Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2016-B-203-z Pembrolizumab

Stand: Dezember 2016

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Pembrolizumab **[zur Behandlung von Chemotherapie-naiven Patienten mit einem lokal fortgeschrittenen oder metastasierten 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.	*Strahlentherapie*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	**Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:** • Necitumumab: Beschluss vom 15. September 2016 **Richtlinien:** Carboplatin: Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie - Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten - (Stand: 8. Juni 2016): Arzneimittel, die unter Beachtung der dazu gegebenen Hinweise in nicht zugelassenen Anwendungsgebieten (Off-Label-Use) verordnungsfähig sind: • Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCL) – Kombinationstherapie
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 Fachinformation)
Zu prüfendes Arzneimittel:	
Pembrolizumab	KEYTRUDA ist als Monotherapie zur Erstlinienbehandlung des metastasierenden nicht-kleinzelligen Lungenkarzinoms (NSCLC) mit PD-L1 exprimierenden Tumoren (Tumor Proportion Score [TPS] ≥ 50 %) ohne EGFR oder ALK-positive Tumormutationen bei Erwachsenen angezeigt.
Chemotherapien:	
Carboplatin L01XA02 (generisch)	Off-Label-Indikation für Carboplatin: Kombinationstherapie des fortgeschrittenen NSCLC (palliativ)
Cisplatin L01XA01 (generisch)	Cisplatin wird angewendet zur Behandlung des: fortgeschrittenen oder metastasierten nichtkleinzelligen Bronchialkarzinoms. Cisplatin kann als Mono- oder Kombinationstherapie angewendet werden. (Cisplatin Teva® 1 mg / ml Konzentrat; Mai 2016)
Docetaxel L01CD02 (generisch)	Nicht-kleinzelliges Bronchialkarzinom: Docetaxel ist in Kombination mit Cisplatin zur Behandlung von Patienten mit nicht resezierbarem, lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Bronchialkarzinom ohne vorausgegangene Chemotherapie angezeigt. (Docetaxel-ratiopharm® 20 mg/ml Konzentrat; Februar 2016)
Etoposid L01CB01 (generisch)	Etoposid ist in Kombination mit anderen antineoplastisch wirksamen Arzneimitteln bei der Behandlung folgender bösartiger Neubildungen angezeigt: Palliative Therapie des fortgeschrittenen nicht-kleinzelligen Bronchialkarzinoms bei Patienten in gutem Allgemeinzustand (Etopophos® 100 mg/1000 mg; September 2015)
Gemcitabin L01BC05 (generisch)	Gemcitabin ist in Kombination mit Cisplatin als Erstlinientherapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nichtkleinzelligen Bronchialkarzinom (NSCLC) angezeigt. Eine Gemcitabin-Monotherapie kann bei älteren Patienten oder solchen mit einem Performance Status 2 in Betracht gezogen werden. (Gemcitabin Kabi 38 mg/ml Konzentrat; März 2015)
Ifosfamid	Nicht-kleinzellige Bronchialkarzinome:

L01AA06 (Holoxan®)	Zur Einzel- oder Kombinationschemotherapie von Patienten mit inoperablen oder metastasierten Tumoren. (Holoxan®; Januar 2015)
Mitomycin L01DC03 (generisch)	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Bei intravenöser Gabe ist es in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei folgenden metastasierenden Tumoren wirksam: […] nicht-kleinzelliges Bronchialkarzinom […]. (Mitomycin Teva® 1 mg/ml; Februar 2016)
Paclitaxel L01CD01 (generisch)	Fortgeschrittenes nicht-kleinzelliges Bronchialkarzinom (NSCLC): Paclitaxel ist, in Kombination mit Cisplatin, zur Behandlung des nicht-kleinzelligen Bronchialkarzinoms bei Patienten angezeigt, für die potentiell kurative chirurgische Maßnahmen und/oder eine Strahlentherapie nicht in Frage kommen. (Paclitaxel-GRY® 6 mg/ml Konzentrat; März 2016)
Paclitaxel Nanopartikel L01CD01 Abraxane®	Abraxane ist in Kombination mit Carboplatin indiziert für die Erstlinienbehandlung des nicht-kleinzelligen Bronchialkarzinoms bei erwachsenen Patienten, bei denen keine potentiell kurative Operation und/oder Strahlentherapie möglich ist. (Abraxane® 5 mg/ml; Juli 2015)
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®; Februar 2016)
Vindesin L01CA03 (Eldesine®)	Kombinationschemotherapie: Lokal fortgeschrittenes oder metastasiertes nicht-kleinzelliges Bronchialkarzinom (Stadium IIIB, IV).
Vinorelbin L01CA04 (generisch)	Behandlung des nicht kleinzelligen Bronchialkarzinoms (Stadium 3 oder 4). (Vinorelbin onkovis 10 mg/ml Konzentrat; Juni 2014)
Proteinkinase-Inhibitoren:	
Afatinib L01XE13 (Giotrif®)	Giotrif® als Monotherapie wird angewendet zur Behandlung von: epidermaler Wachstumsfaktorrezeptor (EGFR)-Tyrosinkinaseinhibitor (TKI)-naiven erwachsenen Patienten mit lokal fortgeschrittenem und/oder metastasiertem nicht-kleinzelligen Lungenkarzinom (NSCLC, non small cell lung cancer) mit aktivierenden EGFR-Mutationen; (Giotrif®; Oktober 2016)

Erlotinib L01XE03 (Tarceva®)	Nicht-kleinzelliges Lungenkarzinom (NSCLC): Tarceva ist zur First-Line-Behandlung bei Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit aktivierenden EGFR-Mutationen angezeigt. Beim Verschreiben von Tarceva sollten Faktoren, die im Zusammenhang mit einer verlängerten Überlebenszeit stehen, berücksichtigt werden. Bei Patienten mit epidermalen Wachstumsfaktor-Rezeptor-(EGFR)-IHC-negativen Tumoren konnten weder ein Überlebensvorteil noch andere klinisch relevante Wirkungen durch die Behandlung gezeigt werden. (Tarceva®; Januar 2016)
Gefitinib L01XE02 (Iressa®)	Iressa® ist angezeigt zur Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Lungenkarzinom (NSCLC) mit aktivierenden Mutationen der EGFR-TK. (Iressa® 250 mg; September 2014)
Osimertinib L01XE35 (Tagrisso®)	Tagrisso ist angezeigt zur Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem, nichtkleinzelligem Lungenkarzinom (NSCLC) und einer positiven T790M-Mutation des epidermalen Wachstumsfaktor-Rezeptors (Epidermal Growth Factor Receptor, EGFR). (Tagrisso®; März 2016)
Ceritinib L01XE28 (Zykadia®)	Zykadia wird angewendet bei erwachsenen Patienten zur Behandlung des fortgeschrittenen, Anaplastische-Lymphomkinase(ALK)-positiven, nicht-kleinzelligen Bronchialkarzinoms (NSCLC), die mit Crizotinib vorbehandelt wurden. (Zykadia®; August 2016)
Crizotinib L01XE16 (Xalkori®)	Xalkori wird angewendet bei Erwachsenen zur Erstlinienbehandlung des Anaplastische-Lymphom-Kinase(ALK)-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, NSCLC). Xalkori wird angewendet bei Erwachsenen zur Behandlung des ROS1-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, NSCLC). (Xalkori®; August 2016)
Antikörper:	
Bevacizumab L01XC07 (Avastin®)	Bevacizumab wird zusätzlich zu einer platinhaltigen Chemotherapie zur First-Line-Behandlung von erwachsenen Patienten mit inoperablem fortgeschrittenem, metastasiertem oder rezidivierendem nicht-kleinzelligem Bronchialkarzinom, außer bei vorwiegender Plattenepithel-Histologie, angewendet. Bevacizumab wird in Kombination mit Erlotinib zur First-Line-Behandlung von erwachsenen Patienten mit inoperablem fortgeschrittenem, metastasiertem oder rezidivierendem nicht-kleinzelligem Nicht-Plattenepithel-Bronchialkarzinom mit Mutationen, die den epidermalen Wachstumsfaktorrezeptor (EGFR) aktivieren, angewendet. (Avastin®; Juni 2016)

Necitumumab L01XC22 (Portrazza®)	Portrazza ist in Kombination mit Gemcitabin- und Cisplatin-Chemotherapie indiziert zur Therapie von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem, den epidermalen Wachstumsfaktor-Rezeptor (EGFR) exprimierenden, plattenepithelialen, nicht-kleinzelligen Lungenkarzinom, wenn diese bislang keine Chemotherapie für dieses Stadium der Erkrankung erhalten haben. (Portrazza®; Februar 2016)

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

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Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation *nicht-kleinzelligem Lungenkarzinom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 06.12.2016 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 976 Quellen, die anschließend in einem zweistufigen Screening Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 59 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Zur Behandlung von Chemotherapie-naiven Patienten mit einem lokal fortgeschrittenen oder metastasierten NSCLC.

Abkürzungen:

ACCP	American College of Chest Physicians
ADK	adenocarcinoma
AE	Unerwünschte Ereignisse (adverse events)
Afl	aflibercept
AIOT	Italian Associatlon of Thoracic Oncology
ALK	Anaplastic Lymphoma Kinase
AM	Arzneimittel
ANITA	*Adjuvant* Navelbine International Trialist Association
AP	pemetrexed + cisplatin
ASCI	Antigen Specific Cancer Immunotherapeutic
ASCO	American Society of Clinical Oncology
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
Bev	Bevacizumab
BSC	Best supportive care
CARB	Carboplatin
CBDCA	carboplatin
CCT	controlled clinical trial
CDDP	cisplatin
CECOG	Central European Cooperative Oncology Group
Cet	cetuximab
CG	clinical gudeline
CI	Konfidenzintervall
CIS	Cisplatin
CR	Complete response
CT	Chemotherapie
CTX	Chemoradiation
DAHTA	Deutsche Agentur für Health Technology Assessment
DART	Documentation and Appraisal Review Tool
DCR	disease control rate
DGHO-Onkopedia	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie
DGP	Gesellschaft für Pneumologie und Beatmungsmedizin
DKG	Deutsche Kresgesellschaft
DC	Docetaxel
DOC	Docetaxel
DP	docetaxel + cisplatin
DSG	Disease Site Group
fNECOG	Eastern cooperative oncology group
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for QLQ Research and Treatment of Cancer Quality of Life Questionnaire
EGFR	Epidermal Growth Factor Receptor
EGFR M+	EGFR-positiv (Vorliegen einer Mutatation)
Enz	enzastaurin
Erl / ERL	erlotinib
ESMO	European Society for Medical Oncology

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

QoL	Lebensqualität (quality of life)
QUADAS	Quality assessment tool for diagnostic studies
RCT	Randomized controlled trial
Ref.	reference
REM	Random effects model
RET	rearranged during transfection
RR	Risk ratio
RR	Relatives Risiko
RT	Radiotherapie
SACT	systemic anticancer therapy
SD	Stable disease; oder: standard deviation
Sel	selumetinib
SR	Systematisches Review
TA	Technology Assessment
TAX	Docetaxel
TC	paclitaxel + carboplatin
TKI	Tyrosinkinsaseinhibitor
TNM	Tumor-Node-Metastasis (Klassifikationssystem)
TOI	Trial outcome index
TRIP	Turn Research into Practice Database
TTP	Time to Progression
UFT	Tegafur/Uracil
UICC	Union for International Cancer Control
Van	vandetanib
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VNB	Vinorelbin
vs.	versus
w	weeks
WJTOG	Western Japan Thoracic Oncology Group
WHO	World Health Organisation
WT	Wild type

G-BA Beschlüsse

G-BA, 2015 [19]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Afatinib	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. 1) Nicht vorbehandelte Patienten mit ECOG-Performance-Status 0 oder 1 **Zweckmäßige Vergleichstherapie:** − Gefitinib oder Erlotinib *oder* − Cisplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel oder Pemetrexed) unter Beachtung des Zulassungsstatus *oder* − Carboplatin in Kombination mit einem Drittgenerationszytostatikum (nur für Patienten mit erhöhtem Risiko für Cisplatin-induzierte Nebenwirkungen im Rahmen einer Kombinationstherapie; vgl. Anlage VI zum Abschnitt K der Arzneimittel- Richtlinie) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Cisplatin in Kombination mit Pemetrexed:** a) PatientengruppemitEGFR-MutationDel19: Hinweis auf einen erheblichen Zusatznutzen. b) PatientengruppemitEGFR-MutationL858R: Ein Zusatznutzen ist nicht belegt. c) Patientengruppe mit anderen EGFR-Mutationen: Ein Zusatznutzen ist nicht belegt. 2) Nicht vorbehandelte Patienten mit ECOG-Performance-Status 2 **Zweckmäßige Vergleichstherapie:** − Gefitinib oder Erlotinib *oder* − alternativ zu den unter 1) angegebenen platinbasierten Kombinationsbehandlungen: Monotherapie mit Gemcitabin oder Vinorelbin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt. 3) Patienten nach Vorbehandlung mit einer Platin-basierten Chemotherapie **Zweckmäßige Vergleichstherapie:** − Gefitinib oder Erlotinib *oder* − Docetaxel oder Pemetrexed **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:**

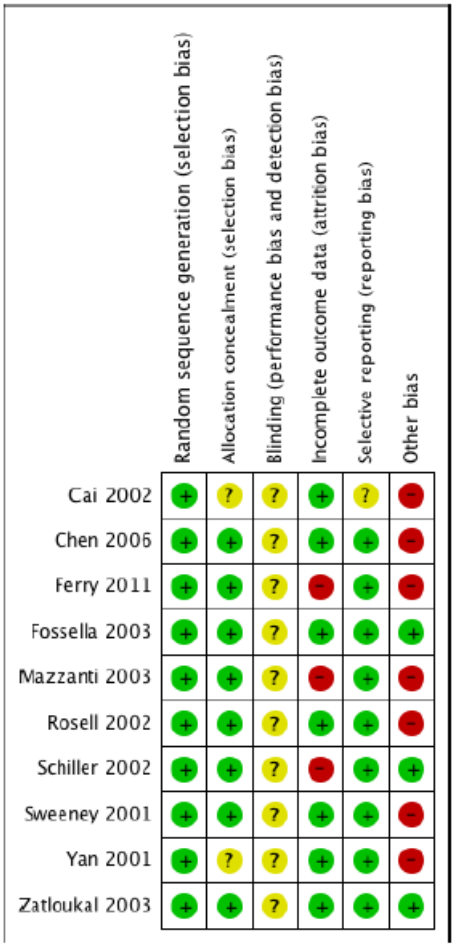
	Ein Zusatznutzen ist nicht belegt.
G-BA, 2015 [20]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Ceritinib	**Zugelassenes Anwendungsgebiet [laut Zulassung vom 6.05.2015]:** Zykadia wird angewendet bei erwachsenen Patienten zur Behandlung des fortgeschrittenen, Anaplastische-Lymphomkinase(ALK)-positiven, nicht-kleinzelligen Bronchialkarzinoms (NSCLC), die mit Crizotinib vorbehandelt wurden. 1) Patienten, für die eine Behandlung mit Docetaxel oder Pemetrexed infrage kommt **Zweckmäßige Vergleichstherapie:** Docetaxel oder Pemetrexed **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Docetaxel oder Pemetrexed:** Ein Zusatznutzen ist nicht belegt. 2) Patienten, für die eine Behandlung mit Docetaxel oder Pemetrexed nicht infrage kommt **Zweckmäßige Vergleichstherapie:** Best-Supportive-Care **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive- Care:** Ein Zusatznutzen ist nicht belegt.
G-BA, 2016 [17]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Crizotinib (neues Anwendungsgebiet)	**Zugelassenes Anwendungsgebiet (laut Zulassung vom 23.11.2015):** XALKORI wird angewendet bei Erwachsenen zur Erstlinienbehandlung des Anaplastische- Lymphom-Kinase(ALK)-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (*non small cell lung cancer*, NSCLC). **Zweckmäßige Vergleichstherapie:** Patienten mit ECOG-Performance-Status 0, 1 oder 2: − Cisplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel oder Pemetrexed) unter Beachtung des Zulassungsstatus *oder* − Carboplatin in Kombination mit einem Drittgenerationszytostatikum (nur für Patienten mit erhöhtem Risiko für Cisplatin-induzierte Nebenwirkungen im Rahmen einer Kombinationstherapie; vgl. Anlage VI zum Abschnitt K der Arzneimittel- Richtlinie) Patienten mit ECOG-Performance-Status 2: − alternativ zur Platin-basierten Kombinationsbehandlung: eine Monotherapie mit Gemcitabin oder Vinorelbin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Cisplatin in Kombination mit Pemetrexed *oder* Carboplatin in Kombination mit Pemetrexed:** Anhaltspunkt für einen beträchtlichen Zusatznutzen.

G-BA 2016 [18]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Osimertinib	**Zugelassenes Anwendungsgebiet (laut Zulassung vom 2. Februar 2016):** TAGRISSO ist angezeigt zur Behandlung von erwachsenen Patienten mit lokal fort geschrittenem oder metastasiertem, nicht-kleinzelligem Lungenkarzinom (NSCLC) und einer positiven T790M-Mutation des epidermalen Wachstumsfaktor-Rezeptors (Epidermal Growth Factor Receptor, EGFR). 1) PatiententnachVorbehandlungmiteinemEGFR-Tyrosinkinase-Inhibitor: **Zweckmäßige Vergleichstherapie:** a) eine zytotoxische Chemotherapie nach Maßgabe des Arztes (unter Beachtung des Zulassungsstatus in Verbindung mit der Verordnungsfähigkeit von Arzneimitteln in Off-Label-Indikationen gemäß Anlage VI der Arzneimittel- Richtlinie) *oder gegebenenfalls* Best-Supportive-Care für Patienten, die bereits eine zytotoxische Chemotherapie erhalten haben als Alternative für eine weitere zytotoxische Chemotherapie. b) für Patienten, für die eine zytotoxische Chemotherapie nicht infrage kommt: Best-Supportive-Care **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt.
G-BA, 2014 [16]. 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	**Teil A:** Arzneimittel, die unter Beachtung der dazu gegebenen Hinweise in nicht zugelassenen Anwendungsgebieten (Off-Label-Use) verordnungsfähig sind: […] Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCL) – Kombinationstherapie 1. Hinweise zur Anwendung von Carboplatin gemäß § 30 Abs. 1 a) Nicht zugelassenes Anwendungsgebiet (Off-Label-Indikation): Fortgeschrittenes nicht-kleinzelliges Bronchialkarzinom (NSCL) - Kombinationstherapie b) Behandlungsziel: palliativ c) Folgende Wirkstoffe sind für die Indikation fortgeschrittenes nicht-kleinzelliges Bronchialkarzinom (NSCL) -Kombinationstherapie zugelassen: − Cisplatin − Docetaxel − Erlotinib − Etoposid − Gemcitabin − Ifosfamid − Mitomycin − Paclitaxel − Pemetrexed − Vindesin

	− Vinorelbin d) Spezielle Patientengruppe: Patienten mit einem erhöhten Risiko für cisplatininduzierte Nebenwirkungen im Rahmen einer Kombinationstherapie (z. B. vorbestehende Neuropathie oder relevante Hörschädigung, besondere Neigung zu Übelkeit, Niereninsuffizienz, Herzinsuffizienz) e) Patienten, die nicht behandelt werden sollten: − Patienten, für die zugelassene Behandlungen in Frage kommen − Monotherapie […]

de Castria TB et al., 2013 [11]. Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer	**1. Fragestellung** To assess the efficacy and safety of carboplatin-based chemotherapy when compared with cisplatin-based chemotherapy, both in combination with a third-generation drug, in people with advanced NSCLC. To compare quality of life in people with advanced NSCLC receiving chemotherapy with cisplatin and carboplatin combined with a third-generation drug.
	2. Methodik **Population:** people with advanced NSCLC **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:** Cochrane risk of bias' tool

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%).

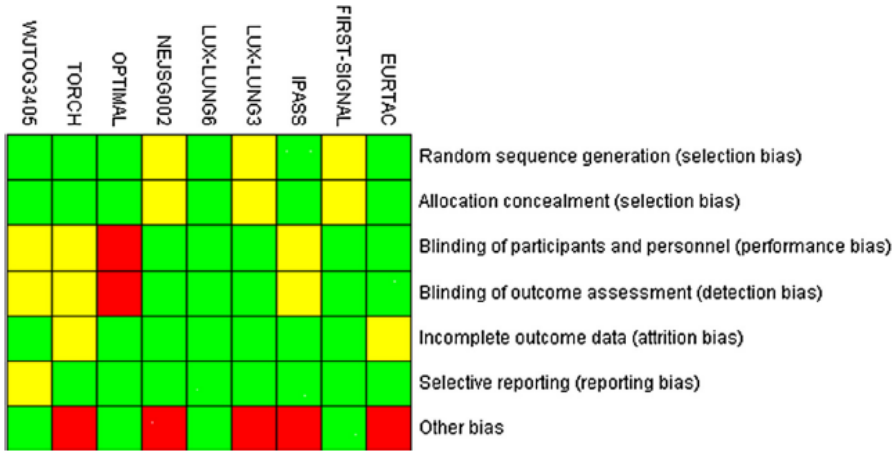
ORR: Cisplatin had higher response rates when we performed an overall analysis (RR 0.88; 95% CI 0.79 to 0.99, I^2 = 3%), but trials using paclitaxel or gemcitabine plus a platin in both arms had equivalent response rates (paclitaxel: RR 0.89; 95% CI 0.74 to 1.07, I^2 = 0%; gemcitabine: RR 0.92; 95% CI 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. **Fazit der Autoren:** The initial treatment of people with advanced NSCLC is palliative, and carboplatin can be a treatment option. It has a similar effect on survival but a different toxicity profile when compared with cisplatin. Therefore, the choice of the platin compound should take into account the expected toxicity profile and the person's comorbidities. In addition, when used with either paclitaxel or gemcitabine, the drugs had an equivalent response rate.

Systematische Reviews

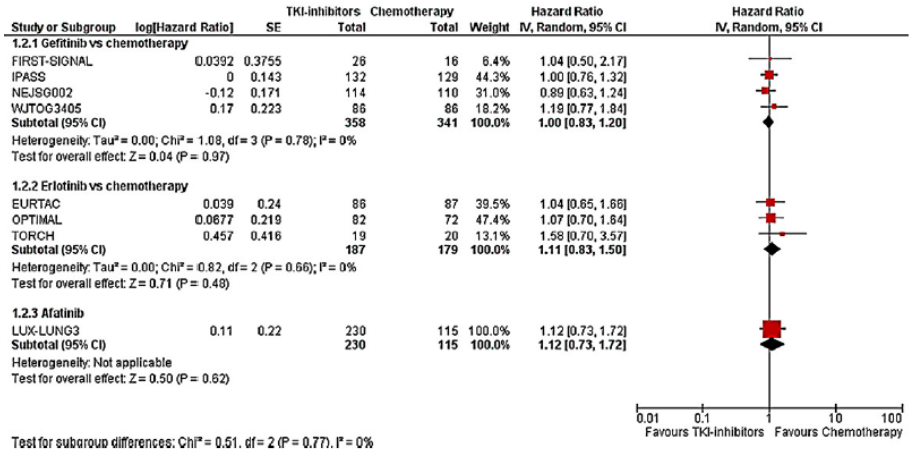
Haspinger ER et al., 2015 [22]. Is there evidence for different effects among EGFR-TKIs? Systematicrevie w and meta-analysis of EGFR tyrosine kinase inhibitors (TKIs)versus chemotherapy as first-line treatment for patients harboring EGFRmutations	1. Fragestellung Three EGFR tyrosine kinase inhibitors have been compared to standard chemotherapy as up-front treatment in patients with advanced EGFR-positive NSCLC. We performed a systematic review and meta-analysis using indirect comparisons to estimate the risk/benefit associated with each drug.
	2. Methodik **Population:** patients of any age and race, with histologicallyproven NSCLC harboring an activating EGFR-mutation **Intervention/Komparator**: First line EGFR-TKI compared with standard chemother-apy (platinum-based doublet, at any dosage or number ofcycles), generally considered of similar clinical efficacy **Endpunkte**: Primary: PFS; Secondary: PFS in exon 19 deletion, PFSin L858R mutation, OS, ORR (complete and/or partialand/or stable assessed using RECIST criteria) and treat-ment related toxic events assessed with the NCI CT Criteria **Suchzeitraum**: PubMed, Cancer-Lit, Embase-databases and Cochrane-Library were searched for RCTs up to June 2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 9 RCTs which involved globally 1774 EGFR-mutated patients **Qualitätsbewertung der Studien:** Cochrane risk of bias tool
	3. Ergebnisdarstellung Qualität der Studien:  **Study characteristics**

Trial	Primary end-point	TKI	Chemotherapy	Patients (TKI/CT)	EGFR + patients (%)	Asiatic patients (%)	Crossover (%)[a]
IPASS Mok, 2009	Progression-free survival	Gefitinib	Carboplatin + paclitaxel	1.217 (609/608)	21.4	99.8	39.5
WJTOG3405 Mitsudomi, 2010	Progression-free survival	Gefitinib	Cisplatin + paclitaxel	177 (88/89)	100	100	59.3
NEJ002 Maemondo, 2010	Progression-free survival	Gefitinib	Carboplatin + paclitaxel	228 (114/114)	100	100	94.6
First-SIGNAL Han, 2012	Overall survival	Gefitinib	Cisplatin + gemcitabine	309 (159/150)	13.6	100	75.0
TORCH Gridelli, 2012	Overall survival	Erlotinib	Cisplatin + gemcitabine	760 (380/380)	5.1	0	60.9
OPTIMAL Zhou, 2011	Progression-free survival	Erlotinib	Carboplatin + gemcitabine	154 (82/72)	100	100	NA
EURTAC Rosell, 2011	Progression-free survival	Erlotinib	Cisplatin/carboplatin + docetaxel/gemcitabine	173 (86/87)	100	0	76.0
LUX-Lung 3 Sequist, 2012	Progression-free survival	Afatinib	Cisplatin + pemetrexed	345 (230/115)	100	100	75.0
LUX-Lung 6 Wu, 2013	Progression-free survival	Afatinib	Cisplatin + gemcitabine	364 (242/122)	100	100	56.0

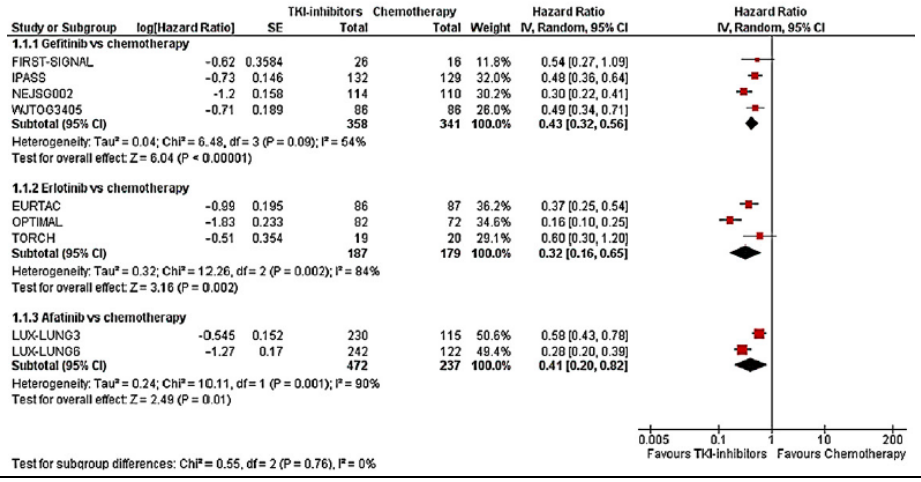
[a] Patients who have been treated with crossover from chemotherapy to TKI in second-line.

Direct comparisons

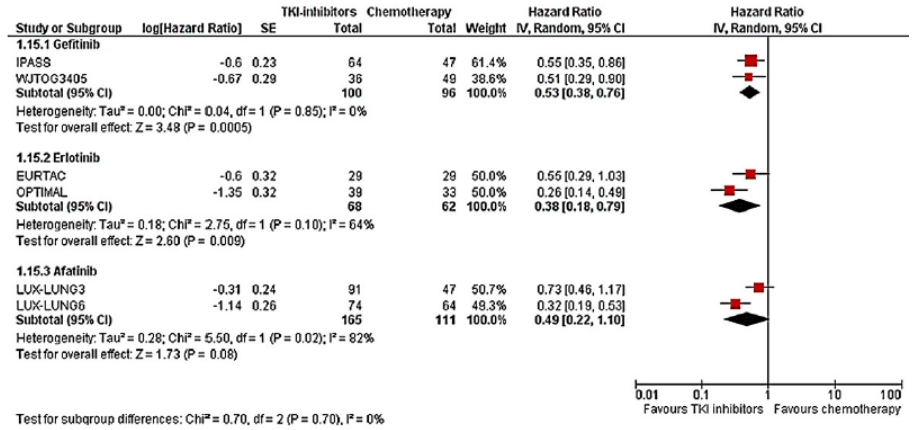
Overall survival



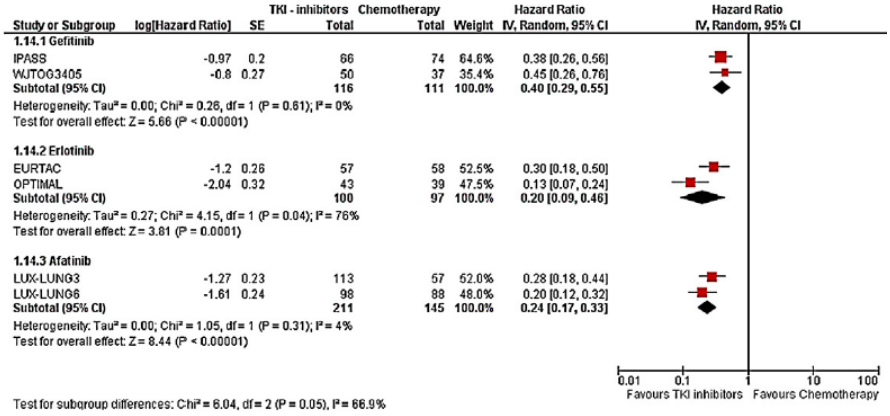
Progressions-free survival



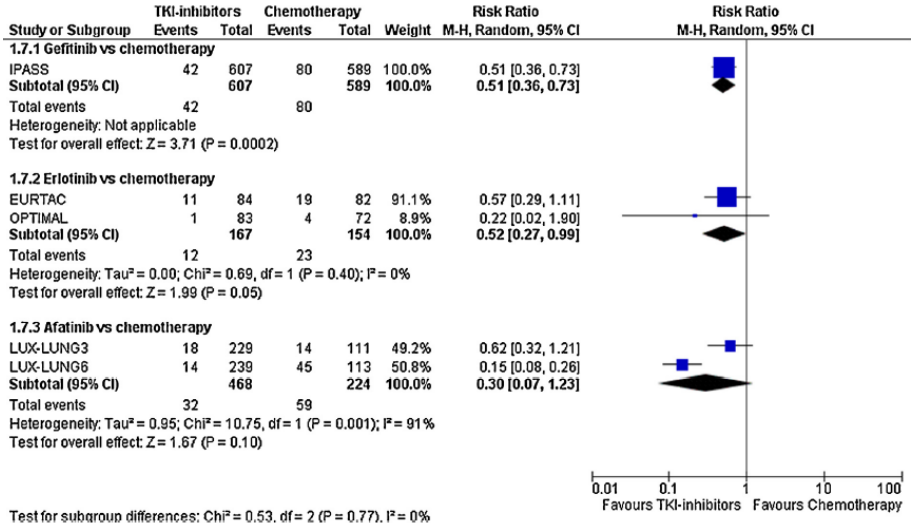
Exon 21



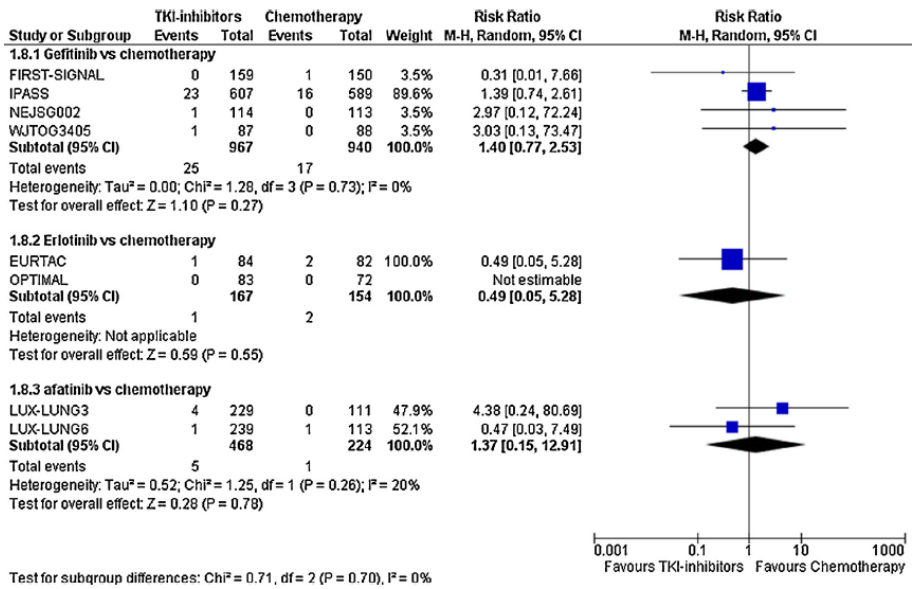
Exon 19



Treatment discontinuation

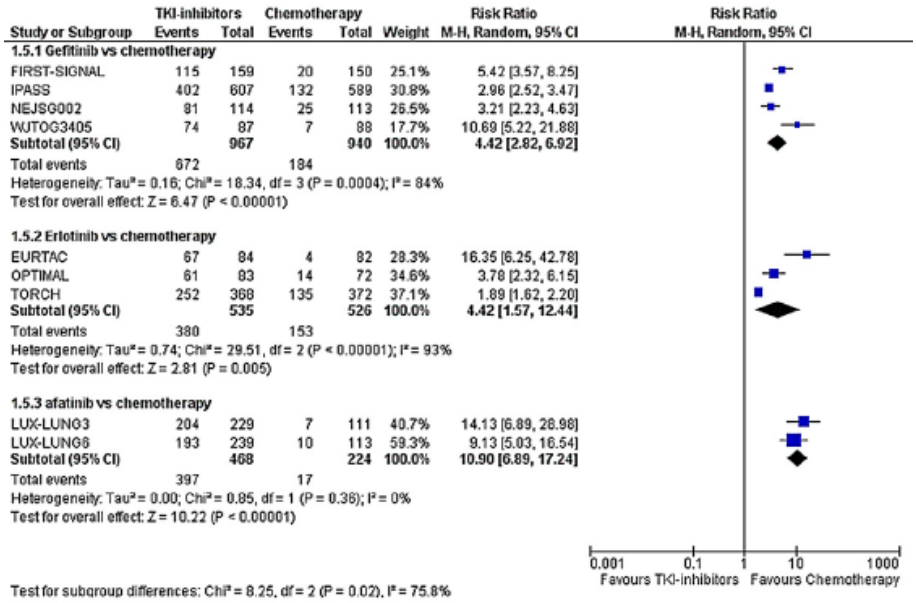


Treatment-related deaths



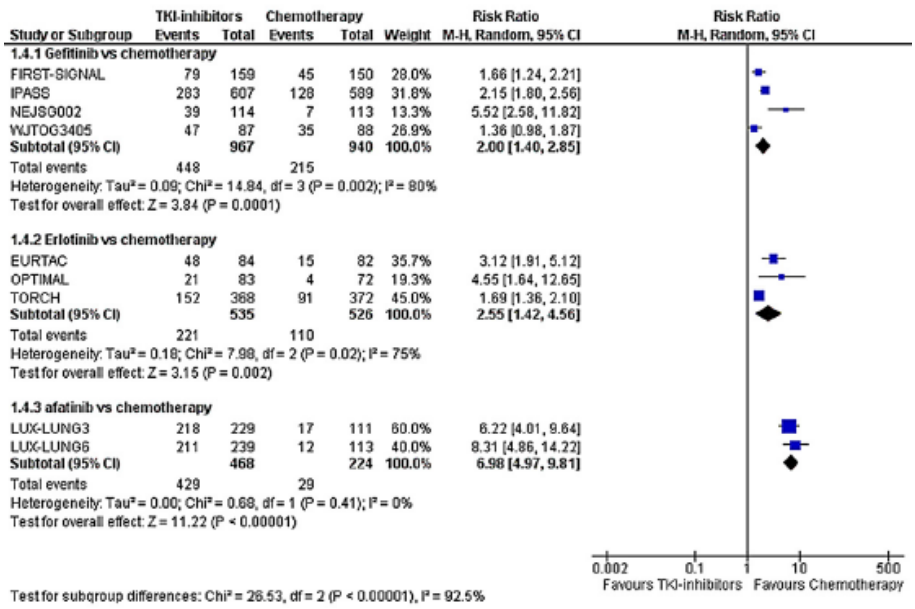
Study or Subgroup	TKI-inhibitors Events	Total	Chemotherapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Gefitinib vs chemotherapy						
FIRST-SIGNAL	0	159	1	150	3.5%	0.31 [0.01, 7.66]
IPASS	23	607	16	589	89.6%	1.39 [0.74, 2.61]
NEJSG002	1	114	0	113	3.5%	2.97 [0.12, 72.24]
WJTOG3405	1	87	0	88	3.5%	3.03 [0.13, 73.47]
Subtotal (95% CI)		**967**		**940**	**100.0%**	**1.40 [0.77, 2.53]**
Total events	25		17			
Heterogeneity: Tau² = 0.00; Chi² = 1.28, df = 3 (P = 0.73); I² = 0%						
Test for overall effect: Z = 1.10 (P = 0.27)						
1.8.2 Erlotinib vs chemotherapy						
EURTAC	1	84	2	82	100.0%	0.49 [0.05, 5.28]
OPTIMAL	0	83	0	72		Not estimable
Subtotal (95% CI)		**167**		**154**	**100.0%**	**0.49 [0.05, 5.28]**
Total events	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.55)						
1.8.3 afatinib vs chemotherapy						
LUX-LUNG3	4	229	0	111	47.9%	4.38 [0.24, 80.69]
LUX-LUNG6	1	239	1	113	52.1%	0.47 [0.03, 7.49]
Subtotal (95% CI)		**468**		**224**	**100.0%**	**1.37 [0.15, 12.91]**
Total events	5		1			
Heterogeneity: Tau² = 0.52; Chi² = 1.25, df = 1 (P = 0.26); I² = 20%						
Test for overall effect: Z = 0.28 (P = 0.78)						
Test for subgroup differences: Chi² = 0.71, df = 2 (P = 0.70), I² = 0%						

Skin toxicity

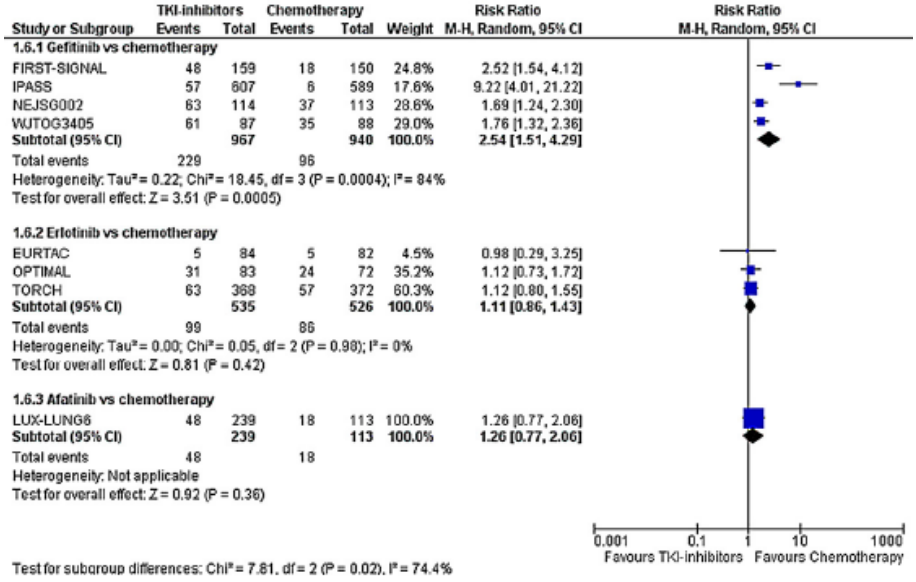


Study or Subgroup	TKI-inhibitors Events	Total	Chemotherapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Gefitinib vs chemotherapy						
FIRST-SIGNAL	115	159	20	150	25.1%	5.42 [3.57, 8.25]
IPASS	402	607	132	589	30.8%	2.96 [2.52, 3.47]
NEJSG002	81	114	25	113	26.5%	3.21 [2.23, 4.63]
WJTOG3405	74	87	7	88	17.7%	10.69 [5.22, 21.88]
Subtotal (95% CI)		**967**		**940**	**100.0%**	**4.42 [2.82, 6.92]**
Total events	672		184			
Heterogeneity: Tau² = 0.16; Chi² = 18.34, df = 3 (P = 0.0004); I² = 84%						
Test for overall effect: Z = 6.47 (P < 0.00001)						
1.5.2 Erlotinib vs chemotherapy						
EURTAC	67	84	4	82	28.3%	16.35 [6.25, 42.78]
OPTIMAL	61	83	14	72	34.6%	3.78 [2.32, 6.15]
TORCH	252	368	135	372	37.1%	1.89 [1.62, 2.20]
Subtotal (95% CI)		**535**		**526**	**100.0%**	**4.42 [1.57, 12.44]**
Total events	380		153			
Heterogeneity: Tau² = 0.74; Chi² = 29.51, df = 2 (P < 0.00001); I² = 93%						
Test for overall effect: Z = 2.81 (P = 0.005)						
1.5.3 afatinib vs chemotherapy						
LUX-LUNG3	204	229	7	111	40.7%	14.13 [6.89, 28.98]
LUX-LUNG6	193	239	10	113	59.3%	9.13 [5.03, 16.54]
Subtotal (95% CI)		**468**		**224**	**100.0%**	**10.90 [6.89, 17.24]**
Total events	397		17			
Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 1 (P = 0.36); I² = 0%						
Test for overall effect: Z = 10.22 (P < 0.00001)						
Test for subgroup differences: Chi² = 8.25, df = 2 (P = 0.02), I² = 75.8%						

Diarrhea

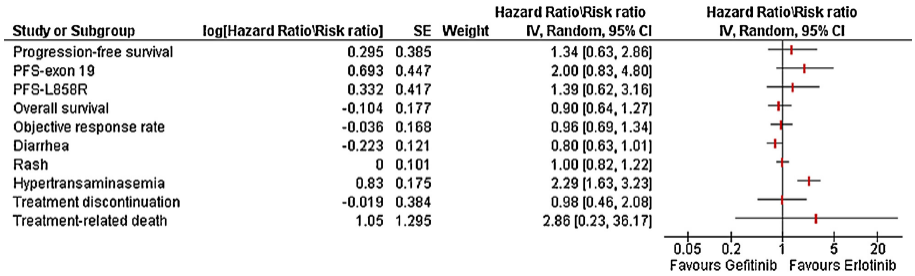


Hypertransaminasemia



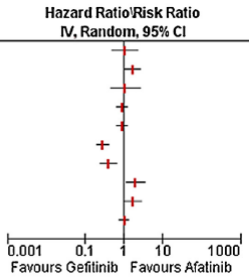
Indirect comparisons

gefitinib versus erlotinib



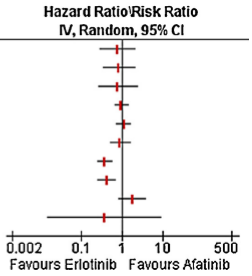
gefitinib versus afatinib

Study or Subgroup	log[Hazard Ratio\Risk Ratio]	SE	Weight	Hazard Ratio\Risk Ratio IV, Random, 95% CI
Progression-free survival	0.048	0.387		1.05 [0.49, 2.24]
PFS-exon 19	0.511	0.235		1.67 [1.05, 2.64]
PFS-L858R	0.078	0.447		1.08 [0.45, 2.60]
Overall survival	-0.099	0.167		0.91 [0.65, 1.26]
Objective response rate	-0.097	0.157		0.91 [0.67, 1.23]
Diarrhea	-1.25	0.187		0.29 [0.20, 0.41]
Rash	-0.903	0.244		0.41 [0.25, 0.65]
Hypertransaminasemia	0.701	0.276		2.02 [1.17, 3.46]
Treatment discontinuation	0.531	0.273		1.70 [1.00, 2.90]
Treatment-related death	0.022	0.136		1.02 [0.78, 1.33]



erlotinib versus afatinib

Study or Subgroup	log[Hazard Ratio\Risk Ratio]	SE	Weight	Hazard Ratio\Risk Ratio IV, Random, 95% CI
Progression-free survival	-0.248	0.507		0.78 [0.29, 2.11]
PFS-exon 19	-0.182	0.449		0.83 [0.35, 2.01]
PFS-L858R	-0.254	0.558		0.78 [0.26, 2.32]
Objective response rate	-0.061	0.186		0.94 [0.65, 1.35]
Overall survival	0.094	0.204		1.10 [0.74, 1.64]
Hypertransaminasemia	-0.127	0.285		0.88 [0.50, 1.54]
Diarrhea	-1.01	0.2		0.36 [0.25, 0.54]
Rash	-0.903	0.245		0.41 [0.25, 0.66]
Treatment discontinuation	0.55	0.395		1.73 [0.80, 3.76]
Treatment-related death	-1.03	1.637		0.36 [0.01, 8.83]



4. Fazit der Autoren: In conclusion, also after this attempt we are unable to select a drug up-front based on clinical evidence. Further-more, the real clinical unmet need on how to treat patients after disease progression and how to overcome acquired resistance remains still unsolved and without any approved drugs. For the 10% of EGFR-mutated patients, after nine phase3 trials we are unable to choose the best drug for first-linetreatment. In fact, due to a lack of direct comparisons madein the research carried out so far, prescriptive choice willnot presently be based on scientific evidence. Therefore, webelieve that “me too” drugs should be accepted by the regu-latory agencies only when there is the final proof of greaterefficacy or demonstrated less toxicity.

Lee JK et al., 2014 [25].

Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors vs Conventional Chemotherapy in Non–Small Cell Lung Cancer Harboring Wild-Type Epidermal Growth Factor Receptor

1. Fragestellung

Current guidelines recommend both epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and cytotoxic chemotherapy drugs as standard treatment options for patients with wild-type (WT) EGFR who were previously treated for non–small cell lung cancer (NSCLC). However, it is not clear that EGFR TKIs are as efficacious as chemotherapy in patients with WT EGFR.

2. Methodik

Population: patients with advanced NSCLC, defined as inoperable locally advanced (stage IIIB) or metastatic or recurrent disease (stage IV); studies were excluded if they only included patients with tumors harboring EGFR mutations

Intervention/Komparator: comparing first-generation EGFR TKI (erlotinib or gefitinib) with a conventional chemotherapy agent

Endpunkte: Primary: PFS; Secondary: objective response rate, which was defined as the proportion of complete response and partial responses among all evaluable patients, and overall survival

Suchzeitraum: PubMed, EMBASE, and Cochrane databases from inception to December 16, 2013

Anzahl eingeschlossene Studien/Patienten (Gesamt): 11 trials including 5471 patients

Qualitätsbewertung der Studien: Cochrane risk of bias tool

3. Ergebnisdarstellung

Study characteristics

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]	No. of Patients: TKI Group Total[b]	No. of Patients: Control Group *EGFR* WT[a]	No. of Patients: 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.

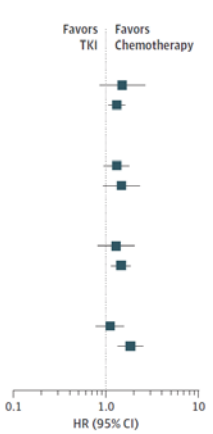
[c] TKI group vs chemotherapy group.

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

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

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 with WT EGFR

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



The treatment effects were calculated with a random-effects model. EGFR indicates epidermal growth factor receptor; HR, hazard ratio; TKI, tyrosine kinase inhibitor.

Critical appraisal

Trial	Sequence generation	Allocation concealment	Blinding[a]	Incomplete outcome data	Selective reporting	Other source of bias[b]
INTEREST[1,2] 2008 and 2010	Adequate (Minimization)	Adequate (Central allocation)	Unclear	Adequate	Adequate	
IPASS[3,4] 2009 and 2011	Adequate (Minimization)	Adequate (Central allocation)[c]	Inadequate (No independent radiologic review)[c]	Adequate	Adequate	
ML20322[5] 2012	Adequate (Computer random number generator)[c]	Adequate (Central allocation)[c]	Adequate (Independent radiologic review)[c]	Adequate	Unclear	Vinorelbine is a less potent comparator; Included only elderly patients
TITAN[6] 2012	Adequate (Minimization)	Adequate (Central allocation)	Unclear	Adequate	Adequate	Premature termination, due to slow accrual of patients
First-SIGNAL[7] 2012	Adequate (Computer random number generator)[c]	Adequate (Sequentially numbered, sealed envelops for treatment allocation)[c]	Adequate (Independent radiologic review)	Adequate	Adequate	
TORCH[8] 2012	Adequate (Minimization)	Adequate (Central allocation)	Unclear	Adequate	Adequate	
KCSG-LU08-01[9] 2012	Adequate (Computer random number generator)	Adequate (Central allocation)	Adequate (Independent radiologic review)	Adequate	Unclear	Premature termination, due to slow accrual of patients; Biased baseline characteristic: patient's median age was lower in the gefitinib arm (58 years versus 64 years).
CT/06.05[10] 2013	Adequate (Computer random number generator)[c]	Adequate (Central allocation)[c]	Adequate (Independent radiologic review)	Adequate	Adequate	

TAILOR[11] 2013	Adequate (Minimization)	Adequate (Central allocation)	Inadequate (Outcome assessor was not blinded)	Adequate	Adequate	
DELTA[12] 2013	Adequate (Minimization)	Unclear	Unclear	Adequate	Adequate	Data from the abstract and the presentation slides
CTONG0806[13] 2013	Unclear	Unclear	Unclear	Adequate	Inadequate (overall survival was a secondary outcome but not reported)	Data from the abstract and the poster; Biased baseline characteristic: pemetrexed arm had more never-smokers (57.9% versus 40.7%, P = 0.032).

[a] The adequacy of blinding was judged by the blindness of outcome assessment, because the PFS is the primary outcome of this study.
[b] Other source of bias was evaluated according to the Cochrane risk of bias assessment tool ("other potential threats to validity" section).
[c] These information, which were not written in the published articles, were obtained by personal communication with the corresponding authors of the articles.

4. Fazit der Autoren: In patients with advanced NSCLC harboring WT EGFR tumors, conventional chemotherapy was associated with improvement in PFS and a higher objective response rate, compared with first-generation EGFR TKI. However, there was no statistically significant difference in terms of overall survival between the 2 treatment groups.

Zhang TT et al., 2016 [57].

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

1. Fragestellung

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

2. Methodik

Population: patients with pathologically confirmed NSCLC

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

Endpunkte: siehe Ergebnisse

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

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

Qualitätsbewertung der Studien: Jadad scale

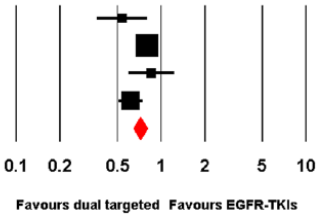
3. Ergebnisdarstellung

Study characteristics and critical appraisal

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

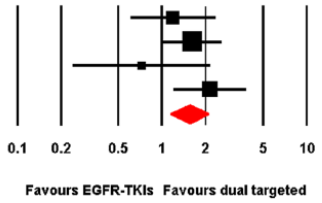
Random-effects model of hazard ratio (95 % confidence interval) of PFS associated with dual targeted therapies versus EGFR-TKIs alone

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Seto T. et al 2014	0.540	0.365	0.800	-3.073	0.002
Scagliotti G.V. et al 2012	0.807	0.695	0.937	-2.813	0.005
Spigel D.R. et al 2011	0.860	0.603	1.226	-0.833	0.405
Herbst R.S. et al 2011	0.620	0.516	0.745	-5.116	0.000
	0.722	0.649	0.802	-6.034	0.000



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

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Group-A	Group-B
Seto T. et al 2014	1.189	0.611	2.313	0.509	0.611	52 / 77	49 / 77
Scagliotti G.V. et al 2012	1.610	1.019	2.544	2.041	0.041	51 / 480	33 / 480
Spigel D.R. et al 2011	0.721	0.243	2.138	-0.590	0.555	9 / 111	6 / 55
Herbst R.S. et al 2011	2.151	1.211	3.819	2.613	0.009	38 / 317	19 / 319
	1.540	1.138	2.084	2.795	0.005	150 / 985	107 / 931



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

5. Anmerkungen FBMed

Nur die Primärstudie von Seto et al. hat Erstlinientherapien untersucht.

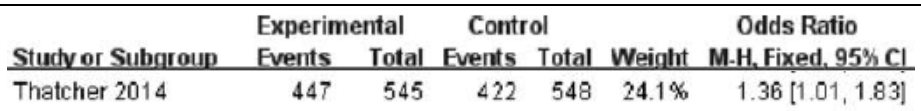
Sheng J et al., 2015 [45].

The Efficacy of Combining EGFR Monoclonal Antibody With

1. Fragestellung

Although epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs) have been proved synergistic effect when combined with cytotoxic agents for advanced nonsmall cell lung cancer (NSCLC), the results of relevant clinical trials remain controversial. The purpose of this meta-analysis was to assess the advantage and toxicity profile of chemotherapy plus EGFR-mAbs versus chemotherapy alone for patients with NSCLC.

Chemotherapy for Patients With Advanced Nonsmall Cell Lung Cancer	2. Methodik **Population:** patients with advanced NSCLC **Intervention/Komparator**: EGFR-mAbs (cetuximab, nectitumumab, panitumumab, or matuzumab) plus standard chemotherapy as experimental group or the corresponding chemotherapy as parallel control **Endpunkte**: OS, progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), or toxicity profile **Suchzeitraum**: PubMed, Embase, and the Central Registry of Controlled Trials of the Cochrane Library (between inception to January 1, 2015), as well as the meeting records related to lung cancer from ASCO and ESMO databases (2010 to January 1, 2015) **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 9 Studien, davon eine Studie mit zugelassener Kombination **Qualitätsbewertung der Studien:** Cochrane risk of bias tool
	3. Ergebnisdarstellung Study characteristics **Study** / **Author and Year** / **Phase** / **Line** / **Study Arms** / **Number of Patients** / **Caucasian Origin, %** / **Histology** / **Primary Outcome** / **PFS (month)** / **OS (month)** / **ORR, %** / **DCR, %** SQIRE / Thatcher 2014 / III / 1 / Necitumumab + GP / 545 / 84 / Squamous cancer / OS / 5.7 vs 5.5 / 11.5 vs 9.9 / 31 / 82 GP alone / 548 / 83 / $P = 0.02$ / $P = 0.012$ / 29 / 77 DCR = disease control rate; EGFR = epidermal growth factor receptor; GP refers to gemcitabine (1250 or 1000 mg/m^2 IV, days 1 and 8) plus cisplatin (75 mg/m^2 IV, day 1) every 3 weeks; GC means gemcitabine plus carboplatin (AUC = 5, IV, day 1) every 3 weeks; NP for cisplatin (80 mg/m^2, day 1) with vinorelbine (25 mg/m^2, days 1 and 8) every 3 weeks; NSCLC = nonsmall cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; TC means taxane/carboplatin chemotherapy, including paclitaxel (200 or 225 mg/m^2 IV, day 1) or docetaxel (75 mg/m^2 IV, day 1) plus carboplatin (AUC = 6, IV, day 1) every 3 weeks; Pem and Doc separately refers to pemetrexed (500 mg/m^2) and docetaxel (75 mg/m^2) IV, day 1, every 3 weeks; AP means pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) IV, day 1, every 3 weeks. All of the chemotherapy regimens were limited to 4 to 6 cycles; TTP = time to progression. HR and 95% CI for OS **Study or Subgroup** / **log[Hazard Ratio]** / **SE** / **Weight** / **Hazard Ratio IV, Fixed, 95% CI** / **Year** **1.1.1 first-line** Thatcher 2014 / -0.1778 / 0.0699 / 21.1% / 0.84 [0.73, 0.96] / 2014 HR and 95% CI for PFS **Study or Subgroup** / **log[Hazard Ratio]** / **SE** / **Weight** / **Hazard Ratio IV, Fixed, 95% CI** Thatcher 2014 / -0.1625 / 0.0707 / 18.1% / 0.85 [0.74, 0.98] OR and 95% CI for ORR **Study or Subgroup** / **Experimental Events** / **Experimental Total** / **Control Events** / **Control Total** / **Weight** / **Odds Ratio M-H, Fixed, 95% CI** Thatcher 2014 / 169 / 545 / 159 / 548 / 29.3% / 1.10 [0.85, 1.42] OR and 95% CI for DCR

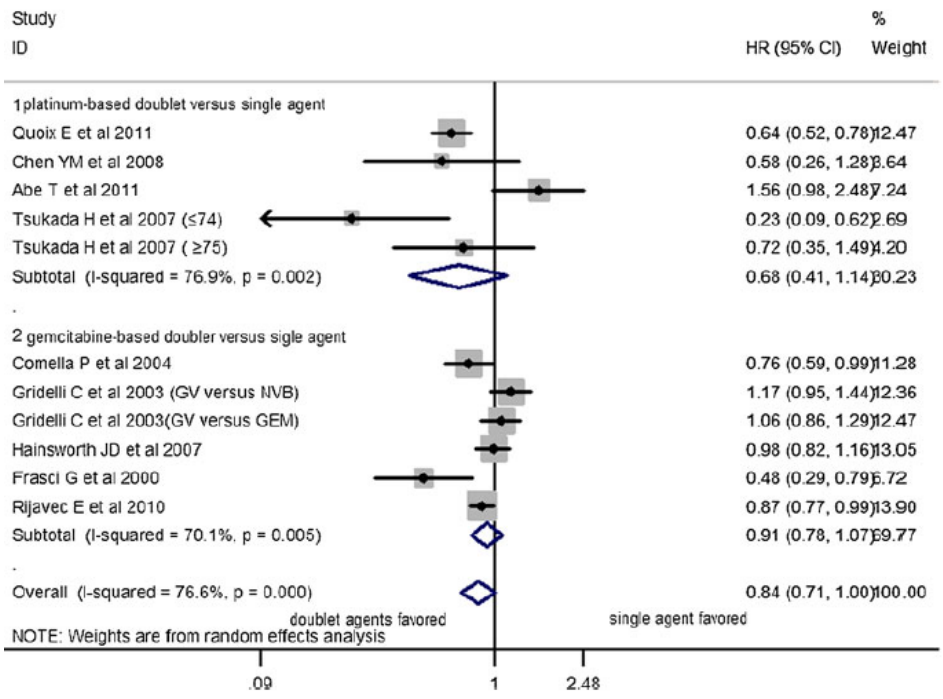
	 Experimental / Control / Odds Ratio Study or Subgroup: Thatcher 2014 Experimental Events 447, Total 545; Control Events 422, Total 548; Weight 24.1%; M-H, Fixed, 95% CI 1.36 [1.01, 1.83]
	4. Fazit der Autoren: The addition of EGFR-mAbs to chemotherapy provided superior clinical benefit along with acceptable toxicities to patients with advanced NSCLC, especially those harboring squamous cancer and treatment-naive. Further validation in front-line investigation, proper selection of the potential benefit population by tumor histology, and development of prognostic biomarkers are warranted for future research and clinical application of EGFR-mAbs. 5. Anmerkung FBMed: Das Fazit der Autoren bezieht sich auf alle von ihnen eingeschlossenen Primärstudien.
Qi WX et al., 2012 [41]. 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 Siehe auch **Xu CA et.al., 2013 [53].** Doublets versus single-agent therapy as first-line therapy for elderly patients with advanced non-small cell lung cancer? A systematic	**1. Fragestellung** to perform a systematic review and meta-analysis of all randomized controlled trials that compared the efficacy of doublet versus single third-generation cytotoxic agent as first-line treatment for elderly patients with advanced non-small-cell lung cancer (NSCLC).
	2. Methodik **Population:** elderly (older than 65 years) patients with advanced non-small-cell lung cancer. First-line **Interventionen:** doublet cytotoxic agents **Komparator:** single third-generation cytotoxic agent **Endpunkte:** OS, TTP, ORR, Toxicity **Suchzeitraum:** 1980-2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 10 (n= 2 510) **Qualitätsbewertung der Studien:** Jadad **Heterogenitätsuntersuchungen:** Between-study heterogeneity was estimated using the v2-based Q statistic. Heterogeneity was considered statistically significant when $p_{heterogeneity} < 0.05$ or I2>50 %. If heterogeneity existed, data were analyzed using a random-effects model. In the absence of heterogeneity, a fixed-effects model was used.
	3. Ergebnisdarstellung There was no placebo-controlled double-blinded trial. Alle Studien wurden mit Jadad 2-3 bewertet. Kein Publikationsbias

review of randomised controlled trials

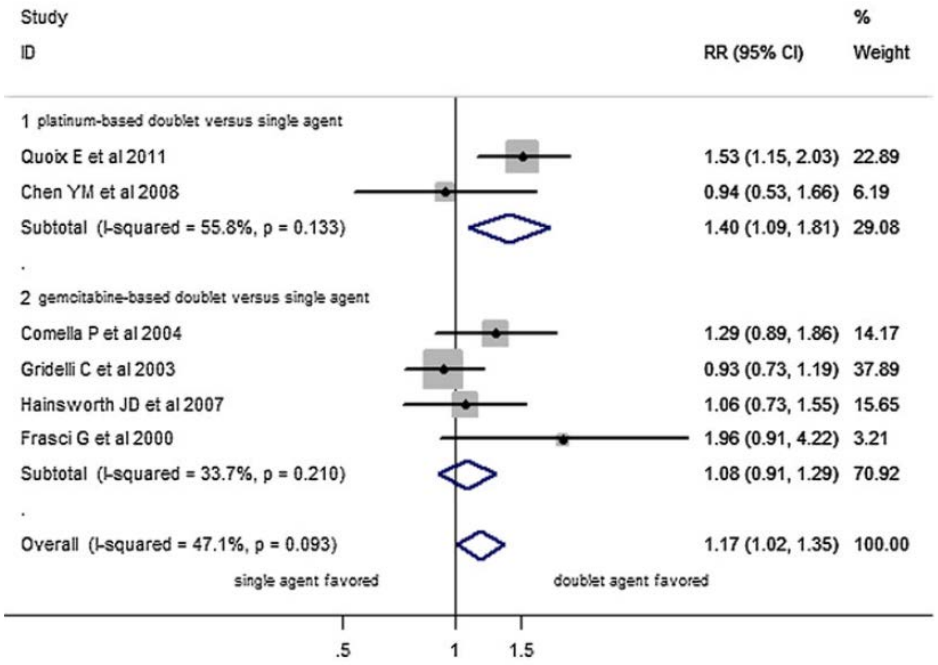
References	Years	Patient age	Chemotherapy regimens	No. of patients
Quoix et al. [18] (IFCT-0501)	2011	≥70	CBP AUC = 6 d1 + PTX 90 mg/m^2, d1,8,15 iv q.4.w.	225
			NVB 25 mg/m^2, d1,8 ivq.3.w. or GEM 1,150 mg/m^2, d1,8 iv q.3.w.	226
Chen et al. [19]	2008	≥70	NVB 22.5 mg/m^2 iv, d1,8 + DDP 50 mg/m^2 iv d1 q.3.w.	34
			NVB 25 mg/m^2, d1,8 iv q.3.w.	31
Comella et al. [20]	2004	≥70 or poor performance status	GEM 1,000 mg/m^2 iv, d1,8 + NVB 25 mg/m^2,d1,8 iv q.3.w.	68
			GEM 1,000 mg/m^2 iv, d1,8 + PTX 80 mg/m^2 iv, d1,8 q.3.w.	65
			GEM 1,200 mg/m^{2}iv, d1,8,15 q.4.w.	68
			PTX 100 mg/m^2 iv, d1,8,15 q.4.w.	63
Gridelli et al. [7] (MILES)	2003	≥70	GEM 1,000 mg/m^2 iv, d1,8 + NVB 25 mg/m^2 iv, d1,8 q.3.w.	232
			GEM 1,200 mg/m^2 iv, d1,8 q.3.w.	233
			GEM 1,000 mg/m^2 iv, d1,8 + NVB 25 mg/m^2 iv, d1,8 q.3.w.	232
			NVB 30 mg/m^2 iv, d1,8q.3.w.	233
Hainsworth et al. [21]	2007	>65 or poor performance status	GEM 800 mg/m^2 iv, d1,8,15 + TXT 30 mg/m^2 iv, d1,8,15 q.4.w.	174
			TXT 36 mg/m^2 iv, d1,8,15 q.4.w.	171
Frasci et al. [22]	2000	≥70	GEM 1,200 mg/m^2 iv, d1,8 + NVB 30 mg/m^2 iv, d1,8 q.3.w.	60
			NVB 30 mg/m^2 iv, d1,8 q.3.w.	60
Rijavec et al. [23]	2010	≥70	TXT 35 mg/m^2 iv, d1,8,15 + GEM 800 mg/m^2 iv, d1,8,15 q.4.w.	36
			TXT 35 mg/m^2 iv, d1,8,15q.4.w.	33
Karampeazis et al. [24]	2010	≥70	TXT 30 mg/m^2 iv, d1,8 + GEM 900 mg/m^2 iv, d1,8 q.3.w.	49
			GEM 1,200 mg/m^2 iv, d1,8 q.3.w.	47
Tsukada et al. [25]	2007	≥70	TXT 20 mg/m^2 iv, d1,8,15 + DDP 25 mg/m^2 iv, d1,8,15 q.4.w.	63
			TXT 25 mg/m^2 iv, d1,8,15 q.4.w.	63
Abe et al. [26]	2011	≥70	TXT 20 mg/m^2 iv, d1,8,15 + DDP 25 mg/m^2 iv, d1,8,15 q.4.w.	139
			TXT 60 mg/m^2 iv, d1 q.3.w.	137

Mortalität (9 Studien)

- no statistically significant difference, HR of 0.84 (95% CI = 0.71–1.00, p = 0.053, I²=76.6%)
- we did a subgroup analysis based on chemotherapy regimens and found that OS was not significantly improved by platinum-based doublet (HR = 0.68, 95 % CI = 0.41–1.14, p = 0.143) or by gemcitabine-based doublet (HR = 0.91, 95 % CI = 0.78–1.07, p = 0.26)
- Stat. signifikanter Vorteil für Kombinationstherapie vs. Monotherapie für 1-Jahres Überleben (RR = 1.17, 95 % CI = 1.02–1.35, p = 0.03; I²=47,7)



Comparison of OS between doublet therapy and single third-generation agent



Comparison of 1-year SR between doublet therapy and single third-generation agent

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)

Toxizität

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. **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.

5. Hinweise durch FB Med

- Alle in **Xu et al.** untersuchten Studien sind auch in **Qi et al.** enthalten. Zusätzlich wurden drei weitere Studien bei Qi et al. betrachtet. Die Gründe für diesen Unterschied sind nicht transparent. Die Ergebnisse der Reviews sind vergleichbar

Lima AB et al., 2011 [28].

Addition of bevacizumab to chemotherapy in advanced non-small cell lung cancer: a systematic review and meta-analysis

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: Advanced NSCLC

Intervention: Chemotherapy with bevacizumab

Komparator: Chemotherapy without bevacizumab

Endpunkte: OS, PFS, RR, Toxizität

Suchzeitraum: Bis 12/2010

Anzahl eingeschlossene Studien/Patienten (Gesamt): 5 (2252); nur RCTs with a parallel design

Qualitätsbewertung der Studien: Details regarding the main methodological dimensions empirically linked to bias as described by Deeks and colleagues were extracted, and the methodological quality of each selected trial were assessed.

Publication bias: Egger's test

Heterogenitätsuntersuchungen: I^2

3. Ergebnisdarstellung

Table 1. Methodological details potentially related to bias.

Authors	Year	Phase	Blindness	Withdrawn description	Alpha error	Beta error	ITT sr]analysis	Multicenter	Sponsor
Johnson et al	2004	II	No	Yes	Yes	Yes	Yes	Yes	Industry
Sandler et al	2006	III	No	Yes	Yes	Yes	No	Yes	Industry
Herbst et al	2007	II	Unclear	Yes	No	No	Yes	Yes	Industry
Reck et al	2009	III	Yes	Yes	Yes	Yes	Yes	Yes	Industry
Nishio et al	2009	II	No	Yes	No	No	No	Yes	No report

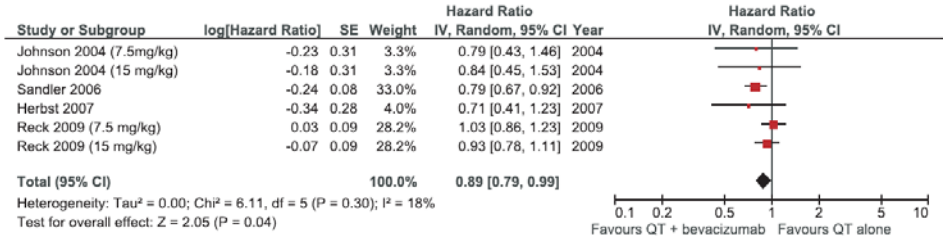
Table 2. Description of interventions and patients included.

Author/year	Study/arm	Patients enrolled	Setting	Primary endpoint	ECOG 0, 1(%)	Histology	Maintenance of bevacizumab (maximum cycles)
Johnson 2004	TP	32	1st line	PFS	93.7	NSCLC	Yes (18)
	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)
	TP+Bev (15)	434			100		
Herbst 2007 *	D or P	41	2nd line	PFS	97.6	Non-squamous NSCLC	Yes (until disease progression)
	D or P+Bev (15)	40			100		
Reck 2009	GP	347	1st line	PFS	100	Non-squamous NSCLC	Yes (until disease progression)
	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)
	TP+Bev (15)	121					

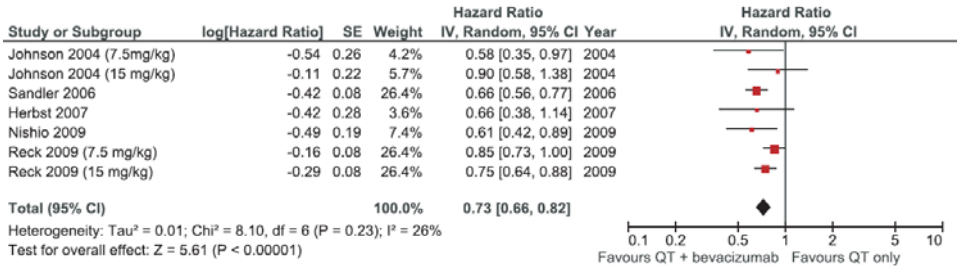
OS:

addition of bevacizumab to chemotherapy resulted in a significant longer OS (HR 0.89; 95% CI 0.79 to 0.99; p = 0.04; I²=18%)

Evaluating only trials studying first-line therapy, the meta-analysis showed similar results, however without statistical significance [HR 0.90 (0.79–1.01), p=0.08].



PFS: addition of bevacizumab to chemotherapy resulted in longer PFS (HR 0.73; 95% CI 0.66 to 0.82; p,0.00001; I²=26%)



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].

	Most important, there was a significant increase in deaths related to treatment associated with the addition of bevacizumab [OR 1.82 (1.04–3.18), p = 0.04] (Figure 6). Most of the deaths in the bevacizumab group were related to bleeding events, neutropenia complications and thromboembolic events.
	4. Fazit der Autoren: The main finding of the present meta-analysis is the homogeneous OS improvement provided by the addition of bevacizumab to chemotherapy when compared to chemotherapy alone in the advanced NSCLC setting, with an 11% reduction in risk of death, but with an estimated absolute benefit of less than 1 month in median survival. 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. **5. Hinweise durch FB Med** Eine Studie (Herbst et al.) mit Patienten in der Zweitlinie. Sonst alle Studien in der Erstlinie
Pilkington G, et. al., 2015 [40]. A systematic review of the clinical effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer <u>Siehe auch</u>: **Brown et al., 2013 [6].**	**1. Fragestellung** Our aim was to evaluate the clinical effectiveness of chemotherapy treatments currently licensed in Europe and recommended by the National Institute for Health and Care Excellence (NICE) for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC)
	2. Methodik **Population:** patients with locally advanced or metastatic NSCLC **Intervention:** first-line chemotherapy treatments. treatments had to be currently licensed for use in Europe and recommended by NICE **Komparator:** first-line chemotherapy treatments. treatments had to be currently licensed for use in Europe and recommended by NICE **Endpunkte:** OS, PFS, time to progression (TTP) **Suchzeitraum:**2001-2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 23 RCTs **Qualitätsbewertung der Studien:** All RCTs were assessed for methodological quality using criteria based on the Centre for Reviews and Dissemination guidance for undertaking reviews in healthcare **Heterogenitätsuntersuchungen:** Statistical heterogeneity was assessed by considering the $\chi 2$ test for heterogeneity with a 10% level of significance, and the I2 statistic with a value of 50% representing moderate heterogeneity
	3. Ergebnisdarstellung

All trials reported the number of patients randomised, however only six RCT were assessed as adequately randomised with adequate concealment of allocation. All trials reported eligibility criteria; 20 trials reported detailed information about baseline comparability and three trials partially reported information about baseline comparability, but only five trials achieved baseline comparability. Seven trials were reported as 'open'. Blinding of participants, investigators or outcome assessors was not reported in 16 studies.

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

Baselinecharakteristika

Trial	Intervention	No. randomised	Median age	% male	Disease stage		Histology	
					IIIB (%)	IV (%)	Squamous (%)	Adeno (%)
Kelly 2001[24]	VNB+CIS	202	61	67	11	89	NR	NR
	PAX+CARB	206	62	70	12	88	NR	NR
Scagliotti 2002[9]	GEM+CIS	205	63	81	19	81	33	67
	PAX+CARB	204	62	76	18	82	32	48
	VNB+CIS	203	63	78	19	81	27	73
Schiller 2002[34]	PAX+CIS	303	62	64	11	89	NR	NR
	GEM+CIS	301	64	62	14	86	NR	NR
	DOC+CIS	304	63	63	14	86	NR	NR
	PAX+CARB	299	63	62	14	86	NR	NR

Trial	Intervention	No. randomised	Median age	% male	Disease stage		Histology	
					IIIB (%)	IV (%)	Squamous (%)	Adeno (%)
Fossella 2003[10]	DOC+CIS	408	61	72	33	67	32	44
	DOC+CARB	406	59	72	33	67	33	42
	VNB+CIS	404	61	75	33	67	35	41
Gebbia 2003[25]	VNB+CIS	140	63	76	46	54	52	34
	GEM+CIS	138	60	78	46	54	52	31
Gridelli 2003*[8]	GEM+CIS or VNB+CIS	126	62	81	20	80	34	42
	VNB+CIS	126						
Smit 2003[11]	PAX+CIS	159	57	60	18	82	19	40
	GEM+CIS	160	57	71	21	79	26	46
Chen 2004[19]	PAX+CIS	70	64.9 (mean)	80	27	66	14	66
	VNB+CIS	70	64.8 (mean)	66	23	67	23	56

Trial	Intervention	No. randomised	Median age	% male	Disease stage		Histology	
					IIIB (%)	IV (%)	Squamous (%)	Adeno (%)
Douillard 2005[20]	DOC+CIS	119	58	83	0	100	33	41
	VNB+CIS	120	57	81	0	100	32	47
Martoni 2005[26]	VNB+CIS	146	62	76	32	66	29	52
	GEM+CIS	146	63	81	36	56	28	54

Trial	Intervention	No. randomised	Median age	% male	Disease stage		Histology	
					IIIB (%)	IV (%)	Squamous (%)	Adeno (%)
Thomas 2006[21]	GEM+CARB	51	60	82	12	86	35	57
	VNB+CIS	49	56	84	4	96	51	35
Chen 2007[22]	VNB+CIS	48	64.9	73	17	83	17	69
	DOC+CIS	46	60.2	57	20	80	26	54
Helbekkmo 2007[27]	VNB +CARB	222	67	59	30	70	27	50
	GEM+CARB	222	67	64	28	72	24	47
Langer 2007[23]	PAX+CARB	54	65	74	9	79	18	51
	GEM+CIS	49	67	59	18	73	21	45
Ohe 2007[28]	PAX+CARB	150	63	68	19	81	21	72
	GEM+CIS	151	61	69	21	79	20	74
	VNB+CIS	150	61	70	18	82	20	75

Trial	Intervention	No. randomised	Median age	% male	Disease stage		Histology	
					IIIB (%)	IV (%)	Squamous (%)	Adeno (%)
Chang 2008[35]	GEM+CIS	39	62.4	71	26	74	24	65
	VNB+CIS	44	61.6	64	36	64	33	62
Scagliotti 2008[4]	PEM+CIS	862	61.1	70	24	76	28	51
	GEM+CIS	863	61	70	24	76	27	48
Gronberg 2009[29]	PEM+CARB	225	64	56	29	71	26	50
	GEM+CARB	221	66	59	28	72	23	50
Mok 2009[5]and Fukuoka 2011[36]	GEF	609	57	21	25	75	NR	95
	PAX+CARB	608	57	21	24	76	NR	97
Tan 2009[30]	VNB+CIS	194	59.4	73	19	81	34	42
	DOC+CIS	196	62.1	76	15	85	34	39

Trial	Intervention	No. randomised	Median age	% male	Disease stage		Histology	
					IIIB (%)	IV (%)	Squamous (%)	Adeno (%)
Maemondo 2010[31]	GEF	115	63.9 (mean)	37	13	77	3	90
	PAX+CARB	115	62.6 (mean)	36	18	74	2	96
Mitsudomi 2010[32]	GEF	88	64	31	12	48	1	97
	DOC+CIS	89	64	30	10	48	0	98
Treat 2010[33]	GEM+CARB	379	64.1	58	10	90	18	NR
	PAX+CARB	379	64.1	61	11	89	16	NR

CARB=carboplatin; CIS=cisplatin; DOC=docetaxel; GEF=gefitinib; GEM=gemcitabine; PAX=paclitaxel; PEM=pemetrexed; VNB=vinorelbine, NR=not reported

NSCLC population with squamous disease

OS (18 RCTs):

- ranged from 6.2 to 15.4 months
- no statistically significant differences in OS between any of the four third-generation chemotherapy treatments
- direct and indirect evidence suggest a potential advantage in terms of OS for gemcitabine+platinum (MA: HR 1.08, 95% CI 0.98 to 1.20) and for docetaxel+platinum (MA: HR 0.89, 95% CI 0.78 to 1.00; MTC-1: HR 0.92, 95% CI 0.81 to 1.03) compared with vinorelbine+platinum, although this advantage is not statistically significant.
- One trial demonstrated significantly favourable survival estimates in a comparison between two regimens. In this study, patients in the docetaxel+cisplatin arm had a longer median OS compared to those in the vinorelbine+cisplatin arm.

Median PFS/TTP (18 RCTs):

- no evidence of any significant difference in PFS between the third-generation chemotherapy comparators.
- Two trials demonstrated differences in PFS/TTP between regimens; in one trial patients treated with gemcitabine+cisplatin had a significantly longer median PFS than those on paclitaxel+cisplatin, while in the other trial it was demonstrated that patients treated with vinorelbine+cisplatin had a significantly longer median PFS than patients treated with paclitaxel+cisplatin.

NSCLC population with non-squamous disease

OS (2RCTs)

- ranged from 7.5 to 11.8
- For patients with non-squamous disease, there is evidence that pemetrexed+platinum increases OS compared with gemcitabine+platinum (MA: HR 0.85, 95% CI 0.73 to 1.00; MTC-1: HR 0.85, 95% CI 0.74 to 0.98).
- There is no evidence to conclude that there is any statistically significant

difference between any of the other chemotherapy treatments in terms of increasing OS for patients with nonsquamous disease.

- The MTC analysis shows a statistically significant difference between paclitaxel+platinum and docetaxel+platinum (HR 0.79, 95% CI 0.66 to 0.93), but the results of MA were not statistically significant.
- One trial demonstrated a statistically significant difference in outcomes in patients with non-squamous disease who received pemetrexed+cisplatin compared with those receiving gemcitabine+cisplatin. Another trial did not show any significant difference in OS when comparing pemetrexed+carboplatin with gemcitabine+carboplatin.

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

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

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

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

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

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

Table 4 Top 10 adverse events by chemotherapy regimen

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

DOC, docetaxel; GEF, gefitinib; GEM, gemcitabine; PAX, paclitaxel; PEM, pemetrexed; PLAT, platinum; VNB, vinorelbine.

4. **Fazit der Autoren:** The results of the review highlight that from a clinical perspective, when examining data from patients with NSCLC, it is often difficult to distinguish between approved treatments in relation to their clinical effectiveness and so the decision about which drug to use will be based on clinicians' judgement and experience. This review highlights the fact that research in this area is now predominantly focussed on histological subpopulations of NSCLC as well as molecular profiling within the NSCLC population. Eighteen out of 23 included trials investigated the treatment of any patient with NSCLC; only recently have trials included and/or reported their results using subpopulations. Recruitment into NSCLC trials will continue to change dramatically over the coming years when further subpopulations are taken into consideration and targeted agents are introduced.

5. **Hinweise durch FB Med**

Der NICE Bericht ist die Langversion zu Pilkington et al. 2015

Zhang et al., 2014 [56].

Antiangiogenic Agents Combined with Chemotherapy in the First-Line Treatment of Advanced Non-Small-Cell Lung Cancer: Overall and Histology Subgroup-Specific Meta-Analysis

1. Fragestellung

This study investigated the overall and histology subtype-specific results of antiangiogenic agents combined with chemotherapy versus chemotherapy alone for the first-line treatment of advanced non-small cell lung cancer (NSCLC).

2. Methodik

Population: advanced NSCLC patients
Intervention / Komparator: antiangiogenic agents plus chemotherapy with chemotherapy alone for first-line treatment
Endpunkte: survival endpoints in terms of tumor response rate, PFS, and overall survival (OS); toxicity endpoints in terms of grade ¾ hematologic laboratory abnormalities and grade 3/4 general non-hematologic toxicities.
Suchzeitraum (Aktualität der Recherche): Systematische Literaturrecherche aber Zeitraum nicht angegeben.
Anzahl eingeschlossene Studien/Patienten (Gesamt): 13 randomized controlled trials comprising 5,451 patients were included

Table 1. Characteristics of the included trials

Study	Antiangiogenic agents	Target	Dosage	Regimen	Number of patients	Median age, years	Disease stage	ECOG PS	Region	Non-squamous, %	Follow-up time, months
Sandler et al. [16]	bevacizumab	VEGFR-1	15 mg/kg	bevacizumab + CP	417	NA	IIIB/IV	0–1	North/South	100	19
				CP	433	NA			America	100	
Reck et al. (AVAiL) [17]	bevacizumab	VEGFR-1	7.5 mg/kg	bevacizumab + CCG	345	57	IIIB/IV	0–1	worldwide	100	33
				CCG + placebo	347	59				100	
Niho et al. (JO19907) [18]	bevacizumab	VEGFR-1	15 mg/kg	bevacizumab + CP	121	61	IIIB/IV	0–1	Japan	100	34
				CP	59	60				100	
Johnson et al. [9]	bevacizumab	VEGFR-1	15 mg/kg	bevacizumab + CP	35	NA	IIIB/IV	0–2	North	78.1	57.8
				CP	32	NA			America	91.4	
Zhou et al (BEYOND) [19]	bevacizumab	VEGFR-1	15 mg/kg	bevacizumab + CP	138	NA	–	0–1	China	100	–
				CP+ placebo	138	NA				100	
Han et al. [20]	endostar	neovascular endothelial cells	7.5 mg/m^2/d	endostar + CP	61	49	IIIB/IV	0–2	China	62.3	38
				CP + placebo	61	38				77	
Goss et al. (BR24) [14]	cediranib	VEGFR-1,2,3, PDGFR, FGFR	30 mg/d	cediranib + CP	126	60	IIIB/IV	0–1	worldwide	81	24
				CP + placebo	125	58				74	
Dy et al. (N0528) [21]	cediranib	VEGFR-1,2,3, PDGFR, FGFR	30 mg/d	cediranib + CG	58	65	IIIB/IV	0–1	North	84.5	
				CG	29	64			America	72.4	51
Scagliotti et al. (MONET1) [22]	motesanib	VEGFR-1,2,3, PDGFR, Kit	125 mg/d	motesanib + CP	541	60	IIIB/IV	0–1	Europe,	100	41
				CP + placebo	549	60			East Asia	100	
Scagliotti et al. [15]	sorafenib	VEGFR-2,3, PDGFR-β, Flt-3, c-Kit	400 mg bid	sorafenib + CP	464	62	IIIB/IV	0–1	worldwide	77	20
				CP + placebo	462	63				75	
Wang et al. [23]	sorafenib	VEGFR-2,3, PDGFR-β, Flt-3, c-Kit	400 mg bid	sorafenib + CCG	18	54	IIIB/IV	0–1	China	83.3	40
				CCG + placebo	12	56				83.3	
Paz-Ares et al. [24]	sorafenib	VEGFR-2,3, PDGFR-β, Flt-3, c-Kit	400 mg bid	sorafenib + CCG	385	60	IIIB/IV	0–1	Europe,	100	38
				CCG + placebo	387	58			Asia	100	
Heymach et al. [25]	vandetanib	VEGFR-2,3, EGFR, RET	300 mg/d	vandetanib + CP	56	60	IIIB/IV	0–1	Europe,	80	32
				CP + placebo	52	59			North America, South Africa	71	

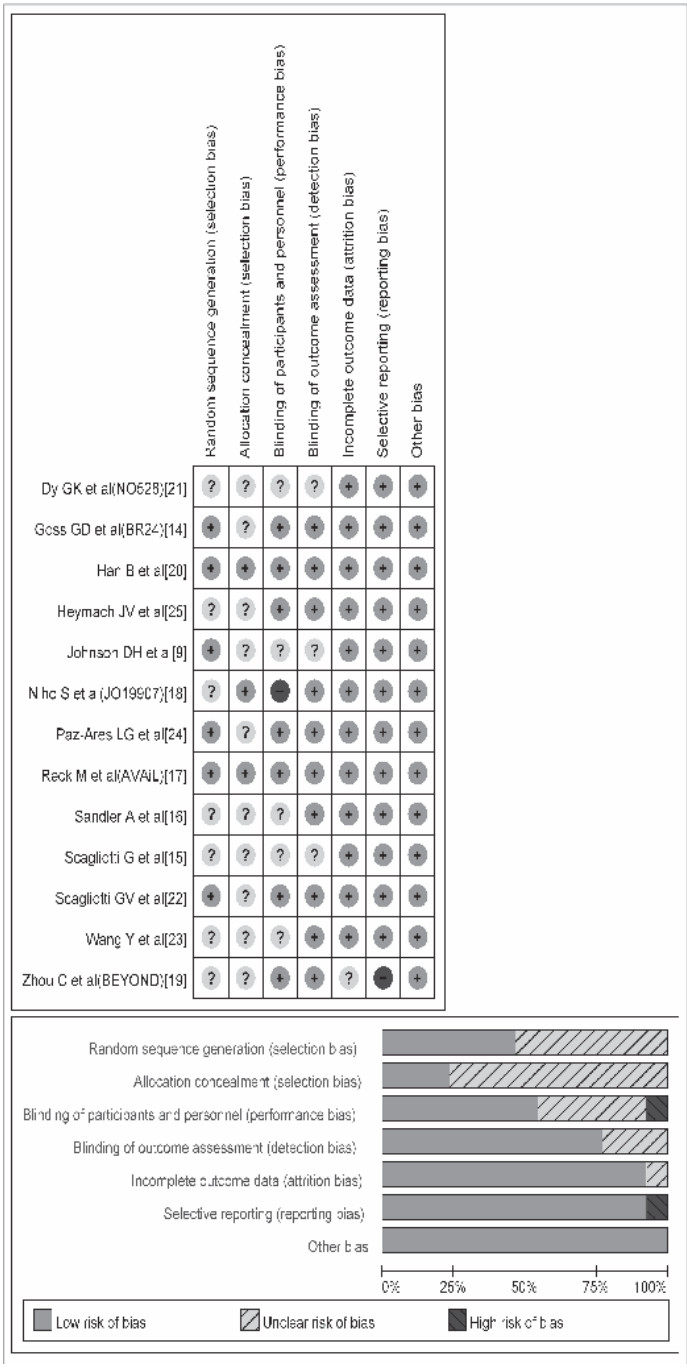
VEGFR = Vascular endothelial growth factor receptor, PDGFR = platelet-derived growth factor receptor, FGFR = fibroblast growth factor receptor, EGFR = epidermal growth factor receptor, bid = twice daily, CP = carboplatin and paclitaxel, CG = carboplatin and gemcitabine, CCG = cisplatin and gemcitabine, ECOG = Eastern Cooperative Oncology Group, NA = not available, PS = performance status.

Qualitätsbewertung der Studien: The risk of bias in each trial was assessed according to Cochrane methodology, considering randomization, allocation concealment, blinding, completeness of follow-up, selective reporting, and other biases. A forest plot demonstrating the risks of bias was generated by Review Manager.

3. Ergebnisdarstellung

Qualität der Studien: In general, the overall methodological quality of the included studies was good. All the included trials applied randomization, but 7 of them did not describe the method of the sequence generation process for randomization. 10 trials did not report adequate concealment of the allocation of outcome

assessments, which might bring selective bias in these trials. Of the 13 included studies, 7 studies applied the method of blinding, 5 did not mention blinding, and 1 was an open-label study. Without double-blinding, high performance bias may appear. Most of the trials mentioned the missing of outcome data; however, the reasons and the proportions of the missing data were unlikely to be related to the true outcomes of the survival and adverse effects. 1 trial did not report the prespecified primary outcome in the present publication, which may produce reporting biases.



- The meta-analysis showed a higher response rate (risk ratio (RR) 0.63, 95% confidence interval (CI) 0.53–0.74) and a significantly prolonged PFS (hazard ratio (HR) 0.75, 95% CI 0.66–0.85) and OS (HR 0.92, 95% CI 0.86–0.98) in

	the groups combining antiangiogenic agents with chemotherapy versus the chemotherapy alone groups. • In the histology subgroup analysis, treatment with antiangiogenic agents plus chemotherapy significantly improved the RR, PFS, and OS as compared with the chemotherapy groups in patients with nonsquamous NSCLC, but not in those with squamous NSCLC. • The risk of grade 3/4 thrombocytopenia, hypertension, bleeding, proteinuria, rash, diarrhea, fatigue, headache, anorexia, and febrile neutropenia was significantly increased in the antiangiogenic agent combination groups as compared with the chemotherapy groups
	4. Fazit der Autoren: Our findings demonstrated that the use of antiangiogenic agents in addition to chemotherapy is a valid option for the first-line treatment of advanced NSCLC, but only in the nonsquamous-cell carcinoma population. However, future clinical studies are still needed to further analyze the efficiency of antiangiogenic agent-based therapies according to subgroups of nonsquamous-histology NSCLC, namely the large-cell and adenocarcinoma histology subgroups. Moreover, biomarkers for selecting patients more suitable for the treatment with antiangiogenic agents also need to be identified in the future.
Yan et al., 2015 [54]. The Efficacy of synchronous Combination of Chemotherapy and EGFR TKIs for the First-Line Treatment of NSCLC: A Systematic Analysis.	1. Fragestellung This systematic review was conducted to compare the efficacy and safety of the synchronous combination of these two treatments with EGFR TKIs or chemotherapy alone in advanced NSCLC.
	2. Methodik Population: NSCLC patients Intervention/Komparator: combination of EGFR TKIs and chemotherapy by synchronous mode vs. EGFR TKIs or chemotherapy alone as the first-line treatment Endpunkte: OS or PFS Suchzeitraum (Aktualität der Recherche): Systematische Literaturrecherche bis 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): A total of 6 randomized controlled trials (RCTs) including 4675 patients were enrolled in the systematic review Five studies compared combination therapy with chemotherapy alone, and two studies compared combination therapy with EGFR TKI monotherapy, and one study compared the efficacy between the three groups. In the six studies, the chemotherapy regimens included gemcitabine/ cisplatin, paclitaxel/carboplatin, and gemcitabine alone,

	whereas the EGFR TKIs applied in the six studies were gefitinib and erlotinib. Qualitätsbewertung der Studien: The quality of the inclusive RCTs was evaluated according to the Cochrane Handbook
	3. Ergebnisdarstellung • The meta-analysis demonstrated that the synchronous combination group of chemotherapy and EGFR TKIs did not reach satisfactory results; there was no significant difference in overall survival (OS), time to progression (TTP) and objective response rate (ORR), compared with monotherapy (OS: HR = 1.05, 95%CI = 0.98–1.12; TTP: HR = 0.94, 95%CI = 0.89–1.00; ORR: RR = 1.07, 95%CI = 0.98–1.17), and no significant difference in OS and progression-free survival (PFS), compared with EGFR TKIs alone (OS: HR = 1.10, 95% CI = 0.83–1.46; PFS: HR = 0.86, 95% CI = 0.67–1.10). • The patients who received synchronous combined therapy presented with increased incidences of grade 3/4 anemia (RR = 1.40, 95% CI = 1.10–1.79) and rash (RR = 7.43, 95% CI = 4.56–12.09), compared with chemotherapy, grade 3/4 anemia (RR = 6.71, 95% CI = 1.25–35.93) and fatigue (RR = 9.60, 95% CI = 2.28–40.86) compared with EGFR TKI monotherapy compared with chemotherapy, grade 3/4 anemia (RR = 6.71, 95% CI = 1.25–35.93) and fatigue (RR = 9.60, 95% CI = 2.28–40.86) compared with EGFR TKI monotherapy
	4. Fazit der Autoren: The synchronous combination of chemotherapy and TKIs is not superior to chemotherapy or EGFR TKIs alone for the first-line treatment of NSCLC. 5. Hinweise durch FB Med the studies did not report the data of patients with EGFR mutations, EGFR wild-type, adenocarcinoma and squamous cell carcinoma.
Xiao et al., 2016 [52]. Efficacy of pemetrexed plus platinum doublet chemotherapy as first-line treatment for advanced nonsquamous non-small-cell-lung cancer: a systematic review and	1. Fragestellung To assess the efficacy of pemetrexed plus platinum doublet chemotherapy as first-line treatment for advanced nonsquamous non-small-cell lung cancer (NSCLC) through a trial-level meta-analysis.
	2. Methodik Population: chemotherapy-naïve advanced nonsquamous NSCLC patients Intervention/ Komparator: Trials that investigating PPC or comparing efficacy of PPC with other platinum-based doublet chemotherapy Endpunkte: ORR, PFS; OS Suchzeitraum (Aktualität der Recherche): Systematische Literaturrecherche zwischen 1990 und 2015

meta-analysis <u>Siehe auch:</u> **Zhou JG et al. 2015 [59].** Treatment on advanced NSCLC: platinum-based chemotherapy plus erlotinib or platinum-based chemotherapy alone? A systematic review and meta-analysis of randomised controlled trials	Anzahl eingeschlossene Studien/Patienten (Gesamt): A total of 2,551 patients with advanced nonsquamous NSCLC from 10 trials Qualitätsbewertung der Studien: Mittels Jadad scale.
	3. Ergebnisdarstellung Qualität der Studien: Four of the included trials did not mention the blinding of allocation clearly in the randomization process and thus had Jadad scores of 3. • Overall, a total of 1,565 patients with advanced nonsquamous NSCLC receiving PPC and 986 with other platinum-based doublet chemotherapy were included; the pooled median PFS and OS were 5.7 and 16.05 months, respectively. • A total of 680 patients from seven trials receiving PPC as first-line chemotherapy were included for ORR analysis. The pooled overall response rate was 37.8% (95% CI: 31.7%–44.3%). There was significant heterogeneity between the trials (*I*2=56.9%, *P*=0.031), and the pooled overall response was performed using a random-effects model. • All of the four RCTs reported OS data. The pooled results demonstrated that PPC significantly improved OS in comparison with other platinum-based doublet chemotherapy treatments (0.86, 95% CI: 0.77–0.97, *P*=0.01) using a fixed-effects model (*I*2=0%, *P*=0.65). • Two of four RCTs reported PFS data. The pooled hazard ratio for PFS demonstrated that PPC tends to improve PFS by giving HR 0.90(not significant), compared with other platinum-based doublet chemotherapy in advanced nonsquamous NSCLC patients. There was no significant heterogeneity between trials (*I*2=0%, *P*=0.95), and the pooled HR for PFS was performed by using fixed-effects model.
	5. Fazit der Autoren: In conclusion, pemetrexed plus platinum doublet regimen is an efficacious treatment for advanced nonsquamous NSCLC patients. Our findings support the use of pemetrexed plus platinum doublet regimens as first-line treatment in advanced nonsquamous NSCLC patients because of its potential survival benefits. Further investigation of this regimen as first-line treatment in nonsquamous NSCLC patients is still warranted.
Zhou JG et al. 2015 [59]. Treatment on advanced NSCLC: platinum-based chemotherapy plus erlotinib or platinum-based chemotherapy	1. Fragestellung to assess the potential of erlotinib plus platinum based chemotherapy relative to platinum-based chemotherapy alone for advanced non-small-cell lung cancer (NSCLC).
	2. Methodik **Population:** advanced NSCLC **Intervention**: erlotinib plus platinum-based chemotherapy **Komparator**: platinum-based chemotherapy alone

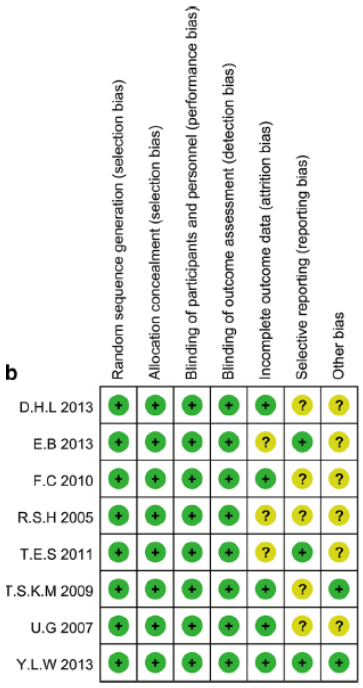
alone? A systematic review and meta-analysis of randomised controlled trials	**Endpunkte**: OS, ORR, PFS **Suchzeitraum**: 2000-2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 8 **Qualitätsbewertung der Studien:** Cochrane risk of bias. Mittlere bis gute Qualität.
<u>Siehe auch:</u> **Wang F et al., 2012 [50].** 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	3. Ergebnisdarstellung Qualität der Studien: 

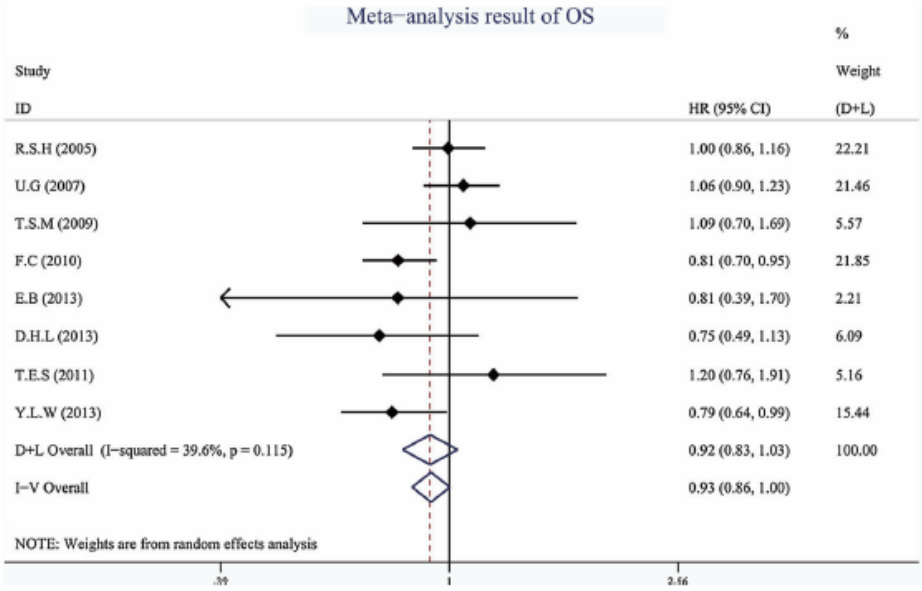
Table 1 Main characteristics of the studies

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

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

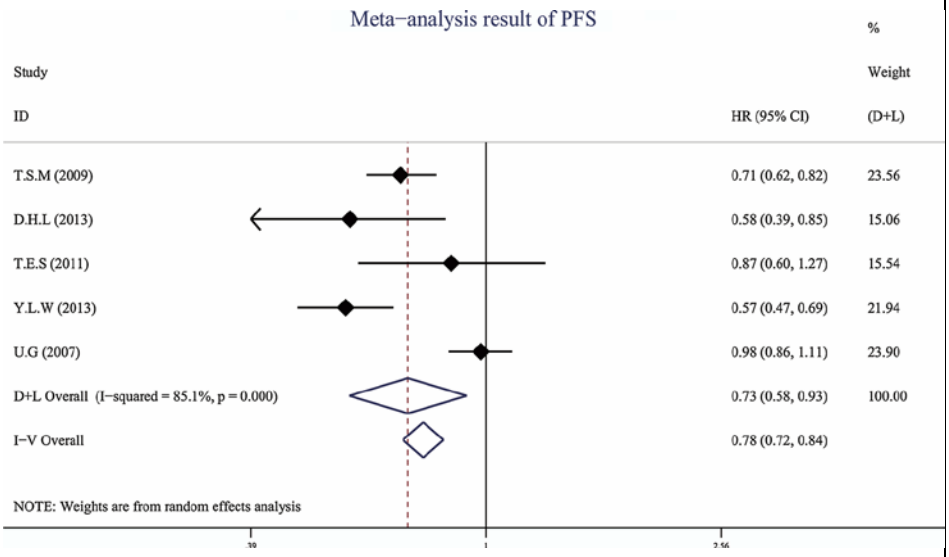
Overall survival:

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



PFS:

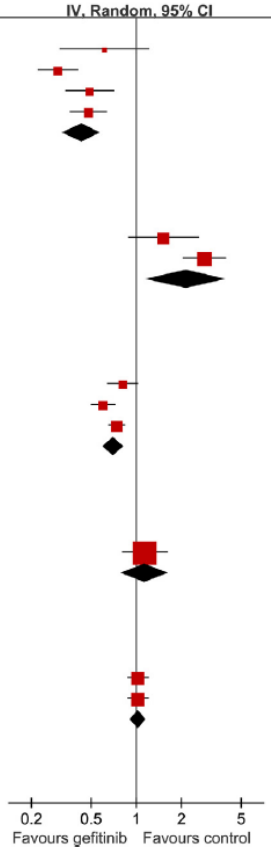
The heterogeneity test indicated that a random effect model could be selected (I^2 = 85.1 %, P<0.0001). The meta-analysis showed that the pooled HR was 0.73 (95 % CI = 0.58, 0.93), P = 0.009) and without statistical significance was identified in terms of the erlotinib platinum-based chemotherapy regimen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



4. Fazit der Autoren: In summary, the current available evidence suggests that erlotinib lacks the potential to improve OS. PFS and objective response rate could be improved by using erlotinib plus chemotherapy in patients with advanced NSCLC. Finally, smoking status and histological type are important evaluation factors that should be considered for evaluating clinical therapy and prognosis.
   This is a systematic review and meta-analysis to further evaluate the efficacy of erlotinib plus platinum-based chemotherapy for advanced NSCLC. The present systematic review and meta-analysis suggested that erlotinib combined with platinum-based chemotherapy was beneficial for advanced NSCLC patient with

	EGFR mutation compared with platinum-based chemotherapy alone regime.
Wang F et al., 2012 [50]. 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 **Sheng Z et al., 2015 [46].** EGFR-TKIs combined with chemotherapy versus EGFR-TKIs single agent as first-line treatment for molecularly selected patients with non-small cell lung cancer	1. Fragestellung To define the efficacy of gefitinib in chemotherapy-naive patients with advanced non-small cell lung cancer, we carried out a meta-analysis of randomized controlled trials.
	2. Methodik **Population:** advanced NSCLC, patients with known EGFRmutation status **Intervention:** gefitinib therapy as first-line treatment **Komparator:** conventional therapy **Endpunkte:** PFS, OS **Suchzeitraum:** bis 01/2011 **Anzahl eingeschlossene Studien/Ptienten (Gesamt):** 7 (4656) **Qualitätsbewertung der Studien:** criterions: (1) generation of allocation concealment, (2) description of drop-outs, (3) masking of randomisation, intervention, outcome assessment, (4) intention-to-treat analyses, (5) final analysis reported. Each criterionwas rated as yes, no or unclear. **Heterogenitätsuntersuchungen:** I^2
	3. Ergebnisdarstellung Characteristics of included studies References; n; Gender (%) Male / Female; Age (year); Therapy regimen; Patient selection*; Publication status; Follow-up period; Ethnicity Gefitinib monotherapy versus platinum-doublet chemotherapy [14] E 115 36.8 63.2 63.9 ± 7.7 G Yes Published 527 days Asian C 115 36.0 64.0 62.6 ± 8.9 PC ≥ 3 cycles [11] E 86 31.4 68.6 64 (34–74) G Yes Published 81 days Asian C 86 30.2 69.8 64 (41–75) CD × (3–6) cycles [16] E 609 20.5 79.5 57 (24–84) G Yes Published 5.6 months Asian C 608 20.9 79.1 57 (25–84) PC × 6 cycles [15] E 159 – – – G Yes Abstract – Asian C 150 GC × 9 cycles Gefitinib combined with systemic chemotherapy [10] E_1 365 72.1 27.9 61 (31–85) (GC + G) × 6 cycles, then G No Published 15.9 months White† E_2 365 76.7 23.3 59 (34–83) (GC + G) × 6 cycles, then G C 363 72.2 27.8 61 (33–81) GC × 6 cycles [9] E_1 347 59.9 40.1 62 (26–82) (PC + G) × 6 cycles, then G No Published >12 months White† E_2 345 57.7 42.3 61 (27–86) (PC + G) × 6 cycles, then G C 345 61.4 38.6 63 (31–85) PC × 6 cycles Gefitinib sequential therapy after chemotherapy [13] E 300 64.0 36.0 62 (25–74) PD × 3 cycles, then G No Published 2 years Asian C 298 64.1 35.5 63 (35–74) PD × 6 cycles G, continued gefitinib; PC, paclitaxel carboplatin; CD, cisplatin docetaxel; GC, gemcitabine cisplatin; PD, continued platinum-doublet chemotherapy. * Patients were selected molecularly or clinically. † Most patients. **PFS**

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



OS

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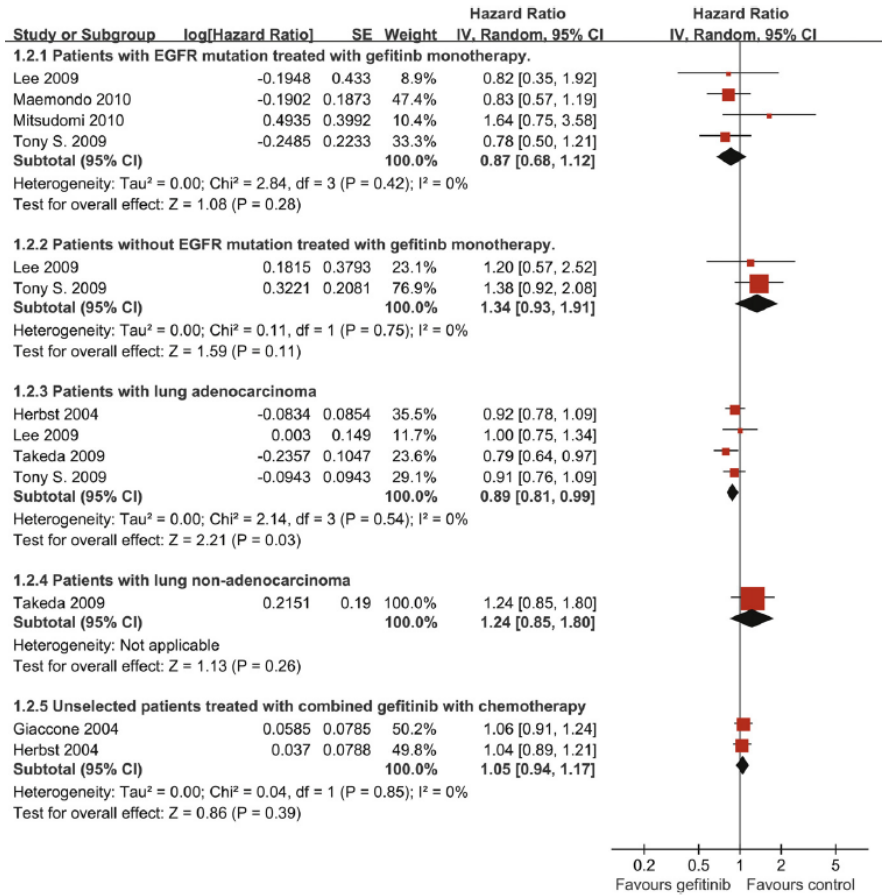


</td></tr>
<tr><td>4. Fazit der Autoren: In conclusion, first-line treatment with gefitinib conferred prolonged progression-free survival than treatment with systemic chemotherapy in a molecularly or histologically defined population of patients with non-small cell lung cancer, and improved survival in the subgroup of patients with lung adenocarcinoma.</td></tr>
<tr><td rowspan="2">Sheng Z et al., 2015 [46].

EGFR-TKIs combined with chemotherapy versus EGFR-TKIs single agent as first-line treatment for molecularly selected patients with non-small cell lung cancer

Petrelli F et al., 2012 [39].

Efficacy of</td><td>1. Fragestellung

EGFR-TKIs added to chemotherapy and EGFR-TKIs single agent have been used as first-line treatment for advanced non-small cell lung cancer patients with and without EGFR mutations. However, direct head-to-head comparison between them is still lacking. We performed indirect comparisons to assess the treatment effects of EGFR-TKIs added to chemotherapy versus EGFR-TKIs alone via common comparator of standard chemotherapy in both subgroups.</td></tr>
<tr><td>2. Methodik

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

EGFR Tyrosine Kinase Inhibitors in Patients With EGFR-Mutated Non–Small- Cell Lung Cancer: A Meta-Analysis of 13 Randomized Trials

independently assessed the quality of selected studies using the following criteria: (1) generation of allocation concealment, (2) description of dropouts, (3) masking of randomization, intervention, outcome assessment, and (4) intention-to-treat (ITT) analyses. Each criterion was rated as yes, no, or unclear.

Heterogenitätsuntersuchungen: I^2

3. Ergebnisdarstellung

Table 1 Demographic characteristics of patients

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

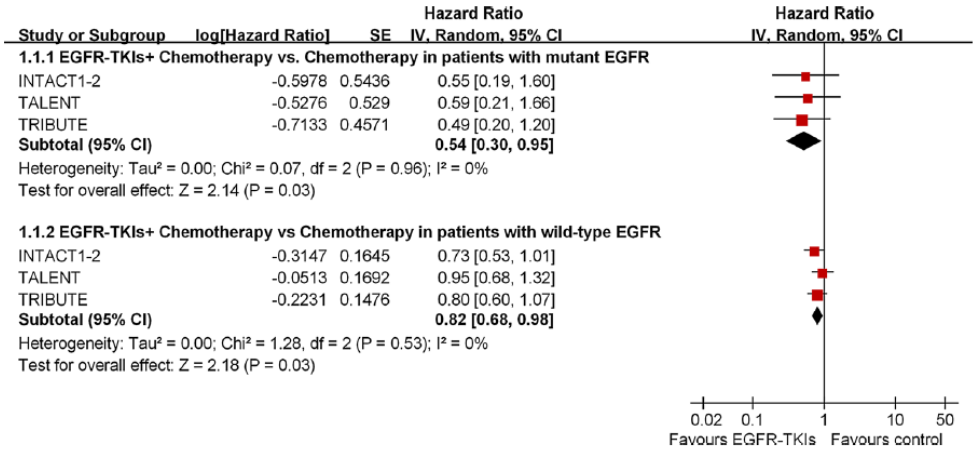
ARMS amplification refractory mutation system, *CisG* cisplatin–gemcitabine, *CP* carboplatin–paclitaxel, *CV* carboplatin–vinorelbine, *CisD* cisplatin–docetaxel, *CG* carboplatin–gemcitabine, *G* gemcitabine, *D* docetaxel, *EGFR*$^+$ presence of epidermal growth factor receptor mutation, *EGFR*$^-$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

[a] Trials reported in abstract format

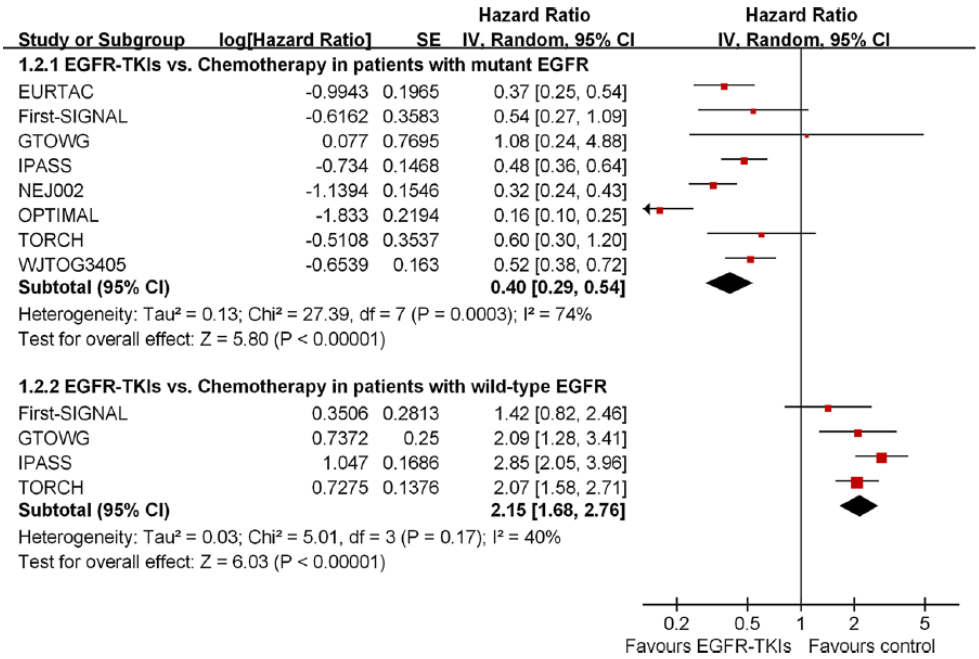
[b] Median age not available; mean age calculated instead

PFS

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

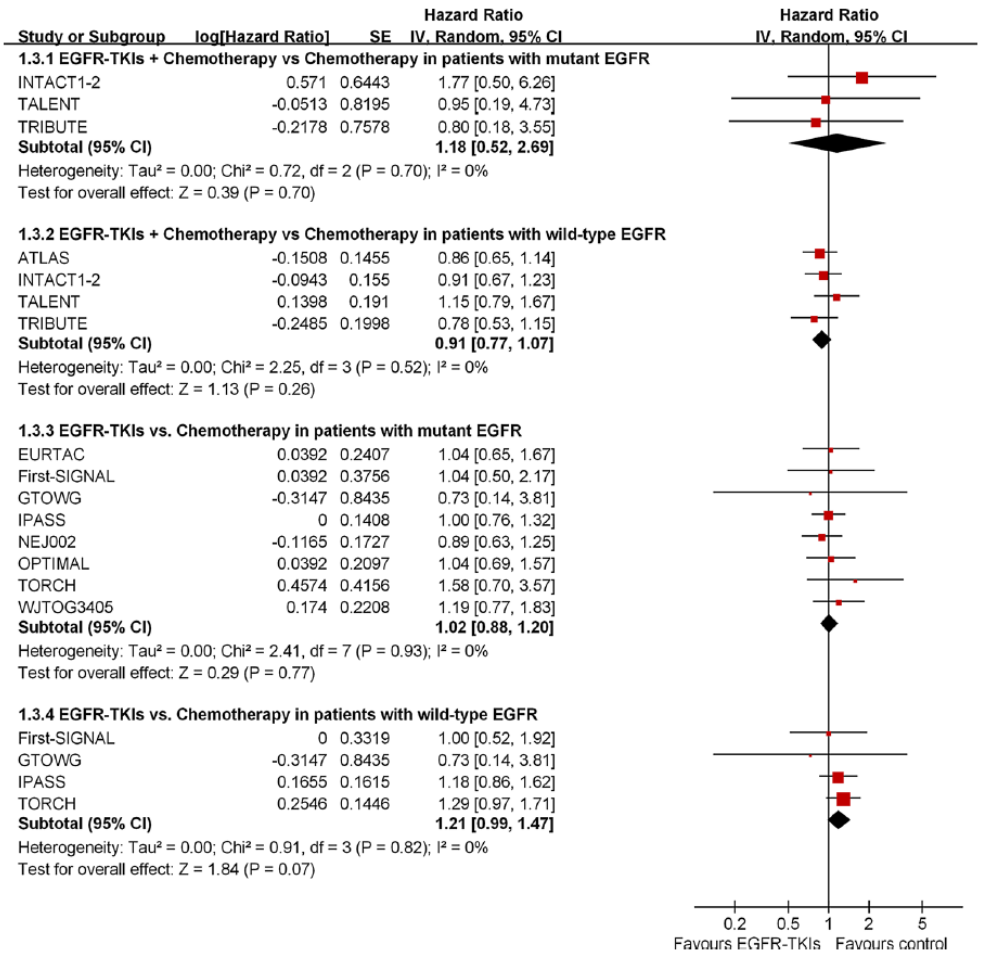


Meta-analysis of the treatment effects (**EGFR-TKIs single agent versus chemotherapy**) on progressionfree survival (PFS) in previously untreated advanced NSCLC patients with and without EGFR mutations. HR hazard ratio, CI 95 % confidence interval. Random, random-effects model

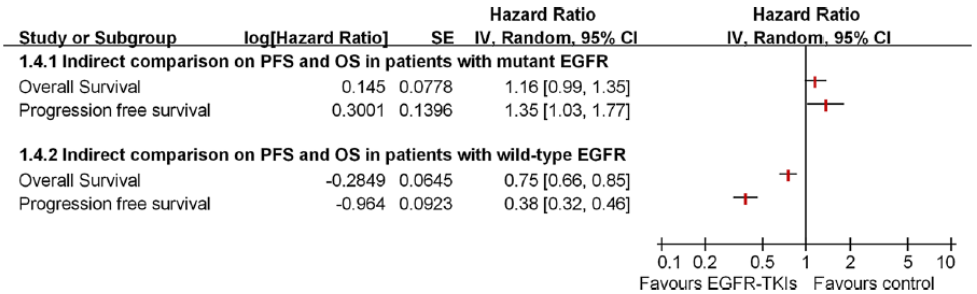


OS

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



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



4. Fazit der Autoren: In summary, addition of chemotherapy to EGFR-TKIs as first-line treatment did confer an additive benefit over EGFR-TKIs alone in patients with wild-type EGFR tumors, but was inferior to EGFR-TKIs alone in patients with mutant EGFR tumors.

Petrelli F et al., 2012 [39].

Efficacy of

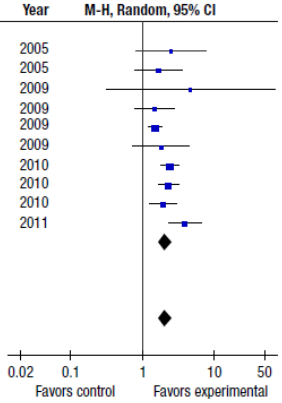
1. Fragestellung

Advanced non–small-cell lung cancer (NSCLC) harboring activating mutations of epidermal growth factor receptor (EGFR) are particularly sensitive to tyrosine kinase inhibitors (TKIs), namely erlotinib and gefitinib. The purpose of

EGFR Tyrosine Kinase Inhibitors in Patients With EGFR-Mutated Non–Small- Cell Lung Cancer: A Meta-Analysis of 13 Randomized Trials **OuYang P-Y et al., 2013 [38].** Combination of EGFR-TKIs and Chemotherapy as First-Line Therapy for Advanced NSCLC: A Meta-Analysis	this metaanalysis was to evaluate the benefit of EGFR TKIs in EGFR-mutated NSCLCs.
	2. Methodik **Population:** previously <u>untreated</u> or pretreated patients with advanced/ metastatic NSCLC subpopulation of patients carrying an activating *EGFR* mutation (mainly exon 19 deletions or exon 21 point mutations) **Intervention:** gefitinib or erlotinib (either in the first-line setting or in subsequent treatment settings) **Komparator:** chemotherapy, placebo, or best supportive care **Endpunkte:** objective response rate, PFS, and OS **Suchzeitraum:** bis 08/2011 **Anzahl eingeschlossene Studien/Ptienten (Gesamt):** 14 (10433) • N=8 first line • N=1 maintenance • N=4 second line **Qualitätsbewertung der Studien:** keine Angaben **Heterogenitätsuntersuchungen:** I^2 statistic
	3. Ergebnisdarstellung *Studiencharakteristika vgl. Anlage* **ORR (all trials and treatment line)**

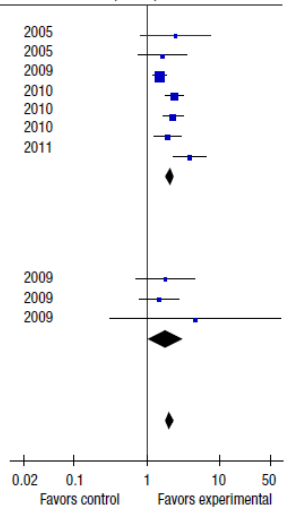
A

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



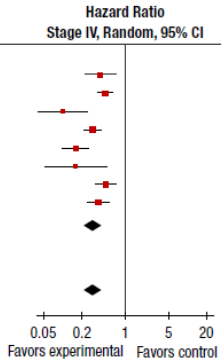
B

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



PFS (all trials)

Study or Subgroup	Log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
7.2.1 meta-analysis of HR for PFS					
Bell 2005	–0.916	0.288	11.9%	0.40 [0.23, 0.70]	2005
Mok 2009	–0.734	0.147	16.2%	0.48 [0.36, 0.64]	2009
Cappuzzo 2010	–2.303	0.468	7.5%	0.10 [0.04, 0.25]	2010
Maemondo 2010	–1.204	0.159	15.9%	0.30 [0.22, 0.41]	2010
Zhou 2010	–1.833	0.244	13.2%	0.16 [0.10, 0.26]	2010
Douillard 2010	–1.833	0.582	5.6%	0.16 [0.05, 0.50]	2010
Mitsudomi 2010	–0.715	0.191	14.9%	0.49 [0.34, 0.71]	2010
Rosell EURTAC 2011	–0.994	0.196	14.7%	0.37 [0.25, 0.54]	2011
Subtotal (95% CI)			**100.0%**	**0.30 [0.22, 0.42]**	
Heterogeneity: $\tau^2 = 0.15$; $\chi^2 = 28.21$, df = 7 ($P = 0.0002$); $I^2 = 75\%$					
Test for overall effect: Z = 7.19 ($P < 0.0001$)					
Total (95% CI)			**100.0%**	**0.30 [0.22, 0.42]**	
Heterogeneity: $\tau^2 = 0.15$; $\chi^2 = 28.21$, df = 7 ($P = 0.0002$); $I^2 = 75\%$					
Test for overall effect: Z =7.19 ($P < 0.0001$)					
Test for subgroup differences: Not applicable					



OS

<table>
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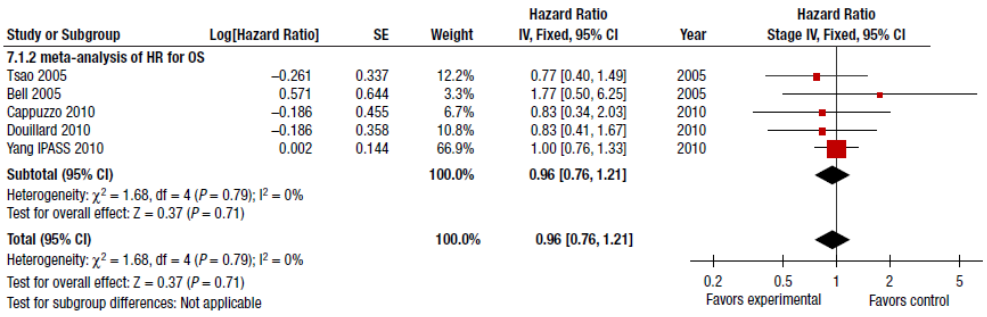


</td></tr>
<tr><td>4. Fazit der Autoren: In conclusion, NSCLCs harboring EGFR mutations derive greater benefit from erlotinib or gefitinib than from chemotherapy, either in first-line or subsequent lines of therapy. These agents double the chance of an objective response and reduce the risk of progression by about 70% but do not increase OS. These results are likely to be influenced by crossover treatments that formally abrogate any survival gain. The paradigm of up-front treatment in this setting has to be shifted from platinum-based chemotherapy to molecular targeted therapies. All patients affected by NSCLC with EGFR mutation–positive analysis in fact should be offered the opportunity to be treated with an EGFR TKI (according to the labeled indications) during the natural course of the disease.

5. Hinweise der FBMed
Keine Angaben zur methodischen Bewertung der Primärstudien</td></tr>
<tr><td rowspan="3">OuYang P-Y et al., 2013 [38].
Combination of EGFR-TKIs and Chemotherapy as First-Line Therapy for Advanced NSCLC: A Meta-Analysis
Normando SRC et al, 2015 [37].
Cumulative meta-analysis of epidermal growth factor receptor-tyrosine kinase inhibitors</td><td>1. Fragestellung
Controversy continues regarding the role of the addition of EGFR–TKIs in patients receiving chemotherapy. Therefore, we conducted this meta-analysis to comprehensively estimate the treatment effect of the combined regimen on PFS and overall survival (OS) based on characteristics of patients.</td></tr>
<tr><td>2. Methodik

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

as first-line therapy in metastatic non-small-cell lung cancer

Siehe auch:

Guetz et al. [21]

und

Zhou et al. [58]

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

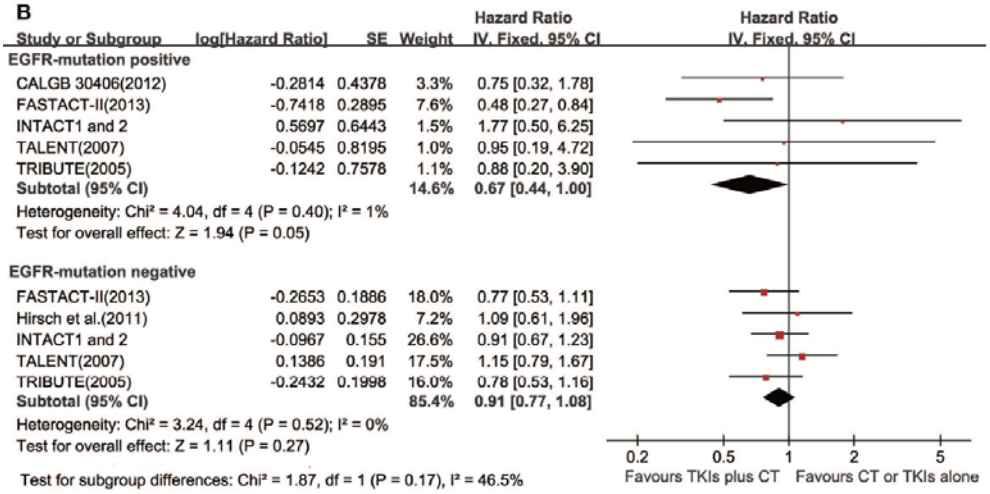
Trials(year)	TKIs	chemotherapy (dose*cycles)	Patients analyzed	Median age (range)	Female	Race (% Asian)	Never/light smoker	EGFR mutation positive
FASTACT(2009) [13]	E†	DDP(75 mg/m^2,d1)/CBP(AUC=5,d1)+GEM1250(mg/m^2,d1,8),q4w*6	76vs78	57.5(33–79) vs57.0(27–79)	22vs24	93vs95	24vs28	2vs5
FASTACT–II (2013) [14]	E†	DDP(75 mg/m^2,d1)/CBP(AUC=5,d1)+GEM1250(mg/m^2,d1,8),q4w*6	226vs225	59.0(31–96)vs57.3(37–88)	94vs85	100vs100	112vs107	49vs48
INTACT 1(2004) [7] [17]	G‡	DDP(80 mg/m^2,d1)+GEM(1250 mg/m^{2}d1,8),q3w*6	365vs363	59(34–83)vs61(33–81)	85vs101	1.6vs0.8	NA	23vs9[&]
INTACT 2(2004) [8] [17]	G‡	CBP(AUC=6)+TAX(225 mg/m^2),q3w*6	345vs345	61(27–86)vs63(31–85)	146vs133	NA	NA	
TALENT(2007) [9]	E	DDP(80 mg/m^2,d1)+GEM(1250 mg/m^{2}d1,8),q3w*6	580vs579	61(26–82)vs60(28–84)	125vs142	3vs4	8vs10	NA
TRIBUTE(2005) [10] [18]	E	CBP(AUC=6)+TAX(200 mg/m^2),q3w*6	539vs540	63(24–84)vs63(26–84)	217vs207	3.9vs2.4	72vs44	15vs14
CALGB30406(2012) [12]	E	CBP(AUC=6)+TAX(200 mg/m^2),q3w*6	100vs81	60(34–81)vs58(32–78)	58vs49	8vs6	100vs81	33vs33
Hirsch et al.2011 [11]	E	CBP(AUC=6)+TAX(200 mg/m^2),q3w*4	71vs72	NA	31vs44	6vs12	NA	6vs9

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

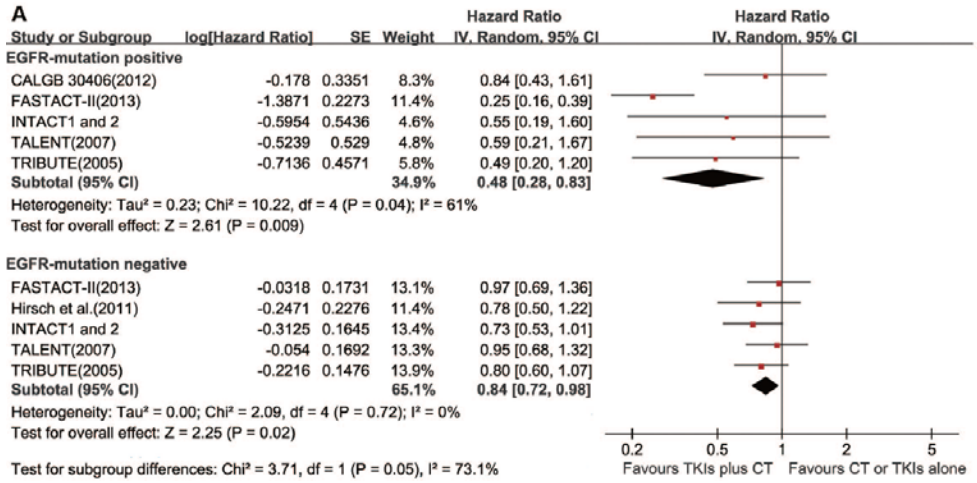
OS

Effect of the Combined Regimen on PFS and OS in Selected Patients by EGFR-Mutation Status Survival data of EGFR-mutation positive patients was only available in the FASTACT–II [14], INTACT 1 and 2 [17], TALENT [9], TRIBUTE [18] and CALGB30406 [12]. Estimates of PFS and OS in EGFR-mutation negative patients could only be calculated in the FASTACT–II [14], INTACT 1 and 2 [17], TALENT [9], TRIBUTE [18] and trial by Hirsch et al [11]. In the EGFR-mutation

positive cohort, the combined regimen was superior over chemotherapy or TKIs monotherapy with a significant improvement in PFS (HR= 0.48, 95% CI 0.28–0.83, P = 0.009; Figure 3a). Interestingly, the combined regimen also showed significant PFS benefit in the EGFR-mutation negative cohort, compared with chemotherapy or TKIs monotherapy (HR =0.84, 95% CI 0.72–0.98, P = 0.02; Figure 3a). Certainly, the magnitude of PFS improvement resulted from the combined regimen in the EGFR-mutation positive cohort was marginally larger than that in the EGFR-mutation negative cohort (P = 0.05). In terms of OS, the combined regimen marginally enhanced OS of EGFR-mutation positive patients (HR =0.67, 95% CI 0.44–1.00, P = 0.05), but not EGFR-mutation negative patients (HR =0.91, 95% CI 0.77–1.08, P =0.27).



PFS



4.Fazit der Autoren: Unfortunately, the combined regimen had no significant impact on overall survival, irrespective of ethnicity, dose schedules or EGFR-mutation status. Severe anorexia (RR = 2.01, 95% CI 1.11–3.63; P = 0.02) and diarrhea (RR = 2.70, 95% CI 1.94–3.76; P<0.001) were more frequent in the combined regimen arm. This strategy of combining EGFR–TKIs and chemotherapy deserved to be considered in the future, although it is not approved for advanced NSCLC at the moment.

Normando SRC

1. Fragestellung

We carried out a meta-analysis to evaluate the benefit of epidermal growth

et al, 2015 [37]. Cumulative meta-analysis of epidermal growth factor receptor-tyrosine kinase inhibitors as first-line therapy in metastatic non-small-cell lung cancer <u>Siehe auch:</u> **Guetz et al. [21]** **und** **Zhou et al. [58]** **Liang W et al,**	factor-tyrosine kinase inhibitors (EGFR-TKI) over the standard first-line platinum-based chemotherapy for metastatic non-small-cell lung cancer (NSCLC).
	2. Methodik **Population:** advanced NSCLC, stages IIIB or IV **Intervention:** standard first-line platinum-based chemotherapy **Komparator:** EGFR-TKI → We excluded studies that used EGFR inhibitors as second-line therapy as well as studies in which the control group received only placebo. **Endpunkte:** OS, PFS **Suchzeitraum:** 2009 - 2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 8 **Qualitätsbewertung der Studien:** Jadad **Heterogenitätsuntersuchungen:** χ2-test
	3. Ergebnisdarstellung All studies were randomized, open, controlled, and phase III trials. A formal review of the eight studies indicated that the quality was high (Jadad score ≥ 3).

2014 [27].

Network Meta-Analysis of Erlotinib, Gefitinib, Afatinib and Icotinib in Patients with Advanced Non-Small-Cell Lung Cancer Harboring EGFR Mutations

Table 1 Population characteristics of the studies

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

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

PFS

Significant differences between the two arms were found when PFS were compared, favoring the EGFR-TKI group [HR = 0.266 (95% CI = 0.20–0.35), P< 0.0001]. Heterogeneity between the analyzed arms was absent (Q = 9.402, P= 0.225). This benefit was sustained in all the subgroups analyzed (Table 2). The analyses of PFS of the different mutations, del Exon 19 [HR = 0.187 (95% CI = 0.131–0.267), P <0.0001, Q =4.436 P= 0.35] and L858R-exon 21 [HR = 0.345 (95% CI = 0.181–0.659), P < 0.001, Q = 0.995 P =0.911], are shown in Figs 3 and 4, respectively. Two studies (IPASS/First-SIGNAL) included patients without the

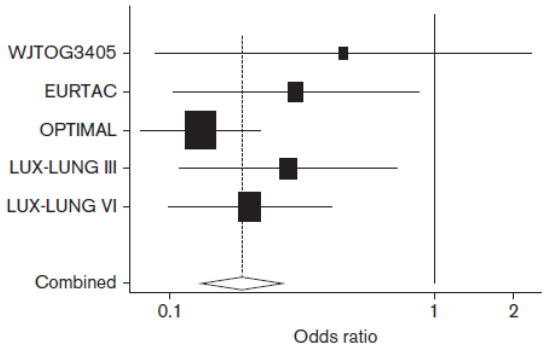
EGFR mutation, where subgroup analysis was carried out according to the status of the EGFR mutation with respect to PFS. Among the patients without the EGFR mutation (n= 230), there was no PFS gain compared with the control group [HR = 1.170 (95% CI = 0.48–2.83), P =0728], (Q =0.008, P= 0.931) (Fig.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

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

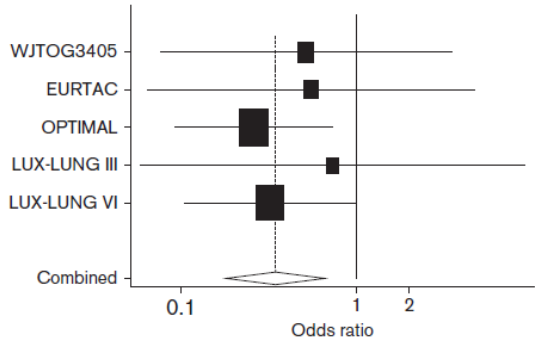
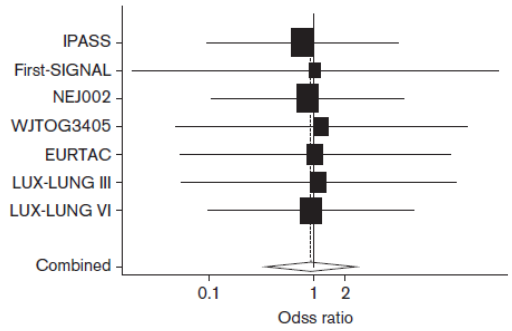
Subgroup	Study	HR (95% CI)	HR bundled (95% CI)
Smokers	WJTOG3405	0.57 (0.29–1.12)	0.29 (0.14–0.62)
	OPTIMAL	0.21 (0.09–0.49)	
	EURTAC	0.56 (0.15–2.15)	
	LUX-LUNG III	1.04 (0.54–1.98)	
	LUX-LUNG VI	0.46 (0.22–1.00)	
Nonsmokers	WJTOG3405	0.46 (0.28–0.73)	0.20 (0.15–0.27)
	OPTIMAL	0.14 (0.08–0.25)	
	EURTAC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

CI, confidence interval; HR, hazard ratio.

Fig. 3



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

	Fig. 4  Progression-free survival in patients with the EGFR mutation (L858R-exon 21 mutation). Odds ratio = 0.345 (0.181–0.659, $P < 0.001$); heterogeneity test: $Q = 0.995$ $P = 0.911$. EGFR, epidermal growth factor receptor. **OS** For OS analysis, an updated WJTOG3405 study was used, available only in abstract form presented at a conference [19]. The other studies were analyzed from full articles mentioned previously. There was no significant difference between the control group and the EGFRTKI in the population with the EGFR mutation [HR = 0.946 (95% CI = 0.35–2.53), P =0.912] (Fig. 7). There was no heterogeneity in the results (Q = 0.073, P = 1.0). Similarly, there was no difference in the OS in the population without any EGFR mutation [HR = 1.16 (95% CI 0.09–14.4), P =0.9] (Fig. 8). There was no significant difference in terms of OS in the cumulative meta-analysis. **Fig. 7**  Overall survival in all groups. Odds ratio = 0.946 (0.353–2.538, $P = 0.91$); heterogeneity test: $Q = 0.073$ $P = 1.0$.
	4. Fazit der Autoren: The cumulative meta-analysis of the studies showed that, since 2011 (OPTIMAL study), the PFS benefit in the EGFR-TKI arm was statistically significantly longer. Toxicity values greater than or equal to 3 in the most prevalent EGFR-TKI group included skin rash, diarrhea, and increased aminotransferase. EGFR-TKI treatment significantly extends PFS, with acceptable toxicities than platinum-based chemotherapy. Thus, they should be considered as the first choice in the first-line treatment for patients with NSCLC and with the EGFR mutation
Liang W et al, 2014 [27]. Network Meta-	1. Fragestellung Several EGFR-tyrosine kinase inhibitors (EGFR-TKIs) including erlotinib, gefitinib, afatinib and icotinib are currently available as treatment for patients with advanced

Analysis of Erlotinib, Gefitinib, Afatinib and Icotinib in Patients with Advanced Non-Small-Cell Lung Cancer Harboring EGFR Mutations

Ellis PM et al. 2015 [13].

Use of the epidermal growth factor receptor inhibitors gefitinib, erlotinib, afatinib, dacomitinib, and icotinib in the treatment of non-small-cell lung cancer: a systematic review

non-small-cell lung cancer (NSCLC) who harbor EGFR mutations. However, no head to head trials between these TKIs in mutated populations have been reported, which provides room for indirect and integrated comparisons.

2. Methodik

Population: advanced NSCLC, patients with known EGFRmutation status
Intervention: erlotinib, gefitinib, afatinib and icotinib
Komparator: - interventionen gegenseitig –
Standard chemotherapy was defined as platinum-based third generation doublets for first-line treatments or pemetrxed/ doctaxel for second-line treatments.
Endpunkte: overall survival (OS), progression free survival (PFS), objective response rate (ORR) and adverse events (rash, grade 3–4 rash, diarrhea, grade 3–4 diarrhea)
Suchzeitraum: bis 03/2013
Anzahl eingeschlossene Studien/Ptienten (Gesamt): 12
Qualitätsbewertung der Studien: Jadad
Heterogenitätsuntersuchungen: forest plot and the inconsistency statistic (I^2)

3. Ergebnisdarstellung

Table 1. Characteristics of included studies regarding TKIs.

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

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

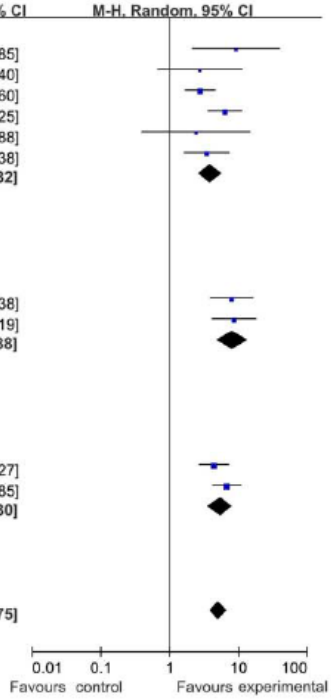
Table 2. Pooled Weighted Outcomes and Direct Meta-Analysis.

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

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

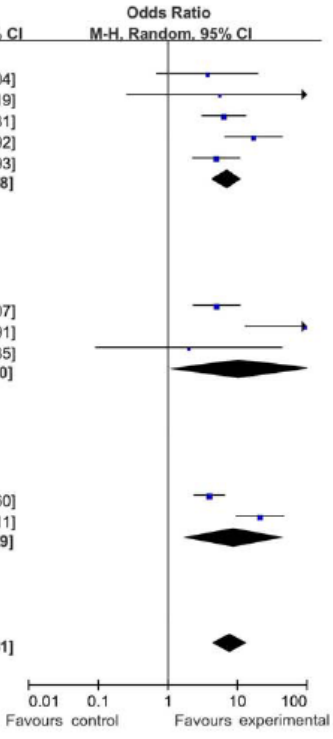
ORR

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Gefitinib						
FIRST SIGNAL	22	26	6	16	3.4%	9.17 [2.11, 39.85]
INTEREST	8	19	4	19	3.5%	2.73 [0.65, 11.40]
IPASS	94	132	61	129	15.5%	2.76 [1.65, 4.60]
NEJ002	84	114	35	114	13.6%	6.32 [3.55, 11.25]
V 15-32	6	9	5	11	2.3%	2.40 [0.39, 14.88]
WJTOG3405	36	58	19	59	9.7%	3.44 [1.61, 7.38]
Subtotal (95% CI)		**358**		**348**	**48.0%**	**3.94 [2.66, 5.82]**
Total events	250		130			
Heterogeneity: Tau² = 0.05; Chi² = 6.37, df = 5 (P = 0.27); I² = 22%						
Test for overall effect: Z = 6.86 (P < 0.00001)						
1.1.2 Erlotinib						
EUTRAC	50	86	13	87	10.2%	7.91 [3.82, 16.38]
OPTIMAL	68	82	26	72	9.9%	8.59 [4.06, 18.19]
Subtotal (95% CI)		**168**		**159**	**20.1%**	**8.23 [4.88, 13.88]**
Total events	118		39			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 7.91 (P < 0.00001)						
1.1.3 Afatinib						
LUX-LUNG3	129	230	26	115	15.6%	4.37 [2.63, 7.27]
LUX-LUNG6	182	242	38	122	16.4%	6.71 [4.14, 10.85]
Subtotal (95% CI)		**472**		**237**	**31.9%**	**5.46 [3.59, 8.30]**
Total events	311		64			
Heterogeneity: Tau² = 0.03; Chi² = 1.43, df = 1 (P = 0.23); I² = 30%						
Test for overall effect: Z = 7.93 (P < 0.00001)						
Total (95% CI)		**998**		**744**	**100.0%**	**5.07 [3.81, 6.75]**
Total events	679		233			
Heterogeneity: Tau² = 0.07; Chi² = 13.94, df = 9 (P = 0.12); I² = 35%						
Test for overall effect: Z = 11.13 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.96, df = 2 (P = 0.08), I² = 59.7%						



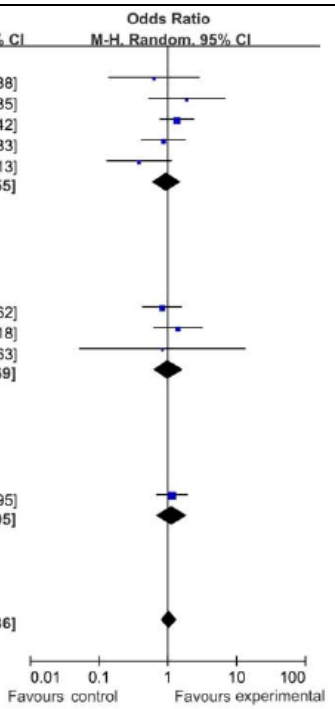
1-year PFS

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 Gefitinib						
FIRST SIGNAL	9	26	2	16	6.8%	3.71 [0.69, 20.04]
INTEREST	2	19	0	19	2.7%	5.57 [0.25, 124.19]
IPASS	46	132	10	129	14.0%	6.37 [3.04, 13.31]
NEJ002	50	114	5	114	11.9%	17.03 [6.46, 44.92]
WJTOG3405	34	86	10	86	13.5%	4.97 [2.26, 10.93]
Subtotal (95% CI)		**377**		**364**	**49.0%**	**7.00 [4.23, 11.58]**
Total events	141		27			
Heterogeneity: Tau² = 0.05; Chi² = 4.63, df = 4 (P = 0.33); I² = 14%						
Test for overall effect: Z = 7.58 (P < 0.00001)						
1.2.2 Erlotinib						
EUTRAC	34	86	10	87	13.5%	5.03 [2.29, 11.07]
OPTIMAL	47	82	1	72	5.3%	95.34 [12.63, 719.91]
TITAN	6	7	3	4	2.7%	2.00 [0.09, 44.35]
Subtotal (95% CI)		**175**		**163**	**21.6%**	**10.62 [1.07, 105.70]**
Total events	87		14			
Heterogeneity: Tau² = 3.09; Chi² = 9.11, df = 2 (P = 0.01); I² = 78%						
Test for overall effect: Z = 2.02 (P = 0.04)						
1.2.3 Afatinib						
LUX-LUNG3	117	230	24	115	16.0%	3.93 [2.34, 6.60]
LUX-LUNG6	136	242	7	122	13.4%	21.08 [9.43, 47.11]
Subtotal (95% CI)		**472**		**237**	**29.4%**	**8.84 [1.65, 47.29]**
Total events	253		31			
Heterogeneity: Tau² = 1.35; Chi² = 12.29, df = 1 (P = 0.0005); I² = 92%						
Test for overall effect: Z = 2.55 (P = 0.01)						
Total (95% CI)		**1024**		**764**	**100.0%**	**7.83 [4.50, 13.61]**
Total events	481		72			
Heterogeneity: Tau² = 0.43; Chi² = 25.46, df = 9 (P = 0.003); I² = 65%						
Test for overall effect: Z = 7.29 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.18, df = 2 (P = 0.91), I² = 0%						



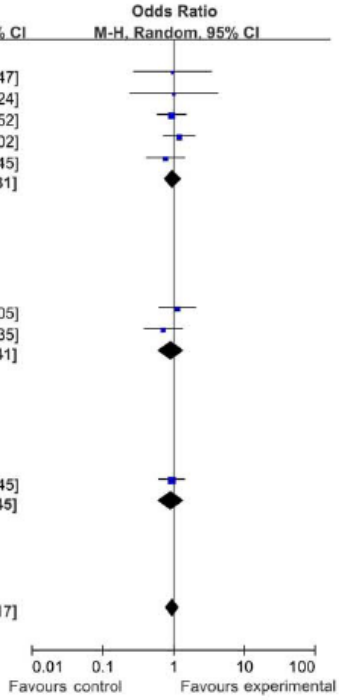
1-year OS

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.3.1 Gefitinib						
FIRST SIGNAL	19	26	13	16	3.1%	0.63 [0.14, 2.88]
INTEREST	11	19	8	19	4.3%	1.89 [0.52, 6.85]
IPASS	106	132	97	129	20.9%	1.34 [0.75, 2.42]
NEJ002	97	114	99	114	12.8%	0.86 [0.41, 1.83]
WJTOG3405	74	86	81	86	6.0%	0.38 [0.13, 1.13]
Subtotal (95% CI)		**377**		**364**	**47.1%**	**0.95 [0.58, 1.55]**
Total events	307		298			
Heterogeneity: Tau² = 0.08; Chi² = 5.45, df = 4 (P = 0.24); I² = 27%						
Test for overall effect: Z = 0.20 (P = 0.84)						
1.3.2 Erlotinib						
EUTRAC	61	86	65	87	15.9%	0.83 [0.42, 1.62]
OPTIMAL	69	82	57	72	10.6%	1.40 [0.61, 3.18]
TITAN	5	7	3	4	0.9%	0.83 [0.05, 13.63]
Subtotal (95% CI)		**175**		**163**	**27.5%**	**1.01 [0.61, 1.69]**
Total events	135		125			
Heterogeneity: Tau² = 0.00; Chi² = 0.96, df = 2 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.05 (P = 0.96)						
1.3.3 Afatinib						
LUX-LUNG6	194	242	95	122	25.4%	1.15 [0.68, 1.95]
Subtotal (95% CI)		**242**		**122**	**25.4%**	**1.15 [0.68, 1.95]**
Total events	194		95			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
Total (95% CI)		**794**		**649**	**100.0%**	**1.04 [0.79, 1.36]**
Total events	636		518			
Heterogeneity: Tau² = 0.00; Chi² = 6.60, df = 8 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.27 (P = 0.79)						
Test for subgroup differences: Chi² = 0.27, df = 2 (P = 0.87), I² = 0%						

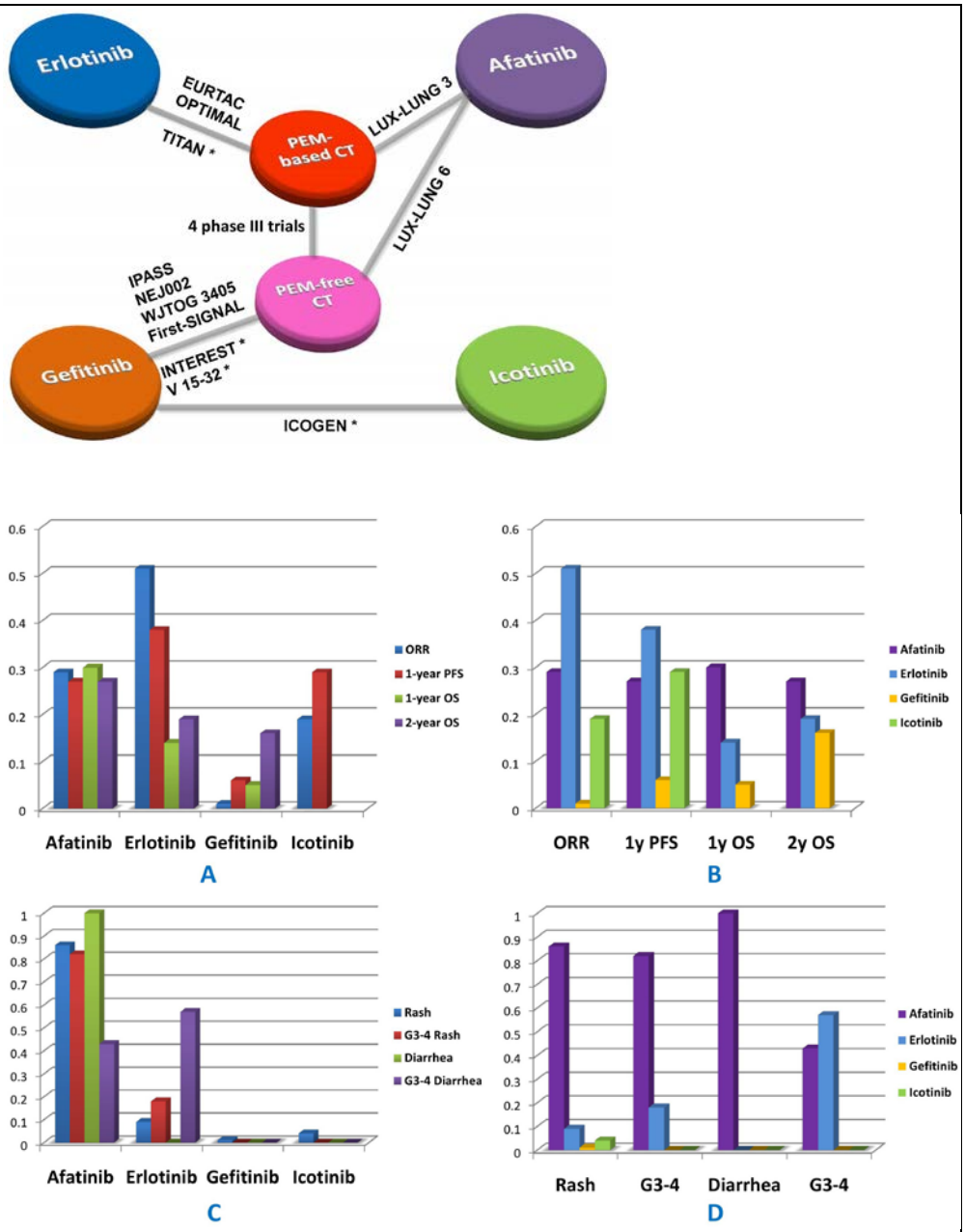


2-year OS

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.4.1 Gefitinib						
FIRST SIGNAL	16	26	10	16	2.8%	0.96 [0.27, 3.47]
INTEREST	5	19	5	19	2.2%	1.00 [0.24, 4.24]
IPASS	57	132	58	129	19.2%	0.93 [0.57, 1.52]
NEJ002	66	114	61	114	16.7%	1.19 [0.71, 2.02]
WJTOG3405	55	86	60	86	11.3%	0.77 [0.41, 1.45]
Subtotal (95% CI)		**377**		**364**	**52.2%**	**0.97 [0.72, 1.31]**
Total events	199		194			
Heterogeneity: Tau² = 0.00; Chi² = 1.15, df = 4 (P = 0.89); I² = 0%						
Test for overall effect: Z = 0.19 (P = 0.85)						
1.4.2 Erlotinib						
EUTRAC	37	86	35	87	12.5%	1.12 [0.61, 2.05]
OPTIMAL	41	82	42	72	11.3%	0.71 [0.38, 1.35]
Subtotal (95% CI)		**168**		**159**	**23.8%**	**0.91 [0.58, 1.41]**
Total events	78		77			
Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 1 (P = 0.31); I² = 1%						
Test for overall effect: Z = 0.44 (P = 0.66)						
1.4.3 Afatinib						
LUX-LUNG6	109	242	57	122	24.0%	0.93 [0.60, 1.45]
Subtotal (95% CI)		**242**		**122**	**24.0%**	**0.93 [0.60, 1.45]**
Total events	109		57			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.30 (P = 0.76)						
Total (95% CI)		**787**		**645**	**100.0%**	**0.95 [0.76, 1.17]**
Total events	386		328			
Heterogeneity: Tau² = 0.00; Chi² = 2.24, df = 7 (P = 0.95); I² = 0%						
Test for overall effect: Z = 0.50 (P = 0.62)						
Test for subgroup differences: Chi² = 0.07, df = 2 (P = 0.96), I² = 0%						



Network established for multiple treatment comparisons


Erlotinib
Afatinib
EURTAC
OPTIMAL
TITAN *
PEM-based CT
LUX-LUNG 3
LUX-LUNG 6
4 phase III trials
IPASS
NEJ002
WJTOG 3405
First-SIGNAL
PEM-free CT
Gefitinib
INTEREST *
V 15-32 *
Icotinib
ICOGEN *
ORR
1-year PFS
1-year OS
2-year OS
Afatinib Erlotinib Gefitinib Icotinib
A
Afatinib
Erlotinib
Gefitinib
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ORR 1y PFS 1y OS 2y OS
B
Rash
G3-4 Rash
Diarrhea
G3-4 Diarrhea
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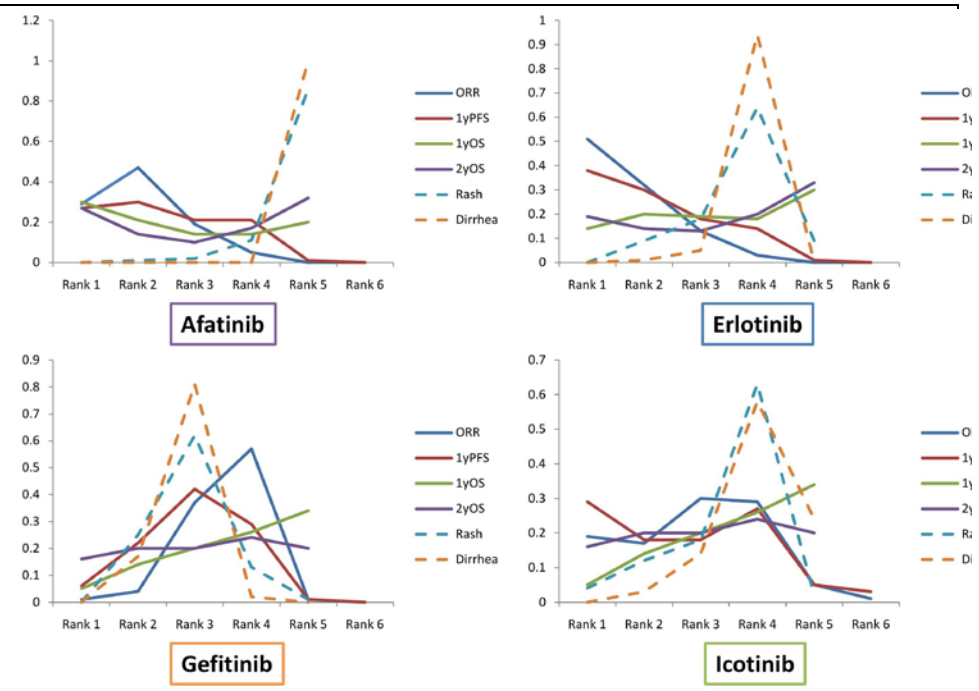


4. Fazit der Autoren

Twelve phase III RCTs that investigated EGFR-TKIs involving 1821 participants with EGFR mutation were included. For mutant patients, the weighted pooled ORR and 1-year PFS of EGFR-TKIs were significant superior to that of standard chemotherapy (ORR: 66.6% vs. 30.9%, OR 5.46, 95%CI 3.59 to 8.30, P,0.00001; 1-year PFS: 42.9% vs. 9.7%, OR 7.83, 95%CI 4.50 to 13.61; P,0.00001) through direct meta-analysis. In the network meta-analyses, no statistically significant differences in efficacy were found between these four TKIs with respect to all outcome measures. Trend analyses of rank probabilities revealed that the cumulative probabilities of being the most efficacious treatments were (ORR, 1-year PFS, 1-year OS, 2-year OS): erlotinib (51%, 38%, 14%, 19%), gefitinib (1%, 6%, 5%, 16%), afatinib (29%, 27%, 30%, 27%) and icotinib (19%, 29%, NA, NA), respectively. However, afatinib and erlotinib showed significant severer rash and diarrhea compared with gefitinib and icotinib. The current study indicated that erlotinib, gefitinib, afatinib and icotinib shared equivalent efficacy but presented different efficacy-toxicity pattern for EGFR-mutated patients. Erlotinib and afatinib revealed potentially better efficacy but significant higher toxicities compared with gefitinib and icotinib.

5. Hinweis der FBMed

Icotinib ist in Deutschland für NSCLC nicht zugelassen. Seine Verwendung in der Netzwerkanalyse kann die Ergebnisse der anderen, in Deutschland zugelassenen Wirkstoffe beeinflusst haben.

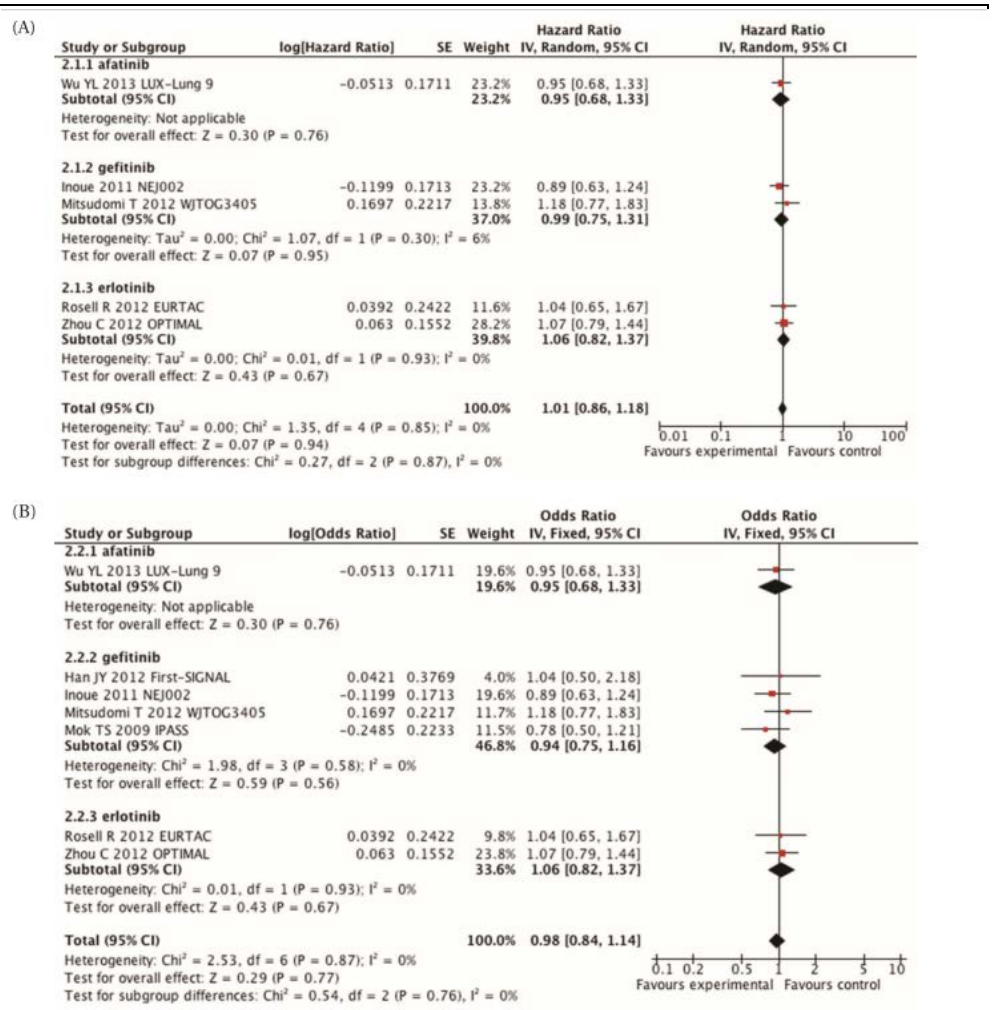
Ellis PM et al. 2015 [13].

1. Fragestellung

This systematic review addresses the use of epidermal growth factor receptor (egfr) inhibitors in three populations of advanced non-small-cell lung cancer

Use of the epidermal growth factor receptor inhibitors gefitinib, erlotinib, afatinib, dacomitinib, and icotinib in the treatment of non-small-cell lung cancer: a systematic review **Yu Y et al., 2012 [55].** Non-platinum regimens of gemcitabine plus docetaxel versus platinum-based regimens in first-line treatment of advanced non-small cell lung cancer: a meta-analysis on 9 randomized controlled trials	(nsclc) patients—unselected, selected, and molecularly selected—in three treatment settings: first line, second line, and maintenance.
	2. Methodik **Population:** NSCLC; patients—unselected, selected, and molecularly selected. In the unselected group, any nsclc patient was allowed to participate in the trial as long as the other trial eligibility criteria were met in the absence of molecular testing. In the clinically selected group, patients were selected based on clinical characteristics predictive of an EGFR mutation such as Asian ethnicity, adenocarcinoma histology, female sex, smoking status, or age. In the mo lecularly selected group, patients were included if their tumours tested positive for an EGFR mutation. **Intervention:** EGFR-TKI (first line, second line, and maintenance) **Komparator:** nicht präspezifiziert **Endpunkte:** nicht präspezifiziert **Suchzeitraum:** 2006 - 3/2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 96, nur RCT **Qualitätsbewertung der Studien:** nicht durchgeführt **Heterogenitätsuntersuchungen:** chi-Quadrat , I^2 **Ergebnisdarstellung** Überwiegend qualitatives Review
	3. **Ergebnisdarstellung** Hinweis: Überwiegend qualitatives Review 1. **Linie** Molecularly Selected Populations: Seven trials used an egfr inhibitor in molecularly selected patients with stage iiib/iv nsclc. One trial selected patients on the basis of egfr protein overexpression (assessed by immunohis- tochemistry) or increased gene copy number (assessed by fluorescence in situ hybridization, Table iii). Six tri- als selected patients with tumours harbouring an EGFR mutation. A meta-analysis of this group of patients was performed because the patients were homogenous, and the treatment comparators were platinum-based chemo- therapy regimens. All six trials observed higher response rates favouring the egfr inhibitor group. Three of the trials (Mitsudomi et al.46, Zhou et al.48 and Yang et al.51) found the results to be statistically significant (p < 0.0001). In every trial, PFS was also statistically significant and favoured the EGFR inhibitor. A meta-analysis [Figure 1(A)] demonstrated a statistically significant im- provement in pfs (hr: 0.35; 95% ci: 0.28 to 0.45; p < 0.00001). However, the I2 is high at 80%, which shows considerable statistical heterogeneity. In each of the subgroup analyses (different egfr inhibitors), the I2 also remains high. The cause of the heterogeneity remains unknown at this time. The addition of the subgroup analyses from both the ipass and First-signal trials in patients with a known EGFR mutation status36,38 resulted in similar findings [hr: 0.38; 95% ci: 0.31 to 0.46; p <

	0.00001; Figure 1(B)]. Evidence of statistical heterogeneity remains, with an I2 of 76%. Six trials reported os. The data are difficult to interpret, because many patients are likely to have crossed over to the other treatment arm, but the actual percentages are not reported. Meta-analysis of those trials demonstrates no difference in survival between the two groups [hr: 1.01; 95% ci: 0.86 to 1.18; p = 0.94; Figure 2(A)]. Inclusion of data from the ipass and First-signal trials did not change that result [hr: 0.98; 95% ci: 0.84 to 1.14; p = 0.77; Figure 2(B)]. One additional study compared an egfr inhibitor plus chemotherapy with an egfr inhibitor alone in patients with egfr protein overexpression or increased gene copy num-ber53. No clear recommendation can be made from that trial. Response rate and pfs were higher in the egfr plus chemotherapy group, but os favoured the egfr-inhibitor- alone group The most significant toxicity was skin rash, which occurred in slightly higher numbers in the egfr- inhibitor-alone group 53. Symptom control and quality of life were discussed in the Yang et al. and Wu et al. studies. A significant delay in time to deterioration of the cancer-related symptoms of cough (hr: 0.60; p = 0.0072) and dyspnea (hr: 0.68; p = 0.0145) was seen with the egfr inhibitor afatinib. A higher proportion of patients in the afatinib group experienced a significantly longer time to deterioration (hr: 0.56; 95% ci: 0.41 to 0.77; p = 0.0002)52. The adverse effects were consistent with those found with EGR inhibitors and chemotherapy.



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

2. Linie

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

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

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

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

Erhaltungstherapie Keine Studien mit EGFR M+ Patienten -

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

5. Hinweis der FBMed

   Es ist keine Qualitätsbewertung der Primärstudien dargelegt.

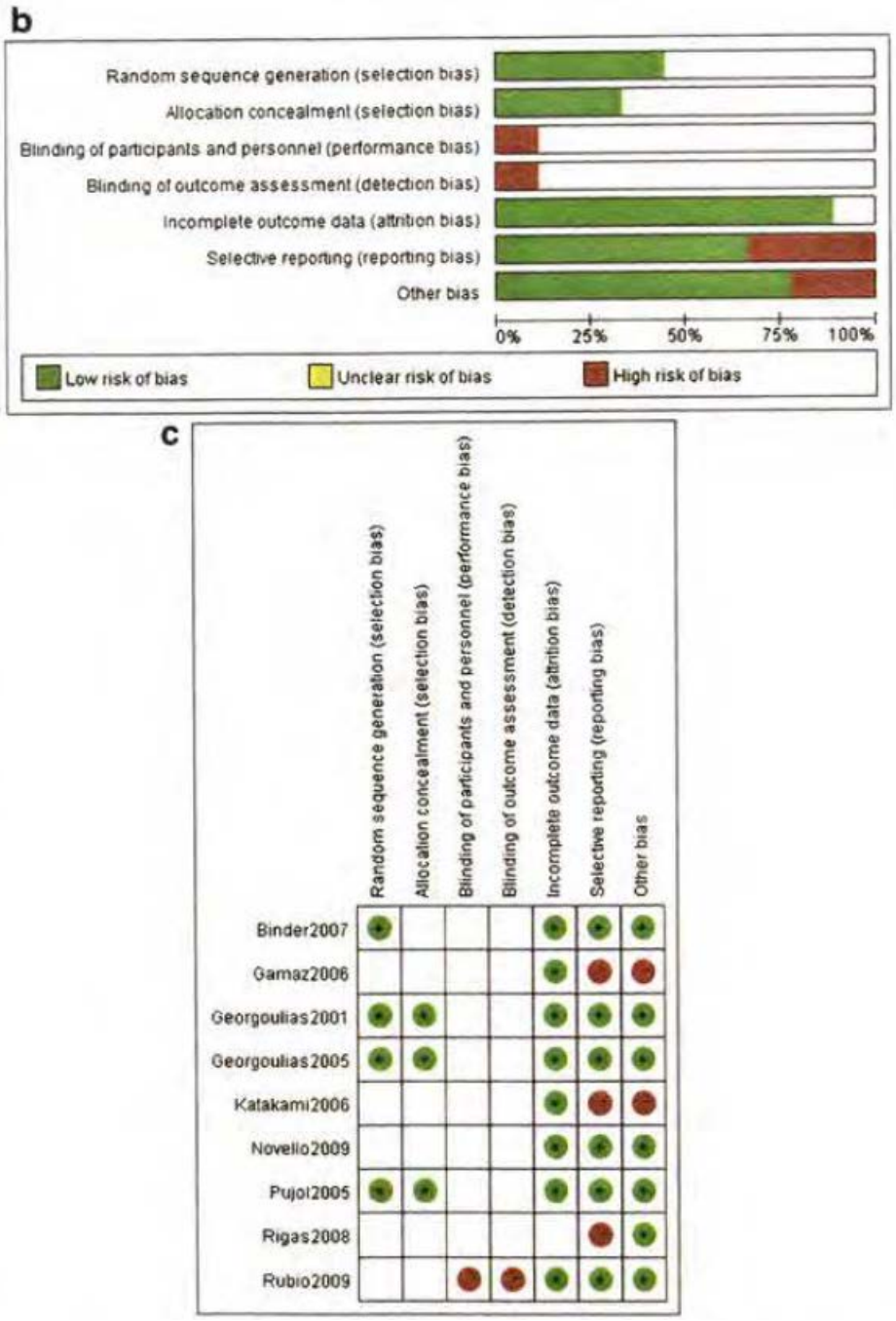
Yu Y et al., 2012 [55].

Non-platinum regimens of

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).

gemcitabine plus docetaxel versus platinum-based regimens in first-line treatment of advanced non-small cell lung cancer: a meta-analysis on 9 randomized controlled trials **Sun L et.al., 2015 [49].** Efficacy and safety of chemotherapy or tyrosine kinase inhibitors combined with bevacizumab versus chemotherapy or tyrosine kinase inhibitors alone in the treatment of non-small cell lung cancer: a systematic review and meta-analysis	**2. Methodik** **Population:** cytologically or pathologically confirmed of NSCLC and in clinical III-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) **Endpunkte:** OS, TTP, ORR, toxicity **Suchzeitraum**: up to 2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 9 (n=2.658) **Qualitätsbewertung der Studien:** Cochrane risk of bias tool **Heterogenitätsuntersuchungen:** Statistical heterogeneity among trials included in the meta-analysis was assessed by using the Cochran Q statistic, and inconsistency was quantified with the e statistic (100% x [Q - df)/Q) that estimates the percentage of total variation across studies due to heterogeneity rather than chance. We considered a p value less than 0.1 as indicative of substantial heterogeneity. When substantial heterogeneity was not observed, the fixed-effect model Mantel-Haenszel method was used to calculate relative risks (RRs) for binary data and fixed effect inverse variance method to calculate HRs for time to-event data. When substantial heterogeneity was observed, the random effect model DerSimonian-Laird method was used for binary data and random effect inverse variance for time-to-event data.
	3. Ergebnisdarstellung


b
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias
c
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Binder2007
Gamaz2006
Georgoulias2001
Georgoulias2005
Katakami2006
Novelio2009
Pujol2005
Rigas2008
Rubio2009

Study ID	Group	Regimens	ITT (n
Novello2009	P	GEM 1,200 mg/m^2 d1,8 +DDP 100 mg/m^2 d2; q3w * 3 cycles → DOC 75 mg/m2, d1; q3w * 3 cycles	54
	GD1	DOC 40 mg/m^2 d1,8 + GEM 1,200 mg/m^2 d1,8; q3w * 6 cycles	54
	GD2	DOC 50 mg/m^2 d1,15 + GEM 1,600 mg/m^2 d1,15; q4w * 6 cycles	57
Rubio2009	P	GEM 1,250 mg/m^2 d1,8 +DDP 75 mg/m^2 d1; q3w * 6 cycles	56
	GD	GEM 1,000 mg/m^2 d1,8 +DOC 85 mg/m^2 d1; q3w * 6 cycles	52
Rigas2008	P	DOC 75 mg/m^2 d1 + CBP AUC 6 d1; q3w	930#
	GD	GEM 1,000 mg/m^2 d1,8 +DOC 40 mg/m^2 d1,8; q3w	
Binder2007	P	GEM 900 mg/m^2 d1,8 +DDP 70 mg/m^2 d1; q3w * 3 cycles → DOC 100 mg/m2 d1; q3w * 3 cycles	58
	GD	GEM 900 mg/m^2 d1,8 +DOC 75 mg/m^2 d1; q3w * 6 cycles	54
Katakami2006	P	DOC 60 mg/m^2 d1 + DDP 80 mg/m^2 d1; q3w to disease progression or unacceptable toxicity	68
	GD	DOC 60 mg/m^2 d8 + GEM 800 mg/m^2 d1,8; q3w to disease progression or unacceptable toxicity	63
Gamaz2006	P	GEM 1,250 mg/m^2 d1,8 +DDP 70 mg/m^2 d1; q3w	22
	GD	GEM 1,250 mg/m^2 d1,8 +DOC 75 mg/m^2 d1; q3w	25
Pujol2005	P	NVB 30 mg/m^2 d1,8,15,22 +DDP 100 mg/m^2 d1; q4w * 6 cycles	156
	GD	GEM 1,000 mg/m^2 d1,8 +DOC 85 mg/m^2 d1; q3w * 8 cycles	155
Georgoulias2005	P	NVB 30 mg/m^2 d1,8 +DDP 80 mg/m^2 d8; q3w * 6 cycles	204
	GD	GEM 1,000 mg/m^2 d1,8 +DOC 100 mg/m^2 d8; q3w * 6 cycles	209
Georgoulias2001	P	DOC 100 mg/m^2 d1 + DDP 80 mg/m2 d2; q3w	219
	GD	GEM 1,100 mg/m^2 d1,8 +DOC 100 mg/m^2 d8; q3w	222

Overall survival (9 trials, 2658 patients):

no statistically significant difference, no heterogeneity (HR = 1.04, 95% CI= 0.96-1.12, p =0.39)

1-year survival (6 trials):

no statistically significant difference, no heterogeneity (RR = 0.94, 95% CI= 0.84-1.06, p = 0.33)

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).

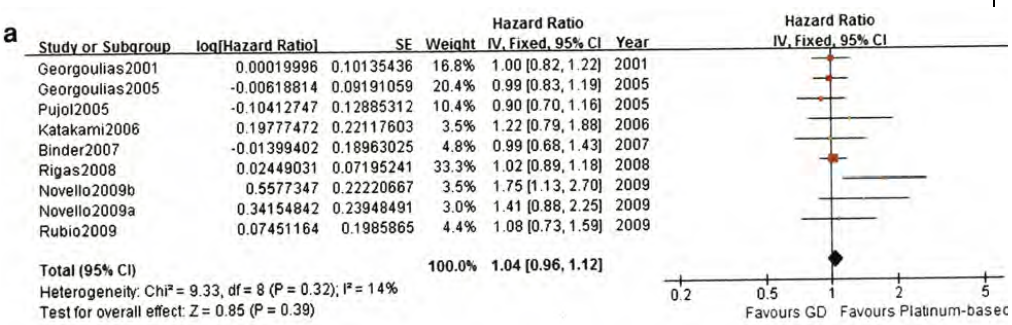


Fig. 2 The efficacy meta -analysis between gemcitabine plus docetaxel (GO) and platinum-based regimens. a The pooled HR for overall did not display a difference between the two groups (HR = 1.04. 95% CI = 0.96-1.1 2. p = 0.39).

4. 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.

Sun L et.al., 2015 [49].

Efficacy and safety of chemotherapy or tyrosine kinase inhibitors combined with bevacizumab versus chemotherapy or tyrosine kinase inhibitors alone in the treatment of non-small cell lung cancer: a systematic review and meta-analysis

Soria JC et al., 2013 [48].

Systematic Review and meta-analysis of

1. Fragestellung

In the present study, we summarized data from randomized controlled clinical trials comparing chemotherapy or EGFR-TKIs plus bevacizumab with chemotherapy or EGFR-TKIs alone in the first- or second-line treatment of NSCLC to provide evidence for the use of bevacizumab in advanced NSCLC.

2. Methodik

Population:

advanced stage IIIB/IV or recurrent NSCLC with ECOG performance status of 0–2 or Karnofsky performance score >60.

Intervention:

bevacizumab plus chemotherapy; bevacizumab plus EGFR-TKIs; first-line or secondline treatment

Komparator:

chemotherapy alone; TKIs alone; first-line or secondline treatment

Endpunkte:

OS, PFS, ORR, Toxizität

Suchzeitraum:

Bis 10/2014

Anzahl eingeschlossene Studien/Patienten (Gesamt):

randomised, phase II/III trials adding Bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer

9 (n=3274)

Qualitätsbewertung der Studien:

Cochrane risk of bias tool und Publikationbias

Heterogenitätsuntersuchungen: Heterogeneity among the studies was assessed by the Cochran Q statistic and the inconsistency index (I2 statistic). The I^2 statistic (0–100 %) was used to assess the proportion of variability in the results that was attributable to heterogeneity between the trials. If the P value was <0.10, I2>50 % or the Q statistic indicated significant heterogeneity, the reason for the heterogeneity was examined using the random-effects model (DerSimonian–Laird method). Otherwise, the fixed-effects model (Mantel– Haenszel method) was used.

3. Ergebnisdarstellung

Trials	Treatment arms	Cases	Endpoints	Histologies
Johnson [23]	PCb	32	TTP/OR	Ade., LCC, SCC, other
	PCb + Bev 7.5 mg/kg	32		
	PCb + Bev 15 mg/kg	35		
Sandler [3]	PCb	433	OS/PFS/OR	Ade., LCC, BAC, other
	PCb + Bev 15 mg/kg	417		
Reck [4]	GCis	347	OS/PFS/OR	Ade., LCC, other
	GCis + Bev 7.5 mg/kg	345		
	GCis + Bev 15 mg/kg	351		
Soria [24]	PCb	41	OS/PFS/OR	Ade., BAC, LCC, other
	PCb + Bev 15 mg/kg	44		
Niho [25]	PCb	59	OS/PFS/OR	Ade., LCC, other
	PCb + Bev 15 mg/kg	121		
Boutsikou [26]	DCb	61	OS/PFS/OR	Ade., LCC
	DCb + Bev 7.5 mg/kg	56		
Seto [8]	Erl	77	PFS/ORR	Ade.
	Erl + Bev 15 mg/kg	77		
Herbst [9]	CT	41	PFS/OS	LCC, Ade., other
	CT + Bev 15 mg/kg	40		
	Erl + Bev 15 mg/kg	39		
Herbst [7]	Erl	317	PFS/OS/ORR	Ade., LCC, SCC, other
	Erl + Bev 15 mg/kg	319		

Study	Randomization	Allocation concealment	Blindness	Follow-up	ITT analysis
Johnson [23]	Interactive voice response system	Unclear	No	Yes	Yes
Sandler [3]	Centralized	Unclear	Unclear	Yes	Yes
Reck [4]	Centralized	Yes	Yes	Yes	Yes
Soria [24]	Centralized	Unclear	No	Yes	Yes
Niho [25]	Centralized	Unclear	Unclear	Yes	Yes
Boutsikou [26]	Centralized	Unclear	No	Unclear	Yes
Seto [8]	Centralized	Unclear	Unclear	Ongoing	Yes
Herbst [9]	Centralized	Unclear	Unclear	Yes	Yes
Herbst [7]	Interactive voice response system	Yes	Yes	Yes	Yes

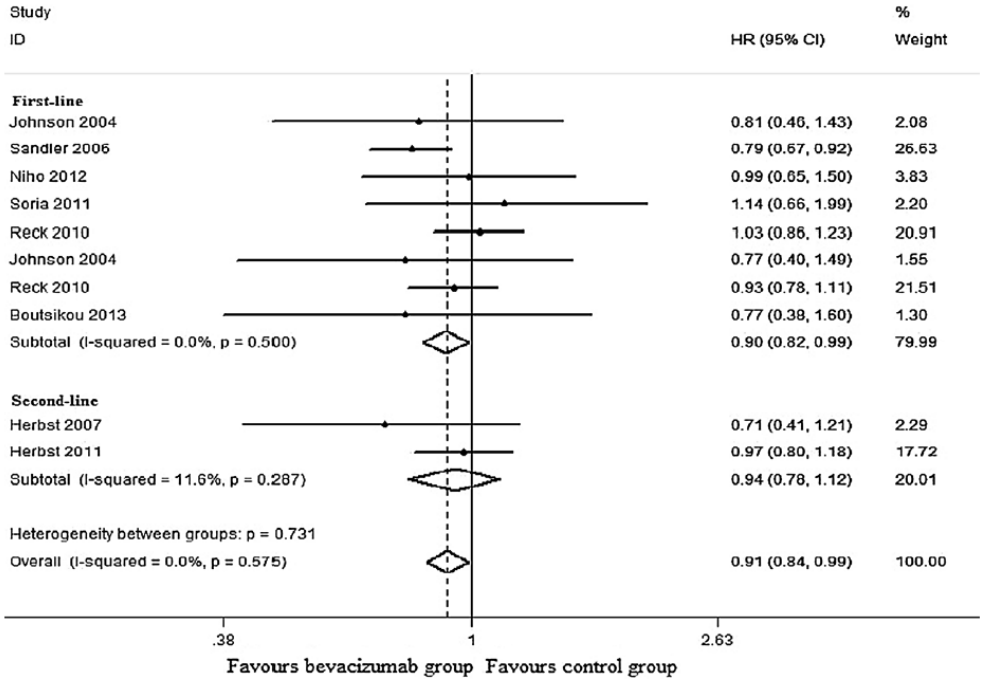
Kein Publikationsbias

There was slight heterogeneity in the pooled analysis of ORR between different treatment protocols and different lines, and a random-effects model was used for final analysis. There was no significant heterogeneity in the analysis of other

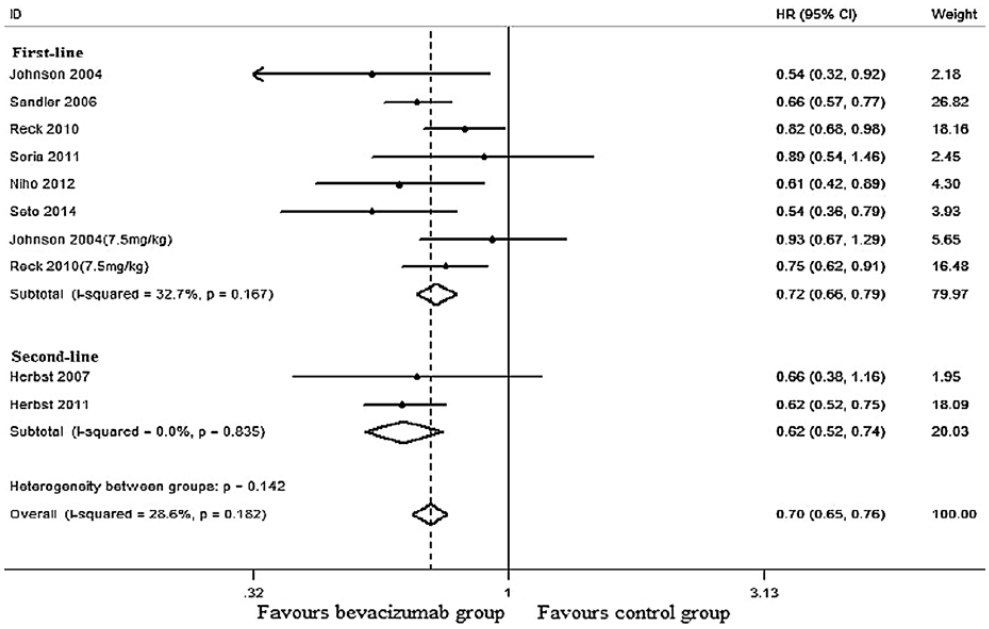
indexes, and a fixed-effects model was used.

Unterscheidung nach Therapielinie

OS (6 RCTs, alle CT + BEV vs. CT allein): stat. signifikanter Vorteil für die Kombination mit Bevacizumab in der Erstlinie (HR 0.90, 95 % CI 0.82–0.99, P = 0.029, keinen Heterogenität).



PFS (5 RCTs, CT + BEV vs. CT allein; 1 RCT Erlotinib + BEV vs. Erlotinib Monotherapie): stat. signifikanter Vorteil für die Kombination mit Bevacizumab in der Erstlinie (HR 0.72, 95 % CI 0.66–0.79, P<0.001)



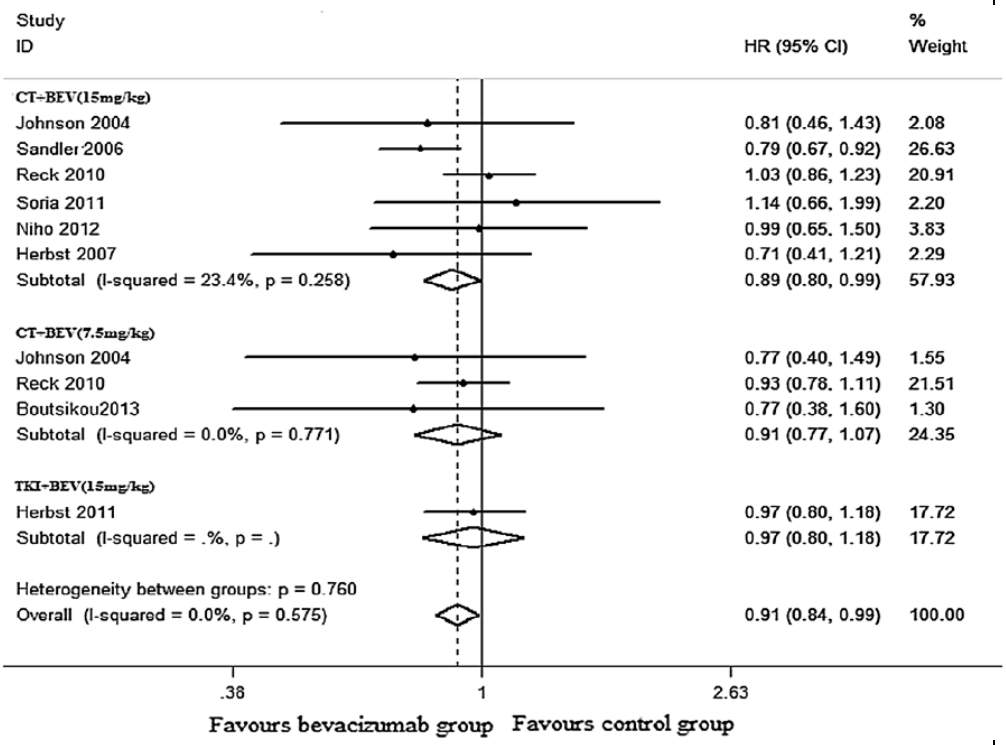
ORR (alle 9 RCTs): stat. signifikanter Vorteil für die Kombination mit Bevacizumab in der Erstlinie (RR 1.58, 95 % CI 1.28–1.95, P<0.001). If the JO25567 trial was excluded from the sensitivity analysis because of moderate heterogeneity (I2 =

65.2 %) in the analysis of ORR, the heterogeneity decreased, with the heterogeneity decreased, with I^2 = 11.5 %, and the ORR results did not change significantly (RR 1.79, 95 % CI 1.57–2.04, P<0.001).

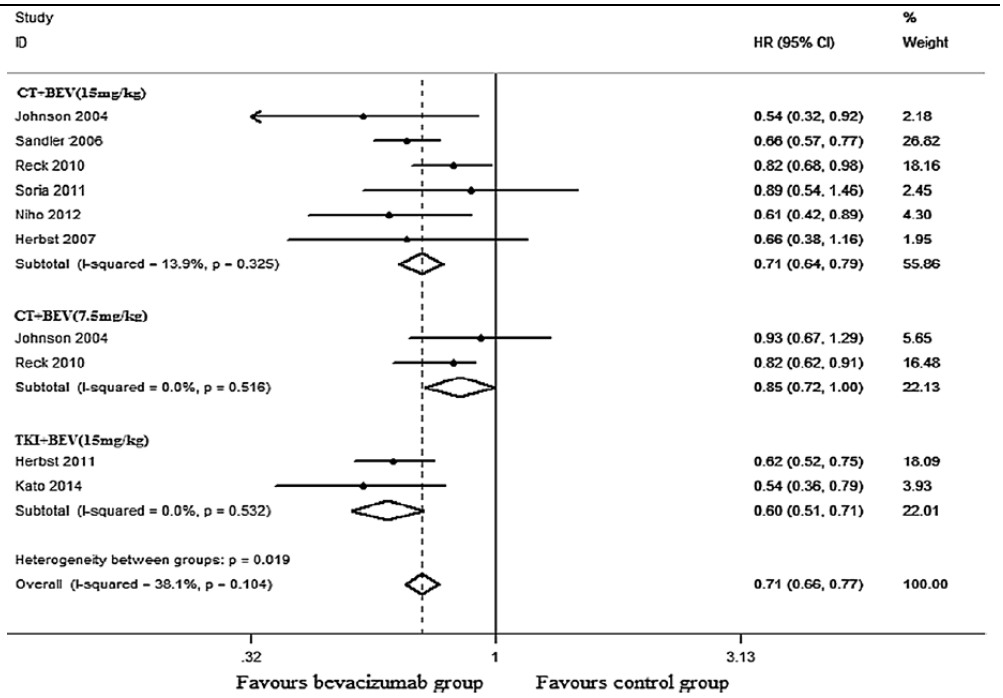
<u>Unterscheidung nach Kombinationspartner</u>

Chemotherapie (6 RCTs): OS, PFS, ORR:

- The results indicated that high doses of bevacizumab significantly prolonged OS, PFS, and ORR (HR 0.89, 95 % CI 0.80–0.99, P = 0.037; HR 0.71, 95 % CI 0.64–0.79, P<0.001; RR 1.85, 95 % CI 1.59–2.15, P<0.01, respectively).
- Among the high-dose group studies, one trial reported on the use of bevacizumab in the second-line treatment of NSCLC. After exclusion of this second-line trial, the results indicated that high doses of bevacizumab significantly improved PFS and ORR (HR 0.71, 95 % CI 0.64–0.79, P<0.001; RR 1.89, 95 % CI 1.61–2.22, P<0.001, respectively), and simultaneously prolonged OS although the difference was not significant (HR 0.90, 95 % CI 0.82–0.99, P = 0.06).
- Low doses of bevacizumab did not improve OS (HR 0.91, 95 % CI 0.77–1.07, P = 0.263), only bringing moderate benefit to PFS and ORR (HR 0.85, 95 % CI 0.72–1.00, P = 0.049; RR 1.60, 95 % CI 1.28–2.0, P<0.001).



Overall survival



PFS

Toxizität

The results indicated that high doses of bevacizumab increased the risk of the CG3 adverse events of leukopenia (RR 1.287, 95 % CI 1.109–1.493, P = 0.001), hypertension (RR 10.306, 95 % CI 4.889–21.725, P<0.01); proteinuria (RR 11.522, 95 % CI 2.377–55.85, P = 0.002), and bleeding events (RR 3.003, 95 % CI 1.508–5.979, P = 0.002). The low-dose bevacizumab group generally showed a lower risk than the high-dose group, and a significantly increased risk of CG3 leukopenia (RR 1.241, 95 % CI 1.019–1.513, P = 0.032), hypertension (RR 3.429, 95 % CI 1.493–7.877, P = 0.004), and bleeding events (RR 3.429, 95 % CI 1.493–7.877, P = 0.005) compared with chemotherapy alone; however, unlike the high-dose bevacizumab group, the low-dose group did not show increased risk of proteinuria (RR 3.115, 95 % CI 0.327–29.672, P = 0.323).

4. **Fazit der Autoren:** In conclusion, the addition of bevacizumab to chemotherapy or erlotinib can significantly improve PFS and ORR in the first- and second-line treatment of advanced NSCLC, with an acceptable and tolerated risk of bleeding events, hypertension, proteinuria, and rash. Bevacizumab plus chemotherapy can also provide an OS benefit; however, whether bevacizumab plus erlotinib can prolong OS needs further validation.

Soria JC et al., 2013 [48].

Systematic Review and meta-analysis of randomised, phase II/III trials

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

adding Bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer **Mörth C et al., 2014 [31].** Single-agent versus combination chemotherapy as first-line treatment for patients with advanced non-small cell lung cancer and performance status 2: a literature-based meta-analysis of randomized studies	**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:** 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:** Random-effect models were used in cases of significant and unexplained heterogeneity. The chi-squared heterogeneity test was used to test for gross statistical heterogeneity between the trials. The I2 statistic (0%–100%) was used to assess the proportion of variability in the results that was attributable to heterogeneity between the trials
	3. Ergebnisdarstellung

Siehe auch:

Luo et al. 2015 [29].

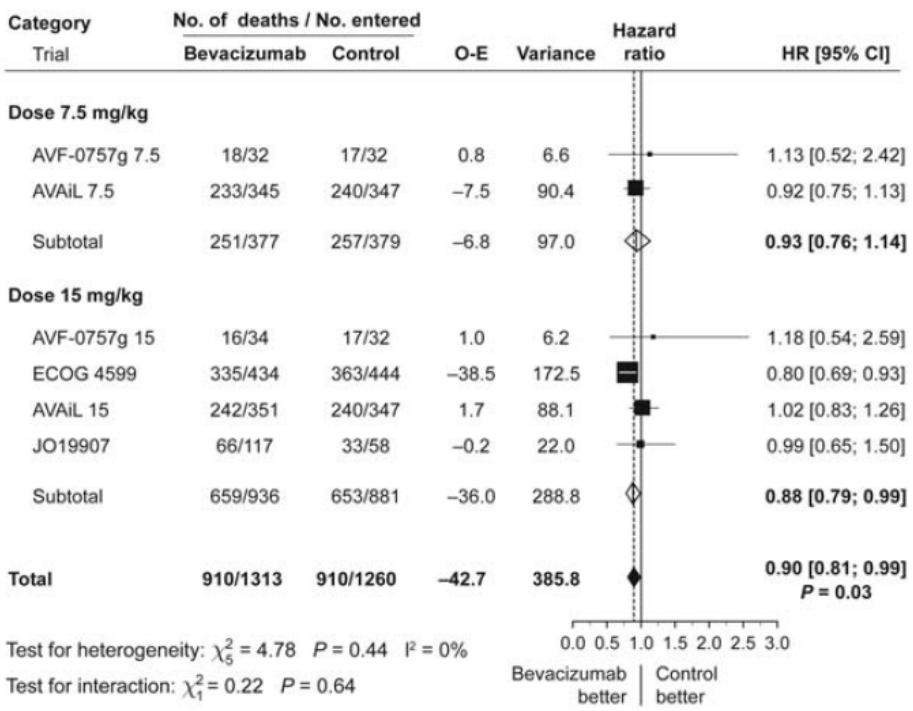
Trial	Design, main inclusion/exclusion criteria, primary end point	Treatment arms[a]	N analysed /randomly assign patients
AVF-0757g [24]	Design: open-label, parallel-group, multicentre, blinded assessment phase II Inclusion critera: histologically confirmed stage IIIB (with pleural effusion), stage IV 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	Bevacizumab 7.5 mg/kg + carboplatin + paclitaxel Bevacizumab 15 mg/kg + carboplatin + paclitaxel Carboplatin + paclitaxel	32/32 34/35 32/32
ECOG 4599 [21]	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	Bevacizumab 15 mg/kg + carboplatin + paclitaxel Carboplatin + paclitaxel	434/434 444/444
AVAiL [22]	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	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]	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	Bevacizumab 15 mg/kg + carboplatin + paclitaxel Carboplatin + paclitaxel	117/121 58/59

aDoses: carboplatin, dosed to a target area under the curve of 6 mg/ml/min; paclitaxel, 200 mg/m2; cisplatin, 80 mg/m2; gemcitabine, 1250 mg/m2. In all trials, treatment was administered in 3-week cycles for 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 bevacizumab 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 the initial six cycles. Patients in the control arms were permitted to receive bevacizumab (15 mg/kg) on disease progression.
bExperimental 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.

All trials used central randomisation stratified using between one and four factors (Table 2). Only one trial was doubleblind. For the main end point of this study, OS, an objective end point, the absence of blinding was not a problem. The proportion of randomly assigned patients excluded from the analysis by trial ranged from 0% to <3% and overall was 0.3%. Follow-up was good without clear imbalance between arms.

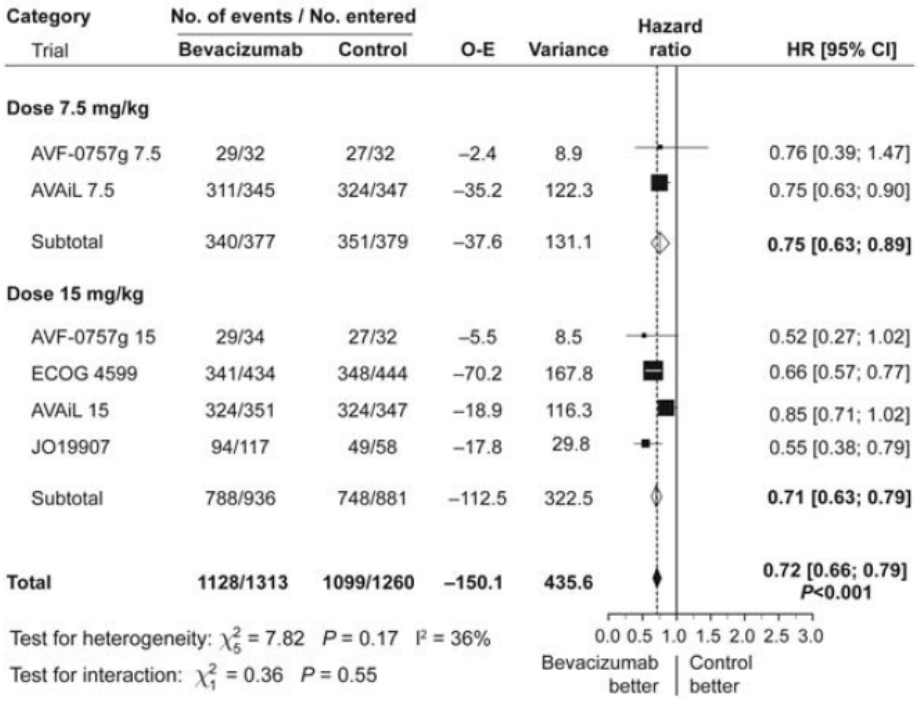
Overall survival (4 trials, 2.194 patients):

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. 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.
Mörth C et al., 2014 [31]. Single-agent versus combination chemotherapy as first-line treatment for patients with advanced non-small cell lung cancer and performance status 2: a literature-based meta-analysis of randomized studies <u>Siehe auch:</u> **Luo et al. 2015 [29].** **Li M, et.al. 2012 [26].** Pemetrexed plus platinum as the first-line	**1. Fragestellung** The purpose of this study was to compare the efficacy and tolerability of first-line treatment with combination versus single agent chemotherapy in patients with advanced non-small cell lung cancer (NSCLC) and performance status (PS) 2
	2. Methodik **Population:** advanced NCSLC mit PS 2 **Intervention:** combination chemotherapy **Komparator:** single agent chemotherapy **Endpunkte:** OS, PFS, ORR **Suchzeitraum:** Bis 07/213 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 12 (1114) **Qualitätsbewertung der Studien:** Cochrane's risk of bias tool **Heterogenitätsuntersuchungen:** I^2
	3. Ergebnisdarstellung **<u>MÖRTH et al.</u>**

treatment option for advanced non-small cell lung cancer: a meta-analysis of randomized controlled trials

Table 1
Characteristics of eligible trials.

Author [trial name] (ref)	Study phase	Treatment arms	Dose and schedule of chemotherapy	PS analysis	No of patients
Kosmidis [8]	II	Gemcitabine	1250 mg/m^2 day 1 + 14, q4w	Dedicated to PS 2	47
		Carboplatin-Gemcitabine	3 AUC – 1250 mg/m^2 day 1 + 14, q4w		43
Morabito [CAPPA-2] [9]	III	Gemcitabine	1200 mg/m^2 day 1 + 8, q3w	Dedicated to PS 2	28
		Cisplatin-Gemcitabine	60–1200 mg/m2 day 1 + 8, q3w		29
Reynolds [USO-03012] [10]	III	Gemcitabine	1250 mg/m^2 day 1+ 8, q3w	Dedicated to PS 2	85
		Carboplatin-Gemcitabine	5 AUC – 1000 mg/m^2 day 1 + 8, q3w		85
Zukin [11]	III	Pemetrexed	500 mg/m^2 day 1, q3w	Dedicated to PS 2	102
		Carboplatin-Pemetrexed	5 AUC – 500 mg/m^2 day 1, q3w		103
Comella [SICOG 9909] [14]	III	Gemcitabine	1200 mg/m^2 day 1 + 8 + 15, q4w	Subset analysis	19
		Paclitaxel	100 mg/m^2 day 1 + 8 + 15, q4w		22
		Gemcitabine-Paclitaxel	1000 mg/m^2–80 mg/m2 day 1 + 8, q3w		15
		Gemcitabine-Vinorelbine	1000 mg/m^2–25 mg/m^2 day 1 + 8, q3w		21
Georgoulias [15]	III	Docetaxel	100 mg/m^2 day 1, q3w	Subset analysis	15
		Cisplatin-Docetaxel	80 mg/m^2 day 2–100 mg/m^2 day 1, q3w		15
Hainsworth [16]	III	Docetaxel	36 mg/m2 day 1 + 8 + 15, q4w	Subset analysis	57
		Docetaxel-Gemcitabine	30 mg/m^2–800 mg/m^2 day 1 + 8 + 15, q4w		65
Le Chevalier [17]	III	Vinorelbine	30 mg/m^2 weekly	Subset analysis	46
		Cisplatin-Vinorelbine	120 mg/m^2 day 1 + 29 –> q6w, 30 mg/m^2 weekly		42
		Cisplatin-Vindesine	120 mg/m^2 day 1 + 29 –> q6w, 3 mg/m^2 weekly for 6 wk –> q2w		33
Lilenbaum [CALGB 9730] [18]	III	Paclitaxel	225 mg/m^2 day 1, q3w	Subset analysis	50
		Carboplatin-Paclitaxel	6 AUC–225 mg/m2 day 1, q3w		49
Perrone [MILES] [19]	III	Vinorelbine	30 mg/m^2 day 1 + 8, q3w	Subset analysis	45
		Gemcitabine	1200 mg/m^2 day 1 + 8, q3w		41
		Vinorelbine-Gemcitabine	25–1000 mg/m^2 day 1 + 8, q3w		44
Quoix [IFCT-0501] [20]	III	Gemcitabine or Vinorelbine	1150 mg/m^2 day 1 + 8, q3w or 25 mg/m^2 day 1 + 8, q3w	Subset analysis	62
		Carboplatin-Paclitaxel	6 AUC day 1–90 mg/m^2 day 1 + 8 + 15, q4w		61
Sederholm [21]	III	Gemcitabine	1250 mg/m^2 day 1 + 8, q3w	Subset analysis	20
		Carboplatin-Gemcitabine	5 AUC day 1–1250 mg/m^2 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 heterogeneity was observed

OS (11 Studien, 1114 Patienten):

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

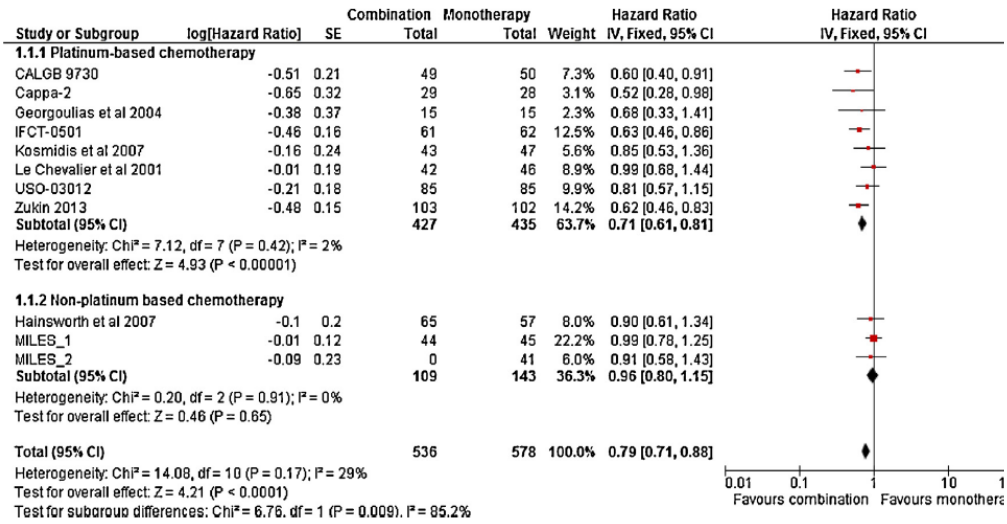


Fig. 2. Forest plot for overall survival (with subgroup analysis based on the administration of platinum-based or non-platinum based chemotherapy in combination arms).The size of the squares indicates the weight of the study. Error bars represent 95% confidence intervals (CIs). The diamond indicates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

PFS (5 Studien, 522 Patienten)

combination chemotherapy resulted in statistically significant 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 chemotherapy 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 could not perform meta-analysis on the incidence of other toxicities.

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

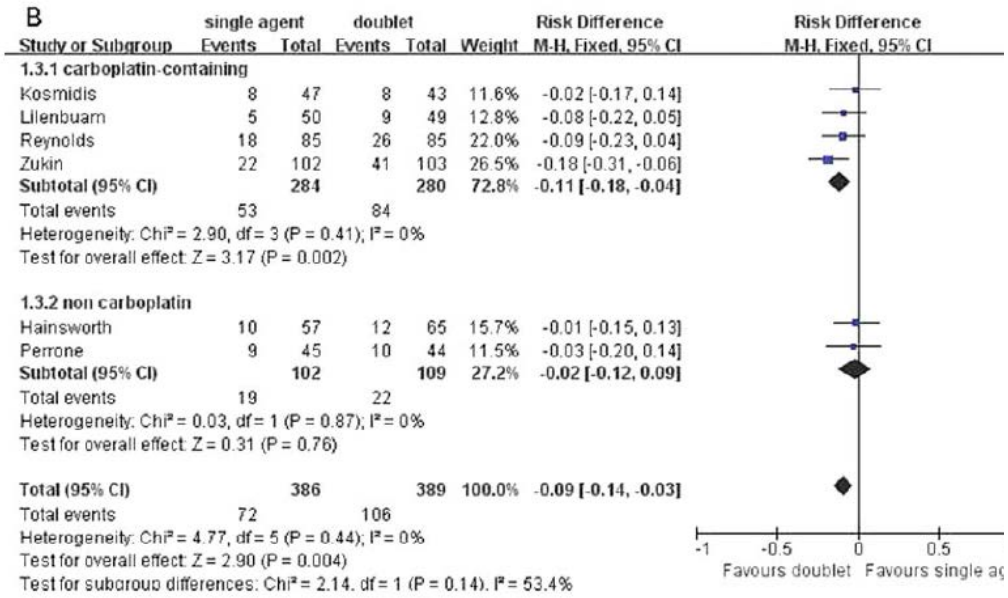
Abbreviations: No: number; OR: odds ratio; CI: confidence interval.

<u>Luo et al.</u>

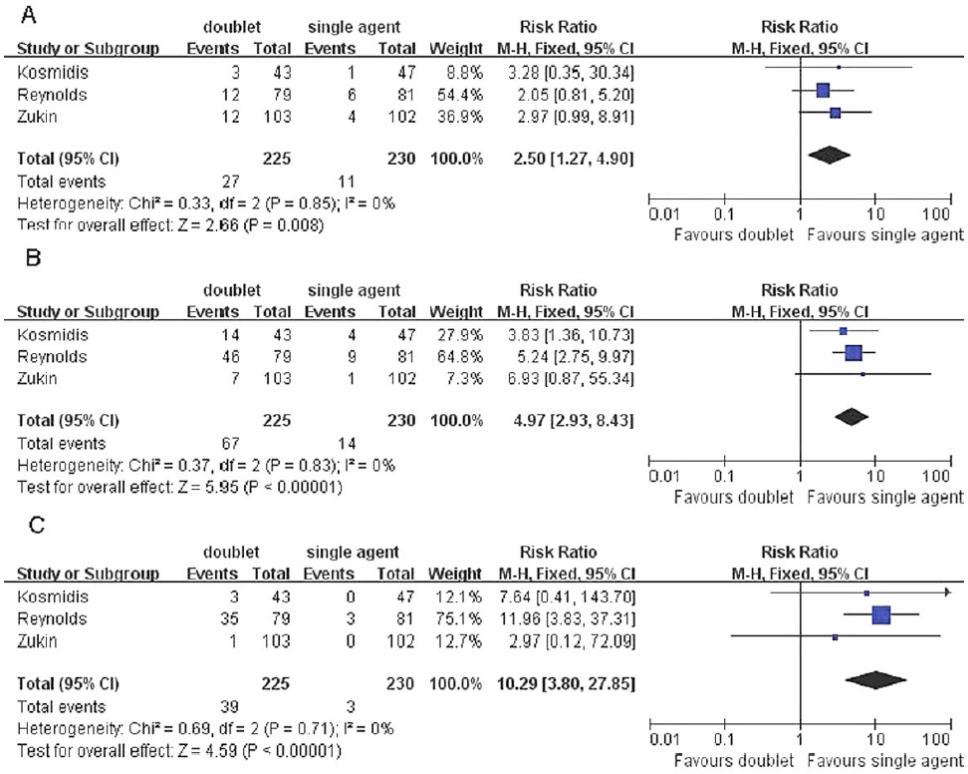
Mortalität:

Für OS vergleichbare Ergebnisse wie Mörth et al.

1-Jahres-Überlebensrate: stat. signifikanter Vorteil mit platinhaltiger Chemotherapie. Kein Unterschied mit nicht-platinhaltiger Chemotherapie



Toxizität:



4. Fazit der Autoren

Mörth et al.: This is the first meta-analysis on the role of combination compared to single-agent chemotherapy as first-line in patients with advanced NSCLC and PS 2. A clear benefit in overall survival was observed in favor of combination chemotherapy. This benefit was substantial irrespectively the type of study. As expected, hematological toxicity was higher in combination chemotherapy. However, the number of deaths due to chemotherapy was low. The observed survival benefit was pronounced when a platinum-based combination was used but disappeared in non-platinum based combinations.

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

Luo et al.: In conclusion, the results from our meta-analysis imply that carboplatin-containing doublet chemotherapy may well be superior to non-carboplatin containing treatment. Additional prospective clinical trials are warranted to evaluate treatment combinations.

5. Hinweise durch FB Med

Die Ergebnisse von Luo et al. sind mit den Ergebnissen von Mörth et al. vergleichbar. Alle in Luo eingeschlossenen Studien (insgesamt 6) wurden auch in Mörth eingeschlossen, jedoch wurden in Mörth noch 6 weitere Studien

eingeschlossen. Diese Diskrepanz lässt sich weder durch den Suchzeitraum noch durch andere Parameter erklären. Luo fand, ohne dies explizit in den Ein- und Ausschlussgründen zu nennen, ausschließlich Studien zu Carboplatin, während bei Mörth auch Studien zu Cisplatin eingeschlossen wurden. Luo untersuchte neben OS auch Ansprechen und die 1-Jahres Überlebensrate.

Li M, et.al. 2012 [26].

Pemetrexed plus platinum as the first-line treatment option for advanced non-small cell lung cancer: a meta-analysis of randomized controlled trials

Jiang J et al., 2013 [24].

Paclitaxel plus platinum or gemcitabine plus platinum in first-line treatment of advanced non-small-cell lung cancer: results from 6 randomized controlled trials

1. Fragestellung

To compare the efficacy and toxicities of pemetrexed plus platinum with other platinum regimens in patients with previously untreated advanced non-small cell lung cancer (NSCLC)

2. Methodik

Population:

previously untreated NSCLC patients stage IIIB or IV

Intervention:

pemetrexed plus cisplatin or carboplatin chemotherapy (PPC)

Komparator:

third-generation agents plus cisplatin or carboplatin regimens (PBR)

Endpunkt:

OS, PFS, Response, Toxizität

Suchzeitraum:

Bis 2011

Anzahl eingeschlossene Studien/Patienten (Gesamt):

4 (n=2518)

Qualitätsbewertung der Studien:

Jadad

Heterogenität: I^2

3. Ergebnisdarstellung

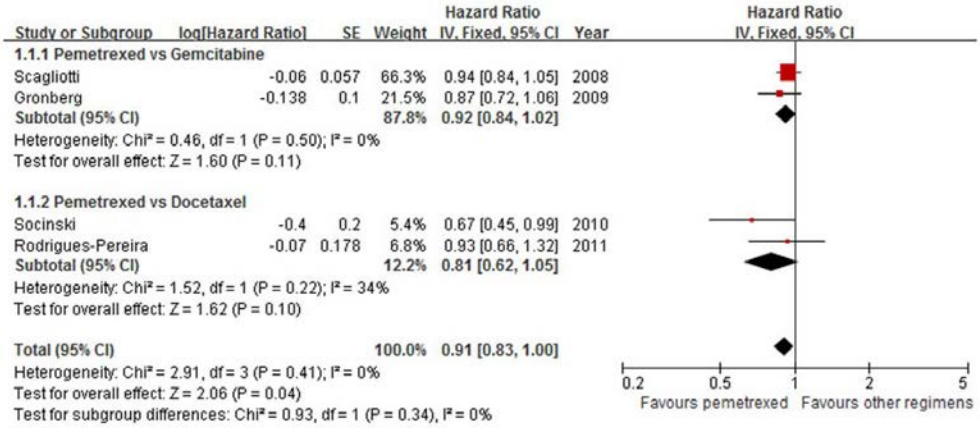
Table 1. Characteristics of Studies Included in the Meta-analysis.

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

OS (4 RCTs):

- statistisch signifikanter Vorteil der Pemetrexed-Regime (HR=0.91, 95% CI:0.83–1.00, p=0.04; I^2=0)
- Subgroup analysis was conducted according to the different drugs used in PBR. Compared with gemcitabine or docetaxel plus platinum, PPC showed a

beneficial trend in terms of OS despite a lack of statistical significance (HR = 0.92, 95% CI: 0.84–1.02, p =0.11; HR= 0.81, 95% CI: 0.62–1.05, p =0.10, respectively). There was no evidence of heterogeneity between the studies (I2 = 0%, p= 0.50; I2 = 34%, p =0.22, respectively). There was no evidence of statistical interaction between the two subgroups (p= 0.36).



PFS (2 RCTs): Kein Unterschied

Toxizität:

- Hematological Toxicity: Chemotherapy toxicity was described as patients experiencing grade 3–4 toxicity. Compared with other PBR, PPC led to less grade 3–4 neutropenia and leukopenia (OR =0.50, 95% CI: 0.34–0.74, p =0.0005; OR=0.41, 95% CI: 0.25–0.65, p= 0.0002, respectively). Compared with the gemcitabine-based regimen, a statistically significant decrease in thrombocytopenia but not in anemia was observed (OR = 0.28, 95% CI: 0.21–0.37, p,0.00001; OR= 0.72, 95% CI: 0.39–1.34, p= 0.30, respectively). Compared with the docetaxel-based regimen, a statistically significant increase in thrombocytopenia and anemia was observed (OR = 5.75, 95% CI: 2.45–13.52, p,0.0001; OR= 9.95, 95% CI: 2.94–33.68, p =0.0002, respectively). The pooled ORs for hematological toxicity were performed using the random-effort model because of heterogeneities.
- Non-hematological Toxicity: Compared with other PBR, PPC led to more grade 3–4 nausea (OR = 1.63, 95% CI: 1.11–2.39, p= 0.01) but not vomiting and diarrhea (OR = 0.98, 95% CI: 0.67–1.44, p= 0.92; OR=0.24, 95% CI: 0.05–1.13, p= 0.07, respectively). There was no significant heterogeneity for all the nonhematological toxicity analyses.

4. Fazit der Autoren

The main finding of the present meta-analysis is that PPC improved OS homogenously and significantly, when compared with other PBR, with a 9% reduction in the risk of death. But the subgroup meta-analysis concerning gemcitabine and docetaxel failed to show positive benefits in PPC. Although the association between histology and survival in NSCLC is controversial, our results

	show a significant 13% OS improvement in non-squamous patients treated with pemetrexed. There were more non-squamous patients than squamous patients in the selected four trials (from 70% to 100%), implying that non-squamous patients might play a greater role in the meta-analysis of OS for all NSCLC patients. In conclusion, this meta-analysis demonstrates that PPC in the first-line setting leads to a significant survival advantage for advanced NSCLC patients and non-squamous patients compared with other PBR. Taking into account less toxicity (such as neutropenia and leukopenia), PPC could be considered as the firstline treatment option for patients with advanced NSCLC, especially those with non-squamous histology.
Jiang J et al., 2013 [24]. Paclitaxel plus platinum or gemcitabine plus platinum in first-line treatment of advanced non-small-cell lung cancer: results from 6 randomized controlled trials **Cui J et al., 2013 [10].** The Efficacy of Bevacizumab Compared with Other Targeted Drugs for Patients with Advanced NSCLC: A Meta-Analysis from 30 Randomized Controlled Clinical Trials	**1. Fragestellung** to compare the efficacy and toxicity of paclitaxel plus platinum (TP) with gemcitabine plus platinum (GP) in untreated advanced non-small-cell lung cancer by a meta-analysis.
	2. Methodik **Population:** patients must be cytologically or pathologically confirmed of NSCLC and in clinical III–IV stage, patients must be chemotherapy-naive **Intervention:** paclitaxel plus platinum (TP) **Komparator:** gemcitabine plus platinum (GP) **Endpunkt:** efficacy, toxicity **Suchzeitraum:** bis 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 6 (n=2.793) **Qualitätsbewertung der Studien:** Jadad **Heterogenität**: I^2
	3. Ergebnisdarstellung As there were no double-blind trials, the highest quality scores of the 6 trials according to Jadad's method were 3, and all 6 trials scored 3. Kein Publikationsbias

Table 1 Characteristics of the 6 trials eligible for the meta-analysis

Study ID [references]	Regimens	*n*(ITT)	*n*(t)	Male (%)	PS 0–1 (%)	Median age (years)	SCC (%)	IV or recurrent (%)	MST (95 % CI) (months)
Scagliotti2002 [19]	G 1250 mg/m^2 d1,8 + P 75 mg/m^2 d1	205	205	81.0	95	63	33.0	81.0	9.8 (8.6–11.2)
	T 225 mg/m2 d1 + C AUC 6.0 d1	204	201	76.0	92	62	32.0	82.0	10.0 (9.0–12.5)
Schiller2002 [20]	G 1000 mg/m^2 d1,8,15 + P 100 mg/m^2 d1[a]	301	293	62.0	95	64	–	86.0	8.1 (7.2–9.4)
	T 135 mg/m^2 d1 + P 75 mg/m^2 d1	303	300	64.0	94	62	–	89.0	7.8 (7.0–8.9)
	T 225 mg/m^2 d1 + C AUC 6.0 d1	299	293	62.0	95	63	–	86.0	8.1 (7.0–9.5)
Smit2003 [21]	G 1250 mg/m^2 d1,8 + P 80 mg/m^2 d1	160	158	70.6	88.8	57	25.6	79.4	8.9 (7.8–10.5)
	T 175 mg/m^2 d1 + P 80 mg/m^2 d1	159	154	59.7	88	57	18.9	81.8	8.1 (6.2–9.9)
Langer2007 [22]	G 1000 mg/m^2 d1,8 + P 60 mg/m^2 d1	49	47	59.0	PS = 2	67	21.0	83.0	6.9
	T 200 mg/m^2 d1 + C AUC 6.0 d1	54	51	74.0	PS = 2	65	18.0	92.0	6.2
Ohe2007 [23]	G 1000 mg/m^2 d1,8 + P 80 mg/m^2 d1	151	151	69.2	100	61	19.9	79.5	14.0
	T 200 mg/m^2 d1 + C AUC 6.0 d1	150	148	68.3	100	63	21.4	80.7	12.3
Treat2010 [24]	G 1000 mg/m^2 d1,8 + C AUC 5.5 d1	379	356	58.3	99.5	64	17.7	90.0	7.9 (7.1–9.2)
	T 225 mg/m^2 d1 + C AUC 6.0 d1	379	366	60.9	98.9	64	16.1	89.4	8.7 (7.7–9.9)

d day, *G* gemcitabine, *T* paclitaxel, *P* cisplatin, *C* carboplatin, *AUC* area under the curve, *n*(*ITT*) number of patients for the intention-to-treatment analysis, *n*(*t*) number of patients receiving at least one dose treatment, *PS* performance status according to ECOG/WHO/Zubrod, *SCC* squamous cell carcinoma, *MST* median survival time

[a] Repeated every 4 weeks, other regimens repeated every 3 weeks

1-Jahres-Überleben (6 trials): no statistically significant difference (RR = 0.99, 95% CI = 0.90–1.09, p = 0.87; I²=6%)

Gesamtüberleben (6 trials): no statistically significant difference (RR = 1.06, 95% CI = 1.00–1.13, p = 0.07; I²=16%)

Response (6 trials): no statistically significant difference (RR = 0.99, 95 % CI = 0.88–1.13, p = 0.92, I²=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. Fazit der Autoren

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.

In order to avoid the bias caused by different platinum, we conducted sensitivity analyses after omitting trials in which paclitaxel was compared with gemcitabine combined with a different platinum. All the sensitivity analyses agreed with the above results.

Cui J et al., 2013 [10].

The Efficacy of Bevacizumab Compared with Other Targeted Drugs for Patients with

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

Advanced NSCLC: A Meta-Analysis from 30 Randomized Controlled Clinical Trials	**Population**: patients with confirmed stage IIIB, stage IV or recurrent NSCLC based on historical or cytological evidence, 1. und 2. Linie **Intervention**: bevacizumab (15 mg/kg) with chemotherapy **Komparator**: standard chemotherapy alone **Endpunkt**: OS, ORR, PFS **Methode**: systematic review and meta-analysis of RCTs (placebo-controlled or other types of superiority trial as well as noninferiorityv trial) **Suchzeitraum**: 1999 to 2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 30 (k.A.) **Qualitätsbewertung der Primärstudien:** Jadad Score
Burotto M, et al., 2015 [8]. Gefitinib and Erlotinib in Metastatic Non-Small Cell Lung Cancer: A Meta-Analysis of Toxicity and Efficacy of Randomized Clinical Trials	3. Ergebnisdarstellung ***Erste Linie (chemotherapy-naive patients)*** the pooled OR of response rate was 2.741(95%CI: 2.046, 3.672), the pooled HR for disease progression was 0.645 (95%CI: 0.561, 0.743), the pooled HR for death was 0.790 (95%CI: 0.674, 0.926), respectively **2. Linie** adjusted HR for previously-treated patients was 0.680 (95%CI: 0.492, 0.942) EGFR-Status **Table 2.** Crude and risk-adjusted hazard ratio of BEV comparing to C/E/G. patients | Response variable | Treatment group | Number of trials | Crude | | Adjusted | | | | | | | HR_{Crude} | 95%CI | $HR_{Adjusted}$ | 95%CI Chemotherapy-naïve | HR_{PFS} | Bev | 3 | 0.753 | (0.570, 0.996) | 0.847* | (0.687, 1.043) | | C/E/G | 18 | 1 | – | 1 | – Previously-treated | HR_{PFS} | Bev | 2 | 0.758 | (0.482, 1.191) | 0.680* | (0.492,0.942) | | C/E/G | 6 | 1 | – | 1 | – Chemotherapy-naïve | HR_{OS} | Bev | 2 | 0.774 | (0.617, 0.972) | 1.151** | (0.828, 1.600) | | C/E/G | 18 | 1 | – | 1 | – Previously-treated | HR_{OS} | Bev | 2 | 0.985 | (0.658, 1.475) | 1.262** | (0.927, 1.710) | | C/E/G | 6 | 1 | – | 1 | – *$HR_{adjusted}$ was adjusted by $\ln(OR_{ORR})$. **$HR_{adjusted}$ was adjusted by $\ln(HR_{PFS})$. Among the 30 clinical trials included in the meta-analysis, 25 reported hazard ratios for PFS and OS (HRPFS and HROS) and the corresponding 95% confidence intervals (CIs). For other 5 trials, 3 reported the HRPFS directly and 2 reported the HROS directly. In terms of the efficacy for patients treated with gefitinib (2 trials [15,17] for EGFR-mutated patients among 14 clinical trials), meta-analysis showed that pooled ORORR in EGFRmutated patients was 4.862 (95%CI: 3.064, 7.715; I2= 20.2%; Figure 3) compared to 1.199 (95%CI: 1.003, 1.434; I2 =43.3%) in EGFR untested patients (P,0.001). Pooled HRPFS in EGFRmutated patients (0.379, 95%CI: 0.235, 0.611; I2 = 74.2%) was smaller than that in EGFR untested patients (0.896, 95%CI: 0.738, 1.087; I2= 79.1%, P= 0.001). In addition, pooled HROS in EGFR-mutated patients was 1.046 (95%CI: 0.509, 2.149; I2 = 63.0%), compared to 1.005 (95%CI: 0.924, 1.093; I2 = 38.5%) in EGFR untested patients (P= 0.914). Therefore, in the following comparison, we compared bevacizumab with other targeted drugs (gefitinib, erlotinib and cetuximab) in EGFR untested patients. However, in terms of HROS, the comparison was made in both EGFR-mutated and EGFR untested patients.

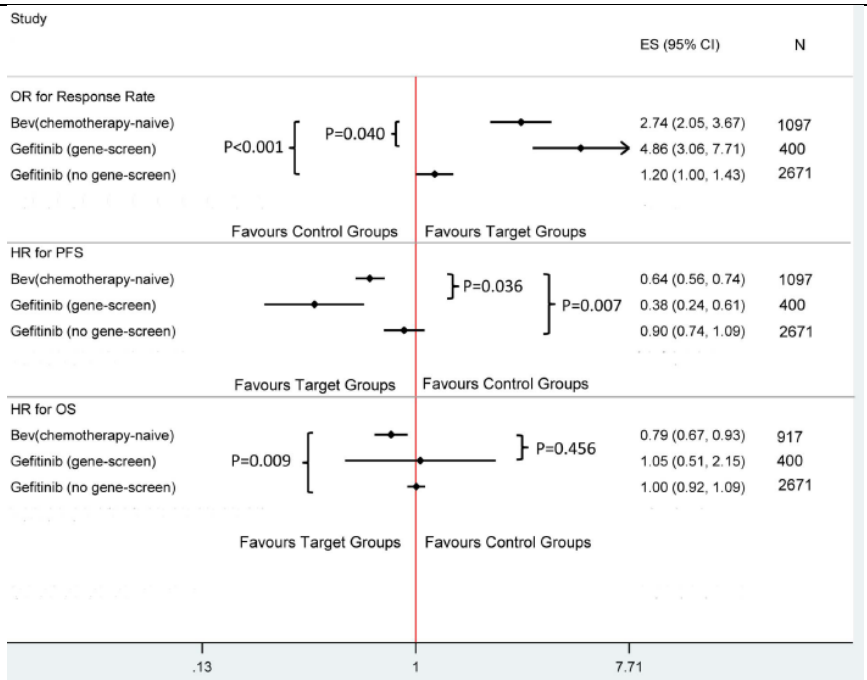


Fig. 3 Response rate, PFS, OS of Bevacizumab versus Gefitinib in NSCLC patients with different EGFR status.

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 HR_{PFS}, and lower HR_{OS} among chemotherapy-naıve patients, and lower HR_{PFS} among previous treated patients. It was also found that in EGFRmutated patients, gefitinib significantly improved OR_{ORR} and reduces HR_{PFS}. However, in general patients with EGFR status untested, bevacizumab showed a clear benefit in OR_{ORR}, HR_{PFS}, as well as HR_{OS}, compared with gefitinib.

5. Hinweise durch FB Med von den Autoren:

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.

Burotto M, et al., 2015 [8].

Gefitinib and Erlotinib in Metastatic Non-Small Cell Lung Cancer: A Meta-Analysis of Toxicity and

1. Fragestellung

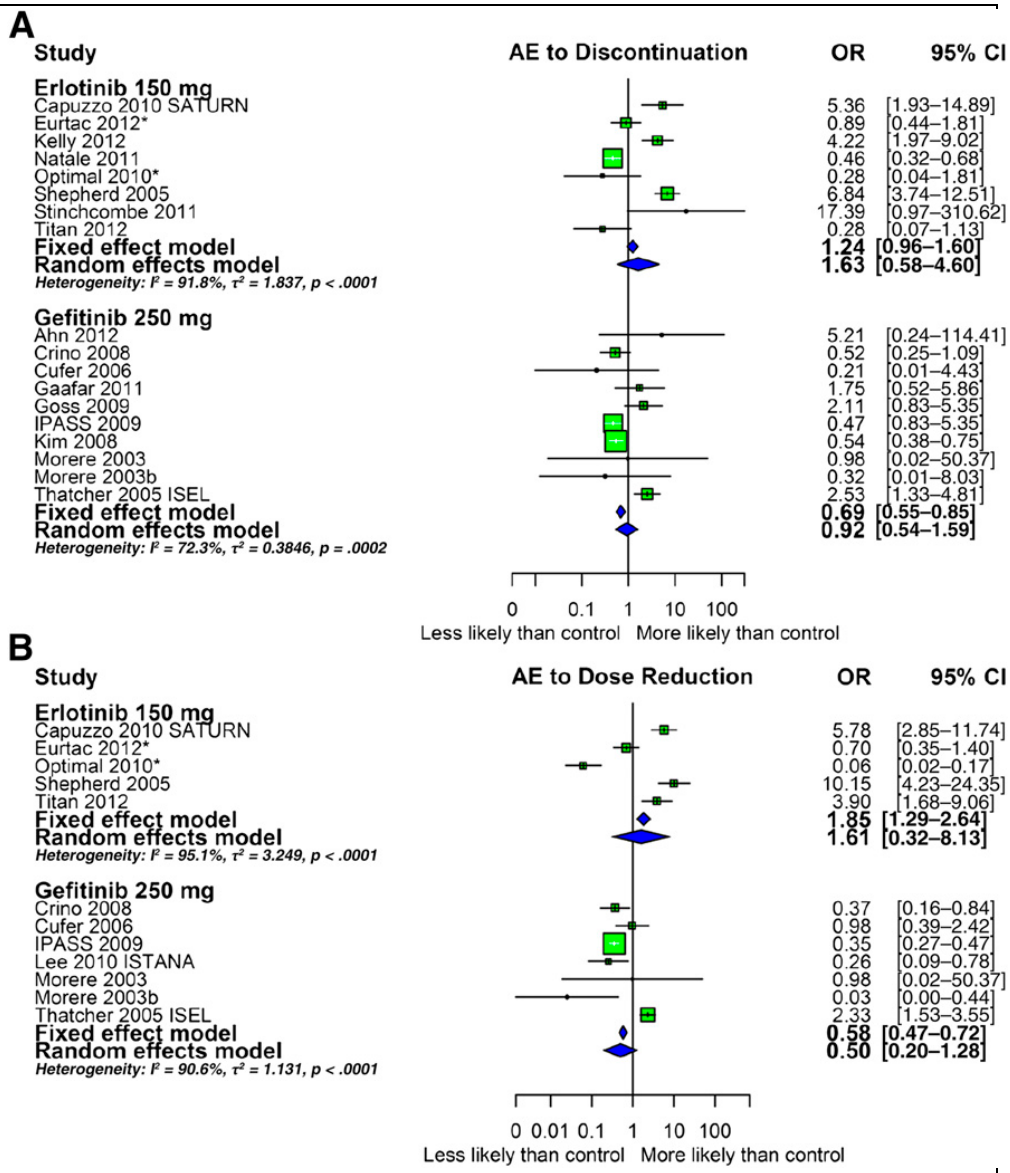
The objective of this study was to compare the efficacy and toxicity of erlotinib, gefitinib, and afatinib in NSCLC.

2. Methodik

Population: advanced or metastatic stage IIIB or IV NSCLC according to the sixth American Joint Committee on Cancer classification

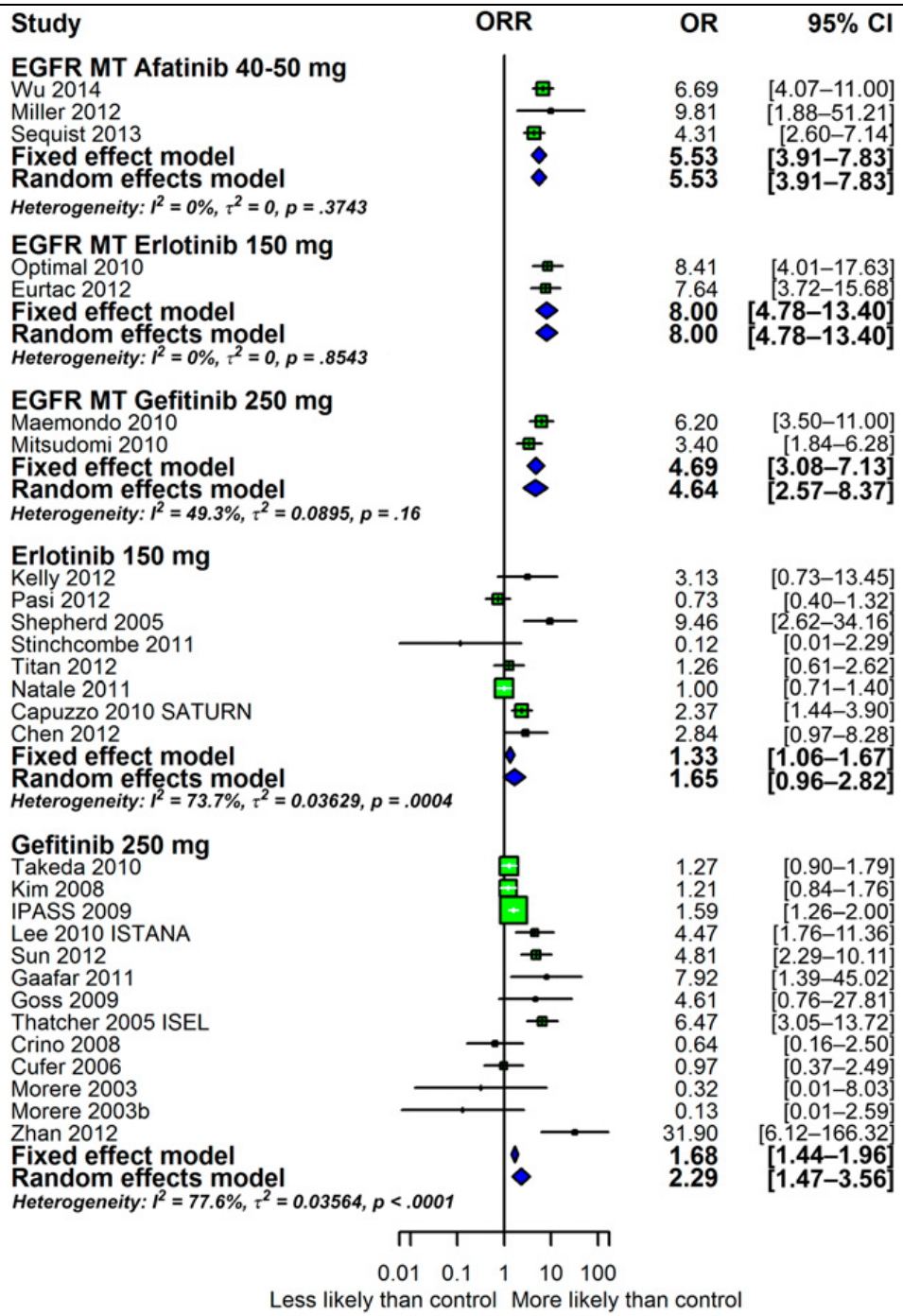
Intervention: erlotinib or gefitinib

Efficacy of Randomized Clinical Trials **Wang F et al, 2012 [50].** 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	**Komparatoren**: control arm did not receive erlotinib, gefitinib, or any other TKI **Endpunkte**: primär: PFS or OS; sekundär: nicht spezifiziert **Suchzeitraum**: 01/2003 – 12/2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** Erlotinib: 12/4 227, Gefitinib: 16/7 043 **Qualitätsbewertung der Studien:** Jadad-Score (phase II and phase III randomized studies; the treatment arm receiving the EGFR TKI had <40 patients) **Heterogenitätsuntersuchungen**: chi-square test
	3. **Ergebnisdarstellung** **Qualität der Studien:** trials had median/mean Jadad scores of 3/3.5 and 3/3 for gefitinib and erlotinib, respectively. 12 erlotinib reports included 7 phase III and 5 randomized phase II trials 16 gefitinib studies were 11 phase III and 5 randomized phase II trials for efficacy analyses comparing median OS and PFS distributions in the experimental arms of the erlotinib and gefitinib studies, we also analyzed trials according to the characteristics of the patients enrolled and the line of treatment, using the following groups: monotherapy in second line, monotherapy in first line (including the four trials in patient with mutated EGFR), maintenance or consolidation in first line, and monotherapy in the elderly population. **Toxitizität** There is no direct comparison between erlotinib and gefitinib. Clinical toxicities, including pruritus, rash, anorexia, diarrhea, nausea, fatigue, mucositis, paronychia, and anemia, were similar between erlotinib and gefitinib, although somestatistical differences were observed.



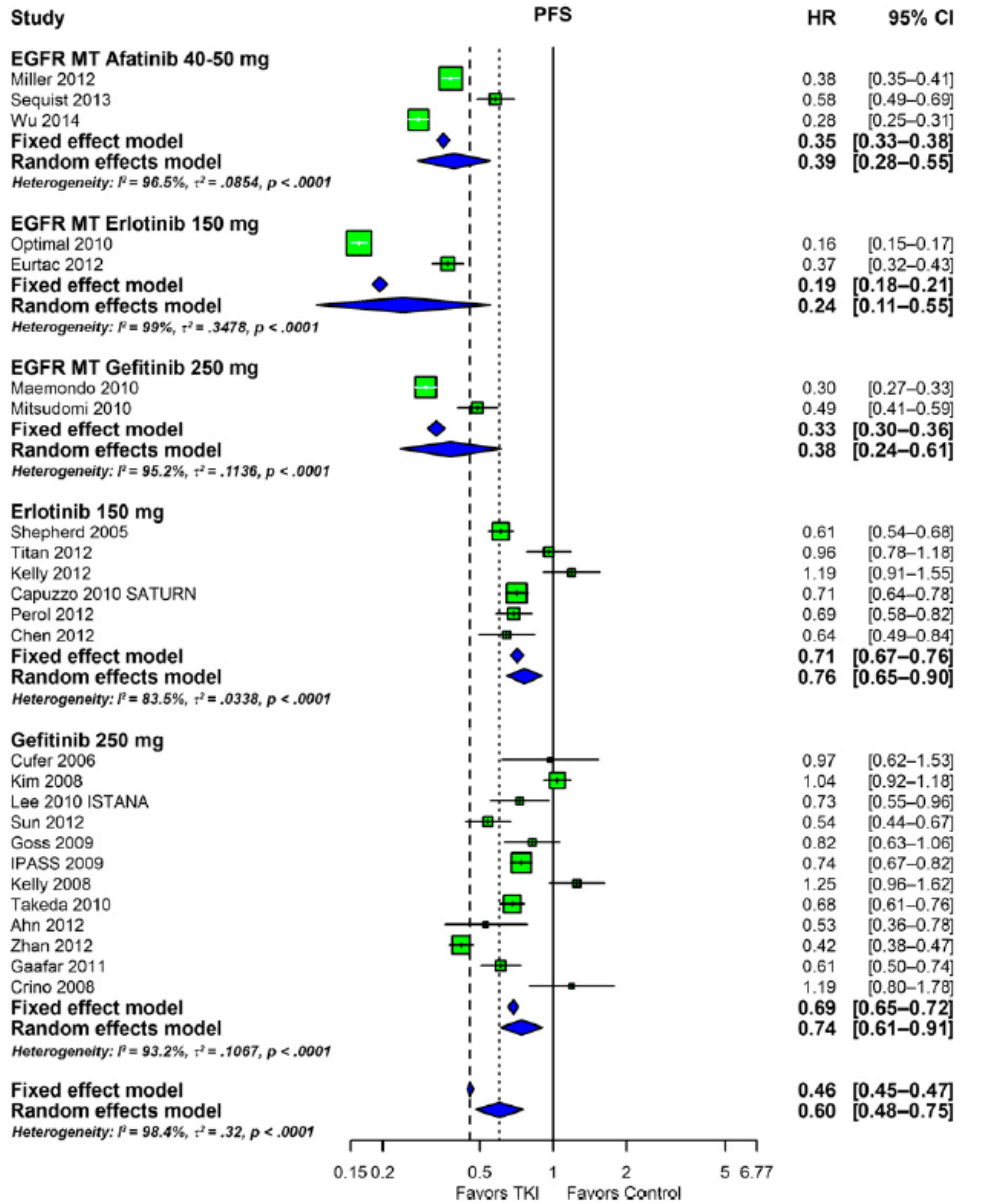
Forest plot depicting the meta-analysis using fixed-and random-effects models for drug discontinuation and dose reduction due to adverse events. An OR>1 indicates that the outcome was morelikely to occur in the arm receiving the tyrosine kinase inhibitor. (A): OR for drug discontinuation. (B): OR for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

ORR



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

PFS



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

OS (OS outcomes have poorer hazard ratios than those for PFS)

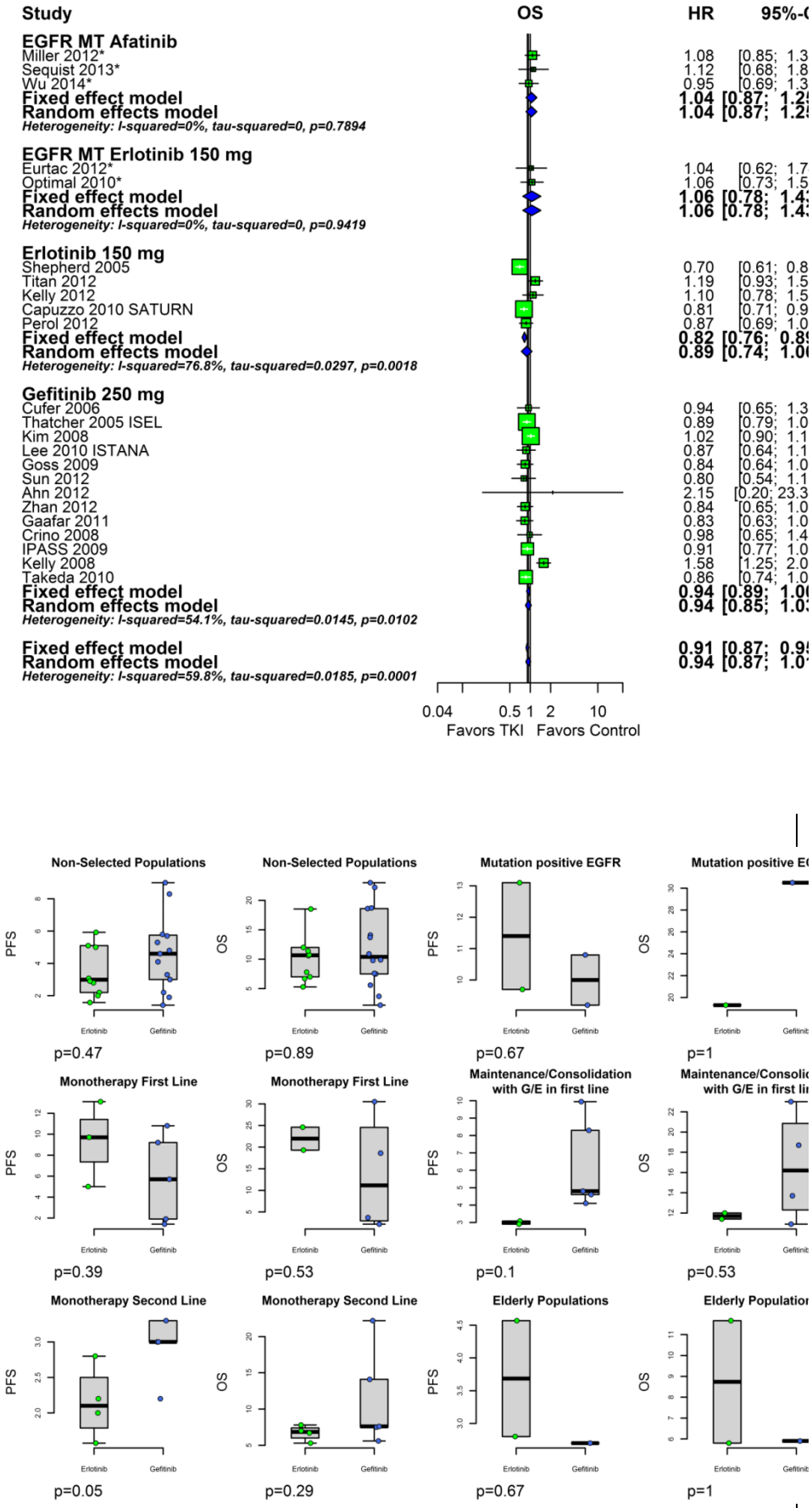


Figure S8: Efficacy analysis in all studies and in various subgroups

	comparing the efficacy of erlotinib and gefitinib. Results are presented for both reported median progression-free survival (PFS) and overall survival (OS) distributions. Boxplots depict the distributions, including the following attributes: the median (solid bar), interquartile range (IQR, box), the range as 1.5 times the IQR (dashed line, excluding any outliers), and the individual study data overlaid as scatterplots.
	4. Fazit der Autoren Gefitinib has similar activity and toxicity compared with erlotinib and offers a valuable alternative to patients with NSCLC. Afatinib has similar efficacy compared with erlotinib and gefitinib in first-line treatment of tumors harboring EGFR mutations but may be associated with more toxicity, although further studies are needed. Gefitinib deserves consideration for U.S. marketing as a primary treatment for EGFR-mutant NSCLC. 5. Hinweise der FBMed von den Autoren: No head-to-head comparisons heterogeneity within subgroups for certain outcomes (i.e., variation between studies exists beyond that forwhich treatment group accounts) some might argue the 150-mg erlotinib dose is the maximum tolerated dose but that the 250-mg gefitinib dose is not, and this may “penalize” erlotinib; however, these are the approved doses and the doses for which data were available inclusion of patients with and without mutations makes analysis more difficult *Anmerkungen der FB Med: Phase II Studien eingeschlossen, Jadad Score aber insgesamt gering DISCLOSURES: The authors indicated no financial relationships.*
Wang F et al, 2012 [50]. Gefitinib Compared with Systemic Chemotherapy as First-line Treatment for Chemotherapy-naive Patients with Advanced Non-small Cell Lung Cancer: A Meta-analysis of Randomised Controlled Trials	1. Fragestellung To define the efficacy of gefitinib in chemotherapy-naive patients with advanced non-small cell lung cancer, we carried out a meta-analysis of randomized controlled trials.
	2. Methodik **Population:** advanced NSCLC, patients with known EGFR mutation status **Intervention:** gefitinib therapy as first-line treatment **Komparator:** conventional therapy **Endpunkte:** PFS, OS **Suchzeitraum:** bis 01/2011 **Anzahl eingeschlossene Studien/Ptienten (Gesamt):** 7 (4656) **Qualitätsbewertung der Studien:** criterions: (1) generation of allocation concealment, (2) description of drop-outs, (3) masking of randomisation, intervention, outcome assessment, (4) intention-to-treat analyses, (5) final analysis reported. Each criterionwas rated as yes, no or unclear. **Heterogenitätsuntersuchungen:** I^2
Al-Saleh K, et	3. Ergebnisdarstellung

al. 2012 [1].

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

Characteristics of included studies

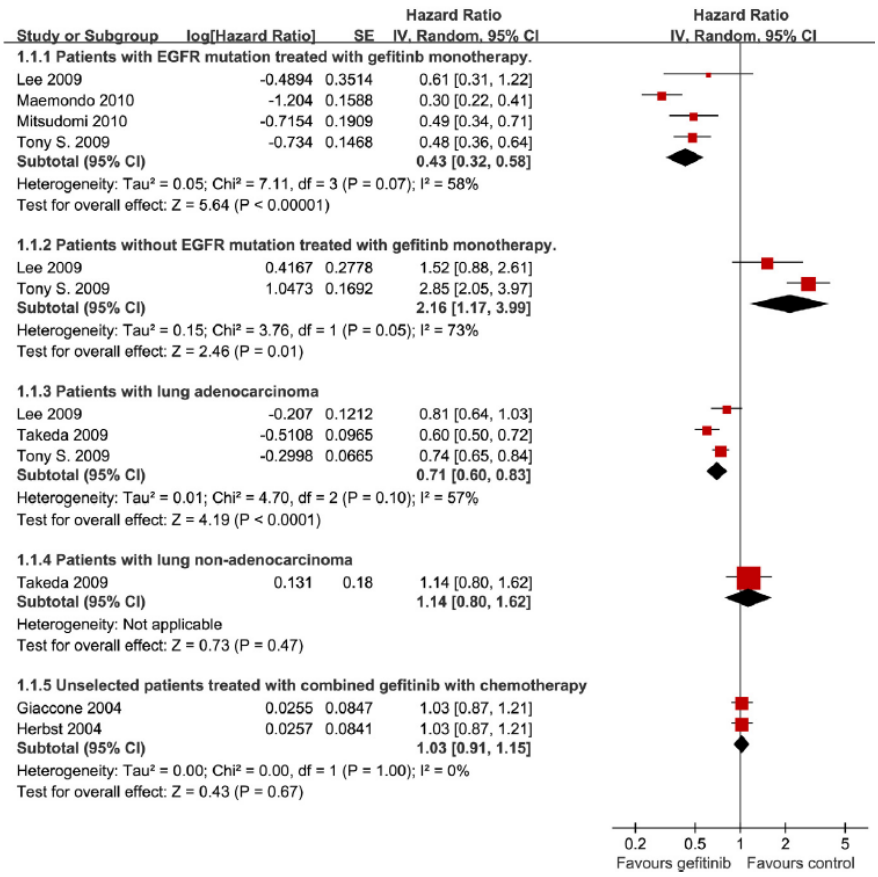
References		n	Gender (%) Male	Gender (%) Female	Age (year)	Therapy regimen	Patient selection*	Publication status	Follow-up period	Ethnicity
Gefitinib monotherapy versus platinum-doublet chemotherapy										
[14]	E	115	36.8	63.2	63.9 ± 7.7	G	Yes	Published	527 days	Asian
	C	115	36.0	64.0	62.6 ± 8.9	PC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

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

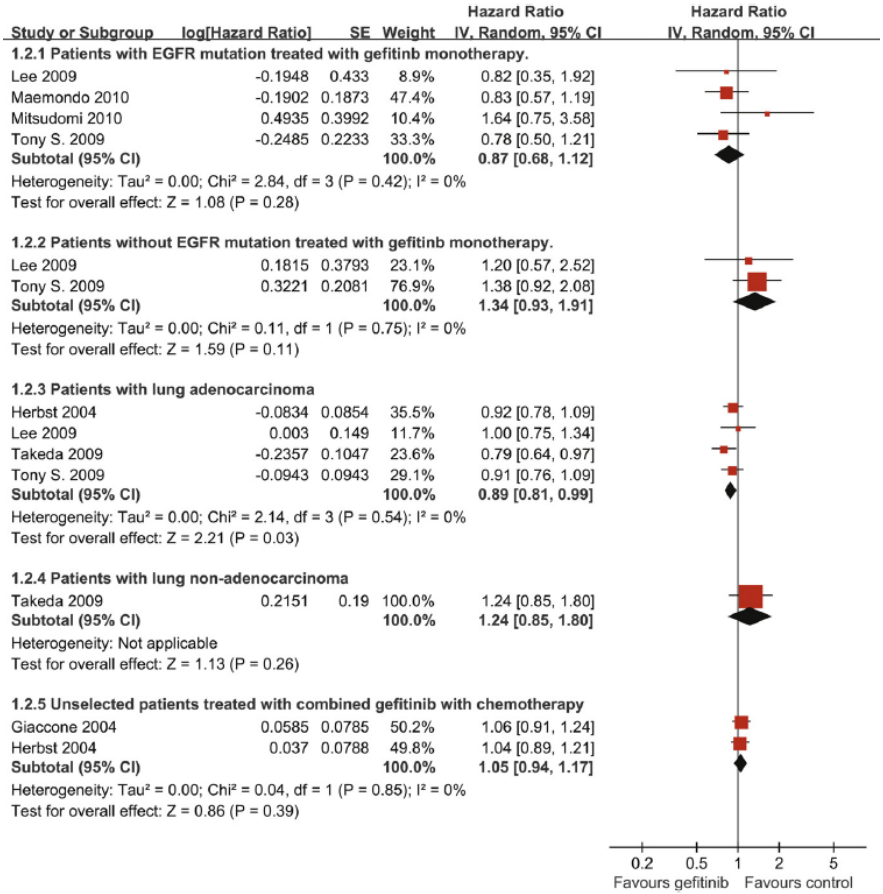
* Patients were selected molecularly or clinically.

† Most patients.

PFS



OS



4. Anmerkungen/Fazit der Autoren
   In conclusion, first-line treatment with gefitinib conferred prolonged progression-free survival than treatment with systemic chemotherapy in a molecularly or histologically defined population of patients with non-small cell lung cancer, and improved survival in the subgroup of patients with lung adenocarcinoma.

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

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

Brown T, et al. 2013 [7].

Clinical

1. Fragestellung

We therefore undertook a systematic review and meta-analysis of the available evidence on the efficacy of pemetrexed compared with other chemotherapeutic agents as first- or second-line treatment in advanced nsclc.

2. Methodik

Population:

advanced NSCLC (stages iii and iv)

Intervention:

pemetrexed

Komparator:

active treatment or with placebo

Endpunkt:

OS (minimum follow up of 12 months)

effectiveness of first-line chemoradiation for adult patients with locally advanced non-small cell lung cancer: a systematic review

Suchzeitraum:

Bis Januar 2010

Anzahl eingeschlossene Studien/Patienten (Gesamt): 5 RCTs (4 Studien: compared pemetrexed with another treatment (three in first-line therapy and one in second-line therapy). 1 Studie: compared pemetrexed as maintenance therapy with a placebo control arm.

Qualitätsbewertung der Studien:

conducted in accordance with the Cochrane handbook guidelines

Heterogenität: I^2

Methodischer Hinweis: a priori hypotheses were established to explore differences in the effectiveness of pemetrexed according to histology (squamous or non-squamous), line of therapy (first or second), and comparator arm (active treatment versus placebo).

3. Ergebnisdarstellung

Eingeschlossen = 5 RCTs (4 Studien: compared pemetrexed with another treatment (three in first-line therapy and one in second-line therapy). 1 Studie: compared pemetrexed as maintenance therapy with a placebo control arm.

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.

OS (5 RCTs):

- Statistisch signifikanter Vorteil in OS for patients treated with pemetrexed compared with either another treatment or placebo [HR: 0.89; 95% CI: 0.80 to 0.99; p=0.04; I²=34%) → no statistically significant heterogeneity (p = 0.19)

OS (4 RCTs; ohne die Erhaltungsstudie):

- Kein statistisch signifikanter Vorteil (pemetrexed vs. active treatment subgroup, HR: 0.93; 95% CI: 0.83 to 1.03; p=0.15; I²=18%)
- The HR for OS was similar whether pemetrexed was used as first- or second-line therapy (hr: 0.89 vs. 0.88; siehe Abb.).

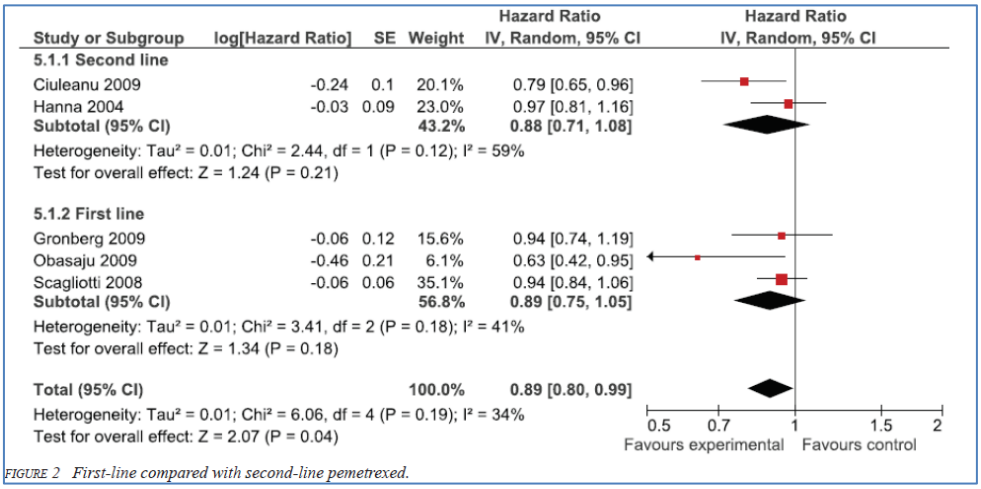


FIGURE 2 *First-line compared with second-line pemetrexed.*

OS based on histologic subtype (4 RCTs)

- Statistisch signifikanter Vorteil in OS for patients with non-squamous histology receiving pemetrexed (HR: 0.82; 95% CI: 0.73 to 0.91; I2 = 12%).
- Three studies reported survival for patients with squamous histology (Figure 4). There was a trend toward inferior survival for patients with squamous histology treated with pemetrexed (HR: 1.19; 95% CI: 0.99 to 1.43) that did not reach statistical significance.

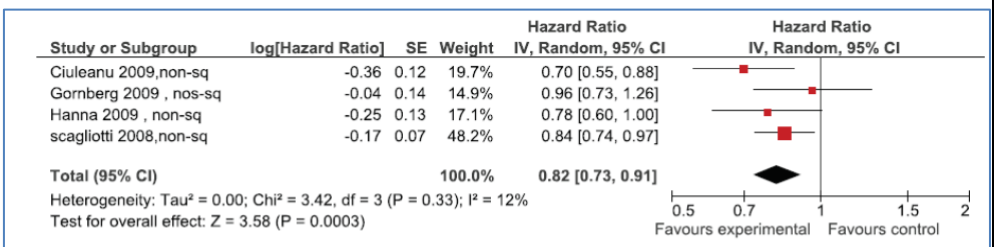


FIGURE 3 *Pemetrexed in non-squamous histology.*

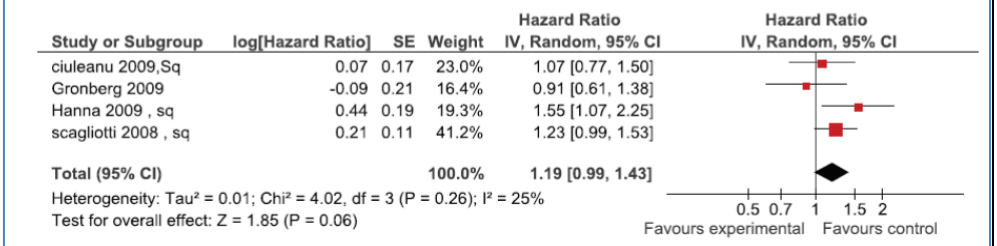


FIGURE 4 *Pemetrexed in squamous histology.*

Toxizität:

	• Nur die aktiv-vergleichenden Studien wurden herangezogen (N=4) • Hematological Toxicity: lower rate of hematologic toxicity was observed in patients treated with pemetrexed • Neutropenia: [odds ratio (OR): 0.41; 95% ci: 0.18 to 0.93], keeping in mind that all studies mandated vitamin B12 and folic acid supplementation for patients receiving pemetrexed. • Anemia: no significant difference (OR: 1.36; 95% CI: 0.73 to 2.52) Alanin-Aminotransferase (ALAT, ALT): more elevation of was observed (or: 11.68; 95% CI: 0.64 to 212.19), although the confidence interval was wide and statistically nonsignificant.
	4. Anmerkungen/Fazit der Autoren This meta-analysis systemically examined the effect of pemetrexed on overall survival in patients with advanced nsclc. A significant improvement in overall survival was observed, but the effect was limited to patients with non-squamous histology. Our findings suggest that, in patients with nonsquamous histology, pemetrexed in various combinations is superior to other chemotherapy regimens for the treatment of advanced nsclc. Patients with squamous cancer treated with pemetrexed appear to have inferior survival. Together, those results support the conclusion that histology is an important determinant in the selection of treatment options in advanced nsclc. **5. Hinweise FbMed** PE has received honoraria and research funding from Eli Lilly and Company. The remaining authors have no financial conflicts of interest to declare.
Brown T, et al. 2013 [7]. Clinical effectiveness of first-line chemoradiation for adult patients with locally advanced non-small cell lung cancer: a systematic review **Hong S, et al., 2015 [23].** Efficacy and safety of angiogenesis	**1. Fragestellung** To evaluate the clinical effectiveness of first-line CTX in addition to radiotherapy (RT) (CTX-RT vs CTX-RT) for adult patients with locally advanced NSCLC who are suitable for potentially curative treatment.
	2. Methodik **Population:** Chemotherapy-naive adult patients with locally advanced NSCLC. **Intervention/ Komperator:** Compared any first-line CTX-RT therapy (induction, sequential, concurrent and consolidation) • sequential CTX-RT compared with concurrent CTX-RT • sequential CTX-RT compared with concurrent/consolidation CTX-RT • sequential CTX-RT compared with concurrent CTX-RT with or without consolidation **Endpunkt:** OS, PFS

inhibitors in advanced non‑small cell lung cancer: a systematic review and meta‑analysis Siehe auch: **Sheng J et al., 2015 [44].**	**Suchzeitraum:** bis September 2010 (American Society for Clinical Oncology (ASCO) was searched from 1998 to 2011) **Anzahl eingeschlossene Studien/Patienten (Gesamt):** N=19 **Qualitätsbewertung der Studien:** criteria based on the Centre for Reviews and Dissemination guidance for undertaking reviews in health care (Centre for Reviews and Dissemination. CRD's guidance for undertaking reviews in health care. York: University of York; 2009). **Heterogenität**: I^2
	3. Ergebnisdarstellung Overall methodological quality of included trials was poor, with nearly all trials failing to report relevant methodology; in particular, methods of randomisation, allocation concealment and blinding were inadequately described (ausführliche Qualitätsbewertung siehe Anhang X). Hinweis: es werden ausschließlich meta-analystische Ergebnisse berichtet **<u>Overall survival data available for inclusion in meta-analyses</u>** **Sequential chemoradiation compared with concurrent chemoradiation (n = 4)[46,51,54,60]** • 2 Studien wurden für die Meta-Analyse berücksichtigt [51,54] • OS advantage for concurrent CTX-RT arms over sequential arms; this result is not statistically significant (HR 0.79; 95% CI 0.50 to 1.25). Visual examination of the forest plot indicates a non-statistically significant chi-squared test for heterogeneity (p = 0.096) and an I2 statistic of 63.9%; the results suggest inconsistency in the direct evidence from the two trials.[51,54] 51 Zatloukal P, Petruzelka L, Zemanova M, Havel L, Janku F, Judas L, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. Lung Cancer 2004;46:87–98. 54. Belderbos J, Uitterhoeve L, van Zandwijk N, Belderbos H, Rodrigus P, van de Vaart P, et al. Randomised trial of sequential versus concurrent chemo-radiotherapy in patients with inoperable non-small cell lung cancer (EORTC 08972–22973). Eur J Cancer 2007;43:114–21. **Sequential chemoradiation compared with concurrent/consolidation chemoradiation (*n* = 4)[49,52,56,57]** • 3 Studien wurden für die Meta-Analyse berücksichtigt [49, 56,57] • The OS HRs for one trial[49] were extracted directly from the published trial paper, while HRs for two trials[56,57] were estimated using summary statistics based on the methods described in the methods section of this report. • statistically significant OS advantage for concurrent/ consolidation CTX-RT treatment over sequential treatment; this result is statistically significant (HR 0.68; 95% CI 0.55 to 0.83). Visual examinations of the forest plot, the chi-squared test for heterogeneity (p = 0.713) and the I2 statistic (0%) all suggest

	very good consistency. 49. Fournel P, Robinet G, Thomas P, Souquet PJ, Lena H, Vergnenegre A, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Francais de Pneumo-Cancerologie NPC 95–01 Study. J Clin Oncol 2005;23:5910–17. 56. Dasgupta A, Dasgupta C, Basu S, Majumdar A. A prospective and randomized study of radiotherapy, sequential chemotherapy radiotherapy and concomitant chemotherapy-radiotherapy in unresectable non small cell carcinoma of the lung. J Cancer Res Ther 2006;2:47–51. 57. Crvenkova S, Krstevska V. Sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small cell lung cancer: our experience. Prilozi 2009;30:197–207. **Sequential chemoradiation compared with concurrent chemoradiation with or without consolidation (n = 8)** [46,49,51,52,54,56,57,60] • 5 Studien wurden für die Meta-Analyse berücksichtigt [49,51,54,56,57] • The HRs for OS for three trials[49,51,54] were extracted directly from the published trial papers, while HRs for two trials[56,57] were estimated using summary statistics based on the methods described in the methods section of this report. • statistically significant OS advantage for concurrent CTX-RT with or without consolidation over sequential treatment; this result is statistically significant (HR 0.72; 95% CI 0.61 to 0.84). Visual examinations of the forest plot, the chisquared test for heterogeneity (p = 0.445) and the I2 statistic (0%) all suggest very good consistency. 49. Fournel P, Robinet G, Thomas P, Souquet PJ, Lena H, Vergnenegre A, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Francais de Pneumo-Cancerologie NPC 95–01 Study. J Clin Oncol 2005;23:5910–17. 51 Zatloukal P, Petruzelka L, Zemanova M, Havel L, Janku F, Judas L, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. Lung Cancer 2004;46:87–98. 54. Belderbos J, Uitterhoeve L, van Zandwijk N, Belderbos H, Rodrigus P, van de Vaart P, et al. Randomised trial of sequential versus concurrent chemo-radiotherapy in patients with inoperable non-small cell lung cancer (EORTC 08972–22973). Eur J Cancer 2007;43:114–21. 56. Dasgupta A, Dasgupta C, Basu S, Majumdar A. A prospective and randomized study of radiotherapy, sequential chemotherapy radiotherapy and concomitant chemotherapy-radiotherapy in unresectable non small cell carcinoma of the lung. J Cancer Res Ther 2006;2:47–51. 57. Crvenkova S, Krstevska V. Sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small cell lung cancer: our experience. Prilozi 2009;30:197–207.

	Adverse events Keine meta-analytischen Ergebnisse. **Quality of life** Only one trial[58] reported on HRQoL and the authors plan to report the results in full in a separate publication. Preliminary analyses showed no statistically significant differences between the trial arms for expected toxicity, dyspnoea, dysphagia and global HRQoL. 58. Nyman J, Friesland S, Hallqvist A, Seke M, Bergstrom S, Thaning L, et al. How to improve locoregional control in stages IIIa-b NSCLC?. Results of a three-armed randomized trial from the Swedish Lung Cancer Study Group. Lung Cancer 2009;65:62–7.
	4. Anmerkungen/Fazit der Autoren This review identified that the research conducted in the area of CTX-RT was generally of poor quality and suffered from a lack of reporting of all important clinical findings, including OS. In addition, there are within- and between-trial variations in treatment protocols including treatment duration, sequencing and length, RT exposure and type of CTX. These wide variations severely limited the combination of trial results. Meta-analyses conducted as part of this review demonstrated a small but statistically significant improvement in OS in patients receiving concurrent/consolidation CTX-RT compared with sequential CTX-RT and statistically significantly improved OS with the use of concurrent CTX-RT (with or without consolidation) over sequential treatment. However, as noted, the variation in treatment protocols and the changes in the diagnostic criteria and staging used in NSCLC mean that the results of comparisons across these trials and with future trials need to be viewed with caution.
Hong S, et al., 2015 [23]. Efficacy and safety of angiogenesis inhibitors in advanced non‑small cell lung cancer: a systematic review and meta‑analysis Siehe auch: **Sheng J et al.,**	**1. Fragestellung** In this study, we performed a systematic review and meta-analysis of RCTs to summarize the up-to-date evidence about the efficacy and safety of angiogenesis inhibitors for advanced NSCLC patients with predefined subgroup analyses
	2. Methodik **Population:** patients with advanced NSCLC **Intervention:** angiogenesis inhibitors **Komparator:** non-angiogenesis inhibitors **Endpunkt:** PFS, OS, ORR, DCR

2015 [44].

Gao et al., 2011 [15].

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

Suchzeitraum:

Bis April 2014

Anzahl eingeschlossene Studien/Patienten (Gesamt): 33 RCTs (N=17,396) → patients (angiogenesis inhibitors: 8,947; control: 8,449)

Qualitätsbewertung der Studien:

Jadad scores

Heterogenität: I^2

3. Ergebnisdarstellung

- 23 Studien analysed TKI-based agents: vandetanib, sunitinib, cediranib, sorafenib, pazopanib, motesanib
- 10 studies focused on antibody-based agents: bevacizumab, aflibercept, ramucirumab
- 13 Studien were performed in first-line settings, 17 in ≥second-line settings and three in maintenance.

Hinweis: ausschließlich Phase-3 Studien, dessen Wirkstoffe zugelassen sind, werden berichtet.

Table 1 Characteristics of all the included randomized controlled trials

First author	Year	Trial phase	Line	Arms	No. of enrolled patients	Median age (years)	Median PFS (months)	Median OS (months)	Jadad score
Bevacizumab									
Boutsikou	2013	3	1	Beva + DC	56	62.5	NM	19.1	2
				DC	61	65	NM	15.3	
Reck	2009	3	1	Beva + GP	351	59	6.5	13.4	5
				Plac + GP	347	59	6.1	13.1	
Sandler	2006	3	2	Beva + TC	417	NM	6.2	12.3	2
				TC	433	NM	4.5	10.3	

OS

Boutsikou (2013): HR 0,77; 95 % CI: 0,38; 1,60

Reck (2009): HR 1,03; 95 % CI: 0,86; 1,23

Sandler (2006): HR 0,79; 95 % CI: 0,67; 0,92 → favour non-angiogenesis inhibitors

PFS

Reck (2009): HR 0,85; 95 % CI: 0,73; 1,00 → favour non-angiogenesis inhibitors

Sandler (2006): HR 0,66; 95 % CI: 0,57; 0,77 → favour non-angiogenesis inhibitors

ORR

Boutsikou (2013): HR 1,33; 95 % CI: 0,80; 2,21

Reck (2009): HR 1,59; 95 % CI: 1,25; 2,04 → favour angiogenesis inhibitors

Sandler (2006): HR 2,33; 95 % CI: 1,80; 3,02 → favour angiogenesis inhibitors

DCR

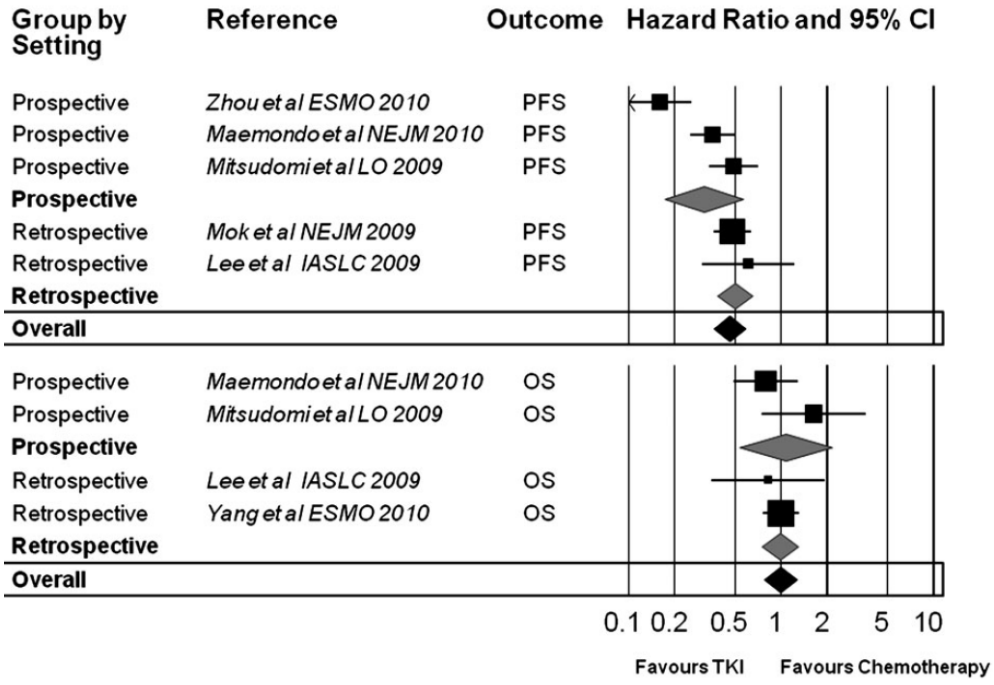
	Boutsikou (2013): HR 1,54; 95 % CI: 1,20; 1,97 → favour angiogenesis inhibitors
	4. Anmerkungen/Fazit der Autoren Angiogenesis inhibitors were superior to non-angiogenesis inhibitors in terms of ORR, DCR, PFS and OS in advanced NSCLC patients. The advantages of anti-angiogenesis therapy were mostly highlighted with antibody-based agents and in ≥second-line settings. Further studies are warranted to explore the predictive biomarkers to pick up those patients who may benefit from angiogenesis inhibition. **5. Hinweise FbMed** Aussage der Autoren für die selektiv-extrahierten Ergebnisse nicht interpretierbar
Gao et al., 2011 [15]. Efficacy of erlotinib in patients with advanced non-small cell lung cancer: a pooled analysis of randomized trials **Bria E et al., 2011 [5].** Outcome of advanced NSCLC patients harboring sensitizing EGFR mutations randomized to EGFR tyrosine kinase inhibitors or chemotherapy as first-line treatment: a meta-analysis	1. Fragestellung to assess the efficacy and safety of erlotinib in patients with advanced NSCLC
	2. Methodik **Population**: advanced NSCLC. Alle Linien **Intervention**: erlotinib alone or based combination therapy **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) **Qualitätsbewertung der Studien:** keine
	3. Ergebnisdarstellung ***First-line therapy (5 trials)*** **Overall survival (4 trials)**: no statistically significant difference between erlotinib-based regimens and other regimens. Significant heterogeneity The subgroup analysis showed a similar OS compared with placebo (HR: 1.02; 95% CI: 0.92–1.13; P=0.73) a decreased OS compared with chemotherapy (HR: 1.39; 95% CI: 0.99–1.94; P=0.05) and a similar OS compared with placebo as maintenance therapy (HR: 0.87; 95% CI: 0.68–1.11; P=0.22) **PFS (3 trials)**: no statistically significant difference between erlotinib-based regimens and other regimens. Significant heterogeneity The pooled estimate showed a similar PFS when compared with placebo (HR: 0.93; 95% CI: 0.85–1.01; P=0.09) a decreased PFS compared with chemotherapy (HR: 1.55; 95% CI: 1.24–1.93; P<0.01) but a prolonged PFS compared with placebo as maintenance therapy (HR: 0.71; 95% CI: 0.60–0.83; P<0.01). **Response rate (9 trials, 5.404 patients):** no statistically significant difference between erlotinib-based regimens and other regimens. Significant heterogeneity The subgroup analysis showed a similar ORR comparing with placebo (OR: 0.90; 95% CI: 0.74–1.09; P=0.29) or chemotherapy (OR: 0.33; 95% CI: 0.64–17.36;

	P=0.15) but an increased ORR comparing with placebo as maintenance therapy (OR: 0.47; 95% CI: 0.31–0.70; P<0.01). ***second/third-line therapy*** compared with placebo: erlotinib-based regimens also significantly increased ORR (OR: 0.10;95% CI: 0.02–0.41; P<0.01), prolonged PFS (HR: 0.61; 95% CI: 0.51–0.73; P<0.01), and improved OS (HR: 0.70; 95% CI: 0.58–0.84; P<0.01). compared with chemotherapy: outcomes were similar between two arms. compared with PF299804: decreased ORR (OR: 3.87; 95% CI: 1.27–11.81; P=0.02), and shortened PFS (HR: 0.58; 95% CI: 0.49–0.95; P=0.02). ***Toxicity**:* All 14 trials including 7261 patients provided results of adverse events. Reported toxicities were analyzed in only 12 trials except for the targeted drugs containing trials. Grade 3/4 diarrhea (OR: 4.87; 95% CI: 3.19–7.44; P<0.01), rash (OR: 28.94; 95% CI: 14.28–58.66; P<0.01), and anemia (OR: 1.39; 95% CI: 1.06–1.82; P=0.02) were significantly prominent in the erlotinib-based regimens.
	4. 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.
Bria E et al., 2011 [5]. Outcome of advanced NSCLC patients harboring sensitizing EGFR mutations randomized to EGFR tyrosine kinase inhibitors or chemotherapy as first-line treatment: a meta-analysis	1. Fragestellung Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) are effective as first-line treatment of advanced non-small-cell lung cancer patients with EGFR mutations (EGFR-M+). We conducted a literature-based meta-analysis to quantify the magnitude of benefit with upfront EGFR TKI in EGFR-M+ patients. Meta-regression and sensitivity analyses were also carried out to identify additional predictors of outcome and to assess the influence of trial design.
	2. Methodik **Population:** advanced NSCLC, patients with known EGFRmutation status; subpopulation of patients carrying an activating EGFR mutation (exon-19 deletions or exon-21 point mutations, EGFR-M+ patients) in the first-line setting **Intervention:** gefitinib or erlotinib **Komparator:** first-line chemotherapy **Endpunkte:** primär: PFS and OS; sekundär: overall response rate (ORR, as reported by trialists) and grades 3–4 toxic effects, **Suchzeitraum:** bis 10/ 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 5 (805) three trials prospectively enrolling EGFR-M+ patients and two retrospective analyses of EGFR-M+ patients **Qualitätsbewertung der Studien:** keine Angabe **Heterogenitätsuntersuchungen:** heterogeneity test was used (nicht spezifiziert)
	3. Ergebnisdarstellung

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

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

PFS/ OS



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

5. Hinweise der FBMed:
   Keine Angaben zur methodischen Bewertung der Primärstudien

Leitlinien

Wauters I et al., 2013 [51]. Belgian Health Care Knowledge Centre (KCE)	Fragestellung/Zielsetzung This study aims to develop a clinical practice guideline (CPG) on lung cancer. The CPG will cover a broad range of topics: staging, treatment of non-small cell lung cancer, treatment of small cell lung cancer and followup. The specific clinical questions (paragraph 2.3) were the result of a scoping review of existing guidelines and consecutive

	discussion within the external expert group.
Non-small cell and small cell lung cancer: diagnosis, treatment and follow-up	Methodik Grundlage der Leitlinie: • The present clinical practice guideline (CPG) was developed by adapting (inter)national CPGs to the Belgian context. In general, and whenever necessary, included guidelines were updated with more recent evidence. In summary, recent evidence-based guidelines of high quality were searched and summarized and served, together with more recent evidence, as basis to formulate the recommendations. Based on the retrieved evidence, draft recommendations were prepared by KCE experts (JR, LV, KHH), and sent for review to the external experts group selected by the College of Oncology. The evidence and the recommendations were discussed during meetings between KCE experts and the group of external experts. • Suchzeitraum: In order to identify published clinical practice guidelines (CPGs) on lung cancer, OVID Medline, the National Guideline Clearinghouse (guideline.gov) and Guidelines International Network (www.g-i-n.net) were searched for both national and international CPGs from 2009 to 20 Gebruary 2012. The update search for peer-reviewed articles included a search in OVID Medline, EMBASE, CENTRAL and the Cochrane Database of Systematic Reviews. For diagnostic and staging research questions, the search was not limited to specific study designs with an aim to include diagnostic accuracy studies. Searches were run between April, 2012 and January, 2013. LoE Table 1 – Levels of evidence according to the GRADE system **Quality level** / **Definition** / **Methodological Quality of Supporting Evidence** **High** – We are very confident that the true effect lies close to that of the estimate of the effect – RCTs without important limitations or overwhelming evidence from observational studies **Moderate** – We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different – RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies **Low** – Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect – RCTs with very important limitations or observational studies or case series **Very low** – We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect – RCTs with very important limitations or observational studies or case series **Source of body of evidence** / **Initial rating of quality of a body of evidence** / **Factors that may decrease the quality** / **Factors that may increase the quality** / **Final quality of a body of evidence** **Randomized trials** – High – 1. Risk of bias 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias – 1. Large effect 2. Dose-response 3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed – High (⊕⊕⊕⊕) Moderate (⊕⊕⊕⊖) Low (⊕⊕⊖⊖) Very low (⊕⊖⊖⊖) **Observational studies** – Low GoR Nach GRADE (strong, weak recommendation)
	Freitext/Empfehlungen/Hinweise

Treatment of locally advanced NSCLC (stage cIIIA-cIIIB)

Treatment of stage cIII NSCLC

Recommendation	Strength of recommendation	Level of evidence
Chemoradiotherapy is recommended for patients with stage III NSCLC.	strong	moderate
Induction therapy followed by surgery can be considered in selected patients with stage IIIA-N2 disease considered resectable at the start of treatment. Optimal treatment in patients with limited stage IIIA-N2 disease should be discussed by a multidisciplinary team taking into account resectability, response to induction treatment, and the availability of surgical expertise.	weak	low
When patients are considered for chemoradiation, it is recommended to offer concurrent chemoradiation in preference to sequential therapy if no contra-indications are present.	strong	moderate
Induction therapy followed by surgery is not recommended in patients with stage IIIA-N2 disease considered unresectable at the start of treatment.	strong	moderate

Good clinical practice
If preoperative chemoradiation is used, timely response assessment should be performed such that the overall treatment scheme is not interrupted in case no surgery is performed.
If preoperative chemotherapy is used and surgery cannot be performed, the time interval between chemotherapy and radiotherapy should be kept as short as possible and not exceed 2-3 weeks.

Treatment of metastatic (stage cIV) and recurrent NSCLC

Treatment of metastatic (stage cIV) and recurrent NSCLC

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

Good clinical practice
It is recommended to offer radiotherapy for palliation of local symptoms to patients with NSCLC.

Australian Government Cancer Council Australia, 2015 [4].

Clinical practice guidelines for the treatment of lung cancer

Fragestellung/Zielsetzung:
What is the optimal first-line chemotherapy regimen in patients with stage IV inoperable NSCLC? Is carboplatin based chemotherapy as effective as cisplatin based chemotherapy for treatment of stage IV inoperable NSCLC? Which new agent or platinum combination regimen is best for treatment of stage IV inoperable NSCLC? Is monotherapy with new third generation (3G) agents as effective as platinum combination therapy for treatment of stage IV inoperable NSCLC? Are three chemotherapy agents better than two chemotherapy agents for treatment of stage IV inoperable NSCLC? Are non-platinum doublet chemotherapy regimens as effective as platinum doublet regimens for treatment of stage IV inoperable NSCLC? Is chemotherapy with a biologic or targeted therapy superior to chemotherapy alone in unselected patients for treatment of stage IV

inoperable NSCLC? What is the optimal chemotherapy regimen for overall quality of life for patients in the treatment of stage IV inoperable NSCLC? What is the optimal second-line therapy in patients with stage IV inoperable NSCLC? What is the optimal third-line therapy in unselected patients with stage IV inoperable NSCLC? What is the optimal systemic therapy regimen for patients with poor performance status for treatment of stage IV inoperable NSCLC? What is the optimal systemic therapy regimen in selected patients for treatment of stage IV inoperable NSCLC?

Methodik

Grundlage der Leitlinie:

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

Suchzeitraum: bis 2015

LoE:

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation	All or none	All or none	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: • Non-randomised, experimental trial • Cohort study • Case-control study • Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: • Non-randomised, experimental trial • Cohort study • Case-control study

III-3	A comparative study without concurrent controls: • Historical control study • Two or more single arm study • Interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: • Historical control study • Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

GoR:

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

Empfehlungen

Stage III inoperable

What is the recommended treatment approach for the definitive management of patients with good performance status and inoperable stage III disease?

Evidence summary	Level	References
In good performance status patients with inoperable stage III NSCLC, surgery does not improve survival in patients who have a radiologic response to induction chemotherapy compared with radiotherapy. Last reviewed December 2015	I	[15]
In good performance status patients with inoperable stage III NSCLC, the addition of chemotherapy to radiation therapy is associated with a statistically significant survival benefit compared with radiation therapy alone Last reviewed December 2015	I	[13], [12], [14]
In good performance status patients with inoperable stage III NSCLC, the concurrent administration of chemotherapy and radiation therapy provides a statistically significant survival benefit compared with the sequential administration of chemotherapy then radiation therapy. Last reviewed December 2015	I	[15], [14]

+ Evidence-based recommendation?	Grade
For patients with good performance status and inoperable stage III NSCLC, the concurrent administration of chemotherapy and radiotherapy is recommended. Last reviewed December 2015	A

✓ Practice point?

In stage III NSCLC patients deemed inoperable at the time of diagnosis, the recommended treatment approach is concurrent chemoradiotherapy. Evidence suggests that the optimal chemotherapy regimen to give concurrently with radiation therapy is a platinum-based doublet.
Last reviewed December 2015

✓ Practice point?

In patients with good performance status and inoperable stage III NSCLC in whom chemotherapy is contra-indicated, treatment with a radical dose of radiation therapy alone is a reasonable option.
Last reviewed December 2015

What is the optimal treatment approach for patients with stage III inoperable NSCLC who, because of patient or tumour factors, are not suitable for curative treatment with concurrent chemo-radiotherapy and who do not have a mutation for targeted therapy?

Evidence summary	Level	References
Palliative radiotherapy achieves reasonable rates of symptom control. Last reviewed December 2015	I	[2]

+ Evidence-based recommendation?	Grade
For patients with stage III disease who because of performance status or disease extent are not suitable for treatment with curative intent and who are experiencing symptoms as a result of chest disease, palliative radiotherapy is recommended. Last reviewed December 2015	A

Evidence summary	Level	References
Higher radiation dose schedules result in a greater likelihood of symptom improvement, a longer duration of symptom relief and an improvement in one year survival compared with lower dose radiation schedules. Last reviewed December 2015	I	[8]

+ Evidence-based recommendation?	Grade
The patient's performance status should be taken into consideration when choosing the radiation dose and fractionation pattern: - Consider treating patients with good performance status with longer radiotherapy regimens because this will lead to a longer duration of symptom relief and may increase survival. Commonly employed radiotherapy regimens include 20Gy/5f, 30Gy/10f, 36Gy/12f, 40Gy/15f, 50Gy/20f. - Patients with poor performance status should be treated with short courses of treatment. Commonly employed radiotherapy regimens include 10Gy/1f, 16Gy/2f (1f/week). Last reviewed December 2015	A

Evidence summary	Level	References
As in metastatic disease, in locally advanced Stage III NSCLC, systemic chemotherapy improves survival and maintains QOL compared with best supportive care. Last reviewed December 2015	I	[10]

+ Evidence-based recommendation?	Grade
For patients with stage III disease who because of performance status or disease extent are not suitable for treatment with curative intent and who are not experiencing symptoms specifically related to chest disease, referral for systemic therapy is recommended. Last reviewed December 2015	A

Evidence summary	Level	References
For patients with locally advanced, inoperable Stage III NSCLC who are not fit for curative radiotherapy, the use of concurrent palliative chemoradiation is superior to chemotherapy alone with respect to survival and HRQOL but is associated with more side effects necessitating admission to hospital. Last reviewed December 2015	II	[12]

+ Evidence-based recommendation?	Grade
For patients with locally advanced, inoperable Stage III NSCLC not fit for curative therapy, consideration should be given to concurrent administration of palliative chemoradiation. Last reviewed December 2015	B

✓ Practice point?

Given the symptomatology experienced by these patients with stage III disease and their poor survival outcomes, referral to palliative care services should be considered.
Last reviewed December 2015

Stage IV inoperable

What is the clinical benefit of radiotherapy to the lung primary in stage IV NSCLC?

Evidence summary	Level	References
Palliative thoracic radiotherapy can relieve symptoms due to primary lung cancer. Last reviewed December 2015	I	[2]
Lower doses of radiotherapy (10Gy in 1 fraction, 17Gy in 2 fractions) are equivalent to higher doses (20Gy in 5 fractions, 30-39Gy in 10-13 fractions and higher) in terms of symptom palliation. Last reviewed December 2015	I	[2]
In patients with good performance status, higher doses of radiotherapy (20Gy in 5 fractions, 30-39Gy in 10-13 fractions) give a modest survival benefit of approximately 5% at one year and 3% at two years and are associated with longer duration of symptom palliation. Last reviewed December 2015	I, II	[2], [7]
Acute toxicity of palliative thoracic radiotherapy is generally mild. Higher doses of radiotherapy are associated with greater acute toxicity particularly oesophagitis. Last reviewed December 2015	I	[2]
Patients with minimal thoracic symptoms do not benefit from immediate thoracic radiotherapy. Last reviewed December 2015	II	[10]
External beam radiotherapy is more effective for palliation of thoracic symptoms than endobronchial brachytherapy. There is no therapeutic advantage in giving both these treatment modalities over external beam radiotherapy alone. Last reviewed December 2015	I	[11]

+ Evidence-based recommendation?	Grade
Patients who have thoracic symptoms of moderate severity from their primary lung cancer should be offered a course of palliative external beam thoracic radiotherapy. Last reviewed December 2015	A

+ Evidence-based recommendation?	Grade
Patients who are of poor performance status should be treated with lower doses of palliative thoracic radiotherapy (8-10Gy in 1 fraction, 16-17Gy in 2 fractions) as this provides equivalent symptomatic response to higher doses of radiotherapy (20Gy in 5 fractions, 30-39Gy in 10-13 fractions). Last reviewed December 2015	A

+ Evidence-based recommendation?	Grade
Patients who are of good performance status should be treated with higher doses (20Gy in 5 fractions, 30-39Gy in 10-13 fractions) of palliative thoracic radiotherapy in order to maximise duration of palliation and survival. Last reviewed December 2015	B

✓ Practice point?

Patients with a centrally located lung cancer who are at risk of major airway obstruction should be considered for palliative thoracic radiotherapy, even in the absence of symptoms.
Last reviewed December 2015

What is the optimal first-line chemotherapy regimen in patients with stage IV inoperable NSCLC?

Evidence summary	Level	References
Platinum-based chemotherapy improves survival in stage IV NSCLC compared with best supportive care. Note that this evidence is based on clinical trials conducted in fit patients, with predominant performance status 0-1, no unstable co-morbidities, adequate organ function and without uncontrolled brain metastases. Last reviewed December 2015	I	[4], [5]

+ Evidence-based recommendation?	Grade
Platinum-based chemotherapy can be used to extend survival in newly diagnosed patients with stage IV NSCLC. Last reviewed December 2015	A

✓ Practice point?

The decision to undertake empirical platinum-based chemotherapy in a given patient should consider factors such as patient performance status (0,1 versus 2 or more) and co-morbidities, their disease extent and symptoms, proposed treatment toxicity and their individual preferences for benefit from specific treatment(s) and toxicities.
Last reviewed December 2015

Is carboplatin based chemotherapy as effective as cisplatin based chemotherapy for treatment of stage IV inoperable NSCLC?

Evidence summary	Level	References
First-line chemotherapy involving cisplatin results in a slightly higher likelihood of tumour response than the same chemotherapy with carboplatin. Last reviewed December 2015	I	[1], [2], [3]
There is no definite overall survival difference between cisplatin or carboplatin based first-line chemotherapy. Last reviewed December 2015	I	[1], [2], [3]
Cisplatin-based chemotherapy is associated with more severe nausea and vomiting and nephrotoxicity; severe thrombocytopaenia is more frequent during carboplatin-based chemotherapy. Last reviewed December 2015	I	[1], [2], [3]

+ Evidence-based recommendation?	Grade
In patients with high tumour burden and symptoms from stage IV NSCLC cisplatin based chemotherapy may be used in preference to carboplatin for the purpose of inducing a response, however, this benefit may be offset by its greater risk of toxicity. Last reviewed December 2015	B

✓ Practice point?

The choice of cisplatin versus carboplatin in a given patient may consider the balance between perceived benefit (in tumour response) versus known toxicity, whilst considering patient preferences.
Last reviewed December 2015

Which new agent or platinum combination regimen is best for treatment of stage IV inoperable NSCLC?

Evidence summary	Level	References
3G platinum-based chemotherapy (vinorelbine, paclitaxel, docetaxel or gemcitabine) is associated with higher response ratio than older 2G platinum-based chemotherapy. Last reviewed December 2015	I	[1], [2], [3]
No 3G platinum-based chemotherapy regimen (vinorelbine, paclitaxel, docetaxel or gemcitabine) has been shown to be superior to another. Last reviewed December 2015	I	[1], [2], [3]
In first-line empirical treatment of advanced NSCLC, chemotherapy with cisplatin and pemetrexed is superior to cisplatin/gemcitabine in patients with non-squamous cell carcinoma histology. Last reviewed December 2015	II	[5]
In first-line empirical treatment of advanced NSCLC, chemotherapy with cisplatin and pemetrexed is inferior to cisplatin/gemcitabine in patients with SCC histology. Last reviewed December 2015	II	[5]

+ Evidence-based recommendation?	Grade
3G platinum-based chemotherapy (with vinorelbine, paclitaxel, docetaxel or gemcitabine) is a standard of care as first-line chemotherapy in fit patients with stage IV NSCLC. Last reviewed December 2015	A

+ Evidence-based recommendation?	Grade
In the first-line setting, chemotherapy with cisplatin and pemetrexed is recommended in preference to cisplatin and gemcitabine in patients with non-squamous cell carcinoma histology. Last reviewed December 2015	B

+ Evidence-based recommendation?	Grade
In the first-line setting, chemotherapy with cisplatin and gemcitabine is recommended in preference to cisplatin and pemetrexed in patients with squamous cell carcinoma histology. Last reviewed December 2015	B

✓ Practice point?
The choice of first-line platinum combination chemotherapy in a given patient may consider patient performance status and co-morbidities, the proposed treatment toxicity, treatment scheduling and individual patient preferences. Last reviewed December 2015

Is monotherapy with new third generation (3G) agents as effective as platinum combination therapy for treatment of stage IV inoperable NSCLC?

Evidence summary	Level	References
3G platinum-based combination chemotherapy (vinorelbine, paclitaxel, docetaxel, irinotecan or gemcitabine) is superior to 3G agent monotherapy. Last reviewed December 2015	I	[1], [4]
3G platinum-based monotherapy (vinorelbine, paclitaxel, docetaxel, or gemcitabine) improves survival compared with best supportive care. Last reviewed December 2015	I	[2]

+ Evidence-based recommendation?	Grade
Patients fit for chemotherapy should be offered 3G platinum-based combination chemotherapy (vinorelbine, paclitaxel, docetaxel, irinotecan or gemcitabine) in preference to 3G agent monotherapy, as it is more effective. Last reviewed December 2015	A

+ Evidence-based recommendation?	Grade
Patients unfit for combination chemotherapy could be considered for 3G monotherapy with vinorelbine, paclitaxel, docetaxel or gemcitabine. Last reviewed December 2015	A

Are three chemotherapy agents better than two chemotherapy agents for treatment of stage IV inoperable NSCLC?

Evidence summary	Level	References
Triplet chemotherapy regimens are associated with higher response rate, but no improvement in survival. Last reviewed December 2015	I	[1]
Triplet chemotherapy regimens are associated with greater grade 3 /4 toxicities. Last reviewed December 2015	I	[2]

+ Evidence-based recommendation?	Grade
Triplet chemotherapy regimens are not recommended, as benefit in response rate does not outweigh extra toxicity. Last reviewed December 2015	A

Are non-platinum doublet chemotherapy regimens as effective as platinum doublet regimens for treatment of stage IV inoperable NSCLC?

Evidence summary	Level	References
Platinum-based doublet 3G chemotherapy is associated with a higher response rate and slightly higher one-year survival than non-platinum doublet chemotherapy. Last reviewed December 2015	I	[1], [2], [3]
Platinum-based doublet 3G chemotherapy is associated with greater risk of anaemia and thrombocytopaenia than non-platinum combination therapy. Last reviewed December 2015	I	[1], [2], [3]
Gemcitabine and paclitaxel improves response ratio without added toxicity, compared with gemcitabine or paclitexel and carboplatin combinations. Last reviewed December 2015	I	[3]

+ Evidence-based recommendation?	Grade
Non-platinum 3G doublet chemotherapy is an effective alternative option for patients unsuitable for platinum-based therapy. Last reviewed December 2015	B

Is chemotherapy with a biologic or targeted therapy superior to chemotherapy alone in unselected patients for treatment of stage IV inoperable NSCLC?

Evidence summary	Level	References
In carefully selected** patients with advanced NSCLC, high dose bevacizumab improves tumour response rate and progression free survival. **Patients with the following criteria were excluded from the trials: SCC histologic type, brain metastases, clinically significant haemoptysis,inadequate organ function, ECOG PS of 1, therapeutic anticoagulation, clinically significant cardiovascular disease, or medically uncontrolled hypertension. Last reviewed December 2015	I	[4], [5]
In carefully selected** patients with advanced NSCLC, treatment with high dose bevacizumab is associated with an increase in treatment related deaths. Last reviewed December 2015	I	[4]

+ Evidence-based recommendation?	Grade
High dose bevacizumab (15 mg/kg three-weekly) may be considered in addition to chemotherapy (carboplatin/paclitaxel or cisplatin/gemcitabine) in carefully selected** patients with non-squamous cell carcinoma. Last reviewed December 2015	B

Evidence summary	Level	References
The addition of the EGFR TKIs gefitinib or erlotinib to a standard chemotherapy regimen does not improve outcomes (OS, RR or time to progression (TTP)) compared with chemotherapy alone. Last reviewed December 2015	II	[7], [8], [10], [9]

+ Evidence-based recommendation?	Grade
The first generation EGFR TKIs gefitinib or erlotinib should not be used in unselected patients in combination with standard chemotherapy. Last reviewed December 2015	A

Evidence summary	Level	References
In patients with advanced NSCLC (selected by the presence of EGFR-positive tumour as measured by immunohistochemistry), the addition of cetuximab to chemotherapy increases response rate and improves overall survival. This overall benefit was modest and observed only in the phase III trial using cisplatin/vinorelbine . Last reviewed December 2015	I	[11], [12]

+ Evidence-based recommendation?	Grade
In patients with advanced NSCLC whose tumours have been shown to express EGFR by immunohistochemistry, cetuximab may be considered in addition to cisplatin/vinorelbine chemotherapy to improve response rate and overall survival. Last reviewed December 2015	B

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

Evidence summary	Level	References
In patients with poor performance status (PS 2), first-line monotherapy with 3G chemotherapy (vinorelbine, gemcitabine, paclitaxel or docetaxel) may improve survival and/or quality of life. Last reviewed December 2015	I, II	[3], [4], [5], [6], [7], [2]

+ Evidence-based recommendation?	Grade
First-line monotherapy with 3G chemotherapy could be offered to selected patients with PS2 for symptom improvement and possible survival gain, who are willing to accept treatment toxicity. Last reviewed December 2015	B

1

Evidence summary	Level	References
There is evidence for benefit with erlotinib 150 mg daily as second or third-line therapy in unselected poor performance status patients (PS2 or 3) . Last reviewed December 2015	II	[8]

+ Evidence-based recommendation?	Grade
Poor performance status patients having received 1 or 2 lines of prior therapy, may be offered erlotinib 150 mg daily. Last reviewed December 2015	B

✓ Practice point?

Decision-making on treatment in poor performance status patients may weigh up benefits against toxicity and patient preferences. Whilst a single agent 3G chemotherapy is an option in unselected patients, patients with known activating EGFR MTs should be considered for first line EGFR TKIs as the magnitude of benefit is greater and toxicity profile more favourable.
Last reviewed December 2015

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

Evidence summary	Level	References
In patients with poor performance status (PS 2), first-line monotherapy with 3G chemotherapy (vinorelbine, gemcitabine, paclitaxel or docetaxel) may improve survival and/or quality of life. Last reviewed December 2015	I, II	[3], [4], [5], [6], [7], [2]

+ Evidence-based recommendation?	Grade
First-line monotherapy with 3G chemotherapy could be offered to selected patients with PS2 for symptom improvement and possible survival gain, who are willing to accept treatment toxicity. Last reviewed December 2015	B

Evidence summary	Level	References
There is evidence for benefit with erlotinib 150 mg daily as second or third-line therapy in unselected poor performance status patients (PS2 or 3) . Last reviewed December 2015	II	[8]

+ Evidence-based recommendation?	Grade
Poor performance status patients having received 1 or 2 lines of prior therapy, may be offered erlotinib 150 mg daily. Last reviewed December 2015	B

✓ Practice point?

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

Last reviewed December 2015

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

Evidence summary	Level	References
First-line single agent vinorelbine (30 mg/m2 on days one and eight, Q3 weekly) in patients over 70 years of age improves survival and reduces disease related symptoms. Last reviewed December 2015	II	[1]
In patients over 70 years of age, first line single agent docetaxel 60 mg/m2 (day one) compared to vinorelbine 25 mg/m2 (days one and eight) every 21 days, improves response rate, progression free survival and disease related symptoms, but not overall survival and is associated with more G3/4 neutropaenia. Last reviewed December 2015	II	[2]
In patients over 65 years of age, gemcitabine doublet chemotherapy improves response rate compared with single agent 3G chemotherapy, but does not improve survival and is associated with greater thrombocytopaenia. Last reviewed December 2015	I	[4]
In patients over 70 years of age, first-line carboplatin/weekly paclitaxel combination improves survival compared with 3G monotherapy (weekly vinorelbine or gemcitabine) but, is associated with more neutropaenia. Last reviewed December 2015	II	[5]

+ Evidence-based recommendation?	Grade
Suitably fit patients over 65 years of age, can be offered first-line mono-chemotherapy with a 3G single agent (vinorelbine (25-30 mg/ m2 day one, eight Q3 weekly), docetaxel (60 mg/m2 day one, Q3 weekly) or gemcitabine (1150 mg/m2 days one and eight, Q3 weekly). Last reviewed December 2015	B

+ Evidence-based recommendation?	Grade
In elderly patients, first-line gemcitabine doublet chemotherapy is not recommended. Last reviewed December 2015	B

+ Evidence-based recommendation?	Grade
In fit elderly patients, first-line carboplatin/weekly paclitaxel may be offered instead of 3G monotherapy, but at the expense of greater neutropaenia. Last reviewed December 2015	B

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

Evidence summary	Level	References
Histology (non-squamous cell carcinoma versus squamous cell carcinoma) is associated with a significant treatment modifying effect for patients treated with pemetrexed based chemotherapy, with superior survival effect of pemetrexed observed in non-squamous cell carcinoma histology and inferior survival effect observed in squamous cell carcinoma histology, compared with other standard regimens when pemetrexed is used first-line, as switch maintenance or as second-line treatment. Last reviewed December 2015	I	[1]

+ Evidence-based recommendation?	Grade
Due to the therapeutic implications, it is important to classify the histologic subtype of NSCLC on diagnostic specimens as accurately as possible, particularly to enable accurate distinction between the key histologic subtypes: adenocarcinoma and squamous cell carcinoma. Last reviewed December 2015	A

✓ Practice point?

Given the importance of accurate histologic diagnosis and the potential need to have sufficient tissue for subsequent molecular testing, it is important to obtain as much tissue as possible at initial diagnosis in patients suspected to have NSCLC.

A multidisciplinary team discussion may be required in order to decide on the most appropriate diagnostic method to obtain adequate tissue.

Last reviewed December 2015

Evidence summary	Level	References
In Asian patients with advanced NSCLC and known common activating EGFR GMs (exon-19 deletions or exon-21 point mutations), first-line therapy with a first generation EGFR TKI (gefitinib or erlotinib) significantly prolongs progression free survival and increases overall response rate, compared with standard platinum-based chemotherapy. Last reviewed December 2015	I	[9]
In regards to progression free survival, first-line gefitinib is not inferior to carboplatin/paclitaxel chemotherapy in Asian patients, particularly females, with adenocarcinoma, who have never smoked. Last reviewed December 2015	II	[5]
In caucasian patients with advanced NSCLC and known activating EGFR GMs (exon-19 deletions or exon-21 point mutations), first-line therapy with erlotinib significantly prolongs progression free survival and increases overall response rate, compared with standard platinum based chemotherapy. Last reviewed December 2015	II	[10]

+ Evidence-based recommendation?	Grade
Patients with known activating gene mutations (exon-19 deletions or exon-21 point mutations) to EGFR should be treated with an EGFR TKI. Last reviewed December 2015	A

Evidence summary	Level	References
Progression free survival is significantly longer among patients treated with initial chemotherapy, than those treated with gefitinib in patients known not to have EGFR mutations. Last reviewed December 2015	II	[5]

+ Evidence-based recommendation?	Grade
Where EGFR mutation status is negative or unknown, patients should be treated with standard chemotherapy. Last reviewed December 2015	B

✓ Practice point?

The evidence in support of large treatment benefits with first-line EGFR TKIs in response rate and progression free survival argues for consideration of obtaining adequate tumour tissue where possible, to enable molecular testing for the presence of activating EGFR gene mutations. This will enable clinicians to offer patients initial EGFR TKIs versus empirical therapy, bearing in mind that overall survival for EGFT GMT + patients does not appear to be compromised, as long they go on to receive EGFR TKIs after chemotherapy.
Last reviewed December 2015

Alberta Provincial Thoracic Tumour Team,	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

2013 [2]. Non-small cell lung cancer - stage III. Alberta Health Services	for patients with inoperable stage III non-small cell lung cancer? 3. When is palliation recommended, and what are the recommend Update der Version von 2008
	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
	Empfehlungen **When is palliation recommended, and what are the recommended palliative treatment options for patients with inoperable stage III non-small cell lung cancer?** **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.
Alberta Provincial Thoracic Tumour Team, 2013 [3]. Non-small cell lung cancer - stage IV. Alberta Health Services	Fragestellungen 1. What is the recommended first-line therapy for patients with stage IV non-small cell lung cancer (NSCLC)? 2. What is the role for EGFR tyrosine kinase inhibitors in first-line treatment of patients with stage IV NSCLC? 3. What is the optimal second-line therapy for patients with stage IV NSCLC? 4. What is the role of palliative radiotherapy in the management of patients with stage IV NSCLC?
	Methodik Grundlage der Leitlinie: - systematic literature search, evidence tables, AGREE used for retrieved guidelines, working group reviewed currency and acceptability of all relevant literature, then circulated a draft of the updated guideline to entire provincial tumour team for final feedback and approval - 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
	Empfehlungen

	3. Combination chemotherapy consisting of a platinum-based doublet is the standard of care for first-line treatment of advanced NSCLC (except for EGFR-positive patients; see recommendation 6 below). The combination of three chemotherapeutic agents for the first-line treatment of advanced NSCLC is not routinely recommended based on current evidence. 5. Acceptable alternatives to combination chemotherapy include non-platinum doublets or monotherapy: - For patients with a borderline performance status (PS=2), single-agent chemotherapy with vinorelbine, gemcitabine, paclitaxel, docetaxel or pemetrexed (for non-squamous cell carcinoma patients only) is recommended over best supportive care alone. - For elderly patients who cannot tolerate a platinum-based combination, single-agent chemotherapy with vinorelbine, gemcitabine, docetaxel, or pemetrexed (for non-squamous cell carcinoma patients only) is associated with improved survival and quality of life when compared to best supportive care alone. However, elderly patients with a good performance status (PS=0-1) should receive combination chemotherapy with a platinum-based doublet. 6. First-line monotherapy with the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib is recommended for patients with EGFR mutation-positive NSCLC. 7. Testing for EGFR mutations should take place for all eligible patients with advanced NSCLC and adenocarcinoma (including adenosquamous) histology who are being considered for first-line therapy with gefitinib, irrespective of their gender, ethnicity, and smoking status. 8. Second-line or subsequent chemotherapy options for advanced NSCLC include single-agent docetaxel or erlotinib for patients with squamous cell carcinoma histology, or single agent treatment with a drug that has not been previously used. 9. Crizotinib has been approved for second-line treatment of patients who are positive for ALK-rearrangements from the pan-Canadian Oncology Drug Review (pCODR) and has also been approved for provincial coverage in Alberta. 10. Testing for ALK mutations should take place for all eligible patients with advanced NSCLC and adenocarcinoma (including adenosquamous) histology who are being considered for second line therapy with crizotinib. 11. Palliative radiotherapy is recommended for relief of specific symptoms and prophylactic prevention of symptom development.

Ellis PM, Vella ET, Ung YT, and the Lung Cancer Disease Site Group. 2016 [14] Systemic Treatment for Patients with Advanced Non-Small Cell Lung Cancer	Fragestellung/Zielsetzung **Clinical Question A1:** Which patients with stage IIIB/IV NSCLC should be treated with chemotherapy? **Clinical Question A2:** What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with NSCC, negative or unknown EGFR-sensitizing mutation and ALK gene rearrangement status, and PS 0 to 1 or possibly PS 2? **Clinical Question A2.a:** What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with negative or unknown EGFR/ALK status, NSCC, and no contraindications to bevacizumab? **Clinical Question A2.b:** What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with PS 2, NSCC, and negative or unknown EGFR-sensitizing mutation and ALK gene rearrangement status? **Clinical Question A3:** What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with SCC, negative or unknown EGFR-sensitizing mutation and ALK gene rearrangement status, and PS 0 to 1 or possibly PS 2? **Clinical Question A3.a:** What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with negative or unknown EGFR/ALK status, SCC, and PS 2? **Clinical Question A4:** What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with an EGFR-sensitizing mutation and PS 0 to 1 or possibly PS 2? **Clinical Question A5:** What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with ALK gene rearrangement and PS 0 to 1 or possibly PS 2? **Clinical Question A6:** What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with ROS1 rearrangement, no ALK gene rearrangement, negative or unknown EGFR-sensitizing mutation status, and PS 0 to 1 or possibly PS 2? **Clinical Question A7:** What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with negative or unknown EGFR/ALK status and large-cell neuroendocrine carcinoma? • The primary outcome for most trials was either OS or PFS.
	Methodik Grundlage der Leitlinie: update von 2009 und 2010, in 2016 Adaptation der aktuellen Leitlinie der American Society of Clinical Oncology (ASCO) mit ergänzenden systematischen Übersichten zu den klinischen Fragestellungen (siehe oben), methodisches Vorgehen orientiert an AGREE II, internes formales Abstimmungsverfahren,

	externes Review, COI z.T. vorhanden
	
	LoE und GoR: Studienqualität geprüft und detailliert dargestellt, Empfehlungsstärken über die Formulierung abgebildet
	
	Sonstige methodische Hinweise
	
	– Further information: PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*
	– The following recommendations were endorsed with no modifications: A1.a, A1.b, A2.a.2, A2.b, A3, A3.a, A4, A5, A6, A7, and do not appear in Table 3-2 (siehe Anhang).
	– Systematisches Review: MEDLINE (1946 to February 16, 2016), EMBASE (1996 to February 16, 2016), and PubMed (February 16, 2016) databases were searched for RCTs.
	– Inclusion Criteria
	  o Phase II or III RCTs comparing treatment with immune checkpoint inhibitors with chemotherapy; and
	  o Stage IIIB or IV NSCLC; and
	  o Fully published papers or published abstracts of trials that reported at least one of the following outcomes by treatment group: OS, PFS, response rate, or adverse events.
	– Exclusion Criteria
	  o Pilot trials, dose-escalation trials, or case series (including expanded access programs) studies.
	  o Letters and editorials that reported clinical trial outcomes.
	  o Conference abstracts published before 2013.
	– Empfehlungen sind mit Literaturstellen verknüpft

	Freitext/Empfehlungen/Hinweise **Recommendation A1.a:** For patients with PS of 0 or 1, a combination of two cytotoxic drugs is recommended. Platinum combinations are recommended over nonplatinum therapy; however, nonplatinum therapy combinations are recommended for patients who have contraindications to platinum therapy. Chemotherapy may also be used to treat selected patients with PS 2 who desire aggressive treatment after a thorough discussion of the risks and benefits of such treatment. **Recommendation A1.b:** Because there is no cure for patients with stage IIIB/IV NSCLC, early concomitant palliative care assistance has improved the survival and well-being of patients and is therefore recommended. **Recommendation A2:** For patients who have the characteristics described in Clinical Question A2 and who have non-squamous histology, the following options are acceptable:

	● Cisplatin-based combinations ● Cisplatin plus docetaxel ● Cisplatin plus paclitaxel ● Cisplatin plus pemetrexed ● Cisplatin plus vinorelbine ● Cisplatin plus gemcitabine ● Carboplatin-based combinations ● Carboplatin plus albumin-bound (nab) –paclitaxel ● Carboplatin plus paclitaxel ● Carboplatin plus pemetrexed ● Carboplatin plus docetaxel ● Carboplatin plus gemcitabine ● Nonplatinum doublets **Recommendation A2.a.1:** For patients receiving carboplatin plus paclitaxel, the addition of bevacizumab 15 mg/kg once every three weeks is recommended, except for patients with SCC histologic type, clinically significant hemoptysis, a known bleeding disorder, inadequate organ function, Eastern Cooperative Oncology Group PS > 1, clinically significant cardiovascular disease, or medically uncontrolled hypertension. Caution should be exercised in patients with brain metastases. Bevacizumab may be continued, as tolerated, until disease progression. An alternative treatment strategy for patients who are eligible for carboplatin, paclitaxel, and bevacizumab would include cisplatin or carboplatin plus pemetrexed and maintenance pemetrexed. **Recommendation A2.a.2:** There is insufficient evidence (for or against) to recommend pemetrexed in combination with bevacizumab plus carboplatin for patients who do not have contraindications to bevacizumab. **Recommendation A2.b:** In the context of shared decision making, combination therapy, single-agent chemotherapy, or palliative therapy alone may be used for patients in this population with PS 2. **Recommendation A3:** Patients with the characteristics listed in Clinical Question A3 and with SCC histology should be offered the following options: ● Cisplatin-based combinations ● Cisplatin plus docetaxel ● Cisplatin plus gemcitabine ● Cisplatin plus paclitaxel ● Cisplatin plus vinorelbine ● Carboplatin-based combinations ● Carboplatin plus gemcitabine ● Carboplatin plus paclitaxel ● Carboplatin plus nab-paclitaxel ● Carboplatin plus docetaxel ● Nonplatinum doublets

	Recommendation A3.a: In the context of shared decision making, combination chemotherapy, single-agent chemotherapy, or palliative therapy alone may be used for patients with the characteristics described in Clinical Question A3.a. **Recommendation A4:** If patients have stage IIIB/IV NSCLC and a sensitizing EGFR mutation, first-line afatinib, erlotinib, or gefitinib is recommended. **Recommendation A5:** If patients have stage IIIB/IV NSCLC and ALK rearrangements, first-line crizotinib is recommended. **Recommendation A6:** If patients have stage IIIB/IV NSCLC with ROS1 rearrangement, single-agent crizotinib is recommended, because it has shown some results indicating improved response rate and duration of response. **Recommendation A7:** Patients with large-cell neuroendocrine carcinoma may receive the same treatment as other patients with NSCLC or treatment with etoposide in platinum combinations.
Masters GA, et al. 2015 [30]. Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update	Diese Leitlinie wurde von Ellis PM, Vella ET, Ung YT, and the Lung Cancer Disease Site Group. 2016 bewertet und adaptiert (siehe oben).
Scottish Intercollegiate Guidelines Network (SIGN). 2014 [43]. Management of lung cancer. A national clinical guideline	Fragestellung/Zielsetzung In patients with NSCLC (locally advanced or metastatic disease), what is the most effective first/second line systemic anticancer therapy (chemotherapy, targeted therapy, EGFR Inhibitors)? Outcomes: Overall survival, progression-free survival, toxicity, quality of life
	Methodik Grundlage der Leitlinie: systematische Recherche und Bewertung der Literatur, Entwicklung durch multidisziplinäre Gruppe von praktizierenden klinischen ExpertInnen, Expertenreview, öffentliche

Konsultation

Suchzeitraum: 2005 - 2012

LoE/GoR:

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

Sonstige methodische Hinweise: aktuelle Entwicklungen zu molekularen Alterationen noch nicht berücksichtigt

Freitext/Empfehlungen/Hinweise

8.2 First line therapy for patients with stage IIIB and IV NSCLC

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

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

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

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

	222. Ranson M, et al. Randomized trial of paclitaxel plus supportive care versus supportive care for patients with advanced non-small-cell lung cancer. J Natl Cancer Inst 2000;92(13):1074-80. 223. Roszkowski K, et al. A multicenter, randomized, phase III study of docetaxel plus best supportive care versus best supportive care in chemotherapynaive patients with metastatic or non-resectable localized non-small cell lung cancer (NSCLC). Lung Cancer 2000;27(3):145-57. 224. Gridelli C. The ELVIS trial: a phase III study of single-agent vinorelbine as first-line treatment in elderly patients with advanced non-small cell lung cancer. Elderly Lung Cancer Vinorelbine Italian Study. Oncologist 2001;6(Suppl 1):4-7. No particular combination of these agents in regimens with platinum has been shown to be more effective. **(LoE 1+)** 225. Schiller JH, et al. Comparison of four chemotherapy regimens for advanced nonsmall- cell lung cancer. N Engl J Med 2002;346(2):92-8. Standard treatment is in four cycles, and exceptionally six cycles. Continuing beyond four cycles may increase progression-free survival but at the expense of an increase in toxicity and worse quality of life without any significant gain in survival. **(LoE 1+/1++)** 226. Goffin J, et al. First-line systemic chemotherapy in the treatment of advanced non-small cell lung cancer: A systematic review. J Thorac Oncol 2010;5(2):260-74. 227. Lima JP, et al. Optimal duration of first-line chemotherapy for advanced non-small cell lung cancer: a systematic review with meta-analysis. Eur J Cancer 2009;45(4):601-7. In patients who have advanced disease and a performance status <2 at the time of diagnosis of NSCLC, first line treatment should be offered according to histology. Patients with non-squamous histology demonstrated a superior survival when treated with cisplatin and pemetrexed compared with cisplatin and gemcitabine (hazard ratio (HR) 0.84, 95% CI 0.74 to 0.96, p=0.011). Patients with squamous histology do not benefit from pemetrexed/platinum combination. **(LoE 1+)** 228. Scagliotti GV, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapynaive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26(21):3541-51. 229. Scagliotti GV, et al. Survival without toxicity for cisplatin plus pemetrexed versus cisplatin plus gemcitabine in chemonaïve patients with advanced non-small cell lung cancer: a risk-benefit analysis of a large phase III study. Eur J Cancer 2009;45(13):2298-303. In patients with adenocarcinoma, overall survival was statistically superior for cisplatin/pemetrexed versus cisplatin/gemcitabine (n=847; 12.6 *v* 10.9 months). **(LoE 1+)** Siehe 228 EGFR tyrosine kinase inhibitors (TKIs) are effective as first line treatment of advanced NSCLC in patients with sensitising EGFR mutations. The optimum treatment is orally delivered single agent therapy. TKIs significantly increased progression-free survival (PFS) (HR 0.45, 95% CI 0.36 to 0.58, P<0.0001) over SACT. In a European trial, the median PFS was 9.4 months in the erlotinib (TKI) group and 5.2 months in the doublet SACT group, (HR 0.42, 95% CI 0.27 to 0.64), p<0.0001. **(LoE 1+)**

	230. Bria E, et al. Outcome of advanced NSCLC patients harboring sensitizing EGFR mutations randomized to EGFR tyrosine kinase inhibitors or chemotherapy as first-line treatment: a meta-analysis. Ann Oncol 2011;22(10):2277-85. 231. Rosell R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13(3):239-46. Randomised evidence does not support the use of sACT in combination with a TKI in any patient group. **(LoE 1++)** Siehe 231 232. Feld R, et al. Use of the epidermal growth factor receptor inhibitors gefitinib and erlotinib in the treatment of non-small cell lung cancer: A systematic review. J Thorac Oncol 2006;1(4):367-76. <u>Recommendations</u> • 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)
Ellis PM et al., 2014 [12]. 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	Fragestellung/Zielsetzung QUESTIONS 1. In patients with advanced non–small-cell lung cancer (NSCLC) who have not received any chemotherapy (chemo-naive), is first-line therapy with the epidermal growth factor receptor (EGFR) inhibitors gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib superior to platinum-based chemotherapy for clinical meaningful outcomes (overall survival, progression-free survival (PFS), response rate and quality of life)? 4. What are the toxicities associated with gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib? TARGET POPULATION This practice guideline applies to adult patients with advanced (stage IIIB or IV) non–small-cell lung cancer.
	Methodik

(Cancer Care Ontario; CCO)	Grundlage der Leitlinie: The PEBC is … using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information. 1. Browman GP, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12. Comment in: Ann Oncol. 2002 Sep;13(9):1507-9; author reply: 1509. 2. Browman GP, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31. Suchzeitraum: bis 2014 LoE und GoR: Studienqualität geprüft und detailliert in Evidenztabellen dargestellt, Empfehlungsstärken über die Formulierung dargestellt
	Empfehlungen **Erstlinientherapie** *Recommendation 1a* First-line therapy with an EGFR tyrosine kinase inhibitor (TKI) is not recommended in unselected (patients who have not undergone mutation testing) or clinically selected populations of patients. Available data would suggest that first-line EGFR TKI is inferior to platinum-based chemotherapy in this group of NSCLC patients. The use of clinical characteristics such as Asian ethnicity, female sex, adenocarcinoma histology and light/never smoking status is not recommended to select patients for first-line EGFR TKI therapy, as this strategy does not reliably select patients who have mutations. *Key Evidence* Twenty-six randomized first-line studies in unselected and clinically selected populations were used to formulate this recommendation. The results of these trials showed no benefit for the use of an EGFR inhibitor in unselected and clinically selected patients (1-26). 26 Quellen zitiert *Recommendation 1b* In patients with EGFR mutation-positive NSCLC, first-line therapy with an EGFR TKI such as gefitinib, erlotinib or afatinib is the preferred

	treatment compared to platinum-based therapies. There is no evidence to support one EGFR TKI over another, so the decision about which EGFR TKI to use should take into consideration the expected toxicity of the drug as well as the cost. EGFR TKI therapy is associated with higher response rates, longer PFS and improved quality of life. *Qualifying Statement* There is no clear difference in overall survival. Many patients in these trials randomized to platinum-doublet chemotherapy, crossed over to an EGFR TKI as subsequent therapy. The likely effect of this cross-over is to dilute any survival difference between the groups, making comparison of overall survival less informative. *Key Evidence* Seven randomized trials and two meta-analyses comprised the evidence base. The trials and meta-analyses based on data from these trials showed that PFS was prolonged in molecularly selected patients when an EGFR was used as first-line treatment (27-33). Six trials were included in the initial meta-analysis that showed a hazard ratio (HR) of 0.35 (95% confidence interval (CI), 0.28-0.45; p<0.00001) (27-30,32,33). A second meta-analysis done on PFS that included subsets of EGFR-positive patients from first-line trials had similar results with an HR of 0.38 (95% CI, 0.31-0.44; p<0.00001) (20,21,28-30,32-34). All seven trials showed a decrease in adverse effects with an EGFR inhibitor compared to chemotherapy (28-34). 27. Inoue A, Kobayashi K, Maemondo M, Sugawara S, Oizumi S, Isobe H, et al. Final overall survival results of NEJ002, a phase III trial comparing gefitinib to carboplatin (CBDCA) plus paclitaxel (TXL) as the first-line treatment for advanced non-small cell lung cancer (NSCLC) with EGFR mutations. J Clin Oncol. 2011;29(abst 7519). 28. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol. 2010;11(2):121-8. 29. 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. 30. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2011;12(8):735-42. 31. Hirsch FR, Kabbinavar F, Eisen T, Martins R, Schnell FM, Dziadziuszko R, et al. A randomized, phase II, biomarker-selected study comparing erlotinib to erlotinib intercalated with chemotherapy in first-line therapy for advanced non-small-cell lung cancer. J Clin Oncol. 2011;29(26):3567-73. 32. Yang JC-H, Schuler MH, Yamamoto N, O'Byrne J, Hirsch V, Mok TS, et al. LUX-Lung 3: A randomized, open label, phase III study of afatinib versus pemetrexed and cisplatin as first-line treatment for patients with advanced adenocarcinoma of the lung harboring EGFR-activating

mutations. J Clin Oncol. 2012;30(abstr LBA7500).

33. Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol. 2014;15(2):213-22.

34. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med. 2010;362(25):2380-8.

Ramnath N, et al. 2013 [42].

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

Fragestellung/Zielsetzung

- updates the published clinical trials since the last American College of Chest Physicians guidelines to make treatment recommendations for this controversial subset of patients

Methodik

Grundlage der Leitlinie: Update der Leitlinie von 2007, Repräsentatives Gremium, systematische Suche, Auswahl und Bewertung der Literatur, iterative Konsensusprozesse, externes Reviewboard, Erklärungen zu möglichen Interessenkonflikten liegen vor und wurden bei der Erstellung der Leitlinie berücksichtigt

Suchzeitraum: Systematische Recherche bis Dezember 2011

LoE/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. Fu research is very unlikely to change confidence in the estimate of effec
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 effec 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 effec 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 dependin on circumstances or patients' or societal values. Further research is very unlikely to change our confid 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 socie values. Higher-quality research ma well have an important impact on confidence in the estimate of effec 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 researc likely to have an important impact our confidence in the estimate of 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 .

Sonstige methodische Hinweise

- Es wurden keine klinischen Fragestellungen formuliert

- Keine Patientenbeteiligung
- Unklar ob die Population des AWG von … hier addressiert ist

Freitext/Empfehlungen/Hinweise

2.0 Infiltrative Stage III (N2,3) Non-small Cell Lung Cancer

Multiple phase 3 trials using platinum-based chemotherapy have confirmed improved survival for patients treated with chemotherapy plus radiotherapy compared with radiotherapy alone (Fig 1).

FIGURE 1. [Section 2.1] Addition of cisplatin-based chemotherapy to radiotherapy improves survival in stage III NSCLC.

First Author	Year	No.	% good PS[a]	Chemo	RT (both arms)	Survival MST (mo) ChRT	MST (mo) RT	2 y (%) ChRT	2 y (%) RT	5 y (%) ChRT	5 y (%) RT	p
Sequential												
Le Chevallier[15]	1991	353	80	CVdPL	65	12	19	21	14	(12)[b]	(4)[b]	0.08
Cullen[13]	1999	446	86	MIP	40-64	12	10	20	16	-	-	.NS
Sause[16, c]	2000	303	(100)[d]	VbP	69.6 HF	14	12	32	24	8	6	0.04
Sause[16, c]	2000	300	(100)[d]	VbP	60	14	11	32	19	8	5	0.04
Mattson[18]	1988	238	69	CAP	55	11	10	19	17	-	-	(NS)[e]
Miller[19]	1998	229	89	FVMCAP	58	9	9	13	18	4	3	NS
Dillman[14]	1996	155	100	VbP	60	14	10	26	13	17	6	0.01
Average[f]						**12**	**10**	**23**	**18**	**9**	**5**	
Concurrent												
Schaake-Koenig[17, c]	1992	210	94	P qd	55 SC	12	12	26	13	10[g]	2[g]	0.003
Trovo[20]	1992	146	(79)[d]	P qd	45	10	10	14	14	-	-	NS
Jeremic[21]	1996	135	49	CbE qd	69.6 HF	22	14	43	26	23[g]	9[g]	0.02
Schaake-Koenig[17, c]	1992	206	94	P q wk	55 SC	13	12	19	13	10[g]	2[g]	NS
Jeremic[22, c]	1995	113	80	CbE q wk	64.8 HF	18	8	35	25	21	5	0.003
Jeremic[22, c]	1995	117	80	CbE q 2wk	64.8 HF	13	8	27	25	16	5	NS
Blanke[23]	1995	215	80	P q 3wk	60-65	11	10	18	13	5	2	NS
Average						**14**	**11**	**26**	**18**	**14**	**4**	

Inclusion criteria: randomized controlled trial of cisplatin-based chemotherapy and RT vs RT alone in >100 patients with stage III NSCLC.
CAP = cyclophosphamide, doxorubicin, cisplatin; CbE = carboplatin, etoposide; Ch = chemotherapy; ChRT = chemoradiotherapy; CVdPL = cyclophosphamide, vindesine, cisplatin, lomustine; ECOG = Eastern Cooperative Oncology Group; FVMCAP = 5-fluorouracil, vincristine, mitomycin c, cyclophosphamide, doxorubicin, cisplatin; HF = hyperfractionated 1.2 Gy per fraction twice daily to 69.6 Gy; MIP = mitomycin C, ifosfamide, cisplatin; MST = median survival time; NS = not significant; NSCLC = non-small lung cancer; P = cisplatin; PS = performance status; RT = radiotherapy; SC = split course; VbP = vinblastine, cisplatin, y=years.
[a]Defined as ECOG 0-1 or Karnofsky 80-100.
[b]Three-year survival.
[c]Three-arm trial.
[d]PS >70.
[e]$P < .05$ if analysis is restricted to only patients with stage III NSCLC.
[f]Excluding values in parentheses.
[g]4-y survival.

13 . Cullen MH , et al . Mitomycin, ifosfamide, and cisplatin in unresectable non-small-cell lung cancer: effects on survival and quality of life . J Clin Oncol . 1999 ; 17 (10): 3188 - 3194 .

14 . Dillman RO , et al. Improved survival in stage III non-small cell lung cancer: a seven-year followup of cancer and leukemia group B (CALGB) 8433 trial . J Natl Cancer Inst . 1996 ; 88 (17): 1210 - 1215 .

15 . Le Chevalier T , et al . Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: fi rst analysis of a randomized trial in 353 patients . J Natl Cancer Inst . 1991 ; 83 (6): 417 - 423 .

16 . Sause WT , et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group . Chest . 2000 ; 117 (2): 358 - 364 .

17 . Schaake-Koning C , et al . Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer . N Engl J Med . 1992 ; 326 (8): 524 - 530 .

18 . Mattson K , et al . Inoperable non-small cell lung cancer: radiation with or without chemotherapy . Eur J Cancer Clin Oncol . 1988 ; 24 (3): 477 - 482 .

	19 . Miller T , et al . A randomized trial of chemotherapy and radiotherapy for stage III non-small cell lung cancer . Cancer Ther . 1998 ; 1 : 229 - 236 . 20 . Trovò MG , et al. Radiotherapy versus radiotherapy enhanced by cisplatin in stage III non-small cell lung cancer. Int J Radiat Oncol Biol Phys . 1992 ;24(3):573-574. 21 . Jeremic B, et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily carboplatin/etoposide for stage III non-smallcell lung cancer: a randomized study . J Clin Oncol . 1996; 14 (4): 1065 - 1070 . 22 . Jeremic B , et al . Randomized trial of hyperfractionated radiation therapy with or without concurrent chemotherapy for stage III non-small-cell lung cancer . J Clin Oncol . 1995 ; 13 (2): 452 - 458 . 23 . Blanke C, et al. Phase III trial of thoracic irradiation with or without cisplatin for locally advanced unresectable non-small-cell lung cancer: a Hoosier Oncology Group protocol . J Clin Oncol . 1995 ; 13 (6): 1425 - 1429. Two meta-analyses reviewing >50 trials confirmed the survival benefit of combined platinum-based chemotherapy with radiotherapy over radiotherapy alone in locally advanced, unresectable NSCLC. [24,25] 24 . Marino P, et al. Randomized trials of radiotherapy alone versus combined chemotherapy and radiotherapy in stages IIIa and IIIb nonsmall cell lung cancer. A meta-analysis . Cancer . 1995 ; 76 (4): 593 - 601 . 25 . Pritchard RS , Anthony SP . Chemotherapy plus radiotherapy compared with radiotherapy alone in the treatment of locally advanced, unresectable, non-small-cell lung cancer. A metaanalysis . Ann Intern Med . 1996 ; 125 (9): 723 - 729 . <u>2.3 Recommendations</u> 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 benefits (Grade 2C). Remark: Patient-related and tumor-related factors can influence the balance of risks vs benefits; patient preferences should also play a significant role. 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).
Socinski MA, et al. 2013 [47]. Treatment of stage IV non-small cell lung cancer: Diagnosis and management of lung cancer. 3rd ed: American College of Chest Physicians	Fragestellung/Zielsetzung PICO 1: Should the choice of first-line chemotherapy be based on histology in patients with advanced stage IV NSCLC? PICO 2: Are EGFR TKIs a more effective first-line treatment than standard or platinum-based chemotherapy for patients with advanced stage IV NSCLC with EGFR mutations? PICO 3: Is bevacizumab with chemotherapy safer for patients with advanced stage IV NSCLC and treated brain metastases, anticoagulation, or a poor PS than chemotherapy alone?
	Methodik Siehe Ramnath N, et al. 2013 [9]

evidence-based clinical practice guidelines	Freitext/Empfehlungen/Hinweise **3.0 First-Line Chemotherapy** *3.1 Histology-Based Chemotherapy Selection* 10 . Sandler A , et al . Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer . N Engl J Med . 2006 ; 355 (24): 2542 - 2550 . 12 . Scagliotti GV , et al . Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advancedstage non-small-cell lung cancer . J Clin Oncol . 2008 ;26 (21): 3543 - 3551 . 13 . Hanna N , 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 . 14 . Peterson P , et al. Is pemetrexed more effective in adenocarcinoma and large cell lung cancer than in squamous cell carcinoma? A retrospective analysis of a phase III trial of pemetrexed vs docetaxel in previously treated patients with advanced non-small cell lung cancer [abstract] . J Thorac Oncol . 2007 ; 2 (8): S851 . 15 . Scagliotti G , et al . Treatment by-histology interaction analyses in three phase III trials show superiority of pemetrexed in nonsquamous non-small cell lung cancer . J Thorac Oncol . 2011 ; 6 (1): 64 - 70 . 17 . Hirsch FR , et al. The prognostic and predictive role of histology in advanced non-small cell lung cancer: a literature review . J Thorac Oncol . 2008 ; 3 (12): 1468 - 1481 . <u>3.1.1 Recommendation</u> 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 Targeted Chemotherapy* 23 . Mok TS , et al . Gefi tinib or carboplatin-paclitaxel in pulmonary adenocarcinoma . N Engl J Med . 2009 ; 361 (10): 947 - 957 . 26 . Inoue A , et al ; North East Japan Gefi tinib Study Group . First-line gefitinib for patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy . J Clin Oncol . 2009 ; 27 (9): 1394 - 1400 . 27 . Sequist LV , et al . First-line gefi tinib in patients with advanced non-small-cell lung cancer harboring somatic EGFR mutations . J Clin Oncol . 2008 ; 26 (15): 2442 - 2449 . 28 . Asahina H , et al . A phase II trial of gefi tinib as fi rst-line therapy for advanced non-small cell lung cancer with epidermal growth factor receptor mutations . Br J Cancer . 2006 ; 95 (8): 998 - 1004 . 29 . Inoue A , et al . Prospective phase II study of gefi tinib for chemotherapy-naive patients with advanced non-small-cell lung cancer with epidermal growth factor receptor gene mutations . J Clin Oncol . 2006 ; 24 (21): 3340 - 3346 . 32 . Thongprasert S , et al . Health-related quality-of-life in a randomized phase III fi rst-line study of gefi tinib versus carboplatin/paclitaxel in clinically selected patients from Asia with advanced NSCLC (IPASS) . J Thorac Oncol . 2011 ; 6 (11): 1872 - 1880 . 33 . Mitsudomi T, et al ; West Japan Oncology Group . Gefi tinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial . Lancet Oncol . 2010 ; 11 (2): 121 - 128 . 34 . Maemondo M , et al ; North-East Japan Study Group . Gefi tinib or chemotherapy for nonsmall-cell lung cancer with mutated EGFR . N Engl J Med . 2010 ; 362 (25): 2380 - 2388 . 35 . Zhou C , et al . Overall survival (OS) results from OPTIMAL (CTONG0802), a phase III trial of erlotinib (E) versus carboplatin plus gemcitabine (GC) as fi rst-line treatment for Chinese

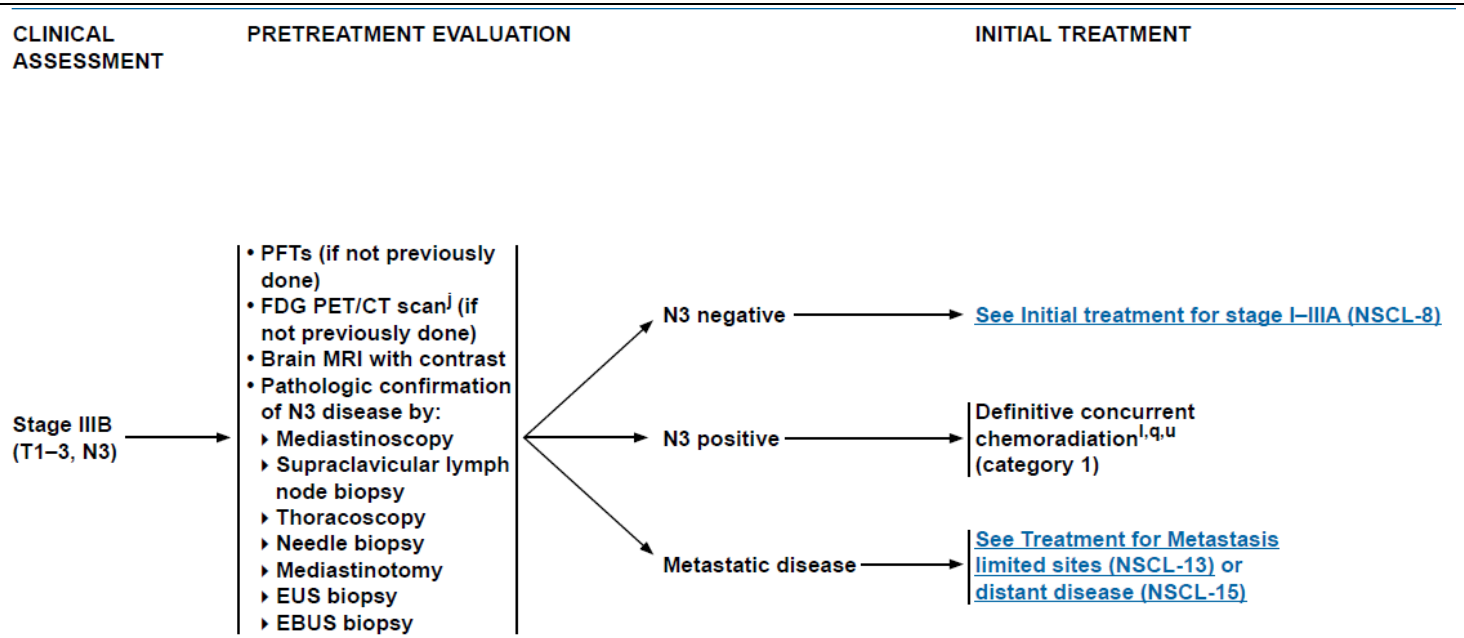
	patients with EGFR mutation-positive advanced non-small cell lung cancer (NSCLC) [abstract 7520] . J Clin Oncol . 2012 ;30: 30 . <u>3.2.1 Recommendation</u> 3.2.1.1. In patients with known EGFR mutations and stage IV NSCLC, first-line therapy with an EGFR TKI (gefitinib or erlotinib) is recommended based on superior response rates, PFS and toxicity profiles compared with platinumbased doublets (Grade 1A). *3.3 Use of Vascular Endothelial Growth Factor Inhibitors* 10 . Sandler A , et al . Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer . N Engl J Med . 2006 ; 355 (24): 2542 - 2550 . 40 . Socinski MA , et al . Safety of bevacizumab in patients with non-small-cell lung cancer and brain metastases . J Clin Oncol . 2009 ; 27 (31): 5255 - 5261 . 41 . Wozniak AJ , et al . Clinical outcomes (CO) for special populations of patients (pts) with advanced non-small cell lung cancer (NSCLC): Results from ARIES, a bevacizumab (BV) observational cohort study (OCS) [abstract] . J Clin Oncol . 2010 ; 28 (15s)(suppl):abstr7618. 42 . Besse B, et al. Bevacizumab safety in patients with central nervous system metastases . Clin Cancer Res . 2010 ; 16 (1): 269 - 278 . 43 . Reck M , et al . Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as fi rst-line therapy for nonsquamous non-small-cell lung cancer: AVAil . J Clin Oncol . 2009 ; 27 (8): 1227 - 1234 . 44 . Crinò L , et al . Safety and effi cacy of fi rst-line bevacizumab-based therapy in advanced nonsquamous non-small-cell lung cancer (SAiL, MO19390): a phase 4 study . Lancet Oncol . 2010 ; 11 (8): 733 - 740 . 45 . Hardy-Bessard AC , et al . Safety and efficacy of bevacizumab combined with taxanes in the fi rst-line treatment of metastatic breast cancer: ATHENA study-France [in French] . Bull Cancer . 2012 ; 99 (6): 609 - 618 . 46 . Miller VA , et al. A randomized, double-blind, placebo-controlled, phase IIIb trial (ATLAS) comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemotherapy with B for fi rstline treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol. 2009 27 (18s)(suppl):abstrLBA8002. 47 . Carden CP , et al. What is the risk of intracranial bleeding during anti-VEGF therapy? Neurooncol . 2008 ; 10 (4): 624 - 630 . 48 . Leighl NB , et al. Bleeding events in bevacizumab-treated cancer patients who received full-dose anticoagulation and remained on study . Br J Cancer . 2011 ; 104 (3): 413 - 418 . 49 . Griesinger F , et al. Safety of fi rst-line bevacizumab- based therapy with concomitant cardiovascular or anticoagulation medication in advanced or recurrent nonsquamous non-small cell lung cancer (NSCLC) in MO19390 (SAiL) [abstract] . J Clin Oncol . 2008 ; 26 (suppl)8049. 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.

National Institute for Health and Care Excellence (NICE). 2011 [32]. The diagnosis and treatment of lung cancer (CG121) UND **National Collaborating Centre for Cancer, National Institute for Health and Care Excellence (NICE), 2012 [33].** Lung cancer: Evidence Update, November 2012. A summary of selected new evidence relevant to NICE clinical guideline 121 'The diagnosis and treatment of lung cancer' (2011)	Fragestellung It offers evidence-based advice on the care and treatment of people with lung cancer.
	Methodik <u>Grundlage der Leitlinie:</u> evidenz- und konsensbasierte Aktualisierung, Entwicklergruppe: „team of health professionals, lay representatives and technical experts", systematische Literatursuche und –bewertung, formaler Konsensprozess, Expertenreview Update: erste Version von 2005, **"This guideline will shortly be checked to see if it needs updating,** Next review date: December 2015" <u>Suchzeitraum:</u> July 2010 <u>LoE/GoR:</u> In den 'qualifying statements' beschrieben: „covering the strength of evidence, the degree of consensus". Bei niedriger Evidenzqualität bzw. fehlender Evidenz informale Konsentierung. "To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations." Sonstige methodische Hinweise: At the start of the guideline development process all GDG members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared new, arising conflicts of interest which were always recorded
	Freitext/Empfehlungen/Hinweise **Combination treatment for non-small-cell lung cancer** 1.4.32 Consider chemoradiotherapy for patients with stage II or III NSCLC who are not suitable for surgery. Balance potential benefit in survival with the risk of additional toxicities. [new 2011] **Chemotherapy for non-small-cell lung cancer** 1.4.40 Chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status (WHO 0, 1 or a Karnofsky score of 80–100), to improve survival, disease control and quality of life. [2005] 1.4.41 Chemotherapy for advanced NSCLC should be a combination of a single third generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Either carboplatin or cisplatin may be administered, taking account of their toxicities, efficacy and

	convenience. [2005] 1.4.42 Patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation drug. [2005] Key references Gao G, Chu H, Zhao L et al. (2012) A meta-analysis of paclitaxel-based chemotherapies administered once every week compared with once every 3 weeks first-line treatment of advanced non-small-cell lung cancer. Lung Cancer 76: 380–6 Li C, Sun Y, Pan Y 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. Lung 188 359–64 Non-Small Cell Lung Cancer Collaborative Group (2010) Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung cancer. Cochrane Database of Systematic Reviews issue 5: CD007309 Supporting reference Centre for Reviews and Dissemination (2011) Gemcitabine plus paclitaxel versus carboplatin plus either gemcitabine or paclitaxel in advanced non-small cell lung cancer: a literature-based meta-analysis. Database of Abstracts of Reviews of Effects. *Gefitinib* Refer to Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (NICE technology appraisal guidance 192 [2010]). *Erlotinib* Refer to Erlotinib for the treatment of non-small-cell lung cancer (NICE technology appraisal guidance 162 [2008]). Key references Chen P, Wang L, Liu B et al. (2011b) EGFR-targeted therapies combined with chemotherapy for treating advanced non-small-cell lung cancer. European Journal of Clinical Pharmacology 67 235–43 Jiang J, Huang L, Liang X et al. (2011) Gefitinib versus docetaxel in previously untreated advanced non-small-cell lung cancer: a meta-analysis of randomised controlled trials. Acta Oncologica 50: 582–8 Lin H, Jiang J, Liang X et al. (2010) Chemotherapy with cetuximab of chemotherapy alone for untreated advanced non-small-cell lung cancer: a systematic review and meta-analysis. Lung Cancer 70: 57–62 Supporting references Centre for Reviews and Dissemination (2012) Gefitinib versus docetaxel in previously untreated advanced non-small-cell lung cancer: a meta-analysis of randomised controlled trials. Database of Abstracts of Reviews of Effects. Centre for Reviews and Dissemination (2011) EGFR-targeted therapies combined with chemotherapy for treating advanced non-small-cell lung cancer. Database of Abstracts of Reviews of Effects. *Pemetrexed* Refer to Pemetrexed for the first-line treatment of non-small-cell lung cancer (NICE technology appraisal guidance 181 [2010]). Key reference Li M, Zhang Q, Fu P et al. Pemetrexed plus platinum as the first-line treatment option for advanced non-small cell lung cancer: a meta-analysis of randomized controlled trials. PLoS one 7: e37229 *Bevacizumab*

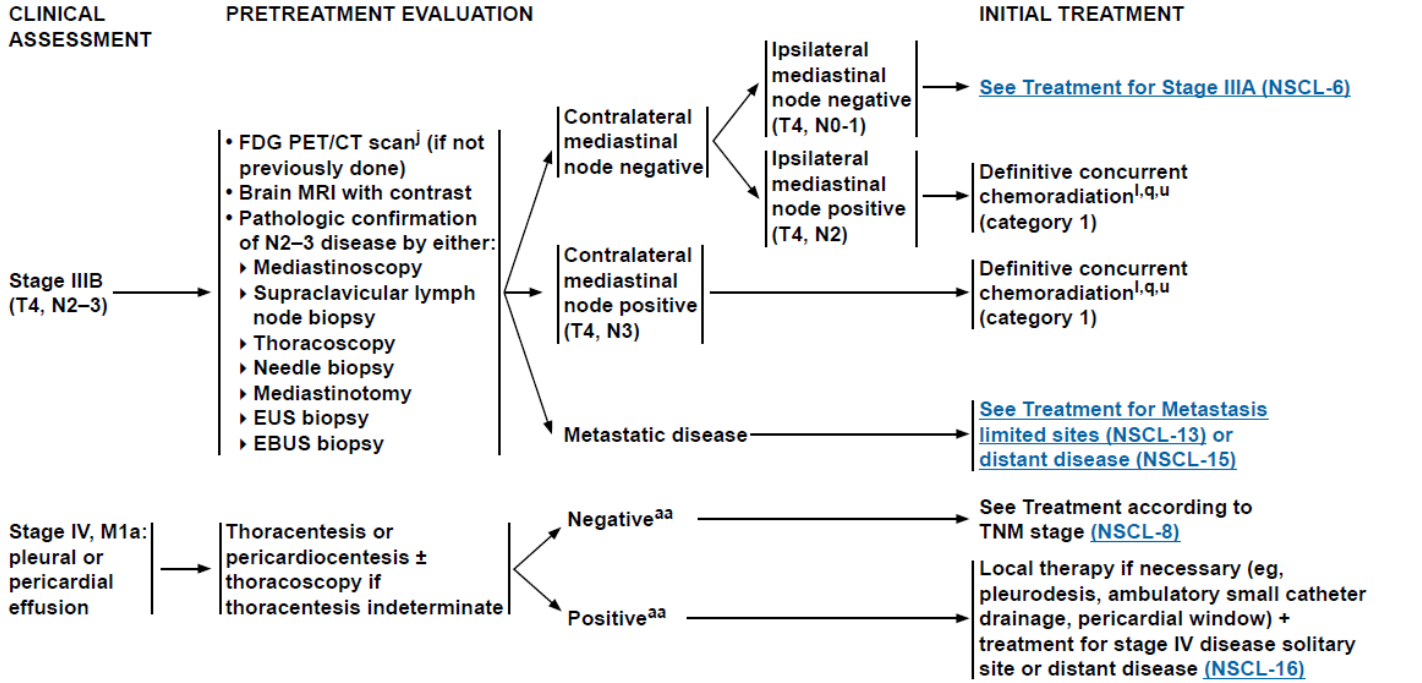
	Bevacizumab was not evaluated for NICE CG121. A NICE technology appraisal of bevacizumab for first-line treatment of locally advanced or metastatic lung cancer was terminated because the manufacturer decided not to launch or promote bevacizumab in this indication; however, bevacizumab has marketing authorisation for this indication in the UK. Key references Botrel TE, Clark O, Clark L 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. Lung cancer 74: 89–97 Cao C, Wang J, Bunjhoo H et al. (2012) Risk profile of bevacizumab in patients with non-small cell lung cancer: a meta-analysis of randomized controlled trials. Acta Oncologica 51: 151–6. Lima AB, Macedo LT, Sasse AD (2011) Addition of bevacizumab to chemotherapy in advanced non-small cell lung cancer: a systematic review and meta-analysis. PLoS one 6: e22681 Supporting reference Centre for Reviews and Dissemination (2012) 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. Database of Abstracts of Reviews of Effects.

National Comprehensive Cancer Network. 2016 [34]. Non-Small Cell Lung Cancer (Version 4.2016)	Fragestellung/Zielsetzung Diagnose, Pathologie, Staging, Therapie des NSCLC
	Methodik Grundlage der Leitlinie: Update der LL von 2015, Systematik der Literatursuche und -bewertung nicht vollständig transparent dargestellt, Diskussion der Literatur und Empfehlungen im Expertenpanel, Interessenkonflikte unklar Literatursuche: in PubMed zwischen 06/2014 und 06/2015 GoR, LoE: Alle Empfehlungen entsprechen der Kategorie 2A, sofern nicht explizit anders spezifiziert. **NCCN Categories of Evidence and Consensus** **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. **Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. **All recommendations are category 2A unless otherwise noted.**
	Empfehlungen **STAGE IIIB (T1-3, N3)**



[j]Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.
[l]See Principles of Radiation Therapy (NSCL-C).
[q]See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).
[u]If full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 2 cycles of full-dose chemotherapy.

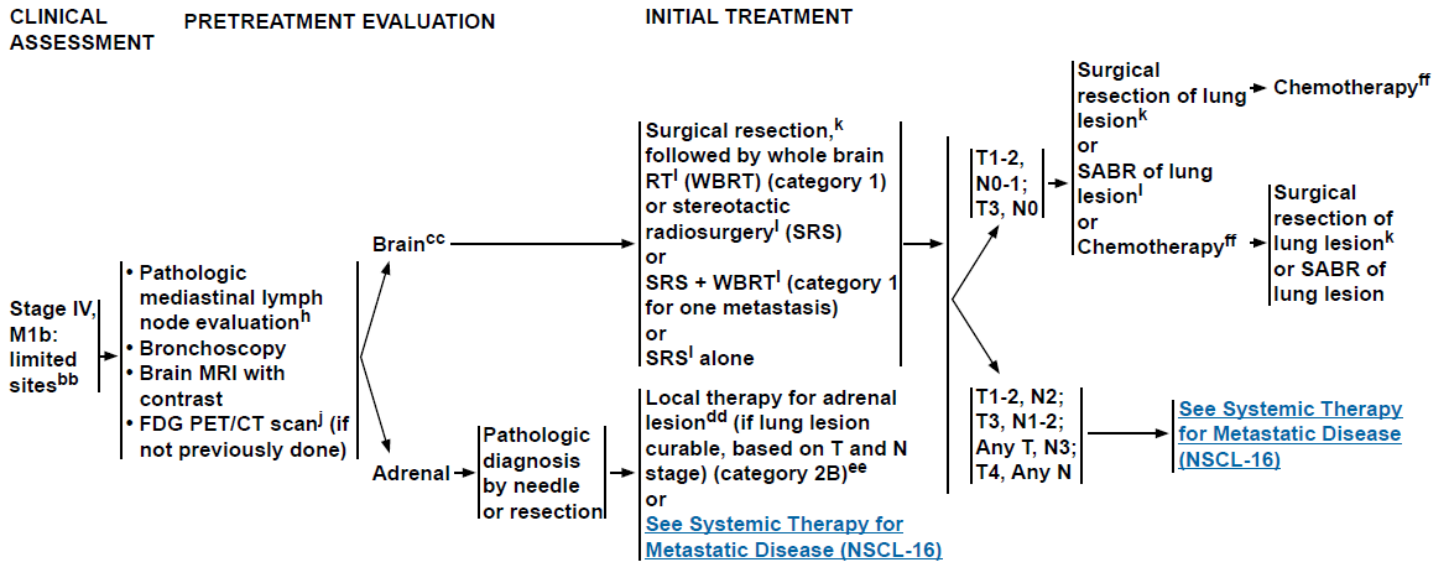
Stage IIIB (T4, N2-3)



[j]Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.
[l]See Principles of Radiation Therapy (NSCL-C).
[q]See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).
[u]If full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 2 cycles of full-dose chemotherapy.

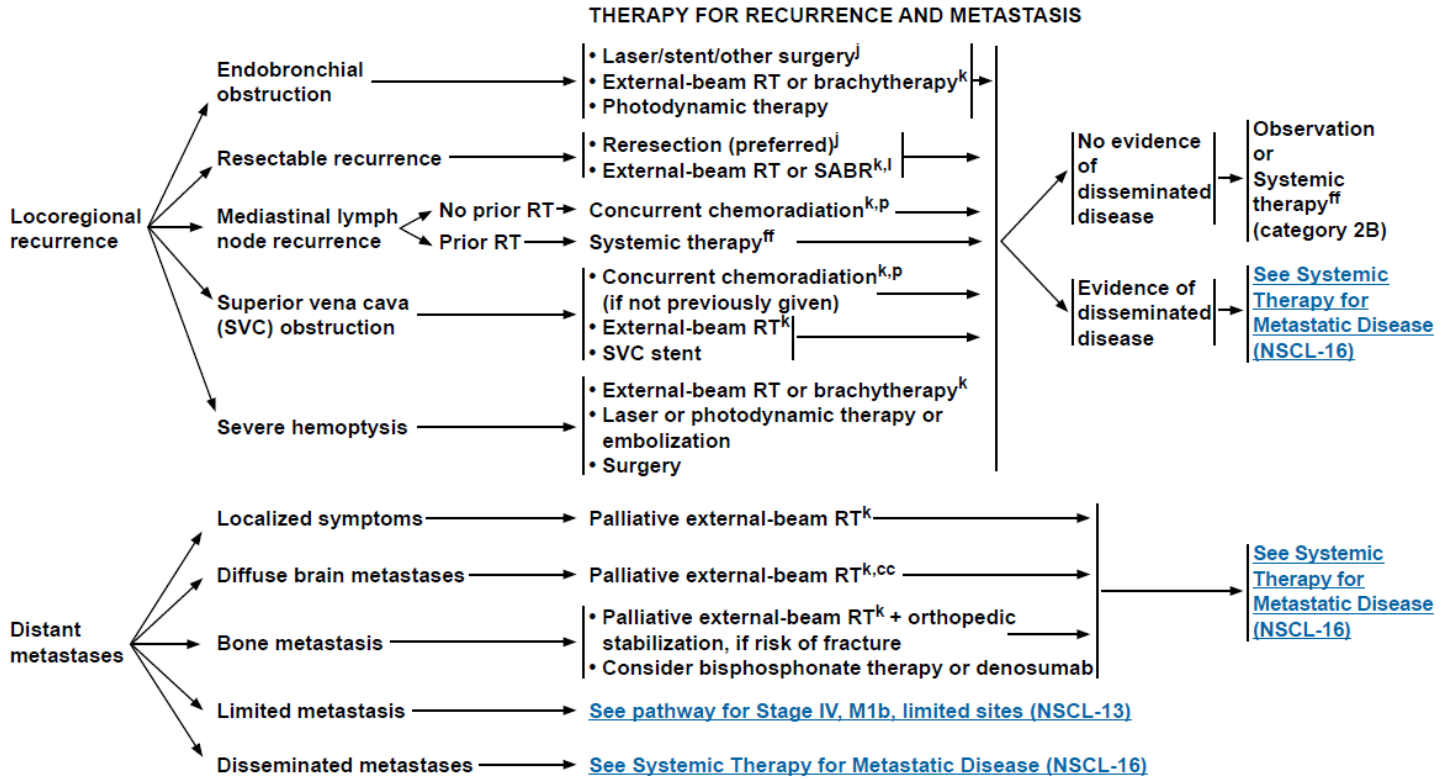
[aa]While most pleural effusions associated with lung cancer are due to tumor, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor and fluid is non-bloody and not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element. Pericardial effusion is classified using the same criteria.

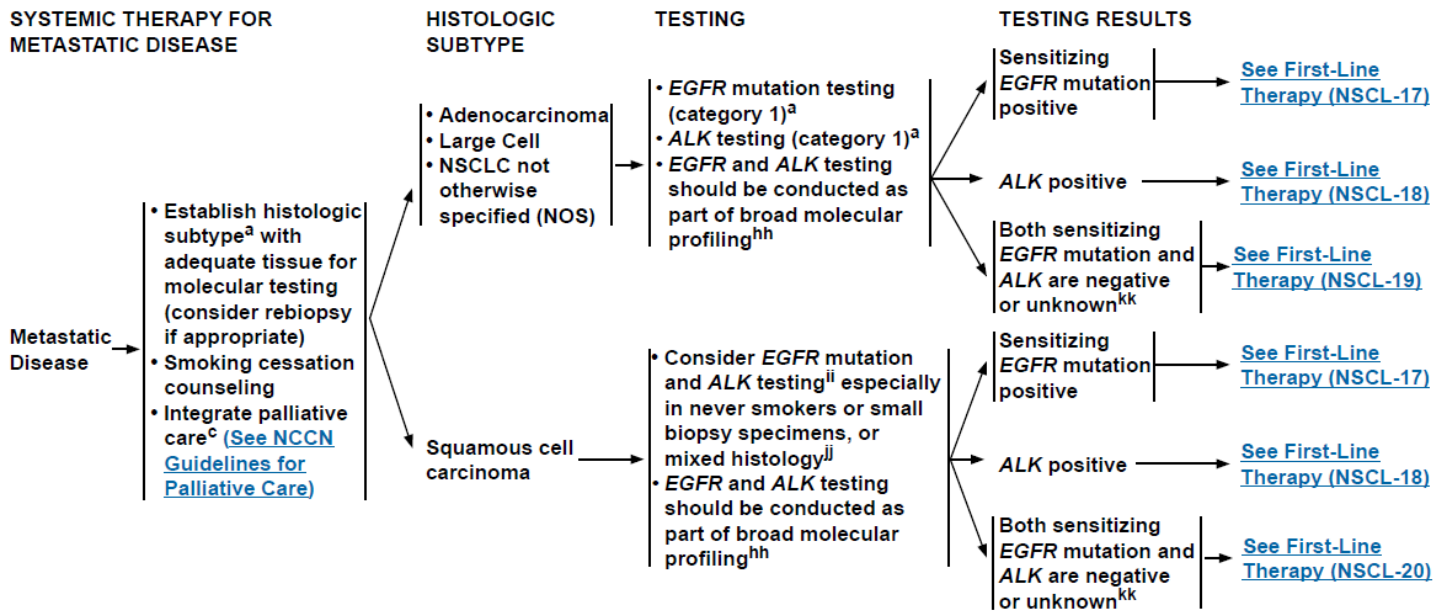
NSCL-13



[h]Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.
[j]Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.
[k]See Principles of Surgical Therapy (NSCL-B).
[l]See Principles of Radiation Therapy (NSCL-C).
[bb]Aggressive local therapy may be appropriate for selected patients with limited-site oligometastatic disease.
[cc]See NCCN Guidelines for Central Nervous System Cancers.
[dd]May include adrenalectomy or RT (including SABR).
[ee]Patients with N2 disease have a poor prognosis and systemic therapy should be considered.
[ff]See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).

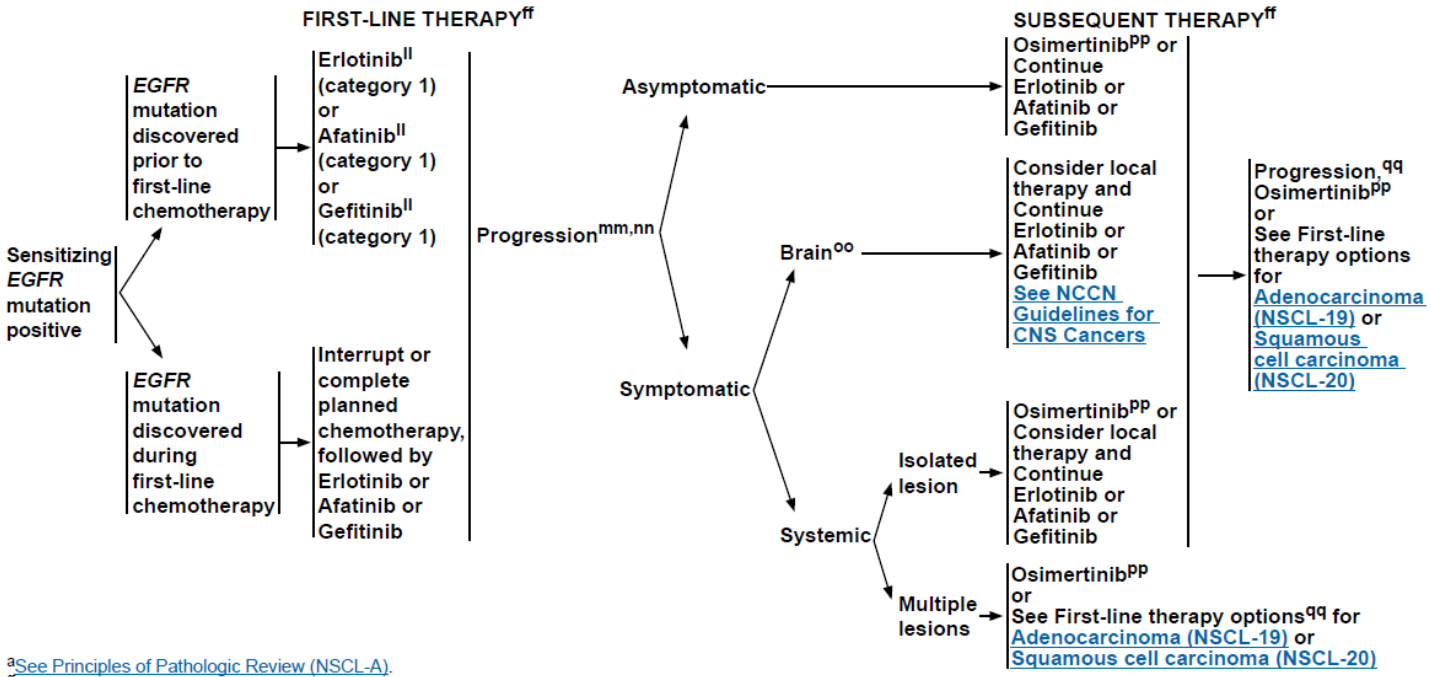
NSCL-15


THERAPY FOR RECURRENCE AND METASTASIS
Locoregional recurrence
Endobronchial obstruction
• Laser/stent/other surgery[j]
• External-beam RT or brachytherapy[k]
• Photodynamic therapy
Resectable recurrence
• Reresection (preferred)[j]
• External-beam RT or SABR[k,l]
Mediastinal lymph node recurrence
No prior RT
Concurrent chemoradiation[k,p]
Prior RT
Systemic therapy[ff]
Superior vena cava (SVC) obstruction
• Concurrent chemoradiation[k,p] (if not previously given)
• External-beam RT[k]
• SVC stent
Severe hemoptysis
• External-beam RT or brachytherapy[k]
• Laser or photodynamic therapy or embolization
• Surgery
No evidence of disseminated disease
Observation or Systemic therapy[ff] (category 2B)
Evidence of disseminated disease
See Systemic Therapy for Metastatic Disease (NSCL-16)
Distant metastases
Localized symptoms
Palliative external-beam RT[k]
Diffuse brain metastases
Palliative external-beam RT[k,cc]
Bone metastasis
• Palliative external-beam RT[k] + orthopedic stabilization, if risk of fracture
• Consider bisphosphonate therapy or denosumab
See Systemic Therapy for Metastatic Disease (NSCL-16)
Limited metastasis
See pathway for Stage IV, M1b, limited sites (NSCL-13)
Disseminated metastases
See Systemic Therapy for Metastatic Disease (NSCL-16)
[j]See Principles of Surgical Therapy (NSCL-B).
[k]See Principles of Radiation Therapy (NSCL-C).
[l]Interventional radiology ablation is an option for selected patients.
[p]See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).
[cc]See NCCN Guidelines for Central Nervous System Cancers.
[ff]See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
NSCL-16



[a]See Principles of Pathologic Review (NSCL-A).
[c]Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742.
[hh]The NCCN NSCLC Guidelines Panel strongly endorses broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).
[ii]In patients with squamous cell carcinoma, the observed incidence of *EGFR* mutations is 2.7% with a confidence that the true incidence of mutations is less than 3.6%. This frequency of *EGFR* mutations does not justify routine testing of all tumor specimens. Forbes SA, Bharma G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). Curr Protoc Hum Genet 2008;chapter 10:unit 10.11.
[jj]Paik PK, Varghese AM, Sima CS, et al. Response to erlotinib in patients with *EGFR* mutant advanced non-small cell lung cancers with a squamous or squamous-like component. Mol Cancer Ther 2012;11:2535-2540.
[kk]Consider ROS1 testing; if positive, may treat with crizotinib. Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in ROS1-rearranged non-small cell lung cancer. N Engl J Med 2014;371:1963-1971.

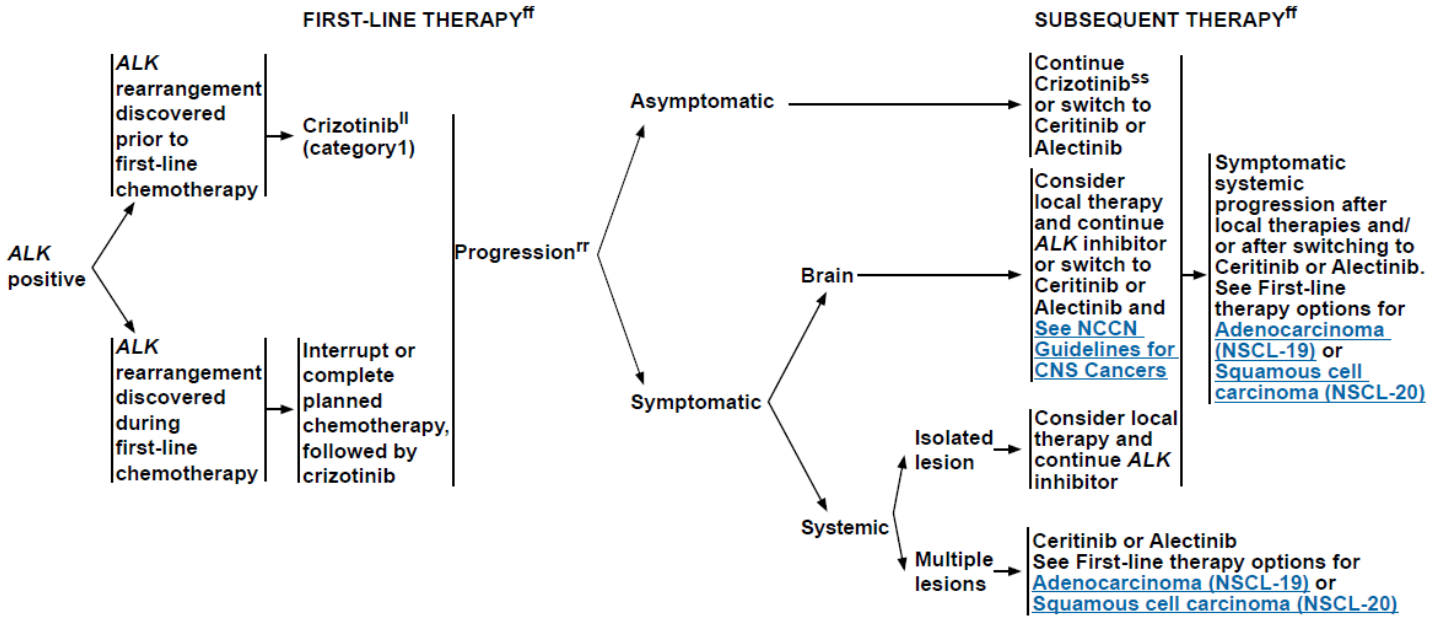
NSCL-17



[a]See Principles of Pathologic Review (NSCL-A).
[ff]See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[ll]For performance status 0-4.
[mm]Prior to changing therapy, a biopsy is reasonable to determine mechanism of acquired resistance.
[nn]Beware of flare phenomenon in subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.
[oo]Consider pulse erlotinib for carcinomatosis meningitis.
[pp]Osimertinib is approved for patients with metastatic EGFR T790M mutation-positive tumors, as determined by an FDA-approved test or other validated laboratory-developed test performed in a CLIA-approved laboratory.
[qq]Afatinib + cetuximab may be considered in patients with disease progression on EGFR TKI therapy.

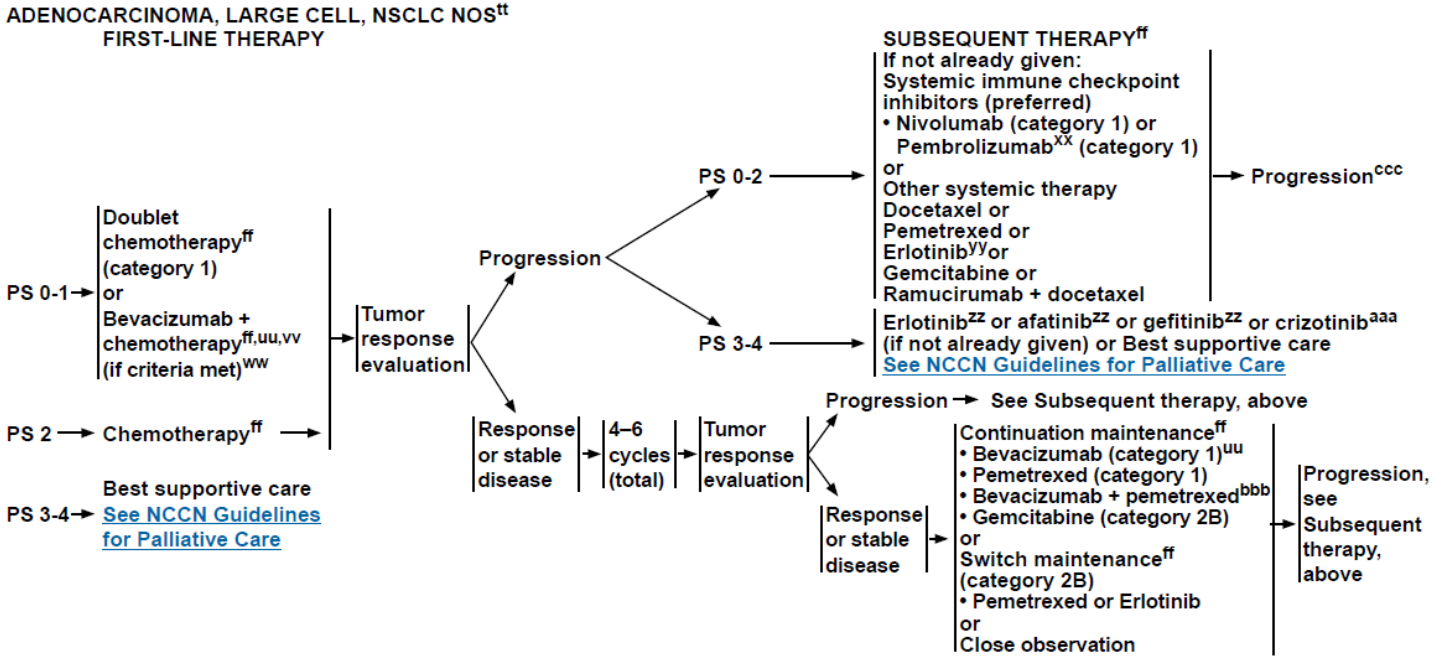
NSCL-18

ALK POSITIVE[a]



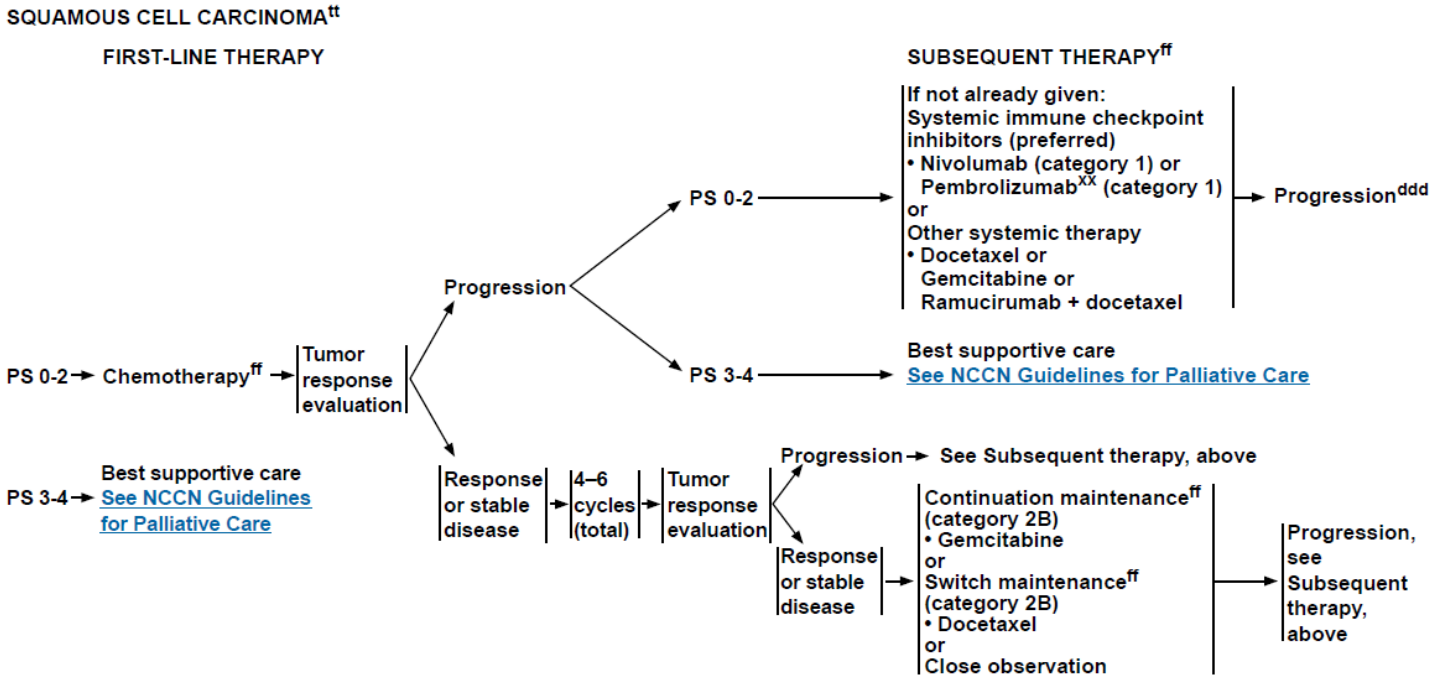
[a]See Principles of Pathologic Review (NSCL-A).
[ff]See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[ll]For performance status 0-4.
[rr]Patients who are intolerant to crizotinib may be switched to ceritinib or alectinib.
[ss]For rapid radiologic progression or threatened organ function, alternate therapy should be instituted.

NSCL-19



[ff]See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[tt]Consider additional mutational testing if only EGFR and ALK were performed. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).
[uu]Bevacizumab should be given until progression.
[vv]Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.
[ww]Criteria for treatment with bevacizumab: non-squamous NSCLC, and no recent history of hemoptysis. Bevacizumab should not be given as a single agent, unless as maintenance if initially used with chemotherapy.
[xx]Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression, as determined by an FDA-approved test for PD-L1 with use of pembrolizumab.
[yy]Recommend proteomic testing for patients with NSCLC and wild-type EGFR or with unknown EGFR status. A patient with a "poor" classification should not be offered erlotinib in the second-line setting. Gregorc V, Novello S, Lazzari C, et al. Lancet Oncol 2014; 15:713-21.
[zz]May be considered for PS 3 and 4 patients with sensitizing EGFR mutations.
[aaa]May be considered for PS 3 and 4 patients if positive for the ALK rearrangement.
[bbb]If bevacizumab was used with a first-line pemetrexed/platinum chemotherapy regimen.
[ccc]If not already given, options for PS 0-2 include erlotinib, nivolumab, pembrolizumab, docetaxel (category 2B), pemetrexed (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include erlotinib or best supportive care. Options for further progression are best supportive care or clinical trial.

NSCL-20



[ff]See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[tt]Consider additional mutational testing if only EGFR and ALK were performed. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).
[xx]Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression, as determined by an FDA-approved test for PD-L1 with use of pembrolizumab.
[ddd]If not already given, options for PS 0-2 include nivolumab, pembrolizumab, docetaxel (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include best supportive care. Options for further progression are best supportive care or clinical trial.

NSCL-F (1 von 4)

	SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (1 OF 4) ADVANCED DISEASE: • The drug regimen with the highest likelihood of benefit with toxicity deemed acceptable to both the physician and the patient should be given as initial therapy for advanced lung cancer. • Stage, weight loss, performance status, and gender predict survival. • Platinum-based chemotherapy prolongs survival, improves symptom control, and yields superior quality of life compared to best supportive care. • Histology of NSCLC is important in the selection of systemic therapy. • New agent/platinum combinations have generated a plateau in overall response rate (≈ 25%–35%), time to progression (4–6 mo), median survival (8–10 mo), 1-year survival rate (30%–40%), and 2-year survival rate (10%–15%) in fit patients. • Unfit patients of any age (performance status 3–4) do not benefit from cytotoxic treatment, except erlotinib, afatinib, or gefitinib for *EGFR* mutation-positive and crizotinib for *ALK*-positive tumors of nonsquamous NSCLC or NSCLC NOS. First-line Therapy • There is superior efficacy and reduced toxicity for cisplatin/pemetrexed in patients with nonsquamous histology, in comparison to cisplatin/gemcitabine. • There is superior efficacy for cisplatin/gemcitabine in patients with squamous histology, in comparison to cisplatin/pemetrexed. • Two drug regimens are preferred; a third cytotoxic drug increases response rate but not survival. Single-agent therapy may be appropriate in select patients. • Response assessment after 1–2 cycles, then every 2–4 cycles. Maintenance Therapy Continuation maintenance refers to the use of at least one of the agents given in first line, beyond 4–6 cycles, in the absence of disease progression. Switch maintenance refers to the initiation of a different agent, not included as part of the first-line regimen, in the absence of disease progression, after 4–6 cycles of initial therapy. Subsequent Therapy • In patients who have experienced disease progression either during or after first-line therapy, the following are established second-line agents. ‣ Nivolumab improves survival when compared with docetaxel. ‣ Pembrolizumab improves overall survival in PD-L1 positive tumors when compared with docetaxel. ‣ Docetaxel is superior to vinorelbine or ifosfamide. ‣ Pemetrexed is considered equivalent to docetaxel with less toxicity in patients with adenocarcinoma and large cell carcinoma. ‣ Ramucirumab + docetaxel improves survival when compared to docetaxel alone. ‣ Erlotinib is superior to best supportive care. **NSCL-F (2 von 4)**

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (2 of 4)†

First-line Systemic Therapy Options

Adenocarcinoma, Large cell, NSCLC NOS (PS 0-1)

- Bevacizumab/carboplatin/paclitaxel (category 1)[1]
- Bevacizumab/carboplatin/pemetrexed[2]
- Bevacizumab/cisplatin/pemetrexed[3]
- Carboplatin/albumin-bound paclitaxel (category 1)[4]
- Carboplatin/docetaxel (category 1)[5]
- Carboplatin/etoposide (category 1)[6,7]
- Carboplatin/gemcitabine (category 1)[8]
- Carboplatin/paclitaxel (category 1)[9]
- Carboplatin/pemetrexed (category 1)[10]
- Carboplatin/vinorelbine (category 1)[11]
- Cisplatin/docetaxel (category 1)[5]
- Cisplatin/etoposide (category 1)[12]
- Cisplatin/gemcitabine (category 1)[9,13]
- Cisplatin/paclitaxel (category 1)[14]
- Cisplatin/pemetrexed (category 1)[13]
- Cisplatin/vinorelbine (category 1)[5,9,15]
- Gemcitabine/docetaxel (category 1)[16]
- Gemcitabine/vinorelbine (category 1)[17]

Adenocarcinoma, Large cell, NSCLC NOS (PS 2)

- Albumin-bound paclitaxel[18]
- Carboplatin/albumin-bound paclitaxel[19,20]
- Carboplatin/docetaxel[5]
- Carboplatin/etoposide[6,7]
- Carboplatin/gemcitabine[8]
- Carboplatin/paclitaxel[9]
- Carboplatin/pemetrexed[10]
- Carboplatin/vinorelbine
- Docetaxel[21,22]
- Etoposide[23]
- Gemcitabine[24-26]
- Gemcitabine/docetaxel[16]
- Gemcitabine/vinorelbine[17]
- Irinotecan[27,28]
- Paclitaxel[29-31]
- Pemetrexed[32]
- Vinorelbine[21]

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

NSCL-F (3 von 4)

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (3 of 4)†

First-line Systemic Therapy Options

Squamous cell carcinoma (PS 0-1)

- Carboplatin/albumin-bound paclitaxel (category 1)[4]
- Carboplatin/docetaxel (category 1)[5]
- Carboplatin/etoposide (category 1)[6,7]
- Carboplatin/gemcitabine (category 1)[8]
- Carboplatin/paclitaxel (category 1)[9]
- Carboplatin/vinorelbine (category 1)[11]
- Cisplatin/docetaxel (category 1)[5]
- Cisplatin/etoposide (category 1)[12]
- Cisplatin/gemcitabine (category 1)[9,13]
- Cisplatin/gemcitabine/necitumumab (category 3)[33]
- Cisplatin/paclitaxel (category 1)[14]
- Cisplatin/vinorelbine (category 1)[5,9,15]
- Gemcitabine/docetaxel (category 1)[16]
- Gemcitabine/vinorelbine (category 1)[17]

Squamous cell carcinoma (PS 2)

- Albumin-bound paclitaxel[18]
- Carboplatin/albumin-bound paclitaxel[19-20]
- Carboplatin/docetaxel[5]
- Carboplatin/etoposide[6,7]
- Carboplatin/gemcitabine[8]
- Carboplatin/paclitaxel[9]
- Carboplatin/vinorelbine
- Cisplatin/gemcitabine/necitumumab (category 3)[33]
- Docetaxel[21-22]
- Etoposide[23]
- Gemcitabine[24-26]
- Gemcitabine/docetaxel[16]
- Gemcitabine/vinorelbine[17]
- Irinotecan[27-28]
- Paclitaxel[29-31]
- Vinorelbine[21]

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

NSCL-F (4 von 4)

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (4 of 4)

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NSCL-H

EMERGING TARGETED AGENTS FOR PATIENTS WITH GENETIC ALTERATIONS

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
BRAF* V600E mutation	**vemurafenib[1,2]** **dabrafenib[2,3]** **dabrafenib + trametinib[4]**
High-level *MET* amplification or MET exon 14 skipping mutation	**crizotinib[5,6,7,8]**
***RET* rearrangements**	**cabozantinib[9,10]**
***ROS1* rearrangements**	**crizotinib[11]**
***HER2* mutations**	**trastuzumab[12] (category 2B)** **afatinib[13] (category 2B)**

*Non-V600E mutations have variable kinase activity and response to these agents.

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Gemeinsamer Bundesausschuss

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

National Institute for Health and Care Excellence (NICE). 2012 [36]. Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer (TA258)	1 Guidance 1.1 Erlotinib is recommended as an option for the first-line treatment of people with locally advanced or metastatic non-small-cell lung cancer (NSCLC) if: • they test positive for the epidermal growth factor receptor tyrosine kinase (EGFRTK) mutation and • the manufacturer provides erlotinib at the discounted price agreed under the patient access scheme (as revised in 2012). NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE GUIDANCE EXECUTIVE (GE) Review of: TA258; Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer, … <u>Final recommendation post consultation</u> TA192 and TA258 should be flagged for further consideration of a review when the results of the LUX Lung 7 trial are available, currently anticipated to be in 2015.
National Institute for Health and Care Excellence, 2014 [35]. Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer (TA310**)**	1 Guidance 1.1 Afatinib is recommended as an option, within its marketing authorisation, for treating adults with locally advanced or metastatic non-small-cell lung cancer only if: • the tumour tests positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation and • the person has not previously had an EGFR-TK inhibitor and • the manufacturer provides afatinib with the discount agreed in the patient access scheme.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 05.12.2016

#	Suchfrage
1	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees
2	((non next small) or nonsmall) next cell next lung:ti,ab,kw
3	tumor* or tumour* or carcinoma* or adenocarcinoma* or neoplasm* or sarcoma* or cancer*:ti,ab,kw
4	advanced:ti,ab,kw or metastat*:ti,ab,kw or metastas*:ti,ab,kw or recurren*:ti,ab,kw or relaps*:ti,ab,kw
5	#2 and #3 and #4
6	nsclc*:ti,ab,kw
7	#1 or #5 or #6
8	#7 from 2011 to 2016

SR, HTAs in Medline (PubMed) am 05.12.2016

#	Suchfrage
1	Carcinoma, Non-Small-Cell Lung[MeSH]
2	(((non[Title/Abstract]) AND small[Title/Abstract]) AND cell[Title/Abstract]) AND lung[Title/Abstract]
3	((((((tumor*[Title/Abstract]) OR tumour*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract]) OR neoplasm*[Title/Abstract]) OR sarcoma*[Title/Abstract]) OR cancer*[Title/Abstract]
4	#2 AND #3
5	#1 OR #4
6	(#5) AND ((((advanced[Title/Abstract]) OR metastat*[Title/Abstract]) OR metastas*[Title/Abstract]) OR recurren*[Title/Abstract])
7	(#6) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract])))))
8	(((#7) AND ("2011/12/01"[PDAT] : "2016/12/05"[PDAT])) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))
9	(#8) AND ((((((drug*[Title/Abstract]) OR (drug therap*)[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR treat[Title/Abstract]) OR treatment*[Title/Abstract])

Leitlinien in Medline (PubMed) am 05.12.2016

#	Suchfrage
1	Carcinoma, Non-Small-Cell Lung[MeSH]
2	(((non[Title/Abstract]) AND small[Title/Abstract]) AND cell[Title/Abstract]) AND lung[Title/Abstract]
3	((((((tumor*[Title/Abstract]) OR tumour*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract]) OR neoplasm*[Title/Abstract]) OR sarcoma*[Title/Abstract]) OR cancer*[Title/Abstract]
4	#2 AND #3
5	#1 OR #4
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title/Abstract])
7	(((#6) AND ("2011/12/01"[PDAT] : "2016/12/05"[PDAT])) NOT ((comment[Publication Type]) OR letter[Publication Type])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))

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Anlage

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

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

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

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

Brown T, et al. 2013 [7].

TABLE 8 Quality assessment

Reference ID	Randomisation			Baseline comparability		Eligibility criteria specified	Co-interventions identified[b]	Blinding				Withdrawals		ITT	Other outcomes
	Truly random	Allocation concealment	Number stated	Presented	Achieved[a]			Assessors	Administration	Participants	Procedure assessed	> 80% in final analysis	Reasons stated		
Jeremic 2001[63]	NS	NS	✓	✓✗	NS	✓	NS	NS	NS	NS	NS	✓	✓	✗	✗
Komaki 2002[50]	NS	✓	✓	✓	NS	✓	NS	NS	NS	NS	NS	✓	✓	✗	✗
Schild 2002[62]	NS	NS	✓	✓	✓	✓	NS	NS	NS	NS	NS	✓	✓	✗	✗
Vokes 2002[47]	NS	✓	✓	✓	NS	✓	NS	NS	NS	NS	NS	✓	✓	✗	✗
Zatloukal 2004[51]	NS	✗	✓	✓	✓	✓	NS	✗	✗	✗	NA	✓	✓	✓	✗
Belani 2005[52]	NS	NS	✓	✓	✓✗	✓	NS	NS	NS	NS	NS	✓	✓	✗	✗
Fournel 2005[49]	NS	✓	✓	✓✗	✓✗	✓	NS	✗	✗	✗	NA	✓	✓	✗	✗
Reinfuss 2005[46]	✓	NS	✓	✓	NS	✓	NS	NS	NS	NS	NS	✓	✓	✗	✗
Dasgupta 2006[56]	NS	NS	✓	✓	NS	✓	✓✗	NS	NS	NS	NS	✓	NA	✗[c]	✗
Gouda 2006[59]	NS	NS	✓	✓	✓	✓	NS	NS	NS	NS	NS	✓	NA	✓	✗

Reference ID	Randomisation			Baseline comparability		Eligibility criteria specified	Co-interventions identified[b]	Blinding				Withdrawals		ITT	Other outcomes
	Truly random	Allocation concealment	Number stated	Presented	Achieved[a]			Assessors	Administration	Participants	Procedure assessed	> 80% in final analysis	Reasons stated		
Belderbos 2007[54]	NS	NS	✓	✓	✓✗	✓	NS	NS	NS	NS	NS	✓	✓	✓	✓
Vokes 2007[48]	NS	✓	✓	✓✗	✓✗	✓	NS	NS	NS	NS	NS	✓	✓	✓	✗
Liu 2008[53]	NS	NS	✓	✓	✓✗	✓	NS	NS	NS	NS	NS	✓	✓	✗	✗
Socinski 2008[55]	NS	NS	✓	✓	✓✗	✓	NS	NS	NS	NS	NS	✓	✓	✗	✗
Berghmans 2009[45]	✓	✓	✓	✓	NS	✓	NS	NS	NS	NS	NS	✓	✓	✗	✗
Crvenkova 2009[57]	NS	NS	✓	✓✗	✓	✓	NS	NS	NS	NS	NS	✓	✗	NS	✗
Nyman 2009[58]	NS	NS	✓	✓	NS	✓	NS	NS	NS	NS	NS	✓	✗	✗	✓
Zhu 2009[60]	NS	NS	NS	✓✗	NS	✓	NS	NS	NS	NS	NS	NS	NA	NS	✗
Movsas 2010[61]	NS	NS	✓	✓	NS	✓	NS	NS	NS	NS	NS	✓	✓	✓	✗

✓, item adequately addressed; ✗, item not adequately addressed; ✓✗, item partially addressed; NA, not applicable; NS, not stated.

a When no *p*-values are reported the trial was assessed as NS.

b This is second-line CTX and/or palliative RT.

c Although trial intended to exclude non-completers from analysis all patients completed treatment.