Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2014-B-076 Afatinib

Stand: Oktober 2014

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Afatinib **zur Behandlung des EGFR-Mutation-positiven nicht-kleinzelligen Lungenkarzinoms (NSCLC)** **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	Beschluss vom 2. Mai 2013 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Crizotinib Beschluss vom 8. Mai 2014 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Afatinib Richtlinie Methoden Krankenhausbehandlung (Stand: 26. Juni 2014); Ausgeschlossene Methoden (§ 4): Protonentherapie beim inoperablen nicht-kleinzelligen Lungenkarzinom des UICC Stadiums IV Protonentherapie bei Hirnmetastasen Protonentherapie bei Lebermetastasen Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie - Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (Stand: 30. Juli 2014): Off-Label-Indikation für Carboplatin: Kombinationstherapie des fortgeschrittenen NSCLC (palliativ)
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:	
Afatinib L01XE13 (Giotrif®)	<u>Zugelassenes Anwendungsgebiet:</u> 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.
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. (FI Cisplatin-HAEMATO, 06-2012)
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. (FI Docetaxel-ratiopharm®, 05-2013)
Etoposid L01CB01 (generisch)	Kombinationstherapie folgender Malignome: Palliative Therapie des fortgeschrittenen NSCLC bei Patienten mit gutem Allgemeinzustand (Karnofsky-Index >80%). (FI Riboposid®, 02-2014)
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. (FI Gemcitabin Kabi, 05-2013)
Ifosfamid L01AA06 (Holoxan®)	Nicht-kleinzellige Bronchialkarzinome: Zur Einzel- oder Kombinationschemotherapie von Patienten mit inoperablen oder metastasierten Tumoren. (FI Holoxan®, 11-2008)
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 […]. (FI Mitomycin 2 medac, 03-2014)
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. (FI Paclitaxel Hospira, 01-2014)

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. (FI Alimta®, 11-2012)
Vindesin L01CA03 (Eldesine®)	Kombinationschemotherapie: Lokal fortgeschrittenes oder metastasiertes nicht-kleinzelliges Bronchialkarzinom (Stadium IIIB, IV). (Lauer Taxe, 02-2014)
Vinorelbin L01CA04 (generisch)	Vinorelbin ist angezeigt zur Behandlung: des nicht kleinzelligen Bronchialkarzinoms (Stadium 3 oder 4). (FI Bendarelbin, 01-2013)
Proteinkinase-Inhibitoren:	
Crizotinib L01XE16 (Xalkori®)	Xalkori® wird angewendet bei Erwachsenen zur Behandlung des vorbehandelten Anaplastische-Lymphom-Kinase (ALK)-positiven, fortgeschrittenen nicht kleinzelligen Bronchialkarzinoms (non small cell lung cancer, NSCLC). (FI Xalkori®, 05-2014)
Erlotinib L01XE03 (Tarceva®)	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 zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC angezeigt, bei denen mindestens eine vorausgegangene Chemotherapie versagt hat. Bei Patienten mit epidermalen Wachstumsfaktor-Rezeptor-(EGFR)-IHC-negativen Tumoren konnten weder ein Überlebensvorteil noch andere klinisch relevante Wirkungen durch die Behandlung gezeigt werden. (FI Tarceva®, 12-2013)
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)
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)

Quellen: AMIS-Datenbank, Lauer-Taxe, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2014-B-076 Afatinib

Stand: Oktober 2014

Recherche und Synopse der Evidenz zur Bestimmung der zVT:

Indikation für die Recherche:

Anwendungsgebiet:

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

Berücksichtigte Wirkstoffe/Therapien:

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

- 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)
- Die Systematischen Reviews sind in alphabetischer Reihenfolge aufgeführt.

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation **„fortgeschrittenes und/oder metastasiertes nicht-kleinzelliges Lungenkarzinom“** durchgeführt. Eine Einschränkung auf das Merkmal des Anwendungsgebietes „aktivierende EGFR-Mutationen“ gemäß Zulassung wurde in dieser Evidenzsynopse nicht vorgenommen. In dieser Recherche und Synopse sind auch alle Therapielinien enthalten.

Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am ***23.07.2014*** 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), Leitlinien.de (ÄZQ), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, TRIP. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien (z.B. NICE, SIGN). Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab **618** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden **261** Quellen eingeschlossen. Insgesamt ergab dies **91** 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
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, 2014: 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 [25]	**Beginn des Verfahrens:** 15.11.2013 **Veröffentlichung der Nutzenbewertung und Beginn des schriftlichen Stellungnahmeverfahrens:** 17.02.2014 **Fristende zur Abgabe einer schriftlichen Stellungnahme:** 10.03.2014 **Beschlussfassung:** 08.05.2014 **Verfahrensstatus:** Verfahren abgeschlossen **Zugelassenes Anwendungsgebiet** Giotrif® als Monotherapie wird angewendet zur Behandlung von EGFR-TKI-naiven erwachsenen Patienten mit lokal fortgeschrittenem und/oder metastasiertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit aktivierenden EGFR-Mutationen. **Zweckmäßige Vergleichstherapie:** 1) Noch nicht vorbehandelte Patienten mit ECOG-Performance-Status 0 oder 1: - Gefitinib oder Erlotinib *oder* - Cisplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin, Gemcitabin, Docetaxel, Paclitaxel, Pemetrexed) unter Beachtung des jeweils zugelassenen Anwendungsgebietes Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Cisplatin in Kombination mit Pemetrexed: a) Patientengruppe mit EGFR-Mutation Del19: Hinweis für einen beträchtlichen Zusatznutzen b) Patientengruppe mit EGFR-Mutation L858R: Anhaltspunkt für einen geringen Zusatznutzen c) Patientengruppe mit anderen EGFR-Mutationen: Hinweis für einen geringeren Nutzen 2) Noch nicht vorbehandelte Patienten mit ECOG-Performance-Status 2: **Zweckmäßige Vergleichstherapie:** - Gefitinib oder Erlotinib *oder* - Gemcitabin Ausmaß und Wahrscheinlichkeit des Zusatznutzens: Ein Zusatznutzen ist nicht belegt. 3) Mit einer oder mehreren Chemotherapie(n) vorbehandelte Patienten: **Zweckmäßige Vergleichstherapie:** Gefitinib oder Erlotinib **Ausmaß und Wahrscheinlichkeit des Zusatznutzens:** Ein Zusatznutzen ist nicht belegt.

G-BA, 2014 Tragende Gründe zum 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 [27]	**Anwendungsgebiet:** EGFR-TKI-naive erwachsenen Patienten mit lokal fortgeschrittenem und/oder metastasiertem nicht-kleinzelligen Lungen-karzinom (NSCLC) mit aktivierenden EGFR-Mutationen <u>2.1 Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie - Begründung auf Basis der Kriterien nach 5. Kapitel § 6 Absatz 3 VerfO:</u> zu 4. Für das vorliegende Anwendungsgebiet wird davon ausgegangen, dass sich die Patienten mit NSCLC im Krankheitsstadium III B bis IV befinden (Stadieneinteilung nach IASLC, UICC), ohne Indikation zur kurativen Resektion, Strahlenbehandlung bzw. Radiochemotherapie. Die Behandlung erfolgt symptomorientiert palliativ sowie in Abhängigkeit von Krankheitsverlauf, Allgemeinzustand, Erfolg und Verträglichkeit der Erstlinientherapie, Begleiterkrankungen, Tumorhistologie, EGFR-Status und Therapiewunsch des Patienten. Tumore mit aktivierenden Mutationen des EGFR weisen in der Regel eine nicht-plattenepitheliale Histologie auf und sind in der Regel ALK-negativ. … Die Nutzenbewertung zu Afatinib beruht auf den vorliegenden Ergebnissen der Studie LUX-Lung 3, die zum Zeitpunkt der Einreichung des Dossiers zur Nutzenbewertung noch nicht abgeschlossen war. Die im Studienprotokoll geplante finale Auswertung des Gesamtüberlebens liegt noch nicht vor. Auch im Hinblick auf die in einer Interimsanalyse beobachteten Unterschiede im Gesamtüberleben in Abhängigkeit vom EGFR-Mutationsstatus bestehen weiterhin Unsicherheiten. Auf Basis der finalen Analyse zum Gesamtüberleben ist eine höhere Aussagesicherheit für die Ergebnisse zum Gesamtüberleben zu erwarten. Auch wird erwartet, dass weitere, differenzierte Ergebnisse im Hinblick auf die heterogene Gruppe der Patienten mit anderen EGFR-Mutationen vorgelegt werden.
G-BA, 2013 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 –	• **Beginn des Verfahrens**: 15.11.2012 • **Veröffentlichung der Nutzenbewertung und Beginn des schriftlichen Stellungnahmeverfahrens**: 15.02.2013 • **Fristende zur Abgabe einer schriftlichen Stellungnahme**: 08.03.2013 • **Beschlussfassung**: 02.05.2013 • **Befristung des Beschluss**es: 02.05.2015 • **Verfahrensstatus**: Verfahren abgeschlossen **Anwendungsgebiet:** Zur Behandlung des vorbehandelten Anaplastische-Lymphom-Kinase (ALK)-positiven, fortgeschrittenen nicht kleinzelligen Bronchialkarzinoms (non small cell lung cancer, NSCLC). **Zweckmäßige Vergleichstherapie:** a) Patienten, bei denen eine Chemotherapie angezeigt ist:

Crizotinib [28]	Docetaxel oder PEM zur Behandlung von Patienten, bei denen eine Chemotherapie angezeigt ist (dies können insbesondere Patienten mit ECOG-PS 0, 1 und gegebenenfalls 2 sein). • <u>Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der Chemotherapie mit Docetaxel oder PEM:</u> Anhaltspunkt für einen *beträchtlichen* Zusatznutzen. b) Patienten, bei denen eine Chemotherapie nicht angezeigt ist: BSC zur Behandlung von Patienten, bei denen eine Chemotherapie nicht angezeigt ist (dies können insbesondere Patienten mit ECOG-PS 4, 3 und gegebenenfalls 2 sein). • <u>Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber BSC:</u> Ein Zusatznutzen ist *nicht belegt.*
G-BA, 2014: Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage VI-Off-Label-Use Teil A Ziffer III. Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) - Kombinationstherapie, Zustimmung eines pharmazeutischen Unternehmers [26]	**Eckpunkte der Entscheidung** Die Firma Sun Pharmaceuticals Germany GmbH hat nachträglich zur Beschlussfassung des G-BA vom 21. November 2006 über die Umsetzung der Empfehlung der Expertengruppe Off-Label zu „Carboplatin-haltigen Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie“ die Anerkennung des bestimmungsgemäßen Gebrauchs nach § 84 AMG ihrer Carboplatin-haltigen Arzneimittel zur Anwendung bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie erklärt. Die Änderung der Arzneimittel-Richtlinie in Bezug auf die Wiedergabe der Zustimmungen pharmazeutischer Unternehmer zum Off-Label-Use Carboplatin-haltiger Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie dient daher der Veröffentlichung der zustimmenden Erklärung des betroffenen pharmazeutischen Unternehmers Sun Pharmaceuticals Germany GmbH gemäß § 35c Abs. 1 Satz 7 SGB V.
IQWiG, 2013 Crizotinib – Nutzenbewertung [34]	Der Gemeinsame Bundesausschuss (G-BA) hat das Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) mit der Nutzenbewertung des Wirkstoffs Crizotinib gemäß § 35a SGB V beauftragt. Die Bewertung erfolgte auf Basis eines Dossiers des pharmazeutischen Unternehmers (pU). Das Dossier wurde dem IQWiG am 15.11.2012 übermittelt. Das Ziel des vorliegenden Berichts ist die Bewertung des Zusatznutzens von Crizotinib bei Patienten mit vorbehandeltem anaplastische Lymphomkinase(ALK)-positiven, fortgeschrittenen nicht kleinzelligen Bronchialkarzinom (NSCLC),

	• bei denen eine Chemotherapie angezeigt ist (dies können insbesondere Patienten mit Eastern Cooperative Oncology Group [ECOG] Performance Status 0, 1 und gegebenenfalls 2 sein), im Vergleich zu Chemotherapie (Docetaxel / Pemetrexed) als zweckmäßiger Vergleichstherapie (Chemotherapie-Population). • bei denen eine Chemotherapie nicht angezeigt ist (dies können insbesondere Patienten mit ECOG Performance Status 4, 3 und gegebenenfalls 2 sein), im Vergleich zu best supportive care (BSC) als zweckmäßiger Vergleichstherapie (BSC-Population). Zusammenfassend ist ein Zusatznutzen für erwachsene Patienten mit vorbehandeltem fortgeschrittenen ALK-positiven NSCLC nicht belegt. Die Gesamtaussage des Zusatznutzens basiert auf der Aggregation des auf Endpunktebene abgeleiteten Ausmaßes des Zusatznutzens in den Teilpopulationen, die sich aus der zweckmäßigen Vergleichstherapie ergaben. Das Vorgehen zur Ableitung einer Gesamtaussage zum Zusatznutzen stellt einen Vorschlag des IQWiG dar. Über den Zusatznutzen beschließt der G-BA. *Vgl. nachfolgend: Addendum*
IQWiG 2013 Addendum zum Auftrag A12-15 (Crizotinib) [35]	Wie bereits in der Dossierbewertung beschrieben, eignet sich die Studie PROFILE 1007 zur Untersuchung des Zusatznutzens von Crizotinib im Vergleich zur Chemotherapie (Docetaxel / PEM) in der Chemotherapie-Population. Das ist eine Population von Patienten mit vorbehandeltem anaplastische Lymphomkinase(ALK)-positiven, fortgeschrittenen nicht kleinzelligen Bronchialkarzinom (NSCLC), bei denen eine Chemotherapie angezeigt ist (dies können insbesondere Patienten mit Eastern Cooperative Oncology Group [ECOG] PS 0, 1 und gegebenenfalls 2 sein). Die Studie kann keine Aussage machen zum Vergleich von Crizotinib und BSC für Patienten in der BSC–Population, bei denen eine Chemotherapie nicht angezeigt ist (dies können insbesondere Patienten mit ECOG PS 4, 3 und gegebenenfalls 2 sein). Für diese Population hat der pU mit der Stellungnahme keine neuen Daten vorgelegt. Das vorliegende Addendum kann deshalb ausschließlich Aussagen zur Chemotherapie-Population machen.
IQWiG, 2014: Afatinib - Nutzenbewertung gemäß § 35a SGB V [36]	Der Gemeinsame Bundesausschuss (G-BA) hat das Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) mit der Nutzenbewertung des Wirkstoffs Afatinib gemäß § 35a SGB V beauftragt. Die Bewertung erfolgte auf Basis eines Dossiers des pharmazeutischen Unternehmers (pU). Das Dossier wurde dem IQWiG am 15.11.2013 übermittelt. Ziel der vorliegenden Nutzenbewertung ist die Bewertung des

	Zusatznutzens von Afatinib bei Epidermal Growth Factor Receptor-Tyrosinkinase-Inhibitor (EGFR-TKI)-naiven erwachsenen Patienten mit lokal fortgeschrittenem und / oder metastasiertem nichtkleinzelligem Lungenkarzinom (NSCLC) mit aktivierenden EGFR-Mutationen. **Mortalität** Für das Gesamtüberleben zeigte sich ein Beleg für eine Effektmodifikation durch die EGFR-Mutation der Patienten, sodass Aussagen nur auf Basis der entsprechenden Subgruppen-ergebnisse sinnvoll sind. Für Patienten mit einer Del19-Mutation ergab sich ein Hinweis auf einen Zusatznutzen von Afatinib im Vergleich zu Cisplatin + Pemetrexed. Für Patienten mit einer L858R-Mutation ergab die Behandlung mit Afatinib keinen statistisch signifikanten Unterschied zwischen den Behandlungsgruppen. Für Patienten mit anderen Mutationen (nicht-Del19 und nicht-L858R) zeigte sich für das Gesamtüberleben ein Hinweis auf einen geringeren Nutzen von Afatinib. **Morbidität** Die Morbidität der Patienten wurde mit den Symptomskalen der krankheitsspezifischen Fragebögen EORTC QLQ-C30 und EORTC QLQ-LC13 erhoben. Ausgewertet wurden die Rate der Patienten mit klinisch relevanter Verbesserung und die Zeit bis zur Verschlechterung der Symptome. Anhaltspunkte für einen Zusatznutzen von Afatinib zeigten sich für die Symptome Dyspnoe, Übelkeit und Erbrechen, Husten (beide Auswertungen), Fatigue und Haarausfall. Für Schmerzen in der Brust (Zeit bis zur Verschlechterung) und Schmerzen in Arm oder Schulter (Verbesserung) wurden zwar Effekte beobachtet, diese waren jedoch nicht mehr als geringfügig, sodass sich daraus kein Zusatznutzen für Afatinib ableiten ließ. Für die Symptome Diarrhö (beide Auswertungen), Mundschmerzen und Schluckbeschwerden (Zeit bis zur Verschlechterung) zeigte sich jeweils ein Anhaltspunkt für einen geringeren Nutzen. Bei den Symptomskalen Schmerzen, Schmerzen (andere als Brust oder Arm / Schulter) Schlaflosigkeit, Appetitverlust, Verstopfung, Bluthusten, sowie periphere Neuropathie zeigte sich kein statistisch signifikanter Unterschied zwischen den Behandlungsgruppen. Die beschriebenen Effekte zeigten sich aufgrund von Effektmodifikationen zum Teil nur in einzelnen Subgruppen. Dies wurde bei der abschließenden Aussage zum Zusatznutzen entsprechend berücksichtigt. **Gesundheitsbezogene Lebensqualität** Die gesundheitsbezogene Lebensqualität wurde mit den Funktionsskalen des Fragebogens EORTC QLQ-C30 erhoben. Ausgewertet wurden die Rate der Patienten mit klinisch relevanter Verbesserung und die Zeit bis zur Verschlechterung der Symptome. Für die Endpunkte körperliche Funktion, Rollenfunktion und globaler Gesundheitsstatus lagen Hinweise auf Effektmodifikationen durch den Faktor Alter, im Falle der körperlichen Funktion außerdem durch den EGFR-Mutationsstatus vor. Bezüglich der körperlichen Funktion und der Rollenfunktion ergab sich bei Patienten < 65 Jahren für beide Auswertungen jeweils ein Anhaltspunkt für einen Zusatznutzen von Afatinib. In der Rollenfunktion zeigte sich bei Patienten ≥ 65 Jahren für die Verbesserung der Funktion hingegen ein Anhaltspunkt für einen

	geringeren Nutzen von Afatinib. Für Patienten mit Del19-Mutation ergab sich hinsichtlich der körperlichen Funktion für beide Auswertungen ein Anhaltspunkt für einen Zusatznutzen von Afatinib; für L858R und andere Mutationen ergaben sich keine statistisch signifikanten Unterschiede zwischen den Behandlungsgruppen. Bei den Endpunkten emotionale Funktion und kognitive Funktion zeigte sich jeweils kein statistisch signifikanter Unterschied zwischen den Behandlungsgruppen. Für die gesundheitsbezogene Lebensqualität gemessen mit dem EQ-5D lagen keine Ergebnisse für die einzelnen Skalen des Fragebogens vor. Die VAS-Daten wurden nicht herangezogen, da zu diesen vom pU keine Subgruppenergebnisse vorgelegt wurden, obwohl sich bei der Erhebung der gesundheitsbezogenen Lebensqualität mittels EORTC QLQ-C30 relevante Effektmodifikationen zeigten. **Nebenwirkungen** Die zwischen den Studienarmen deutlich unterschiedliche Beobachtungsdauer ermöglicht auf Grundlage der vorliegenden Daten keine quantitative Bewertung eines möglichen Schadens von Afatinib gegenüber der zweckmäßigen Vergleichstherapie. Es waren ausschließlich qualitative Aussagen auf Basis der naiven Proportionen möglich. Auf dieser Grundlage ergab sich in der Gesamtschau der Nebenwirkungen weder ein Vorteil noch ein Nachteil von Afatinib gegenüber der zweckmäßigen Vergleichstherapie. Ein größerer oder geringerer Schaden von Afatinib im Vergleich zu Cisplatin + Pemetrexed ist damit insgesamt nicht belegt. ***Fragestellung 1b: nicht vorbehandelte Patienten mit ECOG PS 2*** Für die Fragestellung Afatinib versus Gemcitabin bei nicht vorbehandelten Patienten mit einem ECOG-PS von 2 lagen keine relevanten Daten vor. Damit ist ein Zusatznutzen von Afatinib gegenüber der zweckmäßigen Vergleichstherapie nicht belegt. ***Fragestellung 2: mit einer oder mehreren Chemotherapie(n) vorbehandelte Patienten*** Für die Fragestellung Afatinib versus Erlotinib oder Gefitinib bei mit einer oder mehreren Chemotherapie(n) vorbehandelten Patienten lagen keine relevanten Daten vor. Damit ist ein Zusatznutzen von Afatinib gegenüber der zweckmäßigen Vergleichstherapie nicht belegt. Wahrscheinlichkeit und Ausmaß des Zusatznutzens, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen Auf Basis der dargestellten Ergebnisse werden das Ausmaß und die Wahrscheinlichkeit des Zusatznutzens des Wirkstoffs Afatinib im Vergleich zur zweckmäßigen Vergleichstherapie bewertet wie in Tabelle 3 dargestellt: Tabelle 3: 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

Therapielinie	Patientengruppe	Zweckmäßige Vergleichstherapie[a]	Subgruppe	Ausmaß und Wahrscheinlichkeit des Zusatznutzens
nicht vorbehandelte Patienten	ECOG-PS 0-1	Gefitinib oder Erlotinib oder **Cisplatin +** (Vinorelbin, Gemcitabin, Docetaxel, Paclitaxel oder **Pemetrexed**)	EGFR-Mutation Del19	Hinweis auf erheblichen Zusatznutzen
			EGFR-Mutation L858R, Alter < 65	Anhaltspunkt für geringen Zusatznutzen
			Alter ≥ 65	Zusatznutzen nicht belegt
			andere[b] EGFR-Mutationen	Hinweis auf geringeren Nutzen
	ECOG-PS 2	Gefitinib oder Erlotinib oder **Gemcitabin**	Zusatznutzen nicht belegt	
mit einer oder mehreren Chemotherapie(n) vorbehandelte Patienten		Erlotinib oder Gefitinib	Zusatznutzen nicht belegt	

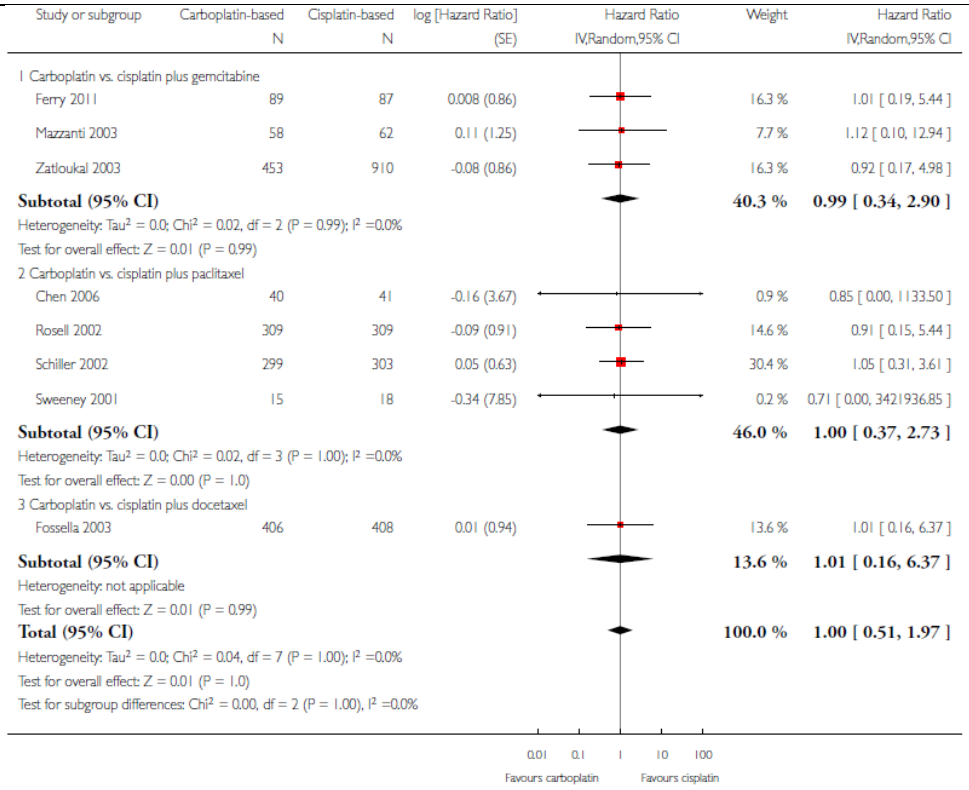
a: Dargestellt ist jeweils die vom G-BA festgelegte zweckmäßige Vergleichstherapie. In den Fällen, in denen der pU aufgrund der Festlegung der zweckmäßigen Vergleichstherapie durch den G-BA aus mehreren Alternativen eine Vergleichstherapie auswählen kann, ist die entsprechende Auswahl des pU fett markiert.
b: nicht L858R, nicht Del19-Mutation
ECOG-PS: Eastern Cooperative Oncology Group Performance Status

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. 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

de Castria TB, 2013: Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer [16]	**1. Fragestellung** To assess the efficacy and safety of carboplatin-based chemotherapy when compared with cisplatin-based chemotherapy, both in combination with a third-generation drug, in people with advanced NSCLC. To compare quality of life in people with advanced NSCLC receiving chemotherapy with cisplatin and carboplatin combined with a third-generation drug.
	2. Methodik ***Population:*** people with advanced NSCLC ***Interventionen und Komparatoren:*** regimens with cisplatin or carboplatin in combination with a third-generation drug (i.e. docetaxel, paclitaxel, vinorelbine, gemcitabine or irinotecan) • Cisplatin plus gemcitabine versus carboplatin plus gemcitabine. • Cisplatin plus docetaxel versus carboplatin plus docetaxel. • Cisplatin plus paclitaxel versus carboplatin plus paclitaxel. • Cisplatin plus vinorelbine versus carboplatin plus vinorelbine. • Cisplatin plus irinotecan versus carboplatin plus irinotecan. We included trials comparing these compounds for any number of cycles or treatment schedules. ***Endpunkte*:** <u>Primär</u>: • Overall survival. • One-year survival rate. • QoL. • Drug toxicities (according to the National Cancer Institute Common Toxicity Criteria v2.0) <u>Sekundär</u>: Objective response rate, classified according to the Response Evaluation Criteria in Solid Tumors (RECIST) (Eisenhauer 2009). ***Suchzeitraum:*** 1966 bis 03/2013 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):***

	10 (5017), nur RCTs ***Qualitätsbewertung der Studien:*** Risk of bias' tool created by The Cochrane Collaboration: mittlere bis gute Qualität ***Heterogenitätsuntersuchungen:*** *durchgeführt (siehe Punkt 3.): geringe Heterogenitäten*
	3. Ergebnisdarstellung ***OS*** There was no difference between carboplatin based and cisplatin-based chemotherapy in overall survival (hazard ratio (HR) 1.00; 95% confidence interval (CI) 0.51 to 1.97, I^2 =0%) and one-year survival rate (risk ratio (RR) 0.98; 95% CI 0.88 to 1.09, I^2 = 24%). ***ORR*** Cisplatin had higher response rates when we performed an overall analysis (RR 0.88; 95% CI 0.79 to 0.99, I^2 = 3%), but trials using paclitaxel or gemcitabine plus a platin in both arms had equivalent response rates (paclitaxel: RR 0.89; 95% CI 0.74 to 1.07, I^2 = 0%; gemcitabine: RR 0.92; 95% CI 0.73 to 1.16, I^2 = 34%). ***Adverse events*** Cisplatin caused more nausea or vomiting, or both (RR 0.46; 95% CI 0.32 to 0.67, I2 = 53%) and carboplatin caused more thrombocytopenia (RR 2.00; 95% CI 1.37 to 2.91, I2 = 21%) and neurotoxicity (RR 1.55; 95% CI 1.06 to 2.27, I^2 = 0%). There was no difference in the incidence of grade III/IV anaemia (RR 1.06; 95% CI 0.79 to 1.43, I2 = 20%), neutropenia (RR 0.96; 95% CI 0.85 to 1.08, I^2 = 49%), alopecia (RR 1.11; 95% CI 0.73 to 1.68, I2 = 0%) or renal toxicity (RR 0.52; 95% CI 0.19 to 1.45, I^2 = 3%). ***QoL*** Two trials performed a quality of life analysis; however, they used different methods of measurement so we could not perform a meta-analysis.



4. Anmerkungen/Fazit der Autoren

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

In Planung/ Durchführung:

- First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer (Protocol 2013)
- Chemotherapy for non-small cell lung cancer in the elderly population (Protocol 2013)
- Chemotherapy with cetuximab versus chemotherapy alone for chemotherapy-naive advanced non-small cell lung cancer (Protocol 2012)

Systematische Reviews

Al-Saleh K et al., 2012: Role of pemetrexed in advanced non-small-cell lung cancer: meta-analysis of randomized controlled trials, with histology subgroup analysis [1]	**1. Fragestellung** To compare the efficacy of pemetrexed with that of other treatments in advanced NSCLC **2. Methodik** ***Population:*** advanced NSCLC ***Intervention:*** pemetrexed ***Komparator:*** other treatments or plecebo ***Endpunkte*:** Primär: OS (survival outcome with a minimum follow up of 12 months ***Suchzeitraum:*** ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 5 (Gesamtzahl nicht angegeben; Range 146 – 1725) Nur RCT ***Qualitätsbewertung der Studien:*** accordance with the Cochrane handbook guidelines and GRADE ***Heterogenitätsuntersuchungen:*** Cochran Q and the *I*2 **3. Ergebnisdarstellung**

TABLE I Studies included in the meta-analysis

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

PS = Performance status.

<u>OS:</u>

pemetrexed was superior to that with other treatments: HR: 0.89; 95%; CI: 0.80 to 0.99

non-squamous histology: HR: 0.82; 95% ci: 0.73 to 0.91.

Pemetrexed was inferior to other chemotherapy options in patients with squamous histology: HR: 1.19; 95% ci: 0.99 to 1.43

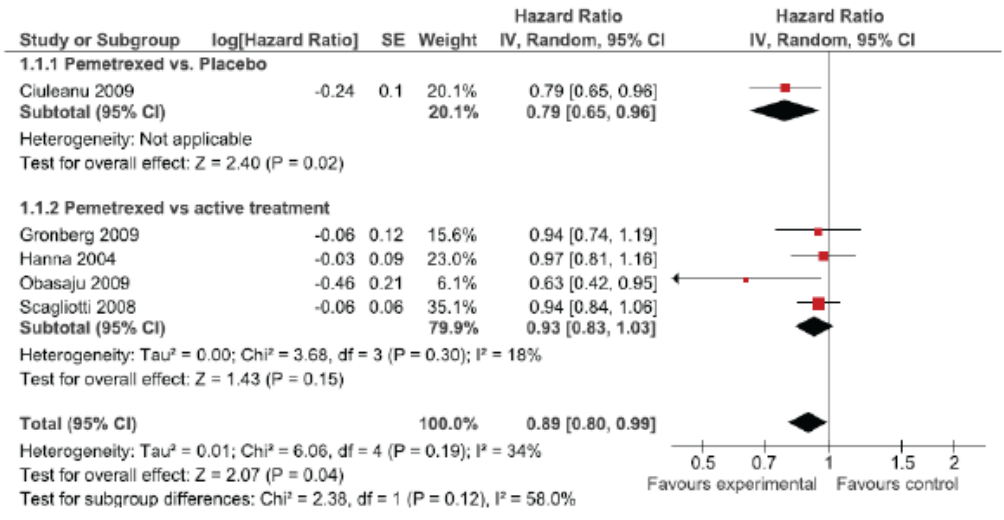


FIGURE 1 *Overall effect of pemetrexed treatment.*

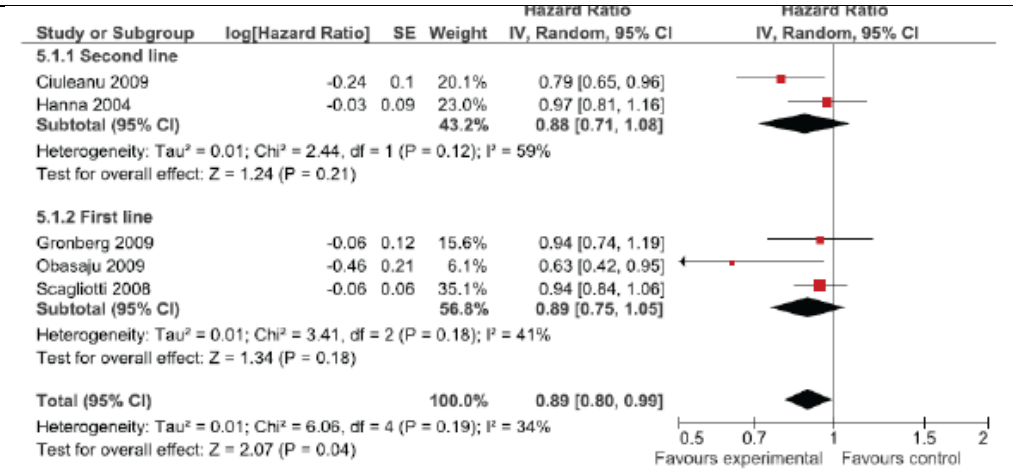


FIGURE 2 *First-line compared with second-line pemetrexed.*

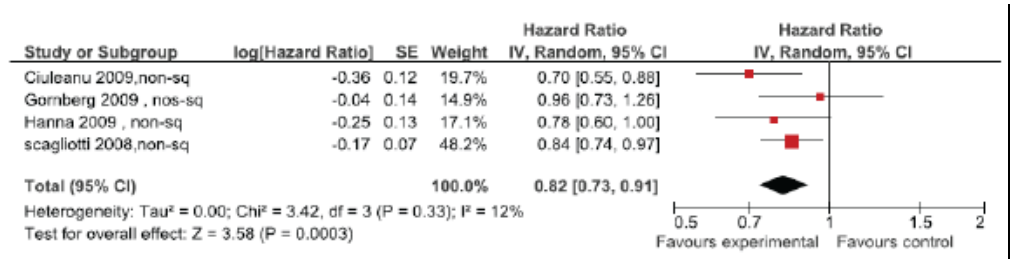


FIGURE 3 *Pemetrexed in non-squamous histology.*

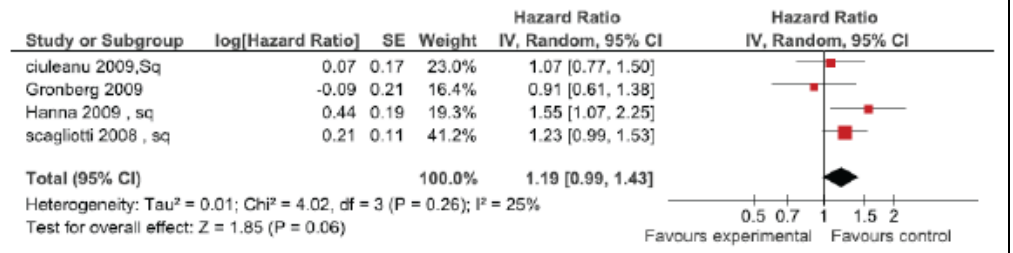


FIGURE 4 *Pemetrexed in squamous histology.*

4. Anmerkungen/Fazit der Autoren

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

Azim HA et al., 2009: Third generation triplet cytotoxic chemotherapy in advanced non-small cell lung cancer: a systematic overview [4]	**1. Fragestellung** to compare the relative efficacy of third generation **triplet therapy** with that of standard **double therapy** in the treatment of advanced NSCLC. **2. Methodik** **Population**: treatment-naïve patients with pathologically proven advanced NSCLC **Intervention**: third generation triplet therapy (vinorelbine, paclitaxel, gemcitabine and docetaxel) **Komparator**: double therapy (platinum and/or third generation cytotoxic drugs)

Endpunkte:
Respone, OS, toxicity
Methode:
systematic review and meta-analysis of RCTs
Suchzeitraum:
k.A.
Anzahl eingeschlossene Studien/Patienten
(Gesamt): 6 (n=2.117)
Qualitätserwertung der eingeschlossenen Primärstudien:
k.A.

3. Ergebnisdarstellung

Table 1
Trials comparing doublet to triplet therapy in patients with advanced NSCLC

Author	Therapy	n
Comella et al. [17]	Cisplatin 50 mg/m^2 + gemcitabine 1000 mg/m^2 + vinorelbine 25 mg/m^2 on days 1, 8 repeated every 3 weeks	60
	Cisplatin 100 mg/m^2 on day 1 + gemcitabine 1000 mg/m^2 on days 1, 8, 15 repeated every 4 weeks	60
	Cisplatin 120 mg/m^2 on day 1, 29 and then every 6 weeks + vinorelbine 30 mg/m^2 weekly for 10 weeks	60
Comella et al. [18]	Cisplatin 50 mg/m^2 + gemcitabine 1000 mg/m^2 + paclitaxel 125 mg/m^2 on days 1, 8 repeated every 3 weeks for 5 cycles	114
	Cisplatin 50 mg/m^2 + gemcitabine 1000 mg/m^2 + vinorelbine 25 mg/m^2 on days 1, 8 repeated every 3 weeks for 5 cycles	117
	Cisplatin 100 mg/m^2 on day 1 + gemcitabine 1000 mg/m^2 on days 1, 8, 15 repeated every 4 weeks for 5 cycles	112
Alberola et al. [19]	Cisplatin 100 mg/m^2 on day 1 + gemcitabine 1000 mg/m^2 on day 1, 8 + vinorelbine 25 mg/m^2 on day 1, 8 every 21 days	188
	Cisplatin 100 mg/m^2 on day 1 + gemcitabine 1250 mg/m^2 on day 1, 8 repeated every 21 days	182
	Gemcitabine 1000 mg/m^2 on day 1, 8 + vinorelbine 30 mg/m^2 on day 1, 8 for three cycles followed by vinorelbine 30 mg/m^2 on day 1, 8 + ifosfamide 3000 mg/m^2 on day 1	187
Laack et al. [20]	Gemcitabine 1000 mg/m^2 + vinorelbine 25 mg/m^2 on days 1, 8 + cisplatin 75 mg/m^2 on day 2 repeated every 3 weeks	144
	Gemcitabine 1000 mg/m^2 + vinorelbine 25 mg/m^2 on days 1, 8 repeated every 3 weeks	143
Paccagnella et al. [21]	Carboplatin AUC 6 + paclitaxel 200 mg/m^2 on day 1 + gemcitabine 1000 mg/m^2 on days 1 and 8 repeated every 3 weeks for at least 6 cycles	163
	Carboplatin AUC 6 + paclitaxel 200 mg/m^2 on day 1 repeated every 3 weeks for at least 6 cycles	156
Comella et al. [22]	Gemcitabine 1000 mg/m^2 + vinorelbine 25 mg/m^2 on days 1, 8 repeated every 3 weeks	110
	Gemcitabine 1000 mg/m^2 + paclitaxel 125 mg/m^2 on days 1, 8 repeated every 3 weeks	107
	Gemcitabine 1000 mg/m^2 + vinorelbine 25 mg/m^2 + cisplatin 50 mg/m^2 on days 1, 8 repeated every 3 weeks	109
	Gemcitabine 1000 mg/m^2 + paclitaxel 125 mg/m^2 + cisplatin 50 mg/m^2 on days 1, 8 repeated every 3 weeks	107

Survival (6 trials, 1.921 patients):

no statistically significant difference

Response (6 trials):

statistically significant difference in favor of triplet therapy (OR: 1.33; 95% CI, 1.50–2.23; p < 0.001, no significant heterogeneity)

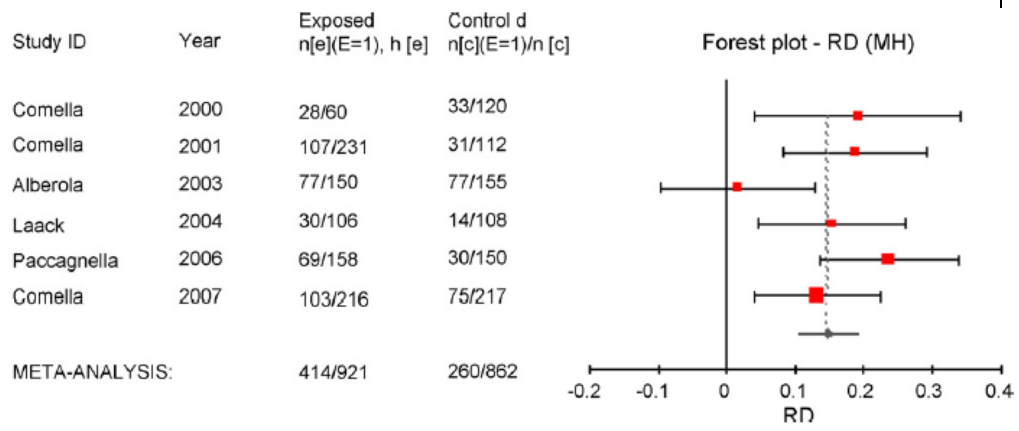


Fig. 2. Response rates.

	Toxicity: Patients who were randomized to receive triplet chemotherapy had significantly more grade III/IV toxicity in terms of myelosuppression, neurological toxicity and diarrhea. However the incidence of oral mucositis, renal dysfunction, nausea and vomiting were not significantly different between the two groups. **4. Anmerkungen/Fazit der Autoren** None of trials were double-blinded. Triplet therapy with third generation cytotoxic drugs is associated with higher tumor response rate at the expense of increased toxicity. Although triplet therapy had a better overall survival compared to doublet therapy, this did not reach statistical significance.
Botrel TEA et al., 2011: 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 [7] Siehe auch **Lima et al. (2011)**. Addition of bevacizumab to chemotherapy in advanced non-small cell lung cancer: a systematic review and meta-analysis [48]	**1. Fragestellung** To perform a systematic review and meta-analysis of all randomized controlled trials comparing the efficacy of **chemotherapy (CT) plus Bevacizumab (Bev) versus CT** alone in previously untreated locally advanced or metastatic non-small cell lung cancer (NSCLC). **2. Methodik** **Population**: Patients with non-small cell lung cancer (NSCLC) previously untreated locally advanced or metastatic (IIIB, with supraclavicular lymph node metastasis or malignant pleural or pericardial effusion or IV). **Intervention**: chemotherapy (CT) plus Bevacizumab (Bev) **Komparator**: chemotherapy alone **Endpunkt**: OS, PFS, ORR, toxicity **Suchzeitraum**: k.A. **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 4 (n=2 200), nur RCTs **3. Ergebnisdarstellung**

Table 1
Characteristics of included studies.

Study	Design	*N*	Patients	Histology	Interventions	Primary endpoi
Johnson et al. [11]	Randomized, double-blind active-controlled, parallel arm	99	Recurrent or advanced non-small-cell lung cancer (stage IIIB or IV)	Adenocarcinoma Large-cell anaplastic Squamous cell Other	CT[a] alone or, CT[a] plus Bev 7.5 mg/kg or, CT[a] plus Bev 15 mg/kg	Time to progression and tumor response rate
Sandler et al. [10]	Randomized, double-blind, active-controlled, parallel arm	878	Recurrent or advanced non-small-cell lung cancer (stage IIIB or IV)	Adenocarcinoma or not other-wise specified Large-cell Bronchioloalveolar Other	CT[a] alone or, CT[a] plus Bev 15 mg/kg	Overall survival
Reck et al. [13,29]	Randomized, double-blind, active-controlled, parallel arm	1043	Recurrent or advanced non-small-cell lung cancer (stage IIIB or IV)	Adenocarcinoma Large-cell Mixed (with predominantly adenocarcinoma component) Other	CT[b] alone or, CT[b] plus Bev 7.5 mg/kg or, CT[b] plus Bev 15 mg/kg	Progression-free survival
Nishio et al. [30,31]	Randomized, open label, multicenter	180	Advanced or recurrent non-squamous	Uninformed	CT[a] alone or, CT[a] plus Bev 15 mg/kg	Progression-free survival

Abbreviations: CT – chemotherapy; Bev – bevacizumab.
[a] Carboplatin and paclitaxel.
[b] Gemcitabine and cisplatin.

Overall survival:

- No statistically significant difference for CT plus Bev at 7.5 mg/kg (2 trials, 721 patients) (fixed effect: HR = 0.92, CI95% = 0.77–1.09; p = 0.33)
- statistically significant difference in favor of CT plus Bev at 15 mg/kg (4 trials, 1.747 patients) (fixed effect: HR = 0.89, CI95% = 0.80–1.00; p = 0.04, I^2=41%; NNT = 9)
- no statistically significant difference for CT plus Bev at 15 mg/kg (4 trials, 1.747 patients) with random effects model (HR = 0.90, CI95% = 0.76–1.07; p = 0.23)

***PFS**:* statistically significant difference in favor of CT plus Bev at 7.5 mg/kg (2 trials, 721 patients) (fixed effect: HR = 0.78, CI95% = 0.68–0.90; p = 0.0005, I^2 = 30%; NNT = 4) and Bev at 15 mg/kg (1.747 patients) (fixed effect: HR = 0.72, CI95% = 0.65–0.80; p < 0.00001, I^2 = 60%; NNT = 3)

***Overall response rate**:* statistically significant difference in favor of combination of CT plus Bev at 7.5 mg/kg doses (2 trials, 721 patients) (fixed effect: RR = 0.58; CI95% = 0.46–0.74; p < 0.00001, I^2=0; NNT = 7) as well as at Bev at 15 mg/kg (4 trials, 1.675 patients) (RR = 0.53; CI95% = 0.45–0.63; p < 0.00001, I^2=30%; NNT = 6)

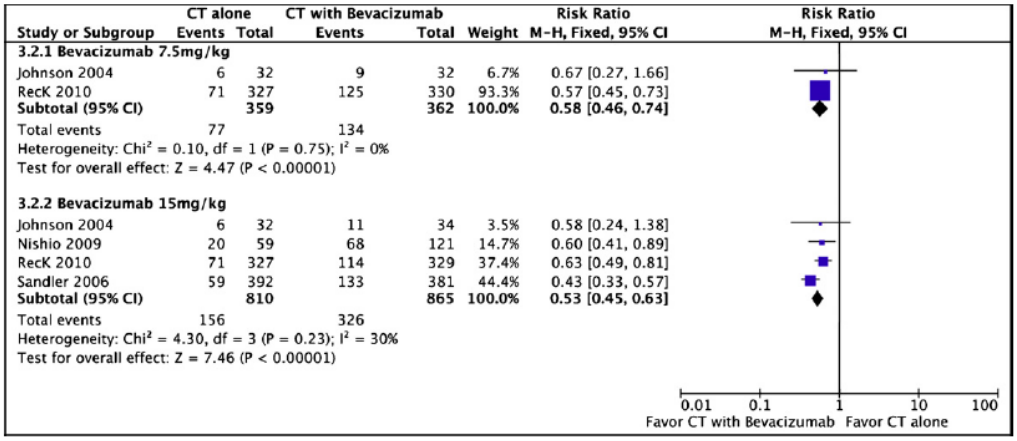


Fig. 2. comparative effect in objective response rates of CT with Bev versus CT alone. Abbreviations: CT – chemotheraphy. Observation: Sandler et al.: only patients with a measurable lesion are assessed

***Toxicity**:*

- the group receiving CT plus Bev in the dose of 7.5 mg/kg had more patients with neutropenia (fixed effect: RR = 0.79; CI95% = 0.65–0.96; p = 0.02). No differences were seen in the rates of patients with thrombocytopenia (fixed effect: RR = 0.86; CI95% = 0.66–1.12; p = 0.27).
- the group receiving CT plus Bev in the dose of 7.5 mg/kg had more patients with hypertension (fixed effect: RR = 0.30; CI95% = 0.13–0.73; p = 0.007) and bleeding events (fixed effect: RR = 0.40; CI95% = 0.16–0.97; p = 0.04).
- The group that received CT plus Bev at 15 mg/kg had more neutropenia (fixed effect: RR = 0.77; CI95% = 0.65–0.91; p = 0.002) and febrile neutropenia (fixed effect: RR = 0.44; CI95% = 0.23–0.84; p = 0.01).
- the group of patients that receiving CT plus Bev at 15 mg/kg had more patients with: haemoptysis (fixed effect: RR = 0.31; CI95% = 0.10–0.92; p = 0.03), hypertension (fixed effect: RR = 0.14; CI95% = 0.07–0.28; p < 0.00001), proteinuria (fixed effect: RR = 0.05; CI95% = 0.01–0.41; p = 0.005), vomiting (fixed effect: RR = 0.41; CI95% = 0.22–0.77; p = 0.005), rash or desquamation (fixed effect: RR = 0.19; CI95% = 0.04–0.88; p = 0.03), and bleeding events (fixed effect: RR = 0.27; CI95% = 0.13–0.56; p = 0.0004).

4. Anmerkungen/Fazit der Autoren

The combination of CT plus Bev increased the response rate and progression-free survival of patients with NSCLC. With respect to overall survival its benefit remains uncertain.

Bria E et al., 2011: Outcome of	**1. Fragestellung** to quantify the magnitude of benefit with upfront **EGFR TKI** in EGFR-M+ patients

advanced NSCLC patients harboring sensitizing EGFR mutations randomized to EGFR tyrosine kinase inhibitors or chemotherapy as first-line treatment: a meta-analysis [9]	**2. Methodik** **Population**: previously untreated patients with advanced/metastatic NSCLC **Interventionen**: Gefitinib, erlotinib **Komparator**: chemotherapy **Endpunkt**: PFS, OS, ORR, toxicity **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: bis 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 5 (n=2 035). 4 trials gefitinib, 3 trials erlotinib **3. Ergebnisdarstellung** **Overall survival**: no statistically significant difference **PFS**: statistically significant difference in favor of EGFR TKI (HR 0.45, 95% CI 0.36–0.58, P < 0.0001, significant heterogeneity) **ORR**: statistically significant difference in favor of EGFR TKI (HR 2.08, 95% CI 1.75–2.46, P < 0.0001) **Toxicity**: Only two of the prospective RCTs reported toxicity data for the EGFR-M+ population: grades 3–4 neutropenia was significantly lower in patients receiving EGFR TKI (RR 0.012, 95% CI 0.002–0.059, P < 0.0001), without significant heterogeneity. **4. Anmerkungen/Fazit der Autoren** **Bria et al. (2011):** This meta-analysis provides a cumulative estimate of the magnitude of benefit obtained with EGFR TKI (gefitinib and erlotinib) when used as front-line treatment in advanced, EGFR-M+, NSCLC patients. In this setting, EGFR TKI provide an unusually large PFS benefit when compared with cytotoxic chemotherapy, with an absolute reduction in the risk of progression of 22%–30%. Similarly an advantage is achieved in terms of ORR, taking into consideration that patients often derive a clinically significant symptomatic benefit from tumor shrinkage. **Gao et al. (2011):** The EGFR-TKI regimen significantly prolonged PFS and increased ORR when compared with platinum-based doublet chemotherapy in the previously untreated advanced NSCLC patients with EGFR mutation. As EGFR mutations are predictor of benefit from TKIs, prospective EGFR mutation should be routinely tested before the initiation of treatment in advanced NSCLC patients. Subgroup analysis revealed statistically significant and robust data for prolonging PFS and improving ORR in patients treated with either gefitinib or erlotinib versus

chemotherapy.

5. Hinweise der FBMed

Dem Review von **Gao et al.** liegen bis auf 1 RCT die gleichen Studien zu Grunde wie bei Petrelli et al. (2012) und Bria et al. (2011). Die Ergebnisse fallen vergleichbar bei den drei Reviews aus.

Chen P et al., 2011:

EGFR-targeted therapies combined with chemotherapy for treating advanced non-small-cell lung cancer: a meta-analysis [13]

1. Fragestellung

to systematically evaluate **EGFR targeted therapies** plus chemotherapy for advanced NSCLC

2. Methodik

Population:
adults (aged 18 or older) with advanced NSCLC. Patients previously exposed to EGFR-directed agents or radiotherapy were excluded (alle first-line)
Intervention:
EGFR targeted therapies plus platinum-based doublet chemotherapy
Komparator:
platinum-based doublet chemotherapy
Endpunkt:
OS, PFS, ORR
Methode:
systematic review and meta-analysis of RCTs
Suchzeitraum:
up to 2010
Anzahl eingeschlossene Studien/Patienten (Gesamt):
10 (n= 5936)

3. Ergebnisdarstellung

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

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

Niedermolekulare TKIs+Chemotherapie vs. Chemotherapie (basierend auf 6 Studien mit 3918 Patienten, 3 trials mit Erlotinib, 2, trials mit Gefitinib, 1 trial mit Vandetanib):

Overall survival: Kein stat. signifikanter Unterschied zwischen den Gruppen

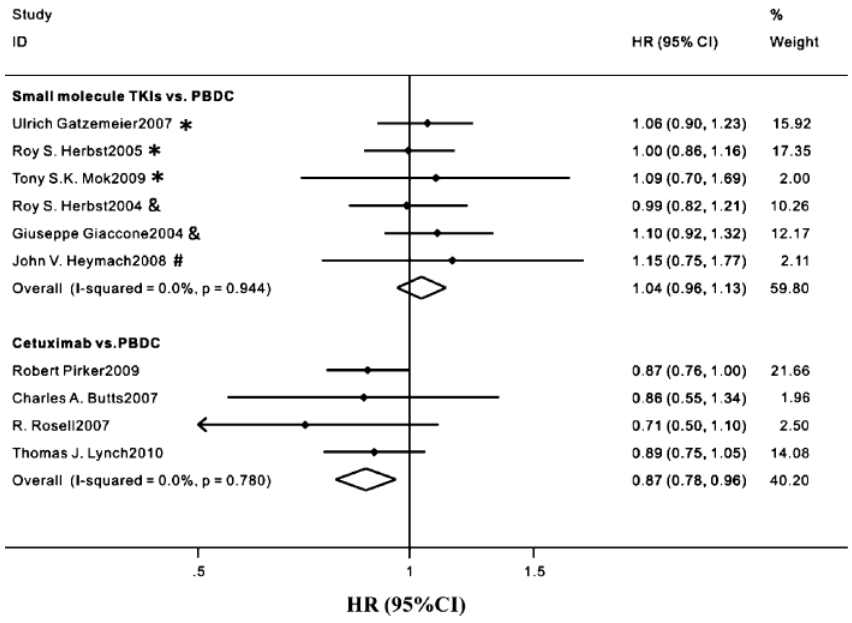


Fig. 2 Overall survival of epidermal growth factor receptor (EGFR)-targeted combination therapies vs. platinum-based doublet chemotherapy (PBDC). *Erlotinib administered, & gefitinib administered, # vandetanib administered, HR hazard ratio, 95% CI 95% confidence interval, HR<1 numerically longer survival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

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

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

4. Anmerkungen/Fazit der Autoren

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

Chen X et al., 2013:

Gefitinib or erlotinib as maintenance therapy in patients with advanced stage non-small cell lung cancer: a systematic

1. Fragestellung

Our aim was to determine the role of maintenance EGFR TKIs in patients with advanced NSCLC and to explore which subgroups of patients who will benefit from EGFR TKIs maintenance.

2. Methodik

Population:

advanced NSCLC

Intervention:

EGFR TKIs

Komparator:

review [14]	*Placebo or Observation* ***Endpunkte*:** PFS, OS ***Suchzeitraum:*** bis 09/2012 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** *5 (2436)* ***Qualitätsbewertung der Studien:*** *k.A.* ***Heterogenitätsuntersuchungen:*** I^2; keine bedeutsame Heretogenität **3. Ergebnisdarstellung** • 2 Studien: gefitinib (250 mg/qd) • 3 Studien: erlotinib (150 mg/qd) maintenance. In all studies maintenance was commenced after 4 cycles' first line chemotherapy in stage IIIB/IV NSCLC. All studies: a mixed population (EGFR mutated and non-mutated) and two of the studies (INFORM and SATURN) reported the outcomes of EGFR patients related to EGFR status. Four studies were double blind and placebo controlled, and only one trial (IFCT-GFPC 0502) [13] was open label.

Table 1. Summary of characteristics and major results of the included studies.

Studies	First author/ year	Number of Pts	Ethnicity Caucasian/ Asian/ Other (%)	Median Age	Non-Smoker n (%)	Adenocarcinoma n (%)	Primary endpoint/ sign	Exp vs control arms	Known EGFR status n (%)	EGFR mut, Exp/control n (%)	RR (%), Exp vs control, *P*	PFS(m), Exp vs control, *P*	OS(m), Exp vs control, *P*	AE≥Grade3, Exp vs control (%)
INFORM [6]	Zhang L 2012	296	0/100/0	55	160 (54%)	209 (71%)	PFS/Yes	G vs placebo	79 (27%)	15(10%)/ 15(10%)	24% vs 1% *P* = 0.0001	4.8 vs 2.6 *P*<0.0001	18.7 vs 16.9 *P* = 0.26	10(7%) vs 5(3%)
EORTC 08021/ILCP 01/03 [8]	Gaafar RM 2011	173	NR	61	38 (22%)	89 (51%)	OS/No	G vs placebo	NR	NR	12% vs 1% *P* = 0.004	4.1 vs 2.9 *P* = 0.0015	10.9 vs 9.4 *P* = 0.2	NR
SATURN [5]	Cappuzzo F 2010	889	84/15/1	60	152 (17%)	403 (45.3%)	PFS/Yes	E vs placebo	446 (50%)	22(5%) 27(6%)	12% vs 5% *P* = 0.0006	12.3 vs 11.3 weeks *P*<0.0001	12 vs 11 *P* = 0.0088	47(11%) vs 34(8%)
IFCT-GFPC 0502 [13]	Perol M 2012	310	NR	58	29 (9%)	200 (65%)	PFS/Yes	E vs placebo	188 (40.5%)†	NR	NR	2.9 vs 1.9 *P* = 0.003	11.4 vs 10.8 *P* = 0.3043	24 (15.5%) vs 4 (2.6%)
ATLAS [7]	Kabbinavar FF 2010	768	78/12/10	64	127 (17%)	609 (82%)	PFS/Yes	E+ Bev vs placebo+ Bev	NR	NR	NR	4.8 vs 3.7 *P* = 0.0012	15.9 vs 13.9 *P* = 0.2686	NR

Abbreviations: Pts, patients; sign, significant; Exp, experimental arm; G, Gefitinib; E, erlotinib; Bev, bevacizumab; PFS, progression free survival in months; OS, overall survival in months; AE, adverse event; NR, not reported.
†This ratio was based on the all included patients in IFCT-GFPC 0502, n = 464.
doi:10.1371/journal.pone.0059314.t001

PFS

TKIs (gefitinib and erlotinib) significantly increased progression-free survival (PFS) [hazard ratio (HR) 0.63, 95% confidence interval (CI) 0.50–0.76, I2 = 78.1%] and

OS

HR = 0.84 (95% CI 0.76–0.93, I2 = 0.0%) compared with placebo or observation.

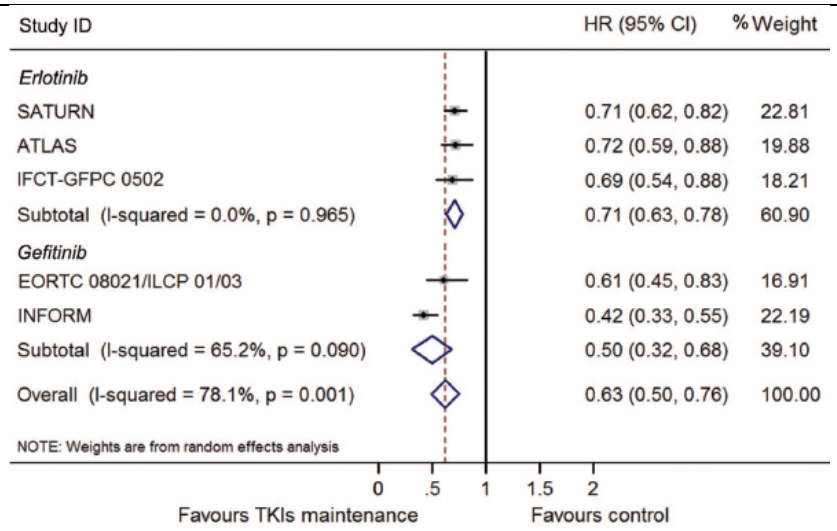
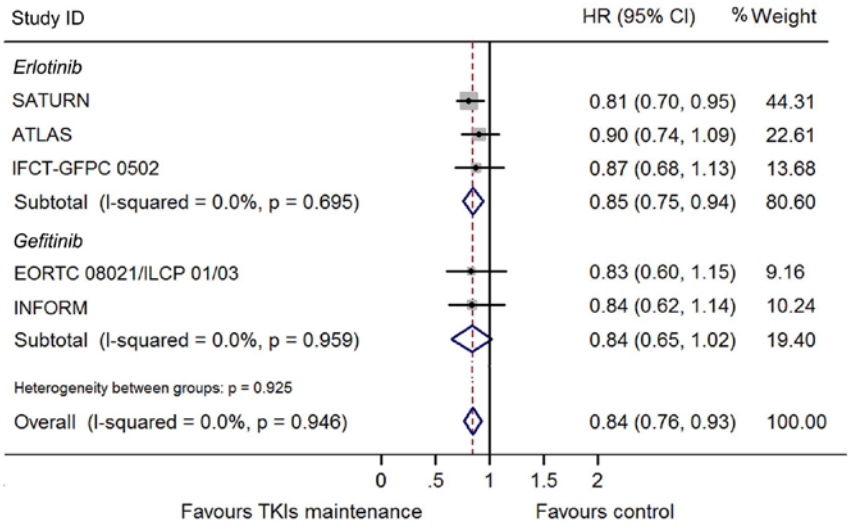


Figure 2. Meta-analysis of hazard ratio (HR) for progression free survival (PFS).



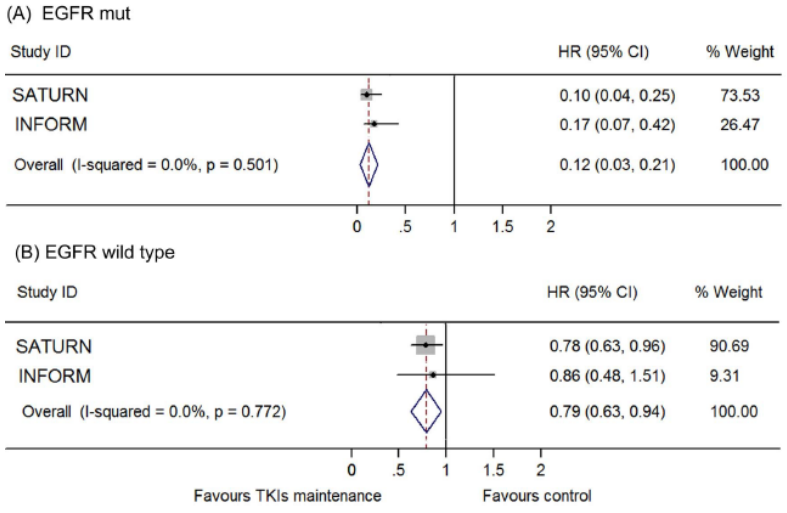
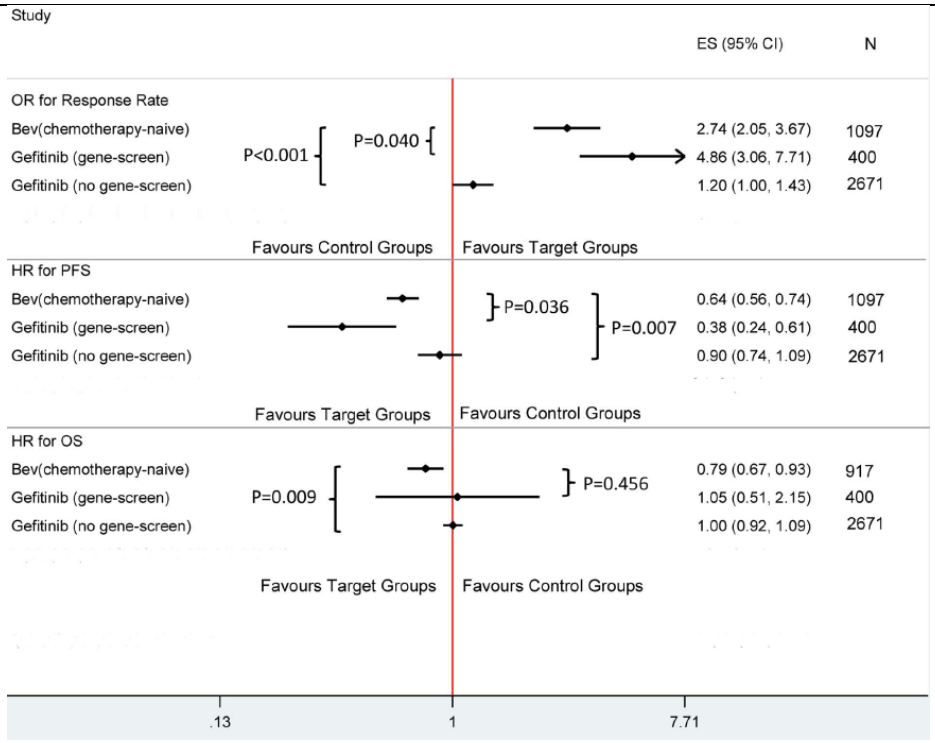


	Figure 3. Meta-analysis of hazard ratio (HR) for progression free survival (PFS) according to EGFR mutation status. (A) EGFR mutation positive. (B) EGFR wild type. **4. Anmerkungen/Fazit der Autoren** The results show that maintenance therapy with erlotinib or gefitinib produces a significant PFS and OS benefit for unselected patients with advanced NSCLC compared with placebo or observation. Given the less toxicity of TKIs than chemotherapy and simple oral administration, this treatment strategy seems to be of important clinical value.
Cui J et al.,2013: The Efficacy of Bevacizumab Compared with Other Targeted Drugs for Patients with Advanced NSCLC: A Meta-Analysis from 30 Randomized Controlled Clinical Trials [15]	**1. Fragestellung** The extent of the benefit of bevacizumab combined with chemotherapy in the treatment of advanced nonsmall- cell lung cancer (NSCLC) is still unclear. We performed this meta-analysis to compare the efficacy of bevacizumab with other commonly used targeted drugs for different patients with advanced NSCLC. **2. Methodik** ***Population***: patients with confirmed stage IIIB, stage IV or recurrent NSCLC based on historical or cytological evidence ***Intervention****:* bevacizumab (15 mg/kg) with chemotherapy ***Komparator****:* standard chemotherapy alone, 1. und 2. Linie ***Endpunkt****:* OS, ORR, PFS ***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 **3. Ergebnisdarstellung** ***1. Linie (chemotherapy-naı¨ve 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



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

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

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

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

4. Fazit der Autoren

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 HRPFS, and lower HR_{OS} among chemotherapy-naı¨ve 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_{PF}S, 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.
Des Guetz G et al., 2012: Comparison of the efficacy and safety of single-agent and doublet chemotherapy in advanced non-small cell lung cancer in the elderly: A meta-analysis [18]	**1. Fragestellung** To compare efficacy (1-Year Overall Survival or OS and Overall Response Rate or ORR) and safety of **doublet vs single-agent chemotherapy** among elderly patients aged 70 years or more. To assess the comparative efficacy and side effects of regimens including platinum derivates or not. **2. Methodik** ***Population***: elderly patients (70 years or older) treated for metastatic or advanced NSCLC (stage IV and IIIB) ***Intervention****:* doublet-agent chemotherapy ***Komparator****:* single-agent chemotherapy ***Endpunkt****:* OS, ORR, toxicity ***Methode****:* systematic review and meta-analysis of RCTs ***Suchzeitraum****:* up to 2012 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 10 (n= 2605) ***Qualitätsbewertung der Primärstudien:*** k.A. **3. Ergebnisdarstellung**

Table 1
Main characteristics of the 13 studies included in the meta-analysis.

	Number Male/female	Patients PS %	Median age	Charlson score	Stage IIIB/IV	Pathological type SCC, AC	Treatment (dose/mg/m^2) schedule	Objective response (%)	1-Year Overall Survival (%)
Abe 2011	276 193/83	>70 yo PS 0–1 = 100%	76	ND	85/191	SCC 72	Docetaxel 60 mg/m^2 D1 D8 D15/22D vs	31/116 (27)	77/134 (58)
						AC 176	Docetaxel 20 mg/m^2 + Cis platin 25 mg/m^2 D1 D8 D15/28D	45/117 (38)	74/138 (54)
Quoix 2010	451 333/118	>70 yo PS 0–1 = 73%	77	1–2: 324 >2: 102	88/363	SCC 151	Vinorelbine 30 mg/m^2 D1 D8/21D vs	23/211 (11)	61/226 (26)
						AC 229	Gemcitabine 1150 mg/m^2 D1 D8/21D vs		
							Paclitaxel 90 mg/m^2 D1 D8 D15 + Carboplatin AUC6 D1/28D	61/210 (29)	101/225 (45)
Karampeazis 2010	94 82/12	>70 yo PS 0–1 = 83%	76 (70–92)	CIRS-G gr 3/4, 0: 35 >1: 21	29/65	SCC34	Gemcitabine 1200 mg/m^2 D1 D8/21D vs	5/45 (11)	23/45 (51)
						AC 35	Gemcitabine 900 mg/m^2 + Docetaxel 30 mg/m^2 D1 D8/21D	13/49 (26)	32/49 (65)
Kang 2009	83 62/21	>70 yo or PS2	72	ND	14/69	SCC 16 AC 43	Docetaxel 75 mg/m^2 D1/21D vs Docetaxel 35 mg/m^2 D1 D8 + Carboplatin AUC 2.5 D1 D8/21D	11/42 (26) 8/41 (19)	16/42 (38) 11/41 (27)
Hainsworth 2007	345 213/132	>65 yo or PS2	74 (45–91)	ND	87/258	SCC 67	Docetaxel 36 mg/m^2 D1 D8 D15/28D vs	22/130 (13)	43/171 (25)
						AC 132	Docetaxel 30 mg/m^2 + Gemcitabine 800 mg/m^2 D1 D8 D15/28D	32/132 (18)	43/174 (25)
Sederholm 2005	119	From Phase 3 >70 yo PS 0–1 = 85%	ND	ND	ND	ND	Gemcitabine 1250 mg/m^2 D1 D8 D 15/28D vs	ND	23/57 (44)
							Gemcitabine 1250 mg/m^2 + Carboplatin D1 D8 D15 (AUC 5)/28D		25/61 (41)
Lilenbaum 2005	155 106/49	From Phase 3 >70 yo PS 0–1 = 82%	ND	ND	ND	ND	Paclitaxel 225 mg/m^2 D1 vs Paclitaxel 35 mg/m^2 + Carboplatin AUC 2.5 D1 D8/21D	16/78 (20) 28/77 (36)	24/78 (31) 27/77 (35)
Comella 2004	264 236/28	>70 yo PS 0–1 = 65%	73	1–2: 161 >2: 16	93/171	SCC 127	Gemcitabine 1200 mg/m^2 D1 D8 D15/28D vs	11/68 (16)	17/68 (25)
						AC 71	Paclitaxel 100 mg/m^2 D1 D8 D15/28D vs	7/63 (11)	13/63 (21)
							Gemcitabine 1000 mg/m^2 + Vinorelbine 25 mg/m^2 D1 D8/21D vs	13/68 (19)	18/68 (26)
							Gemcitabine 1000 mg/m^2 + Paclitaxel 80 mg/m^2 D1 D8/21 D	18/65 (28)	25/65 (38)

Table 1 (*Continued*)

	Number Male/female	Patients PS %	Median age	Charlson score	Stage IIIB/IV	Pathological type SCC, AC	Treatment (dose/mg/m^2) schedule	Objective response (%)	1-Year Over Survival (%)
Gridelli 2003	698 581/117	> 70 yo PS 0–1 = 80%	74	1–2: 305 >2: 315	209/489	SCC 315	Vinorelbine 30 mg/m^2 D1 D8/21D vs	42/233 (18)	89/233 (38)
						AC 235	Gemcitabine 1200 mg/m^2 D1 D8/21D vs	37/233 (16)	65/233 (28)
							Gemcitabine 1200 mg/m^2 + Vinorelbine 30 mg/m^2 D1 D8/21D	49/232 (21)	70/232 (30)
Frasci 2001	120 60/60	>70 yo PS 0–1 = 73%	74 (70–83)	1–2: 69 >2: 22		SCC 57	Vinorelbine 30 mg/m^2 D1 D8/21D vs	9/60 (15)	8/60 (13)
						AC 47	Gemcitabine 1200 mg/m^2 + Vinorelbine 30 mg/m^2 D1 D8/21D	13/60 (22)	18/60 (30)

SCC: squamous cell carcinoma; AC : adenocarcinoma.

Overall survival:

- Overall effect: no statistically significant difference
- Platinum-based therapy (5 trials): no statistically significant difference
- Non-platinum-based therapy (5 trials): no statistically significant difference
- Docetaxel (5 trials): no statistically significant difference
- Paclitaxel (3 trials): statistically significant difference in favor of doublet therapy (HR 0.76; 0.60–0.97; random effect model)

Response rate:

- Overall effect: statistically significant difference in favor of doublet therapy (HR 1.51; 1.22–1.86; $p < 0.001$; random effect model)
- Platinum-based therapy (4 trials): no statistically significant difference
- Non-platinum-based therapy (5 trials): statistically significant difference in favor of doublet therapy (HR 1.36, 95% CI: 1.11–1.67; $p = 0.003$; fixed effect model)
- Docetaxel (5 trials): statistically significant difference in favor of doublet therapy (HR 1.40; 1.07–1.83; fixed effect model)
- Paclitaxel (3 trials): statistically significant difference in favor of doublet

therapy ORR (HR 2.32; 1.71–3.15; fixed effect model)

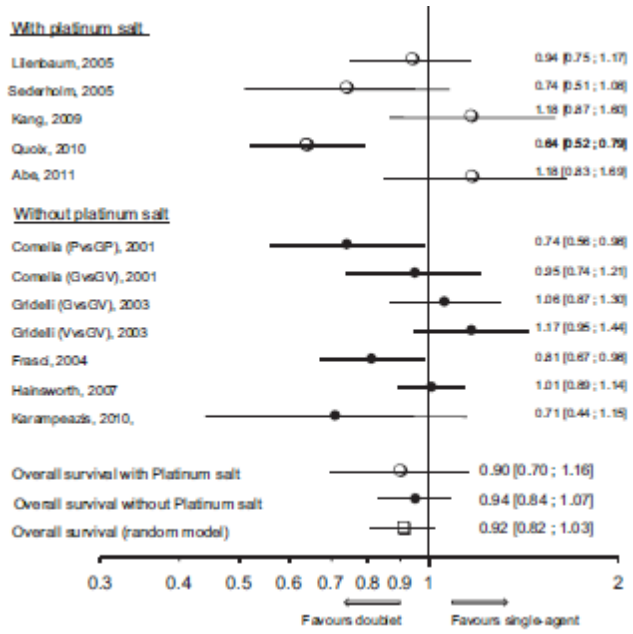


Fig. 2. Forest plot of studies including or not a platinum salt and assessing overall survival. By convention, a Hazard Ratio < 1 corresponds to a higher survival for doublet chemotherapy compared with single agent.

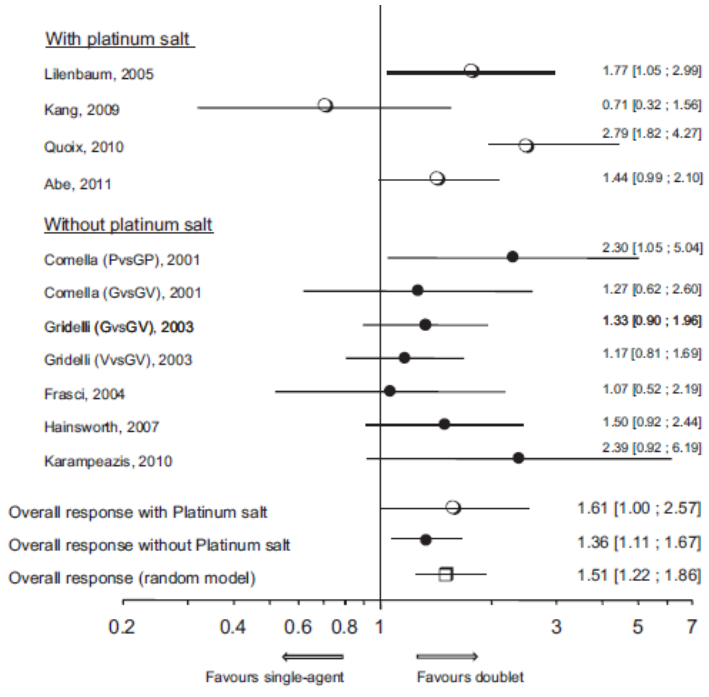


Fig. 3. Forest plot of studies including or not a platinum salt and assessing response rate. By convention, a Hazard Ratio < 1 corresponds to higher response for doublet chemotherapy compared with single agent.

Toxicity:

All grade nausea/vomiting was similar for doublets and single agents,

	whereas neutropenia, thrombocytopenia and anemia were significantly more frequent for doublets compared with single agents (HRs 1.26, 1.15–1.39, fixed effect model; 1.75, CI 1.11–2.77 random effect model; 1.33, CI 1.17–1.52 fixed effect model respectively; all p inferior to 0.001). **4. Anmerkungen/Fazit der Autoren** Platinum-based doublets represent the gold standard of chemotherapy of NSCLC. Our MA does not firmly confirm the superiority of platinum-based doublets among elderly patients. The great majority of studies used carboplatin, which seems preferable since it is devoid of renal toxicity. The benefit to-risk ratio of doublets in advanced NSCLC might be more favorable than that of single agents, at least for doublets including platinum derivates and in elderly patients with good performance status. Doublets not including platinum derivates showed an increased toxicity without improving survival and should therefore be avoided in elderly patients with good performance status. **5. Hinweise durch FB Med** Keine Information über Therapielinie
Di Maio M, et al., 2009: Meta-Analysis of Single-Agent Chemotherapy Compared with combination Chemotherpy as Second-Line Treatment of advanced non-small-cell lung cancer [20]	**1. Fragestellung** **2. Methodik** Basierend auf einer systematischen Literaturrecherche nach RCTs mit Metaanalyse. **Vergleich:** Kombinationschemotherapie (Doxetacel+Gemcitabin, Gemcitabin+Irinotecan, Pemetrexed+Carboplatin, Cisplatin+ Irinotecan, Doxetacel + Irinotecan, Doxetacel+Gemcitabin) **vs**. Monochemotherapie (Doxetacel, Pemetrexed, Cisplatin oder Irinotecan) ***Endpunkte:*** • Gesamtüberleben, • Ansprechrate, • progressionsfreies Überleben, • Nebenwirkungen ***Suchzeitraum:*** 1997 bis 06/2008 ***Anzahl der eingeschlossenen Studien / Patienten:*** 6 (847) Single agent: n=428; Kombination n= 419 **3. Ergebnisse (basierend auf 6 Studien mit 847 Patienten):**

Table 1. Characteristics of the Six Randomized Trials Included in the Meta-Analysis

Parameter	Study					
	Takeda et al[9]	Georgoulias et al[10]	Georgoulias et al[11]	Wachters et al[12]	Gebbia et al[14]	Smit et al[15]
Phase of the study	III	II*	II*	II	III	II*
Treatment dose and schedule						
Single-agent arm	Docetaxel 60 mg/m^2 day 1 every 3 weeks	Irinotecan 300 mg/m^2 day 1 every 3 weeks	Cisplatin 80 mg/m^2 day 1 every 3 weeks	Docetaxel 75 mg/m^2 day 1 every 3 weeks	Docetaxel 33.3 mg/m^2 days 1, 8, 15 every 4 weeks	Pemetrexed 500 mg/m^2 day 1 every 3 weeks
Combination arm	Docetaxel 60 mg/m^2 day 8 + gemcitabine 800 mg/m^2 days 1 and 8 every 3 weeks	Gemcitabine 1,000 mg/m^2 days 1 and 8 + irinotecan 300 mg/m^2 day 8 every 3 weeks	Cisplatin 80 mg/m^2 day 8 + irinotecan 110 mg/m^2 day 1, 100 mg/m^2 day 8, every 3 weeks	Docetaxel 60 mg/m^2 day 1 + irinotecan 200 mg/m^2 day 1 every 3 weeks	Docetaxel 30 mg/m^2 days 1, 8, 15 every 4 weeks + gemcitabine 800 mg/m^2 days 1 and 8 every 4 weeks or vinorelbine 20 mg/m^2 days 1 and 8 every 4 weeks or capecitabine 1,300 mg/m^2 days 5 to 18 every 4 weeks	Pemetrexed 500 mg/m^2 day 1 every 3 weeks + carboplatin AUC5 day 1 every 3 weeks
Primary end point	Overall survival	Overall survival	Overall survival	Response rate	Overall survival	Time to progression
Planned sample size	284	144	130	106	375	240
Actual sample size	130	147	139	108	84	240
Start of the accrual	January 2002	September 1999	July 1999	October 2000	May 2005	October 2005
End of the accrual	April 2003	December 2001	November 2002	January 2003	December 2006	May 2007
Median follow-up, weeks	90.4	59.4	91.6	74.3	70.7	64.0
Trial quality (MERGE criteria)	B1	B1	B1	B1	B1	B1
Eligibility criteria						
Age	20-75	≥ 18	≥ 18	≥ 18	18-75	≥ 18
Performance status	ECOG 0-1	WHO 0-2	WHO 0-2	ECOG 0-2	ECOG 0-2	ECOG 0-2
Previous lines of chemotherapy	1	1-2	1-2	1	1	≥ 1
Previous treatment	Platin based	Platin based	Taxane + gemcitabine	Platin- or nonplatin-based	Platin based	Relapse > 3 months after platin based

Abbreviations: AUC5, area under the time concentration curve 5; MERGE, Method for Evaluating Research and Guideline Evidence; ECOG, Eastern Cooperative Oncology Group.
*Defined randomized phase II, sample size was actually calculated according to phase III design, with formal comparison between treatment arms.

Allgemein: 2 Studien der Phase III und 4 Studien der Phase II. 90% der Patienten hatten einen PS von 0 oder 1; 80% der Patienten hatten vorher eine platinbasierte Chemotherapie erhalten. Alle, bis auf eine Studie, Studien testeten eine von der Erstlilientherapie abweichende Therapie.

- Gesamtüberleben: Es zeigten sich keine stat. signifikanten Unterschiede zwischen den Interventionen.
- Ansprechrate: Es zeigte sich ein stat. signifikanter Vorteil unter einer Kombinationschemotherapie (15.1% vs. 7.1%; p=0.0004).
- Progressionsfreies Überleben: Es zeigte sich ein stat. signifikanter Vorteil unter der Kombinationschemotherapie (14 Wochen vs. 11.7 Wochen; p=0.0009; HR: 0.79; 95%KI: 0.68-0.91).
- Nebenwirkungen: Es traten stat. signifikant mehr hämatologische (41% vs. 25%; p<0.0001) und nicht-hämatologische Nebenwirkungen (28% vs. 22%; p=0.034) Grad 3-4 unter der Kombinationschemotherapie auf.

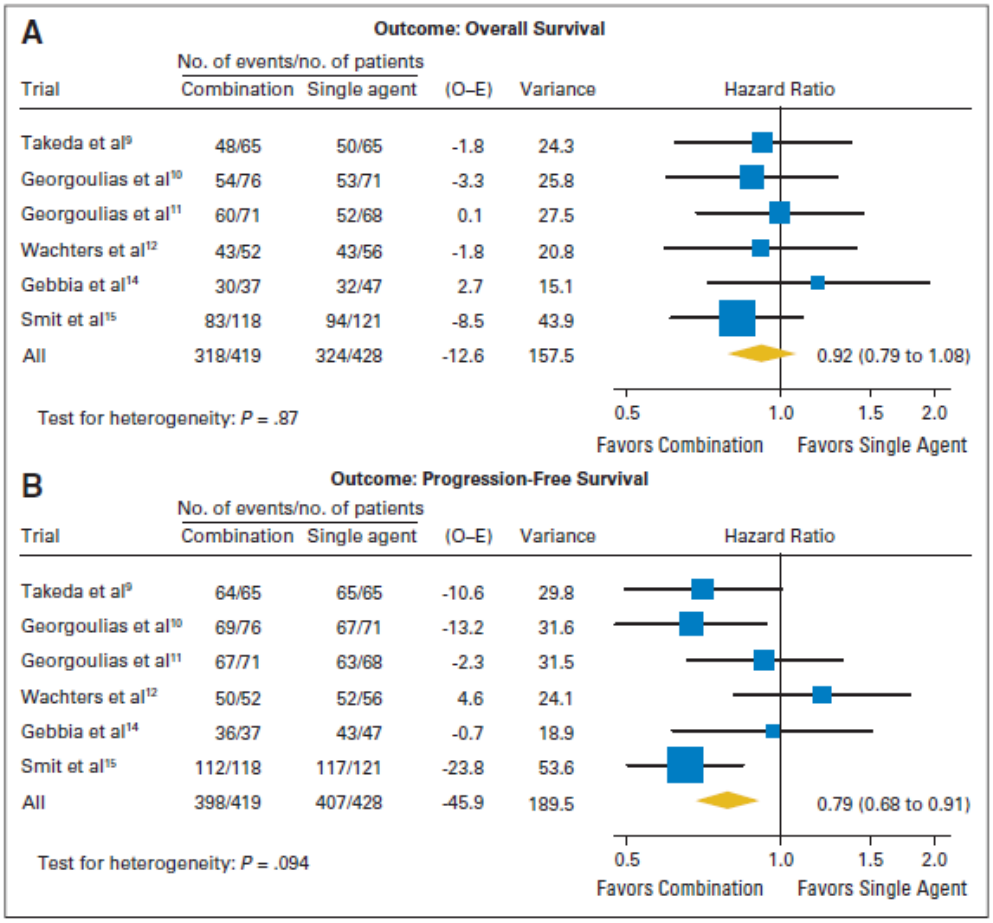


Table 3. Summary of Grade 3-4 Adverse Effects By Treatment

Adverse Effect	No. of Patients With Available Data	Single Agent		Combination		Exact OR	95% CI	*P**	*P* for Homogeneity†
		No.	%	No.	%				
Neutropenia	786	95	24	136	35	2.04	1.38 to 3.04	.0002	.0002
Febrile neutropenia	839	31	7	31	7	1.00	0.57 to 1.76	.99	.032
Anemia	839	9	2	37	9	4.47	2.08 to 10.70	< .0001	.17
Thrombocytopenia	839	7	2	40	10	6.24	2.71 to 16.76	< .0001	.51
Any hematologic	839	106	25	172	41	2.62	1.83 to 3.79	< .0001	.015
Nausea/vomiting	839	12	3	23	6	1.94	0.91 to 4.36	.081	.85
Mucositis	839	2	< 1	1	< 1	0.48	0.01 to 9.31	.62	.99
Diarrhea	839	20	5	42	10	2.28	1.25 to 4.28	.006	.0004
Constipation	839	7	2	3	1	0.42	0.07 to 1.86	.22	.30
Cardiovascular	710	3	1	5	1	1.85	0.35 to 12.04	.49	.66
Pulmonary	700	9	3	10	3	1.15	0.40 to 3.29	.82	.064
Neurological	839	4	1	5	1	1.28	0.27 to 6.50	.75	.67
Liver	839	6	1	6	1	1.01	0.27 to 3.84	.99	.40
Renal	839	—	—	1	< 1	—	—	.48	—
Any nonhematologic	839	92	22	118	28	1.43	1.02 to 2.00	.034	.036

NOTE. Toxicity analysis performed on 839 patients (841 patients received at least one administration of chemotherapy; toxicity data not available in two patients).
Abbreviation: OR, odds ratio.
*Exact text stratified by trial.
†Exact test for homogeneity of ORs.

Fazit der Autoren

'Doublet chemotherapy as second-line treatment of advanced NSCLC significantly increases response rate and progression-free survival, but is more toxic and does not improve overall survival compared to single-agent.'

Hinweis FB Med

- Unterschiede in den Behandlungsschemata

	• no funding information • CoI declared • study quality assessed with standardized method • heterogeneity calculated and reported • publication bias seems unlikely
Ganguli A et al., 2013: The impact of second-line agents on patients' health-related quality of life in the treatment for non-small cell lung cancer: a systematic review [21]	**1. Fragestellung** This review assessed QOL outcomes of approved, guideline- supported 2L chemotherapy with docetaxel, erlotinib, gefitinib, and pemetrexed in advanced NSCLC**.** The purpose of this review is to systematically assess the available literature reporting QOL results in clinical trial studies of guideline-supported 2L chemotherapy with docetaxel, erlotinib, gefitinib, and pemetrexed for the treatment for advanced NSCLC. **2. Methodik** ***Population:*** advanced NSCLC ***Intervention:*** Patients were treated with docetaxel, pemetrexed, erlotinib, or gefitinib; Second-line (2L) ***Komparator:*** Nicht spezifiziert ***Endpunkte*:** quality of life (QOL) ***Suchzeitraum:*** 2000 bis 2010 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 28 (nicht berichtet; Range: 31 – 1692) RCT und CCT nur Studien mit mehr als 20 Patienten, auf QOL wurde im Abstract oder Titel hingewiesen ***Qualitätsbewertung der Studien:*** Checklist for Evaluating QOL Outcomes in Cancer Clinical Trials ***Heterogenitätsuntersuchungen:*** Nicht berichtet **3. Ergebnisdarstellung** • 8 - docetaxel • 4 - erlotinib • 11 - gefitinib and

- 1 – pemetrexed

Table 1 Overview of the key QOL study features

Studies included	*N*	Study type		Population				Agent	QOL instrument
		Trial phase	Design	Age (median)	Male (%)	PS	Stage IV (%)		
Dancey [16]	204	3	AC	62	65	1	NR	D v. BSC	LCSS, EORTC
Fidias [29]	309	3	AC	65	62	0/1	85	D	LCSS
Gebbia [17]	84	3	AC	62	77	0/1	89	D; D/Gem or V; D/C	EORTC
Gridelli [30]	220	3	AC	63	83	1	86	D	EORTC
Krzakowski [31]	551	3	AC-OL	61	75	0	62	D v. V	FACT-L
Lai [32]	50	2	AC	68	76	1	85	D	LCSS
Park [33]	452	3	AC	58	69	0/1	82	D	EORTC
Paz-Ares [34]	849	3	AC	63	72	1	81	D v. P	FACT-L
Bezjak [18]	731	3	PC	62	65	1	NR	E v. Pbo	EORTC
Wheatley-Price [35]	731	3	PC	62	65	1	NR	E v. Pbo	EORTC
Cappuzzo [36]	889	3	PC	60	73	1	74	E v. Pbo	FACT-L
Perez-Soler [37]	57	2	SA	NR	40	1	84	E	EORTC
Cella [38]	216	2	AC	61	59	1	NR	G	FACT-L
Fukuoka [39]	210	2	AC	61	75	1	78	G	FACT-L
Gelibter [40]	57	NR	SA	62	70	1	92	G	EORTC
Kim [19]	1466	3	AC-OL	61	64	1	53	G v. D	FACT-L
Kris [41]	216	2	AC	61	59	1	85	G	FACT-L
Lee [42]	167	3	AC-OL	57	67	1	86	G v. D	FACT-L
Mu [43]	31	NR	SA	64	58	1	84	G	EORTC
Sekine [44]	489	3	AC-OL	NR	62	1	65	G	FACT-L
Takeda [45]	300	3	SA	63	35	1	82	G	FACT-L
Thatcher [46]	1692	3	PC	62	67	1	47	G v. Pbo	FACT-L
Cufer [47]	141	2	OL	63	69	1	60	G v. D	FACT-L
Hanna [12]	571	3	AC	59	69	0/1	75	P v. D	LCSS

AC, active control; *BSC*, best supportive care; *C*, capecitabine; *CT*, clinical trial; *D*, docetaxel; *EORTC*, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; *FACT-L*, Function Assessment of Cancer Therapy-Lung; *Gem*, gemcitabine; *CSS*, Lung Cancer Symptom Scale; *NR*, not reported; *OL*, open-label; *P*, paclitaxel; *PC*, placebo control; *Pbo*, placebo; *PS*, performance status; *QOL*, quality of life; *SA*, single arm; *V*, vinflunine

Table 2 Summary of QOL-related significant results stratified by therapeutic agent

Domain/areas	Docetaxel	Gefitinib	Erlotinib
Overall QOL	T	X	X
Domain specific			
Social functioning		X	
Physical functioning		X	X
Emotional functioning		X	X, T
Role functioning	X	X	
Symptoms			
Pain	X, T	X	X, T
Appetite	X, T	X	
Cough	X, T	X	X, T
Dyspnea	X	X	X, T
Fatigue	X	X	X
Vomiting	X, T		
Sore mouth			X
Constipation			X
Analgesic use	X, T		T
Hair loss	T		T
Hemoptysis	X		
Diarrhea	T		
Trial outcome index		T	

No significant results were found for pemetrexed

QOL, quality of life; *T*, significant effects on time to deterioration; *X*, significant results in QOL score

Table 3 Key findings on overall and domain/symptom QOL outcomes

	Docetaxel	Gefitinib	Erlotinib
Overall QOL	NS reported in 5 studies [16, 29–31, 34]	NS reported in 7 studies [38–42, 46, 47]	
		FACT-L and TOI	
		↑ in FACT-L & TOI was 1.99 and 1.82 times as likely v. D; ($p = 0.0001$ and 0.0026, respectively) [19]	EORTC
		↑ FACT-L & TOI was 1.89 and 2.72 times as likely v. D; ($p = 0.023$, $p = 0.002$, respectively) [44]	↑ v. Pbo ($p = 0.04$) [18]
		↑ in FACT-L/TOI scores (3.7 and 4.3) v. D ($p = 0.022$, 0.001, respectively) [44]	
		EORTC:	
		↑ after 8 weeks ($p = 0.01$), single arm [43]	
Domain or symptomatic QOL	NS reported in 4 studies [16, 30, 31, 34]	NS reported in 7 studies [19, 39–42, 44, 45]	
	Pain	Pain	Pain
	↓ v BSC ($p = 0.005$) [16]	↓ chest, arm, and other ($p = 0.04$, 0.03, 0.02), single arm [43]	↓ v. Pbo $p = 0.006$ [18]
	Appetite	Appetite	↓ in patients < 70 v. Pbo ($p = 0.02$) [35]
	↓ D + V/Gem v. D ($p = 0.05$) [17]	↓ appetite loss ($p = 0.01$), single arm [43]	
	↓ in weekly v. tri-weekly D ($p = 0.03$) [32]	Fatigue	Sore mouth
	Vomiting	↓ ($p < 0.01$), single arm [43]	↑ v. Pbo ($p < 0.0001$) [18]
	↑ w D + V or Gem v. D ($p = 0.05$) [17]	Dyspnea	Dyspnea
	↓ in 4 cycles v. 6 cycles of D ($p < 0.05$) [33]	↓ ($p < 0.01$), single arm [43]	↓ v. Pbo ($p = 0.006$) [18]
	Hemoptysis	Emotional functioning	Diarrhea
	↑ w D + V or Gem v. D ($p = 0.05$) [17]	↑ ($p < 0.01$), single arm [43]	↑ v. Pbo ($p < 0.0001$) [18]
	Use of analgesics	Physical functioning	Constipation
	↑ w D + V or Gem v. D ($p = 0.05$) [17]	↑ ($p = 0.01$), single arm [43]	↓ v. Pbo (0.00) [18]
	Fatigue	Role functioning	Hair loss
	↓ v. BSC ($p = 0.006$) [16]	↑ ($p = 0.03$), single arm [43]	↑ v. Pbo ($p < 0.0001$) [18]
	Role function	Social functioning	Emotional functioning
	↑ in 4 cycles v. 6 cycles of D ($p < 0.05$) [33]	↑ ($p = 0.01$), single arm [43]	↑ v. Pbo ($p = 0.04$) [18]
	Dyspnea	Symptom score	Physical functioning
	↓ in 4 cycles v. 6 cycles of D ($p < 0.05$) [33]	↑ LCS (FACT-L) score v. Pbo ($p = 0.019$) [46]	↑ v. Pbo ($p = 0.006$) [18]
	Sore mouth	Cough	Cough
	↓ in 4 cycles v. 6 cycles of D ($p < 0.05$) [33]	↓ ($p < 0.01$), single arm [43]	↓ v. Pbo ($p = 0.006$) [18]
			↓ in pts < 70 v. Pbo ($p = 0.01$) [35]

Pemetrexed: NS results reported for improvements in average symptom burden index versus docetaxel. No p values reported for anorexia, fatigue, dyspnea, hemoptysis, pain [12, 48]

↑ / ↓ increased/decreased QOL; *BSC*, best supportive care; *D*, docetaxel; *FACT-L*, Functional Assessment of Cancer Therapy-Lung; *Gem*, gemcitabine; *LCS*, lung cancer scale; *NR*, not reported; *NS*, non-significant; *Pbo*, placebo; *QOL*, quality of life; *TOI*, trial outcome index; *Tx*, treatment; *V*, vinorelbine

Table 4 Time to deterioration in QOL

	Docetaxel	Erlotinib
Overall QOL	NS in 3 studies [12, 29, 34]	NS reported in 2 studies [36, 37]
	EORTC	
	Less deterioration in mean QOL today (11.2 v. 27) for D 100 mg/m^2 v. BSC at last available assessment (median time to last assessment NR) [16]	
Domain or symptomatic QOL	Pain	Pain
	Less deterioration in mean pain score v. BSC (2.3 v. 13.6; $p = 0.006$) at last assessment [16]	Median time (months) to deterioration was 2.8 v. 1.9 ($p = 0.03$, full sample; 0.01, pts < 70) v. Pbo [18, 35]
	↓ ($p = 0.04$) in weekly v. 3 weekly therapy at 1 month, NS at last assessment [30]	E treatment and stable disease after prior therapy were associated with ↑ time to deterioration [18]
	Appetite	Time to pain onset (HR 0.61, $p = 0.008$) was sig. ↑ v. Pbo [36]
	↓ at 4 and 8 weeks in D + V or Gem versus D ($p = 0.05$) [17]	Pain was significantly reduced at 2 weeks but returned to baseline levels by study closure [37]
	Vomiting	↓ at 2 wks ($p < 0.05$), ↑ to baseline at last assessment, single arm [37]
	NS at 4 wks, ↑ at 8 weeks ($p = 0.05$) in D + V or Gem versus D [17]	Use of analgesics
	Hemoptysis	Time to analgesic use (HR 0.66, $p = 0.02$) was significantly ↑ v. Pbo [36]
	NS at 4 wks, ↑ at 8 weeks ($p = 0.05$) in D + V or Gem versus D [17]	Cough
	Use of analgesics	Median time (months) to deterioration was 4.9 v. 3.7 ($p = 0.04$) v. Pbo [18]
	NS at 4 wks, ↑ at 8 weeks ($p = 0.05$) in D + V or Gem versus D [17]	E treatment and never having smoked were associated with ↑ time to deterioration [18]
	Hair loss	Median time (months) to deterioration was 7.4 v. 3.2 in pts >70 years v. Pbo ($p = 0.04$) [35]
	↓ hair loss ($p = 0.001$) in weekly v. 3 weekly therapy at 1 month, NS at last assessment [30]	Dyspnea
	Cough	Median time (months) to deterioration dyspnea: 4.7 v. 2.9 ($p = 0.04$) v. Pbo [18]
	↓ cough ($p = 0.007$) in weekly v. 3 weekly therapy at 1 month, NS at last assessment [30]	E treatment, PS 0 or 1 and stable disease after prior therapy were associated with ↑ time to deterioration [18]
	Diarrhea	Median time (months) to deterioration was 4.6 v. 3.1 in pts < 70 ($p = 0.04$) v. Pbo [35]
	↑ ($p = 0.01$) in weekly v. 3 weekly therapy at 1 month, NS at last assessment [30]	Emotional functioning
		↑ at 4 weeks ($p < 0.05$), ↓ to baseline at last assessment, single arm [37]

Gefitinib: Time to worsening of TOI was significantly longer on gefitinib than docetaxel [44]; non-significant results seen in overall QOL, pain, hemoptysis, and hair loss [39–41]

Pemetrexed: Time to deterioration NS v. pemetrexed [48]

↑ / ↓ increased/decreased QOL; *BSC*, best supportive care; *D*, docetaxel; *E*, erlotinib; *FACT-L*, Functional Assessment of Cancer Therapy-Lung; *Gem*, gemcitabine; *HR*, hazard ratio; *NR*, not reported; *NS*, non-significant; *Pbo*, placebo; *PS*, performance status; *Pts*, patients; *QOL*, quality of life; *SS*, statistically significant; *TOI*, trial outcome index; *Tx*, treatment; *V*, vinorelbine; *Wks*, weeks

- Studienqualität sehr heterogen

4. Anmerkungen/Fazit der Autoren

Significant improvements in overall QOL with 2L chemotherapy for advanced NSCLC were infrequent. Single-arm studies and those with less toxic regimens more commonly provided statistically significant improvements in QOL outcomes. Methodological heterogeneity impedes cross-study QOL comparisons.

Gao et al., 2009:

A meta-analysis of platinum plus gemcitabine or vinorelbine in the treatment of advanced non-small-cell

1. Fragestellung

To compare the **gemcitabine plus platinum** with **vinorelbine plus platinum** regimens in first-line treatment of advanced NSCLC.

2. Methodik

Population:
Patients must be pathologically confirmed of NSCLC and in clinical III–IV stage. First-line
Intervention:
gemcitabine plus platinum

lung cancer [22]	***Komparator**:* vinorelbine plus platinum ***Endpunkt**:* ORR, 1-year survival, toxicity ***Methode**:* systematic review and meta-analysis of RCTs ***Suchzeitraum***: 1996 bis 2008 ***Anzahl eingeschlossene Studien/Patienten** :* 9 (n= 2 186) **3. Ergebnisdarstellung** **Survival (9 trials, 2186 patients):** no statistically significant difference In subgroup analysis of seven trials containing gemcitabine or vinorelbine plus cisplatin, the results showed that there was also no statistically significant difference between the two groups **Response (8 trials):** no statistically significant difference **Toxicity (9 trials):** Vinorelbine plus platinum chemotherapy led to more frequent grade 3 or 4 neutropenia, nephrotoxicity, constipation and phlebitis (OR, 0.37; 95%CI, 0.26–0.52; p < 0.00001;OR, 0.38; 95%CI, 0.25–0.57; p < 0.00001;OR, 0.50; 95%CI, 0.27–0.92; p = 0.03 and OR, 0.13; 95%CI, 0.05–0.32; p < 0.00001, respectively), while gemcitabine plus platinum chemotherapy inclined to developing more grade 3 or 4 thrombocytopenia (OR, 11.37; 95%CI, 4.56–28.38; p < 0.00001).

Table 1
Baseline characteristics of the nine trials comparing gemcitabine plus platinum with vinorelbine plus platinum for advanced NSCLC.

First author	Quality scores	Group	*n*	Eligible for evaluation	PS 0-1 (%)	Stage IV (%)	Mean age	Male (%)	CR + PR	1-year OS (%)
Martoni [18]	2	GEM1200 mg/m^2 d1,8 + DDP75 mg/m^2 d1	143	135	100[d]	56.0	63	81.5	36	44
		NVB25 mg/m^2 d1,8 + DDP75 mg/m^2 d1	143	137	100[d]	65.0	62	75.9	44	40
Vokes [19]	2	GEM1250 mg/m^2 d1,8 + DDP80 mg/m^2 d1[a]	62	62	100	0[e]	62	66.0	42	68
		NVB25 mg/m^2 d1,8 + DDP80 mg/m^2 d1[b]	55	55	100	0[e]	58	76.0	38	65
Scagliotti [20]	2	GEM1250 mg/m^2 d1,8 + DDP75 mg/m^2 d1	205	205	95	81.0	63	81.0	62	37
		NVB25 mg/m^2/wk + DDP100 mg/m^2 d1[c]	203	201	92	81.o	63	78.0	61	37
Liu [21]	2	GEM1000 mg/m^2 d1,8 + DDP30 mg/m^2 d1	83	83	100	59.0	59	62.7	36	31
		NVB25 mg/m^2 d1,8 + DDP30 mg/m^2 d1	99	97	100	60.6	56	54.5	41	35
Helbekkmo [22]	2	GEM1000 mg/m^2 d1,8 + CBP4 AUC d1	222	214	71	72.0	67	64.0	–	30
		NVB25 mg/m^2 d1,8 + CBP4 AUC d1	222	218	72	70.0	67	59.0	–	28
Comella [23]	2	GEM1000 mg/m^2 d1,8,15 + DDP100 mg/m^2 d1[c]	70	60	100	60.0	60	90.0	18	40
		NVB30 mg/m^2/wk + DDP120 mg/m^2 d1[c]	68	60	100	56.7	61	93.3	15	34
Thomas [24]	2	GEM1250 mg/m^2 d1,8 + CBP 6AUC d1	51	48	86.3	86.3	60	82.4	10	47
		NVB30 mg/m^2/wk + DDP80 mg/m^2 d1	49	42	87.8	95.9	56	83.7	14	47
Gebbia [25]	2	GEM1400 mg/m^2 d1,8 + DDP100 mg/m^2 d8[c]	138	138	81	54.0	60	78.0	46	20
		NVB25 mg/m^2 d1,8 + DDP100 mg/m^2 d1[c]	140	140	83	53.0	63	76.0	62	24
Ohe [26]	2	GEM1000 mg/m^2 d,1,8 + DDP80 mg/m^2 d1	151	146	100	79.5	61	69.2	44	60
		NVB25 mg/m^2 d,1,8 + DDP80 mg/m^2 d1	150	145	100	82.1	61	69.7	48	48

PS: Zubrod-ECOG-WHO; 1y OS: 1-year survival; DDP: cisplatin; CBP: carboplatin; CR: complete response; PR: partial response.
[a] Gemcitabine 1250 mg/m^2 on days 1, 8, 22, and 29 and 600 mg/m^2 on days 43, 50, 64, and 71.
[b] Vinorelbine 25 mg/m^2 on days 1, 8, 15, 22, and 29 and 15 mg/m^2 on days 43, 50, 64, and 71.
[c] Twenty-eight days every cycle, the rest 21 days every cycle.
[d] Karnofsky ≥ 70.
[e] Stage III = 100%.

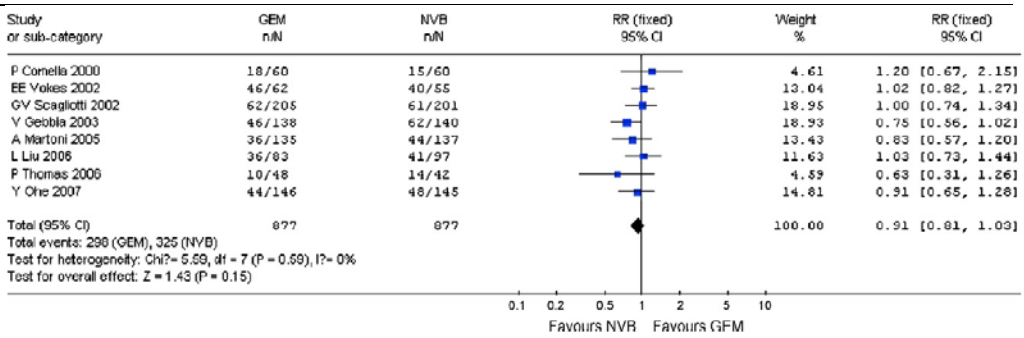


Fig. 2. The overall response rate analysis of platinum plus gemcitabine or vinorelbine for advanced NSCLC.

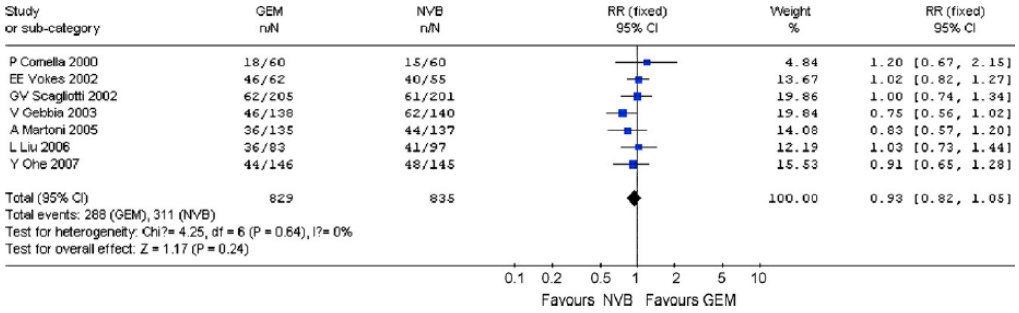


Fig. 3. The sub-analysis of overall response rate of cisplatin plus gemcitabine or vinorelbine for advanced NSCLC.

4. Anmerkungen/Fazit der Autoren

These meta-analyses showed that there was no significant difference between platinum plus gemcitabine or vinorelbine. And the similar results were found in sub-analysis in which gemcitabine and vinorelbine was compared when in combination with cisplatin.

Gemcitabine plus platinum chemotherapy had an equal overall response rate and survival advantage in comparison with vinorelbine plus platinum regimens and the toxicity profiles might play an important role in the decision to choose gemcitabine-based regimens or vinorelbine-based regimens. In conclusion, the gemcitabine plus platinum regimens may be the better choice for the patients whose thrombocytopenia could be taken care, especially for the elder or the people with poor conditions, on the other hand, the vinorelbine plus platinum regimens should be more suitable for the patients who would be apt to bleed or be supersensitive to TPO or IL-11.

Gao H et al., 2011:

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

1. Fragestellung

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

2. Methodik

Population:
advanced NSCLC
Intervention:
erlotinib alone or based combination therapy

analysis of randomized trials [24]

Komparator:
other agent or based combination regimen
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)

3. Ergebnisdarstellung

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

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

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

First-line therapy (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. **4. Anmerkungen/Fazit der Autoren** Our findings demonstrate that erlotinib-based regimens significantly increase ORR and improve PFS as a first-line maintenance therapy or as a second/third-line therapy compared with placebo. Thus, the use of erlotinib may be a new effective therapy in treating advanced NSCLC as first-line maintenance therapy or second/third-line therapy compared with best supportive care.
Gao G et al, 2011: Epidermal	**1. Fragestellung** Gefiinib and erlotinib are two similar small molecules of selective and reversible epidermal growth factor receptor-tyrosine

growth factor receptor-tyrosine kinase inhibitor therapy is effective as first-line treatment of advanced non-small-cell lung cancer with mutated EGFR: a meta-analysis from six phase III randomized controlled trials [23]	kinase inhibitors (EGFR-TKIs), which have been approved for second-line or third-line indication in previously treated advanced Non-small-cell lung cancer (NSCLC) patients. The results of comparing the EGFR-TKI with standard platinum-based doublet chemotherapy as the first-line treatment in advanced NSCLC patients with activated EGFR mutation were still controversial. Ameta-analysis was performed to derive a more precise estimation of these regimens. **2. Methodik** ***Population***: patients >18 years, pathologically proven NSCLC with EGFR mutation-positive, clinical IIIB‑IV stage, previously untreated ***Intervention***: EGFR-TKI, first-line ***Komparator***: platinum-based doublet chemotherapy ***Endpunkt***: PFS, OS, ORR ***Methode***: systematic review mit RCTs ***Suchzeitraum***: 1966 bis 06/2011 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 6 (1021) ***Qualitätsbewertung der Primärstudien*:** All included studies, regardless of whether they were published or not, were assessed for internal validity parameters, with particular emphasis on randomization, masking of patients and clinicians, concealment of allocation, documentation of dropouts and withdrawals and intent-to-treat (ITT) analysis ***Heterogenitätsuntersuchung*** Ist erfolgt (I^2) **3. Ergebnisdarstellung**

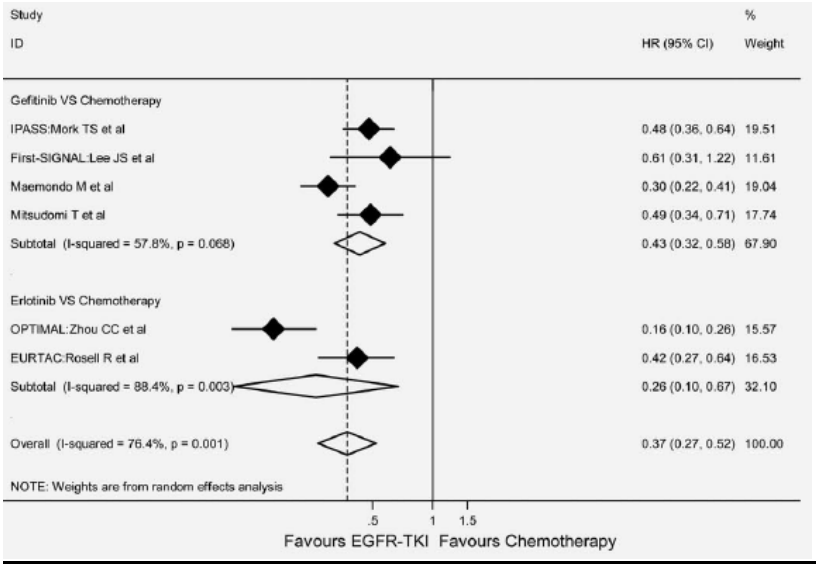
Table 1. Baseline characteristics of the 6 trials comparing Epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) with Chemotherapy for patients with previously untreated NSCLC with mutated EGFR

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

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

PFS

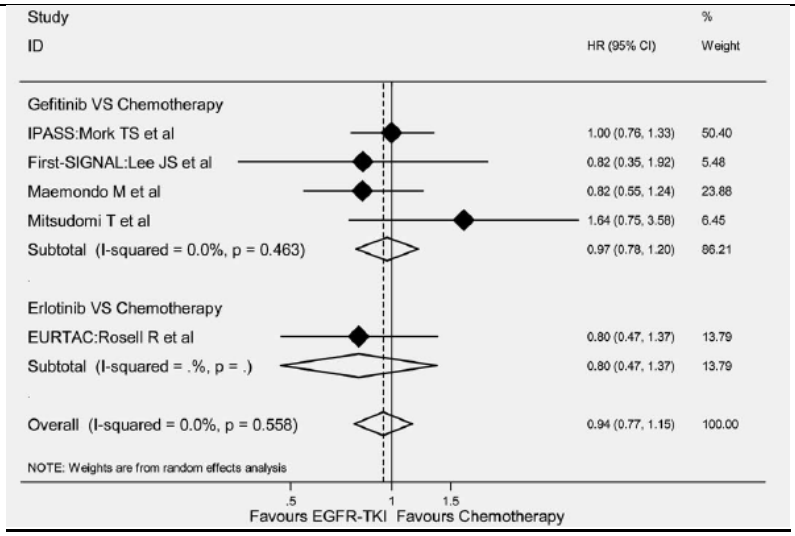
The patients receiving EGFR-TKI as front-line therapy had a significantly longer progression-free survival (PFS) than patients treated with chemotherapy [median PFS was 9.5 versus 5.9 months; hazard ratio (HR) 5 0.37; 95% confidence intervals (CI) 5 0.27–0.52; p < 0.001].



Meta-analysis of PFS among patients receiving EGFR-TKI or Chemotherapy. The pooled HR showed that EGFR-TKI could prolong PFS in patients with previously untreated NSCLC with mutated EGFR (p < 0.001). Subgroup-analysis and sensitivity analysis of Gefitinib vs. Chemotherapy and Erlotinib vs. Chemotherapy also revealed the same conclusion (p < 0.001 and p = 0.005, respectively).

OS

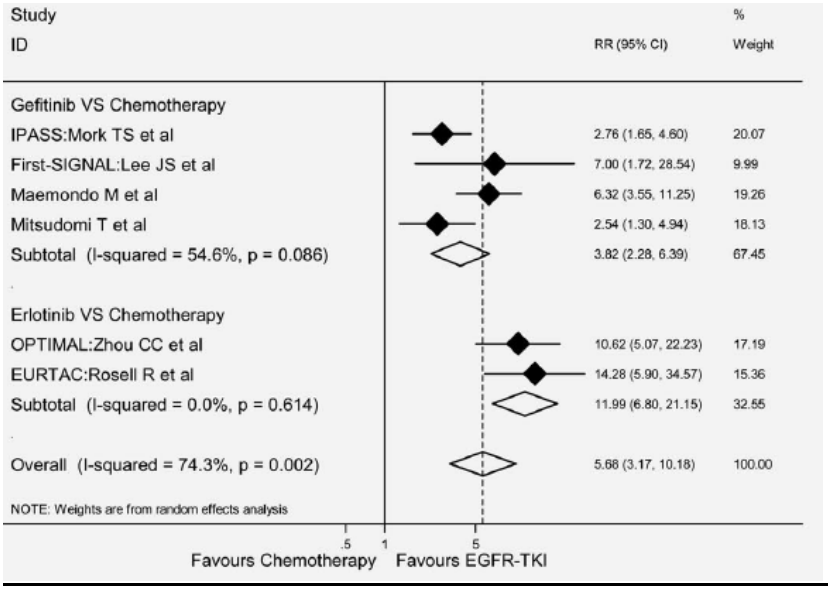
The overall survival (OS) was numerically longer in the patients received EGFR-TKI than patients treated by chemotherapy, although the difference did not reach a statistical significance (median OS was 30.5 vs. 23.6 months; HR= 0.94; 95% CI 5 0.77–1.15; p= 0.57).



Meta-analysis of overall survival (OS) among patients receiving EGFR-TKI or chemotherapy. The pooled HR for OS failed to display a difference between EGFR-TKI and chemotherapy in patients with previously untreated NSCLC with mutated EGFR (p ¼ 0.57). Subgroupanalysis and sensitivity analysis of Gefitinib vs. Chemotherapy also revealed the same conclusion (p = 0.78).

ORR

The overall response rate (ORR) of EGFR-TKI was 66.60%, whereas the ORR of chemotherapy regimen was 30.62%, which was also a statistically significant favor for EGFR-TKI [relative risk (RR) = 5.68; 95% CI = 3.17–10.18; p < 0.001].



Meta-analysis of ORR among patients receiving EGFR-TKI or chemotherapy. The pooled HR showed that EGFR-TKI could prolong ORR in patients with previously untreated NSCLC with mutated EGFR (p < 0.001). Subgroup-analysis and sensitivity analysis of gefitinib vs. chemotherapy and erlotinib vs. chemotherapy also revealed the same conclusion (p < 0.001 and p < 0.001, respectively)

4. Anmerkungen/Fazit der Autoren

Comparing with first-line chemotherapy, treatment of EGFR-TKI achieved a statistical significantly longer PFS, higher ORR and numerically longer OS in the advanced NSCLC patients harboring

	activated EGFR mutations, thus, it should be the first choice in the previously untreated NSCLC patients with activated EGFR mutation. **Limitation**: Nebenwirkungsprofile nicht untersucht
Goffin J et al., 2010: First-line systemic chemotherapy in the treatment of advanced non-small cell lung cancer: a systematic review [29]	**5. Fragestellung** Evidence for first-line treatment in NSCLC **6. Methodik** **Population**: patients with IIIB or IV NSCLC **Intervention**: chemotherapy (mono and doublet, platinum and non-platinum). First-line **Komparator**: k.A. **Endpunkt**: OS, QoL, ORR, toxicity **Methode**: systematic review of evidence based guidelines, systematic reviews and RCTs **Suchzeitraum**: up to 2007 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 2 evidence based guidelinies, 10 systematic reviews, 46 RCTs **7. Ergebnisdarstellung** <u>Does Doublet Chemotherapy Consisting of a Platinum Agent Plus a New Agent Improve Outcomes Compared with Doublets Using Older Agents?</u> Meta-analysis by Baggstrom et al. considered third generation, platinum-based regimens compared with second generation, platinum-based regimens. In a subgroup analysis of six trials (n = 1998) examining only doublet regimens, a 1 -year survival rate risk difference of 6% (95% confidence interval [CI], 2 to 10%) was found in favor of doublet chemotherapy regimens containing platinum and a new agent. Toxicity data were not examined. Five additional trials not included in the meta-analysis of Baggstrom et al. compared new doublet therapies with older regimens. Only one trial, comparing docetaxel plus cisplatin with vindesine plus cisplatin found superior survival with a newer agent. This trial also found superior QOL in the physical domain for the docetaxel-containing arm. <u>Does Doublet Chemotherapy Consisting of a Platinum Agent Plus a New Agent Improve Outcomes Compared with a New Single Agent Alone or to a Platinum Agent Alone?</u> A literature-based meta-analysis of randomized trials by Hotta et al. compared a doublet of platinum plus a new agent with a new agent alone in

	previously untreated patients with ECOG performance status of 0-2. Included were eight trials involving 2374 patients. Platinum-based doublets improved survival (HR, 0.87; 95% CI, 0.80- 0.94; p < 0.001) and produced a higher response rate (odds ratio [OR]. 2.32: 95% Cl. 1.68 -3.20) compared with new single-agent therapy. Platinum-based regimens increased myelosuppression, nephrotoxicity and nausea and vomiting but not treatment-related mortality. Which Doublet Chemotherapy Regimen Consisting of a Platinum Agent Plus a New Agent is most Effective in Improving Clinical Outcomes? Le Chevalier el al. tested the efficacy of gemcitabine plus platinum combinations versus any other platinum-based regimen and survival outcomes. A subgroup analysis of six trials (n = 2481) with a platinum-based third-generation comparator found a trend toward superior survival with gemcitabine-based regimens and improved progression-free survival (HR, 0.89: 95% CI, 0.82-0.96; p value not reported). However, the gemcitabine arms of two studies were counted more than once in the meta-analysis to allow comparison with more than one non-gemcitabine arm, and without weighting. Toxicity was not compared. The second meta-analysis, by Douillard et al. included seven trials (n = 3271) that compared docetaxel containing regimens with vinca-alkaloid regimens. The comparison for overall survival favored docetaxel (HR, 0.89; 95% Cl, 0.82-0.96; p = 0.004), as did the subgroup analysis of three trials (n = 1762) comparing platinum-based docetaxel doublets (HR, 0.87; 95% CI, 0.79-0.96; p value not reported). Does Doublet Chemotherapy Consisting of a Platinum Agent Plus a New Agent Improve Outcomes Compared with Non-platinum Combination Chemotherapy Including a New Agent? A meta-analysis of II phase III RCTs by Pujol et al. assessed 4602 patients treated with a platinum-based new doublet or a combination of new non-platinum agents. Platinum-based regimens had a 2.9% absolute reduction in the risk of death at 1 year (OR, 0.88; 95% CI, 0.78-0.99; p = 0.044). Although the data were statistically heterogeneous, response rates appeared higher with platinum combinations. Toxicity was also more severe with platinum combinations, with significantly worse myelosuppression and gastrointestinal toxicity and trends to worse rates of febrile neutropenia and toxic death. The meta-analysis of D'Addario et al., which included 14 trials (n = 3307), did not find a survival benefit with platinum-based agents over non-platinum chemotherapy regimens (OR, 1.11; 95% Cl, 0.0.96-1.28; p = 0.17). Compared with the meta-analysis by Pujol et al., the meta-analysis by D' Addaria et al. included trials conducted as early as 1983 (whereas Pujol et al. included trials published in 2002 and onward), included phase II studies, and included platinum combinations using three drugs. There is little trial overlap between the meta-analyses (ie, four trials). The meta-analysis by

	Pujol et al. is more representative of new agents. Are New Doublets Containing Cisplatin more Effective than Doublets Containing Carboplatin? The meta-analysis by Jiang et al. showed higher overall response rates with cisplatin-based regimens in two subgroup analyses; platinum plus new drugs (eight trials) and platinum plus the same drug (nine trials) (relative risk [RR], 0.87; 95% CI, 0.78-0.97; p = 0.01 and RR, 0.79; 95% CI, 0.70-0.89; p = 0.0001, respectively). However, these findings did not translate into significant improvements in 1-year survival among the regimens containing any new agent (n = 4364, seven trials) (RR, 0.98; 95% CI, 0.90-1.07; p = 0.66) or the same agent (n = 3752, six trials) (RR, 0.91; 95% CI, 0.82-1.01; p = 0.07). Two other meta-analyses limited inclusion to trials that combined the same non-platinum agent in the cisplatin and carboplatin arms but used different analytic methods. In a subgroup analysis of five trials (n = 2251), Hotta el al. showed that new platinum-based combination regimens containing cisplatin offered superior survival compared with carboplatin plus the same new agent (HR. 1.106: 1 95% CI. 1.005-1.218; p = 0.039). The objective response rate to cisplatin-based regimens was significantly higher than that of carboplatin-based chemotherapy (OR. 1.38: 95% CI. 1.14-1.67: p = 0.001), in the same subgroup of trials but using individual patient data. Is a Single New Agent Superior to Single-Agent or Doublet Therapy Including Older Agents? The 2007 meta-analysis by Baggstrom et al. considered four trials (n = 871) that compared new monotherapy with a second-generation, platinum-based combination regimen. The single agents used were vinorelbine, gemcitabine, and irinotecan, whereas the control arms consisted of cisplatin plus either vindesine or etoposide. Despite an apparent decrease in response rates with new single agents (absolute risk difference estimate for response -6%, 95% CI -11 to 0%), 1-year survival did not differ (risk difference 3%, 95% CI -3 to 10%). Which Single New Agent is Most Effective? Three RCTs, all focused on patients 70 years or older, compared new single-agent chemotherapies. The agents investigated included gemcitabine, vinorelbine, paclitaxel, and docetaxel. No study found a significant survival benefit. Kudoh et al. reported improved response rate with docetaxel over vinorelbine (22.7 versus 9.9, p = 0.019) and an improvement in the overall symptom score (but not global QOL score) in favor of docetaxel. Gridelli et al. found no differences in QOL scores. ln general, toxicity was similar between study arms, apart from alopecia. **8. Anmerkungen/Fazit der Autoren** Despite the plethora of new drug combinations studied, data continue to support the use of a platinum agent plus a new agent as the reference

	standard. This combination seems to have a slight survival advantage over pairs of new agents, although at a cost of additional toxicity. Among new platinum doublets, no particular combination seems to have demonstrated satisfactory or consistent superiority and any may be chosen. There does seem to be a slight response and survival advantage to cisplatin combinations over carboplatin combinations, although the toxicity profile favors the latter. Both conventional cytotoxic agents and EGFR TKl's have been added to doublet chemotherapy, but neither has improved survival. Conversely, in a population carefully chosen to optimize safety, the addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor, may improve survival. Although it is reasonable to use Bevacizumab in combination with paclitaxel and carboplatin in the trial specified population (ie, good performance status [ECOG 0-1], no brain metastasis, no dominant squamous cell histology or hemoptysis, and no history of bleeding diathesis or coagulopathy), data are presently insufficient to recommend that Bevacizumab be used in the general treatment of incurable NSCLC, based on the Iack of a confirmatory trial, the toxicity of the treatment, and its cost. The evidence demonstrates that a new single agent improves survival compared with BSC, although not by more than a median of 2 months. When the use of a platinum agent plus a new agent is considered standard, the use of a single agent may be considered for some patients, including patients aged 70 years or older, patients who have a performance status of two, or patients for whom platinum therapy might be contraindicated. Single new agents also seem comparable in terms of survival with older combinations of a platinum and nonplatinum agent, although they also offer better outcomes when they are combined with a platinum agent. Combinations of new agents are not consistently superior to single agents, although these trials are relatively few and limited to the elderly and poor performance status population.
Grossi et al., 2009: Impact of third-generation drugs on the activity of first-line chemotherapy in advanced non-small cell lung cancer: a meta-analytical approach [30]	**1. Fragestellung** To assess the relative impact of different **third-generation drugs** on the activity of first-line chemotherapy in advanced non-small cell lung cancer by considering both response and progressive disease (PD) rates as outcome measures. **2. Methodik** **Population**: pathologically proven advanced NSCLC, no previous treatment for metastatic disease **Intervention**: two-drug regimen containing at least one third-generation agent. Platinum (defined as cisplatin or carboplatin) and nonplatinum combinations were allowed. Third-generation drugs were defined as gemcitabine,

	vinorelbine, docetaxel, and paclitaxel. **Komparator**: Doublet regimen free of a third generation agent **Endpunkt**: Response rate, disease progression **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: 1980 bis 2007 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 45 (n= k.A.) **Qualitätsbewertung der eingeschlossenen Studien:** k.A. **3. Ergebnisdarstellung** **Overall response** (45 trials, 11.231 patients): no statistically significant difference for gemcitabine-, docetaxel-, vinorelbine-, or paclitaxel-containing arms with the corresponding control groups **Disease progression** • Gemcitabine (23 trials, 6.681 patients): statistically significant difference in favor of gemcitabine (OR 0.86, 95% CI, 0.77– 0.95; p=0.005) • Paclitaxel (16 trials, 5.536 patients): statistically significant difference in favor of paclitaxel-free regimens (OR, 1.22; 95% CI, 1.09 –1.37; p=0.0008) • Docetaxel (12 trials, 4.642 patients): no statistically significant difference • Vinorelbine (23 trials, 6.048 patients): no statistically significant difference **4. Anmerkungen/Fazit der Autoren** Different third-generation regimens provide comparable response rates in chemotherapy-naïve patients with advanced NSCLC. Paclitaxel-based third-generation regimens are associated with a significantly higher risk for immediate progression, whereas gemcitabine-containing regimens may provide superior disease control. Given the impact of first-line chemotherapy on the natural history of the disease, the influence of disease control on treatment-free survival, and the recent evidence of a strong correlation between nonprogression and OS, these data should be considered when new studies are designed comparing standard with innovative regimens or combining them with novel compounds. In view of the results of a cisplatin versus carboplatin meta-analysis, one could object that the apparent superiority of gemcitabine over paclitaxel might be a result of the usual association of the two agents with cisplatin versus carboplatin, respectively.

Haaland B, 2014: Meta-analysis of first-line therapies in advanced non-small-cell lung cancer harboring EGFR-activating mutations [31]	**1. Fragestellung** This meta-analysis compares gefitinib, erlotinib, afatinib, and chemotherapy. **2. Methodik** ***Population:*** advanced non–small-cell lung cancer ***Intervention:*** gefitinib, erlotinib, or afatinib; first-line therapy ***Komparator:*** chemotherapy ***Endpunkte*:** PFS, ORR,OS, AEs ***Suchzeitraum:*** “last five years” (nicht spezifiziert) ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 11 (Gesamtzahl k.A.; Range [42; 251]) Nur: randomized phase 3 clinical trials ***Qualitätsbewertung der Studien:*** *k.A.* ***Heterogenitätsuntersuchungen:*** I^2 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.

PFS

Hazard ratio meta-estimates

- gefitinib versus chemotherapy 0.44 (95% confidence interval [CI] 0.31–0.63; 95% PI, 0.22–0.88),
- erlotinib versus chemotherapy 0.25 (95% CI, 0.15–0.42; 95% PI, 0.11–0.55),
- afatinib versus chemotherapy 0.44 (95% CI, 0.26–0.75; 95% PI, 0.20–0.98),
- erlotinib versus gefitinib 0.57 (95% CI, 0.30–1.08; 95% PI, 0.24–1.36),
- afatinib versus gefitinib 1.01 (95% CI, 0.53–1.92; 95% PI, 0.41–2.42),
- erlotinib versus afatinib 0.56 (95% CI, 0.27–1.18; 95% PI, 0.22–1.46).

Results for overall response rate and disease control rate were similar.

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.

There was no evidence that gefitinib, erlotinib, or afatinib improved overall survival compared with chemotherapy.

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.
Ibrahim EM, 2010: Frontline gefitinib in advanced non-small cell lung cancer: Meta-analysis of published randomized trials [33]	**1. Fragestellung** The inconsistent results and the lack published meta-analysis that systematically examined the overall efficacy of **gefitinib** in the frontline setting in patients with advanced non-small cell lung cancer (NSCLC), have prompted the current meta-analysis. **2. Methodik** **Population**: Chemotherapy naïve patients with locally advanced or metastatic **Intervention**: gefitinib-based therapy (GBT) **Komparator**: placebo or none after initial chemoradiation or chemotherapy induction **Endpunkt**: OS, PFS, ORR, QoL **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: k.A. **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 7 (n=4585) **3. Ergebnisdarstellung** 4 trials compared gefitinib plus chemotherapy vs. chemotherapy alone, 2 trials compared gefitinib alone vs. chemotherapy, 1 trial compared gefitinib plus best supportive care (BSC) vs. BSC alone **Overall survival**: no statistically significant difference. Statistically significant OS survival for GBT was not demonstrated regardless of tumor histology (adenocarcinoma vs. non-adenocarcinoma), or EGFR mutation status **PFS:** no statistically significant difference between GBT and control regardless of trials designs (HR = 0.97, 95% CI: 0.78–1.20, p = 0.78), neither was any PFS advantage was found among patients with mutant or wild EGFR. **Response rate**: no statistically significant difference Quality of life (3 trials): statistically significant difference in favor of GBT. FACT-L questionnaire (OR = 1.38; 95% CI: 1.06‑1.79; p = 0.02), TOI questionnaire (OR = 1.87; 95% CI: 1.13‑3.09; p = 0.02). Rates of reduction in symptoms, as assessed on the basis of the LCS scores, were similar in patients who received GBT and those randomized to the control groups (OR = 1.14; 95% CI: 0.92‑1.42; p = 0.24).

	4. Anmerkungen/Fazit der Autoren GBT cannot be recommended for the management of patients with advanced NSCLC in the first-line setting as compared with other standard interventions in unselected patient population. The significant improvement in QOL shown with GFT would be offset by the involved cost and the potential side effects known to be associated with the use of gefitinib. **5. Hinweise durch FB Med** • Keine Beschreibung zur Evaluation der Qualität der eingeschlossenen Studien • Keine Angabe zum Suchzeitraum. Keine doppelte Datenextraktion
Jiang J et al., 2013: Paclitaxel plus platinum or gemcitabine plus platinum in first-line treatment of advanced non-small-cell lung cancer: results from 6 randomized controlled trials [39]	**1. Fragestellung** to compare the efficacy and toxicity of **paclitaxel plus platinum** (TP) with **gemcitabine plus platinum** (GP) in untreated advanced non-small-cell lung cancer by a meta-analysis. **2. Methodik** **Population**: patients must be cytologically or pathologically confirmed of NSCLC and in clinical III–IV stage, patients must be chemotherapy-naive **Intervention**: paclitaxel plus platinum (TP) **Komparator**: gemcitabine plus platinum (GP) **Endpunkt**: efficacy, toxicity **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: bis 2010 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 6 (n=2.793) **3. Ergebnisdarstellung** **1-Jahres-Überleben (6 trials):** no statistically significant difference (RR = 0.99, 95% CI = 0.90–1.09, p = 0.87; I^2=6%) **Gesamtüberleben (6 trials)**: no statistically significant difference (RR = 1.06, 95% CI = 1.00–1.13, p = 0.07; I^2=16%) **Response (6 trials)**: no statistically significant difference (RR = 0.99, 95 % CI = 0.88–1.13, p = 0.92, I^2=9%) **Toxicity:** Grade 3–4 nausea or vomiting was less frequent in the TP than the GP group (10.5 vs. 17.4 %, RR = 0.53, 95 % CI = 0.35–0.78, p = 0.002). Grade 3–4 sensory neuropathy and fatigue were comparable between the TP and GP arms. Grade 3–4 anemia (8.8 vs. 22.4 %, RR = 0.37, 95 % CI = 0.30–0.45, p<0.00001) and thrombocytopenia (8.8 vs. 47.8 %, RR = 0.20, 95 % CI = 0.14–0.27, p<0.00001) were less frequent in the TP than the GP group. **4. Anmerkungen/Fazit der Autoren** As there were no double-blind trials, the highest quality scores of the 6 trials according to Jadad's method were 3, and all 6 trials scored 3

	Paclitaxel plus platinum had similar efficacy and less toxicity compared with gemcitabine plus platinum in first-line treatment of advanced non-small-cell lung cancer.
Jiang J et al., 2011: Gefitinib versus Docetaxel in previously treated advanced non-small-cell lung cancer: a meta-analysis of randomized controlled trials [37]	**Methodik:** Systematische Literaturrecherche im Jahr 2009 nach RCTs. **Population:** Patienten mit einem NSCLC (Stadium IIIB oder IV), die mindestens ein vorheriges Chemotherapie-Regime erhalten haben, positiver Marker für EGFR-Mutation kein Einschlusskriterium **Vergleich:** Gefitinib vs. Docetaxel **Endpunkte:** OS, PFS, ORR, Lebensqualität und Symptomverbesserung, Nebenwirkungen Es wurden insgesamt 4 Studien mit 2 257 Patienten eingeschlossen. **Ergebnisse:** • OS, PFS: keine statistisch signifikanten Unterschiede; keiner statistische Heterogenität • ORR: statistisch signifikanter Vorteil unter Gefitinib gegenüber Docetaxel (RR: 1.58; 95%KI: 1.02-2.45, p = 0.04), bei signifikanter Heterogenität • Lebensqualität und Symptomverbesserung: statistisch signifikanter Vorteil unter Gefinitib hinsichtlich dem FACT-L und dem TOI Fragebogen (RR: 1.55; 95%KI: 1.27-1.88; p = 0.00 / RR: 1.86; 95%KI: 1.43-2.42; p = 0.00), kein Unterschied hinsichtlich einer Verbesserung der Symptomatik • Nebenwirkungen: Stat. signifikant mehr Risiko hinsichtlich Grad 3/4 Neutropenien und Fatigue unter Docetaxel, verglichen mit Gefinitib (OR: 0.02; 95%KI: 0.01-0.03; p=0.00 / OR: 0.47; 95%KI: 0.32-0.70; p=0.00). Gegensätzlich zeigte sich ein stat. signifikanter Nachteil unter Gefitinib gegenüber Docetaxel hinsichtlich Grad 3/4 Hautausschlägen (OR: 2.87; 95%KI: 1.24-6.63; p=0.01). Grad 3/4 Erbrechen, Übelkeit und Durchfälle waren vergleichbar zwischen den Gruppen. Fazit der Autoren*: 'Although similar OS and PFS, gefitinib showed an advantage over docetaxel in terms of objective response rate, QoL and tolerability. Therefore, gefitinib is an important and valid treatment option for previously treated advanced non-small-cell lung cancer patients.'* Hinweise FB Med: • Notwendigkeit der EGFR-Mutation nicht diskutiert • Ergebnisse nicht nach Erst- oder Zweitlinientherapie unterschieden • Acknowledgements: analysis supported by a grant from the scientific research foundation of Huashan Hospital Fudan University • all authors indicated no potential conflicts of interest • heterogeneity calculated and reported • publication bias was not found
Jiang J et al., 2013: Non-platinum doublets were	**1. Fragestellung** The aim was to compare the efficacy between doublets of third-generation agents (non-platinum) and doublets of platinum plus a third-generation agent (platinum-based) for chemotherapy-naı¨ve advanced

as effective as platinum-based doublets for chemotherapy-naive advanced non-small-cell lung cancer in the era of third-generation agents [38]	non-smallcell lung cancer (NSCLC). **2. Methodik** ***Population:*** • cytologically or pathologically confirmed of NSCLC and in clinical III–IV stage and • chemotherapy-naı¨ve ***Intervention:*** non-platinum doublets (two-thirdgeneration agents combination) ***Komparator:*** platinum-based doublets (cisplatin or carboplatin combined with a thirdgeneration agent) ***Endpunkte*:** Primär: OS, sekundär; PFS, RR; toxicity ***Suchzeitraum:*** 2000 bis 2010 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 16 (Gesamtzahl k.A.) ***Qualitätsbewertung der Studien:*** assessed with the components recommended by the Cochrane Collaboration ***Heterogenitätsuntersuchungen:*** Cochran Q statistic Kein Hinweis auf Publikationsbias (Begg's funnel plot) **3. Ergebnisdarstellung**

Table 1 The characteristics of the 16 studies included in the meta-analysis

Study	Regimens	ITT(n)	E(n)	Male (%)	PS0-1 (%)	Median age	SCC (%)	Stage IV (%)	MST (95 % CI) (m)
VG regimens versus platinum-based regimens subgroup									
Gridelli et al. (2003)	V 30 mg/m^2 d1,8 + DDP 80 mg/m^2 d1 or G 1,200 mg/m^2 d1,8 + DDP 80 mg/m^2 d1	252	250	81	87	62	34	80.0	8.9 (8.2–10.5)
	G 1,000 mg/m^2 d1,8 + V 25 mg/m^2 d1,8	251	251	78	87	61	35	81.0	7.5 (7.0–9.1)
Lilenbaum et al. (2005)	T 200 mg/m^2 d1 + CBP AUC 6 d1	83	83	51	84	63	–	81.0	8.6 (7.0–10.6)
	V 25 mg/m^2 d1,8 + G 1,000 mg/m^2 d1,8	82	82	62	87	66	–	82.0	7.8 (5.7–12.03)
Tan et al. (2005)	V 30 mg/m^2 d1,8 + CBP AUC 5 d1	159	139	77.4	99.3[e]	60	34	–	8.6
	V 25 mg/m^2 d1,8 + G 1,000 mg/m^2 d1,8	157	140	73.2	100[e]	59	31.8	–	11.5
Yamamoto et al. (2006)	G 1,000 mg/m^2 d1,8 + CBP AUC 5 d1	64	64	67.2	100	60	32.8	75.0	14.4
	G 1,000 mg/m^2 d1,8 + V 25 mg/m^2 d1,8	64	64	65.6	100	62	25	75.0	12.8
VT regimens versus platinum-based regimens subgroup									
Stathopoulos et al. (2004)	T 175 mg/m^2 d1 + CBP AUC 6 d1	185	185	86.5	80	65	36.8	55.1	11 (10–12)
	T 135 mg/m^2 d1 + V 25 mg/m^2 d1[a]	175	175	86.9	82.9	65	30.9	53.1	10 (8–11)
Jahnke et al. (2011)	T 175 mg/m^2 d1 + CBP AUC 5 d1	16	11	43.7	81.2[e]	58.5	25	91.8	9 (5.8–12.2)
	T 175 mg/m^2 d1 + V 20 mg/m^2 d1,8	15	9	46.6	93.2[e]	62	13.3	87.5	12 (2.1–21.9)
	T 100 mg/m^2 d1,8,15 + CBP AUC 5 d1[b]	15	13	86.6	86.6[e]	56	0	100	4 (2.1–5.9)
	T 100 mg/m^2 d1,8,15 + V 15 mg/m^2 d1,8,15[b]	15	8	66.7	100[e]	59	13.3	86.6	5 (1.5–8.5)
GT regimens versus platinum-based regimens subgroup									
Kosmidis et al. (2002)	T 200 mg/m^2 d1 + CBP AUC 6 d1	252	238	87	86	63	31	62	10.4 (8.8–12)
	G 1,000 mg/m^2 d1,8 + T 200 mg/m^2 d1	257	241	88	88	62	40	61	9.8 (8.0–11.7)
Smit et al. (2003)	T 175 mg/m^2 d1 + DDP 80 mg/m^2 d1	159	159	59.7	88	57	18.9	81.8	8.1 (6.2–9.9)
	G 1,250 mg/m^2 d1,8 +DDP 80 mg/m^2 d1	160	160	70.6	88.8	57	25.6	78.8	8.9 (7.8–10.5)
	G 1,250 mg/m^2 d1,8 + T 175 mg/m^2 d1	161	161	68.3	88.2	56	21.7	82.0	6.7 (5.9–7.6)
Kosmidis et al. (2008)	G 1,000 mg/m^2 d1,8 + CBP AUC 6 d1	227	189	81	100	63	29.5	86	10.5
	G 1,000 mg/m^2 d1,8 + T 200 mg/m^2 d1	225	183	86	100	63	26	87	10.0
Treat et al. (2010)	G 1,000 mg/m^2 d1,8 + CBP AUC 5.5 d1	379	379	58.3	99.5	64.1	17.7	90.0	7.9 (7.1–9.2)
	T 225 mg/m^2 d1 + CBP AUC 6 d1	379	379	60.9	98.9	64.1	19.6	89.4	8.7 (7.7–9.9)
	G 1000 mg/m^2 d1,8 + T 200 mg/m^2 d1	377	377	62.6	99.2	64.3	16.1	89.9	8.5 (7.6–10.0)
GD regimens versus platinum-based regimens subgroup									
Georgoulias et al. (2001b)	D 100 mg/m^2 d1 + DDP 80 mg/m^2 d2	219	205	89	89	61	66[f]	63.0	10.0
	G 1,100 mg/m^2 d1,8 +D 100 mg/m^2 d8	222	201	87	87	62	63[f]	65.0	9.5
Georgoulias et al. (2005)	V 30 mg/m^2 d1,8 + DDP 80 mg/m^2 d8	204	204	88	90	64	46	64.0	9.7 (8.3–11.2)
	G 1,000 mg/m^2 d1,8 + D 100 mg/m^2 d8	209	209	89	89	63	38	62.0	9.0 (7.7–10.2)

Study	Regimens	ITT(n)	E(n)	Male (%)	PS0-1 (%)	Median age	SCC (%)	Stage IV (%)	MST (95 % CI) (m)
Pujol et al. (2005)	V 30 mg/m^2 d1,8,15,22 +DDP 100 mg/m^2 d1[b]	156	140	79.5	91.7[f]	57	23.7	85.9	9.6 (8.1–12.2)
	G 1,000 mg/m^2 d1,8 + D 85 mg/m^2 d1[c]	155	142	80	92.3[f]	60	31.6	78.7	11.1 (9.6–12.5)
Katakami et al. (2006)	D 60 mg/m^2 d1 + DDP 80 mg/m^2 d1	68	67	66.2	100	65	26.5	73.5	11.4
	D 60 mg/m^2 d8 + G 800 mg/m^2 d1,8	63	60	65.1	100	61	28.6	74.6	13.7
Rigas et al. (2008)	D 75 mg/m^2 d1 + CBP AUC 6 d1	930[d]	–	–	–	–	–	–	7.9
	G 1,000 mg/m^2 d1,8 + D 40 mg/m^2 d1,8		–	–	–	–	–	–	7.9
Rubio et al. (2009)	G 1,250 mg/m^2 d1,8 + DDP 75 mg/m^2 d1	56	55	80	83.3	59.9	–	81.8	8.9 (6.3–10.5)
	G 1,000 mg/m^2 d1,8 + D 85 mg/m^2 d1	52	50	90	84	61.4	–	86.0	8.9 (3.9–10)

ITT intention-to-treatment, *E(n)* numbers eligible for evaluation, *PS* performance status according to Zubrod-ECOG-WHO, *SCC* squamous cell cancer, *MST* median survival time, *CI* confidence interval, *V* vinorelbine, *G* gemcitabine, *platinum-based* platinum-based doublet regimens, *DDP* cisplatin, *CBP* carboplatin, *AUC* area under curve, *T* paclitaxel, *D* docetaxel, – data cannot be acquired

[a] repeated every 2 weeks, maximum treatment of 9 cycles

[b] repeated every 4 weeks, maximum treatment of 6 cycles

[c] repeated every 3 weeks, maximum treatment of 8 cycles; other regimens not noted, repeated every 3 weeks, maximum treatment of 6 cycles

[d] number of the patients in both group

[e] performance status over 80 according to Karnofsky

[f] performance status over 70 according to Karnofsky

[g] Non-adenocarcinoma

OS

pooled HR f (HR = 1.03, 95 % CI = 0.98–1.08, p = 0.29)

RR

Pooled RR = 0.99, 95 % CI = 0.90–1.08, p = 0.24

PFS

pooled HR : platinum-based doublets might have an advantage in PFS compared with non-platinum doublets (HR = 1.06, 95 % CI = 1.01–1.12, p = 0.03).

Toxicity

- The Grade 3–4 nausea or vomiting, anemia, neutropenia, thrombocytopenia, alopecia, and hearing loss of **vinorelbine plus gemcitabine** may be less frequent than platinum-based doublets, while grade 3–4 constipation of vinorelbine plus gemcitabine may be more frequent than platinum-based doublets.
- The grade 3–4 toxicity of **vinorelbine plus paclitaxel** may be comparable with platinum-based doublets excepted for neutropenia and allergy, which might be more frequent in **vinorelbine plus paclitaxel** group.
- **Gemcitabine plus paclitaxel** was more tolerable than platinum-based doublets on the whole according to anemia, neutropenia, thrombocytopenia except grade 3–4 peripheral neuropathy and alopecia.
- **Gemcitabine plus carboplatin** caused especially more grade 3–4 anemia, neutropenia, thrombocytopenia and hemorrhage than gemcitabine plus paclitaxel.
- **Gemcitabine plus docetaxel** caused less nausea or vomiting,

	diarrhea, anemia and neutropenia, but more lung toxicity than platinum-based doublets. • **Vinorelbine plus cisplatin** may cause more grade 3–4 peripheral neuropathy than gemcitabine plus docetaxel. **4. Anmerkungen/Fazit der Autoren** Non-platinum doublets were as effective as platinum-based doublets with different toxicity profile for chemotherapy-naı̈ve advanced NSCLC in the era of thirdgeneration agents.
June KL et al., 2014 Epidermal growth factor receptor tyrosine kinase inhibitors vs conventional chemotherapy in non-small cell lung cancer harboring wild-type epidermal growth factor receptor: a meta-analysis [40]	**1. Fragestellung** Current guidelines recommend both epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and cytotoxic chemotherapy drugs as standard treatment options for patients with wild-type (WT) *EGFR* who were previously treated for non–small cell lung cancer (NSCLC). However, it is not clear that EGFR TKIs are as efficacious as chemotherapy in patients withWT *EGFR*. **2. Methodik** ***Population:*** Patients with advanced NSCLC, defined as inoperable locally advanced (stage IIIB) or metastatic or recurrentdisease (stage IV) ***Intervention:*** first-generation EGFR TKI (erlotinib and gefitinib) ***Komparator:*** chemotherapy ***Endpunkte*:** OS, OR, PFS ***Suchzeitraum:*** Bis 12/2013 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 11 (1605) ***Qualitätsbewertung der Studien:*** Risk of bias assessment (supplement) ***Heterogenitätsuntersuchungen:*** I^2 **3. Ergebnisdarstellung**

Table. Characteristics of the Included Randomized Controlled Trials Comparing EGFR TKI With Chemotherapy

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

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

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

[b] Numbers of randomized patients.

[c] TKI group vs chemotherapy group.

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

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

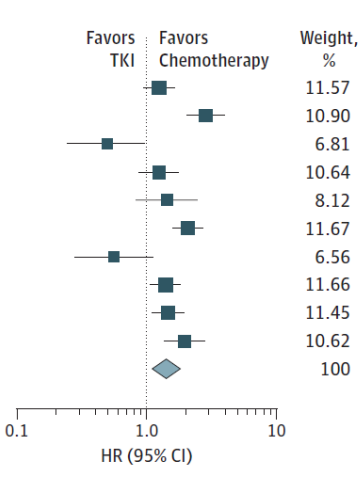
All 11 trials were open-labeled

PFS

- significantly longer PFS with chemotherapy than with TKI in the patients with WT *EGFR* (HR, 1.41; 95% CI, 1.10-1.81);
- a significant statistical heterogeneity was noted in this analysis ($I2$ = 79.1%)

Figure 2. Progression-Free Survival From the 10 Randomized Controlled Trials Comparing EGFR TKI With Chemotherapy

Source	No. of Patients With WT *EGFR*: TKI	Chemotherapy	Progression-Free Survival, HR (95% CI)	Weight, %
INTEREST,[12,27] 2008 and 2010	106	123	1.24 (0.94-1.64)	11.57
IPASS,[5,28] 2009 and 2011	91	85	2.85 (2.05-3.98)	10.90
ML20322,[29] 2012	21	15	0.50 (0.25-0.97)	6.81
TITAN,[13] 2012	75	74	1.25 (0.88-1.78)	10.64
First-SIGNAL,[30] 2012	27	27	1.42 (0.82-2.47)	8.12
TORCH,[14] 2012	119	117	2.07 (1.58-2.71)	11.67
KCSG-LU08-01,[31] 2012	18	20	0.56 (0.28-1.13)	6.56
TAILOR,[15] 2013	109	110	1.39 (1.06-1.82)	11.66
DELTA,[33] 2013	109	90	1.45 (1.09-1.94)	11.45
CTONG-0806,[34] 2013	81	76	1.96 (1.37-2.78)	10.62
Overall: I^2 = 79.1%; P < .001	756	737	1.41 (1.10-1.81)	100



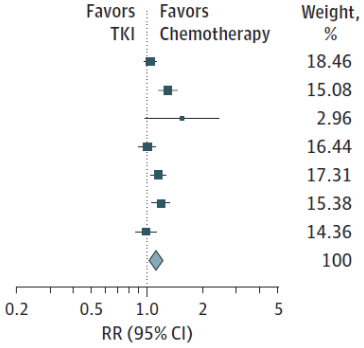
The size of the data markers (squares) corresponds to the weight of the study in themeta-analysis. The treatment effects were calculated with a random-effects model.

OR

OR was significantly higher with chemotherapy (92/549, 16.8%) compared with TKI (39/540, 7.2%; RR of nonresponse for TKI, 1.11; 95% CI, 1.02-1.21)

A Objective response rate

Source	No. of Patients With WT *EGFR* TKI Event[a]	TKI Total	Chemotherapy Event[a]	Chemotherapy Total	RR[a] (95% CI)
INTEREST,[12,27] 2008 and 2010	99	106	111	123	1.03 (0.96-1.12)
IPASS,[5,28] 2009 and 2011	90	91	65	85	1.29 (1.15-1.46)
First-SIGNAL,[30] 2012	20	27	13	27	1.54 (0.98-2.41)
CT/06.05,[32] 2013	51	55	53	57	1.00 (0.90-1.11)
TAILOR,[15] 2013	97	100	82	97	1.15 (1.05-1.26)
DELTA,[33] 2013	100	106	68	85	1.18 (1.05-1.32)
CTONG-0806,[34] 2013	64	75	65	75	0.98 (0.87-1.12)
Overall: $I^2 = 71.7\%$; $P = .002$	521	560	457	549	1.11 (1.02-1.21)

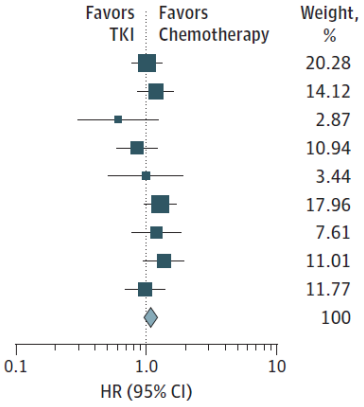


OS

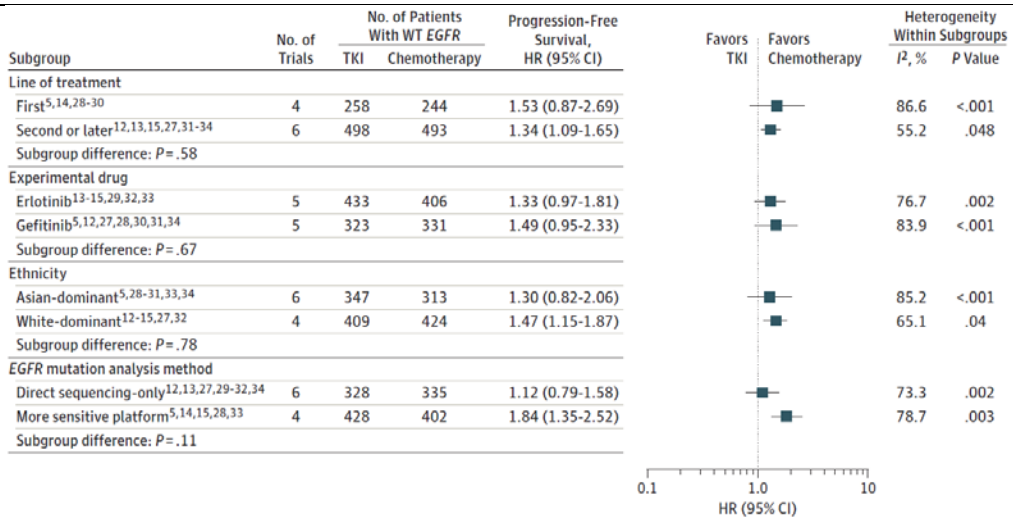
HR for TKI (1.08; 95% CI, 0.96-1.22)

B Overall survival

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



Subgruppen

	 Subgroup / No. of Trials / No. of Patients With WT *EGFR* (TKI, Chemotherapy) / Progression-Free Survival, HR (95% CI) / Heterogeneity Within Subgroups (I^2, %, *P* Value) Line of treatment First[5,14,28-30] 4 258 244 1.53 (0.87-2.69) 86.6 <.001 Second or later[12,13,15,27,31-34] 6 498 493 1.34 (1.09-1.65) 55.2 .048 Subgroup difference: *P* = .58 Experimental drug Erlotinib[13-15,29,32,33] 5 433 406 1.33 (0.97-1.81) 76.7 .002 Gefitinib[5,12,27,28,30,31,34] 5 323 331 1.49 (0.95-2.33) 83.9 <.001 Subgroup difference: *P* = .67 Ethnicity Asian-dominant[5,28-31,33,34] 6 347 313 1.30 (0.82-2.06) 85.2 <.001 White-dominant[12-15,27,32] 4 409 424 1.47 (1.15-1.87) 65.1 .04 Subgroup difference: *P* = .78 *EGFR* mutation analysis method Direct sequencing-only[12,13,27,29-32,34] 6 328 335 1.12 (0.79-1.58) 73.3 .002 More sensitive platform[5,14,15,28,33] 4 428 402 1.84 (1.35-2.52) 78.7 .003 Subgroup difference: *P* = .11 Figure 4. Subgroup Analyses for Progression-Free Survival According to the Line of Treatment (First vs Second or Later), EGFR TKI Agents, Ethnicity, and *EGFR* Mutation Analysis Methods for Patients WithWT *EGFR* **4. Anmerkungen/Fazit der Autoren** Among patients with advanced NSCLC harboringWT *EGFR*, conventional chemotherapy, compared with first-generation EGFR TKI, was associated with improvement in PFS but not overall survival. Limierierungen: • a large number of trials had available data on the *EGFR* mutation status in only a small portion of the enrolled patients • toxitity: not possible to perform an analysis to dealwith such a concern because reports of adverse events from each subgroup were not available
Ku GY et al., 2011: Gefitinib vs. chemotherapy as first-line therapy in advanced non-small cell lung cancer: meta-analysis of phase III trials [41]	**1. Fragestellung** To 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 (stage IIIB/IV) NSCLC ***Intervention:*** gefitinib ***Komparator:*** chemotherapy ***Endpunkte*:** PFS, OS, ORR, toxicity ***Suchzeitraum:***

k.A.

Anzahl eingeschlossene Studien/Patienten (Gesamt):

5 (1617)

Qualitätsbewertung der Studien:

k.A.

Heterogenitätsuntersuchungen:

k.A.

3. Ergebnisdarstellung

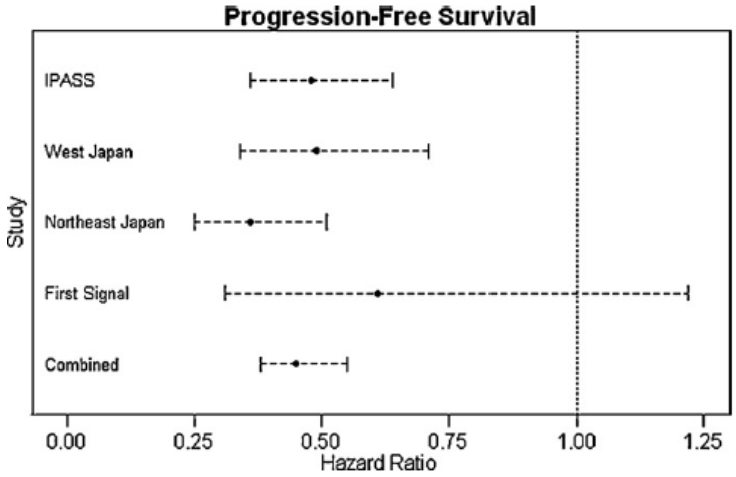
Table 1
Patient demographics.

Characteristic	Gefitinib ($n = 809$)*	Chemotherapy ($n = 808$)*
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.

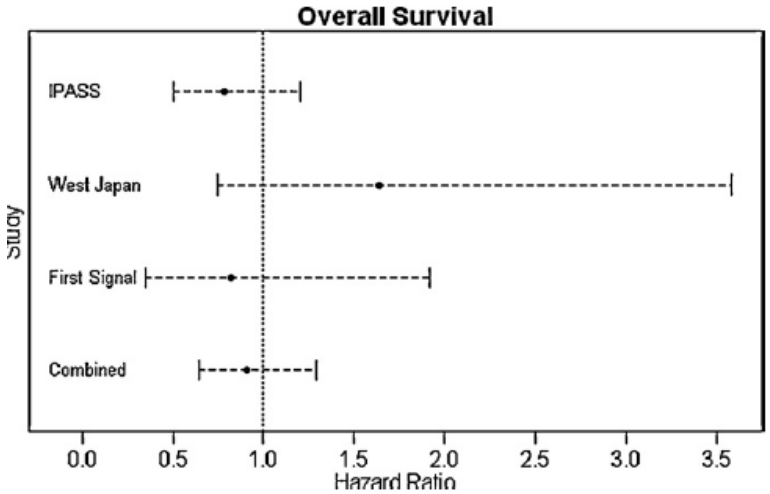
PFS

While median PFS was not different compared to the chemotherapy group (5.7 vs. 5.8 months), the 12-month PFS rate was 25% vs. 7% respectively (hazard ratio for progression 0.74, p < 0.001).



OS

hazard ratio 1.64, p = 0.211



QoL

QoL was analyzed in both the IPASS and first-SIGNAL studies. In the IPASS study, QoL was analyzed using the FACT-L, TOI and LCS instruments. The gefitinib group had better QoL and nominal symptom reduction compared to the chemotherapy group, with odds ratios (p values) for the respective measures of 1.34 (0.01), 1.78 (<0.001) and 1.13 (0.30).

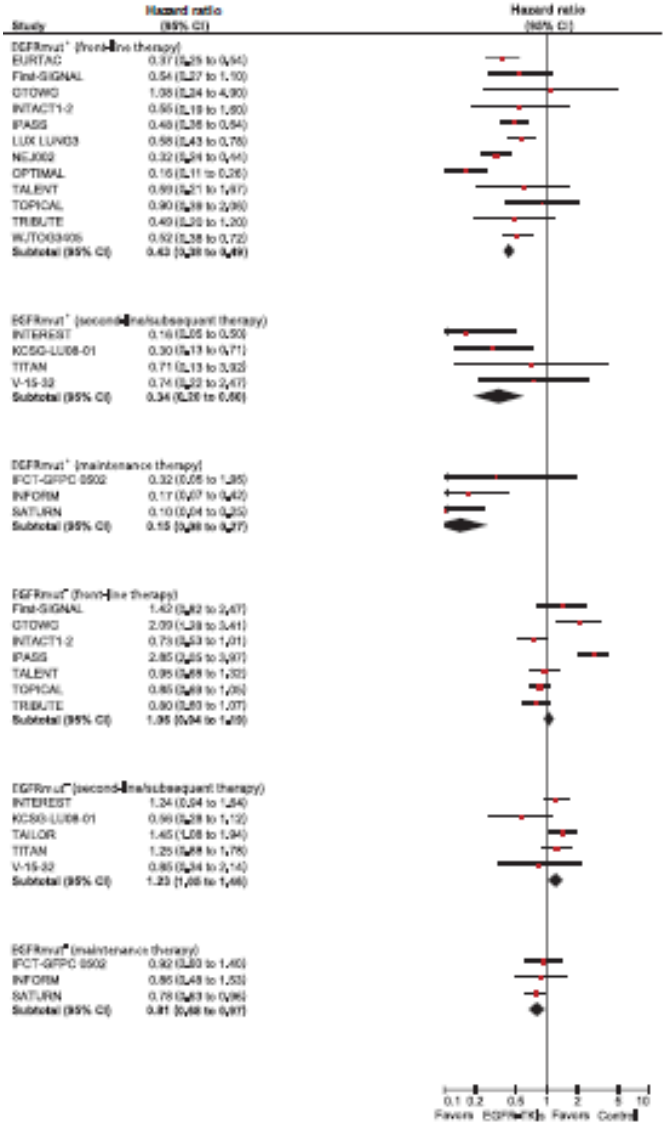
Toxicity

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 ($p < 10^{-15}$).

4. Anmerkungen/Fazit der Autoren

The results of our metaanalysis confirm the results of the individual trials: initial gefitinib is associated with a higher ORR and PFS as well as superior toxicity and QoL profiles as compared to chemotherapy. These benefits are seen in Asian patients who are selected by clinicopathologic characteristics associated with the presence of an EGFR mutation but are even more pronounced in patients with known EGFR mutations. In these studies, there was no OS benefit for upfront

	gefitinib over chemotherapy, quite possibly because most patients treated initially with chemotherapy received and benefited from an EGFR TKI at progression.
Lee CK et al., 2013: Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis [42]	**1. Fragestellung** We examined the impact of **EGFR–tyrosine kinase inhibitors** (TKIs) on progression-free survival (PFS) and overall survival (OS) in advanced NSCLC patients with and without EGFR mutations. **2. Methodik** ***Population****:* advanced NSCLC patients with and without EGFR mutations ***Intervention****:* of EGFR-TKIs monotherapy, EGFR-TKIs and chemotherapy ***Komparator****:* chemotherapy, placebo, best supportive care **Endpunkt**: PFS, OS ***Methode****:* systematic review and meta-analysis of RCTs ***Suchzeitraum****:* 2004 bis 2012 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 23 (n=14 570) ***Bewertung der Studienqualität der Primärstudien:*** k.A. **3. Ergebnisdarstellung** <u>First-line therapy (13 trials)</u> **Overall survival:** no statistically significant difference between EGFR-TKI-based therapy and other therapy. Neither for EGFRmut+ patients (11 trials) nor for EGFRmut- patients (6 trials). **PFS:** • EGFRmut+ patients (12 trials): statistically significant difference in favor of EGFR-TKI-based therapy (HR = 0.43; 95% CI = 0.38 to 0.49; p < 0.001) • EGFRmut- patients (7 trials): no statistically significant difference • Sensitivity analysis (EGFR-TKIs combined with chemotherapy vs. chemotherapy alone): statistically significant difference in favor of EGFR-TKI-based therapy (EGFRmut+: HR = 0.54, 95% CI = 0.30 to 0.95, p = 0.04; EGFRmut–: HR = 0.82, 95% CI = 0.68 to 0.98, p = 0.03 • Sensitivity analysis (EGFR-TKIs monotherapy vs. chemotherapy): statistically significant difference in favor of EGFR-TKI-based therapy in EGFRmut+ subgroup (HR = 0.42; 95% CI = 0.37 to 0.48; p < 0.001). Increased risk in the EGFRmut- subgroup (HR = 1.56; 95% CI = 1.36 to

	1.80; p < 0.001)  **Figure 2.** Forest plot of hazard ratios comparing progression-free survival in subgroups of epidermal growth factor receptor (EGFR) mutation–positive (EGFRmut+) and EGFR mutation–negative (EGFRmut-) patients who received EGFR–tyrosine kinase inhibitors (TKIs) vs control. **4. Anmerkungen/Fazit der Autoren** Treatment with EGFR-TKIs statistically significantly delays disease progression in EGFRmut+ patients but has no demonstrable impact on OS. These findings support assessment of EGFR mutation status before initiation of EGFR-TKIs treatment and indicate that EGFR-TKIs should be considered as front-line therapy in EGFRmut+ patients with advanced NSCLC.
Lee JK et al., 2014: Epidermal growth factor receptor tyrosine kinase	**1. Fragestellung** To determine the association between first-generation EGFR TKI vs chemotherapy and survival in advanced NSCLC patients with WT EGFR. **2. Methodik** ***Population:***

inhibitors vs conventional chemotherapy in non-small cell lung cancer harboring wild-type epidermal growth factor receptor: a meta-analysis [43]	advanced NSCLC with wild type (WT) EGFR ***Intervention:*** EGFR TKI ***Komparator:*** conventional chemotherapy ***Endpunkte:*** primary - progression-free survival (PFS), secondary - objective response rate, overall survival ***Suchzeitraum:*** through December 2013 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 11/1 605 (7 studies on second line treatment or later) ***Qualitätsbewertung der Studien:*** not mentioned ***Heterogenitätsuntersuchungen*:** χ 2 statistic used, I2 statistic also calculated, predefined subgroup analyses performed: line of treatment (first vs second or later), experimental drug (erlotinib vs gefitinib), ethnicity (Asiandominant vs white-dominant trials), and EGFR mutation analysis method (direct sequencing only vs more sensitive platforms; eg, fragment length analysis, amplificationrefractory mutation system, and mass spectrometric genotyping) ***„Publication bias“:*** funnel plot method togetherwith the Egger test for asymmetry to assess the possibility of publication bias **3. Ergebnisdarstellung** • among patients with WT EGFR tumors, chemotherapy associated with improvement of PFS, compared with TKI (HR for TKI, 1.41; 95%CI, 1.10-1.81) • No statistically significant subgroup difference was identified in terms of line of treatment (first-line vs. second- or later-line), experimental drug, dominant ethnicity, or EGFR mutation analysis method • association of chemotherapy with improvement in PFS also significant in second- or later-line trials (HR, 1.34; 95%CI, 1.09-1.65) • objective response rate higher with chemotherapy (92/549, 16.8%, vs 39/540, 7.2%, for TKI; relative risk for TKI, 1.11; 95%CI, 1.02-1.21) • no statistically significant difference observed with respect to overall survival (HR for TKI, 1.08; 95%CI, 0.96-1.22)

	4. Anmerkungen/Fazit der Autoren Among patients with advanced NSCLC harboring WT EGFR, conventional chemotherapy, compared with first-generation EGFR TKI, was associated with improvement in PFS but not overall survival.
Li C et al., 2010: Gemcitabine plus paclitaxel versus carboplatin plus either gemcitabine or paclitaxel in advanced non-small-cell lung cancer: a literature-based meta-analysis [44]	**1. Fragestellung** To compare the activity, efficacy, and toxicity of **gemcitabine plus paclitaxel** versus **carboplatin plus either gemcitabine or paclitaxel** in patients with untreated advanced NSCLC. **2. Methodik** **Population:** Patients were confirmed pathologically to have NSCLC and to be in clinical stage III or IV. **Intervention**: gemcitabine plus paclitaxel **Komparator**: carboplatin plus either gemcitabine or paclitaxel **Endpunkt**: survival, ORR, toxicity **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: up to 2009 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 4 (n=2.186): **3. Ergebnisdarstellung** **Survival**: no statistically significant difference **ORR**: statistically significant difference in favor of gemcitabine plus paclitaxel (OR = 1.20; 95% CI = 1.02–1.42; p = 0.03, I^2=0%) **Toxicity**: Grade 3–4 nausea and vomiting are similar, while significant decreases in grade 3–4 neutropenia, anemia, and thrombocytopenia were observed with the gemcitabine and paclitaxel combination **4. Anmerkungen/Fazit der Autoren** We conclude that adding carboplatin to either gemcitabine or paclitaxel would increase the prevalence of hematologic side effects while not improving on the treatment response of gemcitabine plus paclitaxel. **5. Hinweise durch FB Med** Keine Hinweise zur Qualitätsbewertung der eingeschlossenen Studien,

	keine Angaben zu Interessenskonflikten. Keine Information über Therapielinie in den eingeschlossenen Studien.
Li N et al., 2014 Meta-Analysis of EGFR Tyrosine Kinase Inhibitors Compared with Chemotherapy as Second-Line Treatment in Pretreated Advanced Non-Small Cell Lung Cancer [45]	**1. Fragestellung** We performed this meta-analysis to compare the efficacy and safety of EGFR-TKIs vs. chemotherapy as second-line treatment for pretreated advanced NSCLC. … Preplanned subgroup analyses to explore potential effect on PFS, OS based on EGFR mutation status were scheduled. **2. Methodik** **Population:** advanced NSCLC (previously treated with platinum compounds) **Intervention:** EGFR TKI **Komparator:** standard second-line chemotherapy (docetaxel or PEM) **Endpunkte:** progression-free survival (PFS), overall survival (OS), objective response rate (ORR), grade 3–4 toxicities **Suchzeitraum:** July 2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 10/3 825 **Qualitätsbewertung der Studien:** not mentioned **Heterogenitätsuntersuchungen:** Q statistic and I^2 statistic used, if considered statistically significant, REM used, otherwise FEM **„Publication bias“:** Egger’s test and Begg’s funnel plots used ***3. Ergebnisdarstellung***

Table 1. Information of trials included in this meta-analysis.

Study/Year	Phase	Country	Therapy	N	Male (%)	Ever smoker (%)	IIIB (%)	IV (%)	EGFR M+ (%)	PFS (mo)	OS (mo)	RR (%)	Jadad score
SIGN, 2006	II	International	Gefitinib	68	30.9	67.6	39.7	60.3	NR	3.0	7.5	13.2	3
			Doc	73	30.1	67.1	43.8	56.2	NR	3.4	7.1	13.7	
INTEREST, 2008	III	International	Gefitinib	733	36.4	79.8	25.0	52.9	15.6	2.2	7.6	9.1	3
			Doc	733	33.4	79.6	28.8	52.3	14.1	2.7	8.0	7.6	
V-15-32, 2008	III	Japan	Gefitinib	245	38.4	71.0	19.2	64.9	NR	2.0	11.5	22.5	3
			Doc	244	38.1	64.3	20.5	61.5	NR	2.0	14.0	12.8	
ISTANA, 2010	III	Korea	Gefitinib	82	32.9	63.4	13.4	86.6	NR	3.3	14.1	28.1	3
			Doc	79	43.0	54.4	17.7	82.3	NR	3.4	12.2	7.6	
TITAN, 2012	III	International	Erlotinib	203	20.6	85.2	20.2	79.8	3.4	1.5	5.3	7.9	3
			Doc/Pem	221	27.6	80.1	23.1	76.9	1.8	2.0	5.5	6.3	
KCSG-LU08-01, 2012	III	Korea	Gefitinib	68	85.3	0	8.8	91.2	23.5	9.0	22.2	58.8	3
			Pem	67	85.1	0	9.0	91.0	25.4	3.0	18.9	22.4	
TAILOR, 2012	III	Italy	Erlotinib	109	29.4	81.7	NR	NR	0	2.4	NR	2.2	3
			Doc	110	33.6	71.8	NR	NR	0	3.4	NR	13.9	
HORG, 2013	III	Greece	Erlotinib	166	18.7	74.7	7.2	92.8	8.1	3.6	8.2	9.0	3
			Pem	166	16.9	77.1	11.4	88.6	9.8	2.9	10.1	11.4	
DELTA, 2013	III	Japan	Erlotinib	150	NR	NR	NR	NR	27.3	2.0	14.8	17.0	3
			Doc	151	NR	NR	NR	NR	40.4	3.2	12.2	17.9	
CTONG0806, 2013	II	China	Gefitinib	81	33.3	59.3	4.9	95.1	0	1.6	NR	13.6	3
			Pem	76	38.2	42.1	13.2	86.8	0	4.8	NR	13.2	

Abbreviations: N, number of patients; IIIB, stage IIIB; IV, stage IV; EGFR M+, epidermal growth factor receptor mutation-positive; PFS, progression-free survival; mo, month; OS, overall survival; RR, response rate; Doc, docetaxel; Pem, pemetrexed; NR, no report.

<u>PFS</u>

- HR 1,03; 95 % KI 0,87 – 1,21; p = 0,73; I^2 = 78,7%, p (heterogeneity) = 0,001 - equivalent efficacy
- subgroup analysis
  - HR (second-line chemotherapy for EGFR mutation negative patients) 1,35; 95 % KI 1,09 – 1,66; p = 0,01; I^2 = 55,7%, p (heterogeneity) = 0,046 - significantly improved
  - HR (EGFR-TKIs for EGFR mutation positive patients) 0,28; 95 % KI 0,15 – 0,53; p = 0,001; I^2 = 4,1%, p (heterogeneity) = 0,35 - significantly improved

<u>OS, ORR</u>

- results of main and subgroup analyses equal

<u>grade 3–4 toxicities</u>

- EGFR-TKIs: more grade 3–4 rash, less fatigue/asthenia disorder, leukopenia, thrombocytopenia

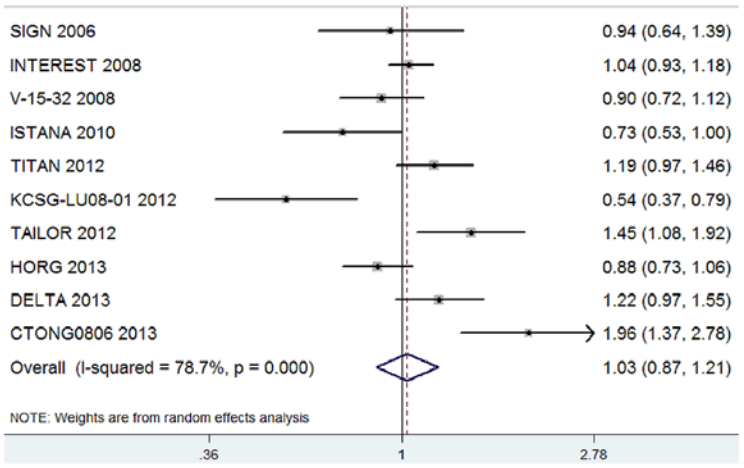


Figure 2. Comparison of PFS between EGFR-TKIs and chemotherapy.
doi:10.1371/journal.pone.0102777.g002

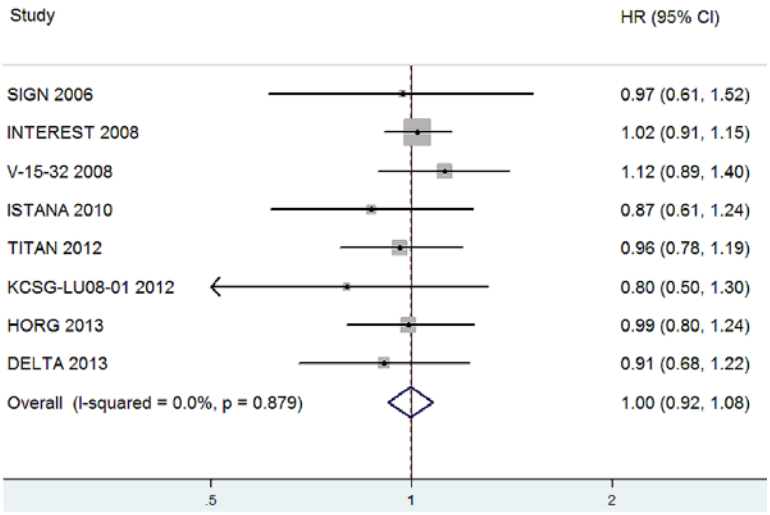


Figure 3. Comparison of OS between EGFR-TKIs and chemotherapy.
doi:10.1371/journal.pone.0102777.g003

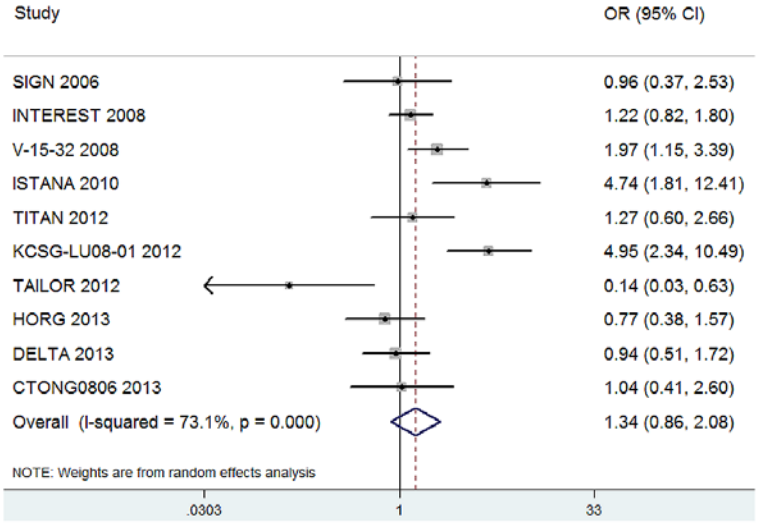


Figure 4. Comparison of ORR between EGFR-TKIs and chemotherapy.
doi:10.1371/journal.pone.0102777.g004

	4. Anmerkungen/Fazit der Autoren Our analysis suggests that chemotherapy in the second-line setting can prolong PFS in EGFR M- patients, whereas it has no impact on OS. EGFR-TKIs seem superior over chemotherapy as second-line therapy for EGFR M+ patients. Our findings support obtaining information on EGFR mutational status before initiation of second-line treatment. *Hinweise durch FB Med:* • *no evidence of publication bias exists*
Li X t al., 2014 Efficacy of combining targeted therapy with pemetrexed or docetaxel as second-line treatment in patients with advanced non-small-cell lung cancer: a meta-analysis of 14 randomized controlled trials [46]	**1. Fragestellung** To compare the effects of adding targeted agents to standard second-line chemotherapy with a single agent (pemetrexed or docetaxel) in patients with advanced NSCLC **2. Methodik** Metaanalyse ***Population:*** NSCLC ***Intervention:*** combination of targeted therapy and standard second-line chemotherapy (pemetrexed or docetaxel) (second-line treatment in NSCLC) ***Komparator:*** chemotherapy alone or chemotherapy plus placebo ***Endpunkte*:** • Objective response rate and disease control rate: Partial response (PR), complete response (CR), and stable disease (SD), • progression free • survival (PFS) • and overall survival (OS), • Sicherheit/ Nebenwirkungen ***Suchzeitraum:*** 2000 – 12/2013 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** *14 (6922)* ***Qualitätsbewertung der Studien:*** Jadad-Score: 8 Studien mit hoher Qualität über 2 Punkte), 6 Studien mit niedriger Qualität (bis 2 Punkte)

Heterogenitätsuntersuchungen:

durchgeführt (vgl. unten): geringe bis mittelgroße Heterogenität

3. Ergebnisdarstellung

All patients had a WHO performance status of 0–2 or Karnofsky performance status of 60–100. Median ages ranged from 59 to 65. Most patients were ever smokers. Anti-angiogenesis and anti-EGFR targeted agents were investigated in 11 of the 14 studies.

Table 1. Randomized trials included in this meta-analysis.

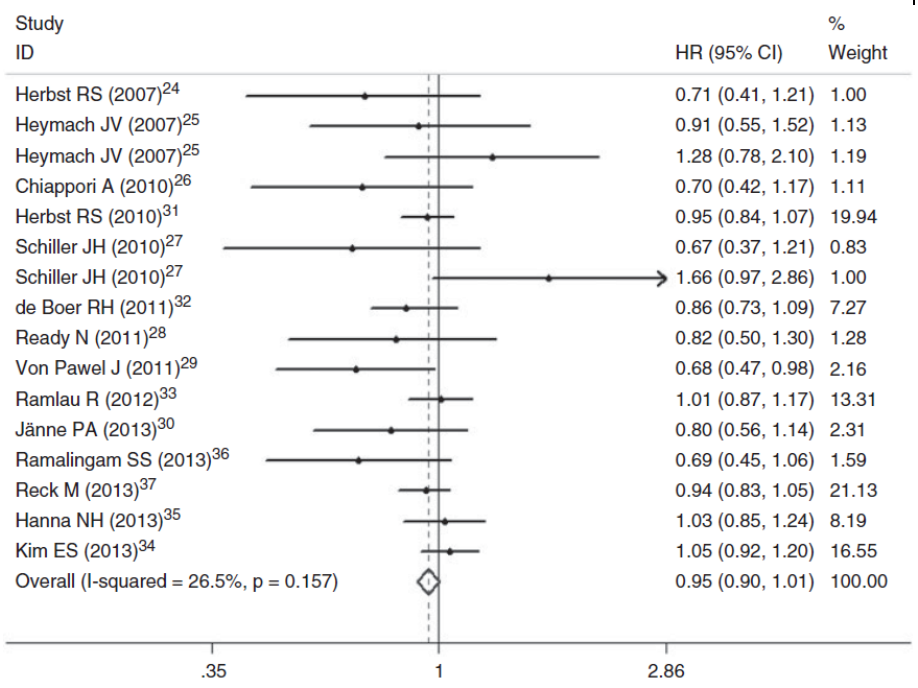
First Author (Year)	Phase	Treatment	No. of patients	Overall Response Rate (%)	Disease Control Rate (%)	Median PFS (months)	Median OS (months)
Herbst RS (2007)[24]	II	Doc/Pem + Pla	41	12.2	39	3.0	8.6
		Doc/Pem + Bev	40	12.5	52.5	4.8	12.6
Heymach JV (2007)[25]	II	Doc + Pla	41	12	56	3.0	13.4
		Doc + Van100	42	26	83	4.7	13.1
		Doc + Van300	44	18	63	4.3	7.9
Chiappori A (2010)[26]	II	Pem + Pla	80	2.6	48.7	3.0	7.4
		Pem + Enz	80	3.9	49.4	3.0	9.6
Herbst RS (2010)[31]	III	Doc + Pla	697	10	55	3.2	9.9
		Doc + Van	694	17	60	4.0	10.3
Schiller JH (2010)[27]	II	Pem	50	4	36	2.7	7.9
		Pem + Mat800	51	16	33	2.3	12.4
		Pem + Mat1600	47	2	34	2.5	5.9
de Boer RH (2011)[32]	III	Pem + Pla	278	8	46	11.9W	10.5
		Pem + Van	256	19	57	17.6W	9.2
Ready N (2011)[28]	II	Doc + Pla	52	2.1	48.9	7.1W	5.9
		Doc + AT101	53	4.3	52.2	7.5W	7.8
Von Pawel J (2011)[29]	II	Pem	83	10.8	51.8	2.9	7.8
		Pem + Erl	76	17.1	55.3	3.2	11.8
Ramlau R (2012)[33]	III	Doc + Pla	457	8.9	54.2	4.1	10.4
		Doc + Afl	456	23.3	61.9	5.2	10.1
Jänne PA (2013)[30]	II	Doc + Pla	44	0	50	2.1	5.2
		Doc + Sel	43	37	81	5.3	9.4
Ramalingam SS (2013)[36]	III	Doc	127	13	68	3.2	7.4
		Doc + Gan	125	19	75	4.5	9.8
Reck M (2013)[37]	III	Doc + Pla	659	4.9	40.2	2.7	9.1
		Doc + Nin	655	2.9	55.2	3.4	10.1
Hanna NH (2013)[35]	III	Pem + Pla	360	8.3	53.3	3.6	12.8
		Pem + Nin	353	9.1	60.9	4.4	12.2
Kim ES (2013)[34]	III	Doc/Pem	470	6.4	30.6	2.27	7.58
		Doc/Pem + Cet	468	10	37.4	2.79	6.74

Doc = doctaxel; Pem = pemetrexed; Pla = placebo; Bev = bevacizumab; Van = vandetanib; Enz = enzastaurin; Mat = matuzumab; Erl = erlotinib; Cet = cetuximab; Afl = aflibercept; Sel = selumetinib; Gan = ganetespib; Nin = nintedanib; W = weeks.

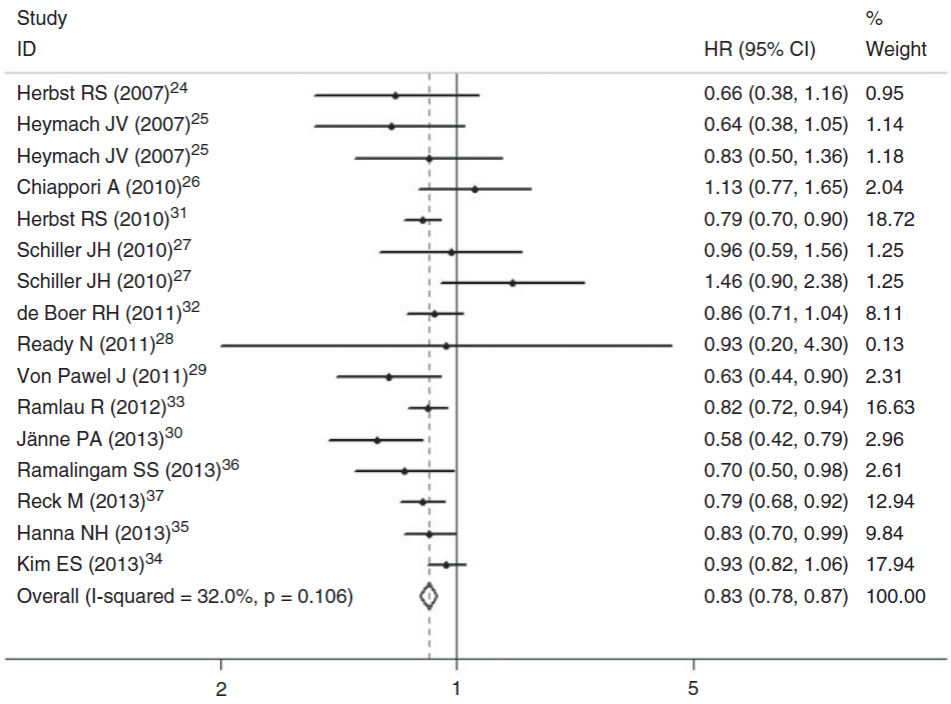
Table 2. Characteristics of studies in the meta-analysis.

First Author (Year)	Treatment	Targets of Bioagents	Median Age, years	Female Sex (%)	Ever Smokers (%)	Squamous (%)
Herbst RS (2007)[24]	CT		65	39	85.4	0
	CT + bevacizumab	VEGF	63.5	42.5	85	0
Heymach JV (2007)[25]	CT		58	34	90.2	26.8
	CT + vandetanib	VEGFR/EGFR/RET	61	50	83.3	28.6
	CT + vandetanib	VEGFR/EGFR/RET	66	43	90.9	31.2
Chiappori A (2010)[26]	CT		62.1	32.5	85.9	22.5
	CT + enzastaurin	PKC/PKB	60.7	32.5	85.9	33.8
Herbst RS (2010)[31]	CT		59	32	75	23
	CT + vandetanib	VEGFR/EGFR/RET	59	28	77	27
Schiller JH (2010)[27]	CT		61	34	NR	36
	CT + matuzumab	EGFR	62	31	NR	22
	CT + matuzumab	EGFR	63	43	NR	36
de Boer RH (2011)[32]	CT		60	38	81	22
	CT + vandetanib	VEGFR/EGFR/RET	60	38	78	21
Ready N (2011)[28]	CT		59.5	25	83	60
	Doc + AT101	Bcl-2 family	58	21	75	53
Von Pawel J (2011)[29]	CT		61	NR	NR	0
	CT + erlotinib	EGFR	64	NR	NR	0
Ramlau R (2012)[33]	CT		59.6	34.4	NR	0
	CT + aflibercept	VEGR	59.6	33.1	NR	0
Jänne PA (2013)[30]	CT		59	53	88	14
	CT + selumetinib	MEK1/MEK2	59.5	52	89	7
Ramalingam SS (2013)[36]	CT		60	44	75	0
	CT + ganetespib	HSP90	60	44	75	0
Reck M (2013)[37]	CT		NR	27.3	76.6	42.2
	CT + nintedanib	VEGFR/PDGFR	NR	27.3	74.8	42.7
Hanna NH (2013)[35]	CT		59	42.2	66.1	0
	CT + nintedanib	VEGFR/PDGFR	60	44.8	69.1	0
Kim ES (2013)[34]	CT		65	40.2	NR	26
	CT + cetuximab	EGFR	64	43.4	NR	25

CT = chemotherapy; NR = not reported; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor; EGFR = epidermal growth factor receptor; RET = rearranged during transfection; PKC = protein kinase C; PKB = protein kinase B; PDGFR = platelet-derived growth factor receptor; HSP = heat shock protein.



Forest plot of overall survival of patients treated with combination arm versus chemotherapy arm.



Forest plot of progression-free survival of patients treated with combination arm versus chemotherapy arm.

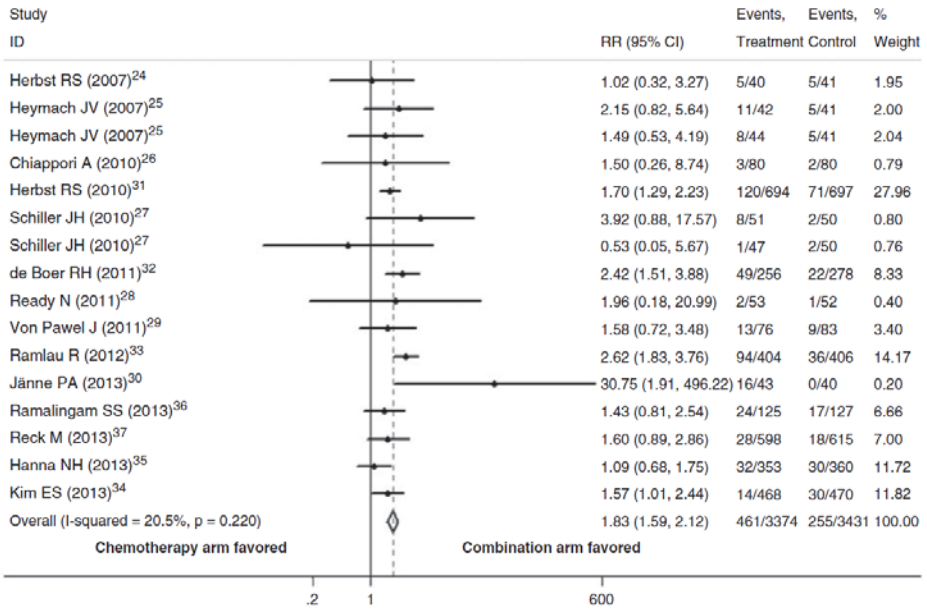


Figure 4. Forest plot of objective response rate of patients treated with chemotherapy arm versus combination arm.

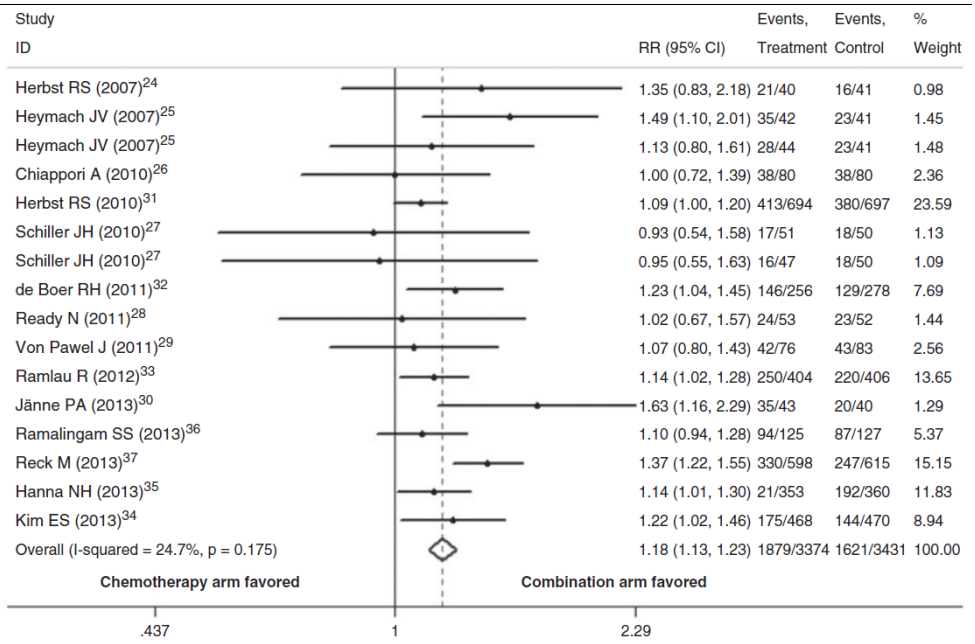
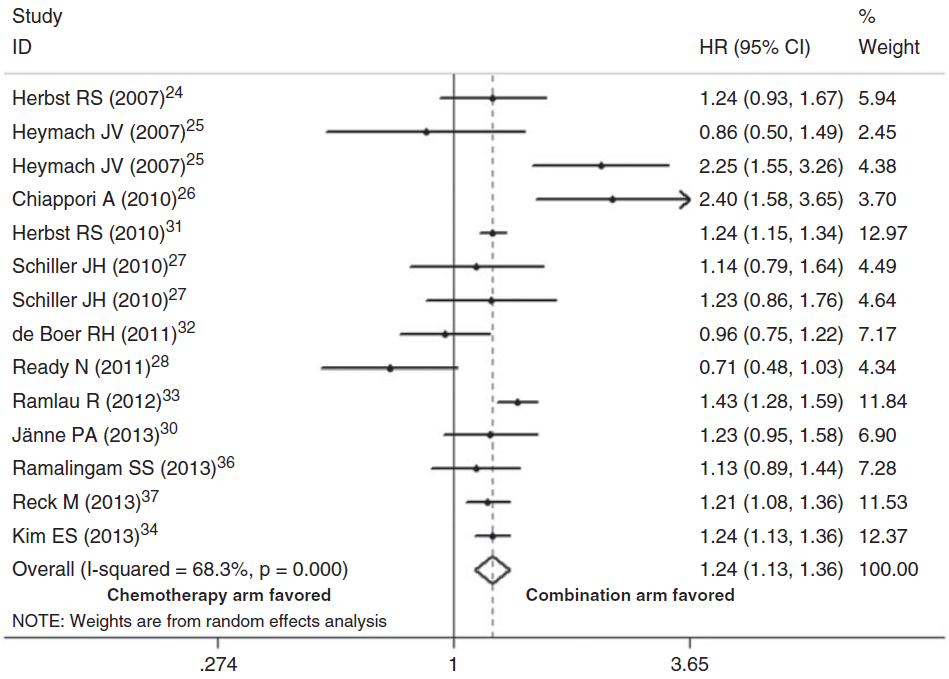


Figure 5. Forest plot of disease control rate of patients treated with chemotherapy arm versus combination arm.



Forest plot of grade 3 or higher toxicity of patients treated with chemotherapy arm versus combination arm.

Table 3. Sub-group analysis for PFS and OS.

Sub-group	PFS		OS
	No. of trials	HR (95% CI)	HR (95% CI)
Phase			
II	7	0.81 (0.65–1.02)	0.85 (0.73–0.99)
III	7	0.83 (0.78–0.88)	0.97 (0.91–1.03)
Chemotherapy			
Docetaxel	8	0.79 (0.74–0.85)	0.96 (0.90–1.03)
Pemetrexed	6	0.92 (0.84–1.00)	0.94 (0.86–1.04)
Targeted agents			
Vandetinib	3	0.80 (0.73–0.89)	0.94 (0.85–1.03)
Nintedanib	2	0.81 (0.72–0.90)	0.96 (0.87–1.07)
Histology			
Squamous	4	0.91 (0.73–1.14)	1.04 (0.91–1.18)
Non-squamous	4	0.83 (0.75–0.91)	0.87 (0.79–0.97)

PFS = Progression free survival, OS = Overall survival, HR = Hazard ratio, CI = Confidence interval

4. Anmerkungen/Fazit der Autoren

In the second-line treatment of advanced NSCLC, the combination of targeted therapy and chemotherapy significantly increased response rates and progression-free survival, but did not improve overall survival and was more toxic.

Liang W et al., 2014:

Network meta-analysis of erlotinib, gefitinib, afatinib and icotinib in patients with advanced non-small-cell lung cancer harboring EGFR mutations [47]

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. Thus, in the current study, we sought to provide some useful information about comparison between these four agents through integrating and indirect methods, expecting this message will be helpful for physicians and patients in decision-making.

2. Methodik

a) pair-wise meta-analyses with a randomeffects model to synthesize studies comparing the same pair of treatments

b) random-effects network within a Bayesian framework using Markov chain Monte Carlo methods (translated binary outcomes of survival analysis and binary outcomes of ORR within studies and specified the relations among the ORs across studies making different comparisons as previously reported

Population:

patients with advanced NSCLC that presents activating EGFR mutations

	advanced NSCLC: defined as stage III or IV disease that was not feasible to surgical treatment or radiotherapy ***Intervention:*** one TKI (including erlotinib, gefitinib, afatinib and icotinib), first-line or second-line ***Komparator:*** • one TKI (including erlotinib, gefitinib, afatinib and icotinib) or • standard chemotherapy (defined as platinum-based third generation doublets for first-line treatments or pemetrxed/ doctaxel for second-line treatments). Since the dominant histological type of patients with EGFR mutation was nonsquamous carcinoma in which pemetrexed were proved to yield superior efficacy compared with other third-generation chemotherapy agents, we also included studies that compared pemetrexed-based regimen with pemetrexed-free regimen in order to optimize the network. ***Endpunkte*:** ORR, OS, PFS ***Suchzeitraum:*** Bis 03/2013 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 12 (1821) Nur phase III RCTs ***Qualitätsbewertung der Studien:*** QUORUM and the Cochrane Collaboration guidelines ***Heterogenitätsuntersuchungen:*** inconsistency statistic (I^2) **3. Ergebnisdarstellung** 12 phase III RCTs that compared elotinib, gefitinib, icotinib, afatinib or chemotherapy in chemo-naı¨ve or previously treated advanced NSCLC patients

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.

Pooled weighted outcomes

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)

- pooled ORR and PFS of EGFR-TKIs were significant higher than standard chemotherapy
- TKIs yielded higher 1-year PFS than standard chemotherapy
- No difference in 1- and 2-year OS

Network Meta-Analyses for Efficacy and Toxicities

elotinib, gefitinib, icotinib and afatinib shared equivalent efficacy in all outcome measures by showing no significant differences in ORs while all TKIs were better than chemotherapy (assessment of icotinib was not available neither in comparison of OS data nor in network 2). Coherence between direct and indirect comparisons based on networks was confirmed.

We selected rash and diarrhea, which are the most common TKIspecific toxicities, as the representative of treatment-related toxicities. Patients who received afatinib experienced more severe diarrhea compared with the other three TKIs. In terms of rash, afatinib is significant severer than gefitinib while no other significant difference was observed among the rest comparisons.

Afatinib and erlotinib had significant more grade 3 to 4 diarrhea or diarrhea compare with gefitinib and icotinib.

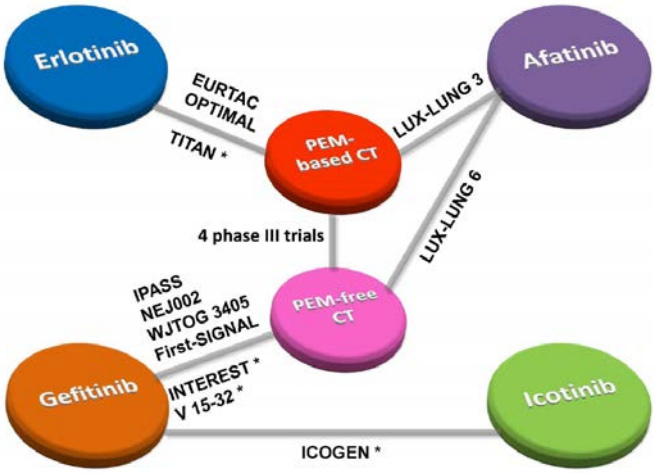


Figure 3. Network established for multiple treatment comparisons. Solid lines between drugs represented the existence of direct comparisons. PEM, pemetrexed; * Second-line studies

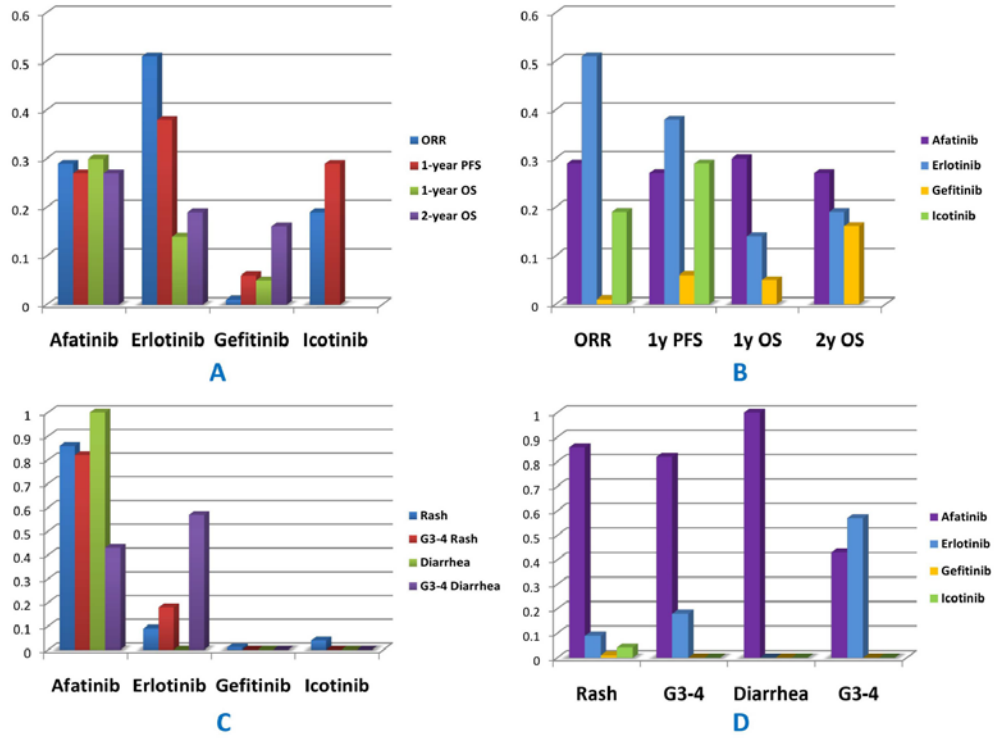


Figure 4. Distribution of probabilities of each agent being ranked the first place based on network 1. A & C were classified by drugs; B & D were classified by outcomes.

Figure 4 was the ranking indicates the probability to be the best treatment, the second best, the third best, and so on, among all the treatment regimens. Agents with greater value in the histogram were associated with greater probabilities for better outcomes.

Based on network 1, the cumulative probabilities of being the most

	efficacious treatments were (ORR, 1-year PFS, 1-year OS, 2-year OS): • erlotinib (61%, 38%, 14%, 19%), • gefitinib (1%, 6%, 5%,16%), • afatinib (29%, 27%, 30%, 27%) and • icotinib (19%, 29%,NA, NA). According to network 2 (1st-line studies only), the results were (ORR, 1-year PFS, 1-year OS, 2-year OS): • erlotinib (61%, 61%, 15%, 19%), • gefitinib (2%, 10%, 7%, 19%), • afatinib (36%, 29%, 30%, 27%), • whereas outcomes of icotinib were not assessable **4. Anmerkungen/Fazit der Autoren** In conclusion, this network meta-analysis indicated that erlotinib, gefitinib, afatinib and icotinib shared equivalent efficacy but presented different efficacy-toxicity pattern for EGFR-mutated patients according to current evidences. **Limitations:** • OS data in mutant population of ICOGEN were not available hence we could not evaluate the survival benefits of icotinib • comparisons in terms of OS were onfounded by subsequent treatments • performance of icotinib in first-line setting was not available could not assess some important molecular markers including T790M status in the population which might have effects on the efficacy of TKIs and cause bias • established networks lacked sufficient direct comparisons between TKIs
Lima AB, 2011: Addition of bevacizumab to chemotherapy in advanced non-small cell lung cancer: a systematic review and meta-analysis[48]	**1. Fragestellung** As the results of clinical trials were not completely consistent, and none of them was large enough to accurately interpret the efficacy and safety of bevacizumab in combination with chemotherapy, the aim of this meta-analysis was to evaluate and to quantify the effectiveness and safety of bevacizumab in patients with advanced NSCLC. **2. Methodik** ***Population:*** ***Intervention:*** Chemotherapy with bevacizumab ***Komparator:*** Chemotherapy without bevacizumab ***Endpunkte*:**

OS, PFS,

Suchzeitraum:

Bis 12/2010

Anzahl eingeschlossene Studien/Patienten (Gesamt):

5 (2252) ; nur RCTs with a parallel design

Qualitätsbewertung der Studien:

ja, Publication bias: Egger's test

Heterogenitätsuntersuchungen:

I^2

3. Ergebnisdarstellung

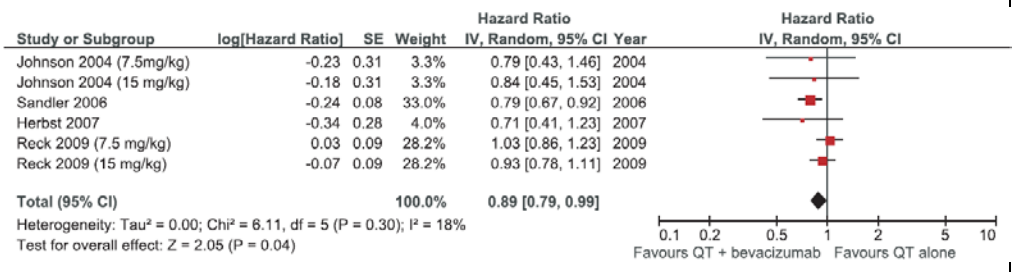
Author/year	Study/arm	Patients enrolled	Setting	Primary endpoint	ECOG 0, 1(%)	Histology	Maintenance of bevacizumab (maximum cycles)	Crossover permitted
Johnson 2004	TP	32	1st line	PFS	93.7	NSCLC	Yes (18)	Yes
	TP+Bev (7.5)	32			96.8			
	TP+Bev (15)	35			88.5			
Sandler 2006	TP	444	1st line	OS	100	Non-squamous NSCLC	Yes (until disease progression)	No
	TP+Bev (15)	434			100			
Herbst 2007 *	D or P	41	2nd line	PFS	97.6	Non-squamous NSCLC	Yes (until disease progression)	Yes
	D or P+Bev (15)	40			100			
Reck 2009	GP	347	1st line	PFS	100	Non-squamous NSCLC	Yes (until disease progression)	No
	GP+Bev (7.5)	345			100			
	GP+Bev (15)	351			100			
Nishio 2009	TP	59	1st line	PFS	NR	Non-squamous NSCLC	Yes (until disease progression)	NR
	TP+Bev (15)	121						

NR: no report; GP: gemcitabine 1,250 mg/m^2 plus cisplatin 80 mg/m^2; TP: paclitaxel 200 mg/m^2 plus carboplatin AUC 6; D: docetaxel 75 mg/m^2; P: pemetrexed 500 mg/m^2; Bev (7.5): bevacizumab 7.5 mg/kg. Bev (15): bevacizumab 15 mg/kg.
*Included patients that had progressed after one platinum-based regimen.

all of them using platinum-based chemotherapy regimens

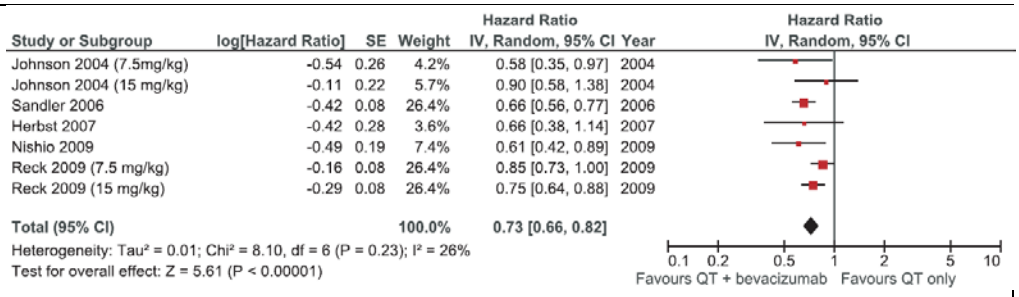
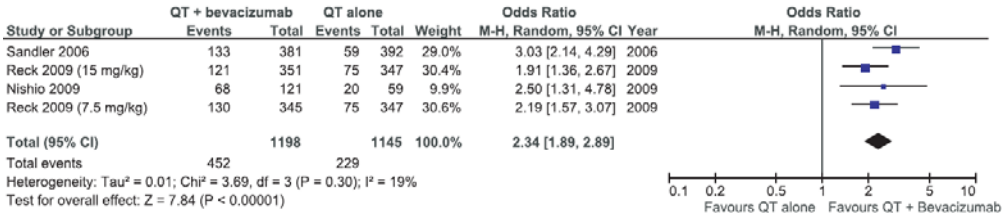
OS

addition of bevacizumab to chemotherapy resulted in a significant longer OS (HR 0.89; 95% CI 0.79 to 0.99; p = 0.04)



PFS

addition of bevacizumab to chemotherapy resulted in longer PFS (HR 0.73; 95% CI 0.66 to 0.82; p,0.00001)

	 ***ORR*** addition of bevacizumab to chemotherapy resulted in higher response rates (OR 2.34; 95% CI 1.89 to 2.89; p,0.00001) high heterogeneity between trials (I2 =53%; p =0.06)  ***Toxicity*** Some of the more clinically relevant grade 3/4 AEs increased by the addition of bevacizumab to chemotherapy were hypertension [OR, 5.51 (3.17–9.55), p,0.00001], bleeding events [OR 3.16 (1.82–5.48); p,0.0001] and febrile neutropenia [OR 2.12 (1.19–3.81), p = 0.01] … **4. Anmerkungen/Fazit der Autoren** The addition of bevacizumab to chemotherapy in patients with advanced NSCLC prolongs OS, PFS and RR. Considering the toxicities added, and the small absolute benefits found, bevacizumab plus platinum-based chemotherapy can be considered an option in selected patients with advanced NSCLC. However, risks and benefits should be discussed with patients before decision making.
Liu S et al., 2011: The safety and efficacy of EGFR TKIs monotherapy versus single-agent chemotherapy using third-generation cytotoxics as the first-line treatment for	**1. Fragestellung** To assess the risk/benefit profiles of EGFR TKIs monotherapy using erlotinib or gefitinib in comparison with single-agent chemotherapy using third-generation cytotoxics (gemcitabine, vinorelbine, taxanes) as the first-line treatment for chemonaÏve patients with advanced non-small cell lung cancer (ANSCLC) and poor performance status (PS). **2. Methodik** A pooled analysis and systematic review, randomized and non-randomized phase II or III clinical trials ***Population:*** advanced non-small cell lung cancer (ANSCLC) and poor performance

patients with advanced non-small cell lung cancer and poor performance status [49]	status (PS). ***Intervention:*** EGFR TKIs monotherapy using erlotinib or gefitinib ***Komparator:*** single-agent chemotherapy using third-generation cytotoxics (gemcitabine, vinorelbine, taxanes) ***Endpunkte*:** DCR, RR, 1-year-survival, PFS/ TTP, AEs ***Suchzeitraum:*** k.A. ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 15 (1425) ***Qualitätsbewertung der Studien:*** k.A. ***Heterogenitätsuntersuchungen:*** k.A. **3. Ergebnisdarstellung** ***RR*** pooled response rate (95% confidence interval) to EGFR TKIs for unselected population was 6% (3–8%), not substantially different from 9% (6–13%) reported by singleagent chemotherapy trials using third-generation cytotoxics **DCR** EGFR TKIs had better disease control rates with a pooled estimate of 40% (33–47%), significantly higher than 30% (20–41%) of the cytotoxics. Single-agent chemotherapy trials enrolling both elderly and poor PS patients had better results with the pooled response rate and the pooled disease control rate was 13% (11–16%) and 41% (36–46%) respectively. ***RR und DCR für Subgruppen***

Response rates and disease control rates of EGFR TKIs monotherapy and single-agent therapy using third-generation cytotoxics in all included studies and in subgroups of patients with certain characteristics.

Regimens	Groups	No	Response rate		Disease control rate	
			Pooled estimate (%)	95% CI (%)	Pooled estimate (%)	95% CI (%)
EGFR TKIs	Unselected population	300	6	3–8	40	33–47
	EGFR mutation	30	66	46–81	90	75–99
	Including PS 3 to 4	172	5	2–9	38	31–46
	PS 2 targeted	128	6	2–10	41	33–50
	all included Studies	330	18	2–34	50	34–66
Single-agent	Poor PS targeted	498	9	6–13	30	20–41
	Together with elderly	597	13	11–16	41	36–46
	Including PS 3 to 4	353	13	7–18	32	22–43
	PS 2 targeted	742	12	10–14	40	34–47
	all included studies	1095	12	9–14	36	30–43

EGFR TKIs: epidermal growth factor receptor tyrosine kinase inhibitor; PS: Eastern Cooperative Oncology Group performance status.

AEs

For safety information, despite both treatments were well-tolerated, the toxicity profile of EGFR TKIs was clearly more favorable than that reported by chemotherapy. The severe hematological adverse events related to EGFR TKIs treatment were rare.

Table 4
Adverse events of EGFR TKIs monotherapy and single-agent therapy using third-generation cytotoxics.

Regimens		Non-hematological toxicity (%)						Hematological toxicity (%)		
		Elevated serum transaminase	ILD	Skin	Fatigue	Diarrhea	Nausea/vomiting	Anemia	Neutro-penia	Thrombo-cytopenia
EGFR TKIs	Pooled estimate (%)	1.2	0.6[b]	4.0	8.7	3.9	2.2	2.4	0.3[a]	0.3[a]
	95% CI (%)	0–2.4	0.2–1.4	0.3–8.3	3.2–14.2	1.8–6.0	0.4–4.0	0.8–4.1	0–1.0	0–1.0
Sing-agent	Pooled estimate (%)	0.1[a]	0.2[b]	0.4[a]	7.8	1.2	3.4	7.7	9.3	3.0
	95% CI (%)	0–0.3	0–0.6	0.1–0.8	6.2–9.4	0.6–1.9	2.4–4.5	3.4–12.0	7.6–11.2	2.1–4.2

[a] Risks estimates corresponding to no event, the pooled probability was calculated.
[b] The beta-binomial distribution was collapsed to a simple binomial distribution, and the Wald confidence intervals was calculated.

4. Fazit der Autoren:

First, we found that the study population was heterogeneous because a small number of good PS elderly patients had been enrolled in 5 chemotherapy trials. Although elderly and poor PS patients have shared several characters, such as the reduced organ function and higher prevalence of comorbid disorders, a small number of good PS elderly patients could change the outcomes for all trials participants because the enormous differential in efficacy of treatment between good PS elderly and their poor PS counterpart.

Specifically for poor PS patients, we found EGFR TKIs had a lower pooled response rate but a significantly higher pooled disease control rate than their cytotoxics counterparts for unselected populations.

Mörth C et al., 2014:

Single-agent versus combination chemotherapy as first-line treatment for patients with

1. Fragestellung

The purpose of this study was to compare the efficacy and tolerability of first-line treatment with combination versus single agent chemotherapy in patients with advanced non-small cell lung cancer (NSCLC) and performance status (PS) 2.

2. Methodik

Population:

advanced non-small cell lung cancer and performance status 2: a literature-based meta-analysis of randomized studies [50]	advanced NCSLC mit PS 2 ***Intervention:*** combination chemotherapy ***Komparator:*** single agent chemotherapy ***Endpunkte*:** Primär: OS; sekundär: PFS, ORR ***Suchzeitraum:*** Bis 07/213 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 12 (1114) ***Qualitätsbewertung der Studien:*** Cochrane's risk of bias tool ***Heterogenitätsuntersuchungen:*** Durchgeführt (I^2) **3. Ergebnisdarstellung** **Table 1** Characteristics of eligible trials. Author [trial name] (ref) / Study phase / Treatment arms / Dose and schedule of chemotherapy / PS analysis / No of patients / Outcomes Kosmidis [8] / II / Gemcitabine / 1250 mg/m² day 1 + 14, q4w / Dedicated to PS 2 / 47 / OS, PFS, ORR, Toxicity Carboplatin-Gemcitabine / 3 AUC – 1250 mg/m² day 1 + 14, q4w / 43 Morabito [CAPPA-2] [9] / III / Gemcitabine / 1200 mg/m² day 1 + 8, q3w / Dedicated to PS 2 / 28 / OS, PFS, ORR, Toxicity Cisplatin-Gemcitabine / 60–1200 mg/m2 day 1 + 8, q3w / 29 Reynolds [USO-03012] [10] / III / Gemcitabine / 1250 mg/m² day 1 + 8, q3w / Dedicated to PS 2 / 85 / OS, PFS, ORR, Toxicity Carboplatin-Gemcitabine / 5 AUC – 1000 mg/m² day 1 + 8, q3w / 85 Zukin [11] / III / Pemetrexed / 500 mg/m² day 1, q3w / Dedicated to PS 2 / 102 / OS, PFS, ORR, Toxicity Carboplatin-Pemetrexed / 5 AUC – 500 mg/m² day 1, q3w / 103 Comella [SICOG 9909] [14] / III / Gemcitabine / 1200 mg/m² day 1 + 8 + 15, q4w / Subset analysis / 19 / ORR Paclitaxel / 100 mg/m² day 1 + 8 + 15, q4w / 22 Gemcitabine-Paclitaxel / 1000 mg/m² -80 mg/m2 day 1 + 8, q3w / 15 Gemcitabine-Vinorelbine / 1000 mg/m² -25 mg/m² day 1 + 8, q3w / 21 Georgoulias [15] / III / Docetaxel / 100 mg/m² day 1, q3w / Subset analysis / 15 / OS, ORR Cisplatin-Docetaxel / 80 mg/m² day 2–100 mg/m² day 1, q3w / 15 Hainsworth [16] / III / Docetaxel / 36 mg/m2 day 1 + 8 + 15, q4w / Subset analysis / 57 / OS Docetaxel-Gemcitabine / 30 mg/m² -800 mg/m² day 1 + 8 + 15, q4w / 65 Le Chevalier [17] / III / Vinorelbine / 30 mg/m² weekly / Subset analysis / 46 / OS Cisplatin-Vinorelbine / 120 mg/m² day 1 + 29 -> q6w, 30 mg/m² weekly / 42 Cisplatin-Vindesine / 120 mg/m² day 1 + 29 -> q6w, 3 mg/m² weekly for 6 wk -> q2w / 33 Lilenbaum [CALGB 9730] [18] / III / Paclitaxel / 225 mg/m² day 1, q3w / Subset analysis / 50 / OS, ORR Carboplatin-Paclitaxel / 6 AUC–225 mg/m2 day 1, q3w / 49 Perrone [MILES] [19] / III / Vinorelbine / 30 mg/m² day 1 + 8, q3w / Subset analysis / 45 / OS, ORR Gemcitabine / 1200 mg/m² day 1 + 8, q3w / 41 Vinorelbine-Gemcitabine / 25–1000 mg/m² day 1 + 8, q3w / 44 Quoix [IFCT-0501] [20] / III / Gemcitabine or Vinorelbine / 1150 mg/m² day 1 + 8, q3w or 25 mg/m² day 1 + 8, q3w / Subset analysis / 62 / OS Carboplatin-Paclitaxel / 6 AUC day 1–90 mg/m² day 1 + 8 + 15, q4w / 61 Sederholm [21] / III / Gemcitabine / 1250 mg/m² day 1 + 8, q3w / Subset analysis / 20 / OS (not adequate data for meta-analysis) Carboplatin-Gemcitabine / 5 AUC day 1–1250 mg/m² day 1 + 8, q3w / 24 *Abbreviations:* ref: reference; PS: performance status; No: number; q4w: every 4 weeks; q3w: every 3 weeks; OS: overall survival; PFS: progression-free survival; ORR: objective response rate. no statistical heterogeneitywas observed ***OS (11 Studien, 1114 Patienten):*** • significant improvement in OS in favor of combina-tion treatment compared with single-agent chemotherapy (HR:0.79, 95% CI: 0.71–0.88, p-value < 0.001) • both for studies dedicated to patients with PS 2 and those that performed subgroup analy-sis based on PS (HR: 0.73, 95% CI: 0.62–0.87 for studies dedicatedto PS 2 and HR: 0.83, 95% CI: 0.72–0.96 for studies with subgroupanalysis, p-value for subgroup difference = 0.30)

- improvement inOS was more pronounced in trials with platinum-based combina-tion versus single-agent therapy (HR: 0.71, 95% CI: 0.61–0.81) whileno difference was observed in studies with non-platinum basedcombination (HR: 0.96, 95% CI: 0.80–1.15) (p-value for subgroupdifference = 0.009) (Fig. 2)

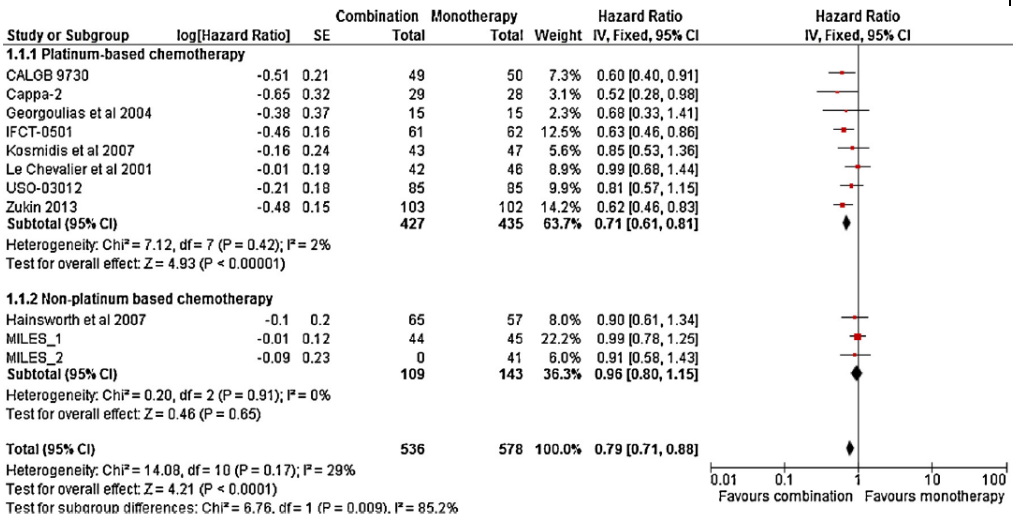


Fig. 2. Forest plot for overall survival (with subgroup analysis based on the administration of platinum-based or non-platinum based chemotherapy in combination arms).The size of the squares indicates the weight of the study. Error bars represent 95% confidence intervals (CIs). The diamond indicates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

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

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

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

combination chemotherapy resulted in statisticallysignificant longer PFS compared with single agent chemotherapy(HR: 0.61, 95% CI: 0.45–0.84, p-value = 0.002)

***ORR** (8 Studien, 822 Patienten)*

was higher in patients that received combination chemother-apy compared with those received single agent (OR: 2.20, 95% CI:1.42–3.39, p-value < 0.001)

***grades III and IV toxicity** (4 Studien)*

Due to lack of adequate data, we couldnot perform meta-analysis on the incidence of other toxicities.

	4. Anmerkungen/Fazit der Autoren This meta-analysis provides evidence supporting the use of combination chemotherapy in patients with NSCLC and PS 2. However, the patients should be informed about the higher risk for toxicity with the combination chemotherapy and the final treatment strategy should be individualized **Limits:** unable to investigate whether the survival benefit with combination chemotherapy is similar on different histological subtypesof lung cancer
NICE, 2013: Clinical effectiveness and cost-effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: a systematic review and economic evaluation [11]	**1. Fragestellung** To evaluate the clinical effectiveness and cost-effectiveness of first-line chemotherapy currently licensed in Europe and recommended by NICE, for adult patients with locally advanced or metastatic nonsmall cell lung cancer (NSCLC). 2. **Methodik** **Population** locally advanced or metastatic NSCLC **Intervention:** chemotherapy drug regimens that are currently licensed in Europe and are recommended by NICE in a monotherapy or in combination, first line **Komparator:** platinum (PLAT) drug **Endpunkte:** Overall survival (OS), OS at 1 and 2 years, progression-free survival (PFS), time to progression (TTP), tumour overall response rate, quality of life (QoL) and adverse events (AEs). **Methode:** Systmatisches Review mit Metaanalyse und Netzwerkmetaanalyse **Suchzeitraum:** 1990 bis 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 23 (11 428); nur RCTs und SRs **3. Ergebnisdarstellung** ***OS*** Among NSCLC patients with squamous disease, there were no statistically significant differences between any of the four chemotherapy regimens (DOC + PLAT, GEM + PLAT, PAX + PLAT, VNB + PLAT) in terms of increasing OS. However, both the direct and indirect evidence suggests a potential non-statistically significant advantage in terms of OS for GEM + PLAT [direct meta-analysis 1: hazard ratio (HR) = 1.08; 95% confidence interval (CI) 0.98 to 1.20] and for DOC + PLAT (direct meta-analysis 1: HR = 0.89; 95% CI 0.78 to 1.00; mixed-treatment comparison 1, HR = 0.92; 95% CI 0.81 to 1.03) compared with VNB + PLAT. Analyses of 1- and 2-year survival support this conclusion. For patients with non-squamous NSCLC there is borderline statistically significant evidence to suggest that PEM + PLAT increases OS compared with GEM + PLAT

	(direct meta-analysis 1, HR = 0.85; 95% CI 0.73 to 1.00). However, there is no statistically significant evidence to suggest that PEM + PLAT compared with GEM + PLAT increases PFS (mixed-treatment comparison 1, HR = 0.85; 95% CI 0.74 to 0.98). Among patients with EGFR M+ status, OS was not statistically significantly different in those treated with GEF and those receiving PAX + PLAT or in those treated with GEF compared with those treatedwith DOC + PLAT. ***PFS*** There was a statistically significant improvement in PFS among those patients treated with GEF compared with those treated with DOC + PLAT or PAX + PLAT. However, there was significant quantitative heterogeneity between the two trials comparing GEF with PAX + PLAT, which requires further exploration. It remains unknown whether or not the clinical effectiveness of PEM + PLAT is superior to that of GEF monotherapy for patients with non-squamous disease. The relative clinical effectiveness of PEM + PLAT in patients who are EGFR M+ is unknown. ***QoL*** (insgesamt 12 Studien) Seven trials reported no significant difference in QoL and four trials reported some significant differences between treatment groups. A lack of reporting of QoL data is a feature of the great majority of trials assessing outcomes of treatment for patients with NSCLC. This, despite its relevance to patients and clinicians, is a major shortcoming of lung cancer research. Measuring QoL outcomes in patients with advanced NSCLC is difficult mainly because of the severity of symptoms, the side effects of chemotherapy and early deaths associated with NSCLC. However, the British Thoracic Oncology Group Trial 2 has shown that it is feasible to collect QoL data in patients with performance status (PS) 0–2, stage IIIB/IV NSCLC disease within a clinical trial setting. A number of instruments/tools that measure QoL were employed in the included trials. The EORTC QLQ-C30 and the lung cancer-specific module QLQ-LC13 were used in five trials, the LCSS by three trials, and the FACT-L32 questionnaire by three trials. Four reported some significant differences between treatment groups for QoL; however, in one of these trials,3 results after two cycles of chemotherapy favoured the PAX + CARB arm over the VNB + CIS arm, and results after four cycles favoured the VNB + CIS arm. In one trial, significantly more patients in the GEF group than in the PAX + CARB group had a clinically relevant improvement in QoL, as assessed by scores on the FACT-L questionnaire (odds ratio = 1.34; 95% CI 1.06 to 1.69; $p = 0.01$) and by scores on the Trial Outcome Index (TOI) (which is the sum of the physical well-being, functional well-being and lung cancer subscale scores of FACT-L; odds ratio = 1.78; 95% CI 1.40 to 2.26; $p < 0.001$). ***AEs*** Across all the chemotherapy arms of the included trials, the most common AEs were neutropenia, anaemia and leucopenia. Rates of haematological AEs were similar for all the chemotherapy drugs with the exception of GEF, which appears to be associated with a significantly lower evere AE rate than some of the other drugs. The trials often varied in the way that AEs were defined, measured and reported.

TABLE 38 Weighted average[a] grade 3–4 AEs of 23 included trials

DOC + PLAT	GEF	GEM + PLAT	PAX + PLAT	PEM + PLAT	VNB + PLAT
Neutropenia, 71.4%	Aminotransferase, elevation, 33.8%	Granulocytopenia, 48.8%	Neutropenia, 62.5%	Granulocytopenia, 37.9%	Neutropenia, 68.3%
Leucopenia, 43.5%	Appetite loss, 5.3%	Asthenia, 40.3%	Leucopenia, 31.9%	Blood transfusions, 26.9%	Leucopenia, 47.2%
Weakness, 16.0%	Rash/acne, 3.3%	Neutropenia, 36.4%	Weakness, 14.5%	Infection, 16.4%	Oedema, 24.0%
Pneumonitis, 11.5%	Toxic deaths, 3.1%	Thrombocytopenia, 34.6%	Cancer pain, 13.2%	Neutropenia, 15.1%	Anaemia, 19.3%
Anaemia, 11.2%	Diarrhoea, 3.1%	Anorexia, 27.0%	Nausea, 10.3%	Alopecia, 11.9%	Phlebitis, 15.7%
Asthenia, 10.2%	Neutropenia, 2.8%	Leucopenia, 20.1%	Anaemia, 10.0%	Leucopenia, 8.2%	Nausea/vomiting, 11.5%
Nausea, 9.9%	Pneumonitis, 2.6%	Transfusion, 18.5%	Lethargy, 9.4%	Thrombocytopenia, 8.1%	Vomiting, 10.3%
Vomiting, 9.8%	Fatigue, 2.5%	Alopecia, 17.2%	Thrombocytopenia, 8.3%	Anaemia, 7.0%	Nausea, 9.9%
Cancer pain, 8.4%	Infection, 1.8%	Weakness, 17.0%	Neuropathy, 7.9%	Fatigue, 6.7%	Asthenia, 9.4%
Infection, 7.5%	Anaemia, 1.6%	Anaemia, 16.5%	Vomiting, 7.4%	Nausea, 6.2%	Pain, 8.3%

a Weighted average – total number of events divided by total number of patients across trial arms.

Mixed-treatment comparison – direct and indirect comparisons

- Vergleiche für verschiedene Patientengruppen (aus Platzgründen hier nicht dargestellt)

Squamöse NSCLC

The PLAT-based doublets of DOC, GEM, PAX and VNB had relatively more data points for all outcomes than the newer PEM + PLAT regimen and GEF monotherapy. In general, there was consistency between the results of the direct meta-analyses and the mixed-treatment comparison analyses, and very good consistency across individual trials in the within-group comparisons.

- ***OS***

  The evidence related to outcomes for patients with squamous disease demonstrates that there are no statistically significant differences in OS between any of the four third-generation chemotherapy treatments (DOC + PLAT, GEM + PLAT, PAX + PLAT or VNB + PLAT). However, both the direct and indirect evidence suggest a potential advantage in terms of OS for GEM + PLAT (direct meta-analysis 1, HR = 1.08; 95% CI 0.98 to 1.20) and for DOC + PLAT (direct meta-analysis 1, HR = 0.89; 95% CI 0.78 to 1.00; mixed treatment comparison 1, HR = 0.92; 95% CI 0.81 to 1.03) compared with VNB + PLAT, although this advantage is not statistically significant. Analyses of 1- and 2-year survival support this conclusion.

- **PFS**

  Only seven trials were included in the PFS analysis and the majority of these trials used slightly different definitions of PFS. There was no

	evidence of any significant difference in PFS for GEM + PLAT compared with VNB + PLAT. There was insufficient evidence to conclude whether or not there were any statistically significant differences in PFS between the other third-generation chemotherapy comparators. ***EGFR-positive*** • ***OS*** For patients with EGFR M+ status, there is no statistically significant difference in OS between GEF compared with PAX + PLAT and between GEF compared with DOC + PLAT. There is evidence of a statistically significant improvement in PFS with GEF compared with DOC + PLAT. • ***PFS*** Although there is also evidence of a statistically significant improvement in PFS with GEF compared with PAX + PLAT the significant heterogeneity between trials means the PFS results should be viewed with caution. **4. Anmerkungen/ Fazit der Autoren** The mix of patient population is now expected to be taken into consideration at the time of trial design as demonstrated in the PEM and GEF trials. Making comparisons across the six available first-line chemotherapy treatments is therefore limited by the comparability of the treatment populations in the published trials. • there were few trials with fully reported methods and the definitions of the health outcomes used often differed between trials • very few trials reported QoL data; AEs from the different trials were difficult to compare; QoL: variety of instruments/tools • CARB and CIS were treated as being similarly effective in the clinical analyses; and owing to the large volumes of data available for patients with lung cancer, • the methods employed in the review do not always match the methods stated in the original protocol
NIHR, 2011: Clinical and cost effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: a systematic review and	**1. Fragestellung** To evaluate the clinical effectiveness and cost-effectiveness of first-line **chemotherapy** currently licensed in Europe and recommended by NICE, for adult patients with locally advanced or metastatic nonsmall cell lung cancer (NSCLC). **2. Methodik** **Population**: Chemotherapy-naive adult patients with locally advanced or metastatic NSCLC **Intervention**: Any first-line chemotherapy treatment currently licensed in Europe and approved by NICE including: • PLAT-based chemotherapy (CARB or CIS) in combination with DOC,

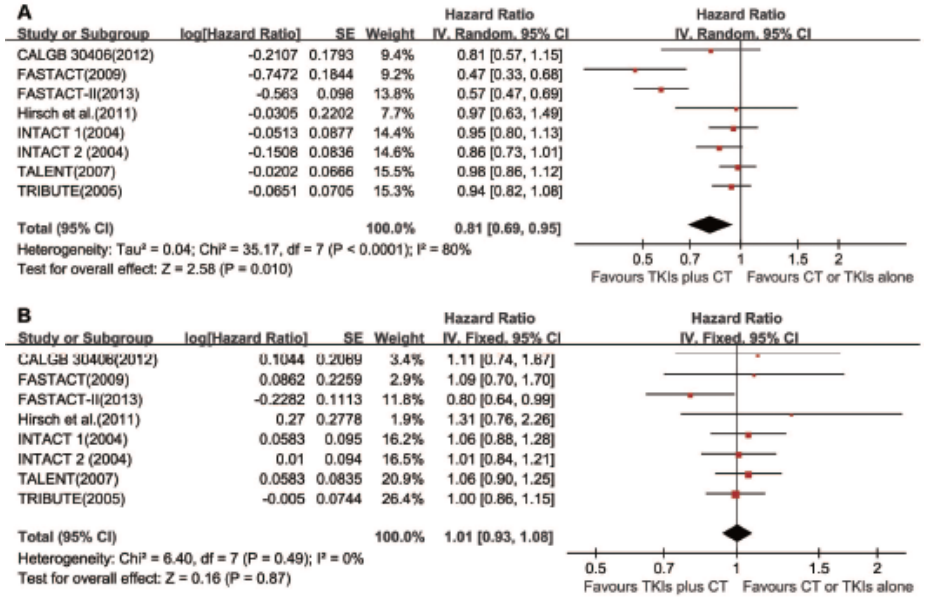
economic evaluation. Health, Technology Assessment [32]	GEM, PAX or VNB • PEM + CIS • Single-agent therapy – GEF **Komparator**: Any first-line chemotherapy treatment currently licensed in Europe and approved by NICE for the first-line treatment of patients with locally advanced and metastatic NSCLC **Endpunkt**: OS, PFS, TTP, ORR, AE, HRQoL **Methode**: Systematic review an meta-analysis of RCTs and systematic reviews **Suchzeitraum**: 2000-2009 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 23 RCTs (n=11.428) **3. Ergebnisdarstellung** <u>Non-small cell lung cancer patients with squamous disease (18 RCTs, 7.382 patients):</u> **Overall survival:** Kein statistisch signifikanter Unterschied zwischen: • Gemcitabine plus platinum compared with paclitaxel plus platinum • Gemcitabine plus platinum compared with docetaxel plus platinum • Vinorelbine plus platinum compared with paclitaxel plus platinum • Vinorelbine plus platinum compared with docetaxel plus platinum • Paclitaxel plus platinum compared with docetaxel plus platinum **PFS:** statistisch signifikanter Zusammenhang zwischen: • Vinorelbine plus platinum compared with paclitaxel plus platinum (1 RCT, 140 patients): statistically significant suggesting an advantage for VNB + CIS (HR = 1.52; 95% CI 1.06 to 2.17) kein statistisch signifikanter Zusammenhang zwischen: • Gemcitabine plus platinum compared with vinorelbine plus platinum • Gemcitabine plus platinum compared with paclitaxel plus platinum • Gemcitabine plus platinum compared with docetaxel plus platinum • Vinorelbine plus platinum compared with docetaxel plus platinum <u>Population 2: non-small cell lung cancer patients with non-squamous disease (20 RCTs, 9553 patients).</u> **Overall survival:** Kein statistisch signifikanter Unterschied zwischen: • Gemcitabine plus platinum compared with pemetrexed plus platinum • Vinorelbine plus platinum compared with pemetrexed plus platinum • Paclitaxel plus platinum compared with pemetrexed plus platinum • Docetaxel plus platinum compared with pemetrexed plus platinum

	PFS: kein statistisch signifikanter Zusammenhang zwischen: • Gemcitabine plus platinum compared with pemetrexed plus platinum • Vinorelbine plus platinum compared with pemetrexed plus platinum • Paclitaxel plus platinum compared with pemetrexed plus platinum • Docetaxel plus platinum compared with pemetrexed plus platinum <u>Epidermal growth factor receptor mutation-positive population.</u> **Overall survival:** Kein statistisch signifikanter Unterschied zwischen: • Paclitaxel plus platinum compared with gefitinib • Docetaxel plus platinum compared with gefitinib • Paclitaxel plus platinum compared with docetaxel plus platinum **PFS:** statistisch signifikanter Zusammenhang zwischen: • Paclitaxel plus platinum compared with gefitinib (2 RCTs, 491 patients) (HR = 0.38; 95% CI 0.24 to 0.60, I^2=78,8%) • Docetaxel plus platinum compared with gefitinib (1 RCT, HR = 0.49; 95% CI 0.33 to 0.73) kein statistisch signifikanter Zusammenhang zwischen: • Paclitaxel plus platinum compared with docetaxel plus platinum **4. Anmerkungen/Fazit der Autoren** Overall, the quality of the included RCTs was poorer than expected – there were few trials with fully reported methods and the definitions of the health outcomes used often differed between trials. In addition, it is generally agreed that RCTs typically include patients who are generally fitter and younger than patients receiving treatment in routine clinical practice and that outcomes from RCTs are not always of the same magnitude as those gained from routine care. Caution is therefore required when interpreting and comparing the results of these trials, in particular the results generated through meta-analysis and mixed-treatment comparison. The evidence related to outcomes for patients with squamous disease demonstrates that there are no statistically significant differences in OS between any of the four third-generation chemotherapy treatments (DOC + PLAT, GEM + PLAT, PAX + PLAT or VNB + PLAT). However, both the direct and indirect evidence suggest a potential advantage in terms of OS for GEM + PLAT (direct meta-analysis 1, HR = 1.08; 95% CI 0.98 to 1.20) and for DOC + PLAT (direct meta-analysis 1, HR = 0.89; 95% CI 0.78 to 1.00; mixedtreatment comparison 1, HR = 0.92; 95% CI 0.81 to 1.03) compared with VNB + PLAT, although this advantage is not statistically significant. Analyses of 1- and 2-year survival support this conclusion.
Ouyang PY et al., 2013: Combination of	**1. Fragestellung** Controversy continues regarding the role of the addition of EGFR–TKIs in patients receiving chemotherapy. Therefore, we conducted this meta-

EGFR-TKIs and Chemotherapy as First-Line Therapy for Advanced NSCLC: A Meta-Analysis [57]	analysis to comprehensively estimate the treatment effect of the combined regimen on PFS and overall survival (OS) based on characteristics of patients. **2. Methodik** ***Population:*** chemotherapy-naı¨ve patients with advanced NSCLC ***Intervention:*** Chemotherapy, first-line treatment ***Komparator:*** EGFR–TKI monotherapy or the combined regimen of EGFR– TKI and chemotherapy ***Endpunkte*:** PFS, OS ***Suchzeitraum:*** Nur: prospective randomized controlled trials (phase II or III) ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 8 (4585) ***Qualitätsbewertung der Studien:*** examined the randomization procedure, estimation of sample size, blinding, loss to follow-up, dropout and if the intention-to-treat analysis ***Heterogenitätsuntersuchungen:*** Chi-square test and I^2 statistic Publication ias: Begg's test and Egger's test **3. Ergebnisdarstellung** **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/m²,d1)/CBP(AUC = 5,d1)+GEM1250(mg/m²,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/m²,d1)/CBP(AUC = 5,d1)+GEM1250(mg/m²,d1,8),q4w*6 | 226vs225 | 59.0(31–96)vs57.3(37–88) | 94vs85 | 100vs100 | 112vs107 | 49vs48 | | INTACT 1(2004) [7] [17] | G‡ | DDP(80 mg/m²,d1)+GEM(1250 mg/m²d1,8),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/m²),q3w*6 | 345vs345 | 61(27–86)vs63(31–85) | 146vs133 | NA | NA | | | TALENT(2007) [9] | E | DDP(80 mg/m²,d1)+GEM(1250 mg/m²d1,8),q3w*6 | 580vs579 | 61(26–82)vs60(28–84) | 125vs142 | 3vs4 | 8vs10 | NA | | TRIBUTE(2005) [10] [18] | E | CBP(AUC = 6)+TAX(200 mg/m²),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/m²),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/m²),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. doi:10.1371/journal.pone.0079000.t001 ***Unselected Patients (4 Studien)*** • ***PFS:*** Significant PFS benefit was observed from the combined regimen of TKIs and chemotherapy (HR= 0.81, 95% CI 0.69–0.95, P = 0.01; Figure 2a) based on random-effects model, due to significant heterogeneity (Chi2 = 35.17, P<0.001; I^2 = 80%).

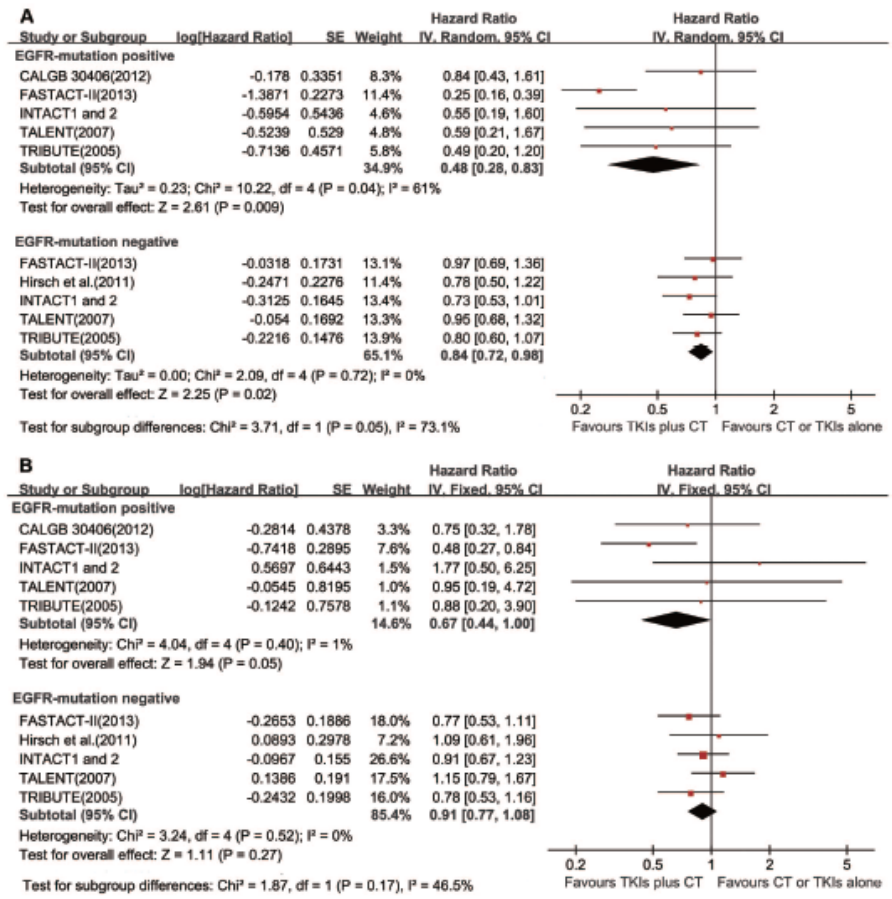
- ***OS:*** no evidence of improvement in OS with the combined regimen (HR= 1.01, 95% CI 0.93–1.08, P = 0.87, fixed-effects model

Figure 2. Forest plots in unselected patients. Figure 2. Forest plots in unselected patients.



Selected Patients by EGFR-Mutation Status (4 Studien)

- ***PFS***: combined regimen was superior over chemotherapy or TKIs monotherapy with a significant improvement in PFS (HR= 0.48, 95% CI 0.28–0.83, P = 0.009); combined regimen also showed significant PFS benefit in the EGFR-mutation negative cohort, compared with chemotherapy or TKIs monotherapy (HR =0.84, 95% CI 0.72–0.98, p= 0.02)
- ***OS:*** combined regimen marginally enhanced OS of EGFR-mutation positive patients (HR =0.67, 95% CI 0.44–1.00, P = 0.05), but not EGFR-mutation negative patients (HR =0.91, 95% CI 0.77–1.08, p= 0.27)



4. Anmerkungen/Fazit der Autoren

In conclusion, on the basis of this meta-analysis, combination of EGFR–TKIs and chemotherapy leads to PFS benefit as first-line treatment for advanced NSCLC, regardless of EGFR-mutation status, but has no demonstrable impact on OS. And there is a larger magnitude of PFS benefit for Asian patients, with sequential administration of EGFR–TKIs and chemotherapy. EGFR-mutation status is still a predictive biomarker of benefit with the combined regimen, for a larger magnitude of improvement in EGFR-mutation positive patients. This strategy deserved to be considered in the future although it is not approved for advanced NSCLC at the moment.

Pan G et al., 2013:

Comparison of the efficacy and safety of single-agent erlotinib and doublet molecular targeted agents based

1. Fragestellung

This study aims to assess the efficacy and safety of doublettargeted agents based on erlotinib in patients with advanced NSCLC.

2. Methodik

Population:

Adult patients with advanced NSCLC

Intervention:

doublets (erlotinib plus another targeted drugs)

on erlotinib in advanced non-small cell lung cancer (NSCLC): a systematic review and meta-analysis [58]	***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:*** *k.A.* ***Heterogenitätsuntersuchungen:*** I^2 **3. Ergebnisdarstellung** 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

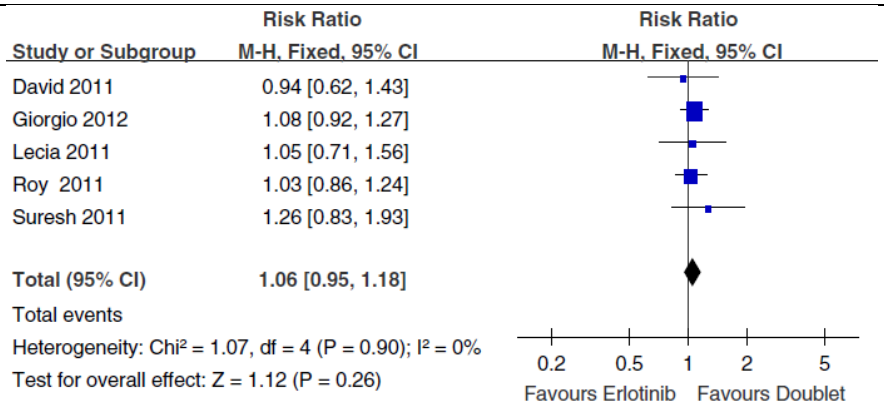
Table 1 Main characteristics of the five studies included in the meta-analysis

	No. of male/female	Median age (years)	ECOG PS score	Stage IIIB/IV	Histology type SCC, AC	Smoking history (Y/N)	No. of prior chemotherapy regimens	Treatment schedule	Objective response rate	Disease control rate	1-year overall survival rate
David 2011		65	48 (0)	ND		139/27		Erlotinib (150 mg daily) + sorafenib (400 mg twice daily) vs erlotinib + placebo			
	166		90 (1)		SCC 50		101 (1)		9/111	60/111	40/111
	88/78		23 (2)		Others 116		65 (2)				
			5 (unknown)						6/55	21/55	21/55
Giorgio 2012		61		74/886	SCC 270	774/186	680 (1)	Erlotinib (150 mg daily) + sunitinib (37.5 mg daily) vs erlotinib + placebo			
	960		359 (0)		AC 506		269 (2)		51/480	206/480	192/480
	581/379		598 (1)		Others 184		11 (≥3)		3/480	68/480	178/480
Lecia 2011		63	40 (0)	19/148	SCC 50	132/35		Erlotinib (150 mg daily) + tivantinib (360 mg twice daily) vs erlotinib + placebo			
	167		126 (1)		AC 101		101 (1)		8/84	22/84	32/84
	100/67		1 (unknown)		Others 16		66 (>1)		6/83	17/83	30/83
Roy 2011		65	250 (0)	ND	SCC 28	569/67	ND	Erlotinib (150 mg daily) + bevacizumab (15 mg/kg iv) vs erlotinib + placebo			
	636		342 (1)		AC 477				38/319	136/319	134/319
	341/295		43 (2)		Others 131				19/317	104/317	129/317
Suresh 2011		62	ND	25/146	SCC 43	149/22		Erlotinib (150 mg/day, daily) + R1507 (9 mg/kg/wk or 16 mg/kg every 3 weeks iv) vs erlotinib + placebo			
	171				AC 87		126 (1)		9/114	60/114	48/114
	114/57				Others 41		45 (2)		5/57	28/57	19/57

Effects: fixed effect models

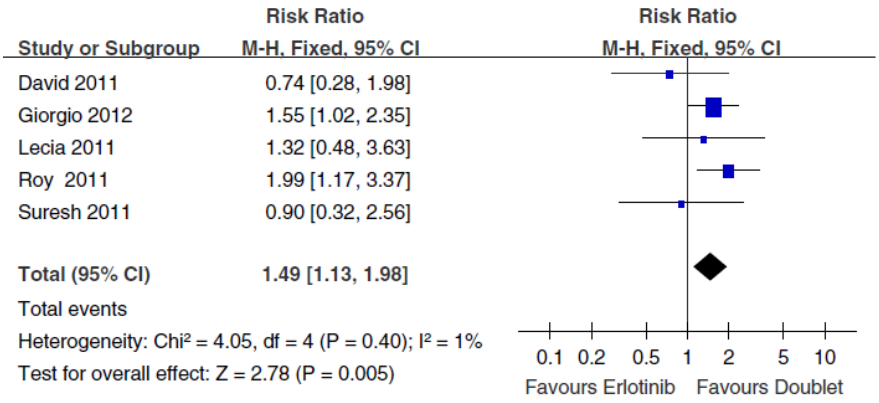
OS

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)



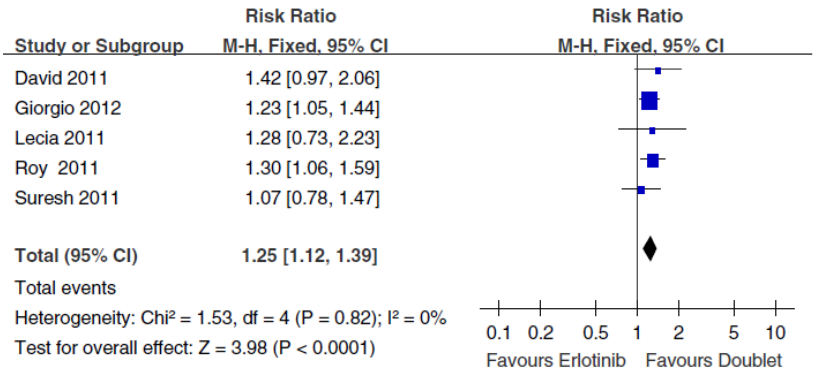
ORR

ORR were significantly superior with doublets (HR 1.49, 95%CI 1.13–1.98, p<0.05;



DCR (disease control rate)

and 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. **4. 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.
Perez-Moreno MA et al., 2014: Systematic review of efficacy and safety of pemetrexed in non-small-cell-lung cancer [59]	**1. Fragestellung** to evaluate the efficacy and safety of pemetrexed therapy in adult patients with advanced stage NSCLC. And the specific objectives were to evaluate the efficacy of pemetrexed in NSCLC in each of the approved indications first-line induction, maintenance and second-line), according to histology (squamous/epidermoid adenocarcima or large cell) and to assess safety according to concomitant therapy administered. **2. Methodik** ***Population:*** NSCLC, Population: age 18 years or older patients ***Intervention:*** *pemetrexed* ***Komparator:*** *Other available therapies* ***Endpunkte*:** Nicht vorab spezifiziert ***Suchzeitraum:*** 04/ 2004 is 04/ 2012 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 5 (3541), nur RCTs ***Qualitätsbewertung der Studien:*** specific assessment scales, Critical Appraisal Skills Program (CASP) adapted for CASP Spain ***Heterogenitätsuntersuchungen:*** **3. Ergebnisdarstellung** Eingeschlossene RCTs in Metaanalyse: nur first line, Studienqualität moderate bis high In first-line induction, treatment with pemetrexed associated with a platinum was similar in terms of efficacy to other alternative

chemotherapy regimens, except in patients with non-squamous histology, in whom survival was higher in the experimental group. In maintenance treatment, greater efficacy was seen with pemetrexed in patients with nonsquamous histology. In second-line treatment, there were no significant differences in terms of efficacy and safety for pemetrexed treatment versus other chemotherapy options. The most frequent adverse reactions were: hematological, gastrointestinal and neurological. All were significantly less frequent with pemetrexed versus other alternative therapies, except for liver toxicity.

Table 5 Efficacy results of PMX in NSCLC

Study	Study objective	Efficacy variables									
Scagliotti et al. [13]	First-line therapy: induction		OS (months)			PSF (months)			Rate response (%)		
		Overall population	CP	CG	*p*	CP	CG	*p*	CP	CG	*p*
			10.3	10.3		9.4	10.8	0.05	30.6	28.2	<0.001
		Non-squamous	11.8	10.4	0.005	5.3	4.7				
		Adenocarcinoma	12.6	10.9	0.03						
		Large cell	10.4	6.7	0.03						
		Squamous	9.4	10.8	0.05	4.4	5.5				
Gronberg et al. [15]			OS (months)								
			CP	CG	*p*						
		Overall population	7.3	7.0	0.63						
		Non-squamous	7.8	7.5	0.77						
Socinski et al. [16]			OS (months)			Time to progression (months)				Rate response	
			ChP	ChD		ChP	ChD			ChP	ChD
			12.7	9.2		6	4.1		Complete response (%)	2.8	0
									Partial response (%)	19.4	27.1
									Stable disease (%)	55.6	30
									Response duration (months)	5.5	5.4
Rodrigues-Pereira et al. [17]					Pemetrexed/Cb		Docetaxel/Cb				p HR
			OS (months)		14.9		14.7				0.933
			PFS (months)		5.8		6.0				0.801
			DoR (months)		5.5		5.4				0.643
			SWT 3–4		3.2		0.7				<0.001
			SWT 4		12.2		2				<0.001
			SWT clínica		3.6		1.3				<0.001
Al-Saleh et al. [22]		HR (OS) favours experimental group = 0.88 [0.81-1.08]									

Table 5 continued

Study	Study objective	Efficacy variables									
Ciuleanu et al. [18]	First-line therapy: maintenance		OS (months)			PSF (months)			Rate response (%)		
			PMX	Placebo	*p*	PMX	Placebo	*p*	PMX	Placebo	*p*
		Overall population	13.4	10.6	0.012	4.0	2.0	<0.0001	52	33	<0.0001
		Non-squamous	15.5	10.3	0.02	4.4	1.8	<0.0001	58	33	<0.0001
		Adenocarcinoma	16.8	11.5	0.026	4.6	2.7	<0.0001	61	33	<0.0001
		Large cell	8.4	7.9	0.964	4.5	1.5	0.125	46	33	0.67
		Squamous	9.9	10.8	0.678	2.4	2.5	0.896	35	35	>0.999
		* % Patients with complete response + partial response + stable disease									
Belani et al. [19]					Pemetrexed			Placebo			pHR
		Overall quality of life			5.75			3.71			<0.267
		Interference with daily life			6.51			3.98			0.512
Paz-Ares et al. [20]		Exitus (%)			PFS (months)				Rate response (%)*		
		PMX	Placebo	*p*	PMX	Placebo	*p*		PMX	Placebo	*p*
		79	74	>0.01	4.1	2.6	<0.001	Complete response(%)	0	0	NE
								Partial response (%)	3	0.6	0.18
								Stable disease (%)	69	59	0.039
								Disease control (%)#	72	60	0.00
								Progression disease(%)	28	39	0.015
Hanna et al. [21]	Second line therapy				Pemetrexed			Docetaxel			*p*
		PFS median (months)			2.9			2.9			0.759
		OS median (months)			8.3			7.9			
		Time to progression (months)			3.4			3.5			0.721
		DoR (months)			4.6			5.3			0.427

Cb carboplatin, *CP* cisplatin/pemetrexed, *CG* cisplatin/gemcitabine, *ChP* carboplatin/pemetrexed, *ChG* carboplatin/gemcitabine, *ChD* carboplatin/docetaxel, *PMX* pemetrexed, *DoR* response duration. *QoL* quality of life, *OS* Overall survival, *PFS* survival progression free, *pHRp* Hazard ratio, *R* response, *SWT* survival without toxicity

* Patients with Complete response + Partial response + stable disease

Disease control (6 weeks)

4. Anmerkungen/Fazit der Autoren

Due to the high degree of uncertainty as to its efficacy in certain subgroups of patients, including conflicting data; to its recent incorporation, and therefore lack of safety data in the medium and long term, and the high budgetary impact of its incorporation into health

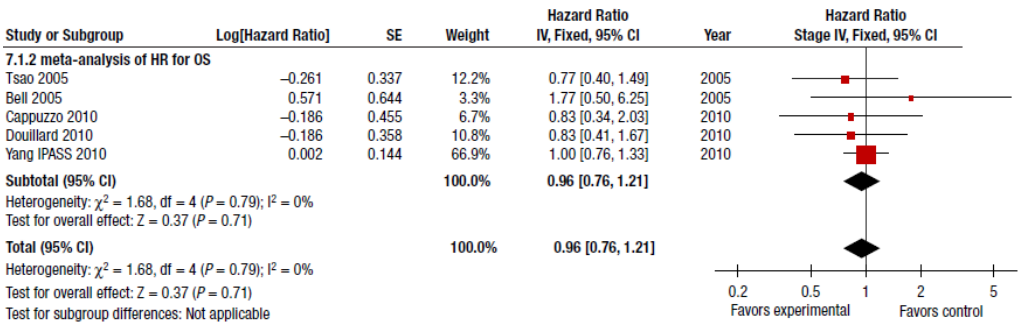
	systems, it seems reasonable to optimize its use, identifying those patients who may benefit most.
Petrelli et al., 2012: Efficacy of EGFR tyrosine kinase inhibitors in patients with EGFR-mutated non-small-cell lung cancer: a meta-analysis of 13 randomized trials [60]	**1. Fragestellung** To evaluate the benefit of **EGFR TKIs** in EGFR-mutated NSCLCs. Eligible studies included published randomized controlled trials in which erlotinib or gefitinib (alone or with chemotherapy) were compared with standard therapy **2. Methodik** **Population**: Patienten mit fortgeschrittenem/metastasiertem NSCLC und EGFR-Mutation, die entweder in der Erstlinie oder in späteren Behandlungslinien mit Erlotinib oder Gefitinib behandelt wurden **Intervention**: TKIs (allein oder + Chemotherapie) **Komparator**: Chemotherapie ohne TKI **Endpunkt**: OS, PFS, ORR **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: bis 2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 13 (n= 10 433) **3. Ergebnisdarstellung** 8 first line trials

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

Response rate (7 trials, 994 patients, 3 trials erlotinib, 4 trials gefitinib): statistically significant difference in favor of EGFR TKI (RR, 2.09 [1.82, 2.39]; p=0.04; fixed-effects model)

OS: Forrest Plot for Hazard Ratio



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.

	5. Hinweise durch FB Med • Keine Beschreibung zur Evaluation der Qualität der eingeschlossenen Studien. • Daten zu OS und PFS liegen für first und second line nicht getrennt vor.
Petrelli F et al., 2013: Platinum rechallenge in patients with advanced NSCLC: A pooled analysis [61]	**1. Fragestellung** This systematic analysis is the first review aiming to assess the clinical efficacy of platinum-doublet re-challenge, by using data pooled from clinical studies that enrolled patients with relapsed NSCLC after the first-line (platinum-based) failure. **2. Methodik** ***Population:*** patients with advanced NSCLC ***Intervention:*** second-line, platinum-based doublets, containing PEM or TAX agents ***Endpunkte:*** OS or PFS and RR ***Studiendesign*:** prospective clinical trials, minimum of 10 patients ***Suchzeitraum*:** between 1998 and 2012 ***Ausschlusskriterien*:** Studies published in a language other than English or that included less than 90% of patients pre-treated with platinum-based first-line doublets were excluded. **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 11 (n = 607) **3. Ergebnisdarstellung** <u>Therapielinie:</u> Zweitlinie: (n = 364), Drittlinie oder mehr: n = 243 (40 %) <u>Studiendesign:</u> 5 phase II trials, 3 prospective series, 1 prospective study, 2 retrospective analysis <u>Therapieschemen:</u> Carboplatin/PEM, Carboplatin/Gemcitabin oder PEM, platinbasiert/PEM, Cisplatin/DOC, Carboplatin/Paclitaxel, Cisplatin/Paclitaxel Time to progression (1st line):

0,8 – 13,7 month or 21,9 % -78,8 % > 6 month

Zweitlinientherapie-Studien - Ergebnisdarstellung

Response Rate (range) 15 – 40 %

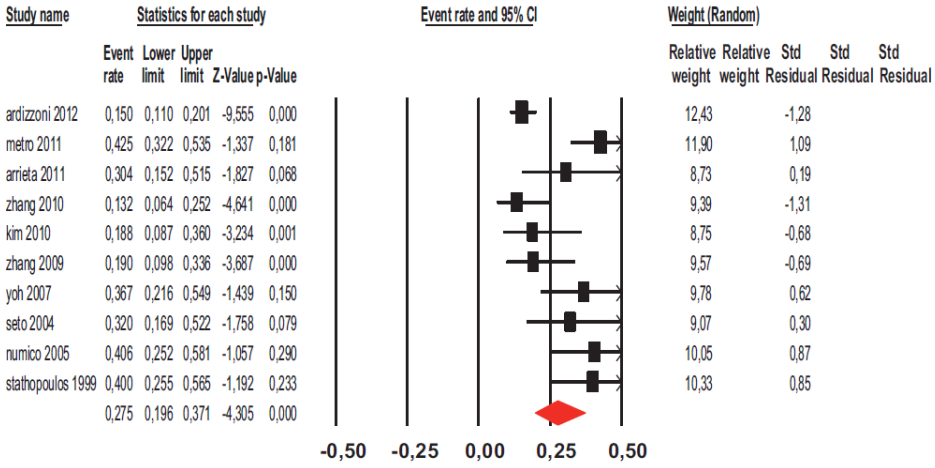
PFS (range): 3,2 – 6,4 month

OS (range): 8,5 – 12,5 month

Ergebnisdarstellung (**gesamt**):

ORR

with platinum-combinations was 27,5 %, with 22 % in (in all histologies) for patients treated with PEM-based doublets (range: 13,4 % – 34,1 %) and 37,8 % (range: 29,7 % – 46,7 %) for TAX-based doublets ($p < 0,0001$).



PFS

overall median PFS and survival time following second-line therapy were 3,9 (range 2,3 – 6,43) and 8,7 (range 8 – 17,4) months with weighted median PFS/OS of 3,9/8,7 months for PEM- and 5,3/8,5 months for TAXs-doublets ($p < 0,0001$ for PFS).

Sensitivity testing:

The median weighted PFS and OS were 3.9 and 8.7 for second-line trials and 5.8 and 10 months for trials that included patients treated both as second-line and beyond.

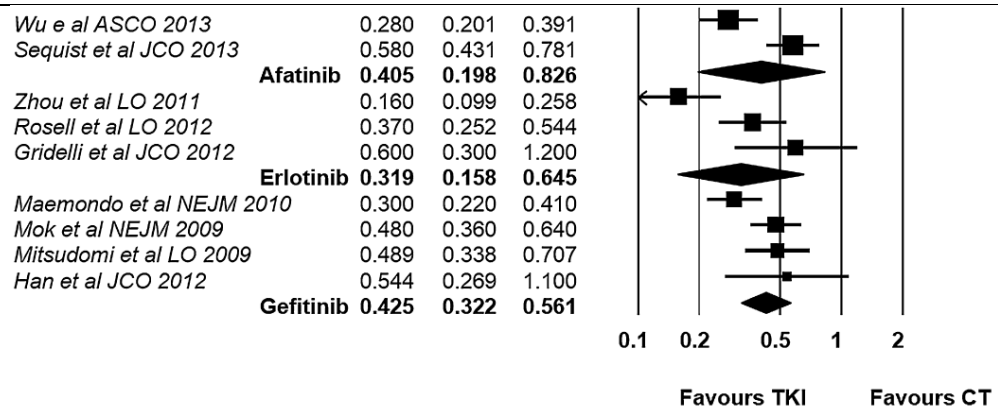
4. Anmerkungen/Fazit der Autoren

With the limitations of small and not randomised trials included, this pooled analysis shows that NSCLC patients who relapsed after a first-line platinum-based chemotherapy obtain a tumour response of 27% from a platinum rechallenge containing PEM or TAXs. Response rate and median PFS appear better with TAXs-than with PEM-doublets.

5. Hinweise durch FB Med:

- no quality assessment of studies

	• using a random-effect model, heterogeneity not further mentioned • inclusion criteria for study design do not match with included studies • only two thirds had adenocarcinoma • no significant publication bias detected
Pilotto S et al., 2014: Predictors of outcome for patients with lung adenocarcinoma carrying the epidermal growth factor receptor mutation receiving 1st-line tyrosine kinase inhibitors: Sensitivity and meta-regression analysis of randomized trials [62]	**1. Fragestellung** We performed a sensitivity and meta-regression analysis, cumulating all randomized trials exploring the benefit of afatinib, erlotinib and gefitinib *versus* chemotherapy in advanced EGFR mutant NSCLC, to investigate the potential role of additional clinico-pathologicalpredictors of TKIs efficacy. **2. Methodik** ***Population:*** advanced EGFR mutant NSCLC ***Intervention:*** afatinib, erlotinib , gefitinib ***Komparator:*** chemotherapy ***Endpunkte*:** PFS, OS, ORR ***Suchzeitraum:*** bis 06/2013 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 7 (1075) ***Qualitätsbewertung der Studien:*** ***Heterogenitätsuntersuchungen:*** Durchgeführt (I^2) **3. Ergebnisdarstellung** **PFS** 9 RCT (1790patients)



ORR 9 RCT (1733 patients)

Overall response rate, risk ratio and interaction test (Cochrane-*Q* and *p* value) according to ethnicity (Asian *versus* Caucasian *versus* mixed), trial design (prospective *versus* retrospective) and drug (gefitinib *versus* erlotinib *versus* afatinib).

Subgroups		ORR (%) [95% CI]		RR (95% CI) *p* value	Interaction [Cochrane-*Q*] *p* value
		TKI	CT		
Ethnicity	Asian	71.2 [66.7–74.7]	34.1 [30.1–38.2]	2.13 (1.69–2.37) <0.0001	[6.129] 0.044
	Caucasian	58.1 [47.7–68.5]	14.9 [7.4–22.4]	3.89 (2.28–6.27) <0.0001	
	Mixed	54.8 [48.6–60.9]	22.4 [15.3–29.4]	2.41 (1.72–3.37) <0.0001	
Trial Design	Prospective	65.1 [61.8–68.4]	25.8 [22.2–29–4]	2.50 (2.16–2.90) <0.0001	[13.633] <0.0001
	Retrospective	69.6 [62.9–76.4]	43.2 [35.7–50.8]	1.57 (1.29–1.92) <0.0001	
Drug	Gefitinib	71.5 [66.6–76.3]	38.0 [32.7–43.3]	1.81 (1.54–2.11) <0.0001	[9.924] 0.007
	Erlotinib	67.0 [60.3–73.7]	24.1 [17.8–30.4]	2.58 (1.98–3.37) <0.0001	
	Afatinib	68.1 [63.7–72.5]	22.8 [17.4–28.1]	2.70 (2.11–3.45) <0.0001	

ORR, overall response rate; CI, confidence intervals; TKI, tyrosine kinase inhibitors; CT, chemotherapy; RR, relative risk.

OS 7 (1075patients)

No statistically significant differences in OS were observed (HR 1.03, 95% CI0.86–1.23, $p = 0.72$).

Meta-regression

None of the putative predictors of outcome as continu-ous variables, Asian ethnicity (*Z*-value = −1.13; $p = 0.25$),female gender (*Z*-value = 1.59; $p = 0.11$), never-smoking sta-tus (*Z*-value = 1.54; $p = 0.12$), and exon-19 EGFR mutation(*Z*-value = 1.15; $p = 0.87$) significantly affected PFS at themeta-regression analysis (Supplementary Fig. II). Con-versely, Asian ethnicity (*Z*-value = −2.23; $p = 0.01$), female gender (*Z*-value = −2.84; $p = 0.044$) and non-smoking status(*Z*-value = −3.23; $p = 0.0012$) significantly correlates withresponse with the exception of the exon-19 deletion (*Z*-value = 0.66; $p = 0.50$)

4. Anmerkungen/Fazit der Autoren

With regard to progression-free survival (PFS), a significant interaction according to ethnicity (Asian *versus* Caucasian *versus*mixed) and to trial design (retrospective *versus* prospective EGFR analysis), was found; a

	trend toward significance with regard to type ofdrug (gefitinib *versus* erlotinib *versus* afatinib) was determined. No statistically significant differences in survival were observed. With regardto response, a significant interaction according to ethnicity, trial design and type of drug, was found.
Qi WX et al., 2012: Erlotinib and pemetrexed as maintenance therapy for advanced non-small-cell lung cancer: a systematic review and indirect comparison [65]	**1. Fragestellung** Two new agents have recently been licensed as maintenance therapy for advanced non-small-cell lung cancer (NSCLC) by the US Food and Drug Administration. This paper aims to systematically review the evidence from all available clinical trials of erlotinib and pemetrexed as maintenance therapy for advanced NSCLC. **2. Methodik** ***Population:*** advanced NSCLC ***Intervention:*** erlotinib or pemetrexed ***Komparator:*** placebo or observation ***Endpunkte*:** Nicht vorab spezifiziert ***Suchzeitraum:*** 1980 bis 03/2011 Nur prospective RCTs ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** *5 (Gesamtzahl: k.A.)* ***Qualitätsbewertung der Studien:*** Jadad scale ***Heterogenitätsuntersuchungen:*** I^2 **3. Ergebnisdarstellung**

Table 1. Characteristics of the five trials in the meta-analysis.

Study/Year	Recruiting time	Initial therapy prior to maintenance	Maintenance therapy	Patients (*n*)	Patients ethnicity		Median age, y	Male sex, %	Median OS, mo	Median PFS/TTP, mo	Jadad score
					Caucasian, *n*	Non-Caucasian, *n*					
Cappuzzo *et al.*, 2010[25] (SATURN)	2005–2008	Platinum based doublet chemotherapy for less than 6 cycles	Erlotinib 150 mg/d, po	438	370	68	60	73%	12	12.3 weeks	3
			placebo	451	376	75	60	75%	11	11.1 weeks	
Herbst *et al.*, 2005[26] (TRIBUTE)	2001–2002	CBP plus PTX for less than 6 cycles plus erlotinib 150 mg/d po	Erlotinib 150 mg/d, po	539	452	87	62.7	59.7%	10.6	5.1	3
		The same treatment schedule without erlotinib	Placebo	540	482	57	62.6	61.6%	10.5	4.9	
Petrel *et al.*, 2010[28] (IFCT-GFPC 0502)	2006–2009	GEM plus DDP for four cycles	GEM 1250 mg/m2 d1,8. iv. q.3.w.	154	–	–	–	–	–	3.7	3
			Erlotinib 150 mg/d po	155	–	–	–	–	–	2.8	
			Observation	155	–	–	–	–	–	2.1	
Ciuleanu *et al.*, 2009[27]	2005–2008	Platinum-based chemotherapy for four cycles	Pemetrexed 500 mg/m2 d1. iv.q.3.w	441	279	162	60.6	73%	13.4	4.3	5
			Placebo	222	149	73	60.4	73%	10.6	2.6	
Paz-Ares *et al.*, 2011[29] (PARAMOUNT)	2008–2010	Pemetrexed plus DDP for four cycles	Pemetrexed 500 mg/m2 d1. iv.q.3.w. + BSC	359	339	20	61	56%	–	3.9	3
			Placebo + BSC	180	171	9	62	62%	–	2.6	

AUC = area under the concentration/time curve; OS = overall survival; PFS = progressice-free survival; TTP = time-to progression; BSC = best support care; GEM = gemcitabine; DDP = cisplatin; CBP = carboplatin; PTX = paclitaxel.

OS (3 Studien, n= 2278)
pooled erlotinib versus placebo and found a pooled HR of 0.90 (95% CI 0.83–0.98, p=0.02

PFS
Pooled analysis favored the erlotinib group giving HR of 0.77 (95% CI 0.70–0.84, p<0.00001)

Indirect comparision
We did not observe a significant difference between erlotinib and pemetrexed in terms of OS (HR 0.88, 95% CI 0.71–1.08, p= 0.22) using placebo as a comparator. But the results of the indirect comparison of PFS data suggested that people taking pemetrexed were less likely to progress than those taking erlotinib (HR 0.71, 95% CI 0.60–0.85, p<0.0001). Pemetrexed might therefore be superior to erlotinib in preventingprogression in this patient population.

4. Anmerkungen/Fazit der Autoren

There is evidence to suggest that maintenance treatment with erlotinib or pemetrexed has clinically relevant and statistically significant advantages over treatment with placebo or observation in patients with advanced NSCLC.

Qi WX et al., 2012:

Doublet versus single cytotoxic agent as first-line treatment for elderly patients with advanced non-small-cell lung cancer: a systematic review and meta-analysis [64]

1. Fragestellung

to perform a systematic review and meta-analysis of all randomized controlled trials that compared the efficacy of **doublet versus single third-generation cytotoxic agent** as first-line treatment for elderly patients with advanced non-small-cell lung cancer (NSCLC).

2. Methodik

Population*:*
elderly (older than 65 years) patients with advanced non-small-cell lung cancer. First-line
Interventionen:
doublet cytotoxic agents
Komparator*:*
single third-generation cytotoxic agent
Endpunkte*:*

OS, TTP, ORR, Toxicity

***Methode**:*

systematic review and meta-analysis of RCTs

***Suchzeitraum**:*

1980-2011

***Anzahl eingeschlossene Studien/Patienten** (Gesamt):*

10 (n= 2 510)

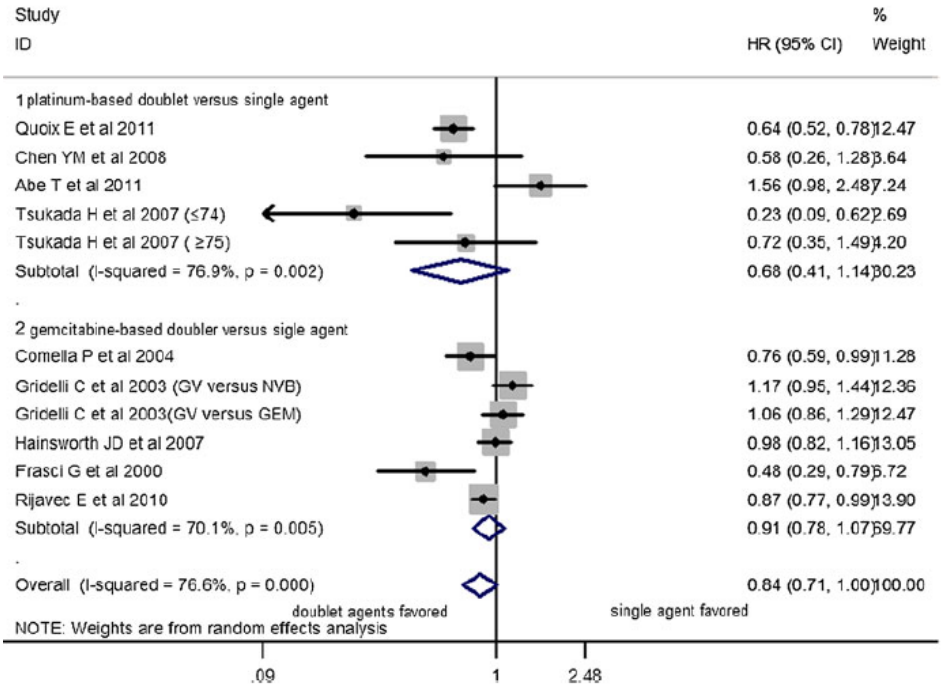
3. Ergebnisdarstellung

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

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

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

Overall survival (9 trials): no statistically significant difference, HR of 0.84 (95% CI = 0.71–1.00, p = 0.053, I²=76.6%)



1-year survival (6 trials statistically significant difference in favor of doublet therapy (RR = 1.17, 95 % CI = 1.02–1.35, p = 0.03, I²=47.1%)

	TTP (3 trials): statistically significant difference in favor of doublet therapy (HR = 0.76, 95 % CI = 0.60–0.96, p=0,022, I^2=72.2%). **ORR (10 trials):** statistically significant difference in favor of doublet therapy (RR = 1.54, 95 % CI = 1.36–1.73, p = 0.0001, I^2=0) **Toxicity**: More incidences of grade 3 or 4 anemia, thrombocytopenia, and neurotoxicity were observed with doublet therapy. With respect to the risk of grade 3 or 4 neutropenia and nonhematologic toxicities such as diarrhea, fatigue, nausea, and vomiting, equivalent frequencies were found between the two groups **4. Anmerkungen/Fazit der Autoren** Our meta-analysis showed that doublet therapy was superior to single-agent therapy as first-line treatment for elderly patients with advanced NSCLC in terms of OS, TTP, ORR, and 1-year SR, but more hematologic toxicities and neurotoxicity were observed with doublet therapy. Due to significant heterogeneity between randomized trials, we performed a subgroup analysis based on different chemotherapy regimens. Similar results were found in platinum-based doublet therapy, although the OS benefit with doublet therapy was not significant. Furthermore, gemcitabine-based doublet significantly increased ORR compared with single agent, but it did not translate into an increase in survival benefit. Platinum-based doublet therapy might be considered as first-line treatment for older patients to improve efficacy, but the optimal drug dosage and treatment schedule should be investigated in future prospective clinical trials. Gemcitabine-based doublet therapy could be considered for elderly patients who were not suitable for platinum-based chemotherapy due to its tendency to improve OS and 1-year SR.
Qi W-X et al., 2013 Overall Survival Benefits for Combining Targeted Therapy as Second-Line Treatment for Advanced Non-Small-	**1. Fragestellung** We thus 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. **2. Methodik** ***Population*:** Patients with pathologically confirmed of advanced NSCLC and previously treated ***Intervention*:** combined targeted therapy

Cell-Lung Cancer: A Meta-Analysis of Published Data [66]	***Komperator*:** erlotinib alone or erlotinib plus placebo ***Endpunkte*:** overall survival (OS), progression-free survival (PFS), overall 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 **Heterogenitätsuntersuchungen:** x2-based Q statistic used, considered statistically significant when p (heterogeneity) < 0,05 or I2>50%, if existed, data analyzed by REM (the DerSimonian and Laird method) **„Publication bias"-Berechnung:** Begg and Egger tests: no evidence of publication bias **3. Ergebnisdarstellung** ***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 **4. 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.
Qi WX et al., 2014: Risk of interstitial lung disease associated with EGFR-TKIs in advanced non-small-cell lung cancer: a meta-analysis of 24 phase III clinical trials [63]	**1. Fragestellung** Since ILD associated with EGFR-TKIs could be fatal in many instances, it is important to carefully recognize and document the incidence and risk of ILD with these drugs to perform an early and adequate intervention. We thus conducted this meta-analysis to investigate the overall incidence and risk of ILD associated with EGFR-TKIs in patients with advanced NSCLC. **2. Methodik** ***Population:*** advanced NSCLC ***Intervention:*** EGFR-TKIs (alone or in combination at any dosage or frequency) ***Komparator:*** *Nicht vorab spezifiziert* ***Endpunkte*:** interstitial lung disease (ILD) (available data regarding events or incidence of ILD and sample size) Four specific findings were required: (1) progressive dyspnea with or without cough or fever; (2) lack of evidence of infection; (3) radiographic findings consistent with drug-induced ILD, and (4) consistent pathologic findings if available ***Suchzeitraum:*** 2000 bis 01/2014, nur: prospective phase III trials ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** *24 (15561)* ***Qualitätsbewertung der Studien:*** ***Heterogenitätsuntersuchungen:*** Publication bias: Egger's test **3. Ergebnisdarstellung** 5265 patients from 18 treatment arms received EGFR-TKIs single agent were available for all-grade ILD analysis Kein Publikationsbias

	Table 2 Odds ratio of ILD with EGFR-TKIs according to prescribed sub-groups All-grade ILD, *n*/total, *n* / High-grade ILD, *n*/total, *n* Groups | Studies, *n* | EGFR-TKIs | Control | OR (95% CI)a | *P* value | Studies, *n* | EGFR-TKIs | Control | OR (95% CI)b | *P* value Overall | 22 | 100/7806 | 46/6024 | 1.74 (1.25–2.43) | 0.001 | 16 | 28/4089 | 4/3717 | 4.38 (2.18–8.79) | <0.001 EGFR-TKIs Gefitinib | 12 | 83/4988 | 37/3666 | 1.76 (1.22–2.54) | 0.003 | 9 | 19/1807 | 3/1768 | 4.23 (1.83–9.78) | <0.001 Erlotinib | 7 | 13/1960 | 9/1939 | 1.41 (0.61–3.28) | 0.42 | 5 | 8/1653 | 1/1641 | 4.77 (1.29–17.66) | 0.019 Afatinib | 3 | 4/858 | 0/419 | 4.43 (0.54–36.06) | 0.16 | 2 | 1/629 | 0/308 | 4.36 (0.066–290.30) | 0.49 EGFR mutation 100% | 6 | 13/836 | 1/579 | 4.87 (1.67–14.25) | 0.004 | 5 | 5/607 | 0/468 | 6.77 (1.14–40.2) | 0.035 <30% | 4 | 3/831 | 2/632 | 1.48 (0.26–8.54) | 0.66 | 3 | 2/605 | 0/410 | 7.36 (0.46–117.67) | 0.16 Not reported | 12 | 84/6139 | 43/4813 | 1.56 (1.09–2.24) | 0.014 | 8 | 21/2877 | 4/2839 | 3.86 (1.76–8.47) | <0.001 Never smoked >50% | 10 | 32/2139 | 9/1661 | 2.89 (1.55–5.38) | <0.001 | 8 | 11/1520 | 1/1355 | 5.00 (1.60–15.64) | 0.006 ≤50% | 8 | 50/3615 | 29/3021 | 1.48 (0.94–2.32) | 0.091 | 6 | 15/1921 | 3/1716 | 3.79 (1.50–9.57) | 0.005 Not reported | 4 | 18/2052 | 8/1342 | 1.25 (0.56–2.82) | 0.59 | 2 | 2/648 | 0/646 | 7.32 (0.46–117.17) | 0.16 Study location Asian | 11 | 44/2238 | 23/2056 | 1.83 (1.13–2.98) | 0.0015 | 9 | 16/1928 | 3/1752 | 3.76 (1.52–9.28) | 0.004 Non-Asian | 11 | 56/5568 | 23/3968 | 1.66 (1.05–2.63) | 0.029 | 7 | 12/2161 | 1/1965 | 5.47 (1.84–16.27) | 0.002 EGFR-TKIs-based regimens EGFR-TKIs monotherapy | 16 | 75/4690 | 35/3619 | 1.83 (1.25–2.68) | 0.002 | 13 | 20/2603 | 3/2230 | 4.23 (1.86–9.63) | <0.001 Combinations | 6 | 25/3116 | 11/2405 | 1.49 (0.75–2.93) | 0.25 | 3 | 8/1486 | 1/1487 | 4.77 (1.29–17.66) | 0.019 Controlled therapy Placebo | 3 | 12/1666 | 6/906 | 1.04 (0.39–2.78) | 0.94 | 2 | 1/390 | 0/343 | 7.44 (0.15–374.94) | 0.32 Non-placebo | 19 | 88/6140 | 40/5118 | 1.86 (1.31–2.65) | <0.001 | 14 | 27/3552 | 4/3374 | 4.31 (2.12–8.73) | <0.001 ILD: interstitial lung disease; OR: odds ratio. [a] *P*=0.50 for variation in ORs by EGFR-TKIs; *P*=0.13 for variation in ORs by percentage of EGFR mutation; *P*=0.044 for variation in ORs by percentage of never-smoked patients; *P*=0.39 for variation in ORs by study locations; *P*=0.30 for variation in ORs by EGFR-TKIs regimens; *P*=0.16 for variation in ORs by controlled therapy. [b] *P*=0.99 for variation in ORs by EGFR-TKIs; *P*=0.48 for variation in ORs by percentage of EGFR mutation; *P*=0.35 for variation in ORs by percentage of never smoked patients; *P*=0.30 for variation in ORs by study locations; *P*=0.43 for variation in ORs by EGFR-TKIs regimens; *P*=0.39 for variation in ORs by controlled therapy. **4. Anmerkungen/Fazit der Autoren** Treatment with EGFR-TKIs is associated with a significantly increased risk of developing ILD.
Russo A et al., 2009: Gemcitabine-based doublets versus single-agent therapy for elderly patients with advanced nonsmall cell lung cancer: a Literature-based Meta-analysis [68]	**1. Fragestellung** To assess the efficacy and tolerability of **gemcitabine-based doublets** compared with **single-agent chemotherapy** for elderly patients with NSCLC **2. Methodik** **Population**: elderly patients with stage IIIB/IV NSCLCs (individuals ages 65 through 79 years). First-line **Intervention**: gemcitabine-based doublets **Komparator**: third generation single-agent chemotherapy (vinorelbine, docetaxel, and paclitaxel) **Endpunkt**: Survival, ORR, toxicity **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: 1966-2008 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 4 (n= 1.436) **3. Ergebnisdarstellung** **1-year survival**: no statistically significant difference (OR, 0.78; 95% CI, 0.57-1.06 [p=0.169]) **Overall response**: statistically significant difference in favor of doublets (OR, 0.65; 95% CI, 0.51-0.82 [p <0 .001]). **Toxicity**: gemcitabine-based doublets were associated with increases in thrombocytopenia (OR, 1.76; 95% CI, 1.12-2.76 [p=0.014]), but not in grade 3 or 4 hematologic or nonhematologic toxicities **4. Anmerkungen/Fazit der Autoren** Gemcitabine-based doublets appeared to be effective and feasible compared with single agents in the treatment of elderly patients with advanced NSCLC who were not suitable for full-dose, platinum-based

	chemotherapy **5. Hinweise durch FB Med** Keine Beschreibung zur Evaluation der Qualität der eingeschlossenen Studien. Keine Angaben zu Interessenskonflikten
Shen et al., 2014: Comparison between cisplatin plus vinorelbine and cisplatin plus docetaxel in the treatment of advanced non-small-cell lung cancer: A meta-analysis of randomized controlled trials [72]	**1. Fragestellung** To compare the VC and DC regimens in the first-line treatment of advanced NSCLC **2. Methodik** ***Population*:** The patients involved were required to have pathological or cytological confirmation of advanced (stage IIIB/IV) NSCLC, with a performance status of 0-2 on the World Health Organization (WHO) scale, or a Karnofsky performance status of ≥80%. ***Intervention*:** cisplatin plus vinorelbine (VC) ***Komparator*:** cisplatin plus docetaxel (DC) ***Endpunkte*:** 1‐year survival rate , 2‐year survival rate , safety ***Suchzeitraum*:** bis Mai 2013 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 9 RCTs (1 886) ***Qualitätsbewertung der Studien:*** Jadad Score **Heterogenitätsuntersuchungen:** Wurden durchgeführt **3. Ergebnisdarstellung** Patients receiving DC therapy exhibited a significantly higher response rate [relative risk (RR)=0.83, 95% CI: 0.73‐0.95 and P=0.007] and 2‐year survival rate (RR=0.65, 95% CI: 0.50‐0.84 and P=0.001). However, the 1‐year survival rate for the two cisplatin‐based regimens were comparable (RR=0.90, 95% CI: 0.81‐1.01 and P=0.07). Patients receiving the VC regimen more frequently developed grade ¾ leucopenia, anemia and vomiting, whereas those receiving DC chemotherapy were more prone to grade ¾ diarrhea. The incidence of grade ¾ neutropenia, thrombocytopenia and nausea were similar between the two arms. In conclusion, our study indicated that DC is superior to the VC regimen in terms of tumor response rate, 2‐year survival rate and safety for the first‐line treatment of advanced NSCLC. **4. Anmerkungen/Fazit der Autoren** In conclusion, our study indicated that DC is superior to the VC regimen in terms of tumor response rate, 2-year survival rate and safety for the first-line treatment of advanced NSCLC.

	Limits: Our study was limited by the number and quality of the available RCTs. Although it may be difficult for phase II studies to produce reliable survival data, no significant heterogeneity was observed in the response rate or in the 1- and 2-year survival rates among the trials included in the analysis. This result of the 2-year survival analysis supports the decision to include all randomized phase II or III trials with prospectively recorded 2-year survival data. Furthermore, the survival data at 2 years of follow-up and some adverse effects were lacking in several trials, which may have led to a biased estimate.
Shi L et al., 2014: Risk of interstitial lung disease with gefitinib and erlotinib in advanced non-small cell lung cancer: A systematic review and meta-analysis of clinical trials [73]	**1. Fragestellung** We performed a systematic review and meta-analysis to determine the incidence and the relative risk (RR) associated with the use of gefitinib and erlotinib. **2. Methodik** **Population:** Patients with advanced NSCLC, assigned to treatment with gefitinib or erlotinib **Intervention:** Gefitinib oder Erlotinib **Komparator:** Platinbasierte Chemotherapie, Pemetrexed, Docetaxel, Paclitaxel, Vinorelbin oder Placebo **Endpunkte:** Overall incidence of interstitial lung disease (ILD) **Suchzeitraum:** Januar 2000 bis Oktober 2012 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 29 RCTs (15 618) **Qualitätsbewertung der Studien:** Jadad Score **Heterogenitätsuntersuchungen:** Wurden durchgeführt **3. Ergebnisdarstellung** The overall incidence for all-grade ILD events was 1.2% (95% CI, 0.9–1.6%) among patients receiving gefitinib and erlotinib, with a mortality of 22.8% (95% CI, 14.6–31.0%). Compared with controls, the RR of all-grade ILD events associated with gefitinib and erlotinib was 1.53 (95% CI, 1.13–2.08; P = 0.006) using a fixed effects model. The RR of fatal ILD events associated with EGFR TKIs treatment was 1.96 (95% CI, 1.03–3.72, P = 0.041) compared with control patients. The analysis was also stratified for drug type, study location, treatment arm, and treatment line, but no significant differences in RRs were observed. **4. Anmerkungen/Fazit der Autoren** Treatment with EGFR TKIs gefitinib and erlotinib is associated with a

	significant increase in the risk of developing both all-grade and fatal ILD events in advanced NSCLC. **Limits:** The National Cancer Institute's common toxicity criteria grading system for ILD has its own limitations. No term specific for ILD is listed in NCI CTCAE v2.0 or v3.0. Also, the majority of trials included in this analysis reported ILD events in combined grades (all-grade, or high-grade), we cannot distinguish cases in each grade. ILD is not a single disease, but encompasses many different pathological diseases. There were no uniform diagnostic criteria of ILD in various studies, also, the trials included in the analysis were performed at various centers, and the ability to detect ILD events might vary among these institutions, which could result in a bias of reported incidence rates. The incidence of ILD events showed significant heterogeneity among the included studies. This might reflect differences in trial designs, sample sizes, concomitant chemotherapy, and many other factors among these studies. Despite these differences, the RRs reported by all of these studies showed remarkable homogeneity. In addition, calculation using the random-effects model for overall incidence estimation might minimize the problem. The study might have a potential observation time bias because EGFR TKIs groups might have longer follow-up time than controls owing to the prolonged PFS that is often associated with the use of EGFR TKIs. However, most ILD events did not occur evenly over time, but in the early phase (first 4 weeks) of EGFR TKIs treatment . This is a meta-analysis at the study level, data were abstracted from published clinical trial results, and individual patient information was not available. Therefore, subgroup analyses according to possible risk factors for the development of ILD, including preexisting pulmonary fibrosis, age, performance status, gender, smoking history, lung cancer histology, and the mutational status of EGFR, are not possible in this analysis.
Soria JC et al., 2013: Systematic Review and meta-analysis of randomised, phase II/III trials adding Bevacizumab to platinum-based chemotherapy as first-line treatment in patients with	**1. Fragestellung** To further assess the efficacy (in terms of OS and PFS) and toxicity of **bevacizumab** used in combination with platinum-based chemotherapy, compared with **chemotherapy** alone, in the first-line treatment of patients with advanced NSCLC **2. Methodik** **Population:** patients with inoperable locally advanced (stage IIIB), recurrent or metastatic NSCLC **Intervention:** first-line bevacizumab plus platinum-based chemotherapy **Komparator:** chemotherapy alone (platinum-based) without bevacizumab **Endpunkte:** OS, PFS **Suchzeitraum:**

advanced non-small-cell lung cancer [75]	bis 04/ 2009 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 4 Phase II und III Studien (2 194) **Qualitätsbewertung der Studien:** The quality of trials and the risk of bias were assessed by considering randomisation methods, stratification factors, blinding, follow-up and intention-to-treat analysis. **Heterogenitätsuntersuchungen:** Wurde durchgeführt **3. Ergebnisdarstellung**

Table 1. Characteristics of the four analysed trials of bevacizumab added to standard chemotherapy as the first-line treatment in patients with advanced NSCLC

Trial	Period of inclusion	Design, main inclusion/exclusion criteria, primary end point	Random-isation	Treatment arms[a]	*N* analysed /randomly ass patients
AVF-0757g [24]	May 1998–Sep 1999	Design: open-label, parallel-group, multicentre, blinded assessment phase II Inclusion criteria: histologically confirmed stage IIIB (with pleural effusion), stage IV or recurrent NSCLC; ECOG PS ≤2; life expectancy ≥3 months; no previous chemotherapy, biological therapy or radiotherapy. Exclusions included: CNS metastasis, therapeutic anticoagulation, uncontrolled hypertension Primary end point: PFS Tumour assessment: every three cycles (i.e. 9 weeks) for the first six cycles and every four cycles (12 weeks) thereafter	1:1:1	Bevacizumab 7.5 mg/kg + carboplatin + paclitaxel Bevacizumab 15 mg/kg + carboplatin + paclitaxel Carboplatin + paclitaxel	32/32 34/35 32/32
ECOG 4599 [21]	Jul 2001–Dec 2005	Design: open-label, parallel-group, multicentre, phase III Inclusion criteria: histologically or cytologically confirmed, predominantly non-squamous stage IIIB (with pleural effusion), stage IV or recurrent NSCLC; ECOG PS 0–1; no previous chemotherapy. Exclusions included: haemoptysis (≥2.5 ml per episode), tumours invading or abutting major blood vessels, CNS metastasis, therapeutic anticoagulation, uncontrolled hypertension Primary end point: OS Tumour assessment: every two cycles (i.e. every 6 weeks) for 24 weeks and then every three cycles thereafter	1:1	Bevacizumab 15 mg/kg + carboplatin + paclitaxel Carboplatin + paclitaxel	434/434 444/444
AVAiL [22]	Feb 2005–Aug 2006	Design: double-blind, parallel-group, multicentre, international, phase III Inclusion criteria: histologically or cytologically confirmed, stage IIIB (with supraventricular lymph node metastasis, or malignant pleural or pericardial effusion), stage IV or recurrent non-squamous NSCLC; ECOG PS 0–1; no previous chemotherapy. Exclusions included: haemoptysis (≥2.5 ml per episode), CNS metastasis, therapeutic anticoagulation, uncontrolled hypertension Primary end point: PFS Tumour assessment: every three cycles	1:1:1	Bevacizumab 7.5 mg/kg + cisplatin + gemcitabine Bevacizumab 15 mg/kg + cisplatin + gemcitabine Cisplatin + gemcitabine + placebo (low or high dose)	345/345 351/351 347/347
JO19907 [31]	Apr 2007– Mar 2008	Design: open-label, parallel-group, multicentre, phase II Inclusion criteria: previously untreated stage IIIB (with pleural and/or pericardial effusion and/or pleural dissemination), IV or recurrent non-squamous NSCLC; ECOG PS 0–1. Exclusions included haemoptysis and CNS metastasis, uncontrolled hypertension Primary end point: PFS Tumour assessment: every 6 weeks for the first 18 weeks and every 9 weeks thereafter	2[b]:1	Bevacizumab 15 mg/kg + carboplatin + paclitaxel Carboplatin + paclitaxel	117/121 58/59

[a]Doses: carboplatin, dosed to a target area under the curve of 6 mg/ml/min; paclitaxel, 200 mg/m^2; cisplatin, 80 mg/m^2; gemcitabine, 1250 mg/m^2. In all trials, treatment was administered in 3-week cy up to six cycles, or until disease progression or unacceptable toxicity. Patients who completed six cycles of bevacizumab-containing therapy in ECOG 4599, AVAiL and JO19907 then received bevac monotherapy until disease progression or unacceptable toxicity. In AVF-0757g, non-progressing patients randomly assigned to bevacizumab could receive up to 18 doses of bevacizumab following th six cycles. Patients in the control arms were permitted to receive bevacizumab (15 mg/kg) on disease progression.
[b]Experimental arm.
CNS, central nervous system; NSCLC, non-small-cell lung cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status; OS, overall survival; PFS, progression-free survival.

Compared with chemotherapy alone, bevacizumab significantly prolonged OS (HR 0.90; 95% CI 0.81-0.99; P = 0.03), and PFS (0.72; 95% CI 0.66-0.79; P<0.001). Bevacizumab showed a significantly greater effect on OS in patients with adenocarcinoma versus other histologies (P = 0.02), and patients with body weight loss ≤5% versus >5% (P = 0.03). Bevacizumab significantly increased the risk of grade ≥3 proteinuria, hypertension, haemorrhagic events, neutropenia, and febrile neutropenia.

Overall survival (4 trials, 2.194 patients):
statistically significant difference in favor of bevacizumab plus chemotherapy, compared with chemotherapy alone, with HR of 0.90 (95% CI 0.81, 0.99; p = 0.03, I^2=0%). No significant difference between the two Bevacizumab doses (7.5 mg, 15 mg).
PFS (4 trials, 2.194 patients):
statistically significant difference in favor of bevacizumab plus chemotherapy, compared with chemotherapy alone HR of 0.72 (95% CI

	0.66, 0.79; P < 0.001). **Toxicity:** Bevacizumab significantly increased the risk of grade ≥3 events of proteinuria (OR 4.81; 95% CI 2.28, 10.1), hypertension (OR 3.69; 95% CI 2.49, 5.47), haemorrhagic events (OR 2.67; 95% CI 1.63, 4.39), neutropenia (OR 1.53; 95% CI 1.25, 1.87) and febrile neutropenia (OR 1.72; 95% CI 1.01, 2.95), compared with chemotherapy alone **4. Anmerkungen/Fazit der Autoren** The effect on OS was greater in adenocarcinoma, compared with other histological types, while that on OS and PFS was greater in patients with a loss in body weight of ≤5%, compared with >5%. In conclusion, this meta-analysis of randomised studies indicates that bevacizumab significantly prolonged OS and PFS when added to standard platinum-based chemotherapy as first-line therapy in patients with advanced NSCLC, with no unexpected toxicity patterns being evident. **Limits:** Our analysis is limited by its use of summary data rather than data from the individual patients from each trial.
Tassinari D et al., 2009: Second-line treatments in non-small cell lung cancer. A systematic review of literature and metaanalysis of randomized clinical trials [78]	**1. Fragestellung** (1) to define the role of second-line treatments in advanced NSCLC in comparison with best supportive care (BSC); and (2) to assess the role of alternative treatments to docetaxel therapy every 3 weeks, assuming docetaxel therapy every 3 weeks as the standard second-line treatment of advanced NSCLC **2. Methodik** **Population:** patients with NSCLC **Intervention:** antineoplastic treatments vs BSC, and a secondary analysis was performed to compare any alternative antineoplastic treatment with three times per week docetaxel, assumed as the “gold standard” **Endpunkte:** One-year survival rate (SR) in the primary analysis was the primary end point; RR and time to progression in the primary analysis, and 1-year SR, RR, and time to progression in the secondary analysis were the secondary end points. **Studiendesign:** randomized phase III trials **Suchzeitraum:**

	from January 2000 to July 2008 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 14 **3. Ergebnisdarstellung** • 3 trials (n = 2 627) comparing antineoplastic treatments with BSC • 11 trials (n = 5 952) comparing docetaxel administration every 3 weeks with other docetaxel schedules or ifosfamide/vinorelbine, pemetrexed, oral topotecan, paclitaxel poliglumex, vinflunine, gefitinib, or docetaxel-gemcitabine combination ***Primary analysis:*** • only methodologic difference: use of chemotherapy in TAX317 trial and EGFR TKIs in the BR21 and ISEL trials • OR of 1-year survival: 0,763 (p = 0,029) in favor of active therapy • translated into an absolute improvement in 1-year survival of approximately 7% and a number needed to treat to achieve 1-year-patient-alive gain of 14 ***Secondary analysis:*** • 1-year survival rate (SR) OR = 0.924 (p = 0.122) and response rate (RR) OR = 1.069 (p = 0.643). **4. Anmerkungen/Fazit der Autoren** *Second-line treatments in NSCLC seem to improve the main outcomes better than supportive care. Docetaxel administration every 3 weeks probably remains the "gold standard" because at present the data in literature are not enough to support a greater efficacy of other alternative options. Further trials are needed to identify a clinical and biological profile that could predict the response to treatments and a criterion to select the patients to be treated with chemotherapy or EGFR inhibitors.* Hinweise durch FB Med: • all trials analyzed and classified using the Nicolucci score (Quality, evaluation and clinical implications of randomized, controlled trials on the treatment of lung cancer: a lost opportunity for metaanalysis) • there is an evident methodological and clinical heterogeneity among the selected trials in the primary and secondary analysis • publication bias found in both the primary and secondary analyses • no funding information • The authors have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Tassinari D et al., 2009: Second Line	**1. Fragestellung** Die folgende Abbildung gibt einen Überblick über die Inhalte der ausgewerteten Studien.

Treatments in Advanced Platinum-Resistant Non Small Cell Lung Cancer. A Critical Review of Literature [76]	

Trial	No. Patients	Comparison Arms	Aims of the Trial	Comments	Nicolucci Score
Hanna et al[11]	571	Every-3-weeks docetaxel versus pemetrexed	Survival (p); toxicity (s); response rate (s); progression-free interval (s); time to progression (s); quality of life (s)	Pemetrexed results in clinically equivalent efficacy outcomes, but with significantly fewer side effects when compared with every-3-weeks docetaxel	54%
Kim et al[17] (INTEREST trial)	1466	Every-3-weeks docetaxel versus gefitinib	Survival (p); response rate (s); time to progression (s); quality of life (s); tolerability (s)	Gefitinib results noninferior to every-3-weeks docetaxel, representing a valid treatment for pretreated patients with advanced NSCLC	100%
Maruyama et al[18] (V-15-32)	489	Every-3-weeks docetaxel versus gefitinib	Survival (p); response rate (s); time to progression (s); quality of life (s); tolerability (s)	Noninferiority of gefitinib in overall survival was not demonstrated	76%
Ramlau et al[19]	829	Every-3-weeks docetaxel versus oral topotecan	Survival (p); time to treatment failure (s); response rate (s); tolerability (s)	Oral topotecan represent an effective and well tolerated alternative to every-3-weeks docetaxel	87%

p indicates primary end point; s, secondary end point.

In this review, we re-analyzed the evidences supporting the different therapeutic options in platinum-resistant NSCLC, focusing on phase III randomized trials and their treatment outcomes.

2. Methodik

Population:
Patients with platinum-resistant NSCLC

Intervention:
Siehe Ergebnisdarstellung

Komparator:
Siehe Ergebnisdarstellung

Endpunkte:
Siehe Ergebnisdarstellung

Suchzeitraum:
Januar 2000 bis Juni 2008

Anzahl eingeschlossene Studien/Patienten (Gesamt):
10 Phase III Studien (4 426)

Qualitätsbewertung der Studien:
Only trials with evidence of efficacy graded I (a-bc) were included into the review. All trials with evidence of efficacy lower than IIA were excluded for the lack of mature data and the low power in addressing clinical practice. All selected trials were analyzed and pondered using the Nicolucci score, with descriptive and qualitative aims.

Heterogenitätsuntersuchungen:
k.A.

3. Ergebnisdarstellung

Die folgende Abbildung gibt einen Überblick über die Inhalte der ausgewerteten Studien.

Trial	Number of Patients	Comparison Arms	Aims of the Trial	Comments	Nicolucci Score
Sheperd *et al.* (TAX317 trial) [6]*	204	3-weekly docetaxel vs best supportive care	Survival (p); Response Rate (s), Time to progression (s); Quality of Life (s).	The treatment with 3 weekly docetaxel is associated with significant prolongation of survival, and at the dose of 75 mg/m^2 the benefits of the treatment outweigh the risks of toxicity.	70%
Dancey *et al.* (TAX317 trial) [22]*	204	3-weekly docetaxel vs best supportive care	Survival (p); Response Rate (s), Time to progression (s); Quality of Life (s).	Second-line docetaxel significantly improves survival with a trend towards less deterioration in Quality of Life compared with best supportive care.	70%
Fossella *et al.* (TAX 320 trial) [7]	373	3-weekly docetaxel (100mg/m^2 or 75mg/m^2) vs vinorelbine or ifosfamide	Survival (p); Time to progression (s).	3-weekly docetaxel 75mg/m^2 significantly improve survival when compared with ifosfamide or vinorelbine.	70%
Gridelli *et al.* [11]	220	3-weekly vs weekly docetaxel	Quality of life (p); Survival (s); Response Rate (s).	The weekly schedule can be preferred by the patients because of some Quality of Life advantage, lower toxicity and no evidence of different effects on survival.	89%
Schuette *et al.* [12]	215	3-weekly vs weekly docetaxel	Survival (p); Response Rate (s); Quality of Life (s).	Weekly docetaxel demonstrated similar efficacy and better tolerability than standard 3-weekly docetaxel and can represent a feasible alternative to 3-weekly schedule.	65%
Camps *et al.* [13]	259	3-weekly vs weekly docetaxel	Survival (p); Time to progression (s); Duration of response (s).	Weekly and 3-weekly docetaxel are effective and well tolerated, with different toxicity profiles. There is no indication to recommend the weekly schedule, with the exception of patients at risk of severe neutropenia.	70%
Chen *et al.* [23]	161	3-weekly vs weekly docetaxel (35mg/m^2 or 40mg/m^2)	Response Rate (p); Survival (s).	Weekly docetaxel produces less myelosuppression and a better compliance and response rate when compared with the 3-weekly schedule.	50%
Hanna *et al.* [14]	571	3-weekly docetaxel vs pemetrexed (non-inferiority design)	Survival (p); Toxicity (s); Response Rate (s); Progression-free Interval (s); Time to progression (s); Quality of Life (s).	Pemetrexed results in clinically equivalent efficacy outcomes, but with significantly fewer side effects when compared with 3-weekly docetaxel.	54%
Thatcher *et al.* (ISEL trial) [17]	1692	Gefitinib (250 mg/day) ve placebo	Survival (p); Time to treatment failure (s); Response Rate (s); Quality of Life (s); Tolerability (s).	No significant improvement of survival was observed in patients treated with gefitinib, when compared with placebo.	67%
Shepherd *et al.* (BR21 trial) [18]	731	Erlotinib (150 mg/day) vs placebo	Survival (p); Progression free interval (s); Response rate (s); Time to progression (s); Quality of Life (s); Tolerability (s).	Erlotinib improved survival in platinum-resistant NSCLC.	67%

Legend.:
*: data from the same trial; p: primary end point; s: secondary end point.

Superiority of primary treatments in comparison with placebo or best supportive care.

Apart from the negative results of the ISEL trial, that are likely due to an unbalanced selection of the patients, the TAX317 and BR21 trials reported a survival improvement of few months in patients treated with docetaxel or erlotinib. However, although the two treatments can not be compared without an ad-hoc trial, some considerations can be made.

- Three-weekly docetaxel improved overall survival, but side effects resulted anything but negligible for frequently frail patients with a short life expectancy.
- Although an improvement in few symptoms was observed in both TAX317 and BR21 trials, the overall benefit in the quality of life was not impressive. Moreover, a treatment-bias (frequently observed in placebo-controlled trials) cannot be excluded.
- Docetaxel or erlotinib are very expensive, and an adhoc pharmacoeconomic analysis should be planned to better define the role of both treatments in platinum-resistant NSCLC.

Role of alternative treatments to 3-weekly docetaxel.

Although weekly docetaxel and 3-weekly pemetrexed seem to be better tolerated than 3-weekly docetaxel, their superiority does not seem conclusive nor enough to recommend these alternative schedules in all

	patients with platinum-resistant NSCLC. Furthermore, it should be kept in mind that pemetrexed is quite expensive, and the safety profile of weekly docetaxel is different but not better than that of 3-weekly docetaxel. The data emerging from the randomized clinical trials seem to state two issues, that clinical research and clinical practice should deal with: • Although recommended by the main clinical guidelines, the need of treating all patients with platinumresistant NSCLC is not so evident, and the old recommendation to treat only patients with good performance status (ECOG 0-1) seems to be still wellgrounded for patients with platinum-resistant NSCLC. • EGFR inhibitors could be an interesting alternative to chemotherapy for patients with platinum-resistant NSCLC, but not all patients are likely to benefit by the treatment. The clinical (women, no-smoking status, asian race, or adenocarcinoma) and even better the biological characterization (EGFR or k-ras mutations) should probably guide the patients selection to obtain the best results, avoiding to treat patients who are likely to be non-responder. **4. Anmerkungen/Fazit der Autoren** Further trials, conjugating the clinical outcomes with the biological features, are needed to better understand the role of second line treatments in patients with platinum-resistant NSCLC. **5. Hinweise der FBMed** Literaturreview ohne Metanalyse, daher nur descriptive Auswertung der Studienergebnisse. Ausgewertet, da spezielles Patientenkollektiv.
Tassinari et al., 2012: Noninferiority Trials in Second-Line Treatments of Nonsmall Cell Lung Cancer. A Systematic Review of Literature With Meta-analysis of Phase III Randomized Clinical Trials [77]	**1. Fragestellung** To assess the role of the novel second-line treatments in nonsmall cell lung cancer (NSCLC). **2. Methodik** **Population:** Patienten mit progredientem NSCLC nach Chemotherapie in der Erstlinie **Intervention:** Any novel treatment (Chemotherapie oder EGFR-Inhibitor) **Komparator:** Every 3 weeks docetaxel **Endpunkte:** One year survival rate (primär) Lebensqualität und Sicherheit (sekundär) **Suchzeitraum:** Bis Juni 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 4 Phase III Studien (3 355)

Qualitätsbewertung der Studien:
Nicolucci Score
Heterogenitätsuntersuchungen:
Wurde untersucht

3. Ergebnisdarstellung

One year survival rate (primär)
The pooled odds ratio for 1-year SR was 0.927 (95% CI = 0.8-1.07, P = 0.313), 0.889 (95% CI = 0.703-1.123, P = 0.323) considering only those trials comparing 3WD versus chemotherapy (pemetrexed or oral topotecan), and 0.953 (95% CI = 0.789-1.151, P = 0.616) considering only those trials comparing 3WD vs gefitinib.

QoL
All the trials reported data about quality of life during the treatment, but only 3 of them reported comparable data that were included in the pooled analysis. The odds ratio for quality of life was 1.623 (95% CI = 1.124-2.343, *P* = 0.01).

AEs
All the 4 selected trials reported data about grade III to IV neutropenia, fatigue, nausea, vomiting, and diarrhea. On the whole, a significant advantage of experimental arms was observed for neutropenia (odds ratio = 35.067, 95% CI = 18.541-66.324, *P* < 0.001), febrile neutropenia (odds ratio = 8.385, 95% CI = 4.525-15.536, *P* < 0.001), fatigue (odds ratio= 1.507, 95% CI = 1.09-2.084, *P*= 0.013), and neurotoxicity (odds ratio= 17.827, 95% CI = 3.813-83.352, *P* < 0.001), whereas a significant advantage of 3WD was observed for hepatic toxicity (odds ratio= 0.068, 95% CI =0.018-0.255, *P* < 0.001) and skin rash (odds ratio= 0.405, 95% CI = 0.166-0.99, *P*= 0.047). Considering the trials comparing 3WD vs other chemotherapies, a significant advantage of the experimental arm was observed only for neurotoxicity (odds ratio = 13.967, 95% CI = 1.804-108.15, *P*= 0.012). In the trials comparing 3WD vs EGFR inhibitors, a significant advantage of the experimental arm was observed for neutropenia (odds ratio = 44.161, 95% CI = 22.576-86.381, *P* < 0.001), febrile neutropenia (odds ratio= 9.291, 95% CI = 4.895-17.637, *P* <0.001), nausea (odds ratio = 2.411, 95% CI = 1.029-5.65, *P*= 0.043), and fatigue (odds ratio = 2.244, 95% CI = 1.462-3.443, *P* < 0.001), whereas a significant advantage of 3WD was observed for skin rash (odds ratio = 0.33, 95% CI = 0.121-0.903, *P*= 0.031).

4. Anmerkungen/Fazit der Autoren
All the noninferiority trials demonstrated the noninferiority of pemetrexed, oral topotecan, or gefitinib in 1-year SR (primary end point), but the improvement in overall survival remains modest. The improvement in quality of life and safety (secondary end points) represents the main value of these treatments, whose aim is mainly palliative.
The main information resulting from our analysis remains the equivocal role of the noninferiority trials, essentially aimed at favoring the registration of novel molecules without any definitive evidence of their

	actual role in improving the main outcomes, as suggested in some interesting warnings recently published in the literature **Limits:** Although no difference among the various treatment options emerged in the primary analysis, the data relating the well-known role of some clinical and biological factors in predicting the clinical response to the EGFR inhibitors were not analyzed, as their predictive value could not be evaluated in the pooled analysis. The data yielded from the secondary analysis have just a descriptive aim, and they should only be considered as an interesting starting point for further trials. Our pooled analysis reports the data of a literature meta-analysis, which are considerably different and less accurate than those of an individual meta-analysis. **5. Hinweise der FBMed** Nur wenige Studien mit unterschiedlichen Interventionen. Es ist fraglich, ob hier die Anwendung metanalytischer Verfahren wirklich angezeigt war.
Tsujino K et al., 2013: Is Consolidation Chemotherapy after Concurrent Chemo-Radiotherapy Beneficial for Patients with Locally Advanced Non–Small-Cell Lung Cancer? A Pooled Analysis of the Literature [79]	**1. Fragestellung** The purpose of this study was to evaluate whether consolidation chemotherapy (CCT) after concurrent chemo-radiotherapy is beneficial for patients with locally advanced non–small-cell lung cancer (LA-NSCLC). **2. Methodik** **Population:** patients with locally advanced non–small-cell lung cancer **Intervention:** Consolidation therapy (CT+) **Komparator:** No Consolidation therapy (CT-) **Endpunkte:** Medianes Gesamtüberleben Toxitizität **Suchzeitraum:** Bis Dezember 2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 41 RCTs (3 479) **Qualitätsbewertung der Studien:** k.A. **Heterogenitätsuntersuchungen:** Wurde untersucht

	3. Ergebnisdarstellung There was no statistical difference in pooled mOS between CCT+ (19.0 month; 95% CI, 17.3−21.0) and CCT− (17.9 month; 95% CI, 16.1−19.9). Predicted hazard ratio of CCT+ to CCT− was 0.94 (95% CI, 0.81−1.09; *p* = 0.40). There were no differences between the two groups with regard to grade 3−5 toxicities in pneumonitis, esophagitis,and neutropenia. **4. Anmerkungen/Fazit der Autoren** These models estimated that addition of CCT could not lead to significant survival prolongation or risk reduction in death for LA-NSCLC patients. We could not clarify the impact of chemotherapy doses on survival, because, in most studies, not fulldose but low-dose/fractionated chemotherapy was offered in the concurrent phase. **Limits:** Pooled analyses on a publication basis, which included heterogeneous studies with different study designs and various patient populations. The impacts of chemotherapy regimens on survival data remain to be solved.
Wang F et al., 2011: 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 [80]	**1. Fragestellung** To define the efficacy of gefitinib in chemotherapy-naive patients with advanced non-small cell lung cancer. **2. Methodik** ***Population***: Chemotherapy-naive patients with NSCLC ***Intervention:*** Gefitinib therapy as first-line ***Komparator:*** Conventional therapy ***Endpunkt:*** PFS, OS ***Methode:*** systematic review and meta-analysis of RCTs ***Suchzeitraum:*** up to 2011 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 7 (n= 4656) **3. Ergebnisdarstellung** <u>Gefitinib monotherapy</u> OS • Patients with lung adenocarcinoma: statistically significant difference in favor of gefitinib monotherapy compared to chemotherapy. HR 0.89

	(0.81, 0.99); p = 0.03 • EGFR mutant treated with gefitinib monotherapy: no statistically significant difference Combination of conventional chemotherapy with gefitinib: no statistically significant difference PFS • EGFR mutant treated with gefitinib monotherapy: statistically significant difference in favor of gefitinib monotherapy compared to chemotherapy HR 0.43 (0.32, 0.58) (p < 0.001) • Patients with lung adenocarcinoma: statistically significant difference in favor of gefitinib monotherapy compared to chemotherapy HR 0.71 (0.60, 0.83) (p < 0.001) • Patients without EGFR mutant: statistically significant difference in favor of chemotherapy compared to gefitinib monotherapy. HR 2.16 (1.17, 3.99) p = 0.01 • Patients with lung non- adenocarcinoma: no statistically significant difference **4. Anmerkungen/Fazit der Autoren** First-line treatment with gefitinib conferred prolonged progression-free survival than treatment with systemic chemotherapy in a molecularly or histologically defined population of patients with non-small cell lung cancer, and improved survival in the subgroup of patients with lung adenocarcinoma.
Xiao Y-Y et al., 2013: Chemotherapy plus multitargeted antiangiogenic tyrosine kinase inhibitors or chemotherapy alone in advanced NSCLC: a meta-analysis of randomized controlled trials [81]	**Fragestellung:** to compare the efficacy and toxicity of chemotherapy plus multitargeted antiangiogenic TKI with chemotherapy alone in patients with advanced NSCLC **Methodik**: Systematische Literaturrecherche bis 2011 ***Population*:** Patients with advanced NSCLC (Erst- und Zweitlinientherapie) ***Intervention***: Chemotherapy plus multitargeted antiangiogenic TKI vs. ***Komparator***: chemotherapy alone ***Endpunkte****:* PFS (primary endpoint), ORR, OS, toxic effects (secondary endpoints) ***Eingeschlossene Studien (Patienten):*** 6 (3 337) Zeitlinientherapie: 3 Studien (2 052) (jeweils mit 5 Punkten JADAD-Score bewertet) ***Qualitätsbwertung der Studien:*** Jadad Scale **Ergebnisse:** • PFS: A significant difference between between the chemotherapy plus multitargeted antiangiogenic TKI and chemotherapy alone groups (HR

	0.83, 95 % CI 0.76–0.90). Chemotherapy plus multitargeted antiangiogenic TKI significantly increased PFS. There was no significant heterogeneity (p= 0.288). • OS: No significant difference between the chemotherapy plus multitargeted antiangiogenic TKI and chemotherapy alone groups with no significant heterogeneity. • ORR: Chemotherapy plus multitargeted antiangiogenic TKI significantly improved the ORR (RR 1.71, 95 % CI1.43–2.05). However, there was significant heterogeneity (p= 0.013). Toxic effects: • The risks of rash, diarrhea, and hypertension were higher in patients receiving chemotherapy plus multitargeted antiangiogenic TKI than in those receiving chemotherapy alone (OR2.78, 95 % CI 2.37–3.26; OR1.92, 95 % CI1.65–2.24; OR2.90, 95 % CI2.19–3.84, respectively). • The risks of nausea and vomiting were higher in patients receiving chemotherapy alone than in those receiving chemotherapy plus multitargeted antiangiogenic TKI (OR0.71, 95 % CI0.60–0.83; OR0.75, 95 % CI0.61–0.92, respectively). • The risk of hemorrhage, fatigue, cough, constipation, anorexia and alopecia were comparable between two groups (OR1.27, 95 % CI 0.98–1.56; OR0.95, 95 % CI0.82–1.11; OR1.08, 95 % CI 0.87–1.34; OR0.95, 95 % CI0.78–1.17; OR1.12, 95 % CI 0.95–1.33; OR0.91, 95 % CI0.75–1.11, respectively). **Fazit der Autoren:** Therapy consisting of chemotherapy plus multitargeted antiangiogenic TKI was found to have specific advantages over chemotherapy alone in terms of PFS and ORR. The toxicity was comparable between the two therapies. Therefore, chemotherapy plus multitargeted antiangiogenic TKI may be a safe and valid therapeutic option for patients with advanced NSCLC.' **Hinweise FB Med:** • Inclusion in our meta-analysis if the chemotherapy plus multitargeted antiangiogenic TKI was compared with chemotherapy alone in first-line or second-line treatment of advanced NSCLC. • only 56 % of included patients in second-line studies had Adenocarcinoma • clinical IIIB–IV stages; phase II and III RCTs included • Publication bias was not found
Xu C et al., 2012: Can EGFR-TKIs be used in first line treatment for advanced non-small cell lung cancer based on selection	**1. Fragestellung** We aimed to determine whether patients could be treated with **TKIs** based on clinical factors in the first-line setting **2. Methodik** ***Population**:* IIIB/IV or post-operational recurrent NSCLC (including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma) patients. First-line ***Intervention**:* gefitinib, erlotinib monotherapy

according to clinical factors? – A literature-based meta-analysis [82]	***Komparator**:* chemotherapy (mono or doublet) ***Endpunkt**:* OS, PFS, ORR ***Methode**:* systematic review and meta-analysis of RCTs ***Suchzeitraum**:* bis 2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 10 (n=3.045) **Qualitätsbewertung der Primärstudien:** k.A. **3. Ergebnisdarstellung**

Table 1 Characters of the eligible trials

Author	Year	Pts	Treatment arm	Control arm
Unselected				
Lilenbaum, R. [10]	2008	103	Erlotinib	Paclitaxel + Carboplatin
Crino, L. (INVITE) [6]	2008	196	Gefitinib	Vinorelbine
Agarwal, S. [4]	2010	35	Gefitinib	Gemcitabine + Carboplatin
Gridelli, C. (TORCH)[15]	2010	760	Erlotinib	Vinorelbine + Carboplatin
Clinical-Selected				
Lee, J. S. (First-SIGNAL) [16]	2009	313	Gefitinib	Gemcitabine + Cisplatin
Mok, T. S. (IPASS) [17,18]	2009	780	Gefitinib	Paclitaxel + Carboplatin
EGFR mutation Selected				
Mitsudomi, T. (WJTOG3405) [19]	2010	177	Gefitinib	Docetaxel + Cisplatin
Maemondo, M. (NEJSG) [20]	2010	230	Gefitinib	Paclitaxel + Carboplatin
Mok, T. S. (IPASS) [17,18]	2009	261	Gefitinib	Paclitaxel + Carboplatin
Zhou, C. (OPTIMAL) [21]	2011	165	Erlotinib	Gemcitabine + Carboplatin
Rosell, R. (EURTAC) [22]	2011	174	Erlotinib	Platium based

Unselected trials: Four studies of randomized NSCLC patients were based on no particular patient criteria in the first-line setting. Among them, three used gemcitabine, vinorelbine, or paclitaxel plus carboplatin.

Selected trials: Two trials selected East Asian patients using the clinical factors of gender and smoking history. Both trials used gefitinib as the treatment arm; the control arm was paclitaxel plus carboplatin in 1 trial and gemcitabine plus cisplatin in the other.

EGFRmut+ trials: Five trials chose patients with an EGFR mutation who were randomized for treatment with TKI or chemotherapy.

First line – unselected patients

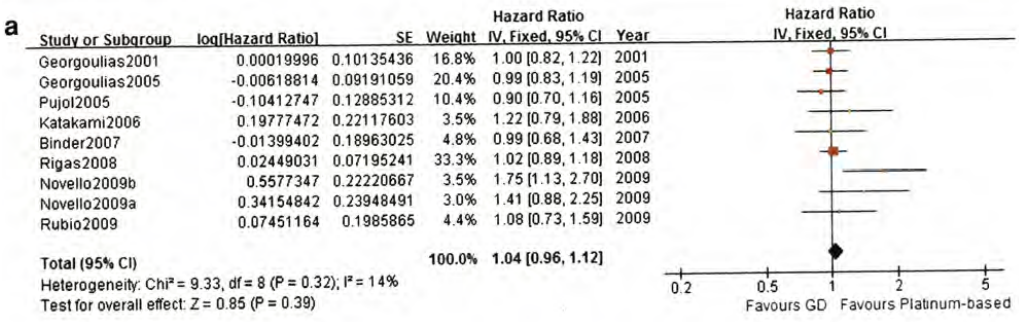
- **Overall survival**: statistically significant difference in favor of chemotherapy. HR 1.35 [95% CI, 1.13–1.61]
- **PFS**: statistically significant difference in favor of chemotherapy. HR 1.29 [95% CI, 1.00–1.66]
- **Response rate**: statistically significant difference in favor of chemotherapy. RR 3.52 [95% CI, 2.41–5.15]

First line – selected patients

	• **Overall survival**: no statistically significant difference. HR 0.92 [95% CI, 0.79–1.07] • **PFS**: statistically significant difference in favor of TKI therapy. HR 0.83 [95% CI, 0.74–0.93] • **Response rate**: statistically significant difference in favor of TKI therapy. RR 0.64 [95% CI, 0.52–0.79] <u>First line – EGFRmut+ patients</u> • **Overall survival**: no statistically significant difference. HR 1.00 [95% CI, 0.79–1.27] • **PFS**: statistically significant difference in favor of TKI therapy. HR 0.36 [95% CI, 0.31–0.43] • **Response rate**: statistically significant difference in favor of TKI therapy. RR 0.47 [95% CI, 0.41–0.55] **4. Anmerkungen/Fazit der Autoren** Our meta-analysis indicates that among NSCLC patients, advanced NSCLC patients with EGFR gene mutations would benefit most from TKI treatment, especially in the first-line setting. Nevertheless, EGFR-TKI treatment is justified for patients with unknown EGFR status, those who cannot tolerate chemotherapy owing to advanced age or who have poor performance status, and those with other medical conditions, when selected according to clinical factors.
Yang K et al., 2010: Effectiveness and safety of bevacizumab for unresectable non-small-cell lung cancer: a meta-analysis [83]	**1. Fragestellung** To evaluate the effectiveness and safety of bevacizumab in patients with unresectable non-small-cell lung cancer (NSCLC) **2. Methodik** **Population**: Patients had to have been confirmed as having NSCLC by pathological examination, and only unresectable NSCLC, such as stage IIIB, stage IV, etc., was considered. Patients treated with prior chemotherapy, immunotherapy, etc. were acceptable, but those who had previously received antiVEGF therapy were excluded **Intervention**: Bevacizumab **Komparator**: k.A. **Endpunkt**: OS, PFS, ORR, toxicity **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: up to 2009 **Anzahl eingeschlossene Studien/Patienten (Gesamt):**

	4 (n=2101) **3. Ergebnisdarstellung** **Overall survival:** • Low dose (7,5 mg/kg): no statistically significant difference at 1-year follow-up nor 2-year follow-up • High dose (15 mg/kg): no statistically significant difference at 1-year follow-up but on 2-year follow-up in favor of bevacizumab (RR= 1.24, 95% CI 1.04, 1.49, p=0.02) **4. Anmerkungen/Fazit der Autoren** In patients with unresectable NSCLC, addition of low-dose bevacizumab may improve progression-free survival whereas high-dose bevacizumab may increase 2-year overall survival rate, prolong progression-free survival, and improve tumour response rate while increasing the risk of treatment-related death. **5. Hinweise durch FB Med** Die eingeschlossenen Studien entsprechen den eingeschlossen Studien bei Botrel et al. Es wurde zusätzlich zu Botrel et al. zwischen 1-Jahres und 2-Jahres Überlebensraten unterschieden. Aufgrund der Überschneidung zu Botrel et al. wurden PFS und ORR nicht dargestellt.
Yang X et al., 2014: The efficacy and safety of EGFR inhibitor monotherapy in non-small cell lung cancer: a systematic review [84]	**1. Fragestellung** Efficacy of (EFGR-TKIs: gefitinib or erlotinib) monotherapy in previously treated non-small-cell lung cancer (NSCLC) **2. Methodik** ***Population:*** advanced NSCLC ***Intervention:*** gefitinib or erlotinib ***Komparator:*** placebo or BSC ***Endpunkte:*** PFS and OS ***Suchzeitraum:*** December 2013 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 14/8 970 (3 front-line, 2 second-line, 9 maintenance)

	Qualitätsbewertung der Studien: scrutinized – no further information ***Heterogenitätsuntersuchungen:*** χ2 test, I2 statistic used, values of 50 % regarded as representing low heterogeneity, FEM with Mantel-Haenszel method used, once the results were homogeneous; otherwise, random-effect model with DerSimonian and Laird method adopted, sensitivity analysis was also conducted to examine the impact of the overall results from this study ***„Publication bias“:*** plotting the HRs against their standard errors, Begg-adjusted rank correlation test and Egger regression asymmetry test performed **3. Ergebnisdarstellung** <u>OS</u> • HR (EGFR-TKIs mono vs. placebo) 0,88, 95 % KI 0,82 – 0,96, I^2 = 50.5% - significantly increased • patients with EGFR mutation positive had more pronounced benefit • second-line therapy group: HR 0,80; 95 % KI 0,63 – 1,01; I^2 = 74,6%, p = 0,047 • EGFR-mutation patients: HR 0,987; 95 % KI 0,881 – 1,105; I^2 = 12,8%, p = 0,330 <u>PFS</u> • HR (EGFR-TKIs) 0,71, 95 % KI 0,63 – 0,81, I2 = 81,2% • patients with EGFR mutation positive had more pronounced benefit <u>adverse reactions (EGFR TKIs vs. placebo)</u> • diarrhea (OR) 3,635; 95 % KI 2,377 to 5,557 • rashes (OR) 5,664; 95 % KI 8,869 to 27,665 • anorexia (OR) 1,555; 95 % KI 1,060 to 2,283 • anemia (OR) 1,481; 95 % KI 1,114 to 1,969 **4. Anmerkungen/Fazit der Autoren** The results show that monotherapy therapy with EFGR-TKIs produce a significant OS and PFS benefit for patients with NSCLC compared with placebo or BSC, especially for the patients who had adenocarcinomas, non-smokers and patients with EGFR gene mutations.
Yu Y et al., 2012: Non-platinum regimens of gemcitabine plus docetaxel	**1. Fragestellung** The aim was to compare the efficacy and toxicity of **gemcitabine plus docetaxel (GD)** with **platinum-based regimens** in patients with untreated advanced non-small cell lung cancer (NSCLC). **2. Methodik**

versus platinum-based regimens in first-line treatment of advanced non-small cell lung cancer: a meta-analysis on 9 randomized controlled trials [85]	**Population**: cytologically or pathologically confirmed of NSCLC and in clinical Ill-IV stage and patients must be chemotherapy naive **Intervention**: gemcitabine plus docetaxel (GD regimens) **Komparator**: cisplatin or carboplatin combined with a cytotoxic drug (platinum-based regimens) **Endpunkt**: OS, TTP, ORR, toxicity **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: up to 2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 9 (n=2.658) **3. Ergebnisdarstellung** **Overall survival (9 trials, 2658 patients):** no statistically significant difference, no heterogeneity ***TTP (5 trials):*** statistically significant difference in favor of platinum-based regimens (HR = 1.12, 95% CI= 1.02-1.24, p = 0.02) ***Response rate (8 trials):*** statistically significant difference in favor of platinum-based regimens (RR = 0.86, 95% CI= 0.74-D.99, p = 0.03) ***Toxicity****:* GD induced less grade 3-4 nausea/vomiting, anemia, neutropenia and febrile neutropenia (RR = 0.36, 95% CI = 0. 15-0.86, p = 0.02; RR = 0.35, 95% CI = 0.23-0.53, p = 0.00; RR = 0.68, 95% CI = 0.52-0.88, p = 0.003; RR = 0.53, 95% CI = 0.34-0.82, p = 0.004. respectively).  a Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio IV, Fixed, 95% CI | Year Georgoulias2001 0.00019996 0.10135436 16.8% 1.00 [0.82, 1.22] 2001 Georgoulias2005 -0.00618814 0.09191059 20.4% 0.99 [0.83, 1.19] 2005 Pujol2005 -0.10412747 0.12885312 10.4% 0.90 [0.70, 1.16] 2005 Katakami2006 0.19777472 0.22117603 3.5% 1.22 [0.79, 1.88] 2006 Binder2007 -0.01399402 0.18963025 4.8% 0.99 [0.68, 1.43] 2007 Rigas2008 0.02449031 0.07195241 33.3% 1.02 [0.89, 1.18] 2008 Novello2009b 0.5577347 0.22220667 3.5% 1.75 [1.13, 2.70] 2009 Novello2009a 0.34154842 0.23948491 3.0% 1.41 [0.88, 2.25] 2009 Rubio2009 0.07451164 0.1985865 4.4% 1.08 [0.73, 1.59] 2009 Total (95% CI) 100.0% 1.04 [0.96, 1.12] Heterogeneity: Chi² = 9.33, df = 8 (P = 0.32); I² = 14% Test for overall effect: Z = 0.85 (P = 0.39) Hazard Ratio IV, Fixed, 95% CI 0.2 0.5 1 2 5 Favours GD Favours Platinum-based Fig. 2 The efficacy meta -analysis between gemcitabine plus docetaxel (GO) and platinum-based regimens. a The pooled HR for overall did not display a difference between the two groups (HR = 1.04. 95% CI = 0.96-1.1 2. *p* = 0.39). **4. Anmerkungen/Fazit der Autoren** In our meta-analysis, we found that the efficacy was comparable between GD regimens and platinum-based regimens according to overall survival and 1-year survival. Although platinum-based regimen had an advantage in TTP and ORR, the advantage was lost when the

	two trials used sequential regimens were removed.
Yuan et al., 2012: Single-agent maintenance therapy in non-small cell lung cancer: a systematic review and meta-analysis [86]	**1. Fragestellung** Can single-agent maintenance therapy be considered as an ideal strategy for non-small cell lung cancer (NSCLC) treatment to achieve prolonged survival and tolerated toxicity? **2. Methodik** ***Population:*** Patients with advanced (stage IIIB or IV) NSCLC ***Intervention:*** Single-agent maintenance therapy (Paclitaxel, Vinorelbin, Gemcitabin, Docetaxel; Gefitinib, Pemetrexed, Erlotinib) ***Komparator:*** Placebo, BSC, Observation ***Endpunkte*:** Progression-free survival (PFS) Overall survival (OS) Objective response rate (ORR) ***Suchzeitraum:*** Bis Oktober 2011 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 11 RCTs (3 686) ***Qualitätsbewertung der Studien:*** Mittels Jadad-Score ***Heterogenitätsuntersuchungen:*** Wurde untersucht (Chi²-Test) **3. Ergebnisdarstellung** **Overall response rate** Data of treatment response were reported in six trials, with 2355 patients included. We found a statistically significant higher probability of tumor response for patients in maintenance groups versus control patients (*OR*: 2.80, 95% *CI*: 2.15–3.64, *P* <0.001). **Progression-free survival** Information concerning PFS was available in ten trials with 3513 patients. Most of the studies presented statistically significant results favoring single-agent maintenance therapy. Patients in maintenance arms had significantly longer PFS (*HR*: 0.67, 95% *CI*: 0.62–0.71, *P*<0.001), with significant

	heterogeneity between trials (*P* <0.001, I^2=70.7%) in our meta-analysis. In the stratified analysis by the type of maintenance therapy, the patients showed significant results when they were treated with cytotoxic agents (*HR*: 0.59, 95% *CI*:0.53–0.65, *P* <0.001) or with molecular targeted therapy (*HR*: 0.75, 95% *CI*: 0.69–0.81, *P* <0.001). When studies were classified by continuous or switch maintenance, we found that patients treated with continuous (*HR*: 0.64,95% *CI*: 0.55–0.74, *P* <0.001) or switch (*HR*: 0.67, 95%*CI*: 0.62–0.72, *P* <0.001) maintenance both showed significantly improved PFS. **Overall survival** The impact of the single-agent maintenance therapy on OS was estimated directly or indirectly for eight trials, with 3177 patients included. Only four single studies demonstrated statistically significant results. In our meta-analysis, there was a significant difference in OS between the two arms (*HR*: 0.84, 95% *CI*: 0.78–0.90, *P*<0.001) with no heterogeneity between trials (*P*=0.463,I^2=0.0%). The patients still had significantly longer OS when the studies were grouped by the types of drugs used in maintenance therapy; cytotoxic agents (*HR*:0.85, 95% *CI*: 0.76–0.94, *P* <0.001) and molecular targeted agents (*HR*: 0.83, 95% *CI*: 0.76–0.91, *P* <0.001). **4. Anmerkungen/Fazit der Autoren** In patients with advanced NSCLC, the use of single-agent maintenance therapy is associated with higher response rate and significantly prolongs PFS and OS despite of the risk of additional toxicity. **Limits:** There were different combinations of platinum-based chemotherapy as first-line therapy. These choices for therapy greatly influence the ORR and PFS for an individual patient. Our findings and interpretations were limited by the quality and quantity of available evidence on the effects of maintenance therapy **5. Hinweise der FBMed** Die Wirkstoffe der Erhaltungstherapie waren sehr vielfältig. Die meisten Wirkstoffe wurden nur in einer Studie untersucht (Paclitaxel, Vinorelbin, Docetaxel, Pemetrexed, Erlotinib). Lediglich Gefitinib und Gemcitabin wurden in mehr als einer Studie eingesetzt.
Zhang et al., 2012: Maintenance erlotinib	**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).

improves clinical outcomes of unresectable advanced non-small cell lung cancer: A meta-analysis of randomized controlled trials [87]	**2. Methodik** ***Population:*** Previously untreated patients with advanced (stage IIIB or IV) NSCLC ***Intervention:*** Erlotinib (mit oder ohne begleitende Chemotherapie) ***Komparator:*** Placebo/Nichtstun (observation) ***Endpunkte*:** PFS, OS, ORR ***Suchzeitraum:*** Bis 2011 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 6 RCTs (4 372) ***Qualitätsbewertung der Studien:*** Anhand von 7 Qualitätskriterien des NHS Center for Reviews and Dissemination (Randomisierung, Verblindung, Loss to follow-up, intention to treat etc.) ***Heterogenitätsuntersuchungen:*** Durchgeführt (Sensitivitäts- und Subgruppenanalysen) 3. **Ergebnisdarstellung** In der folgenden Abbildung sind die Charakteristika der einzelnen Studien dieser Metaanalyse dargestellt.

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.

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]. **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. **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. **5. 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)
Zhang et al., 2012: Pemetrexed plus platinum or gemcitabine plus platinum for advanced non-small cell lung cancer:	**1. Fragestellung** To systematically evaluate **pemetrexed/platinum** as firstline treatment for advanced NSCLC. **2. Methodik** ***Population****:* patients with stage IIIB or stage IV NSCLC. First-line ***Intervention****:* pemetrexed/platinum

final survival analysis from a multicentre randomized phase II trial in the East Asia region and a meta-analysis [89]	***Komparator**:* gemcitabine/platinum ***Endpunkte**:* OS, toxicity ***Methode***: systematic review and meta-analysis of RCTs ***Suchzeitraum***: up to 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 3 (n= 2 412) **3. Ergebnisdarstellung** **Table 4** Characteristics of the trials included in the meta-analysis | Study	Total accrual	Treatment dose and schedule	Stage IV (%)	ECOG PS= 2 (%)	Non-squamous (%)	Female (%)	Median OS (95% CI) (month)	1-year survival rate (%)	2-year survival rate (%)
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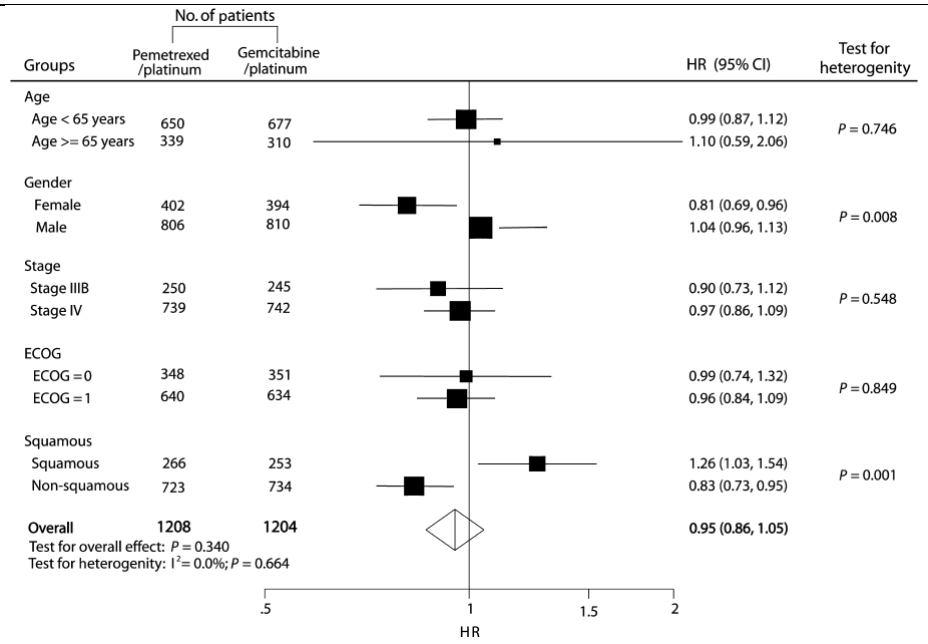
Scagliotti *et al.* (2008)[7]	1725	Pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 on d1, every 3 weeks for up to six cycles	76.2	0	71.7	29.8	10.3 (9.8, 11.2)	43.5	18.9
		Gemcitabine 1,250 mg/m^2 on d1 and d8, plus cisplatin 75 mg/m^2 on d1, every 3 weeks for up to six cycles	75.7	0	73.5	29.9	10.3 (9.6, 10.9)	41.9	14.0
Grønberg *et al.* (2009)[8]	436	Pemetrexed 500 mg/m^2 plus carboplatin AUC5 on d1, every 3 weeks for up to four cycles	71	22	74	44	7.3 (6.1, 8.6)	34	NR
		Gemcitabine 1,000 mg/m^2 on d1 and d8, plus carboplatin AUC5 on d1, every 3 weeks for up to four cycles	72	23	77	41	7.0 (5.8, 8.2)	31	NR
Zhang *et al.* (current study)	251	Pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 on d1, every 3 weeks for up to six cycles	64.6	0	82.7	38.6	15.3 (12.2, 18.9)	59.6	27.3
		Gemcitabine 1,000 mg/m^2 on d1 and d8, plus cisplatin 75 mg/m^2 on d1, every 3 weeks for up to six cycles	71.8	0	80.6	37.9	16.9 (14.6, 20.3)	65.9	27.9	 AUC, area under concentration/time curve; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; NR, not reported; OS, overall survival. **Overall survival**: • Overall population: no statistically significant difference • Female population: statistically significant difference in favor of pemetrexed/platinum (HR 0.81; 95% CI 0.69–0.96, significant heterogeneity) • Non squamous cell lung cancer: statistically significant difference in favor of pemetrexed/platinum (HR 0.83; 95% CI 0.73–0.95, significant heterogeneity) • Squamous cell lung cancer:statistically significant difference in favor of gemcitabine/platinum (HR 1.26; 95% CI 1.03–1.54, significant heterogeneity)



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

Toxicity: pemetrexed-platinum treatment was associated with significantly lower ORs for leukopenia (OR 0.43; 95% CI 0.29-0.65; p < 0.0001), thrombocytopenia (OR 0.28; 95% CI 0.21–0.37; p < 0.001) and neutropenia (OR 0.57; 95% CI 0.45–0.74; p < 0.001).

4. Anmerkungen/Fazit der Autoren

The meta-analysis confirmed that the histological subtype of lung cancer is an important predictor of treatment efficacy.

Zhang JW et al., 2014:

The impact of both platinum-based chemotherapy and EGFR-TKIs on overall survival of advanced non—small cell lung cancer [88]

1. Fragestellung

To understand the impact of PBC and EGFR-TKIs on NSCLC prognosis, we evaluated the association between the receipt of both regimens and overall survival (OS)

evaluate the association between the receipt of both regimens and overall survival (OS)

2. Methodik

Population:

advanced NSCLC

Interventionen:

- platinum-based doublet chemotherapy (PBC)
- epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs)

Komparator:

Plazebo

***Endpunkte*:**

OS

Suchzeitraum:

2001 bis 02/2012

Anzahl eingeschlossene Studien/Patienten (Gesamt):

15 (11456)

Nur: prospective, randomized, controlled phase III clinical trials (und: the percentage of patients treated with both PBC and EGFR-TKIs was available in the trial and OS was reported)

Qualitätsbewertung der Studien:

k.A

Heterogenitätsuntersuchungen:

k.A.

3. Ergebnisdarstellung

Table 1. Characteristics of the trials included in the analysis

First author/year	Study regimens	No. of Pts	PS (%)		Median age (years)	Stage (%)		PFS (months)	Female (%)
			0–1	⩾ 2		IIIB	IV		
Mok TS/2010 [23]	Gefitinib	609	90	10	57	24.6	75.4	5.7	79.5
	TC	608	89.3	10.7	57	23.8	76.2	5.8	79.1
Okamoto I/2010 [31]	TC	281	100	0	63	24.2	75.8	4.8	23.5
	Carboplatin + S–1	282	100	0	64	24.1	75.9	4.1	23.0
Kubota K/2008 [32]	GN followed docetaxel[a]	196	100	0	64	17.0	83	5.5	27.0
	TC	197	100	0	65	17.0	83	5.8	31.0
Ohe Y/2007 [33]	IP	145	100	0	62	21.4	78.6	4.7	33.1
	TC	145	100	0	63	19.3	80.7	4.5	31.7
	GP	146	100	0	61	20.5	79.5	4.0	30.8
	NP	145	100	0	61	17.9	82.1	4.1	30.3
Kubota K/2004 [34]	DP	151	96	4	63	0	100	–	35.8
	Vindesine + cisplatin	151	96.7	3.3	64	0	100	–	31.8
Han JY/2012 [24]	Gefitinib	159	91.2	8.8	57	10.7	89.3	5.8	88.0
	GP	150	90.7	9.3	56.5	9.3	90.7	6.4	89.3
Lara PN Jr/2011 [35]	TC + vadimezan	649	99.7	–	62	8.2	91.8	5.5	37.9
	TC + placebo	650	98.8	–	61	9.1	90.9	5.5	37.7
Reck M/2010 [36]	Placebo + GP	347	100	0	59	23.0	77	6.1	36.0
	Bevacizumab7.5 + GP	345	100	0	57	22.0	78	6.7	35.0
	Bevacizumab15 + GP	351	100	0	59	23.0	77	6.5	38.0
Lynch TJ/2010 [37]	TC + C225	338	98	2	64	12.0	88	4.4	43.0
	TC	338	99	1	65	14.0	86	4.24	40.0
Pirker R/2009 [38]	NP + cetuximab	557	83	17	59	6.0	94	4.8	31.0
	NP	568	82	18	60	6.0	94	4.8	29.0
Tan EH/2009 [39]	NP	194	62.1	37.9	59.4	19.5	80.5	4.9	26.8
	DP	196	62.3	37.7	62.1	15.2	84.8	5.1	23.6
Scagliotti GV/2008 [8]	GP	830	99.9	NA	61.1	24.3	75.7	5.1	29.9
	AP	839	99.8	NA	61	23.8	76.2	4.8	29.8
Ramlau R/2008 [40]	Bexarotene + NP	311	100	0	61	17.0	83.0	4.3	28.0
	NP	312	100	0	61	19.0	81.0	5.0	28.0
Blumenschein GR Jr /2008 [41]	TC + bexarotene	306	100	0	63	13.0	87.0	4.1	34.0
	TC	306	100	0	63	13.0	87.0	4.9	34.0
Sandler A/2011 [42]	TC + bevacizumab	417	100	0	NA	22.0	78.0	6.2	50.0
	TC	433	100	0	NA	26.0	74.0	4.5	42.0

The OS was positively correlated with the percentage of patients treated with both PBC and EGFR-TKIs ($r = 0.797$, $P < 0.001$).

The correlation was obvious in the trials in Asian populations (r = 0.936, P < 0.001) but was not statistically significant in the trials in predominantly Caucasian populations (r = 0.116, P = 0.588).

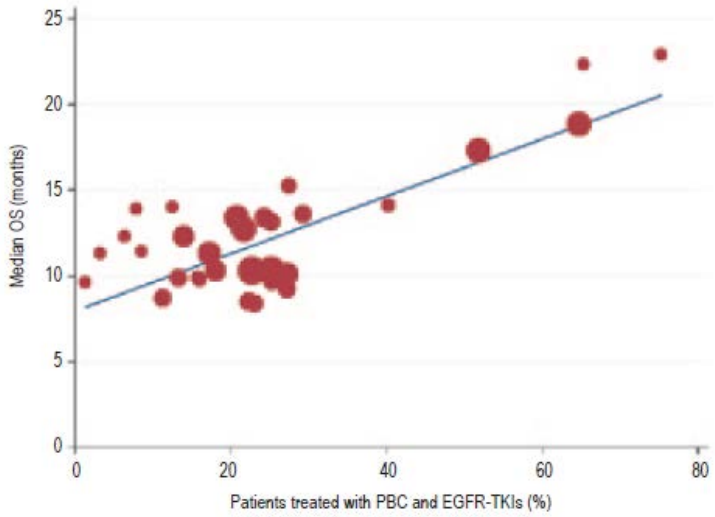


Figure 2. Linear regression curve showing positive correlation between the percentage of patients treated with both PBC and EGFR-TKIs during the course of treatment and the OS (r = 0.797, R2 = 0.636, P < 0.001) in all selected trials. Mathematic equation of regression (based on a weighted model): OS (months) = 8.01 + 16.7 × (percentage of patients treated with both PBC and EGFR-TKIs).

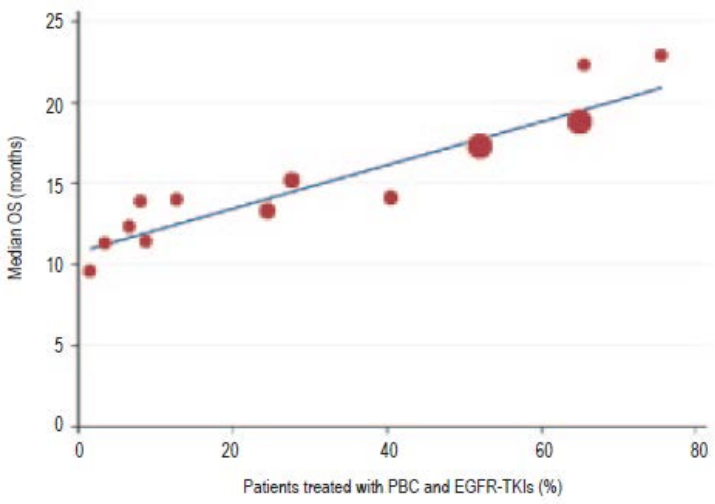


Figure 3. Linear regression curve showing positive correlation between the percentage of patients treated with both PBC and EGFR-TKIs during the course of treatment and the OS (r = 0.936, R2 = 0.876, P < 0.001) in Asian trials. Mathematic equation of regression (based on a weighted model): OS (months) =10.82 + 13.42 × (percentage of patients treated with both PBC and EGFRTKIs).

	4. Anmerkungen/Fazit der Autoren These results suggest that treatment with PBC and EGFR-TKIs may provide a survival benefit to patients with advanced NSCLC, highlighting the importance of having both modalities available for therapy.
Zhao N et al., 2014: Efficacy of epidermal growth factor receptor inhibitors versus chemotherapy as second-line treatment in advanced non-small-cell lung cancer with wild-type EGFR: a meta-analysis of randomized controlled clinical trials [90]	**1. Fragestellung** We sought to evaluate the effectiveness of EGFR-TKI as second-line treatment in EGFR wild-type NSCLC. **2. Methodik** ***Population:*** previously treated advanced NSCLC with wild-type EGFR **Intervention:** EGFR TKIs ***Komparator:*** chemotherapy ***Endpunkte:*** progression-free survival (PFS), overall survival (OS), objective response rate (ORR) ***Suchzeitraum:*** bis 07/ 2013 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 6/990 (5 phase III) ***Qualitätsbewertung der Studien:*** Jadad scale ***Heterogenitätsuntersuchungen:*** x^2-based Q test; $p > 0,05$ indicates low heterogeneity; $p \leq 0,05$ reflects high heterogeneity, if significant random-effects model used, if not significant FEM used ***„Publication bias“:*** tested by funnel plot **3. Ergebnisdarstellung** • all studies reached Jadad score of 3 PFS (EGFR-TKIs vs. chemotherapy) • HR 1,37; 95 % KI 1,20 – 1,56; $p < 0,00001$ – in the second-/third-line treatment of EGFR wild-type NSCLC, PFS significantly inferior in EGFR-TKI group compared with chemotherapy group • gefitinib and erlotinib significantly inferior to chemotherapy

	• erlotinib vs. chemotherapy: HR 1,37; 95 % KI 1,16 – 1,63, p = 0,0003 • gefitinib vs. chemotherapy: HR 1,35; 95 % KI 1,10 – 1,67, p = 0,004 • head-to-head trials: results favored chemotherapy more obviously (HR 1,53; 95 % KI 1,29 – 1,81; p < 0.00001 • subgroup trials, which had only subgroup analyses for EGFR wild-type patients: PFS not significantly different (HR 1,16; 95 % KI 0,94 – 1,43; p = 0,17) <u>OS and ORR</u> • equal results **4. Anmerkungen/Fazit der Autoren** Chemotherapy improves PFS significantly but not OS, compared with EGFR-TKIs as a second-line treatment in advanced NSCLC with wild-type EGFR. Whether EGFR-TKIs should be used in EGFR wild-type patients should be considered carefully. *Hinweise durch FB Med:* • *study quality not further discussed* • *no evidence of publication bias*
Zhong N et al., 2013: Chemotherapy Plus Best Supportive Care versus Best Supportive Care in Patients with Non-Small Cell Lung Cancer: A Meta-Analysis of Randomized Controlled Trials [91]	**1. Fragestellung** We performed a systematic review and meta-analysis to evaluate the effects of chemotherapy plus BSC versus BSC alone on survival of patients with NSCLC. **2. Methodik** ***Population:*** patients with NSCLC (Stage III/IV or advanced) ***Intervention:*** chemotherapy and BSC ***Komparator:*** BSC alone ***Endpunkte*:** OS or treatment-related mortality ***Suchzeitraum:*** Nicht angegeben ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 16 RCTs (4 135) ***Qualitätsbewertung der Studien:*** The quality of the trials was also assessed by pre-defined criteria using

Jadad score

Heterogenitätsuntersuchungen:

Durchgeführt (Sensitivitätsanalysen)

3. Ergebnisdarstellung

Die folgende Abbildung stellt die Charakteristika der ausgewerteten Studien dar, inklusive der jeweils verglichenen Interventionen und der Bewertung der Studien nach Jadad-Score.

Table 1. Design and characteristic of trials included in our meta-analysis.

Source	No. of patients	Sex (male, %)	Mean age, y	Stage of disease	Intervention	Jadad score
H Anderson [17]	300	63.3	64.5	Locally advanced and metastatic NSCLC	Gemcitabine plus BSC; BSC	3
The ELCVIS Group [18]	154	87.0	74.0	IIIB or IV NSCLC	Vinorelbine; BSC	4
RL Woods [19]	188	81.9	61.0	Advanced NSCLC	Cisplatin and vindesine; BSC	2
By Frances A [8,20]	204	67.2	61.0	IIIA, IIIB or IV NSCLC	Docetaxel; BSC	4
M Ranson [21]	157	75.0	64.0	IIIB or IV NSCLC	Paclitaxel Plus BSC; BSC	3
SG Spiro [22]	725	65.5	74.0	Advanced NSCLC	cisplatin-based chemotherapy plus BSC; BSC	4
L Paz-Ares [23]	539	58.1	61.3	IIIB or IV NSCLC	Pemetrexed plus BSC; BSC	4
T Ciuleanu [24]	663	73.0	60.5	IIIB or IV NSCLC	Pemetrexed plus BSC; placebo plus BSC	5
K Roszkowski [25]	207	81.6	59.3	metastatic or non-resectable localized NSCLC	Docetaxel plus BSC; BSC	2
M Helsing [26]	150	59.0	64.0	Advanced NSCLC	Carboplatin, Etoposide plus BSC; BSC	3
G Cartel [27]	102	73.0	56.6	Stage IV NSCLC	Cisplatin, cyclophosphamide, mitomycin plus BSC; BSC	2
S Kaasa [28]	87	79.3	62.0	Inoperable, extensive NSCLC	Cisplatin, etoposide; symptomatic treatment	3
BR Cellerino [29]	123	96.7	60.5	Advanced NSCLC	Cyclophosphamide, epirubicin, cisplatin, methotrexate, etoposide, and lomustine; BSC	2
PA Ganz [30]	48	89.6	NG	advanced metastatic NSCLC	Cisplatin, vinblastine plus BSC; BSC	2
BE Rapp [31]	137	74.5	NG	Advanced NSCLC	vindesine and cisplatin/cyclophosphamide, doxorubicin, and cisplatin; BSC	1
MH Cullen [32]	351	72.4	63	Unresectable NSCLC	Mitomycin, ifosfamide, cisplatin plus palliative care; palliative care	2

Ergebnisse zum Overall Survival:

Von den 16 Studien konnten aus 13 Studien Ergebnisse zum OS ermittelt werden. Hier zeigte sich ein statistisch signifikanter Vorteil für die Kombination aus Chemotherapie plus BSC versus BSC allein (HR, 0.76; 95%CI, 0.69–0.84; P<0.001) bei geringer Heterogenität (I^2=24%, p=0,201).

Ergebnisse zu Nebenwirkungen/Unerwünschten Ereignissen:

Overall, we noted that treatment with chemotherapy plus BSC were associated with significant increase in the risks of neutropenia (RR, 31.01; 95%CI, 10.71–89.75; P<0.001, I^2=0%), leukopenia (RR, 11.49; 95%CI, 3.50–37.69; P<0.001, I^2=14%), anemia (RR, 3.85; 95%CI, 1.58–9.38; P=0.003, I^2=12%), infection (RR, 2,10; 95%CI, 1,04–4.25; P=0.04, I^2=10%), nausea/vomiting (RR, 3.82; 95%CI, 1.31–11.14; P=0.01, I^2=47%), alopecia (RR, 15.84; 95%CI, 1,05–239.49; P00.05, I^2=80%), and ankle swelling (RR, 2,64; 95%CI, 1.61–4.33; P<0.001, I^2=0%). No other significant differences were identified between the effects of chemotherapy plus BSC and BSC alone.

4. Anmerkungen/Fazit der Autoren

Chemotherapy plus BSC increased the OS and reduced the 6-month, 12-

	month, and 2-year mortality of NSCLC patients. Since nearly all the trials in our study included patients with stage III/IV disease or advanced NSCLC, the conclusions should be applicable only to patients with advanced or metastatic NSCLC. **Limits:** First, inherent assumptions were made for all meta-analyses, because the analyses used pooled data,either published or provided by the individual study; individual patient data or original data were unavailable, which did not allow us to perform more detailed analyses and to obtain more comprehensive results. Second, treatments given in those trials included second generation, third generation, and the fourth generation chemotherapy regiments, which prevented us from exploring the association between the type of chemotherapy and survival outcomes. Third, heterogeneity among the trials is another limitation of our study. We applied a random-effect model that took possible heterogeneity into consideration and performed subgroup analyses based on several important factors to further explore the source of heterogeneity. Fourth, data on progression-free survival were rarely available in these trials; therefore, no conclusions could be drawn. **5. Hinweise der FBMed** Kein Suchzeitraum angegeben Es wird nicht dargestellt, welche Interventionen unter BSC subsummiert waren

Scottish Intercollegiate Guidelines Network (SIGN), 2014: Management of lung cancer [69]	**1. Fragestellung** In patients with NSCLC (locally advanced or metastatic disease), what is the most effective second line systemic anticancer therapy (chemotherapy, targeted therapy, EGFR Inhibitors)? Outcomes: Overall survival, progression-free survival, toxicity, quality of life
	2. Methodik ***Grundlage der Leitlinie:*** systematische Recherche und Bewertung der Literatur, Entwicklung durch multidisziplinäre Gruppe von praktizierenden klinischen ExpertInnen, Expertenreview, öffentliche Konsultation ***Suchzeitraum:*** 2005 - 2012 ***LoE/GoR:*** Vgl. *Anlage 1* dieser Synopse ***Sonstige methodische Hinweise*** • *keine Empfehlung zur gesuchten Indikation* • *Hintergrundtext (siehe unten) ohne Quellenangaben*
	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>Molecular testing of predictive biomarkers in patients with NSCLC</u> … Other molecular abnormalities which may be tested for include anaplastic lymphoma kinase (ALK) gene rearrangement …. Drugs targeting these mutations are at various stages of development. <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. <u>Recommendations</u> • Second line systemic anticancer therapy with single agent docetaxel or erlotinib should be considered for patients with performance status 0-2 recurrent NSCLC who have been previously treated with first line SACT for advanced disease. **(A)** • Second line systemic anticancer therapy with pemetrexed should be considered for patients with advanced non-squamous cell NSCLC who have been previously treated with first line SACT for advanced disease. **(A)**
Alberta Provincial Thoracic Tumour Team, 2013: Non-small cell lung cancer stage IV [3]	**Fragestellung** What is the optimal second-line therapy for patients with stage IV NSCLC?
	Methodik ***Grundlage der Leitlinie:*** systematic literature search, evidence tables, AGREE used for retrieved guidelines, working group reviewed currency and acceptability of all relevant literature, then circulated a draft of the updated guideline to entire provincial tumour team for final feedback and approval **Suchzeitraum**: bis 2013 ***LoE/GoR:*** no use of formal rating schemes for describing the strength of the recommendations, rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken

	into consideration when formulating the recommendations *Sonstige methodische Hinweise* • *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* • *Some members of the Alberta Provincial Thoracic Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.*
	Freitext/Empfehlungen <u>Recommendations</u> … 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. … <u>Discussion and literature</u> **Second-line chemotherapy** The Alberta Provincial Thoracic Tumour Team recommends therapy with single-agent docetaxel or erlotinib for patients with squamous cell carcinoma histology, or single-agent PEM for patients with adenocarcinoma tumour histology in the second-line treatment of advanced NSCLC (recommendation #8). All three agents have been reported to produce similar rates of response and overall survival, therefore the choice of which agent to use will depend on the patient's tumour histology, comorbidities, toxicity from previous treatments, risk for neutropenia, smoking history, and patient convenience and preference. **85.** Stinchcombe TE, Socinski MA. Considerations for second-line therapy of non-small cell lung cancer. *Oncologist.* 2008;13 Suppl 1:28-36. **86.** Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol.* May 2000;18(10):2095-2103. **87.** 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.* Jun 2000;18(12):2354-2362. **88.** Dancey J, Shepherd FA, Gralla RJ, Kim YS. Quality of life assessment of second-line docetaxel versus best supportive care in patients with non-small-cell lung cancer previously

treated with platinum-based chemotherapy: results of a prospective, randomized phase III trial. *Lung Cancer.* Feb 2004;43(2):183-194.
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98. Weiss GJ, Langer C, Rosell R, et al. Elderly patients benefit from second-line cytotoxic chemotherapy: a subset analysis of a randomized phase III trial of pemetrexed compared with docetaxel in patients with previously treated advanced non-small-cell lung cancer. *J Clin Oncol.* Sep 20 2006;24(27):4405-4411.
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101. Florescu M, Hasan B, Seymour L, Ding K, Shepherd FA. A clinical prognostic index for patients treated with erlotinib in National Cancer Institute of Canada Clinical Trials Group study BR.21. *J Thorac Oncol.* Jun 2008;3(6):590-598.
102. Ciuleanu T, Stelmakh L, Cicenas S, Esteban E. Erlotinib versus docetaxel or pemetrexed as second-line therapy in patients with advanced non-small-cell lung cancer (NSCLC) and poor prognosis: efficacy and safety results from the phase III TITAN study. . In: Oncol JT, ed. Vol 52010.
103. LeCaer H, Greillier L, Corre R, et al. A multicenter phase II randomized trial of gemcitabine followed by erlotinib at progression, versus the reverse sequence, in vulnerable elderly patients with advanced non small-cell lung cancer selected with a comprehensive geriatric assessment (the GFPC 0505 study). *Lung Cancer.* Jul 2012;77(1):97-103.
104. Parikh PM, Vaid A, Advani SH, et al. Randomized, double-blind, placebo-controlled phase II study of single-agent oral talactoferrin in patients with locally advanced or metastatic non-small-cell lung cancer that progressed after chemotherapy. *J Clin Oncol.* Nov 1 2011;29(31):4129-4136.
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Treatments for ALK-Positive Rearrangements

EML4-ALK fusion gene is present in approximately two to seven percent of such tumours, and is mutually exclusive with K-Ras and EGFR mutations.

112. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature.* Aug 2 2007;448(7153):561-566.

ALK translocations have been noted in never-smokers, patients with adenocarcinoma and younger patients.

113. Kim DW, Ahn MJ, Shi Y, et al. Results of a global phase II study with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC). Paper presented at: 2012 Annual Meeting of the American Society of Clinical Oncology2012.

Patients with ALK translocations appear to be less sensitive to EGFR inhibitors and standard CT than those without.

114. Ramalingam SS, Owonikoko TK, Khuri FR. Lung cancer: New biological insights and recent therapeutic advances. *CA Cancer J Clin.* Mar-Apr 2011;61(2):91-112.

In a recent phase I study, Kwak and colleagues reported a response rate of 57 percent and a stable disease rate of 33 percent in 82 patients with advanced NSCLC who were treated with second-, third-, or fourth-line crizotinib.

115. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med.* Oct 28 2010;363(18):1693-1703.

Lee et al conducted a restrospective analysis of 1 166 patients to investigate outcome rates of patients with advanced NSCLC who were managed in the pre-ALK inhibitor era. OS rates were compared across three groups: patients who were ALK-positive, patients who were EGFR-positive and patients who were ALK and EGFR wild types. The median OS rates in these groups were 12.2 months, 29.6 months and 19.3 months, respectively. Median PFS rates were similar in all groups although PFS rates for patients who received EGFR TKIs was shorter in ALK-positive patients compared to other groups.

116. Lee JK, Park HS, Kim DW, et al. Comparative analyses of overall survival in patients with anaplastic lymphoma kinase-positive and matched wild-type advanced nonsmall cell lung cancer. *Cancer.* Jul 15 2012;118(14):3579-3586.

In the pre ALK-inhibitor era, therefore, ALK-positive patients experienced shorter survival on par with wild type patients. In addition, ALK-positive patients were more resistant to EGFR TKI treatment than wild type patients.

Recently, a phase II clinical trial by Kim et al (see above) and a phase III clinical trial by Shaw et al. investigated the efficacy and safety of crizotinib; building off the results from an earlier phase I, single-arm clinical trial by Camidge et al. In the study by Kim et al, published as an abstract at the ASCO 2012 conference, patients with ALK-positive NSCLC were given 250mg BID crizotinib in three-week cycles. An ORR of 53% and 12-week DCR of 85% was observed with a median PFS of 8.5 months. Significant improvements in post-treatment pain, cough, and global QoL were reported. In the phase III clinical trial conducted by Shaw et al, also published as an abstract, this time at the ESMO 2012 conference, crizotinib was compared to standard CT for advanced NSCLC. Like before, 250mg BID crizotinib was administered to 173 patients with another 174 patients receiving either 500mg/m2 PEM (57%) or 75mg/m2 docetaxel (41%). Crizotinib prolonged PFS to median of 7.7 months from 3 months for those treated with standard CT (HR 0.49, CI 0.37-0.64, $p<0.0001$). The ORR was significantly higher in those treated with crizotinib (65% vs. 20%; $p<0.0001$). The OS data were still not mature. As there was significant crossover from the standard CT group to the crizotinib group it is possible that OS results may not significantly differ. That said, however, the authors believe crizotinib should be the new standard

	of care for individuals with ALK-positive advanced NSCLC. **117.** Shaw AT, Kim DW, Nakagawa K, et al. Phase III study of crizotinib versus pemetrexed or docetaxel chemotherapy in patients with advanced ALK-positive non-small cell lung cancer (NSCLC) (PROFILE 1007). Paper presented at: Congress of the European Society for Medical Oncology 20122012. **118.** Camidge DR, Bang YJ, Kwak EL, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol. Oct 2012;13(10):1011-1019. As a result of these, and other promising results, the US FDA have approved crizotinib for patients with ALK-positive advanced or metastatic NSCLC. **119.** Kimura H, Nakajima T, Takeuchi K, et al. ALK fusion gene positive lung cancer and 3 cases treated with an inhibitor for ALK kinase activity. *Lung Cancer.* 2012;75(1):66-72. The results of these early trials are promising, and, along with other clinical trials currently underway, may strengthen support for the role of prospective genotyping in the selection of therapy for patients with advanced NSCLC. Indeed, guidelines from the National Comprehensive Cancer Network and the European Society for Medical Oncology now recommend ALK gene rearrangement testing to better treat those patients with advanced NSCLC who are ALK-positive.
Brodowicz T et al., 2012: Third CECOG consensus on the systemic treatment of non-small-cell lung cancer [10]	**1. Fragestellung** It is the aim of the present consensus to summarize minimal quality-oriented requirements for individual patients with NSCLC in its various stages based upon levels of evidence in the light of a rapidly expanding array of individual therapeutic options.
	2. Methodik ***Grundlage der Leitlinie:*** evidence-based consensus from experts from Europe and the United States based on systematic literature search ***Suchzeitraum:*** bis 12/2009 ***LoE/GoR:*** Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology *Sonstige methodische Hinweise* • *Kein formaler Konsensusprozess beschrieben* • *Auswahl und Bewertung der Literatur nicht beschrieben* • *14 author disclosures given, remaining authors have declared no conflicts of interest*
	Freitext/Empfehlungen <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. Barlesi F, Jacot W, Astoul P, Pujol JL. Second-line treatment for advanced nonsmall cell lung cancer: a systematic review. Lung Cancer 2006;51(2): 159–172. Weiss GJ, Rosell R, Fossella F et al. The impact of induction chemotherapy on the outcome of second-line therapy with pemetrexed or docetaxel in patients with advanced non-small-cell lung cancer. Ann Oncol 2007; 18(3): 453–460. Shepherd FA, Dancey J, Ramlau R et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000; 18(10): 2095–2103. Fossella FV, DeVore R, Kerr RN et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000; 18(12): 2354–2362. Hanna N, Shepherd FA, Fossella FV et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004; 22(9): 1589–1597. Kim ES, Hirsh V, Mok T et al. Gefitinib versus docetaxel in previously treated nonsmall-cell lung cancer (INTEREST): a randomised phase III trial. Lancet 2008;372(9652): 1809–1818. Shepherd FA, Rodrigues Pereira J, Ciuleanu T et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005; 353(2): 123–132. Thatcher N, Chang A, Parikh P et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet 2005; 366(9496): 1527–1537. Zhu CQ, da Cunha Santos G, Ding K et al. Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol 2008; 26(26): 4268–4275. Hirsch FR, Varella-Garcia M, Bunn PA Jr., et al. Epidermal growth factor receptor in non-small-cell lung carcinomas: correlation between gene copy number and protein expression and impact on prognosis. J Clin Oncol 2003; 21(20): 3798–3807. <u>targeted treatment options</u> … 3 Patients with EML4-ALK fusion tumors benefit from specific targeted therapy against EML4-ALK fusion. The role of routinely carried out EML4-ALK fusion testing for clinical practice is awaiting the results from ongoing clinical trials. EML4-ALK fusion: The fusion gene EML4-Anaplastic Lymphoma Kinase (ALK) was first reported in NSCLC only a few years ago. Soda M, Choi YL, Enomoto M et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007; 448(7153): 561–566. A clinical dose-escalation phase I study with an oral MET and ALK inhibitor PF-02341066 showed for NSCLC patients with tumors harboring an activating ALK gene fusion an objective RR of 64% and a disease control rate of 90%.

	Bang Y, KE , Shaw AT, Kwak EL. Clinical activity of the oral ALK inhibitor PF-02341066 in ALK-positive patients with non-small cell lung cancer (NSCLC). J Clin Oncol (Meeting Abstracts) 2010; 28: 3. Although the ALK fusion either with EML4 or with other fusion partners is relatively infrequent in NSCLC (4%–5%), there still is a substantial number of patients who might have a significant clinical benefit from this well-tolerated therapy. Choi YL, Soda M, Yamashita Y et al. EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors. N Engl J Med 2010; 363(18): 1734–1739.
Ramnath et al., 2013: Treatment of Stage III Non-small Cell Lung Cancer [67]	Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines **1. Fragestellung** updates the published clinical trials since the last American College of Chest Physicians guidelines to make treatment recommendations for this controversial subset of patients
	2. Methodik Siehe *Socinski et al., 2013*
	Infiltrative Stage III (N2,3) Non-small Cell Lung Cancer 2.3.1. In patients with infiltrative stage III (N2,3) non-small cell lung cancer (NSCLC) and performance status 0-1 being considered for curative-intent treatment, radiotherapy alone is not recommended **(Grade 1A**) . 2.3.2. In patients with infi ltrative stage III (N2,3) NSCLC and performance status 0-1 being considered for curative-intent treatment, combination platinum-based chemotherapy and radiotherapy (60-66 Gy) are recommended (**Grade 1A**) . *Remark:* Dose escalation of radiotherapy is not recommended (except in a clinical trial). *Remark:* For patients with stage IIIB NSCLC, once daily thoracic radiotherapy plus platinum-based doublet chemotherapy is recommended. 2.3.3. In patients with infiltrative stage III (N2,3) NSCLC, performance status 0-1, and minimal weight loss being considered for curative-intent treatment, concurrent chemoradiotherapy is recommended over sequential chemoradiotherapy (**Grade 1A**) . *Remark:* We cannot currently recommend for or against induction chemotherapy (ie, before) concurrent chemoradiotherapy, and patients should be referred for clinical trials to answer this question. *Remark:* We cannot currently recommend for or against consolidation chemotherapy (ie, after) concurrent chemoradiotherapy, and patients should be referred to clinical trials to answer this question. 2.3.4. In patients with infiltrative stage III (N2,3) NSCLC with a complete response after treatment with concurrent chemoradiotherapy, we suggest that prophylactic cranial irradiation should not be given (outside of a clinical trial) (**Grade 2C**) . 2.3.5.

	In patients with infiltrative stage III (N2,3) NSCLC and performance status 0-1 being considered for curative-intent treatment, treatment with neoadjuvant (induction) chemotherapy or chemoradiotherapy followed by surgery is not recommended (**Grade 1C**) . 2.3.6. In patients with infiltrative stage III (N2,3) NSCLC and performance status 2 or those with substantial weight loss (. 10%), concurrent chemoradiotherapy is suggested but with careful consideration of the potential risks and benefi ts (**Grade 2C**) . *Remark:* Patient-related and tumor-related factors can infl uence the balance of risks vs benefi ts; patient preferences should also play a significant role. 2.3.7. In patients with infiltrative stage III (N2,3) NSCLC, performance status 0-1, and minimal weight loss being considered for curative-intent treatment, a platinum-based doublet chemotherapy is suggested (**Grade 2C**). *Remark* : An optimal agent to be combined with platinum cannot be defi ned; one should choose a regimen with an acceptable toxicity profi le for the individual patient among several combinations that have demonstrated activity when used concurrently with radiation in stage III NSCLC. 2.3.8. In patients with symptomatic infiltrative stage III (N2,3) NSCLC and either performance status 3-4, comorbidities, or disease too extensive to treat with curative intent, palliative radiotherapy is recommended. The fractionation pattern should be chosen based on the physician's judgment and patient's needs (**Grade 1C**). ***Adjuvant Therapy*** 4.5.3. In patients with resected NSCLC (R0) who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging and who have good performance status, adjuvant platinum-based chemotherapy is recommended (**Grade 1A**) . *Remark* : We suggest this should typically involve a doublet regimen for 3 to 4 cycles initiated within 12 weeks. 4.5.4. In patients with R0 resected NSCLC who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging, sequential adjuvant radiotherapy is suggested when concern for a local recurrence is high (**Grade 2C**) . *Remark* : Adjuvant postoperative radiotherapy reduces the incidence of local recurrence, but it is unclear whether it improves survival. *Remark:* Adjuvant chemotherapy should be used initially followed by radiotherapy; concurrent chemoradiotherapy is not recommended (except in a clinical trial). 4.5.5. In patients with NSCLC who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging and were incompletely resected (R1,2), combined postoperative concurrent chemotherapy and radiotherapy is suggested (**Grade 2C**) . *Remark:* Incomplete resection (R1,2) does not appear to confer a survival benefit over no resection.
Socinski et al., 2013:	Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Treatment of Stage IV Non-small Cell Lung Cancer [74]	**1. Fragestellung** to update the previous edition of the American College of Chest Physicians 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.
	1. **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.
	2. **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)** .
Ellis PM et al., 2014: Use of the Epidermal Growth Factor Receptor Inhibitors Gefitinib (Iressa®), Erlotinib (Tarceva®), Afatinib, Dacomitinib or Icotinib in the Treatment of Non–Small-Cell Lung Cancer: A Clinical Practice Guideline[12]	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)? 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 (47) and one for progression-free survival when combined with bevacizumab against bevacizumab alone (p<0.001) . • One study comparing erlotinib and gemcitabine did not report significance but found a higher response rate with erlotinib (15% vs 7%) and 9.1 months vs 8.3 months for overall survival . • Two trials evaluating gefitinib found a statistically significant benefit for PFS in the maintenance setting, p<0.001 when combined with chemotherapy and against chemotherapy (48) and p<0.0001 compared to a placebo . • Another trial evaluated gefitinib and showed a higher response rate, but this was not significant (p=0.369) . **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%).
Alberta Provincial Thoracic Tumour Team, 2012: Non-small cell	**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

lung cancer - stage III. Alberta Health Services [2]	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
	3. Empfehlungen **Curative Intent Treatment for Inoperable Disease** 6. Combined concurrent chemo-radiation is recommended for inoperable stage III patients with good performance status (ECOG 0-2), minimal weight loss, good pulmonary reserve, and tumour and anatomy conformation permitting radical dose radiation without expected severe normal tissue toxicity. • Cisplatin-based chemotherapy (with either etoposide or vinorelbine) and thoracic radiation of 55Gy in 25 fractions to 66Gy in 33 fractions is the recommended treatment option. 7. For patients with borderline performance status or moderate weight loss (5-10%), concurrent or sequential chemo-radiation or higher dose hypofractionated radiation are options. **Treatment for T1-3N2 Disease** 8. Concurrent chemo-radiation is recommended for pre-operatively diagnosed N2 disease. Cisplatin-based chemotherapy (with either etoposide or vinorelbine) and thoracic radiation of 55 Gy in 25 fractions to 66 Gy in 33

	fractions is the recommended treatment option. Additional cycles of chemotherapy can be considered for bulky disease. 9. In select patients, neoadjuvant chemoradiotherapy followed by lobectomy can be considered. Pre-operative pathologically diagnosed N2 disease is not recommended to undergo surgical resection alone. 10. For patients with N2 disease discovered intra-operatively where complete resection of the lymph nodes and primary tumour is technically possible, completion of the planned lung resection is recommended. 11. In patients with N2 disease discovered intra-operatively, platinum-based adjuvant chemotherapy is recommended. Adjuvant radiotherapy can be considered in select patients. **Palliative Treatment for Inoperable Disease** 12. In patients where lung reserve precludes radical radiotherapy, palliative chemotherapy and/or palliative radiotherapy are recommended. 13. Palliative chemotherapy options include: • 1st line: platinum-based doublets • 2nd line: docetaxel, erlotinib or pemetrexed 14. For symptomatic patients with poor performance status (ECOG>2) and/or significant weight loss (usually defined as >10% in previous 3 months), radiotherapy for symptom palliation is recommended. Dose-fractionation schedule options include: • 20Gy in 5 fractions or 30Gy in 10 fractions • Single fractions of radiotherapy less than 10Gy may be appropriate in some clinical circumstances such as poor performance status or patient travel distance. • Split course radiation can also be used in select cases.
Azzoli et al., 2010: American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer [5]	**1. Fragestellung** To update its recommendations on the use of chemotherapy for advanced stage non–small-cell lung cancer (NSCLC), ASCO convened an Update Committee of its Treatment of Unresectable NSCLC Guideline Expert Panel. ASCO first published a guideline on this topic in 19971 and updated it in 2003.2 The current version covers treatment with chemotherapy and biologic agents and molecular markers for stage IV NSCLC and reviews literature published from 2002 through May 2009.
	2. Methodik 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)
	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., 2011: American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer [6]	**1. 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.
	2. **Methodik** ***focused update:*** zu *Azzoli et al. 2010* **Suchzeitraum:** bis 11/2009
	3. 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 3* dieser Synopse
de Marinis F et al., 2011:	**1. Fragestellung** AIOT (Italian Associatlon of Thoracic Oncology) produces up-to-date,

Treatment of advanced non-small-cell-lung cancer: Italian Association of Thoracic Oncology (AIOT) clinical practice guidelines [17]	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
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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 IA, 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)**

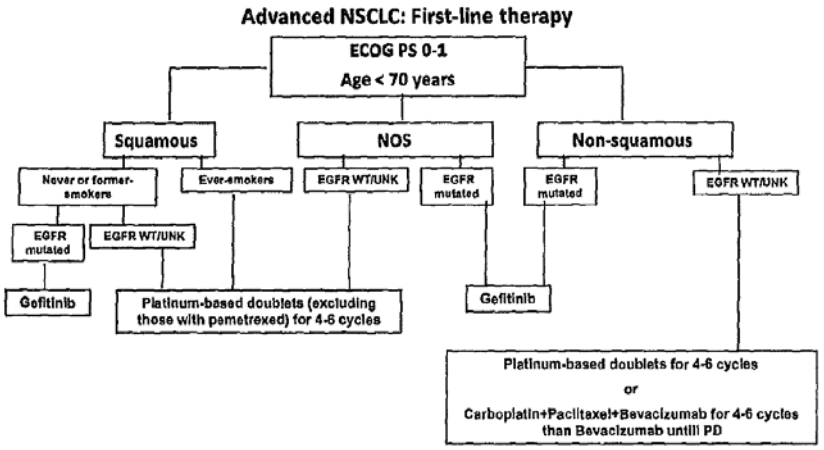


Fig. 1. Suggested algorithm for first-line treatment of advanced non-small-cell lung cancer (ECOG PS: Eastern Cooperative Oncology Group performance status; NOS: not otherwise specified; EGFR: epidermal growth factor receptor; WT: wild type; and UNK: unknown).

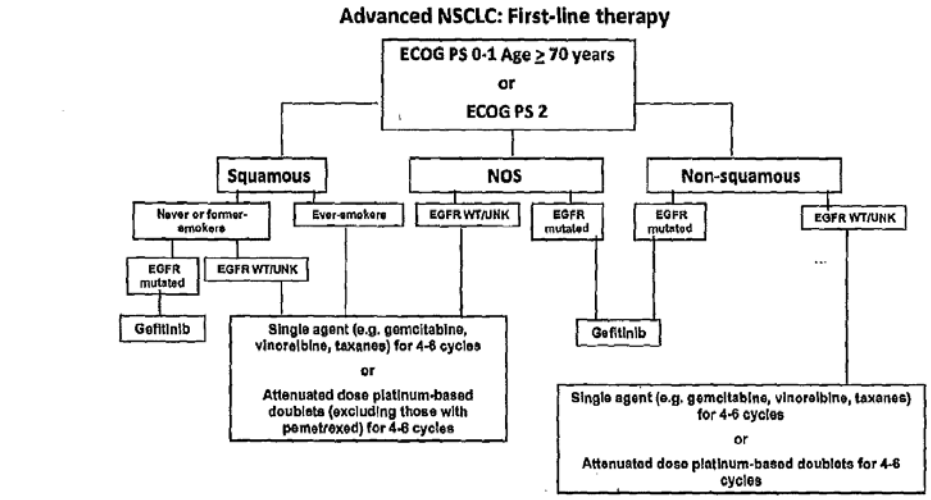


Fig. 2. Suggested algorithm for first-line treatment of advanced non-small-cell lung cancer in special patients population (ECOG PS: Eastern Cooperative Oncology Group performance status; NOS: not otherwise specified; EGFR: epidermal growth factor receptor; WT: wild type; and UNK: unknown).

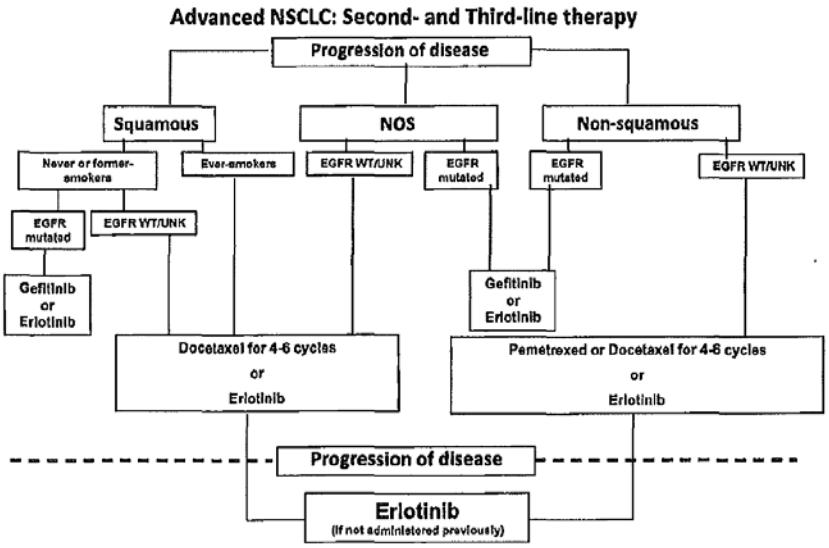


Fig. 3. Suggested algorithm for second- and third-line treatment of advanced non-small-cell lung cancer (NOS: not otherwise specified; EGFR: epidermal growth factor receptor; WT: wild type; and UNK: unknown).

DGP, 2010:

Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms Interdisziplinäre S3-Leitlinie der Deutschen Gesellschaft für Pneumologie und Beatmungsmedizin und der

Fragestellung

Ziel der vorliegenden Leitlinie ist die Verbesserung der Prognose und der Lebensqualität von Patienten mit Lungenkarzinomen durch Optimierung des Einsatzes der derzeitigen diagnostischen und therapeutischen Möglichkeiten in einem interdisziplinären Ansatz. Außerdem soll durch die Empfehlung präventiver Maßnahmen die Häufigkeit des Lungenkarzinoms reduziert werden.

Methodik

Grundlage der Leitlinie:

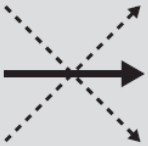
systematische Recherche, formale Konsensusprozesse

Suchzeitraum:

bis 06/2006

Der nachfolgende Zeitraum bis zur Veröffentlichung der Leitlinie wurde hinsichtlich relevanter Publikationen von den Arbeitsgruppen beobachtet.

Deutschen Krebsgesellschaft [19]	Relevante Literatur aus diesem Zeitraum wurde dann in der Leitlinie berücksichtigt, wenn es sich um Studien mit hoher Evidenzstärke (Evidenzgrad 1–2) oder Leitlinien handelte und sich neue Aspekte ergaben. ***LoE, GoR:*** **Tab. 1** Beziehung zwischen Evidenz- und Empfehlungsgrad (modifiziert nach Oxford Center for Evidence-based Medicine 2001 und AWMF).

Evidenzgrad	Evidenz Therapeutische Studien	Diagnostische Studien	Konsensus Modifizierende Kriterien für Empfehlungsgrad	Empfehlungsgrad	
1a	syst. Review von randomisierten kontrollierten klinischen Studien	syst. Review validierende Kohortenstudien	– ethische Aspekte – Patienten-Präferenzen – klin. Relevanz, integr. Outcome – klinisch bedeutsame Abweichung von Studiensituation	A	starke Empfehlung
1b	individ. randomisierte kontrollierte Studie (enges Konfidenzintervall)	validierende Kohortenstudie mit guten Referenzstandards			
1c	Alle-oder-keiner-Prinzip	absolute Spezifität zum Einschluss oder absolute Sensitivität zum Ausschluss der Diagnose			
2a	systematische Review von Kohortenstudien	syst. Review von explorativen Kohortenstudien		B	mittelstarke Empfehlung
2b	individ. Kohortenstudie, randomisierte kontr. Studie geringerer Qualität	exploratorische Kohortenstudie mit guten Referenzstandards			
2c	Outome-Research-Studie				
3a	syst. Review Fall-Kontroll-Studien	syst. Review von nichtkonsekutiven Studien			
3b	individ. Fall-Kontroll-Studie	nicht-konsekutive Studien			
4	Fallserie, Kohortenstudien und Fallkontrollstudien geringerer Qualität	Fall-Kontroll-Studie, schlechter oder nicht-unabhängiger Referenzstandard	– Studien: Konsistenz, Effektstärke – Nutzen, Risiken, Nebenwirkungen – Anwendbarkeit	C	schwache Empfehlung
5	Expertenmeinung ohne explizite kritische Bewertung, physiolog. Modelle etc.	Expertenmeinung ohne explizite kritische Bewertung, physiolog. Modelle etc.		D	fehlende oder inkonsistente Studien, Empfehlung aufgrund von Expertenmeinung

Sonstige methodische Hinweise:

- Rechercheende liegt lange zurück (8 Jahre)
- LoE und GoR nicht direkt verknüpft
- Nach Prüfverfahren keine Interessenkonflikte festgestellt
- Keine Angaben zur Notwendigkeit von der Bestimmung von Markern vor Behandlung mit Gefitinib, Erlotinib
- Evidenztabellen (nur online) nicht verfügbar

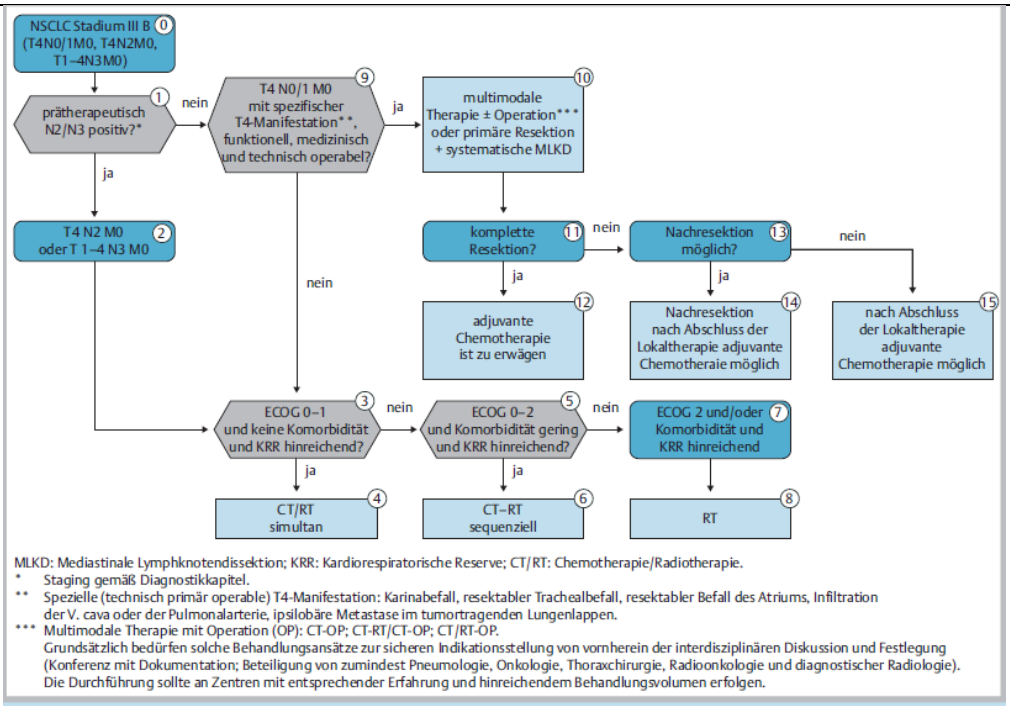
Empfehlungen:

Zusammenfassende Empfehlungen zur Therapie im Stadium III

- Die TNM-Stadienzusammenfassung in IIIA und IIIB unterschied technisch resektable – jedoch prognostisch ungünstige – Tumorausbreitungen im Stadium IIIA von in der Regel technisch inoperablen Erkrankungsausdehnungen (Stadium IIIB). Weiterentwicklungen in Staging, Operationstechnik und multimodalen Ansätzen haben die Grenzen dieser Einteilung für therapeutische Entscheidungen gezeigt. Eine optimale Behandlungswahl für den einzelnen Patienten erfordert vor Therapiebeginn die interdisziplinäre Diskussion und Festlegung (zumindest Beteiligung von Pneumologie, Onkologie, Thoraxchirurgie, Radioonkologie und diagnostischer Radiologie) (**Empfehlungsgrad D**).
- Die Unterscheidung von Subgruppen speziell im Stadium IIIA (N2) ist für Therapiewahl und Prognose von großer Bedeutung (**Empfehlungsgrad B**).
- Eine adjuvante Chemotherapie wird im Stadium IIIA mit inzidentellem N2-Status (IIIA1 bzw. IIIA2) nach kompletter Resektion (R0) und systematischer Lymphknotendissektion empfohlen (**Empfehlungsgrad**

	A). • Ein Beginn der Chemotherapie nach Abschluss der Wundheilung innerhalb von 60 Tagen nach Resektion wird empfohlen (**Empfehlungsgrad D**). • In der adjuvanten Chemotherapie wird die Gabe einer cisplatinhaltigen Kombination über 4 Zyklen empfohlen (**Empfehlungsgrad** A). In der Mehrzahl der positiven Studien wurde eine Kombination mit Vinorelbin verwendet. • Bei Patienten mit bedeutsamer Komorbidität aufgrund der vorangegangenen Resektion oder vorbestehender Erkrankungen wird empfohlen, die adjuvante Chemotherapie in einem interdisziplinär ausgerichteten Behandlungskontext mit entsprechender Erfahrung in der Durchführung von multimodalen Therapien durchführen zu lassen (**Empfehlungsgrad D**). • Für Patienten mit mediastinalem Lymphknotenbefall im Stadium IIIA1 bzw. IIIA2 sollte zusätzlich zur adjuvanten Chemotherapie die Indikation zur postoperativen Mediastinalbestrahlung geprüft werden (**Empfehlungsgrad B**). • Die Bestrahlung sollte bis spätestens 4 Wochen nach Abschluss der adjuvanten Chemotherapie beginnen und eine Dosis von 50–60 Gy nach CT-gestützter 3-dimensionaler Bestrahlungsplanung umfassen. Komorbiditäten müssen bei diesem Vorschlag ausreichend berücksichtigt werden (**Empfehlungsgrad B**). • Patienten im Stadium IIIA3 sollten präferenziell im Rahmen von Studien zur weiteren Definition des Therapiealgorithmus behandelt werden (**Empfehlungsgrad D**). • Außerhalb von Studien können Patienten im Stadium IIIA3 und technisch resektabler Tumorausdehnung individuell mit einem Induktionsprotokoll (Induktionschemotherapie oder Induktionschemostrahlentherapie) behandelt und anschließend operiert werden (**Empfehlungsgrad** B). Grundsätzlich erfordern solche Behandlungsansätze zur sicheren Indikationsstellung vor Therapiebeginn eine interdisziplinäre Diskussion und Festlegung (zumindest Beteiligung von Pneumologie, Onkologie, Thoraxchirurgie Radioonkologie und diagnostischer Radiologie). Präoperativ soll die Indikation zur Resektion im interdisziplinären Kontext gleichermaßen überprüft werden. Die Durchführung sollte an Zentren mit entsprechender Erfahrung und hinreichendem Behandlungsvolumen erfolgen. • In der Subgruppe T4N0/1 des Stadiums IIIB ist die primäre Operation bzw. die Integration der Operation in das Gesamtbehandlungskonzept bei medizinischer und funktioneller Operabilität in folgenden Fällen möglich: Karinabefall, resektabler Trachealbefall, resektabler Befall des Atrium, Infiltration der V. cava oder der Pulmonalarterie, ipsilobäre Metastase im tumortragenden Lungenlappen (**Empfehlungsgrad** B). • Nach Operation und R0-Resektion sollte im Stadium IIIA3 bei alleiniger Induktionschemotherapie eine mediastinale Radiotherapie erfolgen. Bei Induktionschemostrahlentherapieprotokollen sollte nach R0-Resektion keineweitere postoperative Radiotherapie durchgeführt werden (**Empfehlungsgrad B**). • Patienten im Stadium IIIA3 – insbesondere bei multiplem N2-Befall – können gleichermaßen mit einer Kombination aus Strahlentherapie und Chemotherapie (definitive Chemo-/ Radiotherapie) behandelt werden (**Empfehlungsgrad A**). • Patienten im Stadium IIIA4/IIIB sollten – wenn Allgemeinzustand und

	Tumorausdehnung dies zulassen – eine Kombination aus Strahlentherapie und Chemotherapie erhalten (**Empfehlungsgrad A**). • Für selektionierte Patienten im Stadium IIIA4/IIIB kann im begründeten Ausnahmefall ein multimodaler Behandlungsansatz unter Integration der Operation (möglichst nur in Studien) erfolgen (**Empfehlungsgrad D**). • Im direkten Vergleich ist bei geeigneten Patienten die simultane Radio-/Chemotherapie der sequenziellen überlegen. Bei der Patientenselektion ist auf Komorbiditätsspektrum und Allgemeinzustand zu achten (**Empfehlungsgrad A**). • Die Sequenz von Chemotherapie gefolgt von definitiver Strahlentherapie kann im Vergleich zur alleinigen Strahlentherapie sowohl medianes Überleben als auch 5-Jahres-Überlebensraten signifikant verbessern (**Empfehlungsgrad B**). • Für die sequenzielle und simultane Chemostrahlentherapie sollten cisplatinbasierte Chemotherapieprotokolle gewählt werden (Kombinationspartner bei simultaner Therapie in der Regel Etoposid oder Vincaalkaloid) (**Empfehlungsgrad B**). • Sowohl bei der sequenziellen als auch simultanen Behandlung werden typischerweise zwei Zyklen einer voll-dosierten cisplatinhaltigen Kombinationschemotherapie (Zyklusintervall 3–4Wochen) appliziert (**Empfehlungsgrad B**). • Angesichts des hohen systemischen Rezidivrisikos nach definitiver Chemostrahlentherapie kann im Einzelfall eine konsolidierende platinbasierte Kombinationschemotherapie aufgrund der im historischen Vergleich vielversprechenden Daten im Vergleichsarm einer großen randomisierten Phase-IIIStudie (INT 0139) durchgeführtwerden (**Empfehlungsgrad D**). • Im Vergleich zur alleinigen simultanen Chemo-/Radiotherapie ist der Stellenwert einer zusätzlichen konsolidierenden Chemotherapie in randomisierten Studien bisher allerdings nicht gegenüber Beobachtung belegt. Die zusätzliche Konsolidierung in Form der Monotherapie mit einem Taxan nach stattgehabter Radio-/Chemotherapie führt sogar zu deutlicher **und inakzeptabler Toxizität und wird nicht empfohlen (Empfehlungsgrad** A). • Die Strahlentherapie sollte typischerweise eine Dosis zwischen 60 und 66 Gy bei einmal-täglicher Fraktionierung haben (**Empfehlungsgrad A**). Die Zeitdauer hängt von der Einzelfraktionierung ab und liegt typischerweise bei 6–7 Wochen (Empfehlungsgrad B). Eine Unterbrechung der Strahlentherapie sollte vermieden werden (**Empfehlungsgrad C**). […]



MLKD: Mediastinale Lymphknotendissektion; KRR: Kardiorespiratorische Reserve; CT/RT: Chemotherapie/Radiotherapie.

* Staging gemäß Diagnostikkapitel.

** Spezielle (technisch primär operable) T4-Manifestation: Karinabefall, resektabler Trachealbefall, resektabler Befall des Atriums, Infiltration der V. cava oder der Pulmonalarterie, ipsilobäre Metastase im tumortragenden Lungenlappen.

*** Multimodale Therapie mit Operation (OP): CT-OP; CT-RT/CT-OP; CT/RT-OP.
Grundsätzlich bedürfen solche Behandlungsansätze zur sicheren Indikationsstellung von vornherein der interdisziplinären Diskussion und Festlegung (Konferenz mit Dokumentation; Beteiligung von zumindest Pneumologie, Onkologie, Thoraxchirurgie, Radioonkologie und diagnostischer Radiologie). Die Durchführung sollte an Zentren mit entsprechender Erfahrung und hinreichendem Behandlungsvolumen erfolgen.

Abb. 11 Algorithmus zur Therapie des nicht-kleinzelligen Lungenkarzinoms im Stadium IIIB.

Stadium IV/IIIB (ohne Indikation zur definitiven Radiatio)

- Die Lebenszeit von Patienten im Stadium IIIB/IV ist begrenzt (Median 8–12 Monate). Von vornherein sollte in dieser Situation ein stabiler und zuverlässiger Betreuungskontext hergestellt werden. Dafür sollte auch der unmittelbare Zugang zu einem entsprechend ausgerichteten interdisziplinären Betreuungskontext ermöglicht werden (**Empfehlungsgrad D**).
- Neben der medizinischen Behandlung sollten im Rahmen des Aufklärungsgesprächs bzw. im fortlaufenden Gesprächskontakt die Möglichkeiten zur Rehabilitation, psychoonkologischen Unterstützung, Sozialberatung bzw. Unterstützung durch Selbsthilfegruppen angesprochen werden (**Empfehlungsgrad D**).
- Im Stadium IIIB/IV sollte zunächst geprüft werden, ob eine Erkrankungsmanifestation einer zeitnahen Intervention bedarf. Diese sollte dann rasch und vor Einleitung einer systemischen Therapie erfolgen. Der Zugang zu diesen Techniken und Verfahren muss für alle Patienten zeitnah gewährleistet sein (**Empfehlungsgrad D**).
- Bei Vorstellung in einem interdisziplinären Zentrum (Pneumologie; Radioonkologie; Thoraxchirurgie; Onkologie; diagnostische Radiologie; Ernährungsberatung und -therapie; psychologische Beratung und Betreuung; Sozialdienst; Palliativmedizin; im Bedarfsfall Tumororthopädie und Neurochirurgie) sollte eine zeitnahe Entscheidungsfindung und –umsetzung (interdisziplinäre Tumorkonferenz; Dokumentation der Therapiefestlegung) gewährleistet sein (**Empfehlungsgrad D**).

Diskussionspunkte: Für die **rezeptor- und ligandenspezifische Therapie** ist es notwendig, in Zukunft prädiktive Parameter zu entwickeln, die vorhersagen, welche Gruppen von Patienten von der Therapie am ehesten profitieren. Ebenfalls ist eine Verbesserung der Therapieergebnisse zum jetzigen Zeitpunkt mit den vorhandenen Substanzen am ehesten von pharmakogenomischen Ansätzen zu erwarten, die in prospektiven klinischen

	Studien mit standardisierten und validierten Nachweisverfahren erhoben werden sollten. **Empfehlungen** • Bei Patienten im Stadium IIIB/IV in gutem Allgemeinzustand (ECOG 0,1) sollte eine cisplatinbasierte Kombinationschemotherapie zur Verbesserung der Überlebenszeit, der Krankheitskontrolle und der Lebensqualität durchgeführt werden (**Empfehlungsgrad A**). • Bei relevanter Komorbidität (Herzinsuffizienz; Niereninsuffizienz) kann Carboplatin statt Cisplatin eingesetzt werden. Alternativ kann dann auch eine platinfreie Kombination mit Drittgenerationszytostatika eingesetzt werden (**Empfehlungsgrad B**). • In der Erstlinienchemotherapie sollten 4 (–6) Zyklen gegeben werden. Es gibt derzeit keine konsistenten Daten, die im Hinblick auf die Überlebenszeit in der Erstlinienbehandlung eine Erhaltungschemotherapie unterstützen (**Empfehlungsgrad B**). • Patienten in reduziertem Allgemeinzustand (ECOG 2) bzw. mit Kontraindikationen gegen eine platinbasierte Kombinationschemotherapie im Stadium IIIB/IV können eine Monotherapie mit einem Drittgenerationszytostatikum (z. B. Vinorelbin, Gemcitabin) erhalten (**Empfehlungsgrad A**). • Bei Patienten im Stadium IIIB/IV (ECOG 0,1) mit Nicht-Plattenepithelkarzinom führt die Behandlung mit Bevacizumab zusätzlich zur platinbasierten Kombinationschemotherapie zu einer signifikanten Verbesserung der Remissionsrate und der medianen Überlebenszeit bzw. des medianen progressionsfreien Überlebens. Bei selektionierten Patienten im Stadium IIIB/IV mit Nicht- Plattenepithelkarzinom und gutem Allgemeinzustand (ECOG 0,1) kann daher – unter Berücksichtigung der Kontraindikationen – Bevacizumab in der Erstlinienbehandlung zusätzlich zur platinbasierten Kombinationschemotherapie eingesetzt werden (**Empfehlungsgrad B**). • Die weitere Charakterisierung von Patientensubgruppen, die am besten profitieren, ist wünschenswert (**Empfehlungsgrad D**). • Bei Patienten > 70 Jahre kann die therapieassozierte Toxizität und Letalität unter Bevacizumab bedeutsam sein. Daher sollte bei älteren Patienten die Indikation besonders streng unter kritischer Würdigung der Komorbidität gestellt werden (**Empfehlungsgrad B**). • Auch unter einer laufenden Therapie müssen regelmäßige Kontrollen erfolgen, um eine die Lebensqualität kompromittierende Symptomatik frühzeitig zu erkennen und zu behandeln (**Empfehlungsgrad B**). • Unter einer laufenden Therapie sollten die Kontrolluntersuchungen in der Regel in 6-wöchigen Intervallen erfolgen. Nach abgeschlossener Therapie erfolgen Kontrollen nach klinischer Erfordernis, die Kontrollintervalle liegen in der Regel bei 6–12Wochen (**Empfehlungsgrad D**). • Bei Patienten im Stadium IIIB/IV führt die Behandlung mit Cetuximab zusätzlich zur platinbasierten Kombinationschemotherapie zu einer statistisch signifikanten Verbesserung der Remissionsrate und der medianen Überlebenszeit. Bei Patienten im Stadium IIIB/IV kann Cetuximab in der Erstlinienbehandlung zusätzlich zur platinbasierten Kombinationschemotherapie eingesetzt werden (**Empfehlungsgrad B**). • Die weitere Charakterisierung von Patientensubgruppen, die am besten profitieren, sollte erfolgen (**Empfehlungsgrad D**). Zum Zeitpunkt der Publikation der Leitlinie ist Cetuximab nicht zur Therapie des nicht-kleinzelligen Lungenkarzinoms zugelassen. • Bei Patienten mit aktivierenden Mutationen des EGF-Rezeptors

	(insbesondere del. 19; exon 21 L858R) ist Gefitinib im Hinblick auf Remissionsrate und progressionsfreies Überleben in der Erstlinienbehandlung einer Chemotherapie signifikant überlegen (**Empfehlungsgrad B**). Gefitinib ist daraufhin bei positivem Mutationsstatus des EGF-Rezeptors in allen Therapielinien als eine mögliche Behandlungsoption zugelassen worden. In der zulassungsrelevanten Studie erfolgte die Analyse des Mutationsstatus bei Patienten mit einem Adenokarzinom und minimalem Nikotinkonsum (94 % Nieraucher). ***Systemtherapie (Zweitlinie und weitere)*** *Konventionelle Chemotherapie* Bei Erkrankungsprogression nach stattgehabter primärer Chemotherapie kann im Stadium IIIB/IV eine erneute Chemotherapie mit Docetaxel bzw. Pemetrexed oder eine Behandlung mit dem EGF-Rezeptor-Tyrosinkinase-Inhibitor Erlotinib eingeleitet werden. Für Docetaxel (ECOG 2, 24 % der Patienten; platinbasierte Vortherapie, 100%) wurde im Vergleich zu BSC eine signifikante Verbesserung der medianen Überlebenszeit gezeigt. In einer weiteren Studie mit Non-Inferiority-Design wurde im Vergleich zwischen Docetaxel und Pemetrexed (ECOG 2, 12% der Patienten; platinbasierte Vortherapie, 91%) Äquieffektivität für Ansprechen und Überleben bei signifikant günstigerem Toxizitätsprofil für Pemetrexed gezeigt. Die Remissionsraten in diesen Studien liegen in der Größenordnung von 5,8% bis 9,1 %. Dennoch findet sich im Vergleich zu BSC eine signifikante Verbesserung der medianen Überlebenszeit und bestimmter Parameter der Lebensqualität (Schmerz, Husten, Dyspnoe) (**Evidenzgrad 1b**). In einer weiteren Phase-III-Studie wurde Docetaxel gegen Vinorelbin oder Ifosfamid in der Zweitlinie überprüft. Es konnte kein signifikanter Unterschied im primären Studienziel (mediane Überlebenszeit) gezeigt werden, jedoch fanden sich signifikante Unterschiede in den sekundären Studienzielen (1-Jahres-Überleben und progressionsfreies Überleben). In einer Metaanalyse, die 865 Patienten einschloss, konnte gezeigt werden, dass Docetaxel 75 mg/m2 alle 3 Wochen gegenüber einer wöchentlichen Applikation mit 33–36 mg/m2 hinsichtlich Überleben und progressionsfreiem Überleben äquieffektiv ist. Die wöchentliche Applikation von Docetaxel weist gegenüber der 3-wöchentlichen signifikante Vorteile hinsichtlich der hämatologischen Toxizitäten (Granulozytopenie und febrile Granulozytopenie) auf (**Evidenzgrad 1b**). In zwei weiteren Studien wurden Topotecan und Vinflunin im Vergleich zu Docetaxel (Non-Inferiority-Design) untersucht. Für Topotecan 2,3 mg/m2 (oral) d1–5 alle 3 Wochen konnte Äquieffektivität gegenüber Docetaxel 75 mg/m2 alle 3Wochen hinsichtlich des 1-Jahres-Überlebens (25,1vs 28,7 %; HR = 1,23, CI 1,06–1,44) sowie der Zeit bis zur Tumorprogression (11 vs. 13 Wo, p = 0,02, HR = 1,2; CI 1,02–1,39) gezeigt werden. Gleichermaßen wurde für Vinflunin (320 mg/m2) Äquieffektivität gegenüber Docetaxel für das primäre Studienziel (progressionsfreies Überleben 2,3 vs. 2, 3 Monate) und die sekundären Studienziele gezeigt werden. In beiden Studien liegen keine Subgruppenanalysen für PS 2-Patienten vor. Für beide Substanzen ist allerdings bisher keine formale Zulassung erteilt worden. ***Stellenwert rezeptor- bzw. ligandenspezifischer Therapieansätze*** In einer randomisierten Studie (Non-Inferiority-Design) wurde für Gefitinib Äquivalenz im Vergleich zu Docetaxel gezeigt (Hazard Ratio Gesamtüberleben). Im Hinblick auf die Lebensqualität war die Behandlung

	mit Gefitinib günstiger. Die ergänzenden Daten der I-PASS-Studie haben zur Zulassung von Gefitinib bei Patienten mit Nachweis einer aktivierenden EGF-Rezeptor-Mutation (insbesondere del. 19; exon 21 L858R) in allen Therapielinien geführt. In einer randomisierten Studie wurde für Erlotinib im Vergleich zu BSC (ECOG 2, 25%; ECOG 3, 9%; platinbasierte Vortherapie, 92%; ≥ 2 Vortherapien, 50%) eine signifikante Verbesserung der medianen Überlebenszeit gezeigt. Prädiktoren für Ansprechen auf Erlotinib, die in einer multivariaten Analyse definiert wurden, waren Nieraucherstatus, d. h. < 100 Zigaretten lebenslang ($p < 0,001$), Adenokarzinom ($p = 0,01$) und EGFR Expression ($p = 0,03$). Die Expression von EGFR hatte keinen Einfluss hinsichtlich progressionsfreiem Überleben und Überleben. **Empfehlungen** • Bei Patienten in gutem Allgemeinzustand mit einer Erkrankungsprogression nach primärer Chemotherapie wird die Durchführung einer Zweitlinientherapie bis zum Progress oder Auftreten von Toxizitäten empfohlen (**Empfehlungsgrad A**). Trotz niedriger Ansprechraten kann eine Verlängerung des Überlebens und eine Verbesserung tumorbedingter Symptome erreicht werden. In Phase-III-Studien sind mit entsprechender Evidenz geprüft: Docetaxel, Pemetrexed, Topotecan, Vinflunin, Gefitinib und Erlotinib. Zugelassen für die Behandlung sind allerdings nur: Docetaxel, Pemetrexed (Nicht-Plattenepithelkarzinome) und Erlotinib. • Gefitinib ist bei aktivierenden Mutationen des EGF-Rezeptors (insbesondere del. 19; exon 21 L858R) in allen Therapielinien, auch in der Zeitlinientherapie, zur Behandlung zugelassen (**Empfehlungsgrad B**). In der zulassungsrelevanten Studie erfolgte die Analyse des Mutationsstatus bei Patienten mit einem Adenokarzinom und minimalem Nikotinkonsum (94% Nieraucher). • Bei Patienten, die nach einer Zweitlinientherapie progredient sind, kann eine Drittlinientherapie durchgeführt werden (**Empfehlungsgrad B**). • Bei Patienten mit längerfristigem Krankheitsverlauf kann bei entsprechender klinischer Situation und akzeptablem Risikoprofil zur Symptomenkontrolle eine weitere Antitumortherapie auch nach der Drittlinienbehandlung eingesetzt werden (**Empfehlungsgrad D**).

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

NICE technology appraisal guidance, 2013: Crizotinib for previously treated non- small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene [55]	**Guidance** 1.1 Crizotinib is not recommended within its marketing authorisation, that is, for treating adults with previously treated anaplastic-lymphoma-kinase-positiveadvanced non-small-cell lung cancer 1.2 People currently receiving crizotinib that is not recommended according to 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop
Semlitsch T et al., 2013: Crizotinib (Xalkori®) for the treatment of anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) [71]	**Current treatment** As second line therapy the following treatments are recommended: • single agent chemotherapy (docetaxel or PEM) • targeted agent therapy (e.g. erlotinib) • a platinum based combination therapy for patients with EGFR mutation and progressive disease after tyrosine kinase inhibitor treat-ment (e.g. erlotinib) For ALK-positive NSCLC patients the targeted agent crizotinib is the currently recommended treatment option as first or second line therapy. Chemotherapy is an appropriate option for these patients with disease progression on crizotinib. As patients with the ALK fusion oncogene do not appear to respond to EGFR tyrosine kinase inhibitors, erlotinib therapy is not recommended.
Scottish Medicines Consortium (SMC), 2013: Crizotinib (Xalkori) - treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) [70]	crizotinib (Xalkori®) is accepted for use within NHS Scotland. Indication under review: treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). In a phase III clinical study in patients with previously treated anaplastic lymphoma kinase (ALK)-positive advanced NSCLC, crizotinib significantly increased progression-free survival compared with standard chemotherapy. This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of crizotinib. This SMC advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.
Breuer J et al., 2013: Afatinib (Giotrif®)	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

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) [8]	lung cancer (NSCLC) with activating EGFR mutations. **Current treatment** Modalities for the treatment of NSCLC which are generally used are surgery, radiation therapy, chemotherapy and targeted therapy. Depending on disease status, Eastern Cooperative Oncology Group (ECOG) performance status and prognostic factors, these treatments can be used either alone or in combination [12]. First-line therapy of advanced NSCLC depends on a number of factors, such as tumour stage, histo-pathological subtype and performance status. Current treatment options for the first-line therapy of patients with advanced or metastatic lung cancer are: double-agent chemotherapy regimen based on a platinum compound (cisplatin, carboplatin) in addition to one out of numerous other substances (paclitaxel, gemcitabine, vinorelbine or docetaxel and pemetrexed) ☐ other chemotherapy regimens: due to the toxicity of platinum-based regimens, other drug combinations can be used (gemcitabine + docetaxel/paclitaxel/vinorelbine/pemtrexed, paclitaxel + vinorelbine) ☐ single-agent chemotherapy as first-line treatment may be used for elderly patients ☐ targeted therapies: EGFR inhibitors (erlotinib, gefitinib), monoclonal antibodies (bevacizumab) ☐ a combined modality approach [10, 12, 15]. If patients are EGFR mutational status positive, EGFR-TK inhibitors (e.g. erlotinib, gefitinib) are increasingly used as standard first-line therapy, whereas patients with either unknown EGFR status or without EGFR mutation receive chemotherapy doublets, either alone or in combination with a monoclonal antibody (bevacizumab). If patients with driver mutations have initially been treated with chemotherapy, targeted therapy with a specific inhibitor is indicated after progression on the initial chemotherapy regimen either alone or in combination with chemotherapy [15, 16]. [10] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer (V 2.2013). 2013 [24.09.2013]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. [12] Lilenbaum R. Overview of the treatment of advanced non-small cell lung cancer. 2013 [26.09.2013]; Available from: http://www.uptodate.com/contents/overview-of-the-treatment-of-advanced-non-small-cell-lung-cancer?detectedLanguage=en&source=search_result&search=therapy+nsclc&selectedTitle=3~150&provider=noProvider. 15] Lilenbaum R. Systemic therapy for advanced non-small cell lung cancer with an activating mutation in the epidermal growth factor receptor. 2013 [26.09.2013]; Available from: http://www.uptodate.com/contents/systemic-therapy-for-advanced-non-small-cell-lung-cancer-with-an-activating-mutation-in-the-epidermal-growth-factor-receptor?detectedLanguage=en&source=search_result&search=first+line+therapy+nsclc&selectedTitle=8~150&provider=noProvider. [17] Wu YL, Zhou C, Hu CP, Feng JF, Lu S, Huang Y, et al. LUX-Lung 6: A randomized, open-label, phase III study of afatinib (A) versus gemcitabine/cisplatin (GC) as first-line treatment for Asian patients (pts) with EGFR mutation-positive (EGFR M+) advanced adenocarcinoma of the lung. Journal of Clinical Oncology. 2013;31(15).
NICE, 2014: Afatinib for treating epidermal growth	***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:

factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer, TA 310 [56]	• 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, 2012: Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive	**The manufacturer's submission** The manufacturer's submission focussed on a comparison of erlotinib with gefitinib for first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC. The manufacturer's submission did not include pemetrexed plus cisplatin or carboplatin as a comparator because of the declining use in clinical practice of this combination for first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC and the absence of suitable data for comparison in this population.

non-small-cell lung cancer, TA 258 [53]	**Guidance** Erlotinib is recommended as an option for the first-line treatment of people with locally advanced or metastatic non-small-cell lung cancer (NSCLC) if: • they test positive for the epidermal growth factor receptor tyrosine kinase (EGFRTK) mutation and • the manufacturer provides erlotinib at the discounted price agreed under the patient access scheme (as revised in 2012).
NICE, 2010: Pemetrexed for the maintenance treatment of non-smallcell lung cancer. NICE technology appraisal guidance 190 [52]	**The manufacturer's submission The manufacturer's submission** The manufacturer's submission contained evidence on the clinical effectiveness of pemetrexed maintenance therapy compared with best supportive care. The manufacturer stated that pemetrexed is the only chemotherapy currently licensed for the maintenance treatment of non-smallcell lung cancer in the UK and worldwide. Therefore, the comparator used in the clinical trial was placebo plus best supportive care. **Guidance** People who have received pemetrexed in combination with cisplatin as first-line chemotherapy cannot receive pemetrexed maintenance treatment. Pemetrexed is recommended as an option for the maintenance treatment of people with locally advanced or metastatic non-small-cell lung cancer other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel.
NICE, 2009: Pemetrexed for the first-line treatment of non-small-cell lung cancer [51]	**The manufacturer's submission** In the submission the manufacturer compared pemetrexed plus cisplatin (pemetrexed/cisplatin) with gemcitabine plus cisplatin (gemcitabine/cisplatin). The manufacturer justified this choice of comparator with marketing data that suggest gemcitabine plus a platinum drug accounts for 80% of first-line NSCLC treatment, and the fact that according to a meta-analysis and clinical opinion cisplatin is the preferred platinum drug. The manufacturer identified gemcitabine plus carboplatin (gemcitabine/carboplatin) and docetaxel plus cisplatin (docetaxel/cisplatin) as additional comparators. The manufacturer stated that carboplatin is still commonly used in the UK because patients do not need the same hydration that is necessary with cisplatin. It also stated that docetaxel is used occasionally because it requires fewer infusions than gemcitabine. **Guidance** 1.1 Pemetrexed in combination with cisplatin is recommended as an option for the first-line treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) only if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma. 1.2 People who are currently being treated with pemetrexed for NSCLC but who do not meet the criteria in 1.1 should have the option to continue their therapy until they and their clinicians consider it appropriate to stop.
NICE, 2012: Gefitinib for the first-line treatment of locally advanced	**The manufacturer's submission** The manufacturer's decision problem compared gefitinib with gemcitabine and carboplatin, paclitaxel and carboplatin, vinorelbine and cisplatin, and gemcitabine and cisplatin. The decision problem defined the population as patients with locally advanced or metastatic NSCLC who are previously

or metastatic non-small-cell lung cancer, TA 192 [54]	untreated and who test positive for an EGFR-TK mutation (EGFR-TK mutationpositive patients). Outcomes were defined as overall survival, progression-free survival, objective tumour response rates, health-related quality of life and adverse events associated with treatment. In the economic evaluation the incremental cost per quality-adjusted life year (QALY) gained was presented. A lifetime horizon was used, and costs were considered from the perspective of the NHS and personal social services (PSS). **Guidance** Gefitinib is recommended as an option for the first-line treatment of people with locally advanced or metastatic non-small-cell lung cancer (NSCLC) if: they test positive for the epidermal growth factor receptor tyrosine kinase (EGFRTK) mutation **and** the manufacturer provides gefitinib at the fixed price agreed under the patient access scheme.

Primärstudien

Da ausreichend Information aus aggregierter Evidenz vorliegt, wurde eine Suche nach Primärliteratur nicht durchgeführt.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews) am 21.07.2014

Such-schritt	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	#2 and #3
#5	nsclc*:ti,ab,kw (Word variations have been searched)
#6	#1 or #4 or #5
#7	#1 or #4 or #5 Publication Year from 2009 to 2014

Cochrane Library (Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) am 21.07.2014

Such-schritt	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	#2 and #3
#5	nsclc*:ti,ab,kw (Word variations have been searched)
#6	advanced or metastas* or metastat* or recurren* or ((3rd or third or 2nd or second) and line) or (stage next III*) or (stage next IV):ti,ab,kw
#7	(#4 or #5) and #6
#8	#1 or #7
#9	#1 or #7 Publication Year from 2009 to 2014

MEDLINE (PubMed) am 21.07.2014

Such-schritt	Suchfrage
#1	carcinoma, non small cell lung[MeSH Terms]
#2	((((((non[Title/Abstract]) AND small[Title/Abstract])) OR nonsmall[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	nsclc*[Title/Abstract]
#6	(#4) OR #5

Such-schritt	Suchfrage
#7	((((((advanced[Title/Abstract]) OR metastas*[Title/Abstract]) OR metastat*[Title/Abstract]) OR recurren*[Title/Abstract])) OR ((((((3rd[Title/Abstract]) OR third[Title/Abstract]) OR 2nd[Title/Abstract]) OR second[Title/Abstract])) AND line[Title/Abstract])) OR ((stage III*[Title/Abstract]) OR stage IV[Title/Abstract])
#8	(#6) AND #7
#9	(#1) OR #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 ("2009/07/01"[PDAT] : "2014/07/21"[PDAT])

MEDLINE (PubMed) nach Leitlinien am 21.07.2014

Such-schritt	Suchfrage
#1	carcinoma, non small cell lung[MeSH Terms]
#2	((((((non[Title/Abstract]) AND small[Title/Abstract])) OR nonsmall[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	nsclc*[Title/Abstract]
#6	((#1) OR #4) OR #5
#7	(((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type])

Such-schritt	Suchfrage
	OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title])
#8	(#6) AND #7
#9	(#8) AND ("2009/07/01"[PDAT] : "2014/07/21”[PDAT])

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).

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