Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2015-B-063 Nivolumab

Stand: Juni 2015

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Nivolumab zur Behandlung des 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.	*Nicht angezeigt*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	• Afatinib: Beschluss vom 8. Mai 2014 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Crizotinib: Beschluss vom 2. Mai 2013 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie - Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten - (Stand: 30. Juni 2014): Arzneimittel, die unter Beachtung der dazu gegebenen Hinweise in nicht zugelassenen Anwendungsgebieten (Off-Label-Use) verordnungsfähig sind: Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCL) – Kombinationstherapie
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Nivolumab L01XC17 Nivolumab BMS	Nivolumab BMS ist zur Behandlung des lokal fortgeschrittenen oder metastasierten nicht-kleinzelligen Lungenkarzinoms (NSCLC) mit plattenepithelialer Histologie nach vorheriger Chemotherapie bei Erwachsenen indiziert.
Chemotherapien:	
Carboplatin L01XA02 (generisch)	Off-Label-Indikation für Carboplatin: Kombinationstherapie des fortgeschrittenen NSCLC (palliativ)
Cisplatin L01XA01 (generisch)	Cisplatin wird angewendet zur Behandlung des: fortgeschrittenen oder metastasierten nichtkleinzelligen Bronchialkarzinoms. (FI Cisplatin-HAEMATO, 06-2012)
Docetaxel L01CD02 (generisch)	Nicht-kleinzelliges Bronchialkarzinom: Docetaxel ist zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Bronchialkarzinom nach Versagen einer vorausgegangenen Chemotherapie angezeigt. Docetaxel ist in Kombination mit Cisplatin zur Behandlung von Patienten mit nicht resezierbarem, lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Bronchialkarzinom ohne vorausgegangene Chemotherapie angezeigt. (FI Docetaxel-ratiopharm®, 05-2013)
Etoposid L01CB01 (generisch)	Kombinationstherapie folgender Malignome: Palliative Therapie des fortgeschrittenen NSCLC bei Patienten mit gutem Allgemeinzustand (Karnofsky-Index >80%). (FI Riboposid®, 02-2014)
Ifosfamid L01AA06 (Holoxan®)	Nicht-kleinzellige Bronchialkarzinome: Zur Einzel- oder Kombinationschemotherapie von Patienten mit inoperablen oder metastasierten Tumoren. (FI Holoxan®, 11-2008)
Mitomycin L01DC03 (generisch)	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Bei intravenöser Gabe ist es in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei folgenden metastasierenden Tumoren wirksam: […] nicht-kleinzelliges Bronchialkarzinom […]. (FI Mitomycin 2 medac, 03-2014)

Paclitaxel L01CD01 (generisch)	Fortgeschrittenes nicht-kleinzelliges Bronchialkarzinom (NSCLC): Paclitaxel ist, in Kombination mit Cisplatin, zur Behandlung des nicht-kleinzelligen Bronchialkarzinoms bei Patienten angezeigt, für die potentiell kurative chirurgische Maßnahmen und/oder eine Strahlentherapie nicht in Frage kommen. (FI Paclitaxel Hospira, 01-2014)
Vindesin L01CA03 (Eldesine®)	Kombinationschemotherapie: lokal fortgeschrittenes oder metastasiertes nicht-kleinzelliges Bronchialkarzinom (Stadium IIIB oder IV). (FI Eldesine®, 01-2014)
Vinorelbin L01CA04 (generisch)	Vinorelbin ist angezeigt zur Behandlung: des nicht kleinzelligen Bronchialkarzinoms (Stadium 3 oder 4). (FI Bendarelbin, 01-2013)
Proteinkinase-Inhibitoren	
Gefitinib L01XE02 (Iressa®)	Iressa® ist angezeigt zur Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Lungenkarzinom (NSCLC) mit aktivierenden Mutationen der EGFR-TK. (FI Iressa®, 04-2014)
Erlotinib L01XE03 (Tarceva®)	Nicht-kleinzelliges Lungenkarzinom (NSCLC): Tarceva ist zur First-Line-Behandlung bei Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit aktivierenden EGFR-Mutationen angezeigt. Tarceva ist auch als Monotherapie zur Erhaltungsbehandlung bei Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC angezeigt, deren Krankheitszustand nach 4 Behandlungszyklen einer platinbasierten First-Line-Standardchemotherapie unverändert ist. Tarceva ist auch zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC angezeigt, bei denen mindestens eine vorausgegangene Chemotherapie versagt hat. Beim Verschreiben von Tarceva sollten Faktoren, die im Zusammenhang mit einer verlängerten Überlebenszeit stehen, berücksichtigt werden. Bei Patienten mit epidermalen Wachstumsfaktor-Rezeptor-(EGFR)-IHC-negativen Tumoren konnten weder ein Überlebensvorteil noch andere klinisch relevante Wirkungen durch die Behandlung gezeigt werden (siehe Abschnitt 5.1). (FI Tarceva®, 12-2013)
Afatinib L01XE13 (Giotrif®)	Giotrif® als Monotherapie wird angewendet zur Behandlung von EGFR-TKI-naiven erwachsenen Patienten mit lokal fortgeschrittenem und/oder metastasiertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit aktivierenden EGFR-Mutationen. (FI Giotrif®, 09-2013)
Crizotinib L01XE16 (Xalkori®)	Xalkori® wird angewendet bei Erwachsenen zur Behandlung des vorbehandelten Anaplastische-Lymphom-Kinase (ALK)-positiven, fortgeschrittenen nicht kleinzelligen Bronchialkarzinoms (non small cell lung cancer, NSCLC). (FI Xalkori®, 05-2014)
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. (SPC Zykadia®, 05-2015)

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2015-B-063 Nivolumab

Datum: 17.06.2015

Recherche und Synopse der Evidenz zur Bestimmung der zVT:

Indikation für die Recherche:

Anwendungsgebiet:

Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit plattenepithelialer Histologie nach Vorbehandlung mit Chemotherapie.

Die vorliegende Evidenzsynopse beschränkt sich nicht auf Patienten mit plattenepithelialer Histologie. Sofern in den Studien explizite Informationen zu dieser Patientenpopulation vorlagen, wird dies farblich hervorgehoben.

Berücksichtigte Wirkstoffe/Therapien:

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

Systematische Recherche:

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 12.05.2015 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), arztbibliothek.de (ÄZQ), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP.
Aufgrund der onkologischen Indikation wurde zusätzlich in folgenden Datenbanken bzw. Internetseiten folgende Organisationen gesucht: CCO, ESMO, NCI.
Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 655 Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden 110 Quellen eingeschlossen. Insgesamt ergab dies 32 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

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

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

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

Systematische Reviews

Chen X et al., 2013 [7]. Gefitinib or erlotinib as maintenance therapy in patients with advanced stage non-small cell lung cancer: a systematic review

1. Fragestellung

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

2. Methodik

Population: advanced NSCLC
Intervention: EGFR TKIs
Komparator: Placebo or Observation
Endpunkte: PFS, OS
Suchzeitraum: bis 09/2012
Anzahl eingeschlossene Studien/Patienten (Gesamt): 5 (2436)
Qualitätsbewertung der Studien: k.A.
Heterogenitätsuntersuchungen: I^2; keine bedeutsame Heretogenität

3. Ergebnisdarstellung

- 2 Studien: gefitinib (250 mg/qd)
- 3 Studien: erlotinib (150 mg/qd) maintenance.

In all studies maintenance was commenced after 4 cycles' first line chemotherapy in stage IIIB/IV NSCLC.

All studies: a mixed population (EGFR mutated and non-mutated) and two of the studies (INFORM and SATURN) reported the outcomes of EGFR patients related to EGFR status.

Four studies were double blind and placebo controlled, and only one trial (IFCT-GFPC 0502) [13] was open label.

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

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

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

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

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

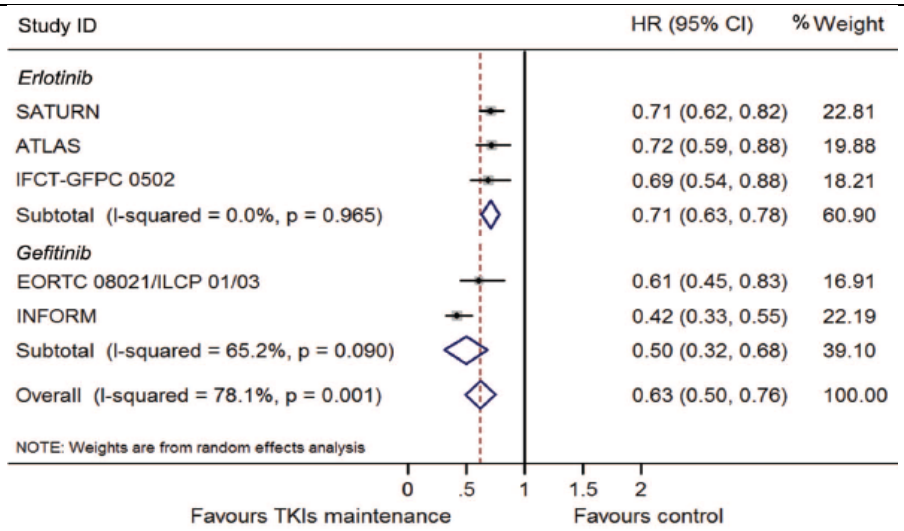
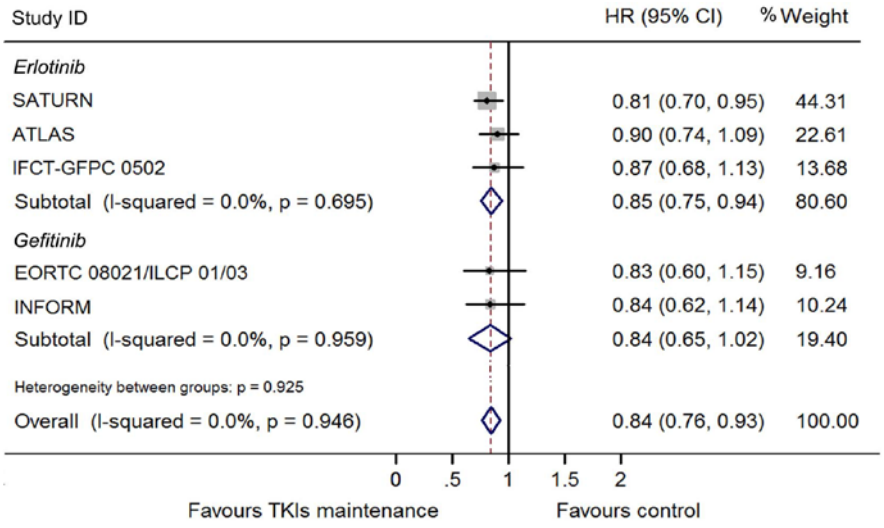


Figure 2. Meta-analysis of hazard ratio (HR) for progression free survival (PFS).



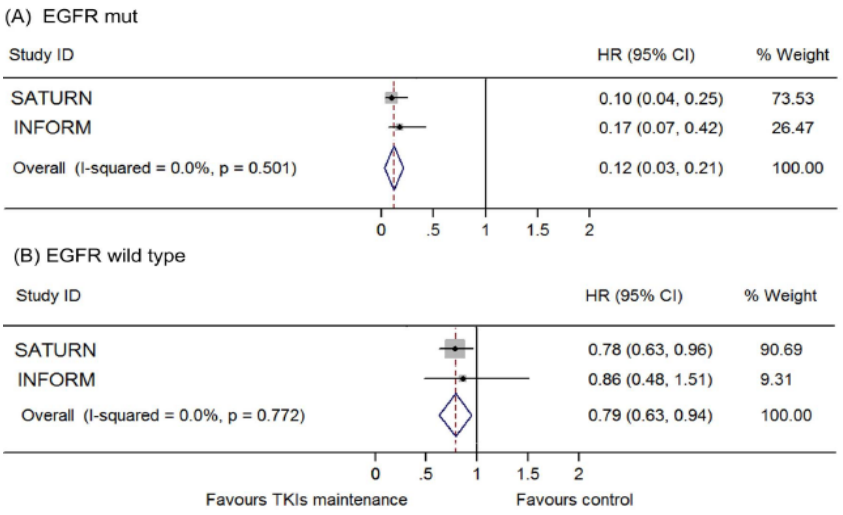


Figure 3. Meta-analysis of hazard ratio (HR) for progression free survival (PFS) according to EGFR mutation status. (A) EGFR mutation positive. (B) EGFR wild type.

	The PFS benefit was consistent in all subgroups including stage, sex, ethnicity, performance status, smoking status, histology, EGFR mutation status, and previous response to chemotherapy. 4. **Fazit der Autoren:** *The results show that maintenance therapy with erlotinib or gefitinib produces a significant PFS and OS benefit for unselected patients with advanced NSCLC compared with placebo or observation. Given the less toxicity of TKIs than chemotherapy and simple oral administration, this treatment strategy seems to be of important clinical value.*
des Guetz G et al., 2012 [9]. Comparison of the efficacy and safety of single-agent and doublet chemotherapy in advanced non-small cell lung cancer in the elderly: A meta-analysis.	**1. Fragestellung** To compare efficacy (1-Year Overall Survival or OS and Overall Response Rate or ORR) and safety of **doublet vs single-agent chemotherapy** among elderly patients aged 70 years or more. To assess the comparative efficacy and side effects of regimens including platinum derivates or not. **2. Methodik** **Population**: Elderly patients (70 years or older) treated for metastatic or advanced NSCLC (stage IV and IIIB) **Intervention**: doublet-agent chemotherapy **Komparator**: single-agent chemotherapy **Endpunkt**: OS, ORR, toxicity **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: up to 2012 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 10 (n= 2605) **Qualitätsbewertung der Primärstudien:** k.A. **3. Ergebnisdarstellung**

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

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

Table 1 (*Continued*)

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

SCC: squamous cell carcinoma; AC: adenocarcinoma.

Overall survival:

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

Response rate:

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

- Paclitaxel (3 trials): statistically significant difference in favor of doublet therapy ORR (HR 2.32; 1.71–3.15; fixed effect model)

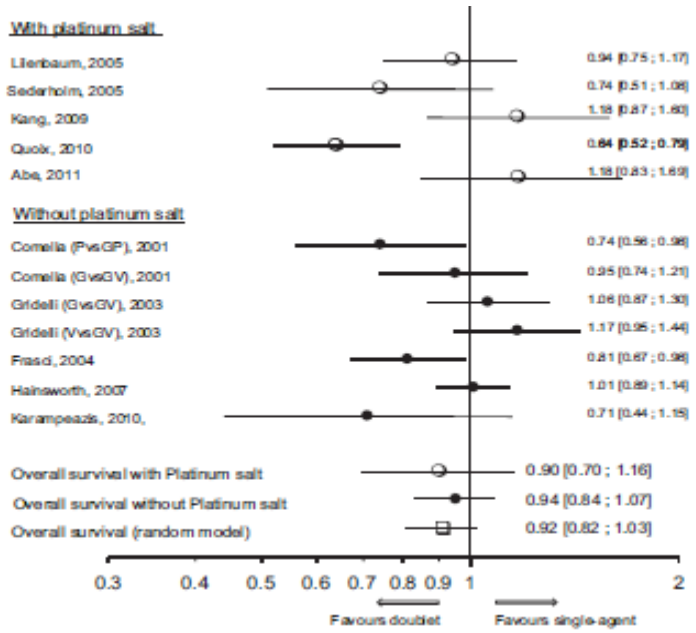


Fig. 2. Forest plot of studies including or not a platinum salt and assessing overall survival. By convention, a Hazard Ratio < 1 corresponds to a higher survival for doublet chemotherapy compared with single agent.

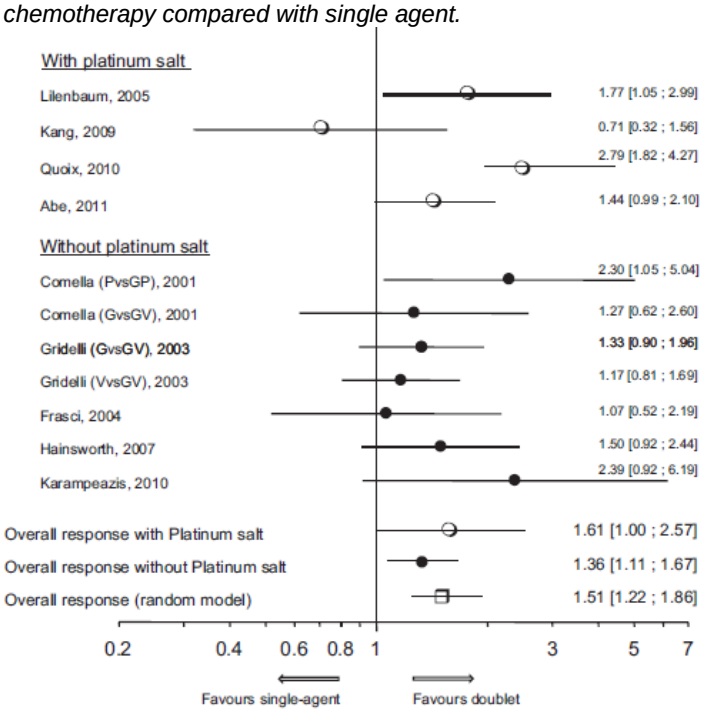


Fig. 3. Forest plot of studies including or not a platinum salt and assessing response rate. By convention, a Hazard Ratio < 1 corresponds to higher response for doublet chemotherapy compared with single agent.

Toxicity:

All grade nausea/vomiting was similar for doublets and single agents, whereas neutropenia, thrombocytopenia and anemia were significantly

	more frequent for doublets compared with single agents (HRs 1.26, 1.15–1.39, fixed effect model; 1.75, CI 1.11–2.77 random effect model; 1.33, CI 1.17–1.52 fixed effect model respectively; all p inferior to 0.001). 4. **Fazit der Autoren:** *Platinum-based doublets represent the gold standard of chemotherapy of NSCLC. Our MA does not firmly confirm the superiority of platinum-based doublets among elderly patients. The great majority of studies used carboplatin, which seems preferable since it is devoid of renal toxicity.* *The benefit to-risk ratio of doublets in advanced NSCLC might be more favorable than that of single agents, at least for doublets including platinum derivates and in elderly patients with good performance status. Doublets not including platinum derivates showed an increased toxicity without improving survival and should therefore be avoided in elderly patients with good performance status.* 5. **Hinweise durch FB Med:** Keine Information über Therapielinie. Die betrachteten Therapieregime weisen Großteils auf eine Erstlinientherapie hin.
Ganguli A et al., 2013 [11]. The impact of second-line agents on patients' health-related quality of life in the treatment for non-small cell lung cancer: a systematic review.	**1. Fragestellung** This review assessed QOL outcomes of approved, guideline- supported 2L chemotherapy with docetaxel, erlotinib, gefitinib, and pemetrexed in advanced NSCLC**.** The purpose of this review is to systematically assess the available literature reporting QOL results in clinical trial studies of guideline-supported 2L chemotherapy with docetaxel, erlotinib, gefitinib, and pemetrexed for the treatment for advanced NSCLC. **2. Methodik** **Population:** advanced NSCLC **Intervention:** Patients were treated with docetaxel, pemetrexed, erlotinib, or gefitinib; Second-line (2L) **Komparator:** Nicht spezifiziert **Endpunkte:** quality of life (QOL) **Suchzeitraum:** 2000 bis 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 28 (nicht berichtet; Range: 31 – 1692) RCT und CCT nur Studien mit mehr als 20 Patienten, auf QOL wurde im Abstract oder Titel hingewiesen **Qualitätsbewertung der Studien:** Checklist for Evaluating QOL Outcomes in Cancer Clinical Trials **Heterogenitätsuntersuchungen:** Nicht berichtet

3. Ergebnisdarstellung

- 8 - docetaxel
- 4 - erlotinib
- 11 - gefitinib and
- 1 – pemetrexed

Table 1 Overview of the key QOL study features

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

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

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

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

No significant results were found for pemetrexed

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

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

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

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

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

Table 4 Time to deterioration in QOL

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

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

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

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

- Studienqualität sehr heterogen

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

Jiang J et al., 2011 [12]

Gefitinib versus Docetaxel in previously treated advanced non-small-cell lung cancer: a meta-analysis of randomized controlled trials

1. **Fragestellung**

2. **Methodik:** Systematische Literaturrecherche im Jahr 2009 nach RCTs.

Population: Patienten mit einem NSCLC (Stadium IIIB oder IV), die mindestens ein vorheriges Chemotherapie-Regime erhalten haben, positiver Marker für EGFR-Mutation kein Einschlusskriterium

Vergleich: Gefitinib vs. Docetaxel

Endpunkte: OS, PFS, ORR, Lebensqualität und Symptomverbesserung, Nebenwirkungen

	Anzahl eingeschlossene Studien/Patienten (Gesamt): Es wurden insgesamt 4 Studien mit 2 257 Patienten eingeschlossen. **3. Ergebnissdarstellung** • OS, PFS: keine statistisch signifikanten Unterschiede; keiner statistische Heterogenität • ORR: statistisch signifikanter Vorteil unter Gefitinib gegenüber Docetaxel (RR: 1.58; 95%KI: 1.02-2.45, p = 0.04), bei signifikanter Heterogenität • Lebensqualität und Symptomverbesserung: statistisch signifikanter Vorteil unter Gefinitib hinsichtlich dem FACT-L und dem TOI Fragebogen (RR: 1.55; 95%KI: 1.27-1.88; p = 0.00 / RR: 1.86; 95%KI: 1.43-2.42; p = 0.00), kein Unterschied hinsichtlich einer Verbesserung der Symptomatik • Nebenwirkungen: Stat. signifikant mehr Risiko hinsichtlich Grad 3/4 Neutropenien und Fatigue unter Docetaxel, verglichen mit Gefinitib (OR: 0.02; 95%KI: 0.01-0.03; p=0.00 / OR: 0.47; 95%KI: 0.32-0.70; p=0.00). Gegensätzlich zeigte sich ein stat. signifikanter Nachteil unter Gefitinib gegenüber Docetaxel hinsichtlich Grad 3/4 Hautausschlägen (OR: 2.87; 95%KI: 1.24-6.63; p=0.01). Grad 3/4 Erbrechen, Übelkeit und Durchfälle waren vergleichbar zwischen den Gruppen. **4. Fazit der Autoren***: 'Although similar OS and PFS, gefitinib showed an advantage over docetaxel in terms of objective response rate, QoL and tolerability. Therefore, gefitinib is an important and valid treatment option for previously treated advanced non-small-cell lung cancer patients.'* **5. Hinweise FB Med:** • Notwendigkeit der EGFR-Mutation nicht diskutiert • Ergebnisse nicht nach Erst- oder Zweitlinientherapie unterschieden • Acknowledgements: analysis supported by a grant from the scientific research foundation of Huashan Hospital Fudan University • all authors indicated no potential conflicts of interest • heterogeneity calculated and reported • publication bias was not found
Lee,JK et al., 2014 [15] Epidermal growth factor receptor tyrosine kinase inhibitors vs conventional chemotherapy in non-small cell lung cancer harboring wild-type epidermal growth factor receptor: a meta-	**1. Fragestellung** Current guidelines recommend both epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and cytotoxic chemotherapy drugs as standard treatment options for patients with wild-type (WT) *EGFR* who were previously treated for non–small cell lung cancer (NSCLC). However, it is not clear that EGFR TKIs are as efficacious as chemotherapy in patients withWT *EGFR*. **2. Methodik** **Population:** Patients with advanced NSCLC, defined as inoperable locally advanced (stage IIIB) or metastatic or recurrentdisease (stage IV) **Intervention:** first-generation EGFR TKI (erlotinib and gefitinib) **Komparator:** chemotherapy **Endpunkte:** OS, OR, PFS **Suchzeitraum:** Bis 12/2013

analysis	**Anzahl eingeschlossene Studien/Patienten (Gesamt):** 11 (1605) **Qualitätsbewertung der Studien:** Risk of bias assessment (supplement) **Heterogenitätsuntersuchungen:** I^2 **3. Ergebnisdarstellung** Table. Characteristics of the Included Randomized Controlled Trials Comparing EGFR TKI With Chemotherapy

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

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

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

[b] Numbers of randomized patients.

[c] TKI group vs chemotherapy group.

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

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

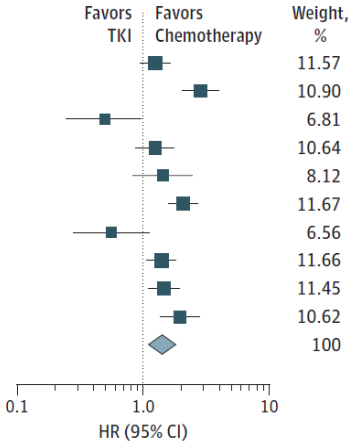
All 11 trials were open-labeled

PFS

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

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

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

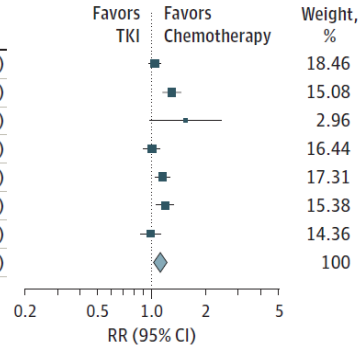


The size of the data markers (squares) corresponds to the weight of the study in themeta-analysis. The treatment effects were calculated with a random-effects model.

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

A Objective response rate

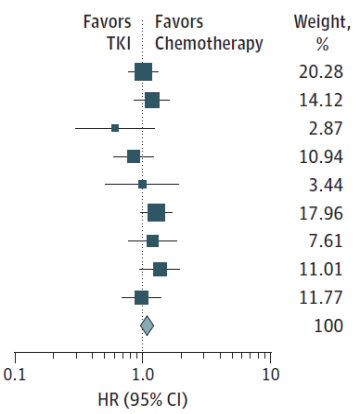
Source	No. of Patients With WT *EGFR* TKI Event[a]	TKI Total	Chemotherapy Event[a]	Chemotherapy Total	RR[a] (95% CI)	Weight, %
INTEREST,[12,27] 2008 and 2010	99	106	111	123	1.03 (0.96-1.12)	18.46
IPASS,[5,28] 2009 and 2011	90	91	65	85	1.29 (1.15-1.46)	15.08
First-SIGNAL,[30] 2012	20	27	13	27	1.54 (0.98-2.41)	2.96
CT/06.05,[32] 2013	51	55	53	57	1.00 (0.90-1.11)	16.44
TAILOR,[15] 2013	97	100	82	97	1.15 (1.05-1.26)	17.31
DELTA,[33] 2013	100	106	68	85	1.18 (1.05-1.32)	15.38
CTONG-0806,[34] 2013	64	75	65	75	0.98 (0.87-1.12)	14.36
Overall: $I^2 = 71.7\%$; $P = .002$	521	560	457	549	1.11 (1.02-1.21)	100



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

B Overall survival

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



Subgruppen

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

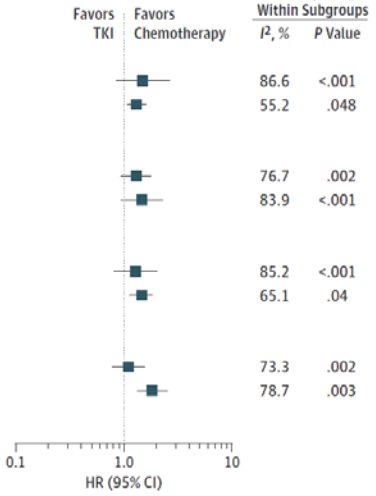
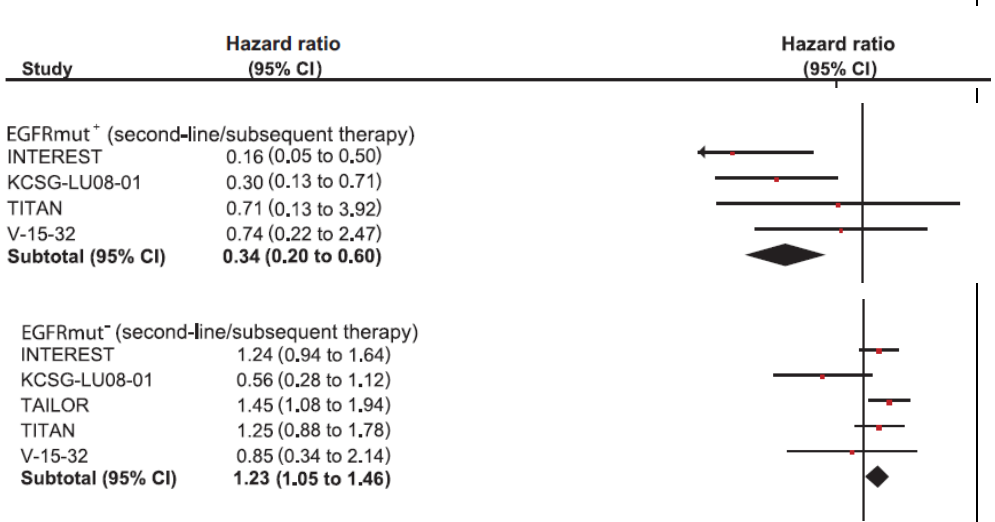


Figure 4. Subgroup Analyses for Progression-Free Survival According to the Line of Treatment (First vs Second or Later), EGFR TKI Agents, Ethnicity, and *EGFR* Mutation Analysis Methods for Patients WithWT *EGFR*

4. **Fazit der Autoren:** *Among patients with advanced NSCLC harboringWT EGFR, conventional chemotherapy, compared with first-generation EGFR TKI, was associated with improvement in PFS but not overall survival.*

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

Lee CK et al., 2013 [14]. Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis	**1. Fragestellung** We examined the impact of **EGFR–tyrosine kinase inhibitors** (TKIs) on progression-free survival (PFS) and overall survival (OS) in advanced NSCLC patients with and without EGFR mutations. **2. Methodik** **Population**: advanced NSCLC patients with and without EGFR mutations **Intervention**: EGFR-TKIs monotherapy, EGFR-TKIs and chemotherapy **Komparator**: chemotherapy, placebo, best supportive care **Endpunkt**: PFS, OS **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: 2004 bis 2012 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 23 (n=14 570) **Bewertung der Studienqualität der Primärstudien:** k.A. **3. Ergebnisdarstellung** <u>Zweitlinientherapie (7 trials)</u> **Overall survival:** no statistically significant difference between EGFR-TKI-based therapy and other therapy. Neither for EGFRmut+ patients nor for EGFRmut- patients **PFS:**  **Figure 2.** Forest plot of hazard ratios comparing progression-free survival in subgroups of epidermal growth factor receptor (EGFR) mutation–positive (EGFRmut+) and EGFR mutation–negative (EGFRmut-) patients who received EGFR–tyrosine kinase inhibitors (TKIs) vs control. **Fazit der Autoren:** EGFR-TKIs treatment is associated with 57% and 66% reduction in the risk of disease progression in EGFRmut+ patients in frontline and second-line settings, respectively, but with no benefit in EGFRmut- patients but has no demonstrable impact on OS
Li N et al., 2014 [16]. Meta-Analysis of	**1. Fragestellung** We performed this meta-analysis to compare the efficacy and safety of EGFR-TKIs vs. chemotherapy as second-line treatment for pretreated

EGFR Tyrosine Kinase Inhibitors Compared with Chemotherapy as Second-Line Treatment in Pretreated Advanced Non-Small Cell Lung Cancer	advanced NSCLC. … Preplanned subgroup analyses to explore potential effect on PFS, OS based on EGFR mutation status were scheduled. **2. Methodik** **Population:** advanced NSCLC (previously treated with platinum compounds) **Intervention:** EGFR TKI **Komparator:** standard second-line chemotherapy (docetaxel or PEM) **Endpunkte:** progression-free survival (PFS), overall survival (OS), objective response rate (ORR), grade 3–4 toxicities **Suchzeitraum:** July 2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 10/3 825 **Qualitätsbewertung der Studien:** not mentioned **Heterogenitätsuntersuchungen:** Q statistic and I^2 statistic used, if considered statistically significant, REM used, otherwise FEM **„Publication bias“:** Egger’s test and Begg’s funnel plots used ***3. Ergebnisdarstellung***

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

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

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

<u>PFS</u>

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

0,15 – 0,53; p = 0,001; I^2 = 4,1%, p (heterogeneity) = 0,35 - significantly improved

<u>OS, ORR</u>

- results of main and subgroup analyses equal

<u>grade 3–4 toxicities</u>

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

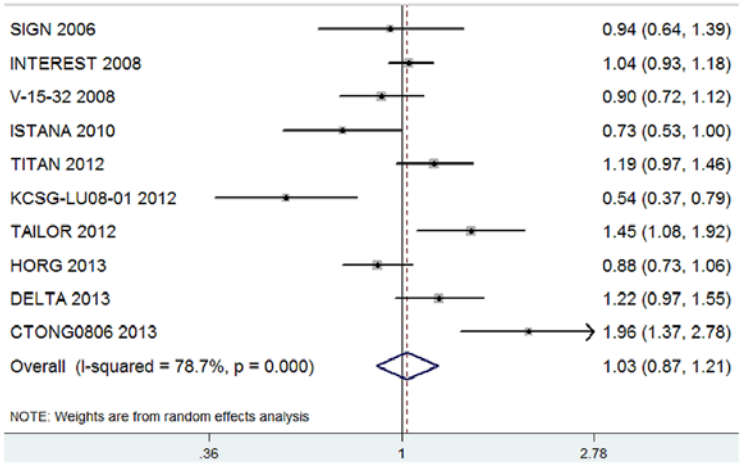


Figure 2. Comparison of PFS between EGFR-TKIs and chemotherapy.
doi:10.1371/journal.pone.0102777.g002

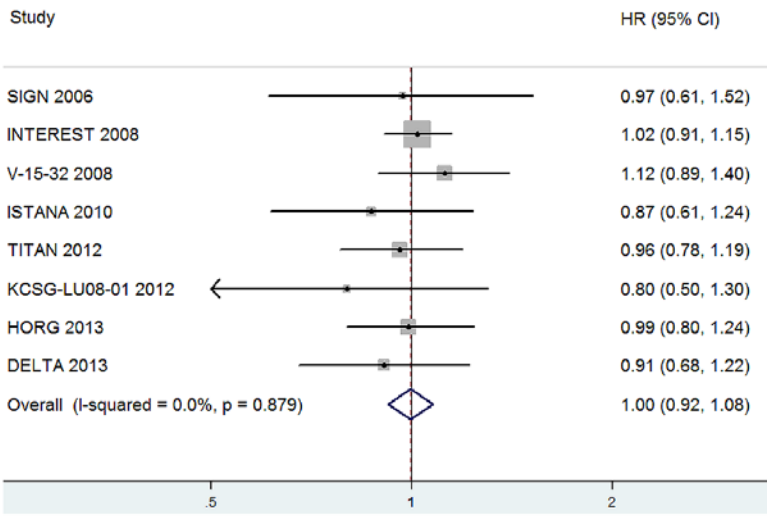
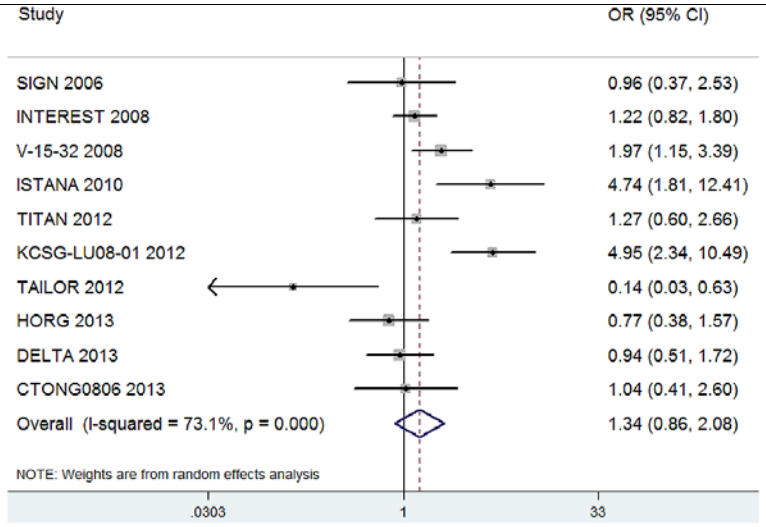


Figure 3. Comparison of OS between EGFR-TKIs and chemotherapy.
doi:10.1371/journal.pone.0102777.g003

	 **Figure 4. Comparison of ORR between EGFR-TKIs and chemotherapy.** doi:10.1371/journal.pone.0102777.g004 4. **Fazit der Autoren:** *Our analysis suggests that chemotherapy in the second-line setting can prolong PFS in EGFR M- patients, whereas it has no impact on OS. EGFR-TKIs seem superior over chemotherapy as second-line therapy for EGFR M+ patients. Our findings support obtaining information on EGFR mutational status before initiation of second-line treatment.* 5. **Hinweise durch FB Med:** • *no evidence of publication bias exists*
Li X t al., 2014 [17]. Efficacy of combining targeted therapy with pemetrexed or docetaxel as second-line treatment in patients with advanced non-small-cell lung cancer: a meta-analysis of 14 randomized controlled trials	**1. Fragestellung** To compare the effects of adding targeted agents to standard second-line chemotherapy with a single agent (pemetrexed or docetaxel) in patients with advanced NSCLC **2. Methodik** Metaanalyse **Population:** NSCLC **Intervention:** combination of targeted therapy and standard second-line chemotherapy (pemetrexed or docetaxel) (second-line treatment in NSCLC) **Komparator:** chemotherapy alone or chemotherapy plus placebo **Endpunkte:** • Objective response rate and disease control rate: Partial response (PR), complete response (CR), and stable disease (SD), • progression free

- survival (PFS)
- and overall survival (OS),
- Sicherheit/ Nebenwirkungen

Suchzeitraum: 2000 – 12/2013

Anzahl eingeschlossene Studien/Patienten (Gesamt): 14 (6922)

Qualitätsbewertung der Studien: Jadad-Score: 8 Studien mit hoher Qualität über 2 Punkte), 6 Studien mit niedriger Qualität (bis 2 Punkte)

Heterogenitätsuntersuchungen: durchgeführt (vgl. unten): geringe bis mittelgroße Heterogenität

3. Ergebnisdarstellung

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

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

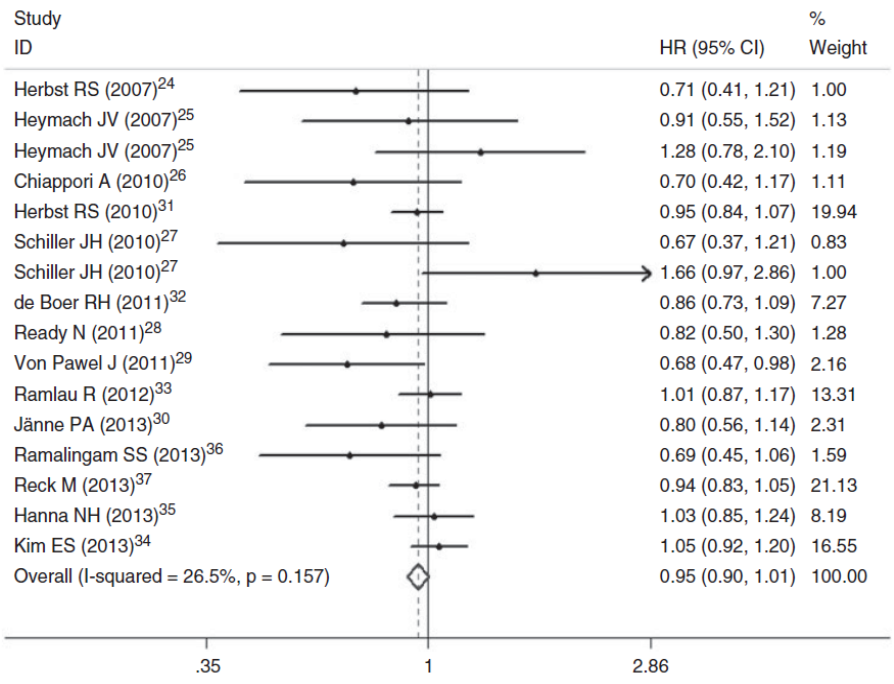
First Author (Year)	Phase	Treatment	No. of patients	Overall Response Rate (%)	Disease Control Rate (%)	Median PFS (months)	Median OS (months)
Herbst RS (2007)[24]	II	Doc/Pem + Pla	41	12.2	39	3.0	8.6
		Doc/Pem + Bev	40	12.5	52.5	4.8	12.6
Heymach JV (2007)[25]	II	Doc + Pla	41	12	56	3.0	13.4
		Doc + Van100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

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

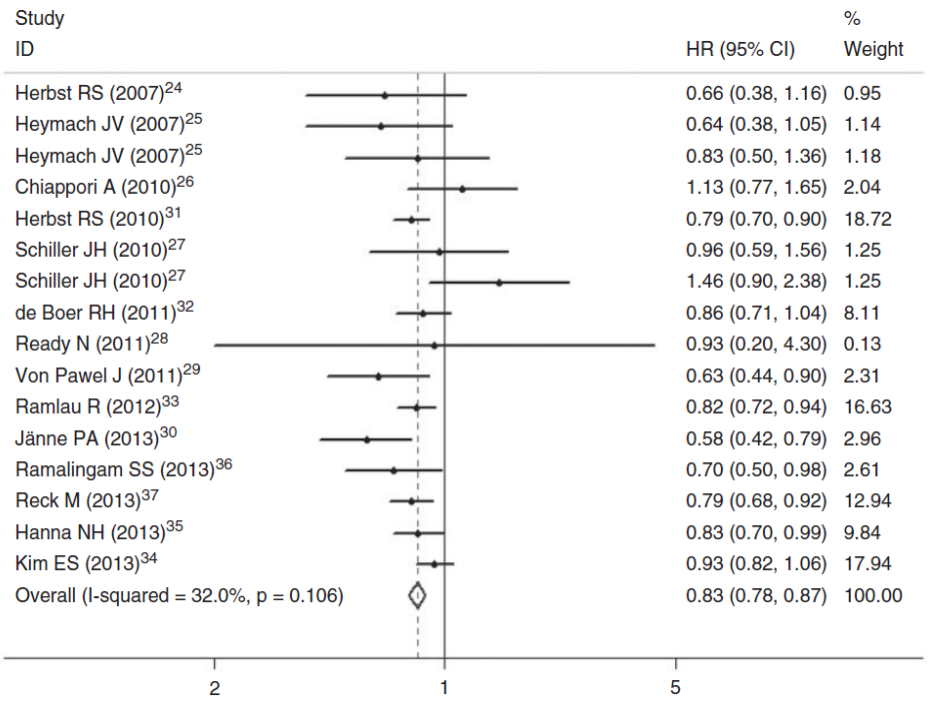
Table 2. Characteristics of studies in the meta-analysis.

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

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



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



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

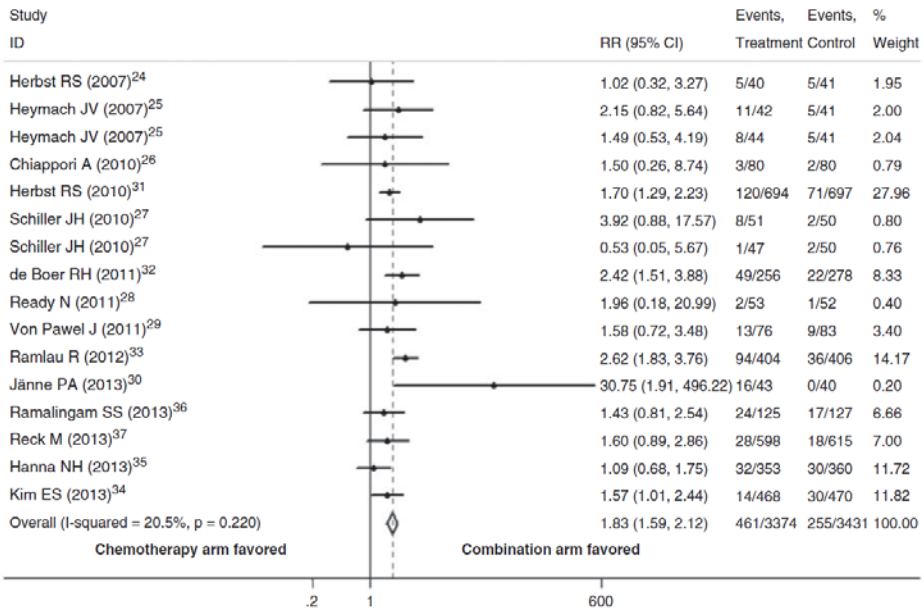


Figure 4. Forest plot of objective response rate of patients treated with chemotherapy arm versus combination arm.

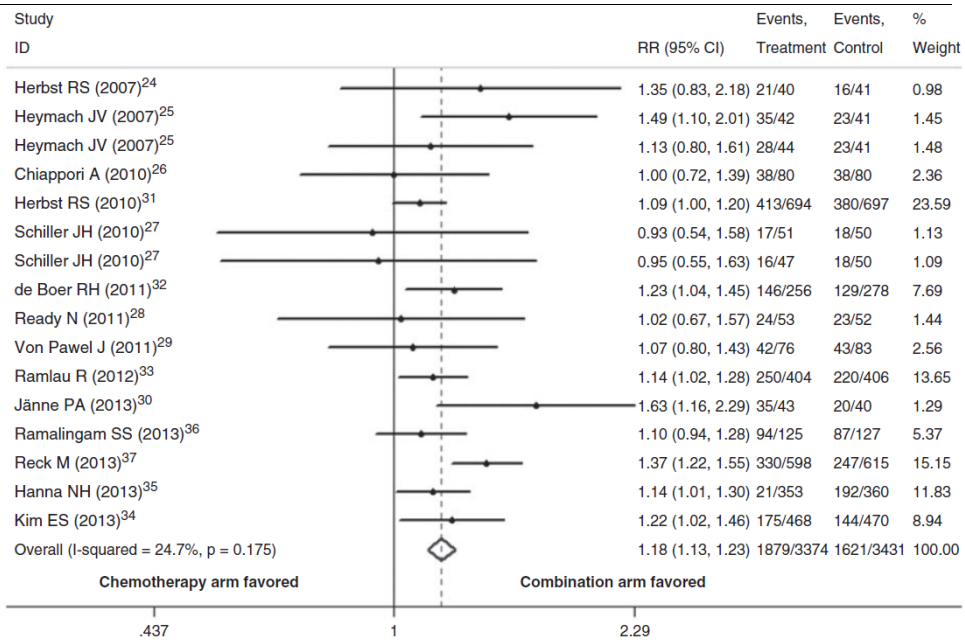
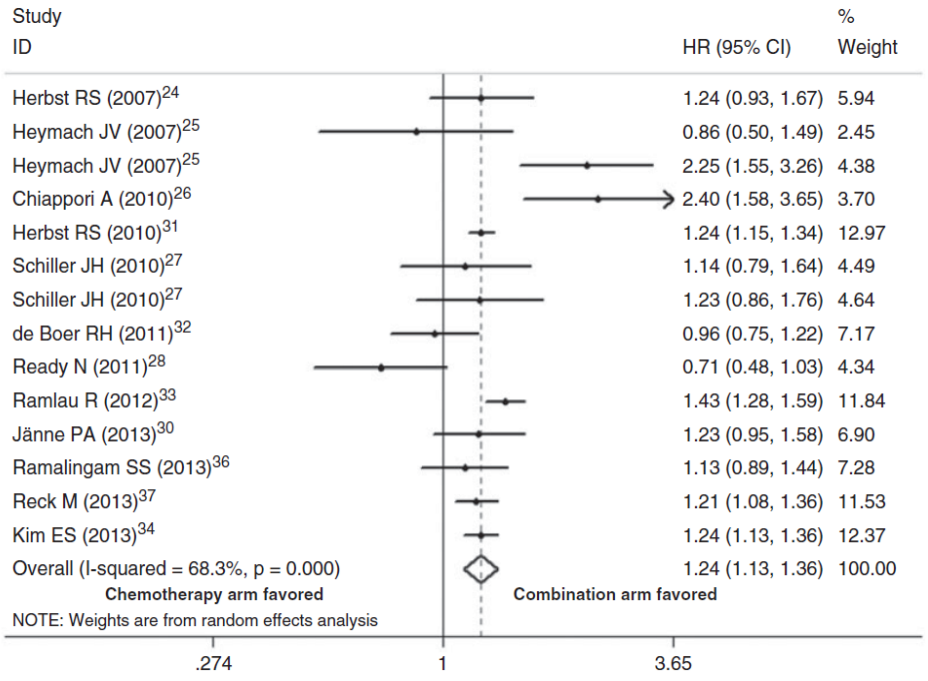


Figure 5. Forest plot of disease control rate of patients treated with chemotherapy arm versus combination arm.



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

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

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

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

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

Pan G et al., 2013 [19].

Comparison of the efficacy and safety of single-agent erlotinib and doublet molecular targeted agents based on erlotinib in advanced non-small cell lung cancer (NSCLC): a systematic review and meta-analysis

1. Fragestellung

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

2. Methodik

Population: Adult patients with advanced NSCLC. Mindestens 2. Linie

Intervention: doublets (erlotinib plus another targeted drugs)

Komparator: erlotinib

Endpunkte: OS, ORR,DCR (disease control rate), side effects

Suchzeitraum: Bis 11/2012, nur RCTs

Anzahl eingeschlossene Studien/Patienten (Gesamt): 5 (2100 Patienten)

Qualitätsbewertung der Studien: k.A.

Heterogenitätsuntersuchungen: I^2

3. Ergebnisdarstellung

Mean age 63; 1,224 men and 876 women; 118 stage IIIB and 1,180 stage IV; 441 squamous cell cancers, 1,287 adenocarcinomas, and 372 other pathological types.

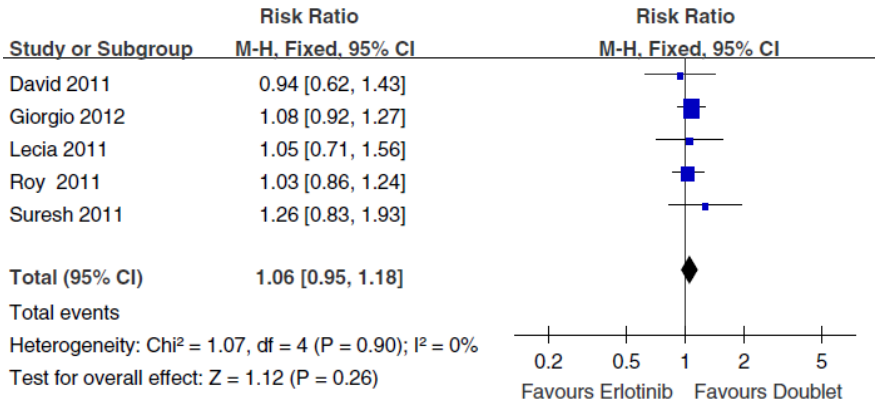
Table 1 Main characteristics of the five studies included in the meta-analysis

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

Effects: fixed effect models

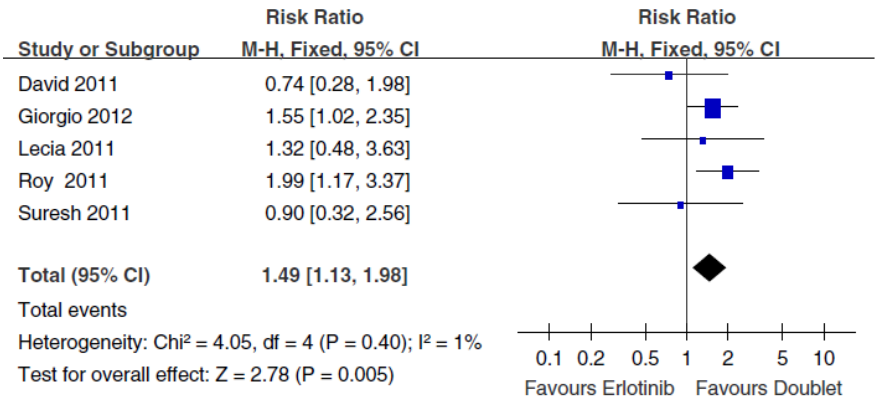
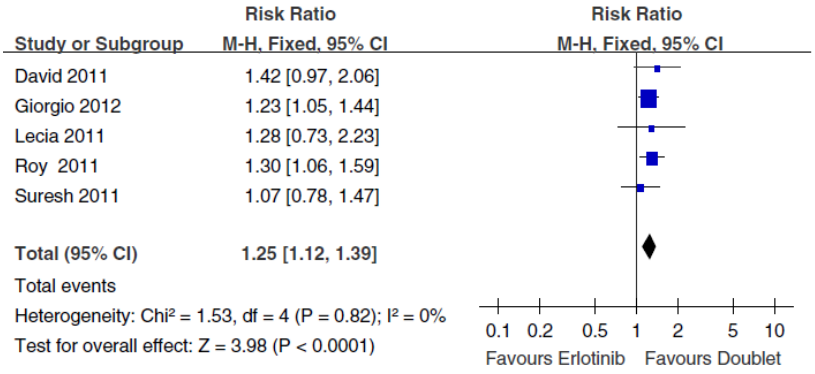
OS

One-year OS did not significantly improve with doublets compared with single erlotinib (HR 1.06, 95 % CI 0.95–1.18, p=0.26; fixed effect model)

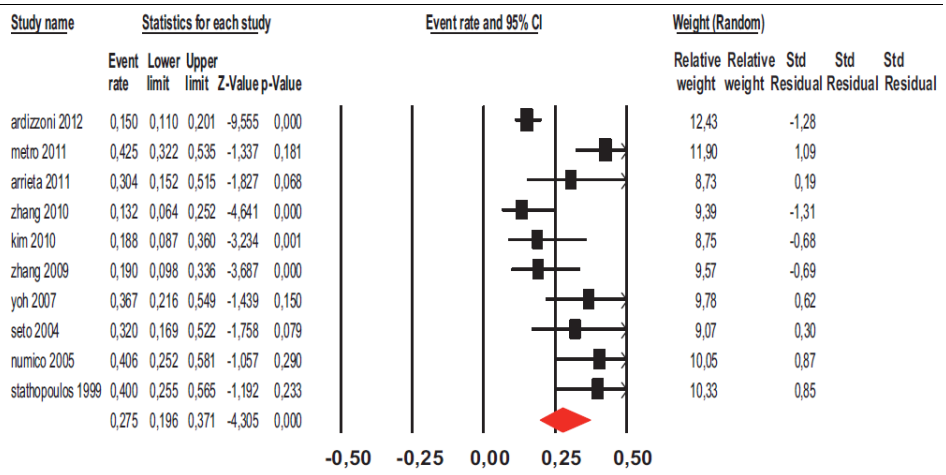


ORR

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

	 ***DCR (disease control rate)*** and HR 1.25, 95%CI 1.12–1.39, p<0.05)  ***Side effects/AEs*** All grades of the most frequent side effects such as rash, anemia, diarrhea, anorexia, and fatigue were similar for two groups (HR 1.25, 95 % CI 0.99–1.58; 0.98, 95 % CI 0.78–1.24; 1.43, 95%CI 0.97–2.11; 1.18, 95%CI 0.84–1.65; 1.23, 95 % CI 0.86–1.77, respectively; random effect model). The grade ≥3 toxicity was not significantly different (HR 1.40, 95 % CI 0.97–2.01; random effect model). Some adverse events (e.g., alopecia, dyspnea, dry skin, hypertension, bleeding complications, stomatitis, interstitial lung disease, and thrombocytopenia) could not be analyzed precisely due to their low incidence. 4. **Fazit der Autoren:** *The results of this systematic review suggest that patients with advanced NSCLC might benefit from doublet-targeted therapy based on erlotinib compared to erlotinib alone. However, an individual patient data systematic review and meta-analysis are needed to give us a more reliable assessment of the size of benefits and to explore whether doublet therapy may be more or less effective for particular types of patients.*
Petrelli F et al., 2013 [20]. Platinum rechallenge in patients with	**1. Fragestellung** This systematic analysis is the first review aiming to assess the clinical efficacy of platinum-doublet re-challenge, by using data pooled from clinical studies that enrolled patients with relapsed NSCLC after the first-

advanced NSCLC: A pooled analysis	line (platinum-based) failure. **2. Methodik** **Population:** patients with advanced NSCLC **Intervention:** second-line, platinum-based doublets, containing PEM or TAX agents **Endpunkte:** OS or PFS and RR **Studiendesign:** prospective clinical trials, minimum of 10 patients **Suchzeitraum:** between 1998 and 2012 **Ausschlusskriterien:** Studies published in a language other than English or that included less than 90% of patients pre-treated with platinum-based first-line doublets were excluded. **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 11 (n = 607) **3. Ergebnisdarstellung** Therapielinie: Zweitlinie: (n = 364), Drittlinie oder mehr: n = 243 (40 %) Studiendesign: 5 phase II trials, 3 prospective series, 1 prospective study, 2 retrospective analysis Therapieschemen: Carboplatin/PEM, Carboplatin/Gemcitabin oder PEM, platinbasiert/PEM, Cisplatin/DOC, Carboplatin/Paclitaxel, Cisplatin/Paclitaxel Time to progression (1st line): 0,8 – 13,7 month or 21,9 % -78,8 % > 6 month **Zweitlinientherapie-Studien -** Ergebnisdarstellung Response Rate (range) 15 – 40 % PFS (range): 3,2 – 6,4 month OS (range): 8,5 – 12,5 month Ergebnisdarstellung (**gesamt**): ***ORR*** with platinum-combinations was 27,5 %, with 22 % in (in all histologies) for patients treated with PEM-based doublets (range: 13,4 % – 34,1 %) and 37,8 % (range: 29,7 % – 46,7 %) for TAX-based doublets (p < 0,0001).



PFS

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

Sensitivity testing:

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

According to histology analysis, RR in PEM trials does not seem largely different in squamous (that represent 10–53% of patients) compared to not-squamous subtypes (as reported by Metro e Kim). However a systemstic investigation was not possible for other trials.

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

5. **Hinweise durch FB Med:**
   - no quality assessment of studies
   - using a random-effect model, heterogeneity not further mentioned
   - inclusion criteria for study design do not match with included studies
   - only two thirds had adenocarcinoma
   - no significant publication bias detected

Qi, WX et al., 2013 [21]. Overall Survival Benefits for	**1. Fragestellung** We thus performed a meta-analysis of RCTs to compare the efficacy and safety of combining targeted therapy vs. erlotinib alone as second-line treatment for advanced NSCLC.

Combining Targeted Therapy as Second-Line Treatment for Advanced Non-Small-Cell-Lung Cancer: A Meta-Analysis of Published Data.	**2. Methodik** **Population:** Patients with pathologically confirmed of advanced NSCLC and previously treated **Intervention:** combined targeted therapy **Komperator:** erlotinib alone or erlotinib plus placebo **Endpunkte:** overall survival (OS), progression-free survival (PFS), overall response rate (ORR), grade 3 or 4 adverse event (AEs) **Suchzeitraum:** 1980 bis 2012 **Anzahl eingeschlossene Studien/Patienten (gesamt):** 8 / 2 417 prospective phase II and III randomized controlled trials (RCTs) **Qualitätsbewertung der Studien:** Jadad score **Heterogenitätsuntersuchungen:** x2-based Q statistic used, considered statistically significant when p (heterogeneity) < 0,05 or I2>50%, if existed, data analyzed by REM (the DerSimonian and Laird method) **„Publication bias"-Berechnung:** Begg and Egger tests: no evidence of publication bias **3. Ergebnisdarstellung** ***Gesamt:*** • significantly improved OS (HR 0.90, 95%CI: 0.82–0.99, p = 0.024), PFS (HR 0.83, 95%CI: 0.72–0.97, p = 0.018), and ORR (OR 1.35, 95%CI 1.01–1.80, p = 0.04) under combined targeted therapy • More incidence of grade 3 or 4 rash, fatigue and hypertension were observed in combining targeted therapy. ***Subgruppen:*** • Sub-group analysis based on phases of trials, EGFR-status and KRAS-status also showed that there was a tendency to improve PFS and OS in combining targeted therapy, except that PFS for patients with EGFR-mutation or wild type KRAS favored erlotinib monotherapy. • because of a small number of patients with EGFR-status reported in these trials, it should be careful when interpreting these results • only 283 patients with EGFR mutation were included in meta-analysis • more trials still needed to identify molecular biomarkers that are predictive of efficacy **4. Fazit der Autoren:** *With the available evidence, combining targeted therapy seems superior over erlotinib monotherapy as second-line treatment for advanced NSCLC. More studies are still needed to identify patients who will most likely benefit from the appropriate combining targeted therapy.*

Shi L et al., 2014 [23]. Risk of interstitial lung disease with gefitinib and erlotinib in advanced non-small cell lung cancer: A systematic review and meta-analysis of clinical trials	**1. Fragestellung** We performed a systematic review and meta-analysis to determine the incidence and the relative risk (RR) associated with the use of gefitinib and erlotinib. **2. Methodik** **Population:** Patients with advanced NSCLC, assigned to treatment with gefitinib or erlotinib **Intervention:** Gefitinib oder Erlotinib **Komparator:** Platinbasierte Chemotherapie, Pemetrexed, Docetaxel, Paclitaxel, Vinorelbin oder Placebo **Endpunkte:** Overall incidence of interstitial lung disease (ILD) **Suchzeitraum:** Januar 2000 bis Oktober 2012 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 29 RCTs (15 618), davon 8 in der Zweit- oder Drittlinie **Qualitätsbewertung der Studien:** Jadad Score **Heterogenitätsuntersuchungen:** Wurden durchgeführt **3. Ergebnisdarstellung** The overall incidence for all-grade ILD events was 1.2% (95% CI, 0.9–1.6%) among patients receiving gefitinib and erlotinib, with a mortality of 22.8% (95% CI, 14.6–31.0%). When stratifying patients for their treatment line, we observed an RR of all-grade ILD events of 1.85 (95% CI, 1.13–3.00) for firstline patients and an RR of 1.36 (95% CI, 0.92–2.00) for non-first line patients. No significant difference was found between the groups stratified by treatment line (P = 0.333). ***4.*** **Fazit der Autoren:** *Treatment with EGFR TKIs gefitinib and erlotinib is associated with a significant increase in the risk of developing both all-grade and fatal ILD events in advanced NSCLC.* **Limits:** The National Cancer Institute's common toxicity criteria grading system for ILD has its own limitations. No term specific for ILD is listed in NCI CTCAE v2.0 or v3.0. Also, the majority of trials included in this analysis reported ILD events in combined grades (all-grade, or high-grade), we cannot distinguish cases in each grade. ILD is not a single disease, but encompasses many different pathological diseases. There were no uniform diagnostic criteria of ILD in various studies, also, the trials included in the analysis were performed at various centers, and the ability to detect ILD events might vary among these institutions, which could result in a bias of reported incidence rates. The incidence of ILD events showed significant heterogeneity among the included studies. This might reflect differences in trial designs, sample sizes, concomitant chemotherapy, and many other factors among these

	studies. Despite these differences, the RRs reported by all of these studies showed remarkable homogeneity. In addition, calculation using the random-effects model for overall incidence estimation might minimize the problem. The study might have a potential observation time bias because EGFR TKIs groups might have longer follow-up time than controls owing to the prolonged PFS that is often associated with the use of EGFR TKIs. However, most ILD events did not occur evenly over time, but in the early phase (first 4 weeks) of EGFR TKIs treatment. This is a meta-analysis at the study level, data were abstracted from published clinical trial results, and individual patient information was not available. Therefore, subgroup analyses according to possible risk factors for the development of ILD, including preexisting pulmonary fibrosis, age, performance status, gender, smoking history, lung cancer histology, and the mutational status of EGFR, are not possible in this analysis.
Tassinari et al., 2012 [25]. Noninferiority Trials in Second-Line Treatments of Nonsmall Cell Lung Cancer. A Systematic Review of Literature With Meta-analysis of Phase III Randomized Clinical Trials.	**1. Fragestellung** To assess the role of the novel second-line treatments in nonsmall cell lung cancer (NSCLC). **2. Methodik** **Population:** Patienten mit progredientem NSCLC nach Chemotherapie in der Erstlinie **Intervention:** Any novel treatment (Chemotherapie oder EGFR-Inhibitor) **Komparator:** Every 3 weeks docetaxel **Endpunkte:** One year survival rate (primär); Lebensqualität und Sicherheit (sekundär) **Suchzeitraum:** Bis Juni 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 4 Phase III Studien (3 355) **Qualitätsbewertung der Studien:** Nicolucci Score **Heterogenitätsuntersuchungen:** Wurde untersucht **3. Ergebnisdarstellung** ***One year survival rate (primär)*** The pooled odds ratio for 1-year SR was 0.927 (95% CI = 0.8-1.07, P = 0.313), 0.889 (95% CI = 0.703-1.123, P = 0.323) considering only those trials comparing 3WD versus chemotherapy (pemetrexed or oral topotecan), and 0.953 (95% CI = 0.789-1.151, P = 0.616) considering only those trials comparing 3WD vs gefitinib. ***QoL*** All the trials reported data about quality of life during the treatment, but only 3 of them reported comparable data that were included in the pooled analysis. The odds ratio for quality of life was 1.623 (95% CI = 1.124-2.343, *P* = 0.01). ***AEs***

	All the 4 selected trials reported data about grade III to IV neutropenia, fatigue, nausea, vomiting, and diarrhea. On the whole, a significant advantage of experimental arms was observed for neutropenia (odds ratio = 35.067, 95% CI = 18.541-66.324, *P* < 0.001), febrile neutropenia (odds ratio = 8.385, 95% CI = 4.525-15.536, *P* < 0.001), fatigue (odds ratio= 1.507, 95% CI = 1.09-2.084, *P*= 0.013), and neurotoxicity (odds ratio= 17.827, 95% CI = 3.813-83.352, *P* < 0.001), whereas a significant advantage of 3WD was observed for hepatic toxicity (odds ratio= 0.068, 95% CI =0.018-0.255, *P* < 0.001) and skin rash (odds ratio= 0.405, 95% CI = 0.166-0.99, *P*= 0.047). Considering the trials comparing 3WD vs other chemotherapies, a significant advantage of the experimental arm was observed only for neurotoxicity (odds ratio = 13.967, 95% CI = 1.804-108.15, *P*= 0.012). In the trials comparing 3WD vs EGFR inhibitors, a significant advantage of the experimental arm was observed for neutropenia (odds ratio = 44.161, 95% CI = 22.576-86.381, *P* < 0.001), febrile neutropenia (odds ratio= 9.291, 95% CI = 4.895-17.637, *P* <0.001), nausea (odds ratio = 2.411, 95% CI = 1.029-5.65, *P*= 0.043), and fatigue (odds ratio = 2.244, 95% CI = 1.462-3.443, *P* < 0.001), whereas a significant advantage of 3WD was observed for skin rash (odds ratio = 0.33, 95% CI = 0.121-0.903, *P*= 0.031). 4. **Fazit der Autoren:** *All the noninferiority trials demonstrated the noninferiority of pemetrexed, oral topotecan, or gefitinib in 1-year SR (primary end point), but the improvement in overall survival remains modest. The improvement in quality of life and safety (secondary end points) represents the main value of these treatments, whose aim is mainly palliative.* *The main information resulting from our analysis remains the equivocal role of the noninferiority trials, essentially aimed at favoring the registration of novel molecules without any definitive evidence of their actual role in improving the main outcomes, as suggested in some interesting warnings recently published in the literature* **Limits:** Although no difference among the various treatment options emerged in the primary analysis, the data relating the well-known role of some clinical and biological factors in predicting the clinical response to the EGFR inhibitors were not analyzed, as their predictive value could not be evaluated in the pooled analysis. The data yielded from the secondary analysis have just a descriptive aim, and they should only be considered as an interesting starting point for further trials. Our pooled analysis reports the data of a literature meta-analysis, which are considerably different and less accurate than those of an individual meta-analysis.

	5. Hinweise der FBMed Nur wenige Studien mit unterschiedlichen Interventionen. Es ist fraglich, ob hier die Anwendung metanalytischer Verfahren wirklich angezeigt war.
Tsujino K et al., 2013 [26]. Is Consolidation Chemotherapy after Concurrent Chemo-Radiotherapy Beneficial for Patients with Locally Advanced Non–Small-Cell Lung Cancer? A Pooled Analysis of the Literature.	**1. Fragestellung** The purpose of this study was to evaluate whether consolidation chemotherapy (CCT) after concurrent chemo-radiotherapy is beneficial for patients with locally advanced non–small-cell lung cancer (LA-NSCLC). **2. Methodik** **Population:** patients with locally advanced non–small-cell lung cancer **Intervention:** Consolidation therapy (CT+) **Komparator:** No Consolidation therapy (CT-) **Endpunkte:** Medianes Gesamtüberleben; Toxitizität **Suchzeitraum:** Bis Dezember 2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 41 RCTs (3 479) **Qualitätsbewertung der Studien:** k.A. **Heterogenitätsuntersuchungen:** Wurde untersucht **3. Ergebnisdarstellung** There was no statistical difference in pooled mOS between CCT+ (19.0 month; 95% CI, 17.3−21.0) and CCT− (17.9 month; 95% CI, 16.1−19.9). Predicted hazard ratio of CCT+ to CCT− was 0.94 (95% CI, 0.81−1.09; *p* = 0.40). There were no differences between the two groups with regard to grade 3−5 toxicities in pneumonitis, esophagitis, and neutropenia. **4. Fazit der Autoren:** *These models estimated that addition of CCT could not lead to significant survival prolongation or risk reduction in death for LA-NSCLC patients. We could not clarify the impact of chemotherapy doses on survival, because, in most studies, not fulldose but low-dose/fractionated chemotherapy was offered in the concurrent phase.* **Limits:** Pooled analyses on a publication basis, which included heterogeneous studies with different study designs and various patient populations. The impacts of chemotherapy regimens on survival data remain to be solved.
Xiao Y-Y et al., 2013 [29]. Chemotherapy	**1. Fragestellung:** to compare the efficacy and toxicity of chemotherapy plus multitargeted antiangiogenic TKI with chemotherapy alone in patients with advanced NSCLC

plus multitargeted antiangiogenic tyrosine kinase inhibitors or chemotherapy alone in advanced NSCLC: a meta-analysis of randomized controlled trials.	**2. Methodik**: Systematische Literaturrecherche bis 2011 **Population:** Patients with advanced NSCLC (Erst- und Zweitlinientherapie) **Intervention**: Chemotherapy plus multitargeted antiangiogenic TKI vs. **Komparator**: chemotherapy alone **Endpunkte**: PFS (primary endpoint), ORR, OS, toxic effects (secondary endpoints) **Eingeschlossene Studien (Patienten):** 6 (3 337) Gesamt 6 Studien (3337 Patienten). Zweitlinientherapie: 3 Studien (2 052) (jeweils mit 5 Punkten JADAD-Score bewertet) **Qualitätsbwertung der Studien:** Jadad Scale **3. Ergebnisse:** Die Ergebnisse wurden nicht getrennt nach Erst- oder Zweitlinientherapie dargestellt. • PFS: A significant difference between between the chemotherapy plus multitargeted antiangiogenic TKI and chemotherapy alone groups (HR 0.83, 95 % CI 0.76–0.90). Chemotherapy plus multitargeted antiangiogenic TKI significantly increased PFS. There was no significant heterogeneity (p= 0.288). • OS: No significant difference between the chemotherapy plus multitargeted antiangiogenic TKI and chemotherapy alone groups with no significant heterogeneity. • ORR: Chemotherapy plus multitargeted antiangiogenic TKI significantly improved the ORR (RR 1.71, 95 % CI1.43–2.05). However, there was significant heterogeneity (p= 0.013). Toxic effects: • The risks of rash, diarrhea, and hypertension were higher in patients receiving chemotherapy plus multitargeted antiangiogenic TKI than in those receiving chemotherapy alone (OR2.78, 95 % CI 2.37–3.26; OR1.92, 95 % CI1.65–2.24; OR2.90, 95 % CI2.19–3.84, respectively). • The risks of nausea and vomiting were higher in patients receiving chemotherapy alone than in those receiving chemotherapy plus multitargeted antiangiogenic TKI (OR0.71, 95 % CI0.60–0.83; OR0.75, 95 % CI0.61–0.92, respectively). • The risk of hemorrhage, fatigue, cough, constipation, anorexia and alopecia were comparable between two groups (OR1.27, 95 % CI 0.98–1.56; OR0.95, 95 % CI0.82–1.11; OR1.08, 95 % CI 0.87–1.34; OR0.95, 95 % CI0.78–1.17; OR1.12, 95 % CI 0.95–1.33; OR0.91, 95 % CI0.75–1.11, respectively). **Aus der Diskussion:** In general, chemotherapy plus multitargeted antiangiogenic TKI showed an advantage over chemotherapy alone in terms of ORR and PFS, despite the toxicities being comparable, but the

	clinical benefit and toxicities of the different multitargeted antiangiogenic TKI therapies were not equal. For example, in contrast to other multitargeted antiangiogenic TKI, in the ESCAPE study, the addition of sorafenib to chemotherapy had no clinical benefit, the PFS was 4.6 months in the paclitaxel and carboplatin plus sorafenib group and 5.4 the months in paclitaxel and carboplatin group, and there was increased mortality in the sorafenib arm in patients with squamous histology (HR1.85; 95 % CI 1.22–o 2.81); this study was terminated after interim analysis. **4. Fazit der Autoren:** Therapy consisting of chemotherapy plus multitargeted antiangiogenic TKI was found to have specific advantages over chemotherapy alone in terms of PFS and ORR. The toxicity was comparable between the two therapies. Therefore, chemotherapy plus multitargeted antiangiogenic TKI may be a safe and valid therapeutic option for patients with advanced NSCLC.'
Yang X et al., 2014 [30]. The efficacy and safety of EGFR inhibitor monotherapy in non-small cell lung cancer: a systematic review	**1. Fragestellung** Efficacy of (EFGR-TKIs: gefitinib or erlotinib) monotherapy in previously treated non-small-cell lung cancer (NSCLC) **2. Methodik** **Population:** advanced NSCLC **Intervention:** gefitinib or erlotinib **Komparator:** placebo or BSC **Endpunkte:** PFS and OS **Suchzeitraum:** December 2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 14/8 970 (3 front-line, 2 second-line, 9 maintenance) **Qualitätsbewertung der Studien:** scrutinized – no further information **Heterogenitätsuntersuchungen:** $\chi 2$ test, I2 statistic used, values of 50 % regarded as representing low heterogeneity, FEM with Mantel-Haenszel method used, once the results were homogeneous; otherwise, random-effect model with DerSimonian and Laird method adopted, sensitivity analysis was also conducted to examine the impact of the overall results from this study **„Publication bias":** plotting the HRs against their standard errors, Begg-adjusted rank correlation test and Egger regression asymmetry test performed **3. Ergebnisdarstellung** OS • HR (EGFR-TKIs mono vs. placebo) 0,88, 95 % KI 0,82 – 0,96, I^2 = 50.5% - significantly increased

	• patients with EGFR mutation positive had more pronounced benefit • second-line therapy group: HR 0,80; 95 % KI 0,63 – 1,01; I^2 = 74,6%, p = 0,047 • EGFR-mutation patients: HR 0,987; 95 % KI 0,881 – 1,105; I^2 = 12,8%, p = 0,330 PFS • HR (EGFR-TKIs) 0,71, 95 % KI 0,63 – 0,81, I2 = 81,2% • patients with EGFR mutation positive had more pronounced benefit adverse reactions (EGFR TKIs vs. placebo) • diarrhea (OR) 3,635; 95 % KI 2,377 to 5,557 • rashes (OR) 5,664; 95 % KI 8,869 to 27,665 • anorexia (OR) 1,555; 95 % KI 1,060 to 2,283 • anemia (OR) 1,481; 95 % KI 1,114 to 1,969 4. **Fazit der Autoren:** *The results show that monotherapy therapy with EFGR-TKIs produce a significant OS and PFS benefit for patients with NSCLC compared with placebo or BSC, especially for the patients who had adenocarcinomas, non-smokers and patients with EGFR gene mutations.*
Zhao N et al., 2014 [31]. Efficacy of epidermal growth factor receptor inhibitors versus chemotherapy as second-line treatment in advanced non-small-cell lung cancer with wild-type EGFR: a meta-analysis of randomized controlled clinical trials	**1. Fragestellung** We sought to evaluate the effectiveness of EGFR-TKI as second-line treatment in EGFR wild-type NSCLC. **2. Methodik** **Population:** previously treated advanced NSCLC with wild-type EGFR **Intervention:** EGFR TKIs **Komparator:** chemotherapy **Endpunkte:** progression-free survival (PFS), overall survival (OS), objective response rate (ORR) **Suchzeitraum:** bis 07/ 2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 6/990 (5 phase III) **Qualitätsbewertung der Studien:** Jadad scale **Heterogenitätsuntersuchungen:** x^2-based Q test; p > 0,05 indicates low heterogeneity; p ≤ 0,05 reflects high heterogeneity, if significant random-effects model used, if not significant FEM used **„Publication bias“:** tested by funnel plot

	3. Ergebnisdarstellung • all studies reached Jadad score of 3 PFS (EGFR-TKIs vs. chemotherapy) • HR 1,37; 95 % KI 1,20 – 1,56; p < 0,00001 – in the second-/third-line treatment of EGFR wild-type NSCLC, PFS significantly inferior in EGFR-TKI group compared with chemotherapy group • gefitinib and erlotinib significantly inferior to chemotherapy • erlotinib vs. chemotherapy: HR 1,37; 95 % KI 1,16 – 1,63, p = 0,0003 • gefitinib vs. chemotherapy: HR 1,35; 95 % KI 1,10 – 1,67, p = 0,004 • head-to-head trials: results favored chemotherapy more obviously (HR 1,53; 95 % KI 1,29 – 1,81; p < 0.00001 • subgroup trials, which had only subgroup analyses for EGFR wild-type patients: PFS not significantly different (HR 1,16; 95 % KI 0,94 – 1,43; p = 0,17) OS and ORR • equal results **4. Fazit der Autoren:** Chemotherapy improves PFS significantly but not OS, compared with EGFR-TKIs as a second-line treatment in advanced NSCLC with wild-type EGFR. Whether EGFR-TKIs should be used in EGFR wild-type patients should be considered carefully.
Zhong N et al., 2013 [32]. Chemotherapy Plus Best Supportive Care versus Best Supportive Care in Patients with Non-Small Cell Lung Cancer: A Meta-Analysis of Randomized Controlled Trials [32]	**1. Fragestellung** We performed a systematic review and meta-analysis to evaluate the effects of chemotherapy plus BSC versus BSC alone on survival of patients with NSCLC. **2. Methodik** **Population:** patients with NSCLC (Stage III/IV or advanced) **Intervention:** chemotherapy and BSC **Komparator:** BSC alone **Endpunkte:** OS or treatment-related mortality **Suchzeitraum:** Nicht angegeben **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 16 RCTs (4 135) **Qualitätsbewertung der Studien:** The quality of the trials was assessed by pre-defined criteria using Jadad score **Heterogenitätsuntersuchungen:** Durchgeführt (Sensitivitätsanalysen) **3. Ergebnisdarstellung**

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

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

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

Ergebnisse zum Overall Survival:

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

Ergebnisse zu Nebenwirkungen/unerwünschten Ereignissen:

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

4. **Fazit der Autoren:** *Chemotherapy plus BSC increased the OS and reduced the 6-month, 12-month, and 2-year mortality of NSCLC patients. Since nearly all the trials in our study included patients with stage III/IV disease or advanced NSCLC, the conclusions should be applicable only to patients with advanced or metastatic NSCLC.*

Limits:

First, inherent assumptions were made for all meta-analyses, because the

	analyses used pooled data, either published or provided by the individual study; individual patient data or original data were unavailable, which did not allow us to perform more detailed analyses and to obtain more comprehensive results. Second, treatments given in those trials included second generation, third generation, and the fourth generation chemotherapy regiments, which prevented us from exploring the association between the type of chemotherapy and survival outcomes. Third, heterogeneity among the trials is another limitation of our study. We applied a random-effect model that took possible heterogeneity into consideration and performed subgroup analyses based on several important factors to further explore the source of heterogeneity. Fourth, data on progression-free survival were rarely available in these trials; therefore, no conclusions could be drawn. **5. Hinweise der FBMed** • Kein Suchzeitraum angegeben • Es wird nicht dargestellt, welche Interventionen unter BSC subsummiert waren • Keine Information zu Therapielinie
Jin et al., 2014 [13]. Meta-Analysis to Assess the Efficacy and Toxicity of Docetaxel-Based Doublet Compared with Docetaxel Alone for Patients with Advanced NSCLC who Failed First-Line Treatment.	1. Fragestellung The goal of this meta-analysis was to assess the efficacy and toxicity of docetaxel-based doublet compared with docetaxel alone for patients with advanced NSCLC who failed to improve with first-line treatment.
	2. Methodik <u>Population</u>: Previously treated patients with locally advanced or metastatic NSCLC <u>Intervention</u>: Docetaxel-based doublet <u>Komparator</u>: Single-agent docetaxel <u>Endpunkt</u>: Overall survival, progression-free survival (PFS), objective response rate, disease control rate, grade3 or 4 adverse events <u>Suchzeitraum (Aktualität der Recherche)</u>: All randomized trials evaluating the effect of the combined regimen of docetaxel and other drugs were eligible for inclusion. Two investigators independently searched the Pub Med database, Cochrane Controlled Trials Register via the Cochrane Library, and ClinicalTrials.gov. The search was limited to randomized controlled trials or clinical trials. Kein Suchzeitraum angegeben! <u>Anzahl eingeschlossene Studien/Patienten (Gesamt):</u> 12 Studien mit 2680

	Patienten. Darunter 1351 mit einer Docetaxel-basierten Kombinationstherapie und 1319 Patienten mit einer Docetaxel Monotherapie. Qualitätsbewertung der Studien: All of the studies were published in peer-reviewed journals. Eight of the12 included trials were PhaseII trials and 4 were large, Phase III, randomized clinical studies. Four of the clinical trials used docetaxel combined with targeted treatment, including vandetanib, selumetinib, and cetuximab; 4 studies used docetaxel combined with anti metabolic agents, including capecitabine,gemcitabine,and S-1; and the other 4 trials used docetaxel combined with oxaliplatin, carboplatin, and irinotecan No publication bias was observed.
	3. Ergebnisdarstellung ORR and Disease Control Rate: The pooled OR for ORR showed that the docetaxel-based doublet group significantly improved ORR more than the docetaxel monotherapy group (OR: 1.73 [95%CI: 1.37–2.18]; P< 0.01). There was no significant heterogeneity. PFS and OS: Only 2 studies reported results for PFS and OS. From the rest oft he studies, PFS and OS were estimated from survival curves. There was a statistically significant benefit regarding PFS and OS in the combined regimen (PFS: HR: 0,79; 95%CI: 0,71-0,89; p<0,01; I^2= 47% / OS: HR: 0,89; 95%CI: 0,83-0,96; p<0,01; I^2=22%). PFS and OS by Drug Type: Docetaxel combined with oxaliplatin, carboplatin and irinotecan: In this cohort, the docetaxel combined regimen had no advantage over docetaxel monotherapy in either PFS or OS. Grade 3andHigherToxicities: There was a higher incidence of grade 3or 4 thrombocytopenia (RR: 4.84 [95%CI: 1.98– 11.83]; P < 0.01) and diarrhea (RR:1.82 [95% CI, 1.22–2.73]; P < 0.01) in the docetaxel-based doublet group.There were no differences in grade 3or 4 anemia, neutropenia, fatigue, nausea, or vomiting between the 2 arms.
	4. Fazit der Autoren: *Based on the available evidence, docetaxel-based doublet therapy seems superior to docetaxel monotherapy as a second-line treatment for advanced NSCLC. More studies should focus on combining docetaxel with targeted therapy to identify patients who will most likely benefit from the appropriate combination targeted therapy.* 5. Anmerkungen der Autoren: • The analysis was based on summary data rather than individual patient data, which tends to overestimate treatment effects.

	• Because most of the HRs and 95% CIs for PFS and OS of the included trials were estimated from survival curves (rather than obtained directly from the article), there might be some errors in the results regarding PFS and OS
Vale et al., 2015 [27] **:** Should Tyrosine Kinase Inhibitors Be Considered for Advanced None Small-Cell Lung Cancer Patients With Wild Type EGFR? Two Systematic Reviews and Meta-Analyses of Randomized Trials.	1. Fragestellung Assessment of the effect of TKIs as second-line therapy and maintenance therapy after first-line chemotherapy in two systematic reviews and meta-analyses, focusing on patients without EGFR mutations.
	2. Methodik Population: None Small-Cell Lung Cancer Patients With Wild Type EGFR Intervention/ Komparator: For the systematic review of second-line treatment, trials should have compared a TKI (erlotinib or gefitinib) versus chemotherapy after first-line chemotherapy. For maintenance treatment, trials should have compared a TKI (erlotinib or gefitinib) versus no TKI after first-line chemotherapy. Endpunkt: PFS (primary endpoint); OS Suchzeitraum (Aktualität der Recherche): Systematic searches16 were conducted in MedLine, EMBASE, Cochrane CENTRAL, clinical trials registers (PDQ, ClinicalTrials. gov), and relevant conference proceedings. We also searched reference lists of relevant randomized controlled trials (RCTs) and clinical reviews. Keine Zeitangabe! Anzahl eingeschlossene Studien/Patienten (Gesamt): We identified 25 potentially eligible RCTs, of TKIs as secondline treatment (n = 18) and maintenance treatment (n = 7) Qualitätsbewertung der Studien: • Tyrosine Kinase Inhibitor Versus Chemotherapy in the Second-Line Setting: No trials were judged to be at high risk for any of the domains assessed • Maintenance TKI Versus No Active Treatment Five trials were judged to be at low risk of bias for allocation concealment, sequence generation, and blinding. One trial was at low risk of bias for all domains except for sequence generation and allocation concealment, which were unclear. No trials were identified as being at high risk of bias.
	3. Ergebnisdarstellung

	<u>Tyrosine Kinase Inhibitor Versus Chemotherapy in the Second-Line Setting</u> Results were based on the 14 remaining eligible trials (4388 patients, 98% of total randomized) Trials compared TKIs with either docetaxel or pemetrexed chemotherapy and were conducted between 2003 and 2012. **PFS:** There was strong evidence of an interaction between the effect of TKIs and EGFR mutational status (interaction HR, 2.69; 95% confidence interval [CI], 1.37-5.29; P = .004; Figure 2A), with the benefit of treatment of TKIs evident only among patients with EGFR mutations. This was consistent across trials (heterogeneity P = .179; I^2=, 39%). Results for patients with wild type EGFR were available for 9 trials and 1302 patients (30% of the total randomized in all trials). There was evidence of a detriment with TKIs compared with chemotherapy (HR, 1.31; 95% CI, 1.16-1.48; P < .0001), with some evidence of variation between the trial results (heterogeneity P = .09; I2, 41%). However, the effect was fairly similar with a random-effects model (HR, 1.27; 95% CI, 1.08-1.51; P = .005). Twelve trials including 3963 patients reported PFS for all patients, irrespective of EGFR status. Metaregression suggested a decreasing effect of TKIs with increasing proportions of wild type patients (P = .014). The treatment effect predicted by the model when 100% of patients had wild type EGFR favors chemotherapy (HR, 1.28; 95% CI, 1.08-1.53; P = .005), whereas when 100% of patients had EGFR mutations, the model predicted a benefit of TKIs (HR, 0.45; 95% CI, 0.25-0.80; P = .007) No differences in the treatment effects of TKIs versus chemotherapy were observed when trials were subdivided according to chemotherapy used: docetaxel alone, pemetrexed alone, or docetaxel and pemetrexed (test for between-subgroup heterogeneity P = .30). There was a difference in the treatment effect according to the TKI used in all randomized patients (test for between-subgroup heterogeneity P= .008). However, when the analysis was adjusted to account for substantial heterogeneity within the group of trials using gefitinib (P < .0001; I2, 82%), there was no longer evidence of this difference between the TKIs (metaregression P = .24; F ratio P = .18). Additionally, when the TKI type was taken into account in the metaregression, there was still evidence of a decreasing effect of TKIs with increasing proportions of patients with wild type EGFR (P= .043). **OS** Based on the available data, there was no evidence of an interaction between the effect of TKIs on OS and EGFR mutational status (interaction HR, 1.15; 95% CI, 0.60-2.18; P = .68. This relationship appeared consistent across trials (heterogeneity P = .37; I2, 4%).

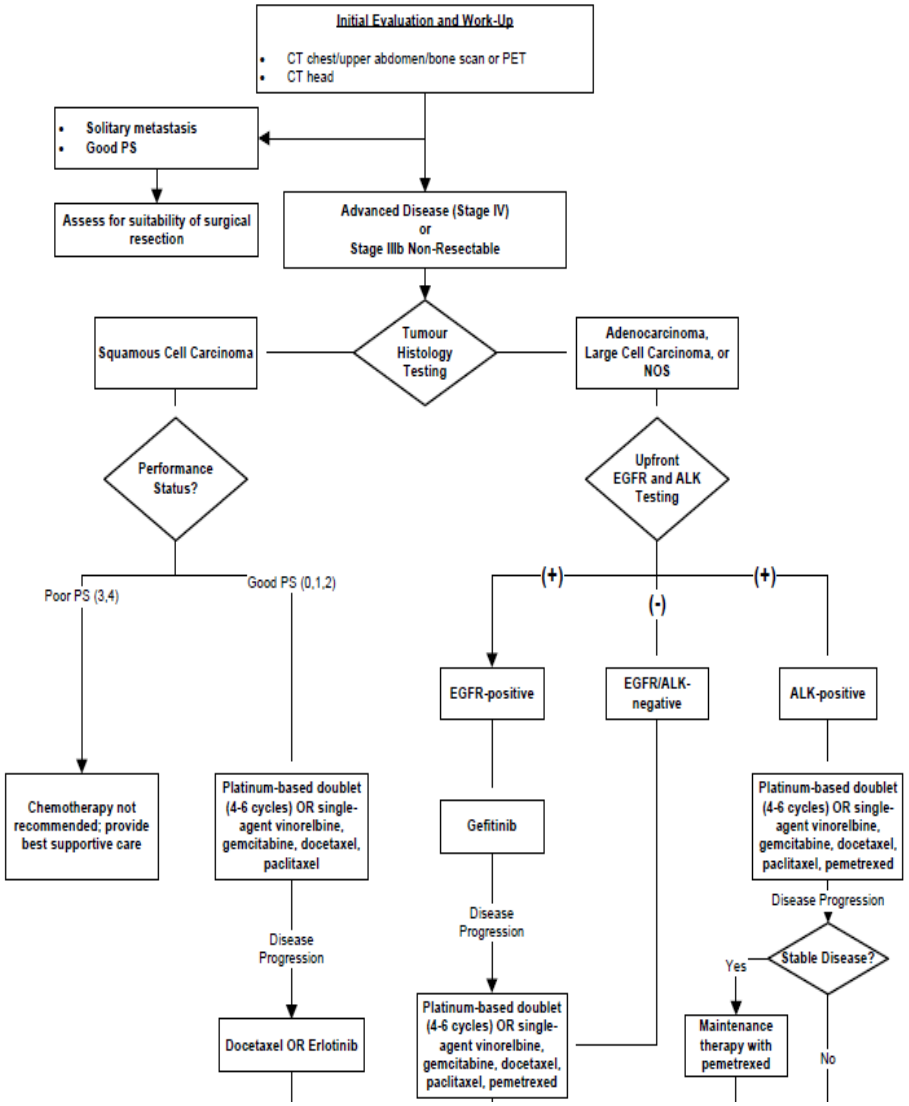
	Maintenance TKI Versus No Active Treatment 6 trials were included (2697 randomized patients, 100% of total). Trials were conducted between 2001 and 2009 and compared TKIs with placebo38,40-43 or observation. **PFS**: Six trials (2672 patients; 99% of total randomized) reported PFS for all patients irrespective of EGFR mutation status. The metaregression suggested that treatment effect varied according to the proportion of patients with wild type EGFR (P= .11). When 100% of patients had wild type EGFR, the model suggested that there is no difference in PFS with TKIs compared with no active treatment (HR, 0.95; 95% CI, 0.65-1.38; P= .78), whereas when 100% of patients had EGFR mutations, a large benefit of TKIs was indicated (HR, 0.12; 95% CI, 0.02-0.66; P= .015). However, the metaregression was based on only 6 trials and was clearly limited. **Interaction Between Treatment Effect and Histology in Patients With Wild Type EGFR** There was a significant difference in effect between the 2 subgroups (interaction HR, 1.41; 95% CI, 1.11-1.80; P=0.004) with little suggestion of variation between trials (heterogeneity P=0.347; I2, 3.8%). We conducted an exploratory analysis to assess whether the benefit of TKIs in patients with wild type EGFR was related to histological type (adenocarcinoma/squamous cell carcinoma). Data were available for 4 trials and 2129 patients (1430 adenocarcinoma; 699 squamous/other nonadenocarcinoma). Benefits of TKI were observed for patients with squamous (HR, 0.77; 95% CI, 0.64-0.92; P=0.004; I^2, 0%; heterogeneity P=0.89) and adenocarcinoma (HR, 0.59; 95% CI, 0.52-0.66; P < .0001; I^2, 79%; heterogeneity P ¼ .002). **OS:** Three trials reported OS according to mutation status. We found no evidence to suggest a difference in the effect of TKIs in patients with mutations compared with those with wild type disease (interaction HR, 1.40; 95% CI, 0.76-2.57; P = .28). This relationship was similar between the trials (heterogeneity P = .49; I2, 0%).
	4. Fazit der Autoren: *There is still uncertainty regarding the best treatment option for the overwhelming majority of advanced NSCLC patients worldwide with wild type EGFR. However, based on these results, TKIs are not an appropriate second-line treatment for patients who are fit to receive chemotherapy, but might offer some scope as maintenance treatment.*

Leitlinien

Scottish Intercollegiate Guidelines Network (SIGN), 2014 [22]. Management of lung cancer.	**1. Fragestellung** In patients with NSCLC (locally advanced or metastatic disease), what is the most effective second line systemic anticancer therapy (chemotherapy, targeted therapy, EGFR Inhibitors)? Outcomes: Overall survival, progression-free survival, toxicity, quality of life
	2. Methodik ***Grundlage der Leitlinie:*** systematische Recherche und Bewertung der Literatur, Entwicklung durch multidisziplinäre Gruppe von praktizierenden klinischen ExpertInnen, Expertenreview, öffentliche Konsultation ***Suchzeitraum:*** 2005 - 2012 ***LoE/GoR:*** Vgl. *Anlage 1* dieser Synopse ***Sonstige methodische Hinweise*** • *keine Empfehlung zur gesuchten Indikation* • *Hintergrundtext (siehe unten) ohne Quellenangaben*
	Empfehlungen ***Second line therapy*** In patients who are PS ≤ 2 at the time of progression of their advanced NSCLC, second line treatment with single agent docetaxel, erlotinib or PEM improve survival rates compared to BSC. **(LoE 1+)** Tassinari D, Scarpi E, Sartori S, Tamburini E, Santelmo C, Tombesi P, et al. Second-line treatments in non-small cell lung cancer. A systematic review of literature and metaanalysis of randomized clinical trials. Chest 2009;135(6):1596-609. Second line docetaxel improved time to progression, survival and quality of life. Patient's opioid requirements and weight loss were reduced with docetaxel compared to BSC only. This was clearest in the patients who received 100 mg/m2 rather than 75 mg/m2 every three weeks, however the higher dose was associated with more overall toxicity, and is not recommended as standard. **(LoE 1+)** Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18(10):2095-103. Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, et al. Randomised phase III trial of docetaxel versus vinorelbine or ifosfamide inpatients with advanced non-small cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000;18(12):2354-62. Weekly docetaxel is not recommended over three-weekly due to increased

	toxicity. **(LoE 1+)** Tassinari D, Carloni F, Santelmo C, Tamburini E, Agli LL, Tombesi P, et al. Second line treatments in advanced platinum-resistant non small cell lung cancer: A critical review of literature. Rev Recent Clin Trials 2009;4(1):27-33. Randomised evidence does not support the use of combination SACT as second line treatment for patients with advanced NSCLC based on an increase in toxicity without any gain in survival. **(LoE 1++)** Di Maio M, Chiodini P, Georgoulias V, Hatzidaki D, Takeda K, Wachters FM, et al. Meta-analysis of single-agent chemotherapy compared with combination chemotherapy as second-line treatment of advanced non-small-cell lung cancer. J Clin Oncol 2009;27(11):1836-43. Second line erlotinib improves overall survival compared to BSC in patients with NSCLC. Median survival was improved with moderate toxicity. The response rate was 8.9% in the erlotinib group and less than 1% in the placebo group (p<0.001); the median duration of the response was 7.9 months and 3.7 months, respectively. Progression-free survival was 2.2 months and 1.8 months, respectively (HR 0.61, adjusted for stratification categories; p<0.001). Overall survival was 6.7 months and 4.7 months, respectively (HR 0.70; p<0.001) in favour of erlotinib. **(LoE 1++)** Noble J, Ellis PM, Mackay JA, Evans WK. Second-line or subsequent systemic therapy for recurrent or progressive non-small cell lung cancer: A systematic review and practice guideline. J Thorac Oncol 2006;1(9):1042-58. Compared with single agent docetaxel, treatment with PEM resulted in clinically equivalent efficacy outcomes, but with significantly fewer side effects in the second-line treatment of patients with advanced predominantly non-squamous cell NSCLC. <u>Recommendations</u> • Second line systemic anticancer therapy with single agent docetaxel or erlotinib should be considered for patients with performance status 0-2 recurrent NSCLC who have been previously treated with first line SACT for advanced disease. **(A)** • Second line systemic anticancer therapy with pemetrexed should be considered for patients with advanced non-squamous cell NSCLC who have been previously treated with first line SACT for advanced disease. **(A)**
Alberta Provincial Thoracic Tumour Team, 2013 [2]. Non-small cell lung cancer stage IV.	**Fragestellung** What is the optimal second-line therapy for patients with stage IV NSCLC?
	Methodik ***Grundlage der Leitlinie:*** systematic literature search, evidence tables, AGREE used for retrieved guidelines, working group reviewed currency and acceptability of all relevant literature, then circulated a draft of the updated guideline to entire provincial tumour team for final feedback and approval **Suchzeitraum**:

	bis 2013 ***LoE/GoR:*** no use of formal rating schemes for describing the strength of the recommendations, rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations *Sonstige methodische Hinweise* • *Kein formaler Konsensusprozess beschrieben* • *Auswahl und Bewertung der Literatur nicht beschrieben* • *no direct industry involvement in the development or dissemination of this guideline* • *authors have not been remunerated for their contributions* • *Some members of the Alberta Provincial Thoracic Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.*
	Freitext/Empfehlungen <u>Recommendations</u> … 8. Second-line or subsequent chemotherapy options for advanced NSCLC include single-agent docetaxel or erlotinib for patients with squamous cell carcinoma histology, or single agent treatment with a drug that has not been previously used. … <u>Discussion and literature</u> **Second-line chemotherapy** The Alberta Provincial Thoracic Tumour Team recommends therapy with single-agent docetaxel or erlotinib for patients with squamous cell carcinoma histology, or single-agent PEM for patients with adenocarcinoma tumour histology in the second-line treatment of advanced NSCLC (recommendation #8). All three agents have been reported to produce similar rates of response and overall survival, therefore the choice of which agent to use will depend on the patient's tumour histology, comorbidities, toxicity from previous treatments, risk for neutropenia, smoking history, and patient convenience and preference.

	TREATMENT ALGORITHM 
Brodowicz T et al., 2012 [5]. Third CECOG consensus on the systemic treatment of non-small-cell lung cancer.	**1. Fragestellung** It is the aim of the present consensus to summarize minimal quality-oriented requirements for individual patients with NSCLC in its various stages based upon levels of evidence in the light of a rapidly expanding array of individual therapeutic options.
	2. Methodik ***Grundlage der Leitlinie:*** evidence-based consensus from experts from Europe and the United States based on systematic literature search ***Suchzeitraum:*** bis 12/2009 ***LoE/GoR:*** Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by

	the American Society of Clinical Oncology *Sonstige methodische Hinweise* • *Kein formaler Konsensusprozess beschrieben* • *Auswahl und Bewertung der Literatur nicht beschrieben* • *14 author disclosures given, remaining authors have declared no conflicts of interest*
	Freitext/Empfehlungen <u>second-line systemic therapy</u> **1 The data from RCTs on second-line therapy are sufficient to recommend either a cytotoxic agent (docetaxel for squamous NSCLC [II,B] or PEM for nonsquamous NSCLC [II,B]) or the EGFR TKI erlotinib [I,B].** Erläuterung aus dem Diskussionteil: […] Docetaxel had initially been established as a standard in NSCLC. However, pemetrexed showed similar efficacy but a more favorable toxicity profile, as compared with docetaxel in a study originally designed to prove noninferiority. In a post hoc analysis, the benefit achieved by pemetrexed was found to occur in patients with nonsquamous tumors and this subsequently resulting in a limitation change of the pemetrexed label. […] Shepherd FA, Dancey J, Ramlau R et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000; 18(10): 2095–2103. Fossella FV, DeVore R, Kerr RN et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000; 18(12): 2354–2362. Hanna N, Shepherd FA, Fossella FV et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004; 22(9): 1589–1597. **2 An EGFR TKI should be strongly considered in patients with EGFR-activating mutations in their tumors who have not received it as first-line treatment [II,B]. Sequencing of chemotherapy after EGFR TKIs has not been defined and remains an important open issue.** Barlesi F, Jacot W, Astoul P, Pujol JL. Second-line treatment for advanced nonsmall cell lung cancer: a systematic review. Lung Cancer 2006;51(2): 159–172. Weiss GJ, Rosell R, Fossella F et al. The impact of induction chemotherapy on the outcome of second-line therapy with pemetrexed or docetaxel in patients with advanced non-small-cell lung cancer. Ann Oncol 2007; 18(3): 453–460. Shepherd FA, Dancey J, Ramlau R et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000; 18(10): 2095–2103. Fossella FV, DeVore R, Kerr RN et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000; 18(12): 2354–2362. Hanna N, Shepherd FA, Fossella FV et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J

	Clin Oncol 2004; 22(9): 1589–1597. Kim ES, Hirsh V, Mok T et al. Gefitinib versus docetaxel in previously treated nonsmall-cell lung cancer (INTEREST): a randomised phase III trial. Lancet 2008;372(9652): 1809–1818. Shepherd FA, Rodrigues Pereira J, Ciuleanu T et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005; 353(2): 123–132. Thatcher N, Chang A, Parikh P et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet 2005; 366(9496): 1527–1537. Zhu CQ, da Cunha Santos G, Ding K et al. Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol 2008; 26(26): 4268–4275. Hirsch FR, Varella-Garcia M, Bunn PA Jr., et al. Epidermal growth factor receptor in non-small-cell lung carcinomas: correlation between gene copy number and protein expression and impact on prognosis. J Clin Oncol 2003; 21(20): 3798–3807.
Socinski et al., 2013 [24]. Treatment of Stage IV Non-small Cell Lung Cancer.	Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines **1. Fragestellung** to update the previous edition of the American College of Chest Physicians Lung Cancer Guidelines Stage IV non-small cell lung cancer (NSCLC) is a treatable, but not curable, clinical entity in patients given the diagnosis at a time when their performance status (PS) remains good.
	1. **Methodik** A writing committee was assembled and approved according to ACCP policies as described in the methodology article of the lung cancer guidelines. **Suchzeitraum:** bis 12/2011 **LoE** nicht ausgeführt, lediglich: Documentation and Appraisal Review Tool (DART) **GoR** ACCP Grading System

Table 1—*Strength of the Recommendations Grading System*

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

Lewis SZ, Diekemper R, Addrizzo-Harris DJ. Methodology for development of guidelines for lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* . 2013 ; 143 (5)(suppl): 41S - 50S .

Literatursuche:

Focused primarily on randomized trials, selected metaanalyses, practice guidelines, and reviews. In addition, phase 2 controlled studies that provided relevant information (eg, for toxicity or particular patient subgroups) were included.

2. **Empfehlungen**

Maintenance Therapy

3.4.4.1. In patients with stage IV non-squamous NSCLC who do not experience disease progression after 4 cycles of platinum-based therapy (which does not include pemetrexed), treatment with switch maintenance pemetrexed is suggested **(Grade 2B)** .

3.4.4.2. In patients with stage IV NSCLC, switch maintenance therapy with chemotherapy agents other than pemetrexed has not demonstrated an improvement in overall survival and is not recommended **(Grade 1B)** .

3.4.4.3. In patients with stage IV non-squamous NSCLC who do not experience disease progression after 4 cycles of platinum-pemetrexed therapy, continuation pemetrexed maintenance therapy is suggested **(Grade 2B)**.

3.4.4.4. In patients with stage IV NSCLC who do not experience disease

	progression after 4 cycles of platinum-based double agent chemotherapy, maintenance therapy with erlotinib is suggested **(Grade 2B)**. 3.5.1.1. In patients with stage IV NSCLC the addition of cetuximab in combination with chemotherapy is suggested not to be used outside of a clinical trial **(Grade 2B).** ***Second and Third Line Treatment*** 4.1.1. In patients with stage IV NSCLC who have good PS (ECOG 0-2), second-line treatment with erlotinib or docetaxel (or equivalent single-agent such as pemetrexed) is recommended **(Grade 1A)** . 4.1.2. In patients with stage IV NSCLC who have good PS (ECOG 0-2), third-line treatment with erlotinib improves survival compared with BSC and is recommended **(Grade 1B)** . *Remark:* No recommendation can be given about the optimal chemotherapeutic strategy in patients with stage IV NSCLC who have received three prior regimens for advanced disease. ***Special Patient Populations and Considerations*** 5.1.1. In elderly patients (age > 69–79 years) with stage IV NSCLC who have good PS and limited co-morbidities, treatment with the two drug combination of monthly carboplatin and weekly paclitaxel is recommended **(Grade 1A)** . *Remark:* In patients with stage IV NSCLC who are 80 years or over, the benefi t of chemotherapy is unclear and should be decided based on individual circumstances. 6.2.1. For patients with stage IV NSCLC with a PS of 2 in whom the PS is caused by the cancer itself, double agent chemotherapy is suggested over single agent chemotherapy **(Grade 2B)** . 6.2.2. In patients with stage IV NSCLC who are an ECOG PS of 2 or greater, it is suggested not to add bevacizumab to chemotherapy outside of a clinical trial (Grade 2B). 7.1.1. In patients with stage IV NSCLC early initiation of palliative care is suggested to improve both QOL and duration of survival **(Grade 2B)**.
CCO/ Ellis PM et al., 2014 [6]. Use of the Epidermal Growth Factor Receptor Inhibitors Gefitinib (Iressa®), Erlotinib	A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO) **1. Fragestellungen** 1. In patients with advanced non–small-cell lung cancer (NSCLC) who have not received any chemotherapy (chemo-naive), is first-line therapy with the epidermal growth factor receptor (EGFR) inhibitors gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib superior to platinum-based chemotherapy for clinical meaningful outcomes (overall survival, progression-free survival (PFS), response rate and quality of life)? 2. In patients with advanced NSCLC who have progressed on platinum-

(Tarceva®), Afatinib, Dacomitinib or Icotinib in the Treatment of Non–Small-Cell Lung Cancer: A Clinical Practice Guideline.	based chemotherapy, does subsequent therapy with EGFR inhibitors gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib improve overall survival or PFS? Is there a preferred sequence for second-line therapy with an EGFR inhibitor or chemotherapy? 3. In patients with advanced stage IIIB or IV NSCLC who have received initial first-line platinum-based chemotherapy, does maintenance therapy with erlotinib, gefitinib, afatinib, dacomitinib or icotinib improve overall survival or PFS? 4. What are the toxicities associated with gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib?
	Empfehlungen ***Recommendation 2*** In patients well enough to consider second-line chemotherapy, an EGFR TKI can be recommended as second- or third-line therapy. There is insufficient evidence to recommend the use of a second EGFR TKI, such as afatinib, in patients whose disease has progressed following chemotherapy and gefitinib or erlotinib, as available data does not demonstrate any improvement in overall survival. *Qualifying Statements:* There are data to support the use of an EGFR TKI in patients who have progressed on platinum-based chemotherapy. Erlotinib is known to improve overall survival and quality of life when used as second- or third-line therapy, in comparison to best supportive care. However, available data would suggest that second-line therapy with either chemotherapy or an EGFR TKI results in similar PFS and overall survival. Available evidence would support the use of either erlotinib or gefitinib in this situation. • Data from a randomized phase II trial suggests improved PFS for dacomitinib versus (vs) erlotinib, but these data require confirmation in a phase III trial. • The Lux Lung 1 study failed to meet its primary outcome of improved overall survival. However, the study showed improved PFS for patients randomized to afatinib and was associated with improvements in lung cancer symptoms. ***Key Evidence*** Three studies examined an EGFR inhibitor as a second-line treatment against a placebo and best supportive care. One study reported on the use of erlotinib and showed a significant improvement in PFS (p=0.001) and overall survival (p=0.001) . The other two studies evaluated gefitinib, with one study finding significant results for response rate (p<0.0001) and the other for PFS (p=0.002) . • A meta-analysis done on seven second-line studies showed no

improvement with EGFR TKIs vs chemotherapy for progression-free survival (HR, 0.99; 95% CI 0.86-1.12, p=0.67) and overall survival (HR, 1.02; 95% CI, 0.95-1.09, p=0.56)

- One phase II study that compared erlotinib to dacomitinib showed significant results for dacomitinib for response rate (p=0.011) and for PFS (p=0.012).
- The Lung Lux 1 study examined the use of afatinib in the third- and fourth-line setting against a placebo. This study showed improved PFS (HR, 0.38; 95% CI, 0.31-0.48, p<0.0001) but no difference in overall survival (HR, 1.08; 95% CI, 0.86-1.35, p=0.74) .

Recommendation 3

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

Qualifying Statements

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

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

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

Key Evidence

Six studies evaluated the use of an EGFR inhibitor in the maintenance setting.

- Two of the trials reported a statistically significant survival benefit with erlotinib: one for response rate (p=0.0006) when compared to placebo (47) and one for progression-free survival when combined with bevacizumab against bevacizumab alone (p<0.001) .
- One study comparing erlotinib and gemcitabine did not report significance but found a higher response rate with erlotinib (15% vs 7%) and 9.1 months vs 8.3 months for overall survival .
- Two trials evaluating gefitinib found a statistically significant benefit for PFS in the maintenance setting, p<0.001 when combined with chemotherapy and against chemotherapy (48) and p<0.0001 compared to a placebo.

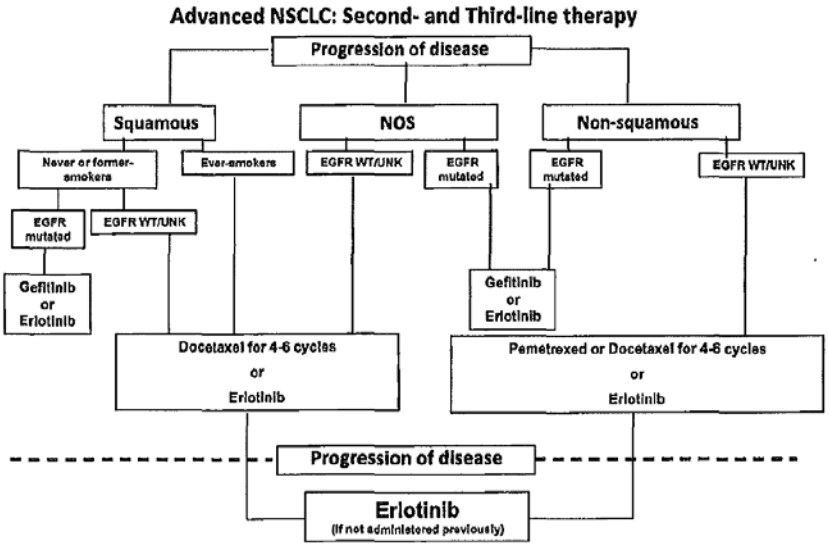
	• Another trial evaluated gefitinib and showed a higher response rate, but this was not significant (p=0.369). **Recommendation 4** The most common toxicities from EGFR inhibitors were diarrhea and rash. Fatigue was also noted to be more prevalent with EGFR inhibitors. Rarer adverse events include interstitial lung disease (ILD). The newer TKIs (icotinib, dacomitinib and afatinib) were noted to have greater incidence of diarrhea, dermatitis and hepatotoxicity. ***Key Evidence*** Two randomized phase II trials, each involving more than 200 patients randomized to either 250 mg or 500 mg of gefitinib daily, identified that grade 3 or 4 toxicity was higher with the higher dose gefitinib. Interstitial lung disease-type events occurred in only one of the two trials, and only with 500 mg/day gefitinib (1% of patients). • One study comparing dacomitinib to erlotinib identified a greater predilection to diarrhea, dermatitis and paronychia with dacomitinib. • One study comparing icotinib to gefitinib identified a greater incidence of elevated liver transaminases with gefitinib (12.6% vs 8%).
Alberta Provincial Thoracic Tumour Team, 2012 [1]. Non-small cell lung cancer - stage III. Alberta Health Services.	**1. Fragestellungen** 1. What are the recommended treatment options for patients with operable stage III non-small cell lung cancer? 2. What are the recommended treatment options with curative intent for patients with inoperable stage III non-small cell lung cancer? 3. When is palliation recommended, and what are the recommend Update der Version von 2008
	2. Methodik ***Grundlage der Leitlinie:*** systematic literature search, evidence tables, AGREE used for retrieved guidelines, working group reviewed currency and acceptability of all relevant literature, then circulated a draft of the updated guideline to entire provincial tumour team for final feedback and approval ***Population:*** NSCLC, adult patients over the age of 18 years ***Suchzeitraum:*** bis 2013 ***LoE/GoR:*** no use of formal rating schemes for describing the strength of the recommendations, rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken

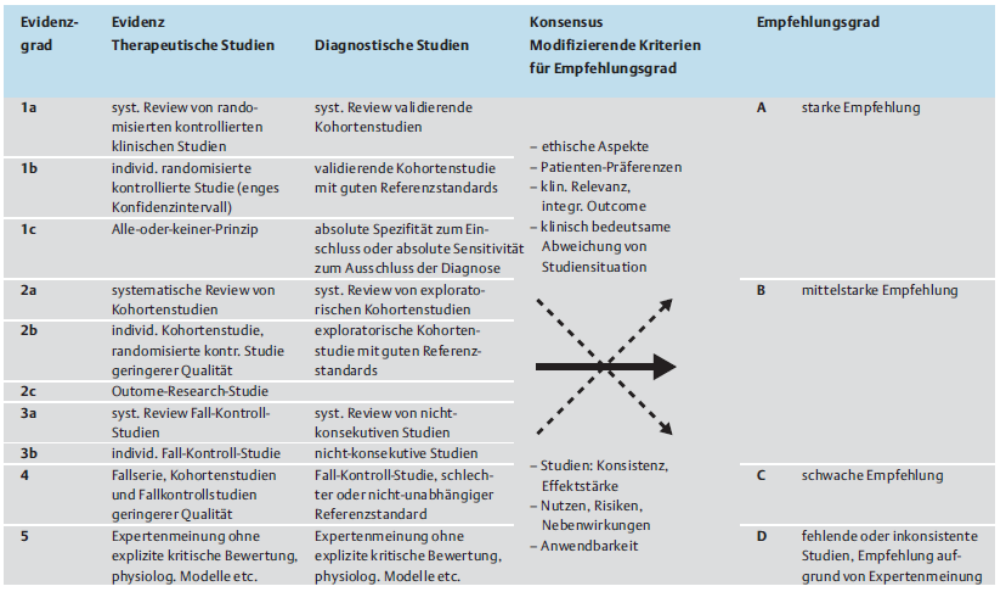
	into consideration when formulating the recommendations ***Sonstige methodische Hinweise*** • Kein formaler Konsensusprozess beschrieben • Auswahl und Bewertung der Literatur nicht beschrieben • no direct industry involvement in the development or dissemination of this guideline • authors have not been remunerated for their contributions
	3. Empfehlungen **Curative Intent Treatment for Inoperable Disease** 6. Combined concurrent chemo-radiation is recommended for inoperable stage III patients with good performance status (ECOG 0-2), minimal weight loss, good pulmonary reserve, and tumour and anatomy conformation permitting radical dose radiation without expected severe normal tissue toxicity. • Cisplatin-based chemotherapy (with either etoposide or vinorelbine) and thoracic radiation of 55Gy in 25 fractions to 66Gy in 33 fractions is the recommended treatment option. 7. For patients with borderline performance status or moderate weight loss (5-10%), concurrent or sequential chemo-radiation or higher dose hypofractionated radiation are options. **Treatment for T1-3N2 Disease** 8. Concurrent chemo-radiation is recommended for pre-operatively diagnosed N2 disease. Cisplatin-based chemotherapy (with either etoposide or vinorelbine) and thoracic radiation of 55 Gy in 25 fractions to 66 Gy in 33 fractions is the recommended treatment option. Additional cycles of chemotherapy can be considered for bulky disease. 9. In select patients, neoadjuvant chemoradiotherapy followed by lobectomy can be considered. Pre-operative pathologically diagnosed N2 disease is not recommended to undergo surgical resection alone. 10. For patients with N2 disease discovered intra-operatively where complete resection of the lymph nodes and primary tumour is technically possible, completion of the planned lung resection is recommended. 11. In patients with N2 disease discovered intra-operatively, platinum-based adjuvant chemotherapy is recommended. Adjuvant radiotherapy can be considered in select patients. **Palliative Treatment for Inoperable Disease** 12. In patients where lung reserve precludes radical radiotherapy, palliative chemotherapy and/or palliative radiotherapy are recommended. 13. Palliative chemotherapy options include: • 1st line: platinum-based doublets • 2nd line: docetaxel, erlotinib or pemetrexed

	14. For symptomatic patients with poor performance status (ECOG>2) and/or significant weight loss (usually defined as >10% in previous 3 months), radiotherapy for symptom palliation is recommended. Dose-fractionation schedule options include: • 20Gy in 5 fractions or 30Gy in 10 fractions • Single fractions of radiotherapy less than 10Gy may be appropriate in some clinical circumstances such as poor performance status or patient travel distance. • Split course radiation can also be used in select cases.
Azzoli et al., 2010 [3]. American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer.	**1. Fragestellung** To update its recommendations on the use of chemotherapy for advanced stage non–small-cell lung cancer (NSCLC), ASCO convened an Update Committee of its Treatment of Unresectable NSCLC Guideline Expert Panel. ASCO first published a guideline on this topic in 19971 and updated it in 2003.2 The current version covers treatment with chemotherapy and biologic agents and molecular markers for stage IV NSCLC and reviews literature published from 2002 through May 2009.
	2. Methodik The recommendations in this guideline were developed primarily on the basis of statistically significant improvements in overall survival (OS) documented in prospective RCTs. Treatment strategies demonstrated to improve only progression-free survival (PFS) prompted greater scrutiny regarding issues such as toxicity and quality of life. ***Suchzeitraum:*** 2002 bis 07/2008 ***GoR, LoE*** Keine Angabe in der zusammenfassenden Darstellung (vgl. Anlage 3)
	3. Empfehlungen **Second-Line Chemotherapy** **Recommendation:** Docetaxel, erlotinib, gefitinib, or pemetrexed is acceptable as second-line therapy for patients with advanced NSCLC with adequate PS when the disease has progressed during or after first-line, platinum-based therapy. **Comment.** In addition to considering optimal regimen, the guideline evaluated data on schedules of administration for second- line therapy, which were available only for docetaxel. These data do not show any differences in efficacy of docetaxel based on schedule. A weekly schedule appears less toxic than a schedule of every 3 weeks, especially for hematologic toxicities. The data on combination biologic therapy as second-line therapy are limited to the combination of bevacizumab and erlotinib. At publication time, there were no published RCTs with positive results for OS using this combination. There are no data available on the optimal duration of second-line therapy.

	Phase III clinical trials of docetaxel, erlotinib, gefitinib, and pemetrexed allowed patients to continue chemotherapy, as tolerated, until disease progression. **Recommendation:** The evidence does not support the selection of a specific second-line chemotherapy drug or combination based on age alone. **Comment.** There is a paucity of research on people considered elderly who are receiving second-line therapy. The available evidence shows that benefits and toxicity do not differ by age. ***Third-Line Chemotherapy*** **Recommendation:** When disease progresses on or after second-line chemotherapy, treatment with erlotinib may be recommended as third-line therapy for patients with PS of 0 to 3 who have not received prior erlotinib or gefitinib. **Comment.** This recommendation is based on the registration trial for erlotinib (Recommendation B1). This trial included participants who had received one or two prior regimens, and an analysis of survival showed no significant difference between prior numbers of regimens. **Recommendation:** The data are not sufficient to make a recommendation for or against using a cytotoxic drug as thirdline therapy. These patients should consider experimental treatment, clinical trials, and best supportive care. **Comment.** Only a retrospective analysis was available on this issue. It found survival and response rates decreased with each subsequent regimen. Patients receiving third- and fourth fourthline cytotoxic therapy have infrequent responses, the responses are of short duration, and the toxicities are considerable.
Azzoli et al., 2011 [4]. American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer	**1. Fragestellung** An American Society of Clinical Oncology (ASCO) focused update updates a single recommendation (or subset of recommendations) in advance of a regularly scheduled guideline update. This document updates one recommendation of the ASCO Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer (NSCLC) regarding switch maintenance chemotherapy.
	2. **Methodik** ***focused update:*** zu *Azzoli et al. 2010* **Suchzeitraum:** bis 11/2009
	3. Empfehlungen ***Intervention*** Switch maintenance (alternative therapy administered to patients who

	have undergone first-line therapy for specified number of cycles [usually four to six] and experienced response or achieved stable disease). ***Recommendation*** In patients with stage IV NSCLC, first-line cytotoxic chemotherapy should be stopped at disease progression or after four cycles in patients whose disease is stable but not responding to treatment. Two-drug cytotoxic combinations should be administered for no more than six cycles. For patients with stable disease or response after four cycles, immediate treatment with an alternative, single-agent chemotherapy such as pemetrexed in patients with nonsquamous histology, docetaxel in unselected patients, or erlotinib in unselected patients may be considered. Limitations of these data are such that a break from cytotoxic chemotherapy after a fixed course is also acceptable, with initiation of secondline chemotherapy at disease progression. Zusammenfassung der aktualisierten Empfehlungen (2011): Vgl. *Anlage 3* dieser Synopse
de Marinis F et al., 2011 [8]. Treatment of advanced non-small-cell-lung cancer: Italian Association of Thoracic Oncology (AIOT) clinical practice guidelines.	**1. Fragestellung** AIOT (Italian Associatlon of Thoracic Oncology) produces up-to-date, cllnlcal practice guidellnes for the management of lung cancer in ltaly. Guidelines were developed by answerlog clinical relevant questions. Here we report only major cllnical issues concerning the management of advanced non-small cell lung cancer (NSCLC). Here we report only eight clinical questions regarding the management of advanced non-small-cell lung cancer (NSCLC) which have been subsequently updated for this manuscrlpt on December 2010.
	2. Methodik Systematische Literatursuche und formaler Konsensusprozess ***Suchzeitraum:*** 2004 bis 2009 ***LoE, GoR*** **Table 1** Level of evidence and strength of recommendation. **Level of evidence** | | **Strength of recommendation** Ia | Evidence from systematic reviews and meta-analysis of randomized controlled trials | A Ib | Evidence from at least one randomized controlled trial | IIa | Evidence from at least one controlled study without randomization | B IIb | Evidence from at least one other type of quasi-experimental study | III | Evidence from observational studies | IV | Evidence from expert committee reports or experts | C
	3. Empfehlungen 3.7.1. Recommendations In patients with advanced NSCLC, after failure of first-line treatment, • Single-agent treatment with docetaxel or pemetrexed (the latter

	limlted to non-squamous tumours) is recommended. **LoE lB, GoR A** • In patients wlth advanced NSCLC, progressing after first-line treatment, combination chemotherapy is not recommended. **LoE lA, GoR A** 3.8.1. Recommendations • In patients wlth advanced NSCLC and EGFR mutation negative or unknown status, with progressive disease after first-line treatment chemotherapy (docetaxel or pemetrexed in non-squamous histology) or erlotinlb should be offered. There are no concluslve data to help the choice between chemotherapy and erlotinib. (**LoE IB, GoR A)** • In patients with advanced NSCLC, with progressive disease after second-line treatment erlotinib is the drug of cholce, lf not administered prevlously, because is the only approved for use ln clinical practice as third-line treatment (**LoE IB, GoR A)**  Fig. 3. Suggested algorithm for second- and third-line treatment of advanced non-small-cell lung cancer (NOS: not otherwise specified; EGFR: epidermal growth factor receptor; WT: wild type; and UNK: unknown).
DGP, 2010 [10]. Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms Interdisziplinäre S3-Leitlinie der Deutschen Gesellschaft für Pneumologie und Beatmungsmedizin und der Deutschen	**Fragestellung** Ziel der vorliegenden Leitlinie ist die Verbesserung der Prognose und der Lebensqualität von Patienten mit Lungenkarzinomen durch Optimierung des Einsatzes der derzeitigen diagnostischen und therapeutischen Möglichkeiten in einem interdisziplinären Ansatz. Außerdem soll durch die Empfehlung präventiver Maßnahmen die Häufigkeit des Lungenkarzinoms reduziert werden.
	Methodik ***Grundlage der Leitlinie:*** systematische Recherche, formale Konsensusprozesse ***Suchzeitraum:*** bis 06/2006 Der nachfolgende Zeitraum bis zur Veröffentlichung der Leitlinie wurde hinsichtlich relevanter Publikationen von den Arbeitsgruppen beobachtet. Relevante Literatur aus diesem Zeitraum wurde dann in der Leitlinie berücksichtigt, wenn es sich um Studien mit hoher Evidenzstärke (Evidenzgrad 1–2) oder Leitlinien handelte und sich neue Aspekte ergaben.

Krebsgesellschaft. ***Hinweis:*** *Ablauf der Gültigkeit. Die LL wird derzeit geprüft.*	***LoE, GoR:*** **Tab. 1** Beziehung zwischen Evidenz- und Empfehlungsgrad (modifiziert nach Oxford Center for Evidence-based Medicine 2001 und AWMF).  **Sonstige methodische Hinweise:** • Rechercheende liegt lange zurück (8 Jahre) • LoE und GoR nicht direkt verknüpft • Nach Prüfverfahren keine Interessenkonflikte festgestellt • Keine Angaben zur Notwendigkeit von der Bestimmung von Markern vor Behandlung mit Gefitinib, Erlotinib • Evidenztabellen (nur online) nicht verfügbar
	Empfehlungen: **Stadium IV/IIIB (ohne Indikation zur definitiven Radiatio)** **Empfehlungen** ***Systemtherapie (Zweitlinie und weitere)*** *Konventionelle Chemotherapie* Bei Erkrankungsprogression nach stattgehabter primärer Chemotherapie kann im Stadium IIIB/IV eine erneute Chemotherapie mit Docetaxel bzw. Pemetrexed oder eine Behandlung mit dem EGF-Rezeptor-Tyrosinkinase-Inhibitor Erlotinib eingeleitet werden. Für Docetaxel (ECOG 2, 24 % der Patienten; platinbasierte Vortherapie, 100%) wurde im Vergleich zu BSC eine signifikante Verbesserung der medianen Überlebenszeit gezeigt. In einer weiteren Studie mit Non-Inferiority-Design wurde im Vergleich zwischen Docetaxel und Pemetrexed (ECOG 2, 12% der Patienten; platinbasierte Vortherapie, 91%) Äquieffektivität für Ansprechen und Überleben bei signifikant günstigerem Toxizitätsprofil für Pemetrexed gezeigt. Die Remissionsraten in diesen Studien liegen in der Größenordnung von 5,8% bis 9,1 %. Dennoch findet sich im Vergleich zu BSC eine signifikante Verbesserung der medianen Überlebenszeit und bestimmter Parameter der Lebensqualität (Schmerz, Husten, Dyspnoe) (**Evidenzgrad 1b**). In einer weiteren Phase-III-Studie wurde Docetaxel gegen Vinorelbin

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

	oder Ifosfamid in der Zweitlinie überprüft. Es konnte kein signifikanter Unterschied im primären Studienziel (mediane Überlebenszeit) gezeigt werden, jedoch fanden sich signifikante Unterschiede in den sekundären Studienzielen (1-Jahres-Überleben und progressionsfreies Überleben). In einer Metaanalyse, die 865 Patienten einschloss, konnte gezeigt werden, dass Docetaxel 75 mg/m2 alle 3 Wochen gegenüber einer wöchentlichen Applikation mit 33–36 mg/m2 hinsichtlich Überleben und progressionsfreiem Überleben äquieffektiv ist. Die wöchentliche Applikation von Docetaxel weist gegenüber der 3-wöchentlichen signifikante Vorteile hinsichtlich der hämatologischen Toxizitäten (Granulozytopenie und febrile Granulozytopenie) auf (**Evidenzgrad 1b**). In zwei weiteren Studien wurden Topotecan und Vinflunin im Vergleich zu Docetaxel (Non-Inferiority-Design) untersucht. Für Topotecan 2,3 mg/m2 (oral) d1–5 alle 3 Wochen konnte Äquieffektivität gegenüber Docetaxel 75 mg/m2 alle 3Wochen hinsichtlich des 1-Jahres-Überlebens (25,1vs 28,7 %; HR = 1,23, CI 1,06–1,44) sowie der Zeit bis zur Tumorprogression (11 vs. 13 Wo, p = 0,02, HR = 1,2; CI 1,02–1,39) gezeigt werden. Gleichermaßen wurde für Vinflunin (320 mg/m2) Äquieffektivität gegenüber Docetaxel für das primäre Studienziel (progressionsfreies Überleben 2,3 vs. 2, 3 Monate) und die sekundären Studienziele gezeigt werden. In beiden Studien liegen keine Subgruppenanalysen für PS 2-Patienten vor. Für beide Substanzen ist allerdings bisher keine formale Zulassung erteilt worden. ***Stellenwert rezeptor- bzw. ligandenspezifischer Therapieansätze*** In einer randomisierten Studie (Non-Inferiority-Design) wurde für Gefitinib Äquivalenz im Vergleich zu Docetaxel gezeigt (Hazard Ratio Gesamtüberleben). Im Hinblick auf die Lebensqualität war die Behandlung mit Gefitinib günstiger. Die ergänzenden Daten der I-PASS-Studie haben zur Zulassung von Gefitinib bei Patienten mit Nachweis einer aktivierenden EGF-Rezeptor-Mutation (insbesondere del. 19; exon 21 L858R) in allen Therapielinien geführt. In einer randomisierten Studie wurde für Erlotinib im Vergleich zu BSC (ECOG 2, 25%; ECOG 3, 9%; platinbasierte Vortherapie, 92%; $\geq$ 2 Vortherapien, 50%) eine signifikante Verbesserung der medianen Überlebenszeit gezeigt. Prädiktoren für Ansprechen auf Erlotinib, die in einer multivariaten Analyse definiert wurden, waren Nieraucherstatus, d. h. < 100 Zigaretten lebenslang (p < 0,001), Adenokarzinom (p = 0,01) und EGFR Expression (p = 0,03). Die Expression von EGFR hatte keinen Einfluss hinsichtlich progressionsfreiem Überleben und Überleben. **Empfehlungen** • Bei Patienten in gutem Allgemeinzustand mit einer Erkrankungsprogression nach primärer Chemotherapie wird die Durchführung einer Zweitlinientherapie bis zum Progress oder Auftreten von Toxizitäten empfohlen (**Empfehlungsgrad A**). Trotz niedriger Ansprechraten kann eine Verlängerung des Überlebens und eine Verbesserung tumorbedingter Symptome erreicht werden. In Phase-III-Studien sind mit entsprechender Evidenz geprüft: Docetaxel, Pemetrexed, Topotecan, Vinflunin, Gefitinib und Erlotinib. Zugelassen für die Behandlung sind allerdings nur: Docetaxel, Pemetrexed (Nicht-Plattenepithelkarzinome) und Erlotinib. • Gefitinib ist bei aktivierenden Mutationen des EGF-Rezeptors (insbesondere del. 19; exon 21 L858R) in allen Therapielinien, auch in der Zeitlinientherapie, zur Behandlung zugelassen (**Empfehlungsgrad B**). In der zulassungsrelevanten Studie erfolgte die Analyse des

	Mutationsstatus bei Patienten mit einem Adenokarzinom und minimalem Nikotinkonsum (94% Nieraucher). • Bei Patienten, die nach einer Zweitlinientherapie progredient sind, kann eine Drittlinientherapie durchgeführt werden (**Empfehlungsgrad B**). • Bei Patienten mit längerfristigem Krankheitsverlauf kann bei entsprechender klinischer Situation und akzeptablem Risikoprofil zur Symptomenkontrolle eine weitere Antitumortherapie auch nach der Drittlinienbehandlung eingesetzt werden (**Empfehlungsgrad D**).
Wauters, 2013 [28]. Small cell and non-small cell lung cancer: diagnosis, treatment and follow-up.	**Fragestellung** This guideline provides recommendations based on current scientific evidence both for the diagnosis, treatment and follow-up of patients with lung cancer.
	Methodik ***Grundlage der Leitlinie:*** The KCE guideline is drawn up according to highly codified principles, based on scientific information regularly updated from the international literature. KCE analyses clinical practices in current use on the basis of existing recommendations. This guideline was developed using a standard methodology based on a systematic review of the evidence. Further details about KCE and the guideline development methodology are available at https://kce.fgov.be/content/kce-processes. The present clinical practice guideline (CPG) was developed by adapting (inter)national CPGs to the Belgian context. This approach was structured in a formal methodology by the ADAPTE group, an international group of guideline developers and researchers. The ADAPTE methodology generally consists of three major phases (www.adapte.org): 1. Set-up Phase: Outlines the necessary tasks to be completed prior to beginning the adaptation process (e.g., identifying necessary skills and resources). 2. Adaptation Phase: Assists guideline developers in moving from selection of a topic to identification of specific clinical questions; searching for and retrieving guidelines; assessing the consistency of the evidence therein, their quality, currency, content and applicability; decision making around adaptation; and preparing the draft adapted guideline. 3. Finalization Phase: Guides guideline developers through getting feedback on the document from stakeholders who will be impacted by the guideline, consulting with the source developers of guidelines used in the adaptation process, establishing a process for review and updating of the adapted guideline and the process of creating a final document. In general, and whenever necessary, included guidelines were updated with more recent evidence. The AGREE II instrument was used to evaluate the methodological quality of the identified CPGs (www.agreetrust.org). Each of the 5 identified CPGs was scored by two independent researchers (JR and KHH or JR and FH) and

	discussed in case of disagreement. Based on an overall assessment – taking into account the AGREE scores – all 5 high quality CPGs were finally selected. However, only two of these five guidelines cover both lung cancer diagnostic, staging and treatment. Thus, three guidelines were selected for their lung cancer guidelines relating to treatment only. The quality of the systematic reviews was assessed using the Dutch Cochrane checklist (www.cochrane.nl). Retrieved diagnostic studies were assessed for the risk of bias with the QUADAS-2 tool. For critical appraisal of randomized controlled trials, the Cochrane Collaboration's Risk of Bias Tool was used Critical appraisal of peer-reviewed articles was performed. ***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 (Appendix 1.1.1). A test search in OVID Medline for guidelines on lung cancer (2001-2011) revealed more than 1000 hits. It was consequently decided to deploy restrictions on language (English, Dutch, French) and date (2009 – current date). All searches for guidelines were run on 20 February 2012. Based on title and abstract, and after removal of duplicate guidelines, a total of 23 guidelines were retained for full-text evaluation. ***LoE, GoR:*** For therapeutic interventions, the quality of evidence was evaluated using the GRADE methodology. A level of evidence was assigned to the body of evidence supporting each conclusion using the GRADE system (Table 1). GRADE for guidelines was used, meaning that the evidence across all outcomes and across studies for a particular recommendation was assessed. The following quality elements for intervention studies were evaluated: study limitations, inconsistency, indirectness, imprecision and publication bias.

Table 1 – Levels of evidence according to the GRADE system

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias	1. Large effect 2. Dose-response 3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	High (⊕⊕⊕⊕) Moderate (⊕⊕⊕⊖) Low (⊕⊕⊖⊖) Very low (⊕⊖⊖⊖)
Observational studies	Low			

Empfehlungen:

- Pemetrexed is preferred to gemcitabine in patients with non-squamous NSCLC. Pemetrexed use should be restricted to non-squamous NSCLC in any line of treatment. (SoE: strong / LoE: low)
- It is recommended to offer second-line chemotherapy for patients with advanced NSCLC with adequate performance status when the disease has progressed during or after first-line therapy. (SoE: strong / LoE: moderate)
- Crizotinib is recommended as second-line therapy in ALK mutation-positive patients. (SoE: strong / LoE: low)
- The use of pemetrexed (only in non-squamous NSCLC) or docetaxel is acceptable as second-line therapy for patients with advanced NSCLC with adequate performance status when the disease has progressed during or after first-line, platinum-based therapy. (SoE: weak / LoE: very low)

NCCN, 2015 [18].

Empfehlungen:

<u>Hinweis aus Leitlinie:</u>

Patients with pure squamous cell carcinoma do not seem to have ALK rarrangements or sensitizing EGFR mutations; therefore, routine testing is not recommended in these patients.

<u>Quellen:</u>

	124. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22896669. 676. Forbes SA, Bhamra G, Bamford S, et al. The Catalogue of Somatic Mutations in Cancer (COSMIC). Curr Protoc Hum Genet 2008;Chapter 10:Unit 10 11. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18428421. 677. Lee SY, Kim MJ, Jin G, et al. Somatic mutations in epidermal growth factor receptor signaling pathway genes in non-small cell lung cancers. J Thorac Oncol 2010;5:1734-1740. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20881644. 678. Rekhtman N, Paik PK, Arcila ME, et al. Clarifying the spectrum of driver oncogene mutations in biomarker-verified squamous carcinoma of lung: lack of EGFR/KRAS and presence of PIK3CA/AKT1 mutations. Clin Cancer Res 2012;18:1167-1176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22228640. However, testing for ALK rearrangements or EGFR mutations can be considered in patients with squamous cell carcinomas who never smoked and those whose histology was determined using small biopsy specimens or mixed histology specimens**.** *Quellen:* 124. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22896669. **Recommendations:** For all histologic subtypes without ALK rearrangements or sensitizing EGFR mutations, docetaxel with (or without) ramucirumab, erlotinib, or gemcitabine are recommended if not already given as subsequent systemic therapy regimens for patients with PS of 0 to 2 who have disease progression during or after first-line therapy. For patients with non-squamous NSCLC but without sensitizing EGFR mutations, pemetrexed is also recommended as subsequent therapy. For the 2015 update, the NCCN Panel added ramucirumab/docetaxel as an additional option for subsequent therapy based on a recent phase 3 randomized trial.[533] The median overall survival was slightly increased

	Pemetrexed (non-squamous only), docetaxel (with or without ramucirumab), gemcitabine, or erlotinib are recommended options for subsequent therapy in patients with advanced NSCLC if these agents have not already been given.[701,711,712] Docetaxel has been proven superior to best supportive care, vinorelbine, or ifosfamide with improved survival and quality of life.[706,707] When compared with docetaxel, pemetrexed has similar median survival but less toxicity.[708] Pemetrexed is recommended in patients with adenocarcinoma or large cell carcinoma (ie, non-squamous NSCLC).[551] Docetaxel is preferred in patients with wild-type EGFR tumors based on 2 randomized trials comparing erlotinib versus docetaxel.[714,715] Proteomic testing can be used to determine whether erlotinib should be used in patients with unknown EGFR status.[716]

Primärstudien

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

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 11.05.2015**

#	Suchfrage	Treffer
1	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees	2540
2	((non next small) or nonsmall) next cell next lung:ti,ab,kw	4952
3	tumor* or tumour* or carcinoma* or adenocarcinoma* or neoplasm* or sarcoma* or cancer*:ti,ab,kw	97911
4	(advanced or metastat* or metastas*or recurren* or relaps*):ti,ab,kw	43783
5	#2 and #3 and #4	2706
6	nsclc*:ti,ab,kw	2990
7	#1 or #5 or #6	4734
8	#7 from 2010 to 2015	1706

SR, HTAs in Medline (PubMed) am 12.05.2015

#	Suchfrage	Treffer
1	Carcinoma, Non-Small-Cell Lung[MeSH]	33732
2	(((non[Title/Abstract]) AND small[Title/Abstract]) AND cell[Title/Abstract]) AND lung[Title/Abstract]	38679
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]	2277556
4	#2 AND #3	38374
5	#1 OR #4	46610
6	squamous[Title/Abstract] AND (lung[Title/Abstract] AND #3)	12729
7	#5 OR #6	
8	(((advanced[Title/Abstract]) OR metastat*[Title/Abstract]) OR metastas*[Title/Abstract]) OR recurren*[Title/Abstract]	911146
9	#7 AND #8	22828
10	(((((drug[Title/Abstract]) OR (drug therap*)[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR treat[Title/Abstract]) OR treatment*[Title/Abstract]	4096685
11	#9 AND #10	14038
12	(#11) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])	613
13	(#11) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))	605
14	#12 OR #13	842
15	(#14) AND ("2010/05/01"[PDAT] : "2015/05/13"[PDAT])	444

Leitlinien in Medline (PubMed) am 12.05.2015

#	Suchfrage	Treffer
1	Carcinoma, Non-Small-Cell Lung[MeSH]	33629
2	(((non[Title/Abstract]) AND small[Title/Abstract]) AND cell[Title/Abstract]) AND lung[Title/Abstract]	38618
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]	2275318
4	#2 AND #3	38314
5	#1 OR #4	46525
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])	188
7	(#6) AND ("2010/05/01"[PDAT] : "2015/05/12"[PDAT])	101

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

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

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

Table 11. Standard Treatment Options for NSCLC

Enlarge

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

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

Anlage 3: Summary of Recommendations aus: *Azzoli et. al 2011*

Table 1. Summary of Recommendations

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

NOTE. Bold font indicates 2011 focused update changes.

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

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

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

Literatur

1. **Alberta Provincial Thoracic Tumour Team**. Non-small cell lung cancer stage III. Edmonton (CAN): Alberta Health Services (AHS) 2012; (Clinical practice guideline; no. LU-003).http://www.albertahealthservices.ca/hp/if-hp-cancer-guide-lu003-nlscs-stage3.pdf, Zugriff am 11.05.2015.

2. **Alberta Provincial Thoracic Tumour Team**. Non-small cell lung cancer stage IV. Edmonton (CAN): Alberta Health Services (AHS) 2013; (Clinical practice guideline; no. LU-004).http://www.albertahealthservices.ca/hp/if-hp-cancer-guide-lu004-nsclc-stage4.pdf, Zugriff am 11.05.2015.

3. **Azzoli CG, Giaccone G, Temin S**. American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer. J Oncol Pract 2010; 6 (1): 39-43.

4. **Azzoli CG, Temin S, Aliff T, Baker S Jr, Brahmer J, Johnson DH, Laskin JL, Masters G, Milton D, Nordquist L, Pao W, Pfister DG, Piantadosi S, Schiller JH, Smith R, Smith TJ, Strawn JR, Trent D, Giaccone G**. 2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer. J Clin Oncol 2011; 29 (28): 3825-31.

5. **Brodowicz T, Ciuleanu T, Crawford J, Filipits M, Fischer JR, Georgoulias V, Gridelli C, Hirsch FR, Jassem J, Kosmidis P, Krzakowski M, Manegold C, Pujol JL, Stahel R, Thatcher N, Vansteenkiste J, Minichsdorfer C, Zochbauer-Muller S, Pirker R, Zielinski CC**. Third CECOG consensus on the systemic treatment of non-small-cell lung cancer. Ann Oncol 2012; 23 (5): 1223-9.

6. **Cancer Care Ontario (CCO)**. 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. Toronto (CAN): Cancer Care Ontario 2014; https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34353, Zugriff am 11.05.2015.

7. **Chen X, Liu Y, Roe OD, Qian Y, Guo R, Zhu L, Yin Y, Shu Y**. Gefitinib or erlotinib as maintenance therapy in patients with advanced stage non-small cell lung cancer: a systematic review. PLoS One 2013; 8 (3): e59314.

8. **de Marinis F., Rossi A, Di MM, Ricciardi S, Gridelli C**. Treatment of advanced non-small-cell lung cancer: Italian Association of Thoracic Oncology (AIOT) clinical practice guidelines. Lung Cancer 2011; 73 (1): 1-10.

9. **Des Guetz G., Uzzan B, Nicolas P, Valeyre D, Sebbane G, Morere JF**. Comparison of the efficacy and safety of single-agent and doublet chemotherapy in advanced non-small cell lung cancer in the elderly: a meta-analysis. Crit Rev Oncol Hematol 2012; 84 (3): 340-9.

10. **Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin, Deutschen Krebsgesellschaft**. Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms. Interdisziplinäre S3-Leitlinie (AWMF Leitlinien-Register Nr.020-007). Pneumologie 2010; 64 (Supplement 2): e1-e164. http://www.awmf.org/uploads/tx_szleitlinien/020-

007_S3_Praevention__Diagnostik__Therapie_und_Nachsorge_des_Lungenkarzinoms_lang_02-2010_02-2015.pdf, Zugriff am 11.05.2015.

11. **Ganguli A, Wiegand P, Gao X, Carter JA, Botteman MF, Ray S**. The impact of second-line agents on patients' health-related quality of life in the treatment for non-small cell lung cancer: a systematic review. Qual Life Res 2013; 22 (5): 1015-26.

12. **Jiang J, Huang L, Liang X, Zhou X, Huang R, Chu Z, Zhan Q**. Gefitinib versus docetaxel in previously treated advanced non-small-cell lung cancer: a meta-analysis of randomized controlled trials. Acta Oncol 2011; 50 (4): 582-8.

13. **Jin Y, Sun Y, Shi X, Zhao J, Shi L, Hong W, Yu X**. Meta-analysis to assess the efficacy and toxicity of docetaxel-based doublet compared with docetaxel alone for patients with advanced NSCLC who failed first-line treatment. Clin Ther 2014; 36 (12): 1980-90.

14. **Lee CK, Brown C, Gralla RJ, Hirsh V, Thongprasert S, Tsai CM, Tan EH, Ho JC, Chu dT, Zaatar A, Osorio Sanchez JA, Vu VV, Au JS, Inoue A, Lee SM, Gebski V, Yang JC**. Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis. J Natl Cancer Inst 2013; 105 (9): 595-605.

15. **Lee JK, Hahn S, Kim DW, Suh KJ, Keam B, Kim TM, Lee SH, Heo DS**. Epidermal growth factor receptor tyrosine kinase inhibitors vs conventional chemotherapy in non-small cell lung cancer harboring wild-type epidermal growth factor receptor: a meta-analysis. JAMA 2014; 311 (14): 1430-7.

16. **Li N, Yang L, Ou W, Zhang L, Zhang SL, Wang SY**. Meta-Analysis of EGFR Tyrosine Kinase Inhibitors Compared with Chemotherapy as Second-Line Treatment in Pretreated Advanced Non-Small Cell Lung Cancer. PLoS One 2014; 9 (7): e102777.

17. **Li X, Wang H, Lin W, Xu Q**. Efficacy of combining targeted therapy with pemetrexed or docetaxel as second-line treatment in patients with advanced non-small-cell lung cancer: a meta-analysis of 14 randomized controlled trials. Curr Med Res Opin 2014; 30 (11): 2295-304.

18. **National Comprehensive Cancer Network (NCCN)**. Non-Small Cell Lung Cancer (Vers. 6.2015). Fort Washington (USA): NCCN 2015; http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf, Zugriff am 11.05.2015.

19. **Pan G, Ke S, Zhao J**. Comparison of the efficacy and safety of single-agent erlotinib and doublet molecular targeted agents based on erlotinib in advanced non-small cell lung cancer (NSCLC): a systematic review and meta-analysis. Target Oncol 2013; 8 (2): 107-16.

20. **Petrelli F, Coinu A, Cabiddu M, Ghilardi M, Ardine M, Barni S**. Platinum rechallenge in patients with advanced NSCLC: a pooled analysis. Lung Cancer 2013; 81 (3): 337-42.

21. **Qi WX, Wang Q, Jiang YL, Sun YJ, Tang LN, He AN, Min DL, Lin F, Shen Z, Yao Y**. Overall survival benefits for combining targeted therapy as second-line treatment for advanced non-small-cell-lung cancer: a meta-analysis of published data. PLoS One 2013; 8 (2): e55637.

22. **Scottish Intercollegiate Guidelines Network (SIGN)**. Management of lung cancer. A national clinical guideline. Edinburgh (UK): SIGN 2014; (SIGN Publication No. 137). http://www.sign.ac.uk/pdf/SIGN137.pdf, Zugriff am 11.05.2015.

23. **Shi L, Tang J, Tong L, Liu Z**. Risk of interstitial lung disease with gefitinib and erlotinib in advanced non-small cell lung cancer: a systematic review and meta-analysis of clinical trials. Lung Cancer 2014; 83 (2): 231-9.

24. **Socinski MA, Evans T, Gettinger S, Hensing TA, Sequist LV, Ireland B, Stinchcombe TE**. Treatment of stage IV non-small cell 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): e341S-e368S.

25. **Tassinari D, Scarpi E, Sartori S, Drudi F, Castellani C, Carloni F, Tombesi P, Lazzari-Agli L**. Noninferiority trials in second-line treatments of nonsmall cell lung cancer: a systematic review of literature with meta-analysis of phase III randomized clinical trials. Am J Clin Oncol 2012; 35 (6): 593-9.

26. **Tsujino K, Kurata T, Yamamoto S, Kawaguchi T, Kubo A, Isa S, Hasegawa Y, Ou SH, Takada M, Ando M**. Is consolidation chemotherapy after concurrent chemo-radiotherapy beneficial for patients with locally advanced non-small-cell lung cancer? A pooled analysis of the literature. J Thorac Oncol 2013; 8 (9): 1181-9.

27. **Vale CL, Burdett S, Fisher DJ, Navani N, Parmar MK, Copas AJ, Tierney JF**. Should Tyrosine Kinase Inhibitors Be Considered for Advanced Non-Small-Cell Lung Cancer Patients With Wild Type EGFR? Two Systematic Reviews and Meta-Analyses of Randomized Trials. Clin Lung Cancer 2015; 16 (3): 173-82.

28. **Wauters I, Robays J, Verleye L, Holdt HK, Hulstaert F, Berghmans T, Wever W, Lievens Y, Pauwels P, Stroobants S, Houtte P, Meerbeeck J, Schil P, Weynand B, Grève J**. Non-small cell and small cell lung cancer: diagnosis, treatment and follow-up. Health Technology Assessment Database 2013; (2): (KCE Reports 206). https://kce.fgov.be/sites/default/files/page_documents/KCE_206_lung_cancer.pdf, Zugriff am 04.06.2015.

29. **Xiao YY, Zhan P, Yuan DM, Liu HB, Lv TF, Song Y, Shi Y**. Chemotherapy plus multitargeted antiangiogenic tyrosine kinase inhibitors or chemotherapy alone in advanced NSCLC: a meta-analysis of randomized controlled trials. Eur J Clin Pharmacol 2013; 69 (2): 151-9.

30. **Yang X, Yang K, Kuang K**. The efficacy and safety of EGFR inhibitor monotherapy in non-small cell lung cancer: a systematic review. Curr Oncol Rep 2014; 16 (6): 390.

31. **Zhao N, Zhang XC, Yan HH, Yang JJ, Wu YL**. Efficacy of epidermal growth factor receptor inhibitors versus chemotherapy as second-line treatment in advanced non-small-cell lung cancer with wild-type EGFR: a meta-analysis of randomized controlled clinical trials. Lung Cancer 2014; 85 (1): 66-73.

32. **Zhong C, Liu H, Jiang L, Zhang W, Yao F**. Chemotherapy plus best supportive care versus best supportive care in patients with non-small cell lung cancer: a meta-analysis of randomized controlled trials. PLoS One 2013; 8 (34): e58466.