzo et al. [23]	III	1	Erl 150 mg/day plus select one of seven standard chemotherapy regimens	Cis75 mg/m^2 D1 or Car AUC = 5, D1	438/451	60/60	116 (26.5)/109 (24.2)	NG	0.81 (0.70–0.95)
Boutsikou et al. [21]	III	NG	Erl 150 mg/day plus (Doc 100 mg/m^2 and Car AUC = 5.5 q28d*4)	Doc 100 mg/m^2 and Car AUC = 5.5 q28d*4	52/61	62.5/65	13 (25.0)/10 (16.4)	NG	0.81 (0.39–1.70)
Lee et al. [20]	II	2	Erl 150 mg/day plus Pem 500 mg/m^2 D1 q21d	Pem 500 mg/m^2 D1 q21d	78/80	55.8/55.9	6 (7.7)/11 (13.8)	0.58 (0.39–0.85)	0.75 (0.49–1.13)
Stinchcombe et al. [22]	II	1	Erl 150 mg/day plus Gem 1,200 mg/m^2 D1,8 q21d	Gem 1,200 mg/m^2 D1,8 q21d	51/44	78/74	10 (19.6)/11 (25.0)	0.87 (0.60–1.27)	1.20 (0.76–1.91)
Wu et al. [3]	III	1	Erl 150 mg/day plus Gem 1,250 mg/m^2 D1,8, six cycles and Car AUC = 5 or Cis 75 mg/m^2, D1	Gem 1,250 mg/m^2, d1,8, six cycles and Car AUC = 5 or Cis 75 mg/m^2, D1	226/255	59/57.3	21 (9.3)/24 (10.7)	0.57 (0.47–0.69)	0.79 (0.64–0.99)

E erlotinib, *G* gemcitabine, *D* docetaxel, *Pr* pralatrexate, *Ca* carboplatin, *V* vinorelbine, *Ci* cisplatin, *Pa* paclitaxel, *Pe* pemetrexed, *NG* not given, *OSR* one-year survival rates, *ORR* objective response rate



Overall survival:

A total of eight RCTs regarding OS were incorporated into this meta-analysis. The heterogeneity test indicated that a fixed effect model could be selected (I^2 = 39.6 %, P = 0.115). The pooled results showed that there was no significant difference between the two groups (HR 0.93; 95 % CI 0.86, 1.00; P = 0.170)

PFS:

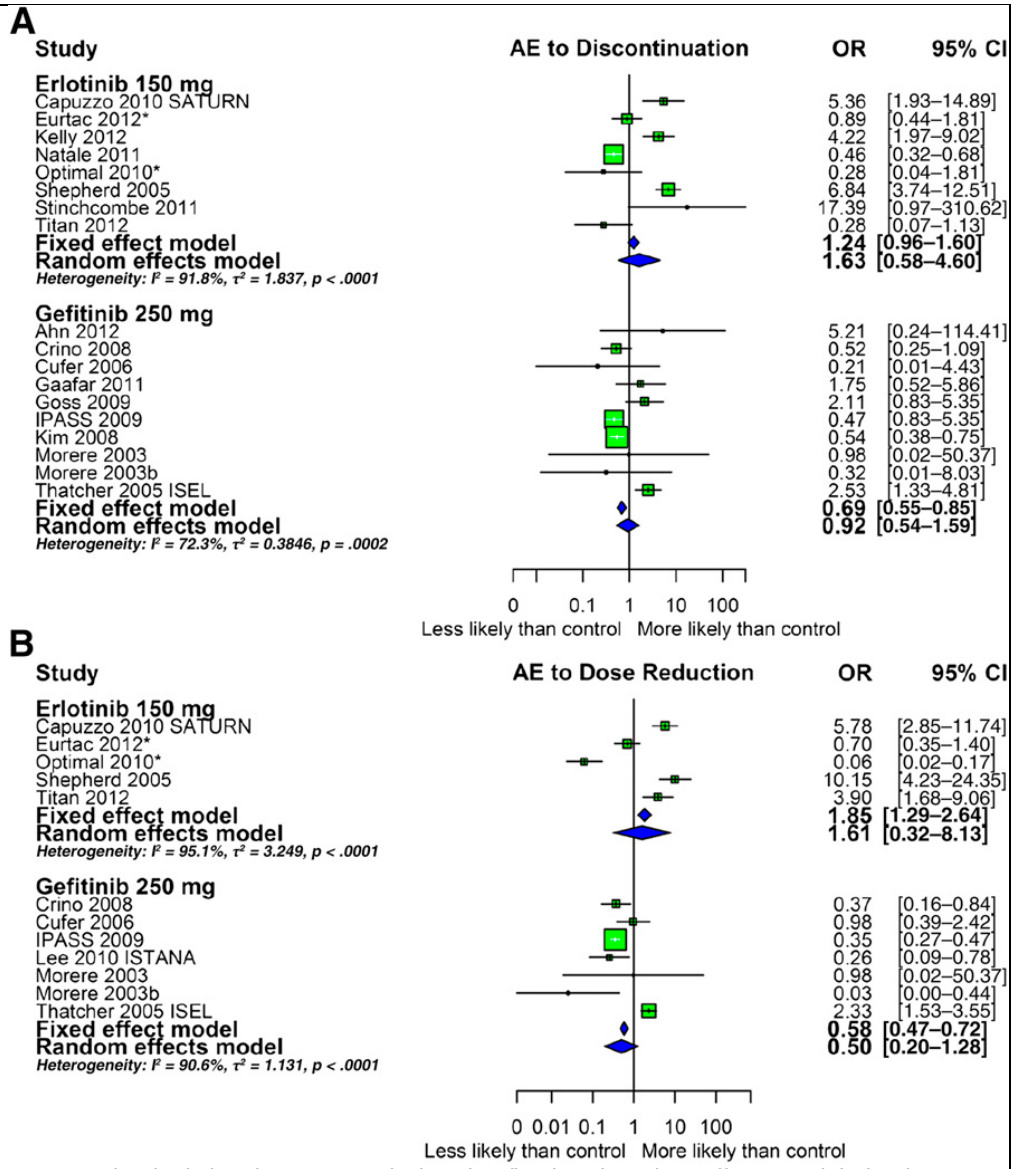
The heterogeneity test indicated that a random effect model could be selected (I^2 = 85.1 %, P<0.0001). The meta-analysis showed that the pooled HR was 0.73 (95 % CI = 0.58, 0.93), P = 0.009) and without statistical significance was identified in terms of the erlotinib platinum-based chemotherapy regimen relative to the platinum-based chemotherapy alone

Anmerkungen/Fazit der Autoren

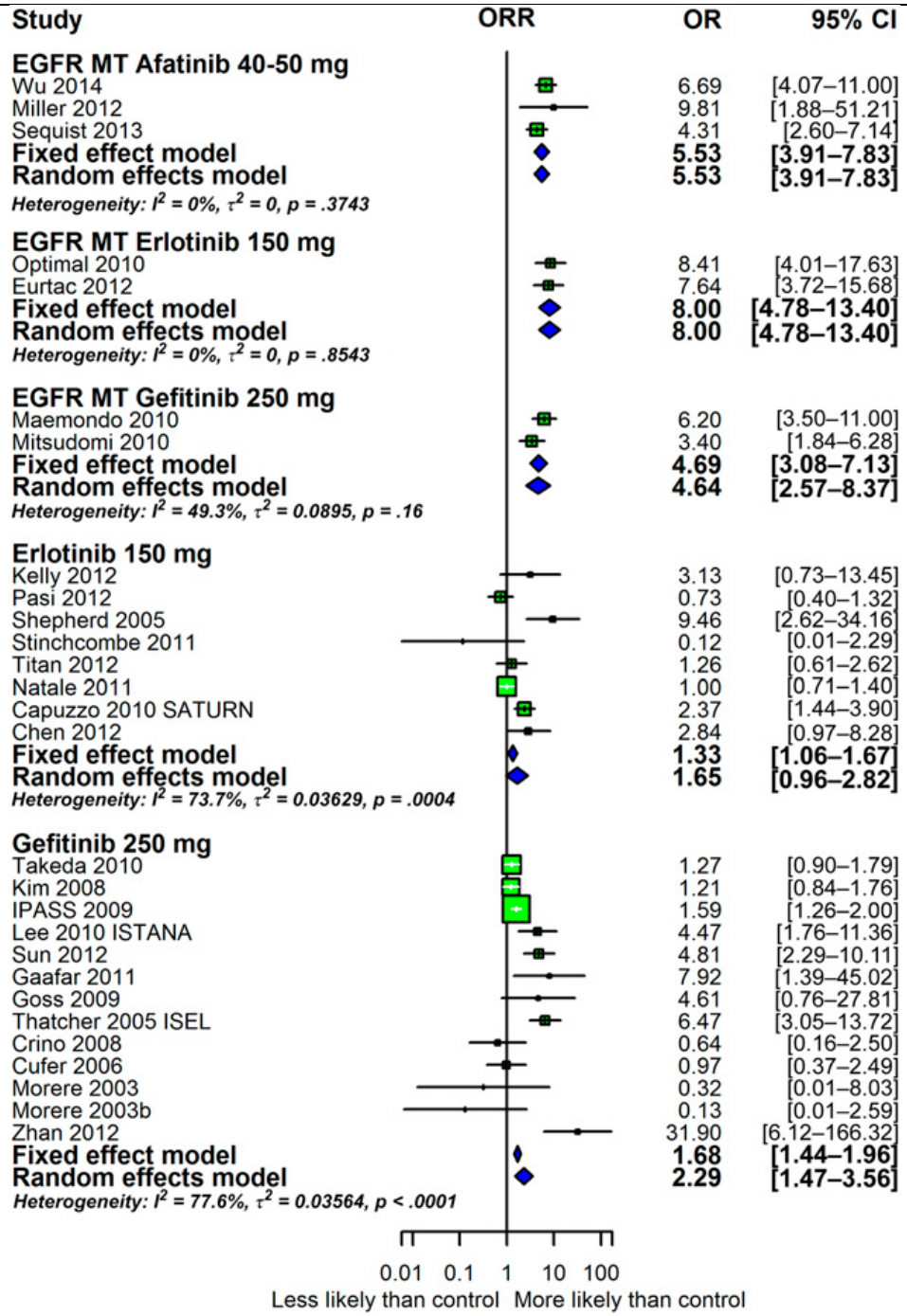
In summary, the current available evidence suggests that erlotinib lacks the potential to improve OS. PFS and objective response rate could be improved by using erlotinib plus chemotherapy in patients with advanced NSCLC. Finally, smoking status and histological type are important evaluation factors that should be considered for evaluating clinical therapy and prognosis.

This is a systematic review and meta-analysis to further evaluate the efficacy of erlotinib plus platinum-based chemotherapy for advanced NSCLC. The present systematic review and meta-analysis suggested that erlotinib combined with platinum-based chemotherapy was beneficial for advanced NSCLC patient with EGFR mutation compared with platinum-based chemotherapy alone regime.

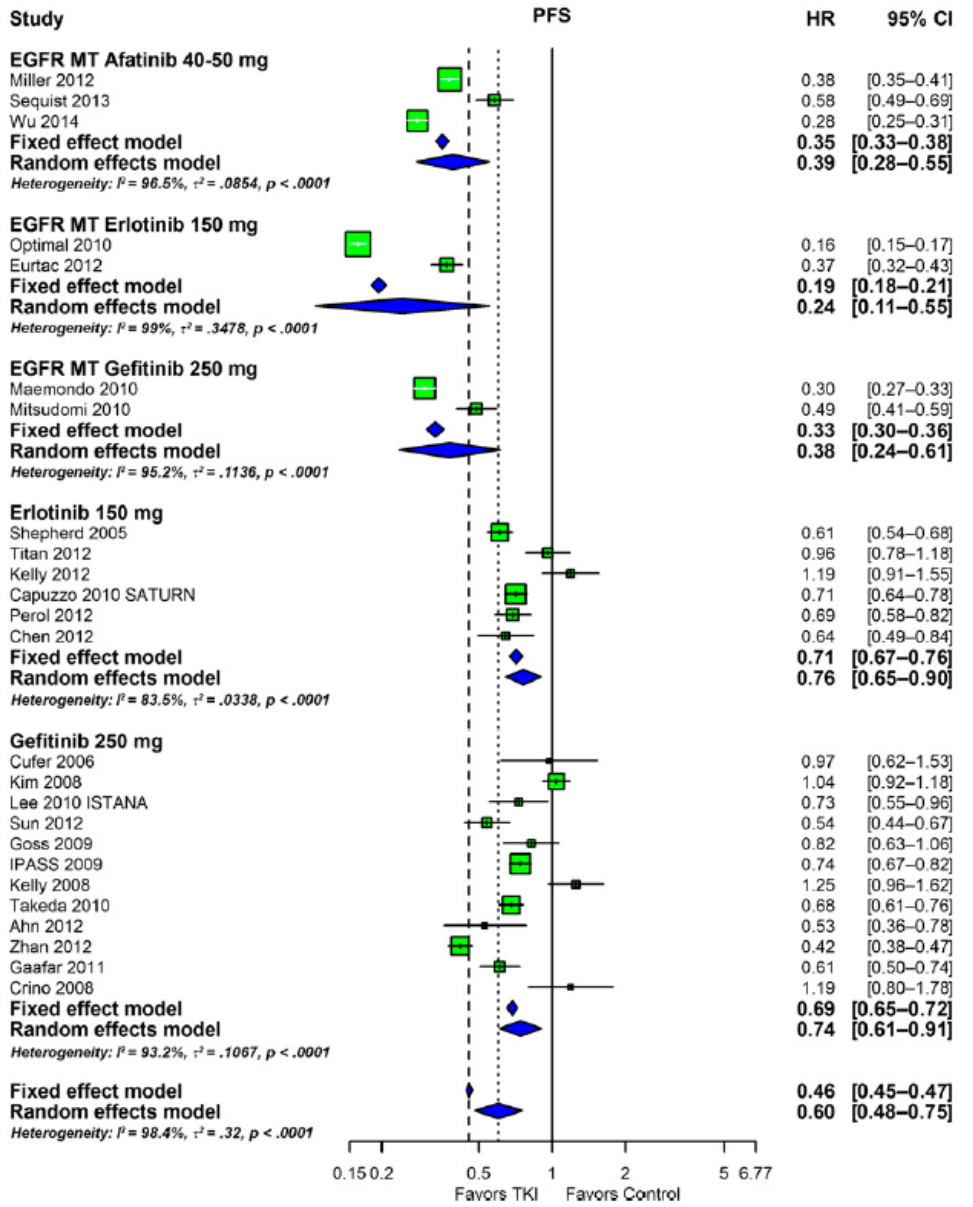
Burotto M, et al., 2015 [8] Gefitinib and Erlotinib in Metastatic Non-Small Cell Lung Cancer: A Meta-Analysis of Toxicity and Efficacy of Randomized Clinical Trials	**Fragestellung** The objective of this study was to compare the efficacy and toxicity of erlotinib, gefitinib, and afatinib in NSCLC.
	Methodik 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
	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: monotherapy in second line, monotherapy in first line (including the four trials in patient with mutated EGFR), maintenance or consolidation in first line, 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**

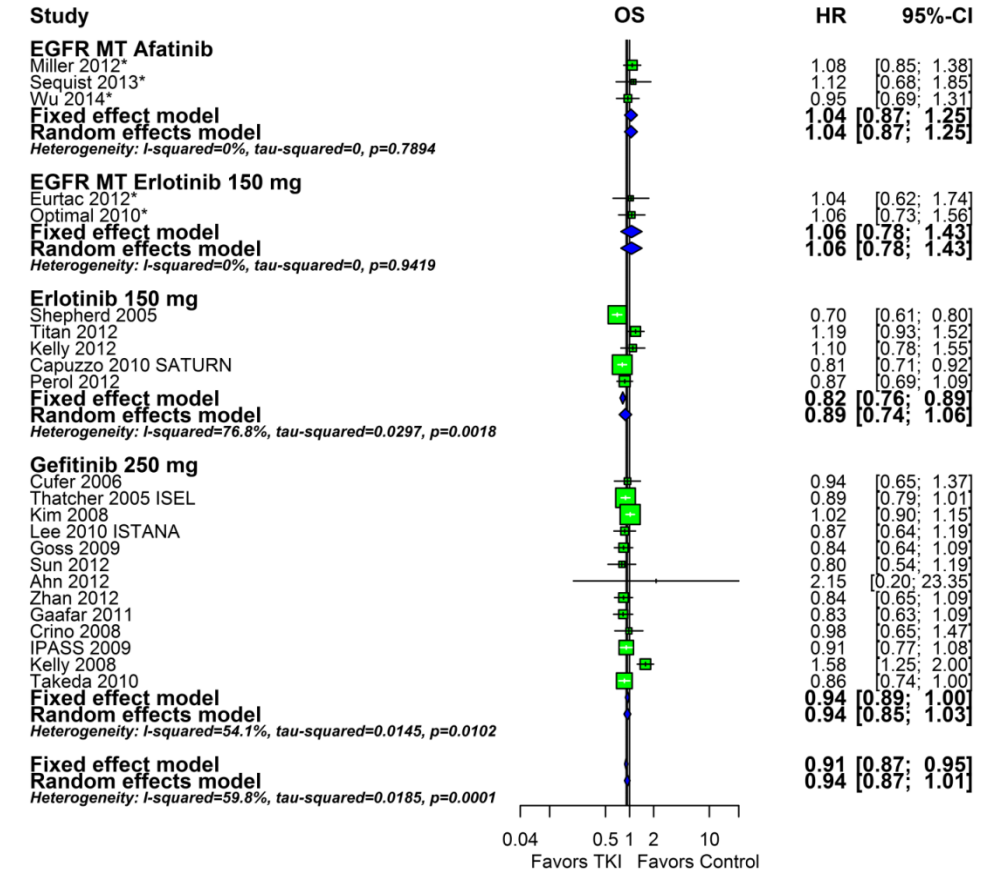


Forest plot depicting the efficacy of afatinib, erlotinib, and gefitinib in the studies evaluated as measured by ORR. An OR of > 1indicates that the arm with the tyrosine kinase inhibitor (TKI) performed better. An OR of <1 indicates that the arm with the TKI performed worse.The three groups at the top 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



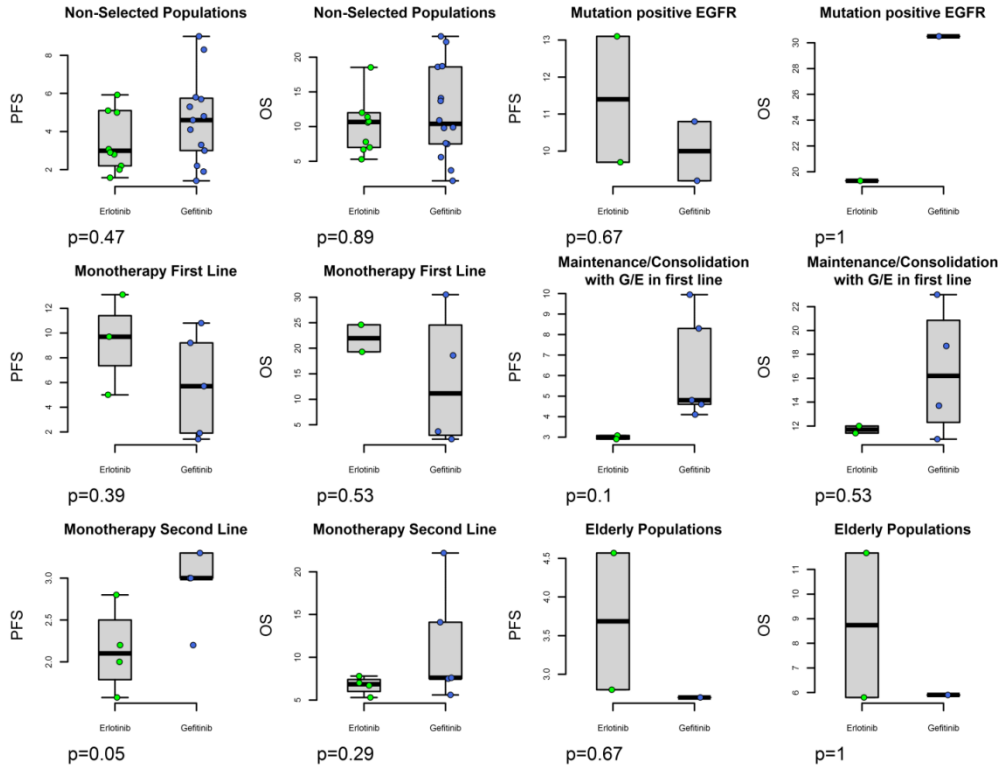


Figure S8: Efficacy analysis in all studies and in various subgroups comparing the efficacy of erlotinib and gefitinib. Results are presented for both reported median

	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.
	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. Limitationen: 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.*
Normando SRC et al, 2015 [27]. Cumulative meta-analysis of epidermal growth factor receptor-tyrosine kinase inhibitors as first-line therapy in metastatic non-small-cell lung cancer	**Fragestellung** We carried out a meta-analysis to evaluate the benefit of epidermal growth factor-tyrosine kinase inhibitors (EGFR-TKI) over the standard first-line platinum-based chemotherapy for metastatic non-small-cell lung cancer (NSCLC). **Methodik** **Population:** advanced NSCLC, stages IIIB or IV **Intervention:** standard first-line platinum-based chemotherapy **Komparator:** EGFR-TKI We excluded studies that used EGFR inhibitors as second-line therapy as well as studies in which the control group received only placebo. **Endpunkte:** OS, PFS **Suchzeitraum:** 2009 - 2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 8 **Qualitätsbewertung der Studien:** Jadad **Heterogenitätsuntersuchungen:** χ^2-test **Ergebnisdarstellung** All studies were randomized, open, controlled, and phase III trials. A formal review of the eight studies indicated that the quality was high (Jadad score $\geq$

3).

Table 1 Population characteristics of the studies

Study	Number of patients	Therapy	Ethnicity, White/ Asian/others	Smokers [*n* (%)]	Adenocarcinomas [*n* (%)]	Phase IV [*n* (%)]	Primary end point/ significance	EGFR mutated Int/control [*n* (%)]	OS mean (Int × control) *P*	PFS mean (Int × control) *P*
IPASS	1217	Gefitinib (*n* = 609) Carboplatin/paclitaxel (*n* = 608)	0/1214/0	77 (6.3)	1.1172 (96)	922 (75.7)	PFS/Yes	132 (21.6)/29 (4.7)	18.6 × 17.3 months	5.7 × 5.8 months *P* < 0.001
First-SIGNAL	309	Gefitinib (*n* = 159) Gemcitabine/cisplatin (*n* = 150)	NR	0	309 (100)	278 (89.9)	OS/No	26 (16.3)/ 16 (10.6)	22.3 × 22.9 months *P* = 0.604	5.8 × 6.4 months *P* < 0.138
Uptade NEJ002	228	Gefitinib (*n* = 114) Carboplatin/paclitaxel (*n* = 114)	NR	87 (38.1)	213 (93.4)	172 (75.4)	PFS/Yes	114 (100)/114 (100)	27.7 × 26.6 months *P* = 0.483	10.8 × 5 4 months *P* < 0.0001
WJTOG3405	172	Gefitinib (*n* = 86) Cisplatin/docetaxel (*n* = 86)	NR	54 (31.3)	167 (97)	82 (47.6)	PFS/Yes	86 (100)/86 (100)	30.9 × not reached *P* = 0.211	9.2 × 6.3 months *P* < 0.001
OPTIMAL	154	Erlotinib (*n* = 82) Gemcitabine/ carboplatin (*n* = 72)	NR	45 (29)	134 (87)	138 (89.6)	PFS/Yes	82 (100)/72 (100)	NR	13.3 × 4.6 *P* < 0.0001
EURTAC	173	Erlotinib (*n* = 86) Cisplatin/docetaxel or gemcitabine (*n* = 87)	NR	53 (30.6)	160 (92.4)	160 (92.4)	PFS/Yes	86 (100)/87 (100)	13.6 × 19.5 months *P* = 0.87	9.7 × 5.2 months *P* < 0.0001
LUX-LUNG III	345	Afatinib (*n* = 230) Cisplatin/pemetrexed (*n* = 115)	91/248/6	109 (31.5)	345 (100)	308 (89.2)	PFS/Yes	230 (100)/115 (100)	16.6 × 14.8 months *P* = 0.6	11.1 × 6.7 months *P* < 0.001
LUX-LUNG VI	364	Afatinib (*n* = 242) Gemcitabine/cisplatin (*n* = 122)	0/364/0	84 (23)	364 (100)	342 (93.9)	PFS/Yes	242 (100)/364 (100)	22.1 × 22.2 months *P* = 0.76	11 × 5.6 months *P* < 0.0001

Control, control group; EGFR, epidermal growth factor receptor; Int, intervention group; NR, not reported; OS, overall survival; PFS, progression-free survival.

PFS

Significant differences between the two arms were found when PFS were compared, favoring the EGFR-TKI group [HR = 0.266 (95% CI = 0.20–0.35), P< 0.0001]. Heterogeneity between the analyzed arms was absent (Q = 9.402, P= 0.225). This benefit was sustained in all the subgroups analyzed (Table 2). The analyses of PFS of the different mutations, del Exon 19 [HR = 0.187 (95% CI = 0.131–0.267), P <0.0001, Q =4.436 P= 0.35] and L858R-exon 21 [HR = 0.345 (95% CI = 0.181–0.659), P < 0.001, Q = 0.995 P =0.911], are shown in Figs 3 and 4, respectively. Two studies (IPASS/First-

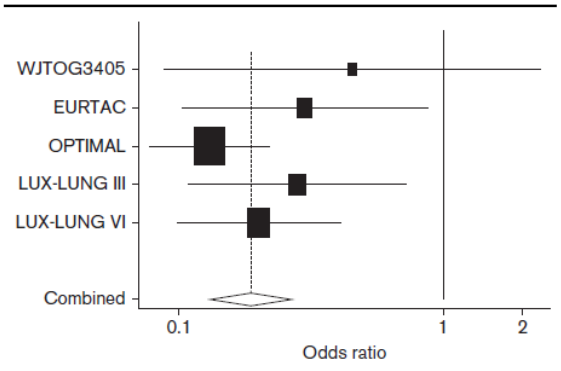
SIGNAL) included patients without the EGFR mutation, where subgroup analysis was carried out according to the status of the EGFR mutation with respect to PFS. Among the patients without the EGFR mutation (n= 230), there was no PFS gain compared with the control group [HR = 1.170 (95% CI = 0.48–2.83), P =0728], (Q =0.008, P= 0.931) (Fig. 5). The cumulative meta-analysis of the studies showed that, since 2011 (OPTIMAL study), the PFS gain for EGFRTKI compared with chemotherapy was statistically significant.

Table 2 Patient subgroup analysis in relation to progression-free survival

Subgroup	Study	HR (95% CI)	HR bundled (95% CI)
Smokers	WJTOG3405	0.57 (0.29–1.12)	0.29 (0.14–0.62)
	OPTIMAL	0.21 (0.09–0.49)	
	EURTAC	0.56 (0.15–2.15)	
	LUX-LUNG III	1.04 (0.54–1.98)	
	LUX-LUNG VI	0.46 (0.22–1.00)	
Nonsmokers	WJTOG3405	0.46 (0.28–0.73)	0.20 (0.15–0.27)
	OPTIMAL	0.14 (0.08–0.25)	
	EURTAC	0.24 (0.15–0.39)	
	LUX-LUNG III	0.47 (0.33–0.67)	
	LUX-LUNG VI	0.24 (0.16–0.34)	
Adenocarcinoma	OPTIMAL	0.17 (0.11–0.28)	0.19 (0.12–0.30)
	EURTAC	0.37 (0.24–0.56)	
Nonadenocarcinoma	OPTIMAL	0.22 (006–0.73)	0.22 (0.06–0.80)
	EURTAC	0.27 (0.05–1.44)	
Phase IIIb	WJTOG3405	0.333 (0.203–0.544)	0.20 (0.13–0.31)
	OPTIMAL	0.18 (0.11–0.28)	
Phase IV	WJTOG3405	0.333 (0203–0.544)	0.32 (0.13–0.78)
	OPTIMAL	0.27 (0.06–1.16)	
ECOG 0	OPTIMAL	0.16 (0.10–0.26)	0.19 (0.30–0.27)
	EURTAC	0.26 (0.12–0.59)	
	LUX-LUNG III	0.50 (0.31–0.82)	
	LUX-LUNG VI	0.22 (0.12–0.41)	
ECOG 1	OPTIMAL	0.16 (0.10–0.26)	0.21 (0.15–0.30)
	EURTAC	0.37 (0.22–0.62)	
	LUX-LUNG III	0.63 (0.43–0.91)	
	LUX-LUNG VI	0.29 (020–0.43)	
ECO 2	OPTIMAL	0.21 (0.04–1.28)	0.30 (0.04–1.95)
	EURTAC	0.48 (0.15–1.48)	
Feminine	WJTOG3405	0.671 (0.337–1.334)	0.18 (0.13–0.25)
	OPTIMAL	0.13 (0.07–0.24)	
	EURTAC	0.35 (0.22–0.55)	
	LUX-LUNG III	0.61 (0.37–1.01)	
	LUX-LUNG VI	0.24 (0.16–0.35)	
Masculine	WJTOG3405	0.418 (0.267–0.654)	0.35 (0.21–0.59)
	OPTIMAL	0.26 (0.14–0.50)	
	EURTAC	0.38 (0.17–0.84)	
	LUX-LUNG III	0.54 (0.38–0.78)	
	LUX-LUNG VI	0.36 (0.21–0.63)	
EGFR wild type	First-SIGNAL	1.419 (0.817–2.466)	–
Mutation: exon 19 del	WJTOG3405	0.453 (0.268–0.768)	0.19 (0.14–0.25)
	EURTAC	0.30 (0.18–0.50)	
	OPTIMAL	0.13 (0.07–0.25)	
	LUX-LUNG III	0.28 (0.18–0.44)	
	LUX-LUNG VI	0.20 (0.13–0.33)	
Mutation: L858R/exon 21	WJTOG3405	0.514 (0.294–0.899)	0.34 (0.20–0.60)
	EURTAC	0.55 (0.29–1.02)	
	OPTIMAL	0.26 (0.14–0.49)	
	LUX-LUNG III	0.73 (0.46–1.17)	
	LUX-LUNG VI	0.32 (0.19–0.52)	
Mutation Del19/L858R uncommon	LUX-LUNG III	0.47 (0.34–0.65)	–

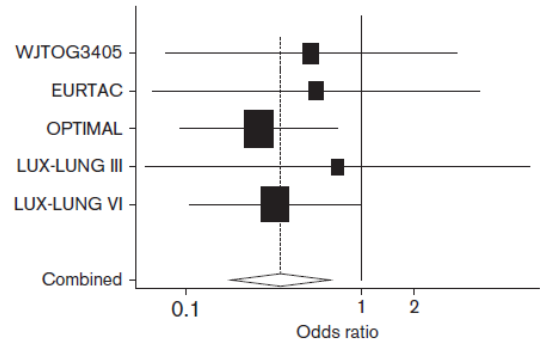
CI, confidence interval; HR, hazard ratio.

Fig. 3



Progression-free survival in patients with the EGFR mutation (del Exon 19 mutation). Odds ratio = 0.187 (0.131–0.267, $P < 0.0001$); heterogeneity test: $Q = 4.436$ $P = 0.35$. EGFR, epidermal growth factor receptor.

Fig. 4

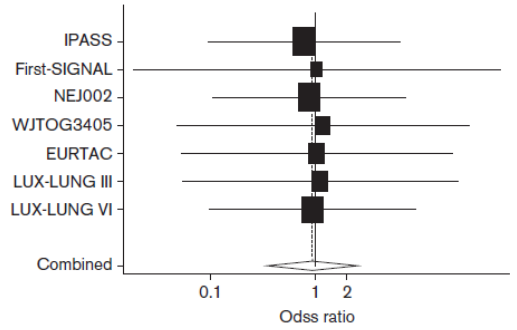


Progression-free survival in patients with the EGFR mutation (L858R-exon 21 mutation). Odds ratio = 0.345 (0.181–0.659, $P < 0.001$); heterogeneity test: $Q = 0.995$ $P = 0.911$. EGFR, epidermal growth factor receptor.

OS

For OS analysis, an updated WJTOG3405 study was used, available only in abstract form presented at a conference [19]. The other studies were analyzed from full articles mentioned previously. There was no significant difference between the control group and the EGFRTKI in the population with the EGFR mutation [HR = 0.946 (95% CI = 0.35–2.53), P =0.912] (Fig. 7). There was no heterogeneity in the results (Q = 0.073, P = 1.0). Similarly, there was no difference in the OS in the population without any EGFR mutation [HR = 1.16 (95% CI 0.09–14.4), P =0.9] (Fig. 8). There was no significant difference in terms of OS in the cumulative meta-analysis.

Fig. 7



Overall survival in all groups. Odds ratio = 0.946 (0.353–2.538, $P = 0.91$); heterogeneity test: $Q = 0.073$ $P = 1.0$.

Anmerkungen/Fazit der Autoren

The cumulative meta-analysis of the studies showed that, since 2011 (OPTIMAL study), the PFS benefit in the EGFR-TKI arm was statistically significantly longer. Toxicity values greater than or equal to 3 in the most prevalent EGFR-TKI group included skin rash, diarrhea, and increased aminotransferase. EGFR-TKI treatment significantly extends PFS, with acceptable toxicities than platinum-based chemotherapy. Thus, they should be considered as the first choice in the first-line treatment for patients with NSCLC and with the EGFR mutation.

Cui J et al., 2013 [10].

The Efficacy of Bevacizumab Compared with Other Targeted Drugs for Patients with Advanced NSCLC: A Meta-Analysis from 30 Randomized Controlled Clinical Trials

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.

Methodik

Population: patients with confirmed stage IIIB, stage IV or recurrent NSCLC based on historical or cytological evidence, 1. und 2. Linie
Intervention: bevacizumab (15 mg/kg) with chemotherapy
Komparator: standard chemotherapy alone
Endpunkt: OS, ORR, PFS **Methode**: systematic review and meta-analysis of RCTs (placebo-controlled or other types of superiority trial as well as noninferiorityv trial) **Suchzeitraum**: 1999 to 2011
Anzahl eingeschlossene Studien/Patienten (Gesamt): 30 (k.A.)
Qualitätsbewertung der Primärstudien: Jadad Score

Ergebnisdarstellung

Erste 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 **2. Linie** adjusted HR for previously-treated patients was 0.680 (95%CI: 0.492, 0.942) 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 $\ln(HR_{PFS})$.

Among the 30 clinical trials included in the meta-analysis, 25 reported hazard ratios for PFS and OS (HRPFS and HROS) and the corresponding 95% confidence intervals (CIs). For other 5 trials, 3 reported the HRPFS directly and 2 reported the HROS directly. In terms of the efficacy for patients treated with gefitinib (2 trials [15,17] for EGFR-mutated patients among 14 clinical trials), meta-analysis showed that pooled ORORR in EGFRmutated patients was 4.862 (95%CI: 3.064, 7.715; I2= 20.2%; Figure 3) compared to 1.199 (95%CI: 1.003, 1.434; I2 =43.3%) in EGFR untested patients (P,0.001). Pooled HRPFS in EGFRmutated patients (0.379, 95%CI: 0.235, 0.611; I2 = 74.2%) was smaller than that in EGFR untested patients (0.896, 95%CI: 0.738, 1.087; I2= 79.1%, P= 0.001). In addition, pooled HROS in EGFR-mutated patients was 1.046 (95%CI: 0.509, 2.149; I2 = 63.0%), compared to 1.005 (95%CI: 0.924, 1.093; I2 = 38.5%) in EGFR untested patients (P= 0.914). Therefore, in the following comparison, we compared bevacizumab with other targeted drugs (gefitinib, erlotinib and cetuximab) in EGFR untested patients. However, in terms of HROS, the comparison was made in both EGFR-mutated and EGFR untested patients.

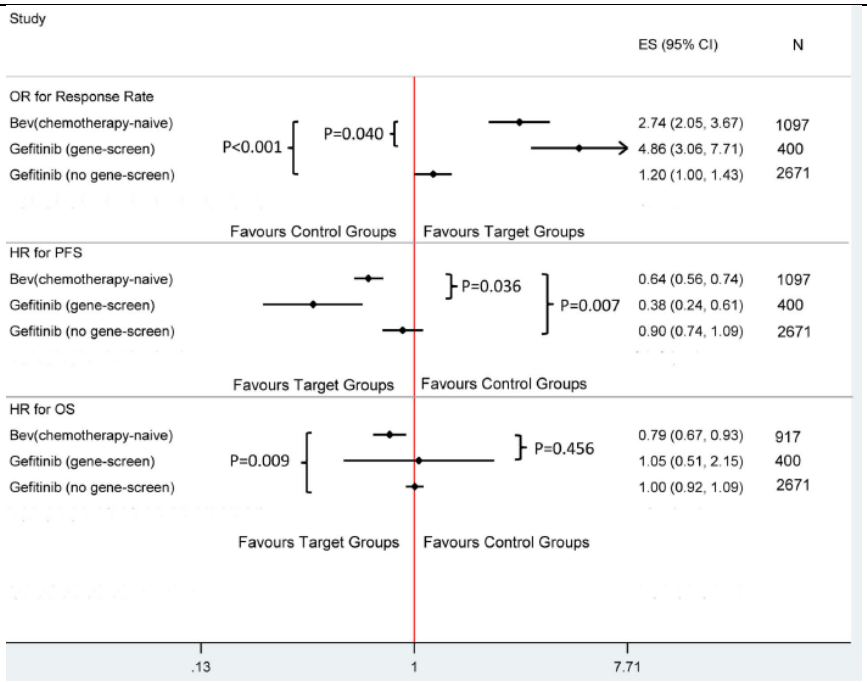


Fig. 3 Response rate, PFS, OS of Bevacizumab versus Gefitinib in NSCLC patients with different EGFR status.

Fazit der Autoren

Our meta-analyses showed that compared to other commonly used targeted drugs, chemotherapy with bevacizumab significantly improved patients' response rate, PFS and OS. In addition, bevacizumab provided significantly higher OR_{ORR}, lower HR_{PFS}, and lower HR_{OS} among chemotherapy-naive patients, and lower HR_{PFS} among previous treated patients. It was also found that in EGFRmutated patients, gefitinib significantly improved OR_{ORR} and reduces HR_{PFS}. However, in general patients with EGFR status untested, bevacizumab showed a clear benefit in OR_{ORR}, HR_{PFS}, as well as HR_{OS}, compared with gefitinib.

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.

Gao H et al., 2011 [13].

Efficacy of erlotinib in patients with advanced non-small cell lung cancer: a pooled

Fragestellung

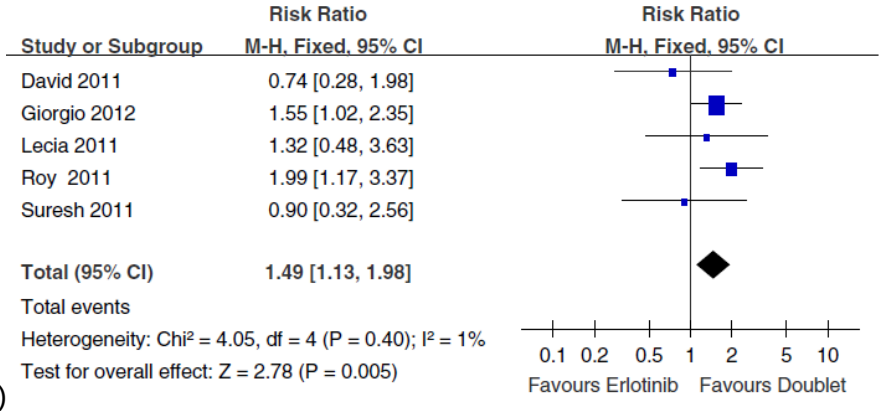
to assess the efficacy and safety of erlotinib in patients with advanced NSCLC

Methodik

Population: advanced NSCLC. Alle Linien

Intervention: erlotinib alone or based combination therapy **Komparator**: other agent or based combination regimen

analysis of randomized trials	**Endpunkt**: OS, PFS, ORR, toxicity **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: 1997 bis 2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 14 (n= 7974) **Qualitätsbewertung der Studien:** keine **Ergebnisdarstellung** ***First-line therapy (5 trials)*** **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) and a similar OS compared with placebo as maintenance therapy (HR: 0.87; 95% CI: 0.68–1.11; P=0.22) **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). **Response rate (9 trials, 5.404 patients):** no statistically significant difference between erlotinib-based regimens and other regimens. Significant heterogeneity The subgroup analysis showed a similar ORR comparing with placebo (OR: 0.90; 95% CI: 0.74–1.09; P=0.29) or chemotherapy (OR: 0.33; 95% CI: 0.64–17.36; P=0.15) but an increased ORR comparing with placebo as maintenance therapy (OR: 0.47; 95% CI: 0.31–0.70; P<0.01). ***second/third-line therapy*** compared with placebo: erlotinib-based regimens also significantly increased ORR (OR: 0.10;95% CI: 0.02–0.41; P<0.01), prolonged PFS (HR: 0.61; 95% CI: 0.51–0.73; P<0.01), and improved OS (HR: 0.70; 95% CI: 0.58–0.84; P<0.01). compared with chemotherapy: outcomes were similar between two arms. compared with PF299804: decreased ORR (OR: 3.87; 95% CI: 1.27–11.81; P=0.02), and shortened PFS (HR: 0.58; 95% CI: 0.49–0.95; P=0.02). ***Toxicity****:* All 14 trials including 7261 patients provided results of adverse events. Reported toxicities were analyzed in only 12 trials except for the targeted drugs containing trials. 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), and anemia (OR: 1.39; 95% CI: 1.06–1.82; P=0.02) were significantly prominent in the erlotinib-based regimens. **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.
Pan G et al., 2013 [29]. Comparison of the efficacy and safety of single-agent erlotinib and doublet molecular targeted agents based on erlotinib in advanced non-small cell lung cancer (NSCLC): a systematic review and meta-analysis	**Fragestellung** This study aims to assess the efficacy and safety of doublettargeted agents based on erlotinib in patients with advanced NSCLC. **Methodik** **Population:** Adult patients with advanced NSCLC **Intervention:** doublets (erlotinib plus another targeted drugs) **Komparator:** erlotinib **Endpunkte:** OS, ORR,DCR (disease control rate), side effects **Suchzeitraum:** Bis 11/2012, nur RCTs **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 5 (2100 Patienten) **Qualitätsbewertung der Studien:** Cochrane risk of bias. Insgesamt gute Qualität der Studien **Heterogenitätsuntersuchungen:** I^2 **Ergebnisdarstellung** The RCTs included in this systematic review all seem to be of fairly good methodological quality mean age 63; 1,224 men and 876 women; 118 stage IIIB and 1,180 stage IV; 441 squamous cell cancers, 1,287 adenocarcinomas, and 372 other pathological types Effects: fixed effect models ***OS:*** One-year OS did not significantly improve with doublets compared with single erlotinib (HR 1.06, 95 % CI 0.95–1.18, p=0.26; fixed effect model) ***ORR:*** ORR were significantly superior with doublets (HR 1.49, 95%CI 1.13–1.98, p<0.05) 

	DCR (disease control rate): HR 1.25, 95%CI 1.12–1.39, p<0.05 ***Side effects/ AEs:*** All grades of the most frequent side effects such as rash, anemia, diarrhea, anorexia, and fatigue were similar for two groups (HR 1.25, 95 % CI 0.99–1.58; 0.98, 95 % CI 0.78–1.24; 1.43, 95%CI 0.97–2.11; 1.18, 95%CI 0.84–1.65; 1.23, 95 % CI 0.86–1.77, respectively; random effect model). The grade ≥3 toxicity was not significantly different (HR 1.40, 95 % CI 0.97–2.01; random effect model). Some adverse events (e.g., alopecia, dyspnea, dry skin, hypertension, bleeding complications, stomatitis, interstitial lung disease, and thrombocytopenia) could not be analyzed precisely due to their low incidence. **Anmerkungen/Fazit der Autoren** The results of this systematic review suggest that patients with advanced NSCLC might benefit from doublet-targeted therapy based on erlotinib compared to erlotinib alone. However, an individual patient data systematic review and meta-analysis are needed to give us a more reliable assessment of the size of benefits and to explore whether doublet therapy may be more or less effective for particular types of patients. From out MA and these studies, we can conclude that patients with advanced NSCLC can benefit from doublettargeted therapy, whereas having no notable impact on OS in unselected patients according to EGFR or KRAS status, the EGFR-negative or KRAS-positive group may benefit more from the combination therapy. Therefore, the predictive biomarkers are essential for further development of combined inhibition.
Pilkington G et al., 2015 [31]. A systematic review of the clinical effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer	**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 non-small cell lung cancer **Methodik** **Population:** adult patients with locally advanced or metastatic NSCLC **Intervention:** first-line chemotherapy treatments for NSCLC; treatments had to be currently licensed for use in Europe and recommended by NICE **Komparator:**. Andere first-line Chemotherapie **Endpunkte:** OS or PFS and TTP **Suchzeitraum:** 2001-2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 23 **Methode:** In terms of direct evidence syntheses, standard meta-analysis (MA) was undertaken for each pair-wise treatment comparison. An insufficient number of trials directly compared all chemotherapy treatment options and so multiple treatment comparison (MTC) methodology was undertaken in order to synthesise information on the relative efficacy of all included chemotherapy regimens. **Qualitätsbewertung der Studien:** All RCTs were assessed for

methodological quality using criteria based on the Centre for Reviews and Dissemination guidance. 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.

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.

	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. Table 4 Top 10 adverse events by chemotherapy regimen DOC+PLAT / GEM+PLAT / PAX+PLAT / PEM+PLAT / VNB+PLAT / GEF Neutropenia 71.4% / Granulocytopenia 48.8% / Neutropenia 62.5% / Granulocytopenia 37.9% / Neutropenia 68.3% / Aminotransferase elevation 33.8% Leucopenia 43.5% / Asthenia 40.3% / Leucopenia 31.9% / Blood transfusions 26.9% / Leucopenia 47.2% / Appetite loss 5.3% Weakness 16.0% / Neutropenia 36.4% / Weakness 14.5% / Infection 16.4% / Oedema 24.0% / Rash/acne 3.3% Pneumonitis 11.5% / Thrombocytopenia 34.6% / Cancer pain 13.2% / Neutropenia 15.1% / Anaemia 19.3% / Toxic deaths 3.1% Anaemia 11.2% / Anorexia 27.0% / Nausea 10.3% / Alopecia 11.9% / Phlebitis 15.7% / Diarrhoea 3.1% Asthenia 10.2% / Leucopenia 20.1% / Anaemia 10.0% / Leucopenia 8.2% / Nausea/vomiting 11.5% / Neutropenia 2.8% Nausea 9.9% / Transfusion 18.5% / Lethargy 9.4% / Thrombocytopenia 8.1% / Vomiting 10.3% / Pneumonitis 2.6% Vomiting 9.8% / Alopecia 17.2% / Thrombocytopenia 8.3% / Anaemia 7.0% / Nausea 9.9% / Fatigue 2.5% Cancer pain 8.4% / Weakness 17.0% / Neuropathy 7.9% / Fatigue 6.7% / Asthenia 9.4% / Infection 1.8% Infection 7.5% / Anaemia 16.5% / Vomiting 7.4% / Nausea 6.2% / Pain 8.3% / Anaemia 1.6% DOC, docetaxel; GEF, gefitinib; GEM, gemcitabine; PAX, paclitaxel; PEM, pemetrexed; PLAT, platinum; VNB, vinorelbine. **Anmerkungen/Fazit der Autoren** In earlier trials that assessed the clinical effectiveness of third generation chemotherapy drugs, there was very little analysis of outcomes by factors such as histology or genetic markers and patients with NSCLC were classed as a homogeneous patient population. However, it is now accepted that NSCLC patients can be divided into at least three subpopulations: patients with squamous disease, patients with non-squamous disease and EGFR M+ patients. Our comparisons of available drugs for different subpopulations of patients with NSCLC are therefore extremely timely and should prove useful for decision-makers. The evidence relating to patients with EGFR M+ status is based on the results from three trials conducted in East Asian countries. It is questionable whether the results of these trials are generalisable to UK clinical practice as evidence suggests that East Asian populations with NSCLC have a more favourable prognosis compared with non-East Asian populations.
Qi W-X et al., 2013 [32]. Overall Survival Benefits for Combining Targeted Therapy as Second-Line Treatment for	**Fragestellung** We performed a meta-analysis of RCTs to compare the efficacy and safety of combining targeted therapy vs. erlotinib alone as second-line treatment for advanced NSCLC. **Methodik** **Population:** Patients with pathologically confirmed of advanced NSCLC and previously treated **Intervention:** combined targeted therapy **Komperator:** erlotinib alone or erlotinib plus placebo **Endpunkte:** overall survival (OS), progression-free survival (PFS), overall

Advanced Non-Small-Cell-Lung Cancer: A Meta-Analysis of Published Data	response rate (ORR), grade 3 or 4 adverse event (AEs) **Suchzeitraum:** 1980 bis 2012 **Anzahl eingeschlossene Studien/Patienten (gesamt):** 8 / 2 417. prospective phase II and III randomized controlled trials (RCTs) **Qualitätsbewertung der Studien:** Jadad score. Insgesamt gute Studienqualität **„Publication bias"-Berechnung:** Begg and Egger tests: no evidence of publication bias **Ergebnisdarstellung**

Table 1. overview of studies in the pooled analysis (N = 2417).

Study/year	Phase	Primary endpoint	Treatment regimen	No.of patients	CR+PR (%)	PFS, mo	OS, mo	1- Year SR (%)	Jadad score
Lynch T.J.et al 2009	II	ORR	Erlotinib/Bortezomib	25	9	1.3	8.5	40	3
			Erlotinib	25	16	2.7	7.3	30	
Bennouna J. et al 2010	II	NR	Erlotinib/Everolimus	66	12.1	2.9	NR	NR	3
			Erlotinib	67	10.4	2.0	NR	NR	
HerBst, Roy S. et al 2011	III	OS	Erlotinib/bevacizumab	319	13	3.4	9.3	42.1	5
			Erlotinib/placebo	317	6	1.7	9.2	40.7	
Sequist L.V. et al. 2011	II	PFS	Erlotinib/tivantinib	84	10	3.8	8.5	NR	5
			Erlotinib/placebo	83	7	2.3	6.9	NR	
Spigel D.R. et al. 2011	II	ORR and PFS	Erlotinib/sorafenib	112	8	3.38	7.62	NR	5
			Erlotinib/placebo	56	11	1.94	7.23	NR	
Ramalingam S.S. et al. 2011	II	PFS	Erlotinib/R1507(IGF-1R) weekly	57	8.8	1.6	8.1	NR	5
			Erlotinib/R1507(IGF-1R) Q 3 weekly	57	7	2.7	12.1	NR	
			Erlotinib/placebo	57	8.8	1.5	8.1	NR	
Scagliotti G.V. et al. 2011	III	OS	Erlotinib/sunitinib	480	10.6	3.6	9.0	NR	5
			Erlotinib/placebo	480	6.9	2.0	8.5	NR	
Witta S.E.et al. 2012	II	OS	Erlotinib/Entinostat	67	3.0	1.97	8.9	NR	5
			Erlotinib/placebo	65	9.2	1.88	6.7	NR	

Abbreviations: OS: overall survival; ORR: overall response rate; PFS: progression-free survival; CR: complete response; PR: partial response; 1-year SR: 1-year survival rate; NR: not reported.

Table 2. Characteristics of patients in the pooled analysis (N = 2417).

Study/year	Treatment arm	No.of patients	Female Sex (%)	Median age, y	History of smoking, %	KRAS mutation, n (%)	EGFR mutation, n (%)
Lynch T.J. et al. 2009	Combination	25	56	62	84	NR	NR
	Single	25	48	64	80	NR	NR
Bennouna J. et al. 2010	Combination	66	NR	59	80	NR	NR
	Single	67	NR	60	82	NR	NR
HerBst, Roy S. et al. 2011	Combination	319	46	64.8	89	48 (25)	33(32)
	Single	317	46	65	90	38 (21)	43(42)
Sequist L.V. et al. 2011	Combination	84	39	64	80	10 (17)	38(52)
	Single	83	41	62	78	5 (10)	59 (40)
Spigel D.R. et al. 2011	Combination	112	44	65	NR	5 (4.5)	22(19.6)
	Single	56	53	65	NR	6(10.7)	14(25)
Ramalingam S.S. et al. 2011	Combination(weekly)	57	32	63	86	16 (27)	NR
	Combination (every 3 weekly)	57	33	62	91	12(36)	NR
	Single	57	35	62	84	8 (19)	NR
Scagliotti G.V. et al 2011	Combination	480	38.1	61	80	NR	28(5.8)
	Single	480	40.8	61	81.3	NR	30(6.3)
Witta S.E.et al. 2012	Combination	67	42	66	84	4(9)	18(60)
	Single	65	34	67	83	7(21)	11(38)

Gesamt: significantly improved OS (HR 0.90, 95%CI: 0.82–0.99, p = 0.024), PFS (HR 0.83, 95%CI: 0.72–0.97, p = 0.018), and ORR (OR 1.35, 95%CI 1.01–1.80, p = 0.04) under combined targeted therapy More incidence of grade 3 or 4 rash, fatigue and hypertension were observed in combining

	targeted therapy. ***Subgruppen:*** Sub-group analysis based on phases of trials, EGFR-status and KRAS-status also showed that there was a tendency to improve PFS and OS in combining targeted therapy, except that PFS for patients with EGFR-mutation or wild type KRAS favored erlotinib monotherapy. because of a small number of patients with EGFR-status reported in these trials, it should be careful when interpreting these results only 283 patients with EGFR mutation were included in meta-analysis more trials still needed to identify molecular biomarkers that are predictive of efficacy **Table 3.** Sub-group analysis based on study characteristics. **Sub-group** / **No. of studies for PFS** / **HR (95%CI)** / **No. of studies for OS** / **OS (95%CI)** **Phases** **Phase II** / 4 [28,29,31,32] / 0.94 (0.80–1.09) / 4 [28,29,31,32] / 0.82 (0.70–0.97) **Phase III** / 2 [27,30] / 0.71 (0.55–0.92) / 2 [27,30] / 0.94 (0.84–1.06) **EGFR-status** **Wild type** / 3 [28,29,30] / 0.65 (0.42–0.88) / 5 [27,28,29,30,31] / 0.92 (0.75–1.12) **Mutation** / 2 [28,30] / 1.20 (0.41–1.97) / 3 [27,30,31] / 0.91 (0.40–1.43) **KRAS status** **Wild type** / 1 [28] / 1.01 (0.63–1.60) / 1 [32] / 0.71 (0.43–1.18) **Mutation** / 1 [28] / 0.18 (0.05–0.70) / 2 [28,32] / 0.37 (0.12–1.09) **Anmerkungen/Fazit der Autoren** With the available evidence, combining targeted therapy seems superior over erlotinib monotherapy as second-line treatment for advanced NSCLC. More studies are still needed to identify patients who will most likely benefit from the appropriate combining targeted therapy.
Haaland B et al., 2014 [16]. **Meta-Analysis of First-Line Therapies in Advanced Non‐Small-Cell Lung Cancer Harboring EGFR-Activating Mutations**	**1. Fragestellung** Tyrosine kinase inhibitors gefitinib, erlotinib, and afatinib have been compared with chemotherapy as first-line therapies for patients with advanced non–small-cell lung cancer harboring epidermal growth factor receptor–activating mutations. This meta- analysis compares gefitinib, erlotinib, afatinib, and chemotherapy. **2. Methodik** **Population:** patients with advanced NSCLC whose tumors present with an EGFR-activating mutation **Intervention:** gefitinib, erlotinib, or afatinib **Komparator:** chemotherapy or one EGFR-TKI with another as first-line therapy **Endpunkte:** PFS, OS, DCR, ORR **Suchzeitraum:** nicht genau angegeben („within the last 5 years“) **Anzahl eingeschlossene Studien/Ptienten (Gesamt): 1**1 **Qualitätsbewertung der Studien:** keine Angaben **Heterogenitätsuntersuchungen:** I2 statistics and predictive intervals (PIs) **3. Ergebnisdarstellung**

TABLE 1. Summary of Studies Comparing Gefitinib, Erlotinib, and Afatinib with Chemotherapy as First-Line Therapies for Patients with Advanced NSCLC Harboring *EGFR*-Activating Mutations

			Progression-Free Survival	Response	Disease Control	Overall Survival
Study	**Patient Population**	**Treatment Arms**	**HR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**HR (95% CI)**
IPASS	East Asian nonsmoking or formerly light-smoking patients with advanced pulmonary adenocarcinoma[a]	Gefitinib ($n = 132$) Carboplatin + paclitaxel ($n = 129$)	0.48 (0.36–0.64)	2.8 (1.7–4.6)	1.6 (0.7–3.5)	1.00 (0.76–1.33)
West Japan	Japanese patients with advanced or recurrent NSCLC with *EGFR*-activating mutations	Gefitinib ($n = 86$) Cisplatin + docetaxel ($n = 86$)	0.49 (0.34–0.71)	3.4 (1.6–7.4)	3.8 (1.2–12.5)	1.64 (0.75–3.58)
North-East Japan	Japanese patients with metastatic NSCLC with *EGFR*-activating mutations	Gefitinib ($n = 114$) Carboplatin + paclitaxel ($n = 114$)	0.32 (0.24–0.44)	6.3 (3.6–11.2)	2.1 (1.0–4.6)	0.89 (0.63–1.24)
First-SIGNAL	Korean never-smoking patients with advanced or metastatic lung adenocarcinoma[a]	Gefitinib ($n = 26$) Gemcitabine + cisplatin ($n = 16$)	0.54 (0.27–1.10)	9.2 (2.1–39.8)	0.0 (0.0–16.6)	1.04 (0.50–2.18)
OPTIMAL	Chinese patients with advanced NSCLC with *EGFR*-activating mutations	Erlotinib ($n = 82$) Gemcitabine + carboplatin ($n = 72$)	0.16 (0.10–0.26)	8.6 (4.1–18.2)	5.8 (1.6–21.3)	1.07 (0.79–1.44)
EURTAC	Caucasian patients with advanced NSCLC with *EGFR*-activating mutations	Erlotinib ($n = 86$) Platinum-based doublet chemotherapy ($n = 87$)	0.37 (0.25–0.54)	7.9 (3.8–16.4)	2.0 (1.0–3.9)	1.04 (0.65–1.68)
LUX-Lung 3	Patients with advanced lung adenocarcinoma with *EGFR*-activating mutations	Afatinib ($n = 230$) Pemetrexed + cisplatin ($n = 115$)	0.58 (0.43–0.78)	4.4 (2.6–7.3)	2.1 (1.1–4.0)	1.12 (0.73–1.73)
LUX-Lung 6	Asian patients with advanced lung adenocarcinoma with *EGFR*-activating mutations	Afatinib ($n = 242$) Gemcitabine + cisplatin ($n = 122$)	0.28 ($p < 0.0001$)[b]	6.8 (4.1–11.2)	3.9 (2.1–7.3)	0.95 (0.68–1.32)

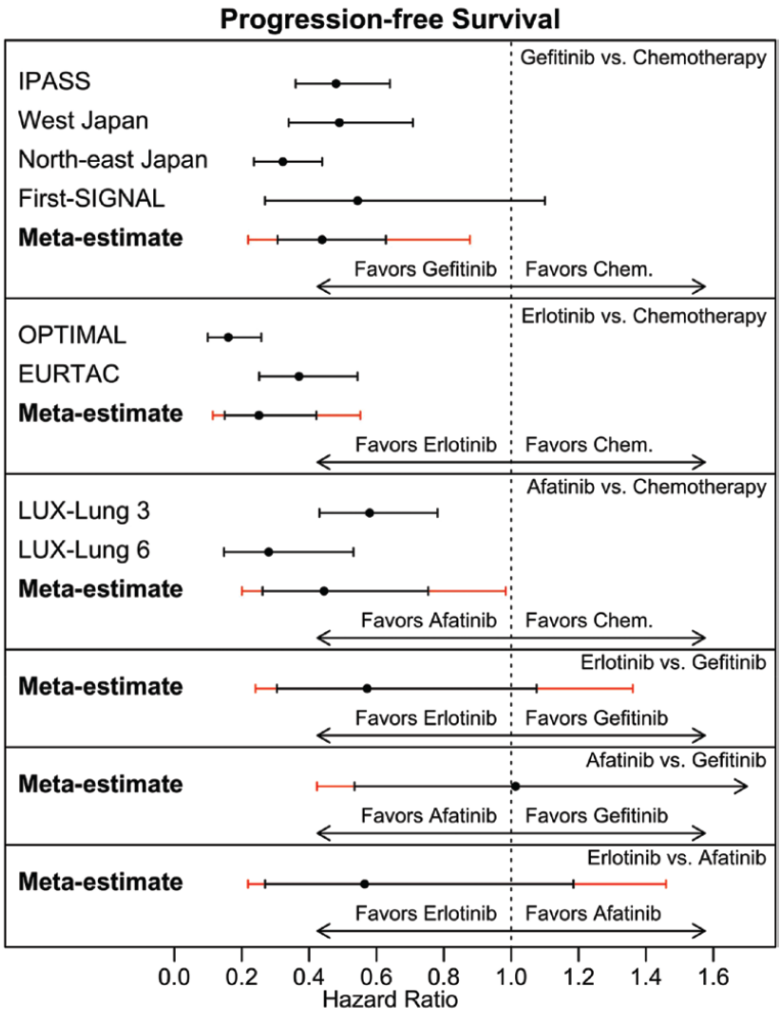
[a]Only the subgroup with *EGFR*-activating mutations considered.
[b]$p = 0.0001$ used to construct conservative standard error.
HR, hazard ratio; CI, confidence interval; OR, odds ratio; NSCLC, non–small-cell lung cancer; EGFR, epidermal growth factor receptor.

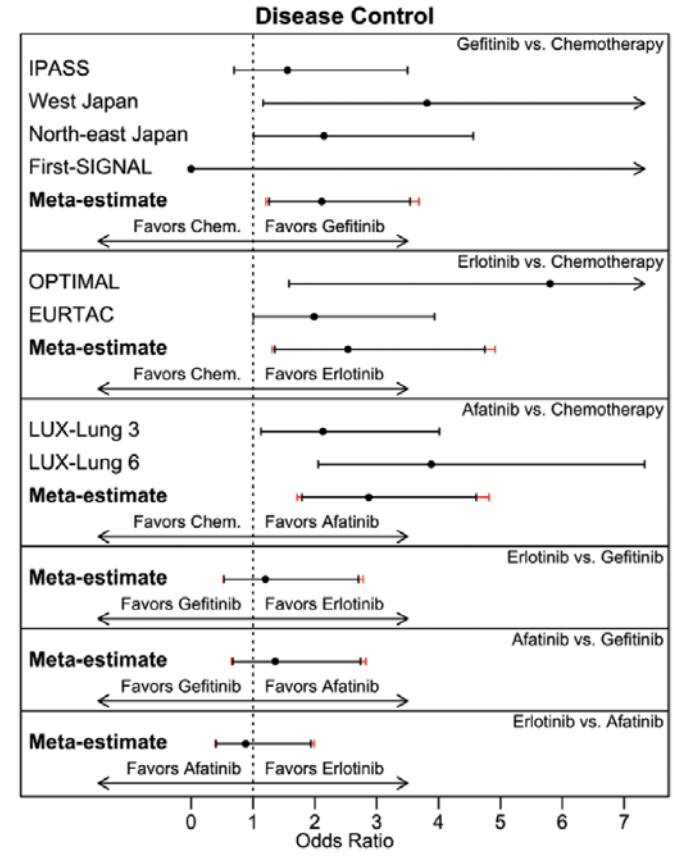
TABLE 2. Comparisons of Gefitinib, Erlotinib, Afatinib, and Chemotherapy as First-Line Therapies for Patients with Advanced NSCLC Harboring *EGFR*-Activating Mutations

	Progression-Free Survival	Response	Disease Control	Overall Survival
Comparison	**HR (95% CI; 95% PI)**	**OR (95% CI; 95% PI)**	**OR (95% CI; 95% PI)**	**HR (95% CI; 95% PI)**
Gefitinib vs. chemotherapy	0.44 (0.31–0.63; 0.22–0.88)	4.1 (2.7–6.3; 2.3–7.6)	2.1 (1.3–3.5; 1.2–3.7)	0.99 (0.81–1.21; 0.81–1.21)
Erlotinib vs. chemotherapy	0.25 (0.15–0.42; 0.11–0.55)	8.2 (4.5–15.1; 3.9–17.5)	2.5 (1.4–4.7; 1.3–4.9)	1.06 (0.82–1.37; 0.82–1.37)
Afatinib vs. chemotherapy	0.44 (0.26–0.75; 0.20–0.98)	5.5 (3.4–8.8; 2.9–10.5)	2.9 (1.8–4.6; 1.7–4.8)	1.01 (0.78–1.31; 0.78–1.31)
Erlotinib vs. gefitinib	0.57 (0.30–1.08; 0.24–1.36)	2.0 (0.9–4.1; 0.8–4.7)	1.2 (0.5–2.7; 0.5–2.8)	1.07 (0.77–1.47; 0.77–1.47)
Afatinib vs. gefitinib	1.01 (0.53–1.92; 0.42–2.42)	1.3 (0.7–2.5; 0.6–2.8)	1.4 (0.7–2.7; 0.7–2.8)	1.02 (0.73–1.41; 0.73–1.41)
Erlotinib vs. afatinib	0.56 (0.27–1.18; 0.22–1.46)	1.5 (0.7–3.3; 0.6–3.7)	0.9 (0.4–1.9; 0.4–2.0)	1.05 (0.73–1.51; 0.73–1.51)

OR, odds ratio; NSCLC, non–small-cell lung cancer; EGFR, epidermal growth factor receptor; HR, hazard ratio; CI, confidence interval; PI, predictive interval.

Individual study hazard ratiosalong with comparative meta-estimates forprogression-free survival in first-line therapyfor patients with advanced NSCLC harboringEGFR-activating mutations. 95% confidence intervalsshown in black and 95% predictive intervals in red.NSCLC, non‐small-cell lung cancer.


Progression-free Survival
Gefitinib vs. Chemotherapy
IPASS
West Japan
North-east Japan
First-SIGNAL
Meta-estimate
Favors Gefitinib
Favors Chem.
Erlotinib vs. Chemotherapy
OPTIMAL
EURTAC
Meta-estimate
Favors Erlotinib
Favors Chem.
Afatinib vs. Chemotherapy
LUX-Lung 3
LUX-Lung 6
Meta-estimate
Favors Afatinib
Favors Chem.
Erlotinib vs. Gefitinib
Meta-estimate
Favors Erlotinib
Favors Gefitinib
Afatinib vs. Gefitinib
Meta-estimate
Favors Afatinib
Favors Gefitinib
Erlotinib vs. Afatinib
Meta-estimate
Favors Erlotinib
Favors Afatinib
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
Hazard Ratio


Disease Control
Gefitinib vs. Chemotherapy
IPASS
West Japan
North-east Japan
First-SIGNAL
Meta-estimate
Favors Chem.
Favors Gefitinib
Erlotinib vs. Chemotherapy
OPTIMAL
EURTAC
Meta-estimate
Favors Chem.
Favors Erlotinib
Afatinib vs. Chemotherapy
LUX-Lung 3
LUX-Lung 6
Meta-estimate
Favors Chem.
Favors Afatinib
Erlotinib vs. Gefitinib
Meta-estimate
Favors Gefitinib
Favors Erlotinib
Afatinib vs. Gefitinib
Meta-estimate
Favors Gefitinib
Favors Afatinib
Erlotinib vs. Afatinib
Meta-estimate
Favors Afatinib
Favors Erlotinib
0
1
2
3
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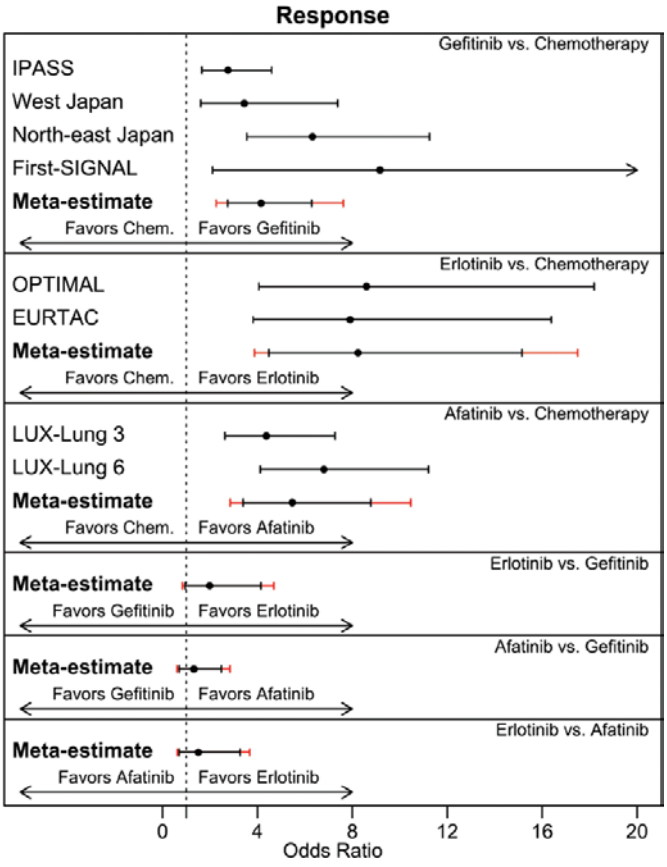
5
6
7
Odds Ratio


Response
Gefitinib vs. Chemotherapy
IPASS
West Japan
North-east Japan
First-SIGNAL
Meta-estimate
Favors Chem.
Favors Gefitinib
Erlotinib vs. Chemotherapy
OPTIMAL
EURTAC
Meta-estimate
Favors Chem.
Favors Erlotinib
Afatinib vs. Chemotherapy
LUX-Lung 3
LUX-Lung 6
Meta-estimate
Favors Chem.
Favors Afatinib
Erlotinib vs. Gefitinib
Meta-estimate
Favors Gefitinib
Favors Erlotinib
Afatinib vs. Gefitinib
Meta-estimate
Favors Gefitinib
Favors Afatinib
Erlotinib vs. Afatinib
Meta-estimate
Favors Afatinib
Favors Erlotinib
0
4
8
12
16
20
Odds Ratio

	Adverse Events The more common adverse events with TKIs were diarrhea,rash or acne, dry skin, and pruritis, whereas anorexia,anemia, fatigue, nausea, vomiting, alopecia, and neutropeniawere more common with chemotherapy. Liver enzyme elevationswere more common with gefitinib and erlotinib thanwith chemotherapy, but not reported for afatinib. Grade 3and 4 adverse events were more common with chemotherapythan with TKIs. Broadly, adverse event profiles were similaramong TKIs although there was some indication that gefitinibwas associated with more anemia and afatinib was associatedwith more stomatitis or mucositis. **4. Anmerkungen/Fazit der Autoren** Gefitinib, erlotinib, and afatinib out-performed chemotherapy in terms of progression-free survival, overall response rate, and disease control rate. Differences among gefitinib, erlotinib, and afatinib were not statistically significant.
Liang W et al, 2014 [20]. Network Meta-Analysis of Erlotinib, Gefitinib, Afatinib and Icotinib in Patients with Advanced Non-Small-Cell Lung Cancer Harboring EGFR Mutations	**1. Fragestellung** Several EGFR-tyrosine kinase inhibitors (EGFR-TKIs) including erlotinib, gefitinib, afatinib and icotinib are currently available as treatment for patients with advanced non-small-cell lung cancer (NSCLC) who harbor EGFR mutations. However, no head to head trials between these TKIs in mutated populations have been reported, which provides room for indirect and integrated comparisons. **2. Methodik** **Population:** advanced NSCLC, patients with known EGFRmutation status **Intervention:** erlotinib, gefitinib, afatinib and icotinib **Komparator:** - interventionen gegenseitig – Standard chemotherapy was defined as platinum-based third generation doublets for first-line treatments or pemetrxed/ doctaxel for second-line treatments. **Endpunkte:** overall survival (OS), progression free survival (PFS), objective response rate (ORR) and adverse events (rash, grade 3–4 rash, diarrhea, grade 3–4 diarrhea) **Suchzeitraum:** bis 03/2013 **Anzahl eingeschlossene Studien/Ptienten (Gesamt):** 12 **Qualitätsbewertung der Studien:** Jadad **Heterogenitätsuntersuchungen:** forest plot and the inconsistency statistic (I^2) **3. Ergebnisdarstellung**

Table 1. Characteristics of included studies regarding TKIs.

Studies	TKI	Control	Year	Sample size	Patients status	EGFR Pts analyzed
IPASS[5]	Gefitinib	TC	2009	1217	CT-naive	261
First-SIGNAL[6]	Gefitinib	GP	2012	309	CT-naive	42
NEJ002[7]	Gefitinib	TC	2010	228	CT-naive	228
WJTOG 3405[8]	Gefitinib	DP	2010	172	CT-naive	117
INTEREST[9]	Gefitinib	DOC	2008	1466	Previously treated	38
V 15–32[10]	Gefitinib	DOC	2008	490	Previously treated	20
OPTIMAL[11]	Erlotinib	GC	2011	165	CT-naive	154
EUTRAC[12]	Erlotinib	CT	2012	174	CT-naive	173
TITAN[13]	Erlotinib	PEM/DOC	2012	424	Previously treated	11
LUX-lung 3[25]	Afatinib	AP	2013	345	CT-naive	345
LUX-lung 6[26]	Afatinib	GP	2013	364	CT-naive	364
ICOGEN[15]	Icotinib	Geftinib	2012	399	Previously treated	68

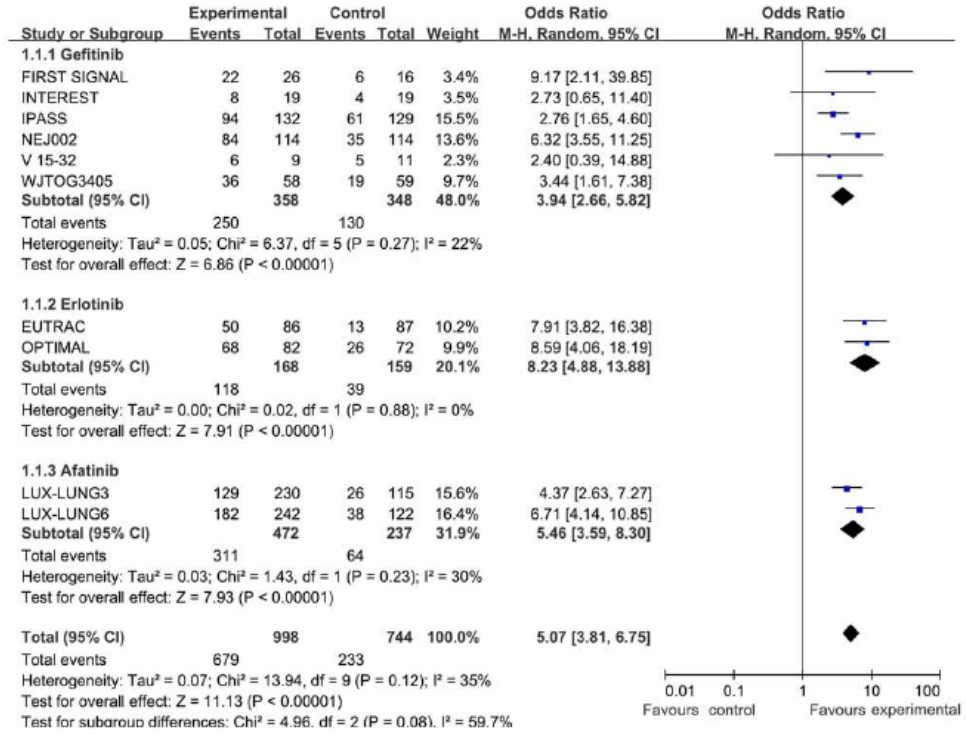
TKI, tyrosine kinase inhibitors; TC, carboplatin plus palitaxel; GP, cisplatin plus gemcitabine; DP, cisplatin plus docetaxel; DOC, docetaxel; GC, carboplatin plus gemcitabine; CT, chemotherapy (not specific); PEM, pemetrexed; AP, cisplatin plus pemetrexed.

Table 2. Pooled Weighted Outcomes and Direct Meta-Analysis.

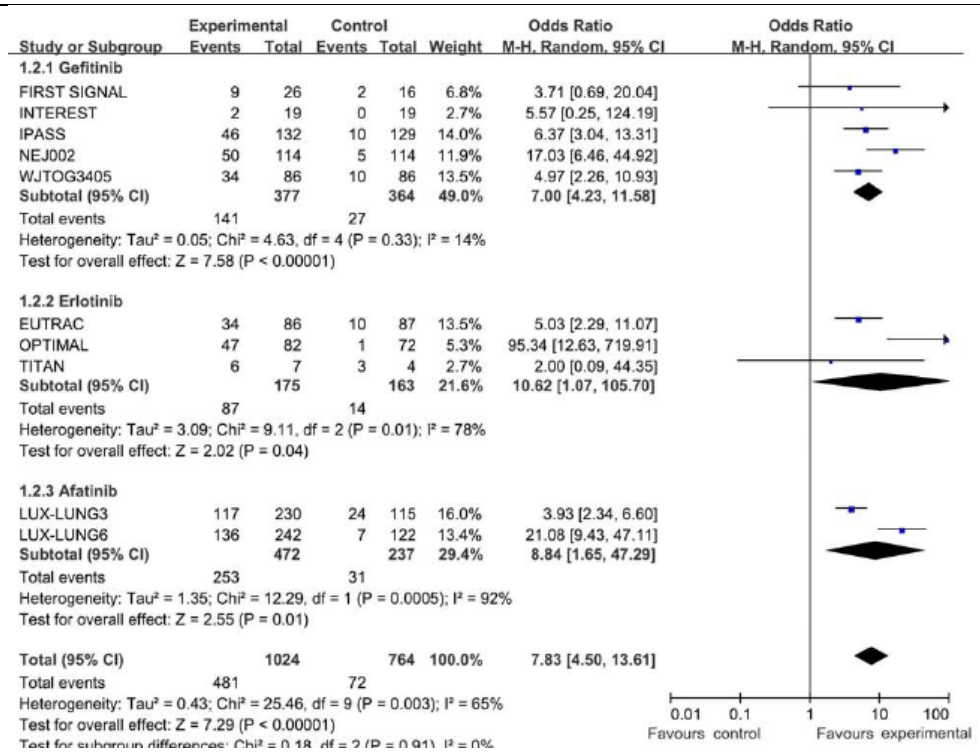
	TKIs (95% CI)	Chemotherapy (95% CI)	Odds Ratio (95% CI, P value)
ORR	66.6% (0.596, 0.729)	30.9% (0.245, 0.381)	5.46 (3.59, 8.30; P<0.00001)
1-year PFS	42.9%(0.366, 0.494)	9.7% (0.058, 0.158)	7.83 (4.50, 13.61; P<0.00001)
1-year OS	79.2% (0.745, 0.833)	78.9% (0.709, 0.852)	1.04 (0.79, 1.36; P=0.79)
2-year OS	49.7% (0.432, 0.563)	51.0% (0.431, 0.589)	0.95 (0.76, 1.17; P=0.62)

CI, confidence interval; ORR, objective response rate; PFS, progression free survival; OS, overall survival.

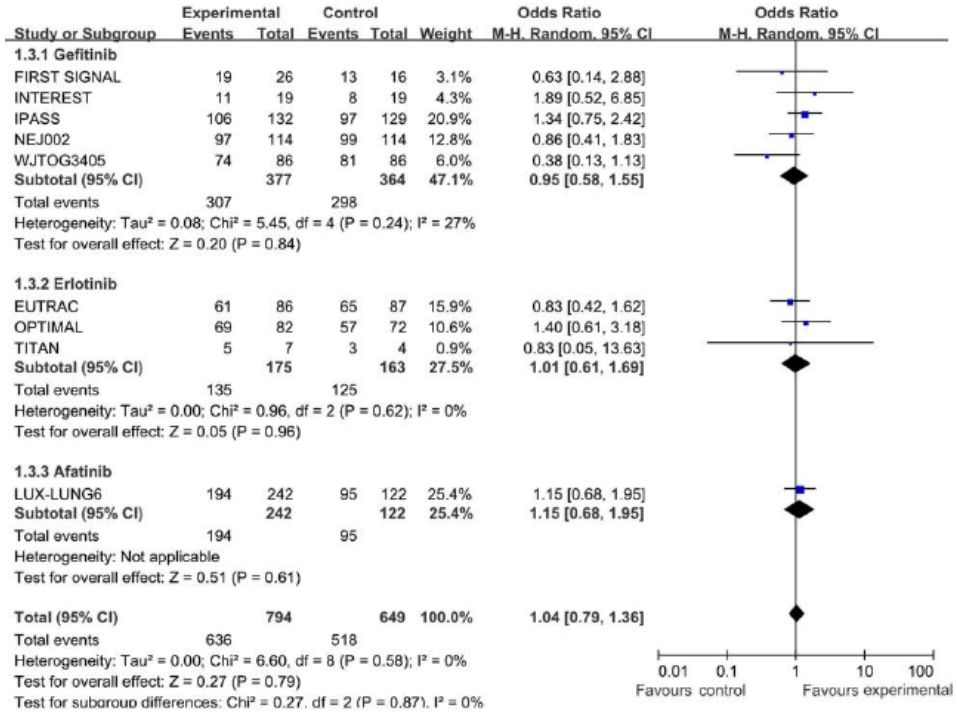
ORR



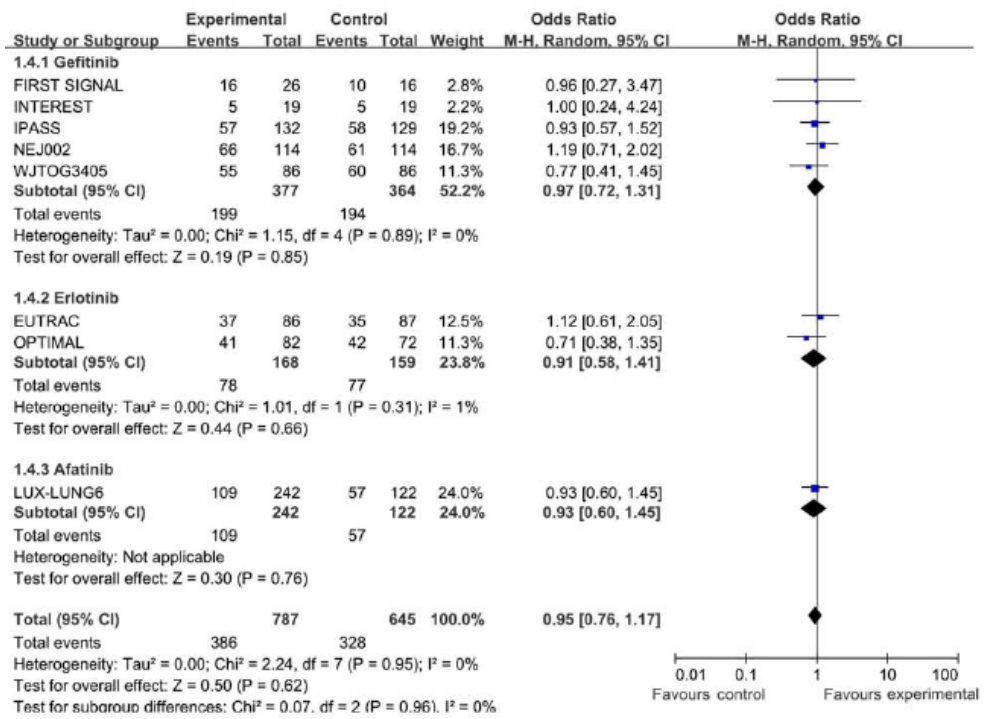
1-year PFS



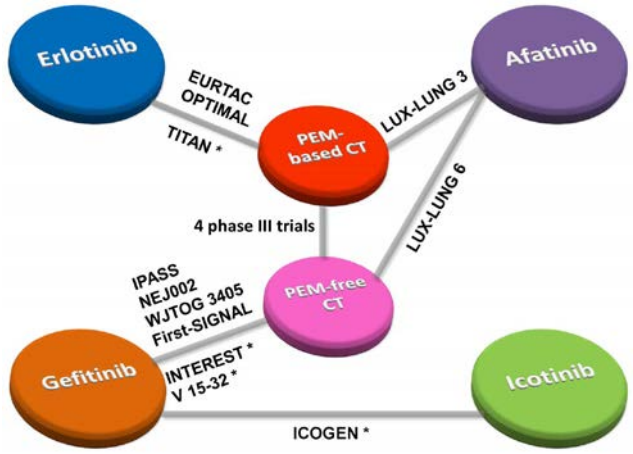
1-year OS

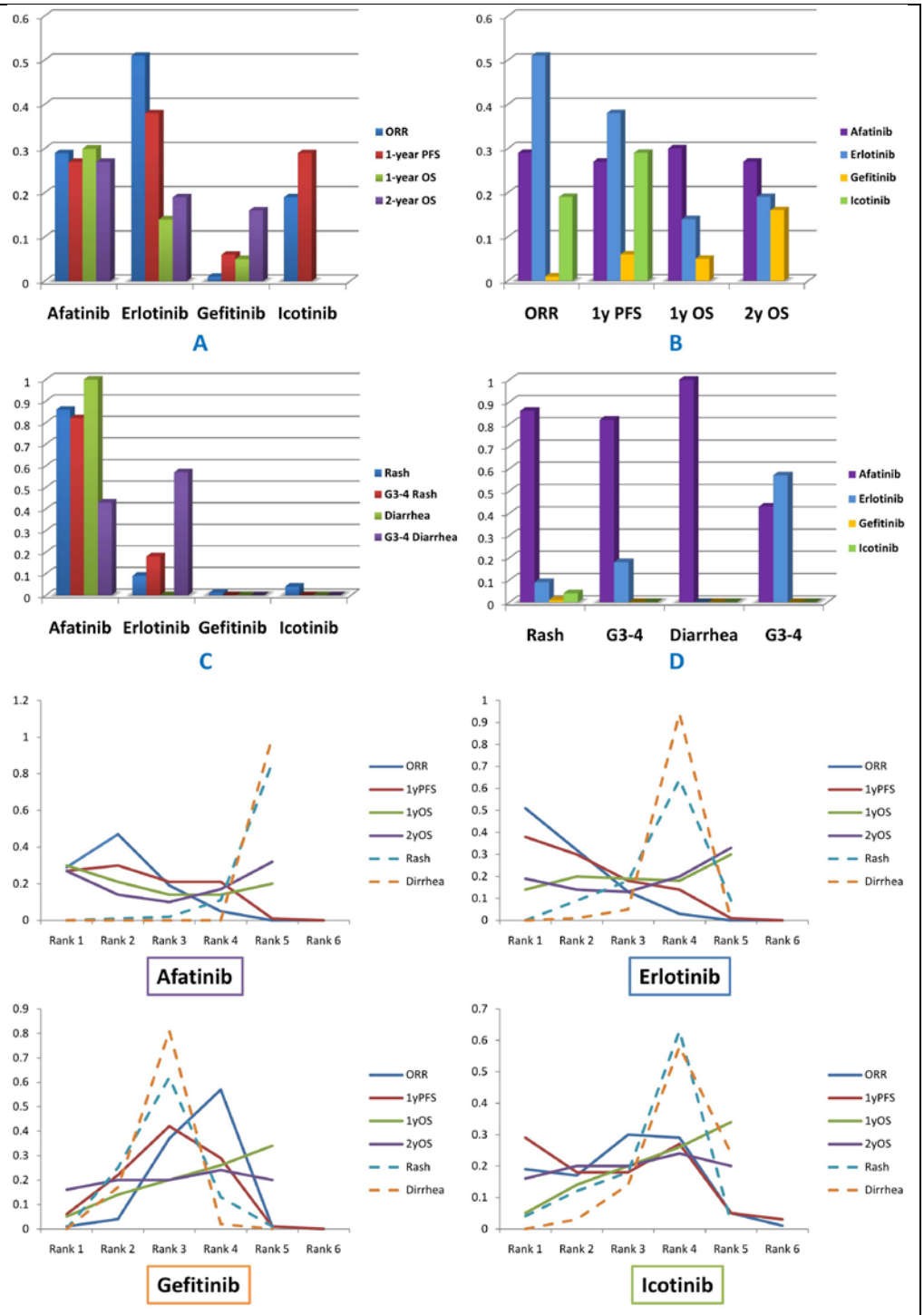


2-year OS



Network established for multiple treatment comparisons





4. Anmerkungen/Fazit der Autoren

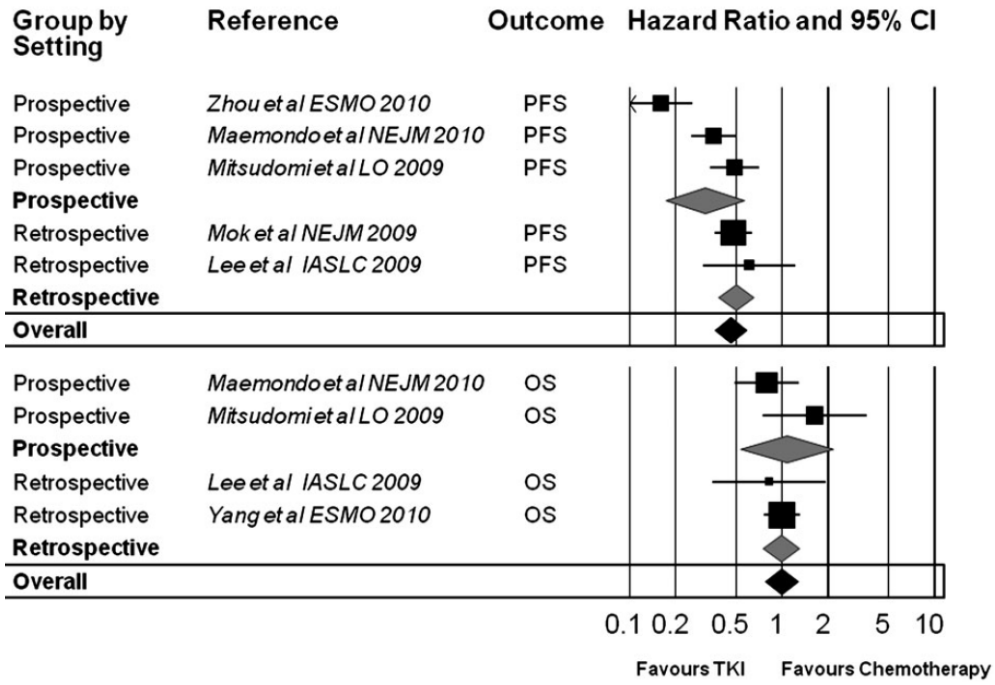
Twelve phase III RCTs that investigated EGFR-TKIs involving 1821 participants with EGFR mutation were included. For mutant patients, the weighted pooled ORR and 1-year PFS of EGFR-TKIs were significant superior to that of standard chemotherapy (ORR: 66.6% vs. 30.9%, OR 5.46, 95%CI 3.59 to 8.30, P,0.00001; 1-year PFS: 42.9% vs. 9.7%, OR 7.83, 95%CI 4.50 to 13.61; P,0.00001) through direct meta-analysis. In the network meta-analyses, no statistically significant differences in efficacy were found between these four TKIs with respect to all outcome measures. Trend analyses of rank probabilities revealed that the

	cumulative probabilities of being the most efficacious treatments were (ORR, 1-year PFS, 1-year OS, 2-year OS): erlotinib (51%, 38%, 14%, 19%), gefitinib (1%, 6%, 5%, 16%), afatinib (29%, 27%, 30%, 27%) and icotinib (19%, 29%, NA, NA), respectively. However, afatinib and erlotinib showed significant severer rash and diarrhea compared with gefitinib and icotinib. The current study indicated that erlotinib, gefitinib, afatinib and icotinib shared equivalent efficacy but presented different efficacy-toxicity pattern for EGFR-mutated patients. Erlotinib and afatinib revealed potentially better efficacy but significant higher toxicities compared with gefitinib and icotinib. **5. Hinweis der FBMed** Icotinib ist in Deutschland für NSCLC nicht zugelassen. Seine Verwendung in der Netzwerkanalyse kann die Ergebnisse der anderen, in Deutschland zugelassenen Wirkstoffe beeinflusst haben.
Bria E et al., 2011 [6]. Outcome of advanced NSCLC patients harboring sensitizing EGFR mutations randomized to EGFR tyrosine kinase inhibitors or chemotherapy as first-line treatment: a meta-analysis	**1. Fragestellung** Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) are effective as first-line treatment of advanced non-small-cell lung cancer patients with EGFR mutations (EGFR-M+). We conducted a literature-based meta-analysis to quantify the magnitude of benefit with upfront EGFR TKI in EGFR-M+ patients. Meta-regression and sensitivity analyses were also carried out to identify additional predictors of outcome and to assess the influence of trial design. **2. Methodik** **Population:** advanced NSCLC, patients with known EGFRmutation status; subpopulation of patients carrying an activating EGFR mutation (exon-19 deletions or exon-21 point mutations, EGFR-M+ patients) in the first-line setting **Intervention:** gefitinib or erlotinib **Komparator:** first-line chemotherapy **Endpunkte:** primär: PFS and OS; sekundär: overall response rate (ORR, as reported by trialists) and grades 3–4 toxic effects, **Suchzeitraum:** bis 10/ 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 5 (805) three trials prospectively enrolling EGFR-M+ patients and two retrospective analyses of EGFR-M+ patients **Qualitätsbewertung der Studien:** keine Angabe **Heterogenitätsuntersuchungen:** heterogeneity test was used (nicht spezifiziert) **3. Ergebnisdarstellung**

Authors	Pts	Arms	Analysis in EGFR mutant patients	Female gender (%)	Nonsmokers (%)	Exon-19 mutation (%)
Mok et al. [10, 26]	132	Gefitinib	Retrospective	80.8	94.2	53.6
	129	CBDCA-P				
Lee et al. [9]	26	Gefitinib	Retrospective	42.3	100.0	NR
	16	DDP-GEM				
Maemondo et al. [12]	98	Gefitinib	Prospective	63.0	61.6	50.5
	100	CBDCA-P				
Mitsudomi et al. [11]	87	Gefitinib	Prospective	74.0	75.0	50.0
	88	DDP-D				
Zhou et al. [13]	82	Erlotinib	Prospective	59.0	70.5	53.0
	72	CBDCA-GEM				

Pts, patients; G, gefinitib; CBDCA, carboplatin; P, paclitaxel; DDP, cisplatin; GEM, gemcitabine; D, docetaxel; NR, not reported.

PFS/ OS



4. Anmerkungen/Fazit der Autoren

In EGFR-M+ patients, first-line TKI increase both PFS and ORR by _25%, while significantly decreasing toxicity. The role of additional predictive factors and the influence of trial design on the magnitude of the observed benefit warrant further investigation.

5. Hinweise der FBMed

Keine Angaben zur methodischen Bewertung der Primärstudien

Zhang J et al., 2012 [40].

Maintenance erlotinib improves clinical outcomes of

1. Fragestellung

The aim of this study was to evaluate the efficacy and safety of erlotinib as maintenance therapy in patients with unresectable non-small cell lung cancer (NSCLC) by evidence‑based methodology.

2. Methodik

Population: patients with unresectable NSCLC at baseline levels

unresectable advanced non-small cell lung cancer: A meta-analysis of randomized controlled trials	**Intervention/ Komparator:** maintenance therapy with vs. without erlotinib after the first-line chemotherapy Studies were excluded based on the following criteria; i) patients previously treated with targeted agents, ii) phase I clinical trial, iii) retrospective trial or iv) any review, comment or case report **Endpunkte:** OS, PFS, ORR and adverse events (AEs) **Suchzeitraum:** bis 06/2011 **Anzahl eingeschlossene Studien/Ptienten (Gesamt):** 6 (4372) **Qualitätsbewertung der Studien:** durchgeführt (siehe unten: Ergebnisdarstellung) **Heterogenitätsuntersuchungen:** chi Quadrat, I Quadrat

3. Ergebnisdarstellung

Table I. Characteristics of included studies.

Study	Design	n	Patients	Intervention	Outcomes
Herbst *et al* (21)	Multi-center, randomized placebo-controlled phase III trial	1079	CT-naive advanced (stage IIIB or IV) NSCLC	GP concurrent with Erl or placebo and followed by Erl or placebo	OS, TTP, ORR, safety, duration of response
Gatzemeier *et al* (20)	Multi-center, randomized placebo-controlled, double-blind, phase III trial	1172	CT-naive unresectable or recurrent or advanced (stage III or IV) NSCLC	PC concurrent with Erl or placebo and followed by Erl or placebo	OS, TTP, ORR, QOL, safety, duration of response
Mok *et al* (30)	Multi-center, randomized placebo-controlled phase II trial	154	Previously untreated advanced (stage IIIB or IV) NSCLC	Sequential Erl or placebo and CT, followed by Erl or placebo	NPR, RR, OS, PFS, safety, duration of response
Cappuzzo *et al* (16)	Multi-center, randomized placebo-controlled phase III trial	889	Unresectable or advanced (stage IIIB or IV) NSCLC	Maintenance Erl vs. placebo after 4 cycles of standard platinum-doublet CT	PFS, OS, safety, QOL
Perol *et al* (32)	Randomized, three group phase III trial	310	Stage IIIB or IV NSCLC	Maintenance Erl vs. Gem vs. observation after 4 cycles	PFS, OS, safety symptom control of GP
Kabbinavar *et al* (31)	Randomized, double-blind, placebo-controlled, phase IIIb trial	768	Previously untreated recurrent or advanced (stage IIIB or IV) NSCLC	Maintenance Erl plus Bev vs. after 4 cycles of first-line CT combined Bev	PFS, OS, safety

NSCLC, non-small cell lung cancer; CT, chemotherapy; GP, gemcitabine + cisplatin; PC, paclitaxel + carboplatin; Erl, erlotinib; Bev, bevacizumab; Gem, gemcitabin; RR, response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression; NPR, non-progression rate; QOL, quality of life.

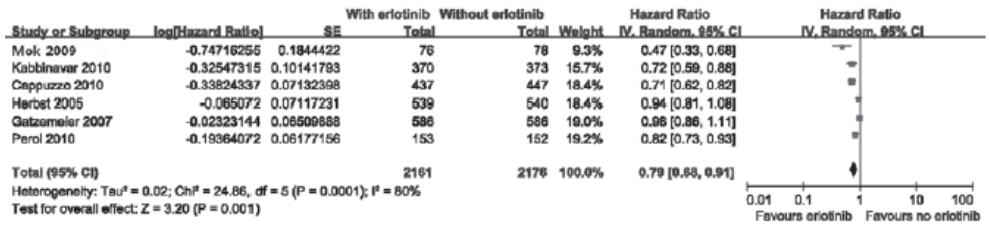
Table II. Quality of included studies.

Study	Truly random	Random allocation	Equivalence of baseline features	Eligibility criteria	Blinding assessment	Loss to follow-up	Intent to treat	Study quality
Herbst *et al* (21)	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	High
Gatzemeier *et al* (20)	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	High
Mok *et al* (30)	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	High
Cappuzzo *et al* (16)	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	High
Perol *et al* (32)	Yes	No	Yes	Yes	Yes	Unclear	Yes	Fair
Kabbinavar *et al* (31)	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Fair

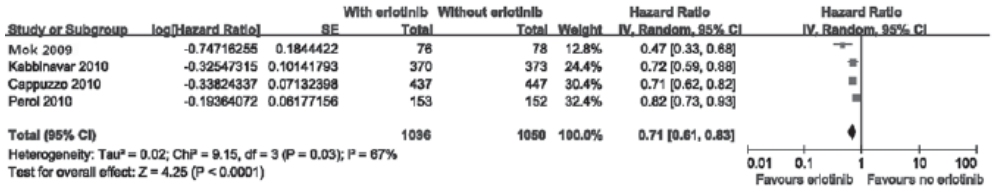
PFS

Comparative effect of progression-free survival of maintenance with erlotinib

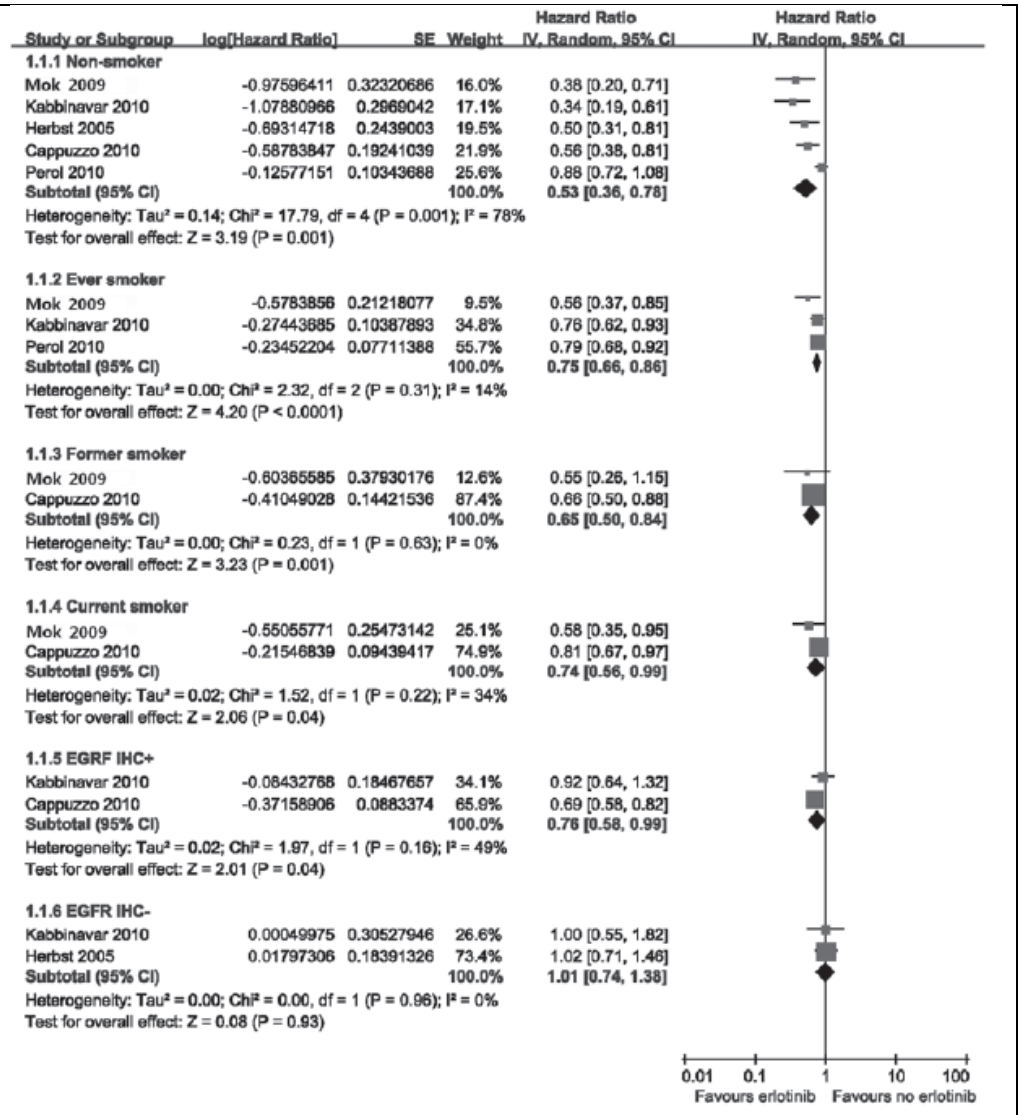
vs. control



Comparative effect of progression-free survival of maintenance with erlotinib vs. control after excluding the two studies using erlotinib concurrent with chemotherapy.

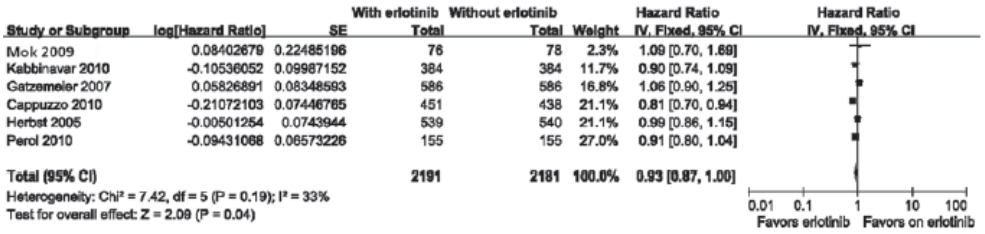


Subgroup analyses in progression-free survival of maintenance with erlotinib vs. control, stratified by EGFR status (positive, negative) and smoking history (current, former, ever, non-smokers).

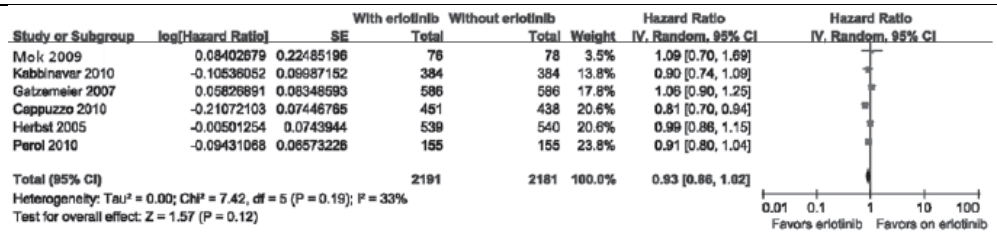


OS

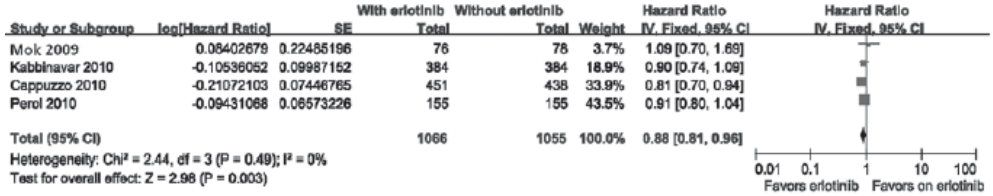
Comparative effect of overall survival of maintenance with erlotinib vs. control using fixed effects model.



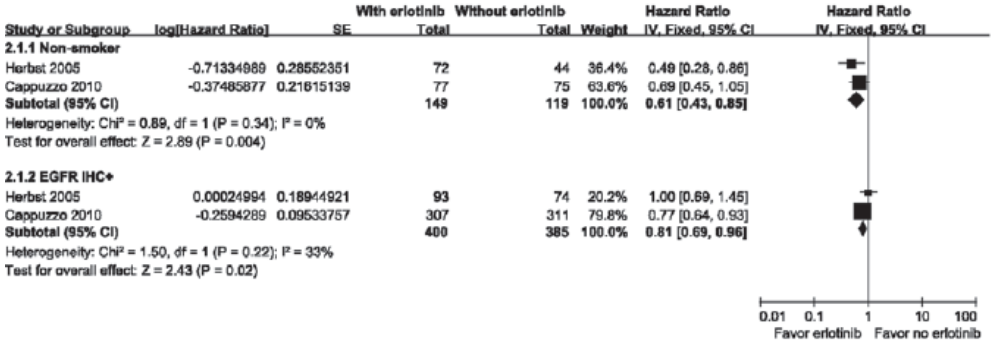
Comparative effect of overall survival of maintenance with erlotinib vs. control using random effects model.



Comparative effect of overall survival of maintenance with erlotinib vs. control after excluding the two studies using erlotinib concurrent with chemotherapy.



Subgroup analyses in overall survival of maintenance with erlotinib vs. control for non-smokers and the immunohistochemistry-positive (IHC+) patients.



IHC+, immunohistochemistry-positive; IHC-, immunohistochemistry-negative.

Qualitätsbewertung der Studien: Anhand von 7 Qualitätskriterien des NHS Center for Reviews and Dissemination (Randomisierung, Verblindung, Loss to follow-up, intention to treat etc.). Qualität wurde als mittel bis hoch eingestuft.

Gesamtpopulation

Ergebnisse zum PFS: The meta-analysis showed a longer PFS in patients who received erlotinib as maintenance therapy [random effects: HR=0.79 (95% CI=0.68-0.91); P=0.001; NNT=5], showing a high heterogeneity level [χ^2=24.86, df=5 (P=0.0001); I^2=80%].

Ergebnisse zum OS: The OS was slightly longer for patients who received erlotinib as maintenance therapy [fixed effect: HR=0.93 (95% CI=0.87-1.00); P=0.04; NNT=15] with moderate heterogeneity [χ^2=7.42, df=5 (P=0.19);

	I^2=33%]. However, the random effects model indicated **no significant difference** [random effects: HR=0.93 (95% CI=0.86-1.02); P=0.12]. Nach Ausschluss der beiden Studien, in denen Erlotinib zusätzlich zu einer platinbasierten Chemotherapie verabreicht wurde, ergab sich ein signifikanter Vorteil für das Gesamtüberleben von [fixed effects: HR=0.88 (95% CI=0.81-0.96); P=0.003; NNT=8] ohne die zuvor beobachtete Heterogenität [χ2=2.44, df=3 (P=0.49); I2=0%]. **Ergebnisse zur ORR:** Es gab keinen signifikanten Unterschied in der ORR zwischen der Erlotinib und der Kontrollgruppe [random effects OR=1.39; (95% CI=1.00-1.94);p=0,05]. **Ergebnisse zu Sicherheitsendpunkten:** The group receiving erlotinib had a higher incidence of anemia [fixed effect: RR=1.36; (95% CI=1.06-1.75); P=0.02]. No difference was observed in patients with other hematological toxicities including neutropenia, thrombocytopenia and leukopenia. With regard to the non-hematological toxicities, patients receiving erlotinib experienced a significantly higher incidence of diarrhea, skin toxicity and renal impairment with a pooled HR of 5.10 [fixed effect: (95% CI=3.20-8.14); P<0.00001], 17.67 [fixed effect: (95% CI=9.22-33.86); P<0.00001] and 4.84 [fixed effect: (95% CI=2.09-11.18); P=0.0002], respectively. There was no significant difference in the incidence of treatment-related deaths [fixed effect: RR=1.51 (95% CI=0.73-3.12); P=0.27]. **Limits:** Due to limited data, we failed to perform pooled analyses of quality-of-life and cost-effectiveness, which are useful for doctors to determine whether the involved patients should receive maintenance therapy or a 'treatment holiday'. Subsequent therapy may affect the OS of patients, but this issue was not analyzed in the present study. In addition, the number of included studies is small with little difference in design and one study did not achieve the mature OS data. **Hinweise der FBMed** Keine Hinweise auf Publikationsbias (Egger test, p>0,05) Vier Studien wiesen eine hohe Qualität auf (6-7 Qualitätskriterien erfüllt) und zwei Studien eine moderate Qualität (4-5 Qualitätskriterien erfüllt) **4. Anmerkungen/Fazit der Autoren** Erlotinib produced significant clinical benefits with acceptable toxicity as a maintenance strategy in patients with unresectable NSCLC, particularly when sequentially administered with chemotherapy. However, more well-designed randomized control trials (RCTs) are required to identify patients that may derive greater benefits from maintenance with erlotinib, and whether the use of erlotinib as maintenance therapy is more efficient than second-line treatment should also be investigated.

Wang F et al, 2012 [38].

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, we carried out a meta-analysis of randomized controlled trials.

2. Methodik

Population: advanced NSCLC, patients with known EGFRmutation status

Intervention: gefitinib therapy as first-line treatment

Komparator: conventional therapy

Endpunkte: PFS, OS

Suchzeitraum: bis 01/2011

Anzahl eingeschlossene Studien/Ptienten (Gesamt): 7 (4656)

Qualitätsbewertung der Studien: criterions: (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 criterionwas rated as yes, no or unclear.

Heterogenitätsuntersuchungen: I^2

3. Ergebnisdarstellung

Characteristics of included studies

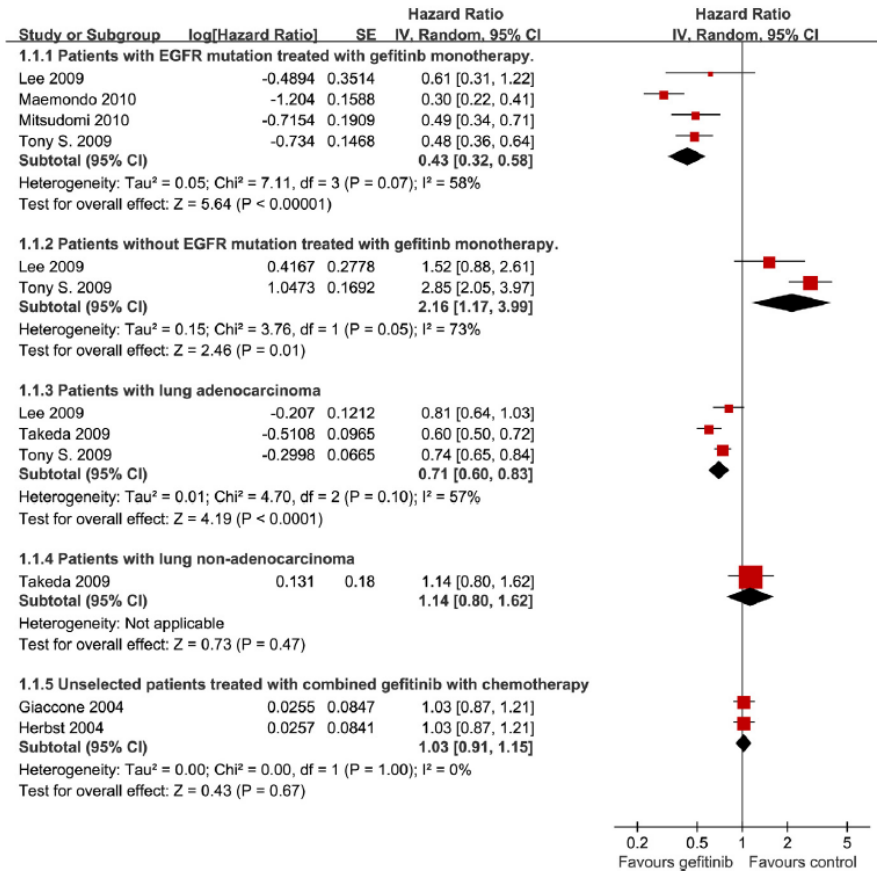
References		*n*	Gender (%)		Age (year)	Therapy regimen	Patient selection*	Publication status	Follow-up period	Ethnicity
			Male	Female						
Gefitinib monotherapy versus platinum-doublet chemotherapy										
[14]	E	115	36.8	63.2	63.9 ± 7.7	G	Yes	Published	527 days	Asian
	C	115	36.0	64.0	62.6 ± 8.9	PC ≥ 3 cycles				
[11]	E	86	31.4	68.6	64 (34–74)	G	Yes	Published	81 days	Asian
	C	86	30.2	69.8	64 (41–75)	CD × (3–6) cycles				
[16]	E	609	20.5	79.5	57 (24–84)	G	Yes	Published	5.6 months	Asian
	C	608	20.9	79.1	57 (25–84)	PC × 6 cycles				
[15]	E	159	–	–	–	G	Yes	Abstract	–	Asian
	C	150				GC × 9 cycles				
Gefitinib combined with systemic chemotherapy										
[10]	E_1	365	72.1	27.9	61 (31–85)	(GC + G) × 6 cycles, then G	No	Published	15.9 months	White†
	E_2	365	76.7	23.3	59 (34–83)	(GC + G) × 6 cycles, then G				
	C	363	72.2	27.8	61 (33–81)	GC × 6 cycles				
[9]	E_1	347	59.9	40.1	62 (26–82)	(PC + G) × 6 cycles, then G	No	Published	>12 months	White†
	E_2	345	57.7	42.3	61 (27–86)	(PC + G) × 6 cycles, then G				
	C	345	61.4	38.6	63 (31–85)	PC × 6 cycles				
Gefitinib sequential therapy after chemotherapy										
[13]	E	300	64.0	36.0	62 (25–74)	PD × 3 cycles, then G	No	Published	2 years	Asian
	C	298	64.1	35.5	63 (35–74)	PD × 6 cycles				

G, continued gefitinib; PC, paclitaxel carboplatin; CD, cisplatin docetaxel; GC, gemcitabine cisplatin; PD, continued platinum-doublet chemotherapy.

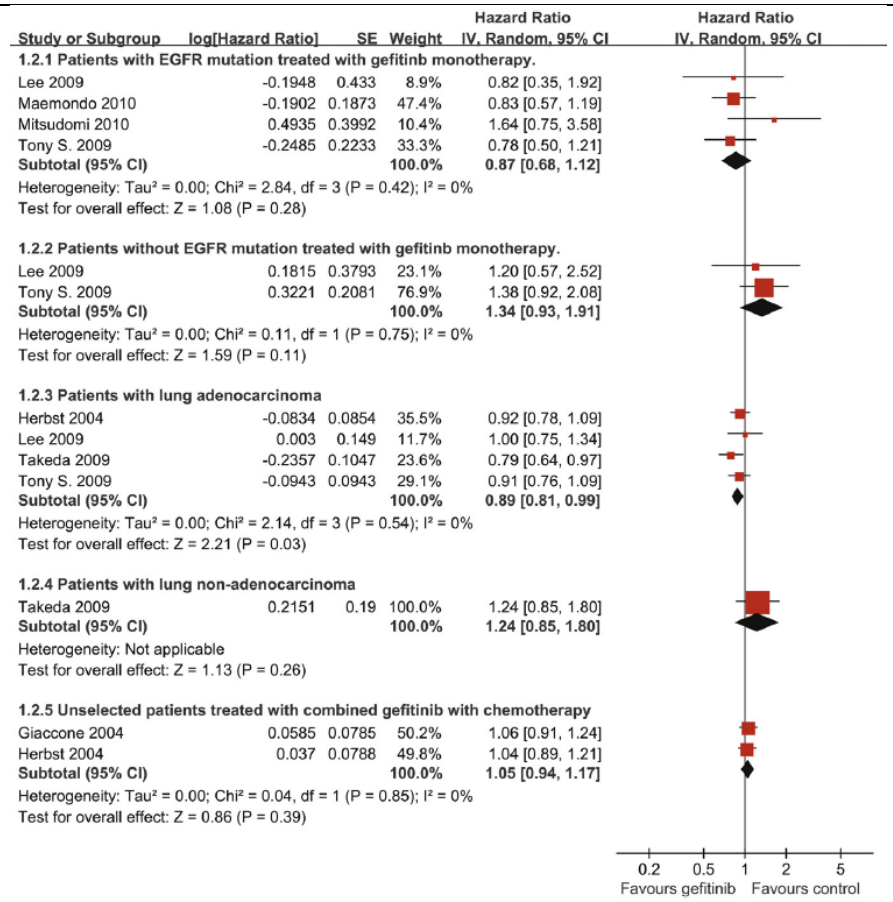
* Patients were selected molecularly or clinically.

† Most patients.

PFS


Hazard Ratio
Hazard Ratio
Study or Subgroup log[Hazard Ratio] SE IV, Random, 95% CI
IV, Random, 95% CI
1.1.1 Patients with EGFR mutation treated with gefitinb monotherapy.
Lee 2009 -0.4894 0.3514 0.61 [0.31, 1.22]
Maemondo 2010 -1.204 0.1588 0.30 [0.22, 0.41]
Mitsudomi 2010 -0.7154 0.1909 0.49 [0.34, 0.71]
Tony S. 2009 -0.734 0.1468 0.48 [0.36, 0.64]
Subtotal (95% CI) 0.43 [0.32, 0.58]
Heterogeneity: Tau² = 0.05; Chi² = 7.11, df = 3 (P = 0.07); I² = 58%
Test for overall effect: Z = 5.64 (P < 0.00001)
1.1.2 Patients without EGFR mutation treated with gefitinb monotherapy.
Lee 2009 0.4167 0.2778 1.52 [0.88, 2.61]
Tony S. 2009 1.0473 0.1692 2.85 [2.05, 3.97]
Subtotal (95% CI) 2.16 [1.17, 3.99]
Heterogeneity: Tau² = 0.15; Chi² = 3.76, df = 1 (P = 0.05); I² = 73%
Test for overall effect: Z = 2.46 (P = 0.01)
1.1.3 Patients with lung adenocarcinoma
Lee 2009 -0.207 0.1212 0.81 [0.64, 1.03]
Takeda 2009 -0.5108 0.0965 0.60 [0.50, 0.72]
Tony S. 2009 -0.2998 0.0665 0.74 [0.65, 0.84]
Subtotal (95% CI) 0.71 [0.60, 0.83]
Heterogeneity: Tau² = 0.01; Chi² = 4.70, df = 2 (P = 0.10); I² = 57%
Test for overall effect: Z = 4.19 (P < 0.0001)
1.1.4 Patients with lung non-adenocarcinoma
Takeda 2009 0.131 0.18 1.14 [0.80, 1.62]
Subtotal (95% CI) 1.14 [0.80, 1.62]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.47)
1.1.5 Unselected patients treated with combined gefitinib with chemotherapy
Giaccone 2004 0.0255 0.0847 1.03 [0.87, 1.21]
Herbst 2004 0.0257 0.0841 1.03 [0.87, 1.21]
Subtotal (95% CI) 1.03 [0.91, 1.15]
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.67)
0.2
0.5
1
2
5
Favours gefitinib
Favours control

OS

	 **4. Anmerkungen/Fazit der Autoren** In conclusion, 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.
Petrelli F et al., 2012 [30]. Efficacy of EGFR Tyrosine Kinase Inhibitors in Patients With EGFR-Mutated Non–Small-Cell Lung Cancer: A Meta-Analysis of 13 Randomized Trials	**1. Fragestellung** Advanced non–small-cell lung cancer (NSCLC) harboring activating mutations of epidermal growth factor receptor (EGFR) are particularly sensitive to tyrosine kinase inhibitors (TKIs), namely erlotinib and gefitinib. The purpose of this metaanalysis was to evaluate the benefit of EGFR TKIs in EGFR-mutated NSCLCs. **2. Methodik** **Population:** previously untreated or pretreated patients with advanced/ metastatic NSCLC; subpopulation of patients carrying an activating *EGFR* mutation (mainly exon 19 deletions or exon 21 point mutations) **Intervention:** gefitinib or erlotinib (either in the first-line setting or in subsequent treatment settings) **Komparator:** chemotherapy, placebo, or best supportive care **Endpunkte:** primär: objective response rate, PFS, and OS **Suchzeitraum:** bis 08/2011

Anzahl eingeschlossene Studien/Ptienten (Gesamt): 14 (10433)

- N=8 first line
- N=1 maintenance
- N=4 second line

Qualitätsbewertung der Studien: keine Angaben

Heterogenitätsuntersuchungen: I^2 statistic

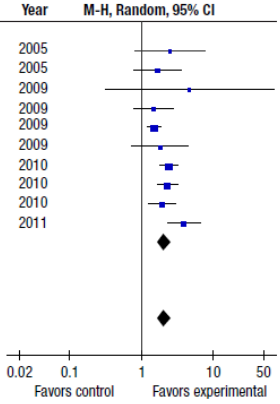
3. Ergebnisdarstellung

Studiencharakteristika vgl. Anlage

ORR (all trials and treatment line)

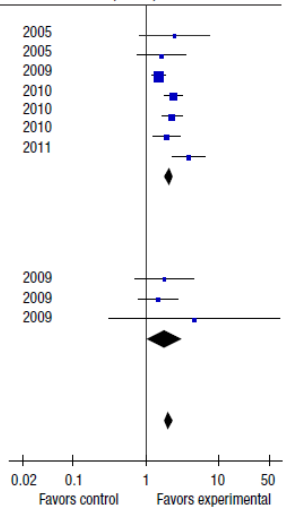
A

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year	Risk Ratio M-H, Random, 95% CI
7.3.2 meta-analysis of RR for response rate								
Eberhard 2005	8	15	3	14	3.3%	2.49 [0.82, 7.55]	2005	
Bell 2005	17	23	4	9	6.1%	1.66 [0.77, 3.59]	2005	
Kris ISEL 2009	8	21	0	5	0.6%	4.64 [0.31, 69.37]	2009	
Kris V 15-32 2009	11	16	7	15	8.0%	1.47 [0.78, 2.78]	2009	
Mok IPASS 2009	94	132	61	129	20.6%	1.51 [1.22, 1.86]	2009	
Douillard INTEREST 2009	9	22	5	22	4.6%	1.80 [0.72, 4.52]	2009	
Maemondo 2010	84	114	35	114	17.3%	2.40 [1.78, 3.23]	2010	
Zhou 2010	68	82	26	72	16.4%	2.30 [1.66, 3.17]	2010	
Mitsudomi 2010	36	58	19	59	13.0%	1.93 [1.26, 2.94]	2010	
Rosell EURTAC 2011	50	86	13	87	10.1%	3.89 [2.28, 6.63]	2011	
Subtotal (95% CI)		**569**		**526**	**100.0%**	**2.06 [1.66, 2.56]**		
Total events	385		173					
Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 17.40$, $df = 9$ ($p = .04$); $I^2 = 48\%$								
Test for overall effect: $Z = 6.53$ ($p < .00001$)								
Total (95% CI)		**569**		**526**	**100.0%**	**2.06 [1.66, 2.56]**		
Total events	385		173					
Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 17.40$, $df = 9$ ($p = .04$); $I^2 = 48\%$								
Test for overall effect: $Z = 6.53$ ($p < .00001$)								
Test for subgroup differences: Not applicable								

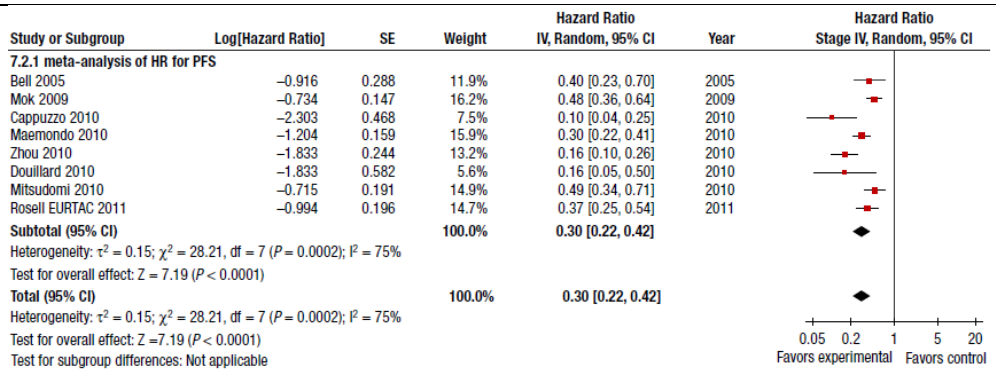


B

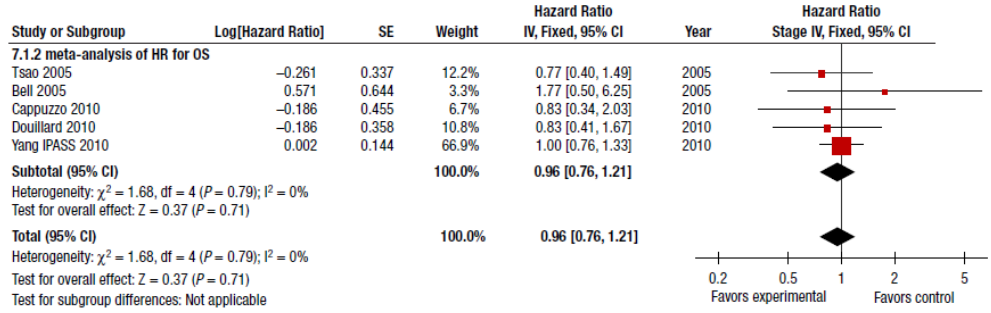
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year	Risk Ratio M-H, Fixed, 95% CI
7.3.1 meta-analysis of RR for response rate (1st-line trials)								
Eberhard 2005	8	15	3	14	1.7%	2.49 [0.82, 7.55]	2005	
Bell 2005	17	23	4	9	3.2%	1.66 [0.77, 3.59]	2005	
Mok IPASS 2009	94	132	61	129	34.7%	1.51 [1.22, 1.86]	2009	
Maemondo 2010	84	114	35	114	19.7%	2.40 [1.78, 3.23]	2010	
Zhou 2010	68	82	26	72	15.6%	2.30 [1.66, 3.17]	2010	
Mitsudomi 2010	36	58	19	59	10.6%	1.93 [1.26, 2.94]	2010	
Rosell EURTAC 2011	50	86	13	87	7.3%	3.89 [2.28, 6.63]	2011	
Subtotal (95% CI)		**510**		**484**	**92.7%**	**2.09 [1.82, 2.39]**		
Total events	357		161					
Heterogeneity: $\chi^2 = 16.11$, $df = 6$ ($p = .01$); $I^2 = 63\%$								
Test for overall effect: $Z = 10.52$ ($p < .00001$)								
7.3.2 meta-analysis of RR for response rate (2nd-line trials)								
Douillard INTEREST 2009	9	22	5	22	2.8%	1.80 [0.72, 4.52]	2009	
Kris V 15-32 2009	11	16	7	15	4.1%	1.47 [0.78, 2.78]	2009	
Kris ISEL 2009	8	21	0	5	0.4%	4.64 [0.31, 69.37]	2009	
Subtotal (95% CI)		**59**		**42**	**7.3%**	**1.79 [1.04, 3.09]**		
Total events	28		12					
Heterogeneity: $\chi^2 = 0.84$, $df = 2$ ($p = .66$); $I^2 = 0\%$								
Test for overall effect: $Z = 2.09$ ($p = .04$)								
Total (95% CI)		**569**		**526**	**100.0%**	**2.07 [1.81, 2.36]**		
Total events	385		173					
Heterogeneity: $\chi^2 = 17.40$, $df = 9$ ($p = .04$); $I^2 = 48\%$								
Test for overall effect: $Z = 10.69$ ($p < .00001$)								
Test for subgroup differences: $\chi^2 = .29$, $df = 1$ ($p = .59$); $I^2 = 0\%$								



PFS (all trials)



OS



4. Anmerkungen/Fazit der Autoren

In conclusion, NSCLCs harboring *EGFR* mutations derive greater benefit from erlotinib or gefitinib than from chemotherapy, either in first-line or subsequent lines of therapy. These agents double the chance of an objective response and reduce the risk of progression by about 70% but do not increase OS. These results are likely to be influenced by crossover treatments that formally abrogate any survival gain. The paradigm of up-front treatment in this setting has to be shifted from platinum-based chemotherapy to molecular targeted therapies. All patients affected by NSCLC with *EGFR* mutation– positive analysis in fact should be offered the opportunity to be treated with an EGFR TKI (according to the labeled indications) during the natural course of the disease.

5. Hinweise der FBMed

Keine Angaben zur methodischen Bewertung der Primärstudien

OuYang P-Y et al., 2013 [28]. Combination of EGFR-TKIs and Chemotherapy as First-Line	**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**

Therapy for Advanced NSCLC: A Meta-Analysis	**Population:** advanced NSCLC, **Intervention:** EGFR–TKI monotherapy **Komparator:** EGFR–TKI and chemotherapy **Endpunkte:** OS, PFS **Suchzeitraum:** k.A. **Anzahl eingeschlossene Studien/Ptienten (Gesamt):** 4 **Qualitätsbewertung der Studien:** Jadad **Heterogenitätsuntersuchungen:** square test and I^2 **3. Ergebnisdarstellung** Overall, these studies were of high quality – blinding, showing randomization procedure, conducting estimation of sample size, mostly reporting dropout and following the principle of intentionto-treat analysis

Table 1. Baseline characteristics of the included trials in the meta-analysis.

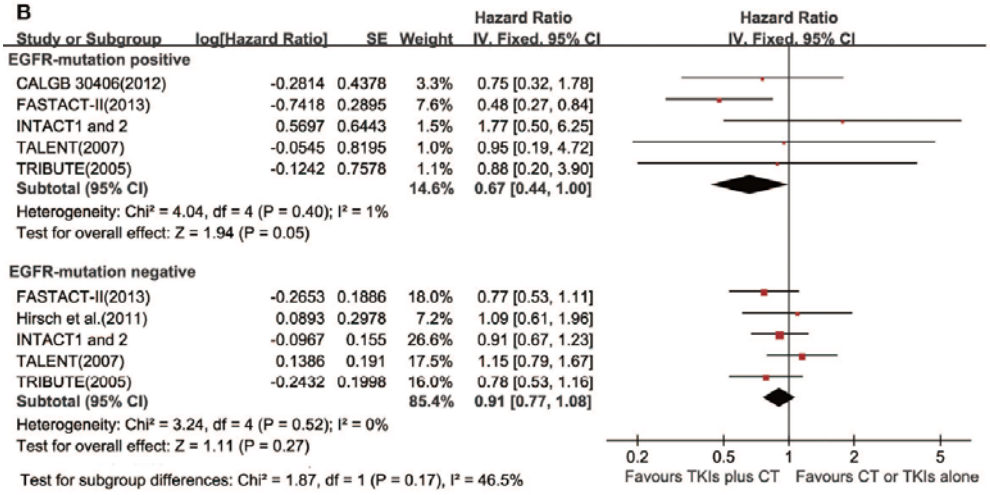
Trials(year)	TKIs	chemotherapy (dose*cycles)	Patients analyzed	Median age (range)	Female	Race (% Asian)	Never/light smoker	EGFR mutation positive
FASTACT(2009) [13]	E[†]	DDP(75 mg/m^2,d1)/CBP(AUC = 5,d1)+GEM1250(mg/m^2,d1,8),q4w*6	76vs78	57.5(33–79) vs57.0(27–79)	22vs24	93vs95	24vs28	2vs5
FASTACT–II (2013) [14]	E[†]	DDP(75 mg/m^2,d1)/CBP(AUC = 5,d1)+GEM1250(mg/m^2,d1,8),q4w*6	226vs225	59.0(31–96)vs57.3(17–88)	94vs85	100vs100	112vs107	49vs48
INTACT 1(2004) [7] [17]	G[‡]	DDP(80 mg/m^2,d1)+GEM(1250 mg/m^{2}d1,8),q3w*6	365vs363	59(34–83)vs61(33–81)	85vs101	1.6vs0.8	NA	23vs9[&]
INTACT 2(2004) [8] [17]	G[‡]	CBP(AUC = 6)+TAX(225 mg/m^2),q3w*6	345vs345	61(27–86)vs63(31–85)	146vs133	NA	NA	
TALENT(2007) [9]	E	DDP(80 mg/m^2,d1)+GEM(1250 mg/m^{2}d1,8),q3w*6	580vs579	61(26–82)vs60(28–84)	125vs142	3vs4	8vs10	NA
TRIBUTE(2005) [10] [18]	E	CBP(AUC = 6)+TAX(200 mg/m^2),q3w*6	539vs540	63(24–84)vs63(26–84)	217vs207	3.9vs2.4	72vs44	15vs14
CALGB30406(2012) [12]	E	CBP(AUC = 6)+TAX(200 mg/m^2),q3w*6	100vs81	60(34–81)vs58(32–78)	58vs49	8vs6	100vs81	33vs33
Hirsch et al.2011 [11]	E	CBP(AUC = 6)+TAX(200 mg/m^2),q3w*4	71vs72	NA	31vs44	6vs12	NA	6vs9

Note: TKIs = tyrosine kinase inhibitors, PS = performance status, E = erlotinib, G = gefitinib, DDP = cisplatin, CBP = carboplatin, AUC = area under the curve, GEM = gemcitabine, q4w = every four weeks, vs = the combined regimen versus chemotherapy or TKIs monotherapy, NA = not available, TAX = paclitaxel.
[*]Sequential administration of erlotinib following gemcitabine/platinum chemotherapy, rather than concurrent administration as the other trials.
[‡]Only included patients treated with gefitinib 250 mg/d.
[&]Data from trials INTACT 1and 2 together.

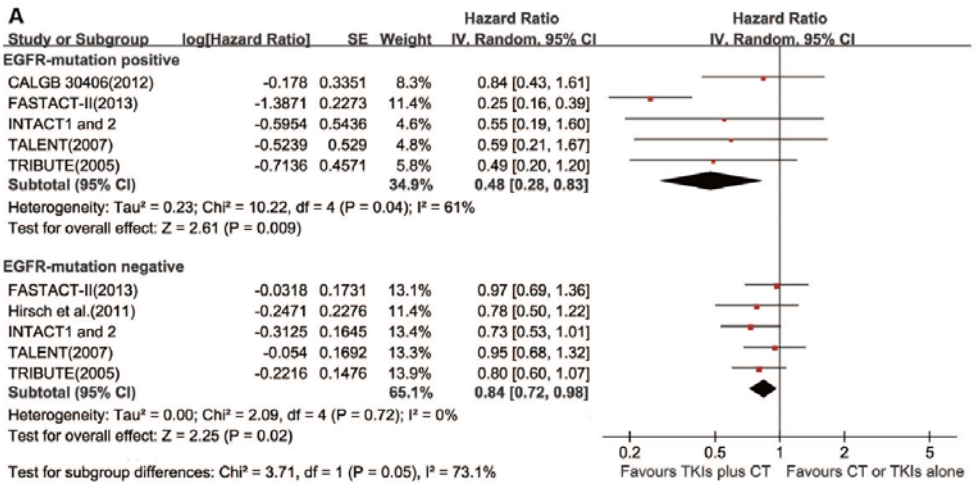
OS

Effect of the Combined Regimen on PFS and OS in Selected Patients by EGFR-Mutation Status Survival data of EGFR-mutation positive patients was only available in the FASTACT–II [14], INTACT 1 and 2 [17], TALENT [9], TRIBUTE [18] and CALGB30406 [12]. Estimates of PFS and OS in

EGFR-mutation negative patients could only be calculated in the FASTACT–II [14], INTACT 1 and 2 [17], TALENT [9], TRIBUTE [18] and trial by Hirsch et al [11]. In the EGFR-mutation positive cohort, the 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; Figure 3a). Interestingly, the 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). Certainly, the magnitude of PFS improvement resulted from the combined regimen in the EGFR-mutation positive cohort was marginally larger than that in the EGFR-mutation negative cohort (P = 0.05). In terms of OS, the 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).



PFS



	4. Anmerkungen/Fazit der Autoren Unfortunately, the combined regimen had no significant impact on overall survival, irrespective of ethnicity, dose schedules or EGFR-mutation status. Severe anorexia (RR = 2.01, 95% CI 1.11–3.63; P = 0.02) and diarrhea (RR = 2.70, 95% CI 1.94–3.76; P<0.001) were more frequent in the combined regimen arm. This strategy of combining EGFR–TKIs and chemotherapy deserved to be considered in the future, although it is not approved for advanced NSCLC at the moment.
Ku GY et al., 2011 [18]. Gefitinib vs. chemotherapy as first-line therapy in advanced non-small cell lung cancer: Meta-analysis of phase III trials	**1. Fragestellung** Here, we perform a meta-analysis of the most updated results of these studies to better quantify the toxicities and clinical benefits of gefitinib over chemotherapy. **2. Methodik** **Population:** advanced NSCLC, patients with known EGFRmutation status **Intervention:** Gefitinib **Komparator:** Chemotherapie **Endpunkte:** nicht präspezifiziert **Suchzeitraum:** k.A. **Anzahl eingeschlossene Studien/Ptienten (Gesamt):** 4 (ca. Gefitinib 969 / Chemotherapie 960) **Qualitätsbewertung der Studien:** k.A. **Heterogenitätsuntersuchungen:** k.A. **3. Ergebnisdarstellung** - Qualitatives Review Patient demographics. | Characteristic	Gefitinib ($n=809$)*	Chemotherapy ($n=808$)*
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Sex		
Male	194 (24%)	194 (24%)
Female	615 (76%)	614 (76%)
Smoking history		
Never	707 (87%)	692 (86%)
Former/current	102 (13%)	116 (14%)
ECOG/WHO performance status		
0	267 (33%)	270 (33%)
1	480 (59%)	471 (58%)
2	62 (8%)	67 (8%)
Stage		
IIIB	175 (22%)	174 (22%)
IV/recurrent	634 (78%)	633 (78%)
Unknown	0	1 (0%)	 ECOG/WHO, Eastern Cooperative Oncology Group/World Health Organization. * Complete demographic data are available only for the North-East Japan, West Japan and IPASS studies. **3.2. EGFR mutations** Both the North-East Japan and West Japan studies mandated the presence of an activating EGFR mutation prior to study entry. The IPASS and first-SIGNAL studies selected light- or neversmokers (≤10 pack-years) with

	adenocarcinoma histology and subsequently analyzed available tumor tissue from consenting patients for EGFR mutations. The IPASS study recruited in East and South-east Asia (but not Korea) while the first-SIGNAL study exclusively enrolled Korean patients. In the IPASS study, analysis was performed on 36% of patients; of these patients, 57% were found to have activating EGFR mutations. In the first-SIGNAL study, 31% of patients had analyzable tumors; activating mutations were found in 44%. From the four studies, data on specific activating EGFR mutations are available for 650 patients. Fifty-three percent were deletions in exon 19, 45% were the L858R mutation in exon 21 and 4% were other mutations (some tumor samples had multiple mutations). Of note, 11 of 437 samples (2.5%) analyzed in the IPASS study were found to contain the exon 20 T790M mutation, which is known to confer resistance to EGFR TKIs. **3.3. Toxicities** Toxicities reported on these trials are consistent with the known toxicities of gefitinib and the respective chemotherapy regimens. Representative toxicities include fatigue, which was significantly more common in the chemotherapy arms. In the North-East Japan, West Japan and IPASS studies, the cumulative incidence of fatigue of any grade in the gefitinib arms was 18% (148 of 808) vs. 46% (363 of 790) in the chemotherapy arms (odds ratio 0.24, $p < 10^{-15}$). Nausea was also more common in the chemotherapy arms of the North-East Japan and IPASS trials, where 51% (344 of 677) of the patients experienced any grade nausea vs. 17% (116 of 694) in the gefitinib arms (odds ratio 0.19, $p < 10^{-15}$). Patients receiving chemotherapy also experienced significantly more myelosuppression. As an example, the incidence of all-grade and grade ≥ 3 neutropenia was much less common in the gefitinib arms (7% vs. 84% and 3% vs. 69%, respectively). Across the studies, the odds ratio for grade ≥ 3 neutropenia for gefitinib vs. chemotherapy was 0.01 ($p < 10^{-15}$). On the other hand, rash and diarrhea were more common in the gefitinib arms. Sixty-nine percent (557 of 808) of patients in the gefitinib arms experienced any-grade rash vs. 21% (164 of 790) of patients in the chemotherapy arms (odds ratio 8.19, $p < 10^{-15}$). There was a similarly increased incidence of grade ≥ 3 rash for the gefitinib arms (3% vs. 1% odds ratio 3.39, $p = 0.003$). Any-grade diarrhea occurred in 46% (369 of 808) of the gefitinib-treated patients vs. 22% (170 of 790) of patients who received chemotherapy (odds ratio 3.15, $p < 10^{-15}$); grade ≥ 3 diarrhea was also more common (3% vs. 1%, odds ratio 3.12, $p = 0.006$). Pneumonitis, a rare but serious toxicity associated with gefitinib, was reported in the North-East Japan study in 5% (6 of 114) of gefitinib-treated patients vs. 0 of 113 patients in the chemotherapy arm (odds ratio ∞, $p = 0.03$). In the IPASS study, interstitial lung disease events (which included pneumonitis) occurred in 2.6% of gefitinib treated patients vs. 1.4% of those who received chemotherapy (odds ratio 1.97, $p = 0.15$). **4. Anmerkungen/Fazit der Autoren** This meta-analysis confirms the results of each individual study and narrows

	the confidence intervals of these results. In patients with known EGFR mutations or whose tumors are likely to harbor a mutation, upfront gefitinib or chemotherapy are associated with similar OS. Gefitinib is associated with less fatigue, myelosuppression and nausea than chemotherapy (but produces more skin rash, diarrhea and pneumonitis). Patients receiving gefitinib have improved quality-of-life compared to those receiving chemotherapy, making it an appropriate first-line choice. **5. Hinweis der FBMed** Dieses Review wurde trotz methodischer Mängel eingeschlossen, weil es die Mutation T790M thematisiert. Die methodischen Mängel sind: • Vermischung zwischen Methoden und Ergebnissen, • fehlende Angabe zum Suchzeitraum • fehlende Studienbewertung • keine Angaben zu eingesetzten Methoden der Heterogenitätsanalyse • Einbeziehung von auch Primärstudien, deren Publikation nicht als Volltext vorgelegen hat Es wurden nur die Ergebnisse der zur Mutation T790M extrahiert.

b) TKI-vorbehandelte Patienten

Es wurden keine Systematischen Reviews gefunden.

Australian Government, Cancer Council Australia, 2015 [2].

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 toxicity, compared with gemcitabine or paclitexel and carboplatin combinations.	I
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. **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.	I
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 previously treated patients 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

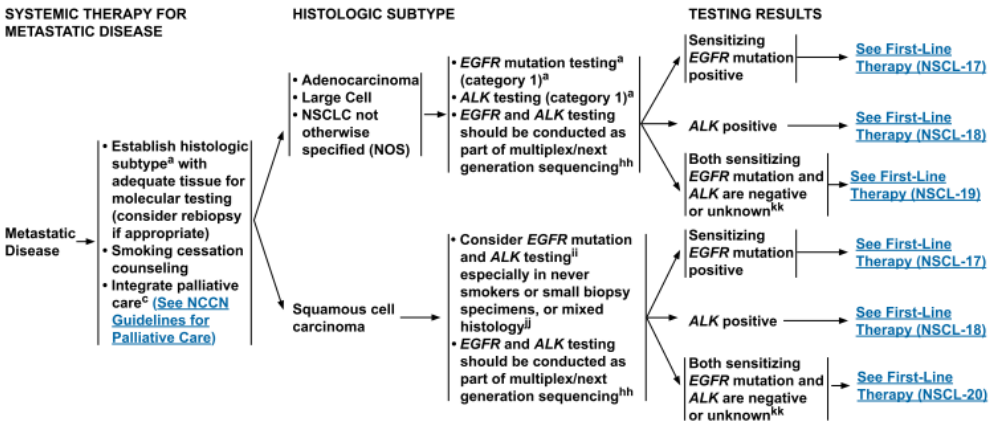
Evidence summary	LoE
In patients with poor performance status (PS 2), first-line monotherapy with 3G chemotherapy (vinorelbine, gemcitabine, paclitaxel or docetaxel) may improve survival and/or quality of life.	I, II
Recommendation	Grade
First-line monotherapy with 3G chemotherapy could be offered to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

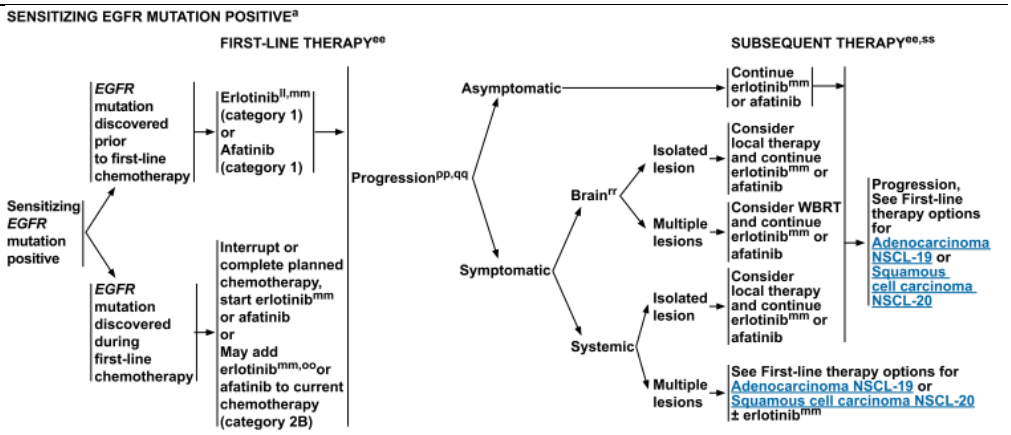
Baggstrom MQ, et al. 2007 Crawford J, O'Rourke M, Schiller JH, Spiridonidis CH, Yanovich S, Ozer H, et al. Randomized trial of vinorelbine compared with fluorouracil plus leucovorin in patients with stage IV non-small-cell lung cancer. J Clin Oncol 1996 Oct;14(10):2774-84 Effects of vinorelbine on quality 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	I

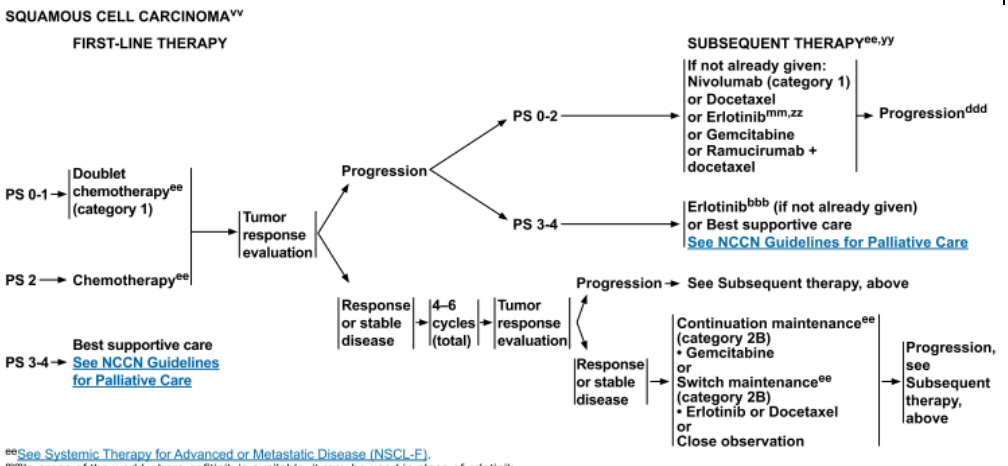
	of pemetrexed observed in non-squamous cell carcinoma histology and inferior survival effect observed in squamous cell carcinoma histology, compared with other standard regimens when pemetrexed is used first-line, as switch maintenance or as second-line treatment. Recommendation — Grade Due to the therapeutic 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
NCCN, 2015 [23]. NCCN Guidelines Version Version	– Leitlinie des National Comprehensive Cancer Network Hier: Empfehlungen zu TKI-vorbehandelten Patienten
	Methodik Grundlage der Leitlinie Update 2015 Suchzeitraum 06/2013 –

7.2015 Non-small cell lung cancer	06/2014 Recherche in Pubmed nach ‚key literature', search term: NSCLC, Auswahl der Literatur unklar LoE: depends on *extent* of data (e.g., number of trials, size of trials, clinical observations only) *consistency* of data (e.g., similar or conflicting results across available studies or observations), *quality* of data based on trial design and how the results/observations were derived (e.g., RCTs, non-RCTs, meta-analyses or systematic reviews, clinical case reports, case series) 2 categories: high level of evidence and lower level of evidence; Bewertung der Studien und Einteilung in LoE unklar GoR: 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.
	Empfehlungen  [a]See Principles of Pathologic Review (NSCL-A). [c]Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742. [hh]The NCCN NSCLC Guidelines Panel strongly endorses broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H). [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. [jj]Paik PK, Varghese AM, Sima CS, et al. Response to erlotinib in patients with *EGFR* mutant advanced non-small cell lung cancers with a squamous or squamous-like component. Mol Cancer Ther 2012;11:2535-2540. [kk]Consider ROS1 testing; if positive, may treat with crizotinib. Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in ROS1-rearranged non-small cell lung cancer. N Engl J Med 2014;371:1963-1971. **Note: All recommendations are category 2A unless otherwise indicated.** **Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.** NSCL-16



[a]See Principles of Pathologic Review (NSCL-A).
[ee]See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[ll]For performance status 0-4.
[mm]In areas of the world where gefitinib is available, it may be used in place of erlotinib.
[oo]Janne PA, Wang X, Socinski MA, et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who are never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial. J Clin Oncol 2012;30:2063-2069.
[pp]Prior to changing therapy, a biopsy is reasonable to determine mechanism of acquired resistance.
[qq]Beware of flare phenomenon in subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.
[rr]Consider pulse erlotinib for carcinomatosis meningitis.
[ss]Afatinib appears to have some efficacy in patients who progressed on EGFR therapy. Miller VA, Hirsh V, Cadrenal J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol 2012;13:528-38.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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)**

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]**

[1]Bonomi P, Kim K, Fairclough D, et al. Comparison of survival and quality of life in advanced non-small cell lung cancer patients treated with two dose levels of paclitaxel combined with cisplatin versus etoposide with cisplatin:results of an Eastern Cooperative Oncology Group trial. J Clin Oncol 2000;18:623-631.
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[3]Cardenal F, Lopez-Cabrerizo MP, Anton A, et al. Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small cell lung cancer. J Clin Oncol 1999;17:12-18.
[4]Belani CP, Lee JS, Socinski MA, et al. Randomized phase III trial comparing cisplatin-etoposide to carboplatin-paclitaxel in advanced or metastatic non-small cell lung cancer. Ann Oncol 2005;16:1069-1075.
[5]Sandler AB, Nemunaitis J, Denham C, et al. Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small cell lung cancer. J Clin Oncol 2000;18:122-130.
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[8]Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. N Engl J Med 2002;346:92-98.
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[11]Belani CP, Ramalingam S, Perry MC, et al. Randomized, phase III study of weekly paclitaxel in combination with carboplatin versus standard every-3-weeks administration of carboplatin and paclitaxel for patients with previously untreated advanced non-small-cell lung cancer. J Clin Oncol 2008;26:468-473.
[12]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;18:2354-2362.
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[15]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 NSCLC. J Clin Oncol 2008;26:3543-3551.
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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.

Nach vorheriger TKI Therapie: Empfehlung 1 (Category 2A): in patients with asymptomatic progression after treatment with TKI (erlotinib, gefitinib, or afatinib): continuation of either erlotinib, gefitinib, or afatinib; in patients with symptomatic progression after treatment with TKI (erlotinib, gefitinib, or afatinib): continuation of either erlotinib, gefitinib, or afatinib plus addition/substitution therapy (whole brain RT, local therapy, systemic therapy) recommendation based on following studies: **Riely 2007** Einarmige Interventionsstudie (n=13); Studienpopulation: NSCLC patients treated with gefitinib or erlotinib monotherapy for > 6 months; acquired resistance to erlotinib or gefitinib (defined by a prior radiographic response to treatment with gefitinib or erlotinib or, in cases where radiographs were not available, documentation of either an EGFR exon 19 deletion or an EGFR L858R mutation) Intervention: Discontinuation for 3w and reinitiation of erlotinib or gefitinib. 3 w after retreatment of TKI: initiation of 5 mg/d orally everolimus (RAD001, Novartis) Outcome: changes in tumor size, metabolic

activity of NSCLC Results:
based on 10/13 pts. (3 excluded [due to death (1) or back pain (1) after discontinuation or due to cough/dyspnea (1) after TKI retreatment but before everolimus] Clinical findings after discontinuation and reinitiation of gefitinib or erlotinib. increase in symptoms after discontinuing erlotinib or gefitinib in 7/ 10 patients; all 7 improved or stabilized symptoms after restarting of efitinib or erlotinib) after discontinuation: increase in tumor diameter in 8/10; increase in tumor volume in 9/10 patients Response to combined treatment with everolimus plus gefitinib or erlotinib 0/10 patient (95% CI 0-32%) had a confirmed partial response after combined treatment with 5 mg/d everolimus plus gefitinib or erlotinib Results with respect to tumor diameter and volume

Table 3. Changes in tumor on CT and FDG-PET

	After stopping gefitinib or erlotinib	After restarting gefitinib or erlotinib	3 wks after adding everolimus
Median change in tumor diameter	+9%	-1%	-8%
Mean change in tumor diameter	+9%	1%	-9%
Range in change in tumor diameter	-13% to +29%	-14% to +23%	-34% to +15%
Median change in tumor volume	+50%	-1%	-11%
Mean change in tumor volume	+61%	-4%	-10%
Range in change in tumor volume	-4% to +260%	-27% to 15%	-40% to +26%
Median change in SUV_{max}	+18%	-4%	-18%
Mean change in SUV_{max}	+23%	-11%	-11%
Range in change in SUV_{max}	-17% to +87%	-45% to +62%	-39% to +82%

Authors conclusion: in patients with acquired resistance, stopping of erlotinib or gefitinib therapy results in symptomatic progression; No responses were observed with combined everolimus and erlotinib or gefitinib **Chaft et al. 2011** Observational, retrospective study (n=61) Study population: patients with EGFR-mutant lung cancer who participated in trials for patients with acquired resistance to erlotinib or gefitinib that mandated TKI discontinuation before administration of study therapy. Finding: 23 % (95% CI: 14–35) had a disease flare (hospitalization or death attributable to disease progression) after discontinuation of the TKI **Zur EGFR-Mutation T790M**

PRINCIPLES OF PATHOLOGIC REVIEW (3 of 4)

Molecular Diagnostic Studies in Lung Cancer.

- ***EGFR*** **and** ***KRAS***
  - ***EGFR*** **is normally found on the surface of epithelial cells and is often overexpressed in a variety of human malignancies. Presence of** ***EGFR*****-activating mutations represents a critical biological determinant for proper therapy selection in patients with lung cancer.**
  - **There is a significant association between** ***EGFR*** **mutations—especially exon 19 deletion and exon 21 (L858R, L861), exon 18 (G719X, G719), and exon 20 (S768I) mutations—and sensitivity to EGFR TKIs.[16-19]**
  - **The exon 20 insertion mutation may predict resistance to clinically achievable levels of TKIs.[20,21]**
  - **Overlapping** ***EGFR*** **and** ***KRAS*** **mutations occur in <1% of patients with lung cancer.[22]**
  - ***KRAS*** **mutations are associated with intrinsic EGFR TKI resistance, and** ***KRAS*** **gene sequencing could be useful for the selection of patients as candidates for EGFR TKI therapy.[23]** ***KRAS*** **testing may identify patients who may not benefit from further molecular diagnostic testing.**
  - **The prevalence of** ***EGFR*** **mutations in adenocarcinomas is 10% of Western and up to 50% of Asian patients, with higher** ***EGFR*** **mutation frequency in non-smokers, women, and non-mucinous cancers.** ***KRAS*** **mutations are most common in non-Asians, smokers, and in mucinous adenocarcinoma.[24] The most common** ***EGFR*** **mutations result in an arginine for leucine substitution at amino acid 858 in exon 21 (L858R) and in frame deletions at exon 19. Mutations are more common in non-mucinous lung adenocarcinoma with lepidic pattern (former BAC pattern) and in lung adenocarcinoma with papillary (and or micropapillary) pattern.**
  - **Primary resistance to EGFR TKI therapy is associated with** ***KRAS*** **mutation. Acquired resistance is associated with second-site mutations within the** ***EGFR*** **kinase domain (such as T790M), amplification of alternative kinases (such as** ***MET***), **histologic transformation from NSCLC to SCLC, and epithelial to mesenchymal transition (EMT).**
- ***ALK***
  - **Anaplastic lymphoma kinase (*ALK*) gene rearrangements represent the fusion between** ***ALK*** **and various partner genes, including echinoderm microtubule-associated protein-like 4 (*EML4*).[25] ALK fusions have been identified in a subset of patients with NSCLC and represent a unique subset of NSCLC patients for whom** ***ALK*** **inhibitors may represent a very effective therapeutic strategy.[26] Crizotinib and ceritinib are oral** ***ALK*** **inhibitors that are approved by the FDA for patients with metastatic NSCLC who have the** ***ALK*** **gene rearrangement (ie,** ***ALK*** **positive).**
  - ***ALK*** **NSCLC occurs most commonly in a unique subgroup of NSCLC patients who share many of the clinical features of NSCLC patients likely to harbor** ***EGFR*** **mutations.[27,28] However, for the most part,** ***ALK*** **translocations and** ***EGFR*** **mutations are mutually exclusive.[27, 29-31]**
  - **The current standard method for detecting** ***ALK*** **NSCLC is fluorescence in situ hybridization (FISH), although other methods are currently being evaluated, including polymerase chain reaction (PCR) and IHC. The appropriate antibody and detection method for** ***ALK*** **protein expression can be used for rapid prescreening of ALK-rearranged lung adenocarcinomas and selection of cases that will subsequently be confirmed by FISH testing.[32]**

including EGFR and HER2.[149,150] The FDA has approved afatinib for first-line treatment of patients with metastatic non-squamous NSCLC who have sensitizing EGFR mutations.[151,152]

These sensitizing EGFR mutations are found in approximately 10% of Caucasian patients with NSCLC and up to 50% of Asian patients.[153] Other drug-sensitive mutations include point mutations at exon 21 (L861Q) and exon 18 (G719X).[154] Primary resistance to TKI therapy is associated with KRAS mutations and ALK gene rearrangements. Patients with exon 20 insertion mutations are also resistant to TKIs.[155-158] The EGFR T790M mutation is associated with acquired resistance to TKI therapy and has been reported in about 50% of patients with disease progression after initial response to erlotinib.[159-164] Most patients with sensitizing EGFR mutations become resistant to erlotinib (or gefitinib) after about 8 to 16 months of TKI therapy.[159] However, studies suggest the T790M mutation may also occur in patients who have not previously received TKI therapy.[165] Acquired resistance may be associated with histologic transformation from NSCLC to SCLC and with epithelial to mesenchymal transition (see *Principles of Pathologic Review* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[166-168]

DNA mutational analysis is the preferred method to assess for EGFR status.[169-171] Various DNA mutation detection assays can be used to determine the EGFR mutation status in tumor cells. Direct sequencing of DNA corresponding to exons 18 to 21 (or just testing for exons 19 and 21) is a reasonable approach; however, more sensitive methods are available.[153,170,172-174] Mutation screening assays using multiplex PCR (eg, Sequenom's MassARRAY® system, SNaPshot® Multiplex System) can detect more than 50 point mutations, including EGFR.[130] NGS can also be used to detect EGFR mutations.[132]

The predictive effects of the drug-sensitive EGFR mutations—Exon19del (LREA deletion) and L858R—are well defined. Patients with these mutations have a significantly better response to erlotinib, gefitinib, or afatinib.[148] Retrospective studies have shown an objective response rate of approximately 80% with a median progression-free survival (PFS) of 13 months to single-agent therapy in patients with a bronchioloalveolar variant of adenocarcinoma and a sensitizing EGFR mutation.[113] A prospective study has shown that the objective response rate in North American patients with non-squamous NSCLC and sensitizing EGFR mutations (53% Exon19del [LREA deletion], 26% L858R, 21% other mutations) is 55% with a median PFS of 9.2 months.[114] EGFR mutation testing is not usually recommended in patients with pure squamous cell carcinoma unless they never smoked, if only a small biopsy specimen (ie, not a surgical resection) was used to assess histology, or if the histology is mixed.[124] Data suggest that EGFR mutations can occur in patients with adenosquamous carcinoma, which is harder to discriminate from squamous cell carcinoma in small specimens.[124]

Recent data suggest that erlotinib (or gefitinib) or afatinib (instead of standard first-line chemotherapy) should be used as first-line systemic therapy in patients with sensitizing EGFR mutations documented before first-line therapy.[152,175-180] Data show that PFS is improved with use of EGFR TKI in patients with sensitizing EGFR mutations when compared with standard chemotherapy, although overall survival is not statistically different.[152,175] Patients receiving erlotinib have fewer treatment-related severe side effects and deaths when compared with those receiving chemotherapy.[175,181] Based on this data and the FDA approval, erlotinib (or gefitinib) is recommended (category 1) as first-line systemic therapy in patients with sensitizing EGFR mutations.[175] In a recent phase 3 randomized trial, patients receiving afatinib had decreased cough,

Masters GA et al., 2015 [22].

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

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).

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**

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

GoR

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

Formal Consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong,"
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
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

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

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

Empfehlungen

First-Line Treatment for Patients:

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: intermediate; strength of recommendation: moderate).

With ROS1 rearrangement: crizotinib is recommended (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).

Recommendation A4 If patients have stage IV NSCLC and a sensitizing

	EGFR mutation, first-line afatinib (type: evidence based, benefits outweigh harms; evidence quality: high; strength of recommendation: strong), erlotinib (type: evidence based, benefits outweigh harms; evidence quality: high; strength of recommendation: strong), or gefitinib (type: evidence based, benefits outweigh harms; evidence quality: high; strength of recommendation: strong) is recommended. *Literature review update and analysis.* Since the publication of the ASCO 2009 guideline and the ASCO EGFR provisional clinical opinion, results from seven trials of first-lineEGFRTKIs for patients with EGFR mutations have been published. Three studies specifically required evidence that all participants had EGFR mutations. Two trials, in which PFS was the primary end point, compared first-line erlotinib with chemotherapy. In one small study, there was a PFS benefit with erlotinib (9.7 v 5.2 months;HR,0.37;95% CI, 0.25 to 0.54; P = .001); OS had not been reached by the time of publication. There was incidence of higher fatigue, rash, and diarrhea with erlotinib compared with chemotherapy. In the second small study, which was a publication of an abstract in the provisional clinical opinion, there was a longer PFS (erlotinib: 13.7 months; 95% CI, 10.6 to 15.3; control: 4.6 months; 95% CI, 4.2 to 5.4; HR, 0.164; 95% CI, 0.11 to 0.26; P = .001); OS had not yet been reached. Rash incidence was higher with erlotinib, although only small numbers of participants experienced grade 3 to 4 rash. In both studies of selected patients, incidence of neutropenia, thrombocytopenia, and anemia was higher with chemotherapy. Afatinib is a second-generation, irreversible ErbB family inhibitor. One study, with PFS as primary outcome, compared first-line afatinib with cisplatin plus pemetrexed. The results showed improvement with afatinib (11.1 v 6.9 months; HR, 0.58; 95% CI, 0.43 to 0.78; P=.001). Survival was not significantly longer (16.6 v 14.8 months). Afatinib was approved by the FDA on the basis of this study for patients with L858R mutations and/or exon 19 deletions. A prespecified analysis of patients with these common mutations showed a PFS of 13.6 versus 6.9 months for chemotherapy (HR, 0.47; 95% CI, 0.34 to 0.65; P=.001). Briefly, theASCOprovisional clinical opinion discussed results of the IPASS trial comparing gefitinib with carboplatin plus paclitaxel. A statistically significant PFS was found for all patients in the trial treated with gefitinib, including those whose tumors were EGFR mutation positive. The updated systematic review included final OS results, which were not statistically significantly different (overall: 18.8 v 17.4 months; EGFR positive: 21.6 v 21.9 months). The report also noted that “although these values [PFS] were reported in the original publications, a single HR is not readily interpretable because the survival curves cross, suggesting a violation of the proportional hazards assumption.”(p4) Updated results of another trial discussed in the EGFR provisional clinical opinion that compared gefitinib versus carboplatin plus paclitaxel continued to show statistically significant outcomes for PFS but not OS and will not be further discussed here. Two studies of gefitinib as switch maintenance found PFS but not OS benefits. *Clinical interpretation.* There is overwhelming and consistent evidence now from multiple trials that gefitinib, erlotinib, or

	afatinib have greater activity than platinum-based chemotherapy in the first-line treatment of patients with advanced NSCLC with activating EGFR mutations. There have been significant improvements in response rate and TTP favoring gefitinib, erlotinib, or afatinib. These agents have more favorable toxicity profiles than platinum-based chemotherapy and have demonstrated improvements in QoL. Despite the absence of clear improvements in OS, gefitinib, erlotinib, or afatinib is a preferred treatment based on large improvements in other outcomes. The choice of whichEGFRTKI to recommend to patients should be based on the availability and toxicity of the individual agent. Whereas gefitinib is not licensed in the United States, it is still widely used in Asia and other regions. There are no results from direct comparative trials of different EGFR TKIs. Therefore, it is not possible to make a recommendation favoring one EGFR TKI over another. RCTs are ongoing, comparing gefitinib with afatinib, as well as gefitinib with dacomitinib, another pan-HER inhibitor. The results of these trials may help refine this recommendation in the future. ***Second-Line Treatment for Patients:*** 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). *Vgl. Unten: B3.b* 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. **T790M** *Recommendation B3.b* Patients who received an EGFR TKI in the first-line setting, had an initial response, and subsequently experienced disease progression may be switched to chemotherapy or another EGFR TKI as secondline therapy (type: informal consensus, balance of benefits and harms; evidence quality: low; strength of recommendation: weak). *Literature review update and analysis.* Given that there were no data

	meeting the inclusion criteria to inform this question, the Update Committee relied on clinical experience, training, and judgment to formulate this recommendation. Afatinib has shown preclinical activity in*EGFR*-mutant models with the exon 20 T790M mutation, which has been shown to confer resistance to EGFR-reversible TKIs.Aphase IIB/III randomized clinical trial (LUX-Lung 1) investigated the role of afatinib for patients whose disease had progressed with both chemotherapy and an EGFR inhibitor. This study included many participants whose tumors had developed resistance to treatment with an EGFR TKI; however, *EGFR* mutation status was not an eligibility criterion. The study found no improvement in the primary end point of OS between patients randomly assigned to afatinib and those randomly assigned to placebo, although PFS was longer in the afatinib group (3.3 *v* 1.1 months; HR, 0.38; 95% CI, 0.31 to 0.48; *P* =.001). Response rate was 7% versus 0.5%. Ninety-six patients had tumors that were positive for *EGFR* mutations. Among these 96 patients, PFS was 3.3 months for those who received afatinib and 1.0 month for those who received placebo (HR, 0.55; 95% CI, 0.31 to 0.85; *P* = .009). In a prespecified analysis, participants with a complete or partial response to a first-line EGFR TKI whose tumors also had known *EGFR* mutation test results (58 [88%] of 66), the HR for PFS was significant (0.23), but the HR for OS was not (0.90) in the afatinib arm. Sixty-three percent of the patients in the afatinib group and 76% in the control group received ≥ one subsequent regimen (all mutation statuses). *Clinical interpretation.* There is a lack of conclusive data for treating this population, especially with a second TKI. In the afatinib trial, response rates in both arms were lower than in studies with chemotherapy; however, given the longer PFS, afatinib after gefitinib or erlotinib in patients with *EGFR*-sensitizing mutations who experienced an initial response may be an option. There are indications that it is not beneficial to continue an EGFR inhibitor after acquired resistance. European Society for Medical Oncology results from IMPRESS (Iressa Mutation Positive Multicenter Treatment Beyond Progression Study; ClinicalTrials.gov identifier NCT01544179), in which the control arm, composed of patients with resistance to an EGFR TKI (gefitinib) and chemotherapy, continued to receive an EGFR inhibitor with chemotherapy, the addition of (or continuation) of the TKI did not add efficacy or adverse event benefits. These results have not yet been released in a peer-reviewed publication. **Future directions** As a result of the lack of data in certain areas, the Update Committee hopes new results will inform future versions of this guideline, including in the following specific areas: Results of studies comparing gefitinib with afatinib and gefitinib with dacomitinib Further study of the optimal integration of chemotherapy and targeted agents in the treatment of patients with gene mutations in various lines of therapy Further study of third-line therapy Results from examples of ongoing studies on resistance mechanics and new agents (note this is not comprehensive list): Third-generation EGFR inhibitors,154,155 for example, AZD9291 (AURA3 trial [AZD9291 *v* platinum-based doublet chemotherapy in locally advanced or metastatic NSCLC]; ClinicalTrials.gov identifier NCT02151981) and

	CO1686, now in phase II trials (TIGER-2 [Open Label Safety and Efficacy Study of CO-1686 in Patients With T790M Positive NSCLC Who Have Failed One Previous EGFR-Directed TKI]; ClinicalTrials.gov identifier NCT0214799d0; TIGER-1 [Safety and Efficacy Study of Rociletinib (CO-1686) or Erlotinib in Patients Eith EGFR Mutant NSCLC Who Have Not Had Any Previous EGFR Directed Therapy]; ClinicalTrials.gov identifier NCT02186301; and TIGER-X [Study to Evaluate Safety, Pharmacokinetics, and Efficacy of CO-1686 in Previously Treated Mutant Epidermal Growth Factor Receptor (EGFR) Non-Small Cell Lung Cancer (NSCLC)]; ClinicalTrials.gov NCT01526928) […]
Scottish Intercollegiate Guidelines Network (SIGN), 2014 [33]. Management of lung cancer	**1. Fragestellung** In patients with NSCLC (locally advanced or metastatic disease), what is the most effective anticancer therapy (chemotherapy, targeted therapy, EGFR Inhibitors)? Outcomes: Overall survival, progression-free survival, toxicity, quality of life
	2.* Methodik** ***Grundlage der Leitlinie: systematische Recherche und Bewertung der Literatur, Entwicklung durch multidisziplinäre Gruppe von praktizierenden klinischen ExpertInnen, Expertenreview, öffentliche Konsultation ***Suchzeitraum:*** 2005 - 2012 ***LoE/GoR:*** Vgl. *Anlage 1* dieser Synopse
	3. Empfehlungen ***First line treatment*** <u>Kernempfehlung</u> Systemische Therapie: 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) <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++)** Burdett S, Stephens R, Stewart L, Tierney J, Auperin A, Le Chevalier T, 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+)** 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 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. Ranson M, Davidson N, Nicolson M, Falk S, Carmichael J, Lopez P, 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. 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 chemotherapynaive patients with metastatic or non-resectable localized non-small cell lung cancer (NSCLC). Lung Cancer 2000;27(3):145-57. 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+)** Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, 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++)** Goffin J, Lacchetti C, Ellis PM, Ung YC, Evans WK. 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. Lima JP, dos Santos LV, Sasse EC, Sasse AD. 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+)** 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 chemotherapynaive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26(21):3541-51. Scagliotti GV, Park K, Patil S, Rolski J, Goksel T, Martins R, 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+)** Scagliotti GV, Park K, Patil S, Rolski J, Goksel T, Martins R, 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. 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.230 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+)** Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, 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.

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)

second line therapy

In patients who are PS ≤ 2 at the time of progression of their advanced NSCLC, second line treatment with single agent docetaxel, erlotinib or PEM improve survival rates compared to BSC. **(LoE 1+)** Tassinari D, Scarpi E, Sartori S, Tamburini E, Santelmo C, Tombesi P, et al. Second-line treatments in non-small cell lung cancer. A systematic review of literature and metaanalysis of randomized clinical trials. Chest 2009;135(6):1596-609.

Second line docetaxel improved time to progression, survival and quality of life. Patient's opioid requirements and weight loss were reduced with docetaxel compared to BSC only. This was clearest in the patients who received 100 mg/m2 rather than 75 mg/m2 every three weeks, however the higher dose was associated with more overall toxicity, and is not recommended as standard. **(LoE 1+)** Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18(10):2095-103. Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, et al. Randomised phase III trial of docetaxel versus vinorelbine or ifosfamide inpatients with advanced non-small cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000;18(12):2354-62.

Weekly docetaxel is not recommended over three-weekly due to increased toxicity. **(LoE 1+)** Tassinari D, Carloni F, Santelmo C, Tamburini E, Agli LL, Tombesi P, et al. Second line treatments in advanced platinum-resistant non small cell lung cancer: A critical review of literature. Rev Recent Clin Trials 2009;4(1):27-33. Randomised evidence does not support the use of combination SACT as second line treatment for patients with advanced NSCLC based on an increase in toxicity without any gain in survival. **(LoE 1++)** Di Maio M, Chiodini P, Georgoulias V, Hatzidaki D, Takeda K, Wachters FM, et al. Meta-analysis of single-agent chemotherapy

	compared with combination chemotherapy as second-line treatment of advanced non-small-cell lung cancer. J Clin Oncol 2009;27(11):1836-43. Second line erlotinib improves overall survival compared to BSC in patients with NSCLC. Median survival was improved with moderate toxicity. The response rate was 8.9% in the erlotinib group and less than 1% in the placebo group (p<0.001); the median duration of the response was 7.9 months and 3.7 months, respectively. Progression-free survival was 2.2 months and 1.8 months, respectively (HR 0.61, adjusted for stratification categories; p<0.001). Overall survival was 6.7 months and 4.7 months, respectively (HR 0.70; p<0.001) in favour of erlotinib. **(LoE 1++)** Noble J, Ellis PM, Mackay JA, Evans WK. Second-line or subsequent systemic therapy for recurrent or progressive non-small cell lung cancer: A systematic review and practice guideline. J Thorac Oncol 2006;1(9):1042-58. Compared with single agent docetaxel, treatment with PEM resulted in clinically equivalent efficacy outcomes, but with significantly fewer side effects in the second-line treatment of patients with advanced predominantly non-squamous cell NSCLC. 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)** **T790M** Keine Hinweise (auch nicht zur Frage der TKI-Resistenzen generell)
Brodowicz T et al., 2012 [7]. Third CECOG consensus on the systemic treatment of non-small-cell lung cancer	**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 therapeutic options.
	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 Auswahl und Bewertung der Literatur nicht beschrieben 14 author*

	disclosures given, remaining authors have declared no conflicts of interest
	Freitext/Empfehlungen First line 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]. 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. 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]. <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]. 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.
Socinski et al., 2013 [35]. Treatment of Stage IV Non-	Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines **1. Fragestellung** to update the previous edition of the American College of Chest Physicians

small Cell Lung Cancer	Lung Cancer Guidelines Stage IV non-small cell lung cancer (NSCLC) is a treatable, but not curable, clinical entity in patients given the diagnosis at a time when their performance status (PS) remains good.
	Methodik A writing committee was assembled and approved according to ACCP policies as described in the methodology article of the lung cancer guidelines. **Suchzeitraum:** bis 12/2011 **LoE** nicht ausgeführt, lediglich: Documentation and Appraisal Review Tool (DART) **GoR** ACCP Grading System **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. 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 . ***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.
	Empfehlungen ***General Approach*** 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. 3.2.1.1. In patients with known epidermal growth factor receptor (EGFR) mutations and stage IV NSCLC, first-line therapy with an EGFR tyrosine kinase inhibitor (gefitinib or erlotinib) is recommended based on superior response rates, progression-free survival and toxicity profiles compared with platinum-based doublets **(Grade 1A)** . 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. ***Maintenance Therapy*** 3.4.4.1. In patients with stage IV non-squamous NSCLC who do not experience disease progression after 4 cycles of platinum-based therapy (which does not include pemetrexed), treatment with switch maintenance pemetrexed is suggested **(Grade 2B)** . 3.4.4.2. In patients with stage IV NSCLC, switch maintenance therapy with chemotherapy agents other than pemetrexed has not demonstrated an improvement in overall survival and is not recommended **(Grade 1B)** .

	3.4.4.3. In patients with stage IV non-squamous NSCLC who do not experience disease progression after 4 cycles of platinum-pemetrexed therapy, continuation pemetrexed maintenance therapy is suggested **(Grade 2B)** . 3.4.4.4. In patients with stage IV NSCLC who do not experience disease progression after 4 cycles of platinum-based double agent chemotherapy, maintenance therapy with erlotinib is suggested **(Grade 2B)** . 3.5.1.1. In patients with stage IV NSCLC the addition of cetuximab in combination with chemotherapy is suggested not to be used outside of a clinical trial **(Grade 2B) .** ***Second and Third Line Treatment*** 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)** .
Cancer Care Ontario, 2014 [9]. Use of the Epidermal Growth Factor Receptor Inhibitors Gefitinib (Iressa),	A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO) **1. Fragestellungen** 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)?

Erlotinib (Tarceva), Afatinib, Dacomitinib or Icotinib in the Treatment of Non-Small-Cell Lung Cancer: A Clinical Practice Guideline	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?
	Empfehlungen ***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 **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. 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). 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). All seven trials showed a decrease in adverse effects with an EGFR inhibitor compared to chemotherapy. ***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) . **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 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 and $p<0.0001$ compared to a placebo. Another trial evaluated gefitinib and showed a higher response rate, but this was not significant ($p=0.369$).

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%).

T790M

Ongoing Trials

Genius Study to Compare Efficacy and Safety of Gefitinib/ Pemetrexed With Pemetrexed Alone as Maintenance Therapy in Patients With Stage IV EGFR Mutation Negative or T790M Single Mutation Who Respond to Pemetrexed/ Platinum as First-	The study aims to randomize 122 patients with advanced (Stage IV) EGFR mutation negative nonsquamous non-small-cell lung cancer (NSCLC) who respond (CR/PR/SD) to 4 cycles of pemetrexed / cisplatin or pemetrexed/carboplatin as first-line

	line Therapy NCT01579630	therapy. In order to achieve that, approximately 338 treatment naive patients with advanced non-squamous NSCLC need to be enrolled from around 5-7 investigational sites in Taiwan that have expertise in lung cancer diagnosis.
Alberta Provincial Thoracic Tumour Team, 2013 [1]. Non-small cell lung cancer - stage III. Alberta Health Services	**1. Fragestellungen** 1. What are the recommended treatment options for patients with operable stage III non-small cell lung cancer? 2. What are the recommended treatment options with curative intent for patients with inoperable stage III non-small cell lung cancer? 3. When is palliation recommended, and what are the recommend Update der Version von 2008	
	• **2. 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 ***Population:*** NSCLC, adult patients over the age of 18 years ***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*** Kein formaler Konsensusprozess beschrieben Auswahl und Bewertung der Literatur nicht beschrieben no direct industry involvement in the development or dissemination of this guideline authors have not been remunerated for their contributions	
	4. Empfehlungen 2. Patients with a solitary metastasis as the basis for stage IV disease with good performance status and otherwise resectable and limited thoracic disease may benefit from more aggressive management, including surgical intervention and/or stereotactic radiotherapy. 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. 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. 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. 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. 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.

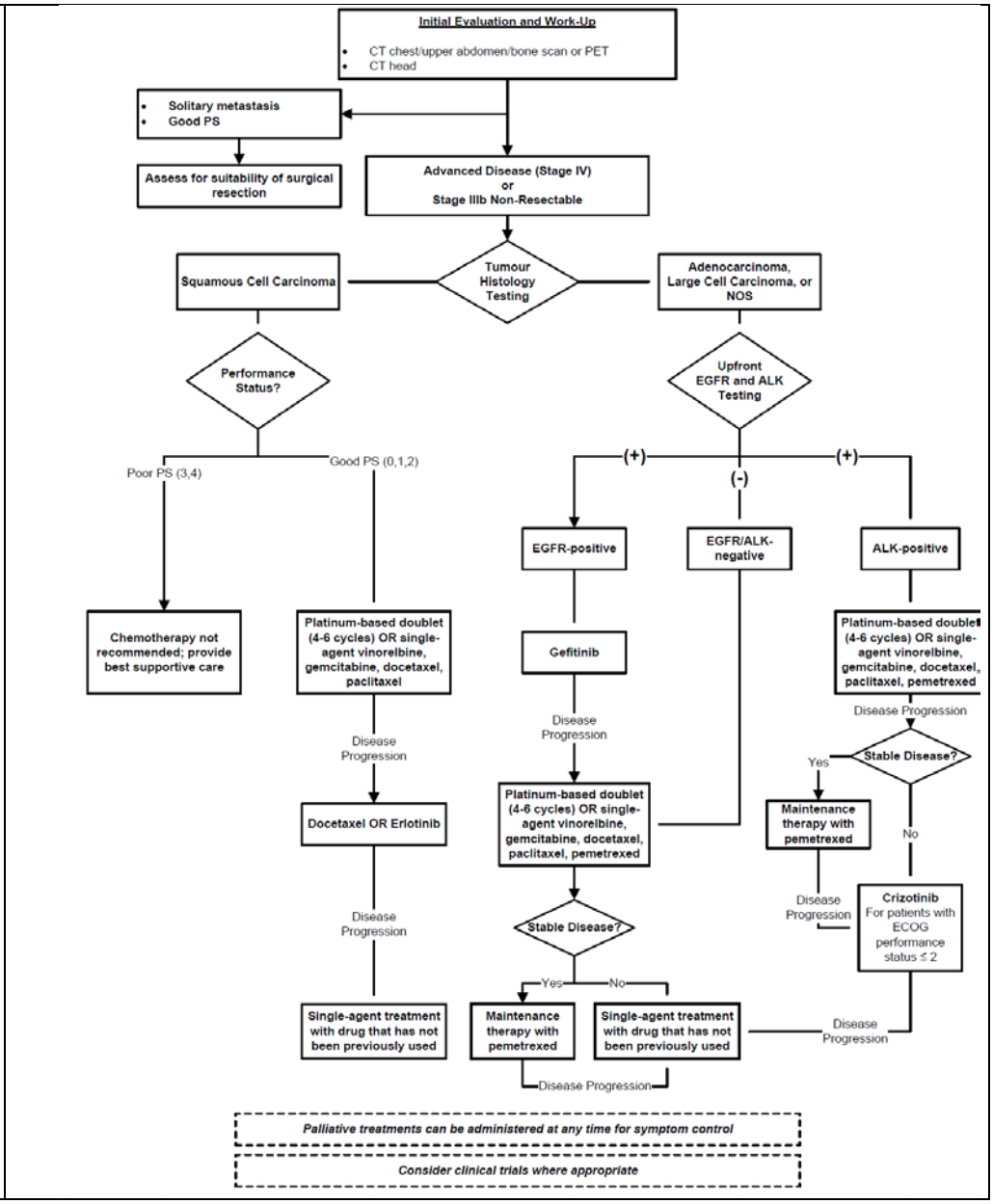

Initial Evaluation and Work-Up
CT chest/upper abdomen/bone scan or PET
CT head
Solitary metastasis
Good PS
Assess for suitability of surgical resection
Advanced Disease (Stage IV) or Stage IIIb Non-Resectable
Tumour Histology Testing
Squamous Cell Carcinoma
Adenocarcinoma, Large Cell Carcinoma, or NOS
Performance Status?
Poor PS (3,4)
Good PS (0,1,2)
Chemotherapy not recommended; provide best supportive care
Platinum-based doublet (4-6 cycles) OR single-agent vinorelbine, gemcitabine, docetaxel, paclitaxel
Disease Progression
Docetaxel OR Erlotinib
Disease Progression
Single-agent treatment with drug that has not been previously used
Upfront EGFR and ALK Testing
(+)
(-)
(+)
EGFR-positive
EGFR/ALK-negative
ALK-positive
Gefitinib
Disease Progression
Platinum-based doublet (4-6 cycles) OR single-agent vinorelbine, gemcitabine, docetaxel, paclitaxel, pemetrexed
Stable Disease?
Yes
No
Maintenance therapy with pemetrexed
Single-agent treatment with drug that has not been previously used
Disease Progression
Platinum-based doublet (4-6 cycles) OR single-agent vinorelbine, gemcitabine, docetaxel, paclitaxel, pemetrexed
Disease Progression
Stable Disease?
Yes
No
Maintenance therapy with pemetrexed
Disease Progression
Crizotinib For patients with ECOG performance status ≤ 2
Disease Progression
Palliative treatments can be administered at any time for symptom control
Consider clinical trials where appropriate

Table 1. Summary of Phase III Clinical Trials Assessing First-Line Monotherapy with Gefitinib or Erlotinib in Patients with Advanced NSCLC and Positive EGFR Mutational Status.

Author, Year	Inclusion Criteria	Disease Stage	N	Treatment	Median PFS (months)	Median OS (months)
Gefitinib Therapy						
Mitsudomi, 2010[61] (West Japan Oncology Group)	CT-naïve, ≤75 years, PS 0-1, Japanese, EGFR-positive	IIIB, IV, or post-op recurrence	88	gefitinib 250mg/day q21 days x 3-6 cycles	9.2	30.9
			89	cisplatin 80mg/m^2 + docetaxel 60mg/m^2 q21 days x 3-6 cycles	6.3 HR=0.489; 95% CI 0.336-0.71, p<0.001	not reached HR=1.638; 95% CI 0.749-3.582, p=0.211
Maemondo, 2010[62] (North East Japan Study Group)	CT-naïve, ≤75 years, PS 0-1, EGFR-positive	IIIB, IV, or post-op recurrence	114	gefitinib 250mg/day q21 days	10.8	30.5
			114	carboplatin AUC6 + paclitaxel 200mg/m^2 q21 days	5.4 HR=0.30; 95% CI 0.22-0.41, p<0.001	23.6 p=0.31
Mok, 2009[63] (IPASS)	CT-naïve, adeno-carcinoma, non- or former light smoker	IIIB, IV	132*	gefitinib 250mg/day q21 days x 6 cycles	9.5	21.6
			129*	carboplatin AUC5-6 + paclitaxel 200mg/m^2 q21 days x 6 cycles	6.3 HR= 0.45; 95% CI 0.36-0.64, p<0.001	21.9 HR=1.002; 95% CI 0.756-1.328, p=0.990
Lee, 2009[59] (First SIGNAL)	CT-naïve, adeno-carcinoma, PS 0-2, never-smoker	IIIB, IV	26*	gefitinib 250mg/day	8.4	30.6
			16*	cisplatin 80mg/m^2 day1, q21 days x 9 cycles + gemcitabine 1250mg/m^2 days1,8	6.7 HR=0.613; 95% CI 0.308-1.221, p=0.084	26.5 HR=0.823; 95% CI 0.352-1.922, p=0.648
Erlotinib Therapy						
Rosell, 2011[58] (EURTAC)	CT-naïve, PS 0-2, Caucasian, EGFR-positive	advanced	77	erlotinib	9.4	22.9
			76	platinum-based chemotherapy	5.2 HR=0.42; p<0.0001	18.8 HR=0.80; p=0.42
Zhou, 2011[64]	CT-naïve, EGFR-positive	IIIB, IV	82	erlotinib (150mg/d)	13.1	not reported
			72	gemcitabine + carboplatin	4.6 HR=0.16; p<0.0001	
Zhou, 2010[57] (OPTIMAL)	CT-naïve, PS 0-2, EGFR-positive	advanced	82	erlotinib 150 mg/day until unacceptable toxicity or PD	13.1	not reported
			76	carboplatin AUC5 + gemcitabine 1000 mg/m^2 days 1,8 q21 days x 4 cycles	4.6 HR=0.16; 95% CI 0.10-0.26, p<0.0001	

Abbreviations. *PFS=progression-free survival, OS=overall survival, CT=chemotherapy, PS=performance status, HR=hazard ratio, CI=95% confidence interval, AUC=area under the curve, PD=progressive disease.*
** Subset of patients in trial with positive EGFR mutational status; patients not pre-selected for mutational status.*

Azzoli et al., 2010 [3].

American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer

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.

Methodik

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.

Suchzeitraum: 2002 bis 07/2008

GoR, LoE Keine Angabe in der zusammenfassenden Darstellung (vgl. Anlage 3)

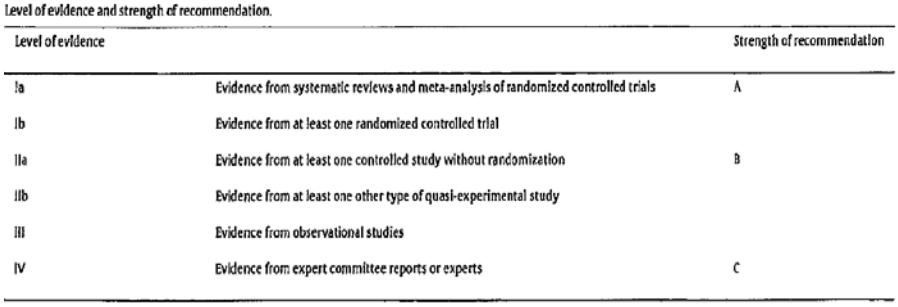
Empfehlungen

	The recommendations are designated as follows: First-line therapy recommendations begin with A, second-line recommendations with B, third-line recommendations with C, and molecular analysis recommendations with D. **First-Line Chemotherapy** In this summary, the term chemotherapy refers to any anticancer drug, regardless of its mechanism of action (ie, cytotoxic and biologic drugs are included). **Recommendation A1.** Evidence supports the use of chemotherapy in patients with stage IV non–small-cell lung cancer with Eastern Cooperative Oncology Group (ECOG)/Zubrod PS 0, 1, and possibly 2. (Note: Stage IV as defined by the International Association for the Study of Lung Cancer Lung Cancer Staging Project, for the seventh edition of the TNM Classification of Malignant Tumors.) **Recommendation A2.** In patients with PS 0 or 1, evidence supports using a combination of two cytotoxic drugs for firstline 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. **Recommendation A3.** Available data support use of singleagent chemotherapy in patients with a PS of 2. Data are insufficient to make a recommendation for or against using a combination of two cytotoxic drugs in patients with a PS of 2. **Comment.** PS is the most important prognostic factor for patients with stage IV NSCLC; patients with a PS of 0 to 1 live longer than patients with a PS of 2, regardless of therapy. Use of single-agent vinorelbine, docetaxel, or paclitaxel has led to improved survival in phase III comparisons versus best supportive care in patients with a PS of 0 to 2. Because of concerns about toxicity and drug tolerance, patients with stage IV NSCLC and a PS of 2 are routinely excluded from prospective trials of novel **Recommendation A4.** The evidence does not support the selection of a specific first-line chemotherapy drug or combination based on age alone. **Comment.** Clinical trial data since the 2003 update reinforce the recommendation that age alone should not be used to select chemotherapy for patients with stage IV NSCLC. Older patients may experience more toxicity from cytotoxic chemotherapy than younger patients but may garner an equal amount of benefit. The guideline emphasizes that physiologic age and PS are more important in treatment selection. **Recommendation A5.** The choice of either cisplatin or carboplatin is acceptable. Drugs that may be combined with platinum include the third-generation cytotoxic drugs docetaxel, gemcitabine, irinotecan, paclitaxel, pemetrexed, and vinorelbine. The evidence suggests that cisplatin combinations have a higher response rate 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. **Comment.** Cisplatin is slightly more effective than carboplatin but also has more adverse effects. Therefore, either is acceptable, depending on the individual. **Recommendation 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 not responding to treatment. Two-drug cytotoxic combinations should be administered for no more than six cycles. For patients who have stable disease or who respond to first-line therapy, evidence does not support the continuation of cytotoxic chemotherapy until disease progression or the initiation of a different chemotherapy before disease progression. **Comment.** With the advent of drugs that improve survival for patients with progressive cancer after first-line chemotherapy (ie, second-line drugs), there is renewed interest in whether initiation of a non–cross-resistant drug immediately after completion of first-line therapy may improve survival. There have been some preliminary results on such a strategy, but until more mature data are presented showing a survival benefit, these results suggest that PFS, but not OS, may be improved either by continuing an effective chemotherapy beyond four cycles or by immediately initiating alternative chemotherapy. The improvement in PFS is tempered by an increase in adverse effects from additional cytotoxic chemotherapy. Special announcement: The FDA approved a new indication for pemetrexed for maintenance therapy in patients with advanced NSCLC on July 2, 2009, when this guideline went to press. The data supporting this change were recently presented and were outside the scope of the comprehensive data review for this guideline. The recommendation recommendation on maintenance therapy in this guideline will be updated pending consideration of recently published relevant data. **Recommendation 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. The first-line use of gefitinib may be recommended for patients with activating *EGFR* mutations. If *EGFR* mutation status is negative or unknown, then cytotoxic chemotherapy is preferred (see Recommendation A2). **Comment.** There is no current evidence that adding an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor to cytotoxic chemotherapy as first-line treatment is beneficial. In addition, there is no current evidence that erlotinib monotherapy is beneficial in the first-line setting in unselected patients. There is evidence that first-line gefitinib monotherapy improves PFS and has less adverse events compared with carboplatin and paclitaxel in patients of Asian ethnicity who are former or light smokers or have never smoked. In a recent trial, patients with tumors with *EGFR* mutations receiving gefitinib experienced longer PFS, and those whose tumors lacked

	EGFR mutations had longer PFS with chemotherapy. The *EGFR* mutation status of most patients' tumors, however, is negative or unknown. Current evidence is insufficient to recommend the routine use of molecular markers to select systemic treatment for patients with metastatic NSCLC (Recommendation D1). In cases in which the *EGFR* mutation status is negative or unknown, cytotoxic chemotherapy is preferred. **Recommendation A8.** Based on the results of one large phase III RCT, the Update Committee recommends the 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 PS greater than 1, therapeutic anticoagulation, clinically significant cardiovascular disease, or medically uncontrolled hypertension. Bevacizumab may be continued, as tolerated, until disease progression. **Comment.** Because of bleeding events and deaths observed in earlier clinical trials using bevacizumab for NSCLC, use of this drug was restricted in phase III testing, which informed the list of exclusion criteria in the recommendation. A recent trial suggested that there may be differences in outcomes depending on which chemotherapy regimen is combined with bevacizumab and also suggested that a lower dose of bevacizumab may be as effective as a high dose; however, OS benefit has not yet been shown from combining bevacizumab with other cytotoxic chemotherapy regimens. The duration recommendation is based on the design of RCTs of bevacizumab. The optimal duration of bevacizumab beyond chemotherapy has not yet been determined. **Recommendation A9.** On the basis of the results of one large phase III RCT, clinicians may consider the addition of cetuximab to cisplatin/ vinorelbine in first-line therapy in patients with an EGFR-positive tumor as measured by immuno- histochemistry. Cetuximab may be continued, as tolerated, until disease progression. **Comment.** Eligibility for this phase III RCT required that all patients have their tumor tested for EGFR expression by immunohistochemistry and that at least one tumor cell stained positive. This trial showed a benefit in OS and response rate with the addition of cetuximab to this chemotherapy doublet. The OS benefit may not directly translate to all chemotherapy regimens. The duration recommendation is based on the design of RCTs on cetuximab. However, the optimal duration of treatment with cetuximab beyond chemotherapy is not known. **Second-Line Chemotherapy Recommendation B1.** 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 B2.** 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 C1.** 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 C2.** 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.
Azzoli et al., 2012 [4]. American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer	**Fragestellung** An American Society of Clinical Oncology (ASCO) focused update updates a single recommendation (or subset of recommendations) in advance of a regularly scheduled guideline update. This document updates one recommendation of the ASCO Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer (NSCLC) regarding switch maintenance chemotherapy.
	Methodik *focused update:* zu *Azzoli et al. 2010* **S** **Suchzeitraum:** bis 11/2009
	Empfehlungen *Intervention* Switch maintenance (alternative therapy administered to patients who have undergone first-line therapy for specified number of cycles [usually four to six] and experienced response or achieved stable disease). ***Recommendation*** 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 an 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 these data are such that a break from cytotoxic chemotherapy after a fixed course is also acceptable, with initiation of secondline chemotherapy at disease progression. Zusammenfassung der aktualisierten Empfehlungen (2011): Vgl. *Anlage* dieser Synopse
de Marinis F et al., 2011 [11]. Treatment of advanced non-small-cell-lung cancer: Italian Association of Thoracic Oncology (AIOT) clinical practice guidelines	**1. Fragestellung** AIOT (Italian Associatlon of Thoracic Oncology) produces up-to-date, cllnlcal practice guidellnes for the management of lung cancer in ltaly. Guidelines were developed by answerlog clinical relevant questions. Here we report only major cllnical issues concerning the management of advanced non-small cell lung cancer (NSCLC). Here we report only eight clinical questions regarding the management of advanced non-small-cell lung cancer (NSCLC) which have been subsequently updated for this manuscrlpt on December 2010.
	2. Methodik Systematische Literatursuche und formaler Konsensusprozess ***Suchzeitraum:*** 2004 bis 2009 ***LoE, GoR*** **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

	3. Empfehlungen Platinum-based (cisplatin or carboplatin) chemotherapy is the standard treatment for adult patients with advanced NSCLC, with good peformance status (PS 0-1). Chemotherapy should be stopped at disease pragression or after 4 cycles in patients who do not obtain an objective response, and continued for maximum 6 cycles in patients achieving an objective response. Treatment options are different according to tumour histotype (squamous versus non squamous). ***A. Treatment options for patients with squamous tumour*** Patients with advanced squamous NSCLC are eligible for firstline platinum-based doublets with a third-generation drug, with the exception of pemetrexed. ***B. Treatment options for patients with non-squamous tumours***

	Patients with advanced non-squamous NSCLC are eligile for first-line platinum-based doublets with a third-generation drug, including pemetrexed. Bevacizumab in combination with carboplatin plus paclitaxel or cisplatin plus gemicitabine is a further option for patients considered eligible to this therapy. Carboplatin plus paclitaxel should be considered the chemotherapy backbone [or bevacizumab. (**LoE lA GoR A)** ***3.2. Question 2, Cisplatin* or *carboplatin for first-line treatment?*** Several randomized trials compared cisplatin- versus carboplatin-based chemotherapy in advanced NSCLC. Those trials were lncluded in two meta-analyses. The one based on individual patient data showed a statistically slgnificant increase in objective response rate with cisplatin. Difference in overall sutvival between the two drugs did not reach statistical significance, although carboplatin was associated with a statistically significant increase in mortallty ln patients with non-squamous tumours andin patients receiving third-generation regimens. As expected, cispiatin *was* associated with higher lncidence of nausea, vomiting and renal toxicity, whilst carboplatin was associated with higher incidence of thrombocytopenia. Based on these data, cispiatin-containing third-generation regimens represent the standard treatment for patients with advanced NSCLC. 3.2.1. Recommendations Third-generation cisplatin-based regimens are recommended for the treatment of advanced NSCLC patients, with PS 0-1 and without major co-morbidities. Where the use of cisplatin is contra-indicated third-generation carboplatin-based regimens are a valid therapeutic option. (**LoE lA, GoR A**) 3.3.1. Recommendations Gefitinib is recommended as first-line therapy of patients with EGFR mutat!on positive NSCLC EGFR analysfs is recommended, if adequate tumoursampie is available, espedaily in patients selected on the basis of clinical and/or pathological charaeteristics known to be assodated with higher frequency of EGFR mutation (never or former smokers, adenocardnoma). (**LoE IB, GoR A)** 3.4.1. Recommendations in patients with advanced non-squamoiis NSCLCwho have an objective response or a stable disease after completing first-line treatment consisting of 4 cycles of platinum-based chemotherapy, notincluding pemetrexed, maintenance therapy wlth pemetrexed can be considered (if aliowed by reimbursement procedures) and discussed with patients. (**LoE B, GoR A**) in patients with a/1 histotypes advanced NSCLC who have stable disease after completing first-line chemotherapy consisting of 4 eycles of platinum-based chemotherapy, maintenance therapy w!th erlotinlb can be considered (if allowed by reimbursement procedures) and discussed with patients. (**LoE B, GoR A)** 3.5.1. Recommendations In elderly patients (older than 70 years) with advanced NSCLC, single-ogent treatment with a third-generation drug is the recommended optionfor 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 B; GoR A)** In elderly patients (older than 70years), with EGFR mutation positive advanced NSCLC, gefitinib ls the recommended treatment. (**LoE lA, GoR A)**

3.6.1. Recommendations First-line chemotherapy is recommended in patients wlth advanced NSCLC and ECOG PS 2 because lt is associated 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 cisplatln is a reasonable alternative. (**LoE 1/B, GoR B)** ln PS 2 patients, with EGFR mutationpositive advanced NSCLC, gefitlnib ls the recommended treatment. (**LoE IB, GoR A)**

3.7.1. Recommendations In patients with advanced NSCLC, after failure of first-line treatment, single-agent treatment with docetaxel orpemetrexed (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**

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 ln 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)**

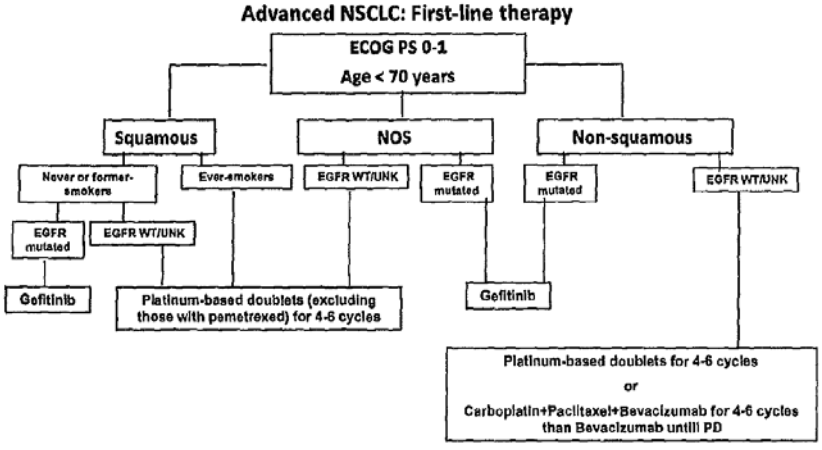


Fig. 1. Suggested algorithm for first-line treatment of advanced non-small-cell lung cancer (ECOG PS: Eastern Cooperative Oncology Group performance status; N otherwise specified; EGFR: epidermal growth factor receptor; WT: wild type; and UNK: unknown).

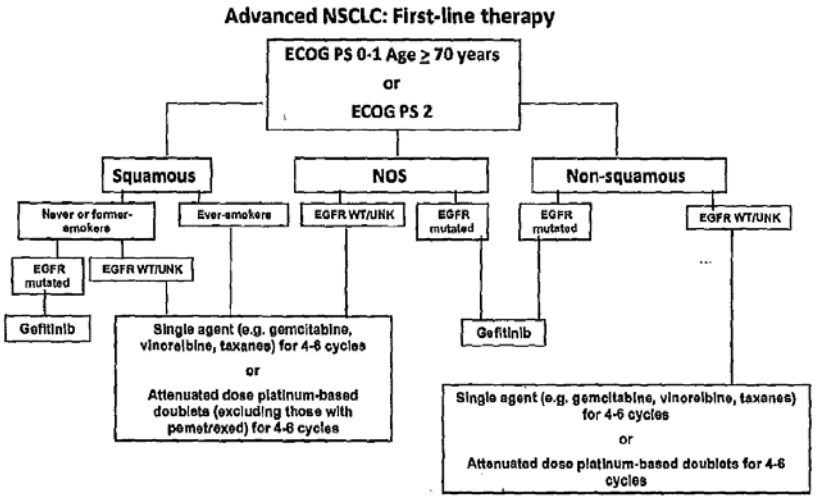


Fig. 2. Suggested algorithm for first-line treatment of advanced non-small-cell lung cancer in special patients population (ECOG PS: Eastern Cooperative Oncology performance status; NOS: not otherwise specified; EGFR: epidermal growth factor receptor; WT: wild type; and UNK: unknown).

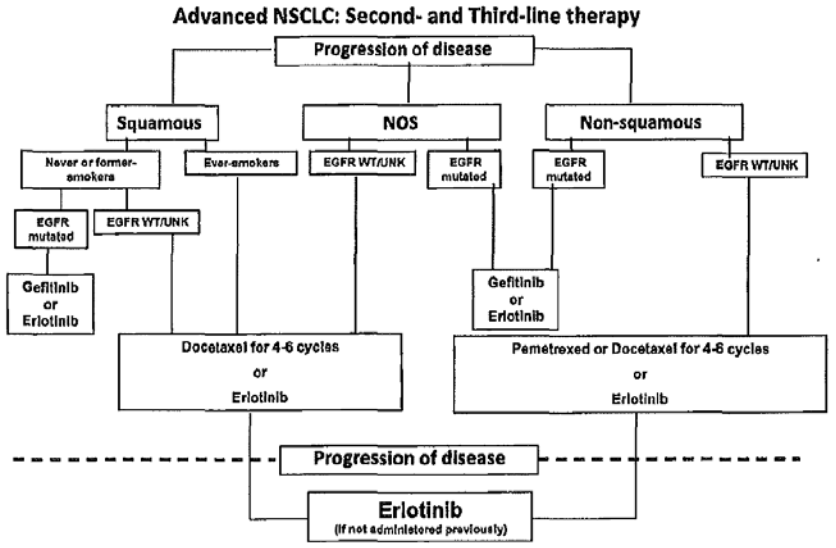


Fig. 3. Suggested algorithm for second- and third-line treatment of advanced non-small-cell lung cancer (NOS: not otherwise specified; EGFR: epidermal growth receptor; WT: wild type; and UNK: unknown).

National Institute for Health and Care Excellence (NICE), 2011 [25]. 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 <u>Grundlage der Leitlinie:</u> 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: March 2016 <u>Suchzeitraum:</u> July 2010 <u>LoE/GoR:</u> 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

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Greenhalgh J et al. 2015 [15]. **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**	Fragestellung HTA Methodik Population: advanced NSCLC Intervention: Gefitinib, Erlotinib Komparator: gegeneinander, gegen Docetexal oder BSC Endpunkte: ORR, OS, PFS, QoL Suchzeitraum: bis 03 /2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 12 (Erlotinib vs. Chemo = 3; Erlotinib vs. BSC = 1; Gefitinib vs. Erlotinib = 1; Gefitinib vs. Chemo = 6; Gefitinib vs. BSC = 1) Ergebnisdarstellung No trials were identified that were conduded in a population of solely EGFR M + patients. Limited EGFR mutation Status data were retrospectively derived from relatively small rubgroup analyses of RCTs that induded patients of unknown EGFR mutation Status at the time of randomisation. Four Studies reported OS outcomes none of which was statistically significantly different for anyof the comparissonsdescribed. Five Studies reported PFS, but only one trial found a statistically significant improvernent for any comparison considered, and the results favoured gefitinib over docetaxel. Anmerkungen/Fazit der Autoren Ihe Iack of dinical data available for distinct patient populations limited the condusions of the assesssment. Future trials should distinguish between patients with B3FR M + and B3FR M- diease.
Breuer J et al., 2013 [5]. 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. 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).
NICE, 2014 [24]. Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer, TA 310.	***Guidance*** 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. Afatinib for treating epidermal growth factor receptor mutationpositive locally advanced or metastatic non-small-cell lung cancer The Appraisal Committee considered evidence submitted by the manufacturer of afatinib and a review of this submission by the Evidence Review Group. Because there was no head-to-head randomised controlled trial comparing the effectiveness of afatinib with erlotinib or gefitinib for progression-free survival or overall survival, the manufacturer presented a mixed treatment comparison. This was based on a previous mixed treatment comparison conducted for Gefitinib for the first-line treatment of locally advanced or metastatic non-smallcell lung cancer (NICE technology appraisal guidance 192), which was adapted to include data on the effectiveness of afatinib based on the LUXLung 3 and 6 studies and erlotinib.The studies used to populate the mixed treatment comparison were identified through systematic review. The manufacturer identified 20 randomised controlled trials, 4 of which included gefitinib (first SIGNAL trial, IPASS trial, Mitsudomi 2010, Maemondo 2010) and 1 that included erlotinib (EURTAC trial). ***Clinical effectiveness*** The Committee discussed current clinical practice for treating EGFR mutationpositive locally advanced or metastatic NSCLC. The clinical specialists highlighted that the standard first choice of treatment for NSCLC with EGFR positive tyrosine kinase mutations was a tyrosine kinase inhibitor, which is in line with Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer (NICE technology appraisal guidance 258) and Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (NICE technology appraisal guidance 192). The

	Committee was also aware of evidence presented in the manufacturer's submission which stated that 99% of eligible patients receive either erlotinib or gefitinib as a first-line treatment. The Committee concluded that treatment with erlotinib and gefitinib is standard practice for most people presenting with EGFR mutation-positive locally advanced or metastatic NSCLC. ***Conclusion:*** The Committee concluded that on balance afatinib is likely to have similar clinical efficacy to erlotinib and gefitinib.
NICE 2015 [26]. Erlotinib and gefinitib for treating nonsmall-cell lung cancer that has progressed after prior chemotherapy. Technology appraisal guidance	This guidance replaces TA175 and TA162. 1.1 Erlotinib is recommended as an option for treating locally advanced or metastatic non-small-cell lung cancer that has progressed in people who have had non-targeted chemotherapy because of delayed confirmation that their tumour is epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation-positive, only if the company provides erlotinib with the discount agreed in the patient access scheme revised in the context of NICE technology appraisal guidance 258. 1.2 Erlotinib is recommended as an option for treating locally advanced or metastatic non-small-cell lung cancer that has progressed after non-targeted chemotherapy in people with tumours of unknown EGFR-TK mutation status, only if: the result of an EGFR-TK mutation diagnostic test is unobtainable because of an inadequate tissue sample or poor-quality DNA and the treating clinician considers that the tumour is very likely to be EGFR-TK mutation-positive and the person's disease responds to the first 2 cycles of treatment with erlotinib and the company provides erlotinib with the discount agreed in the patient access scheme revised in the context of NICE technology appraisal guidance 258. 1.3 Erlotinib is not recommended for treating locally advanced or metastatic non-small-cell lung cancer that has progressed after non-targeted chemotherapy in people with tumours that are EGFR-TK mutation-negative. 1.4 Gefitinib is not recommended for treating locally advanced or metastatic non-small-cell lung cancer that has progressed after non-targeted chemotherapy in people with tumours that are EGFR-TK mutation-positive. 1.5 People whose treatment with erlotinib or gefitinib is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

Recherchestrategien

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 12.10.2015**

#	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 2015

SR, HTAs in Medline (PubMed) am 13.10.2015

#	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	(((advanced[Title/Abstract]) OR metastat*[Title/Abstract]) OR metastas*[Title/Abstract]) OR recurren*[Title/Abstract]
7	#5 AND #6
8	(((((drug[Title/Abstract]) OR (drug therap*)[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR treat[Title/Abstract]) OR treatment*[Title/Abstract]
9	#7 AND #8
10	(#9) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
11	(#9) AND (((((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]))))
12	#10 OR #11
13	(#12) AND ("2010/10/01"[PDAT] : "2015/10/13"[PDAT])

Leitlinien in Medline (PubMed) am 13.10.2015

#	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])
7	(#6) AND ("2010/10/01"[PDAT] : "2015/10/13"[PDAT])

Anlagen

Anlage 1: Levels of Evidence and Grades of Recommendation, aus: *SIGN 2014*

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

Anlage 2: Standard Treatment Options for NSCLC aus: *National Cancer Institut 2014*

Table 11. Standard Treatment Options for NSCLC

Enlarge

Stage (TNM Staging Criteria)		Standard Treatment Options
Occult NSCLC		Surgery
Stage 0 NSCLC		Surgery
		Endobronchial therapies
Stages IA and IB NSCLC		Surgery
		Radiation therapy
Stages IIA and IIB NSCLC		Surgery
		Neoadjuvant chemotherapy
		Adjuvant chemotherapy
		Radiation therapy
Stage IIIA NSCLC	Resected or resectable disease	Surgery
		Neoadjuvant therapy
		Adjuvant therapy
	Unresectable disease	Radiation therapy
		Chemoradiation therapy
	Superior sulcus tumors	Radiation therapy alone
		Radiation therapy and surgery
		Concurrent chemotherapy with radiation therapy and surgery
		Surgery alone (for selected patients)
	Tumors that invade the chest wall	Surgery
		Surgery and radiation therapy
		Radiation therapy alone
		Chemotherapy combined with radiation therapy and/or surgery
Stage IIIB NSCLC		Sequential or concurrent chemotherapy and radiation therapy
		Chemotherapy followed by surgery (for selected patients)
		Radiation therapy alone
Stage IV NSCLC		Cytotoxic combination chemotherapy (first line)
		Combination chemotherapy with bevacizumab or cetuximab
		EGFR tyrosine kinase inhibitors (first line)
		EML4-ALK inhibitors in patients with EML-ALK translocations

Stage (TNM Staging Criteria)	Standard Treatment Options
	Maintenance therapy following first-line chemotherapy
	Endobronchial laser therapy and/or brachytherapy (for obstructing lesions)
	External-beam radiation therapy (primarily for palliation of local symptomatic tumor growth)
Recurrent NSCLC	Radiation therapy (for palliation)
	Chemotherapy or kinase inhibitors alone
	EGFR inhibitors in patients with/without EGFR mutations
	EML4-ALK inhibitors in patients with EML-ALK translocations
	Surgical resection of isolated cerebral metastasis (for highly selected patients)
	Laser therapy or interstitial radiation therapy (for endobronchial lesions)
	Stereotactic radiation surgery (for highly selected patients)

Anlage 3: Summary of Recommendations aus *Azzoli 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).

Anlage 4 Ergebnisse zu PFS und OS aus *Liu et al., 2015*

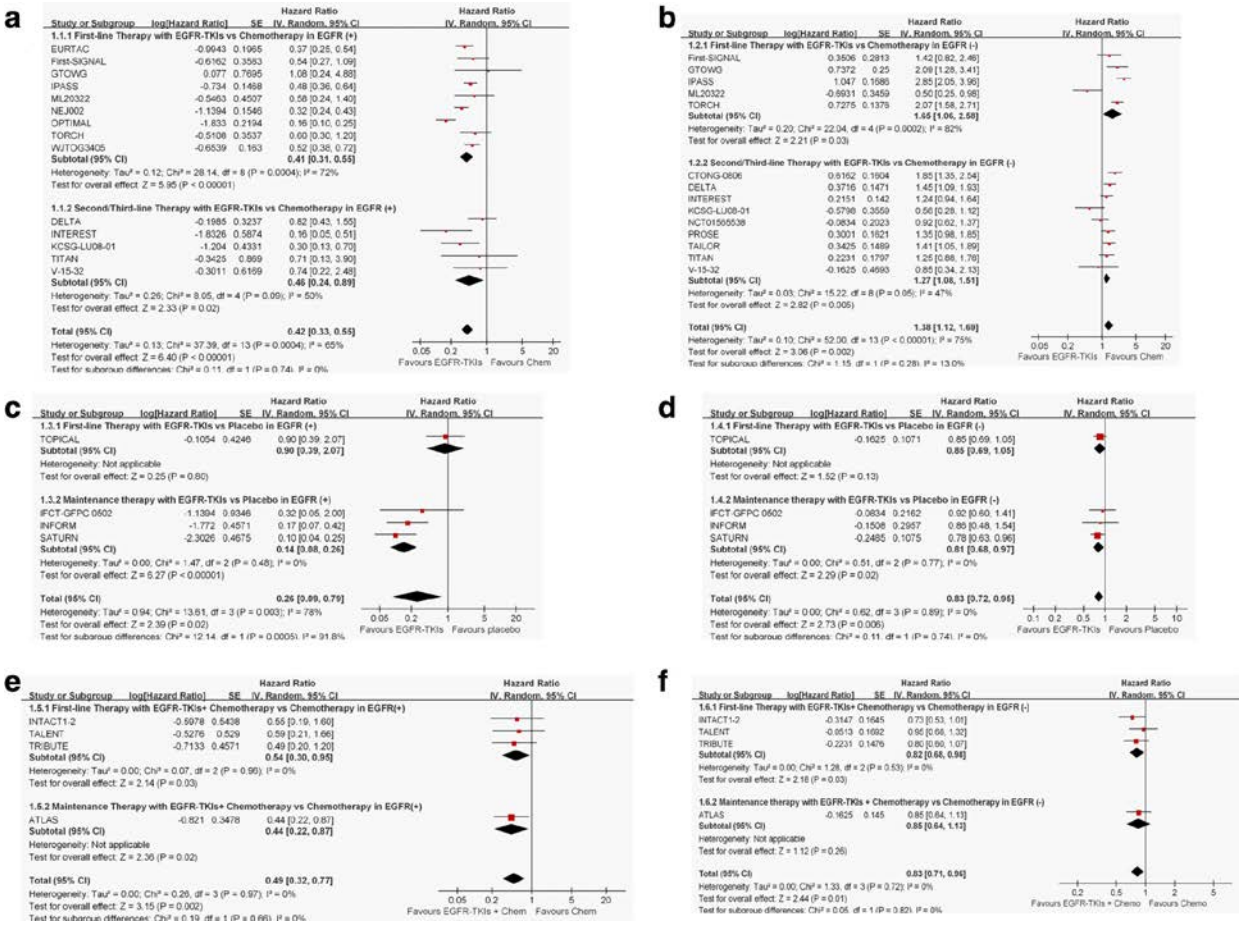


Fig. 2 Meta-analysis of the treatment effects on progression-free survival (PFS) in molecularly selected patients with advanced non-small cell lung cancer. a EGFR-TKIs vs. chemotherapy in patients with mutant EGFR. b EGFR-TKIs vs. chemotherapy in patients with wild-type EGFR. c EGFR-TKIs vs. placebo in patients with mutant EGFR. d EGFR-TKIs vs. placebo in patients with wild-type EGFR. (e) EGFR-TKIs + chemotherapy vs. chemotherapy in patients with mutant EGFR. f EGFR-TKIs + chemotherapy vs. chemotherapy in patients with wild-type EGFR. HR, Hazard Ratio; CI, 95 % confidence interval; Random, random-effects model

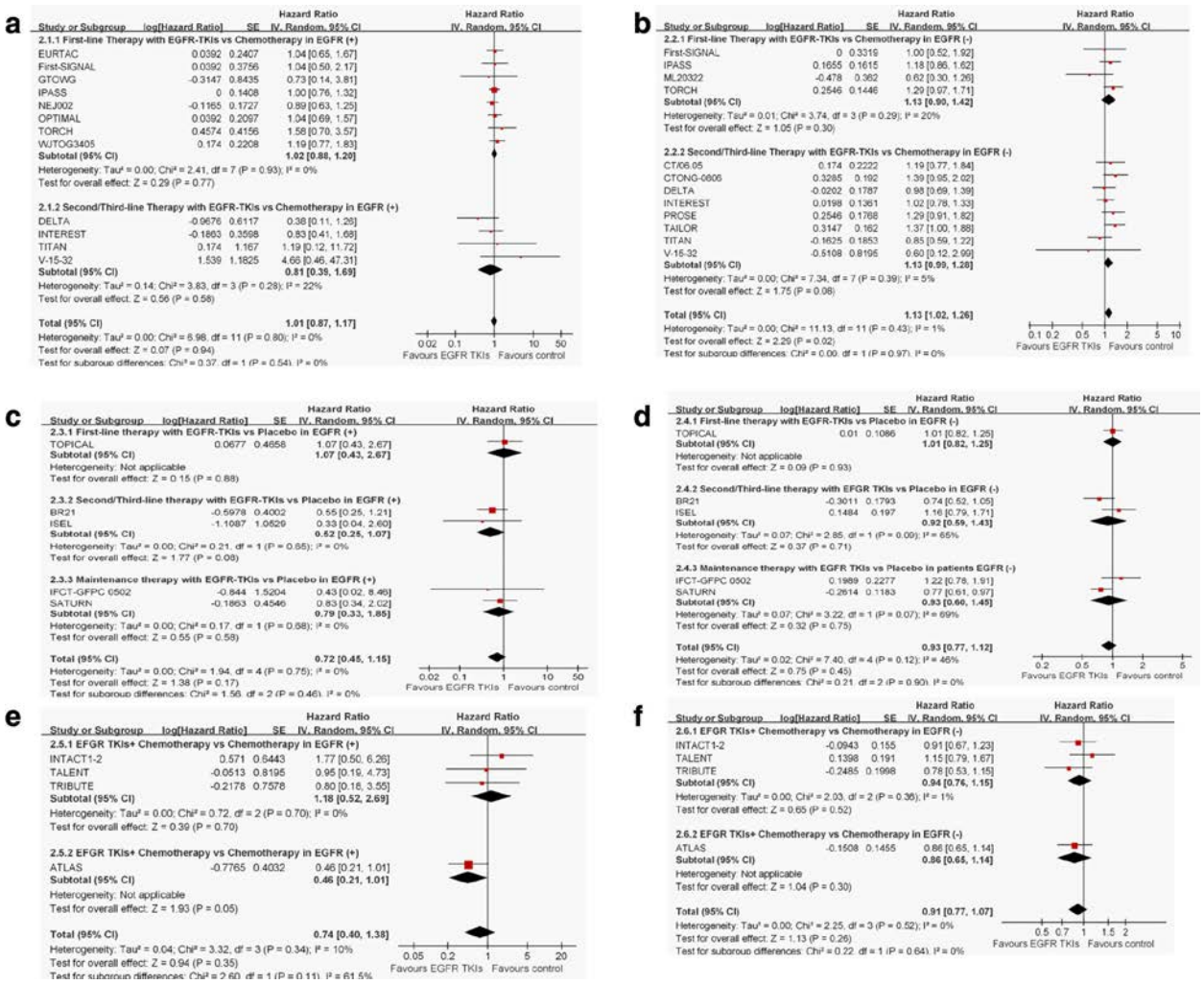


Fig. 3 Meta-analysis of the treatment effects on overall survival (OS) in molecularly selected patients with advanced non-small cell lung cancer. A EGFR-TKIs vs. chemotherapy in patients with mutant EGFR. b EGFRTKIs vs. chemotherapy in patients with wild-type EGFR. c EGFR-TKIs vs. placebo in patients with mutant EGFR. d EGFR-TKIs vs. placebo in patients with wild-type EGFR. e EGFR-TKIs + chemotherapy vs. chemotherapy in patients with mutant EGFR. f EGFR-TKIs + chemotherapy vs. chemotherapy in patients with wild-type EGFR. HR, Hazard Ratio; CI, 95 % confidence interval; Random, random-effects model

Anlage 5 Studiencharakteristika der Primärstudien in *Petrelli er al., 2012*

Table 1 Characteristics of the 11 Randomized Trials Included in the Metanalysis

Study author–year (ref.)	Trial N° enrolled pts PS 0-1/ median age	ADK Histology (%)	Treatment arms	Crossover to TKI (%)	EGFR mut screened pts	tot. EGFR mut. pts exp + control arms N° (%)	% EGFR mut. 19-21	Response rate % exp/control RR (p)	PFS mo (exp/control) HR (p)	OS mo (exp/ control) HR (p)
Mok TS–2009 (19) Yang CH–2010 (28)	IPASS 1217 90%/57	96,3%	A: Gefitinib 250 mg/day B: CBDCA AUC 5-6+Paclitaxel 200 mg/m^2 BSA	39,5%	437	261 (59,7%)	96,1%	71,2%/47,3% RR 1.51 (p<0.001)	9,5/6,3 HR 0.48 (p<0.001)	mo N.A. HR 1.002 (p=0.990)
Maemondo M–2010 (22)	228 98,7%/63	93,4%	A: Gefitinib 250 mg/day B: CBDCA AUC 6 +Paclitaxel 200 mg/m^2 BSA	94,6%	228 (all enrolled pts)	228 (100%)	93,8%	73,7%/30,7% RR 2.4 (p< 0.001)	10.8/5.4 HR 0.3 (p<0,001)	30.5/23.6 HR N.A. (p=0.31)
Douillard JY–2010 (23)	INTEREST 1466 88,4%/60,5	56,6%	A: Gefitinib 250 mg/day B: Docetaxel 75 mg/m^2 BSA (2nd line)	37%	297	44 (15%)	86%	42,1%/21,1% RR 2 (p=0.04)	7/4.1 HR 0.16 (p=0.001)	14,2/16,6 HR 0,83 (p=0,59)
Mitsudomi T–2010 (24)	WJTOG3405 172 100%/64	83,5%	A: Gefitinib 250 mg/day B: Docetaxel 60 mg/m^2 BSA–CDDP 80 mg/m^2 BSA	59,3%	172 (all enrolled pts)	172 (100%)	100%	62,1%/32,2% RR 1.93 (n=117 with measurable disease) (p<0.0001)	9.2/6.3 HR 0.489 (p<0.0001)	N.A.
Cappuzzo F–2010 (25)	SATURN 889 100%/60	45,3%	A: Erlotinib 150 mg/day B: Placebo	67%	518	58 (11,1%)	84,4%	N.A.	mo N.A. HR 0.10 (p< 0.0001)	mo N.A. HR 0.83 (p=0.6810)
Tsao MS–2005 (26)	BR.21 731 66%/61	50%	A: Erlotinib 150 mg/day B: Placebo	7,4%	177	40 (22,6%)	80%	N.A.	N.A.	mo N.A. HR 0.77 (p=0.54)
Bell DW–2005 (27)	INTACT 1 INTACT 2 2130 90%/60,6	52,3%	A: CDDP 80 mg/m^2 BSA + GEM 1250 mg/m^2 BSA +/- Gefitinib 250 mg/day B: CBDCA AUC 6 + Paclitaxel 200 mg/m^2 BSA +/- Gefitinib 500 mg/day	N.A.	312	32 (10%)	87,5%	72%/40% RR 1,81 (p=0,3)	6.7/4.5 HR 0.4 (p=N.A.)	mo N.A. HR 1.77 (p=N.A.)
Zhou C–2010 (29)	OPTIMAL 165 N.A./N.A.	87%	A: CBDCA AUC 5–GEM 1000 mg/m^2 BSA B: Erlotinib 150 mg/day	N.A.	165 (all enrolled pts)	165 (100%)	91%	83%/36% RR 2.3 (p 0,0000)	13.1/4.6 HR 0.16 (p < 0.0001)	N.A.
Kris MG–2009 (31)	ISEL 1692 66,5%/61,8	45%	A: Gefitinib 250 mg/day B: Placebo (pretreated)	3%	215	26 (12%)	82%	37.5%/0% RR N.A.	10.8/3.8 HR N.A.	N.A.
Maruyama R–2008 (46) Kris MG–2009 (31)	V 15-32 490 95,7%/56% <64y	77,7%	A: Gefitinib 250 mg/day B: Docetaxel 60 mg/m^2 BSA (2nd line)	53%	57	31 (54,4%)	96%	66.7%/45.4% RR N.A.	7.5/9.0 HR N.A.	N.A.
Eberhard DA–2005 (33)	TRIBUTE 1079 99,9%/62,6	61%	A: CBDCA AUC 6 +Paclitaxel 200 mg/m^2 BSA + Erlotinib 150 mg/day B: CBDCA AUC 6 +Paclitaxel 200 mg/m^2 BSA + Placebo	N.A.	228	29 (12,7%)	86,2%	53%/21% RR 2.5 (p=0,13)	N.A.	mo N.A. HR N.A. (p=0.96)
Rosell R (45)	EURTAC 174/ 86%/ 66	N.A.	A: erlotinib 150 mg/day B: cisplatinum-based doublets	N.A.	1,227	174 (14.1%)	100%	58%/15% RR 3.89 (p=N.A.)	5.2/9.7 HR 0.37 (p<0.0001)	NA for updated analysis

Ref.: reference; n°=number; Pts=patients; PS=performance status; ADK=adenocarcinoma; TKIs=tyrosine kinase inhibitors; EGFR=epidermal growth factor receptor; mut=mutatated; RR= risk ratio; PFS=progression free survival; OS=overall survival; mo=months; N.A.=data not available; CBDCA=carboplatin; CDDP=cisplatin; GEM=gemcitabine.

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