Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2014-B-129 Crizotinib

Stand: Februar 2015

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Crizotinib **zur Behandlung des ALK-positiven, fortgeschrittenen NSCLCs (Erstlinientherapie)**	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	*Nicht angezeigt.*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschluss vom 2. Mai 2013 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Crizotinib Beschluss vom 8. Mai 2014 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Afatinib Richtlinie Methoden Krankenhausbehandlung (Stand: 6. September 2014); Ausgeschlossene Methoden (§ 4): Protonentherapie beim inoperablen NSCLC des UICC Stadiums IV Protonentherapie bei Hirnmetastasen Protonentherapie bei Lebermetastasen Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie - Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (Stand: 8. Oktober 2014): Off-Label-Indikation für Carboplatin: Kombinationstherapie des fortgeschrittenen NSCLC (palliativ)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche.*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Beratungsanforderung/Fachinformation)
Zu prüfendes Arzneimittel:	
Crizotinib L01XE16 XALKORI®	XALKORI wird angewendet bei Erwachsenen zur Erstlinienbehandlung des Anaplastische-Lymphom-Kinase (ALK)-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, NSCLC).
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 in Kombination mit Cisplatin zur Behandlung von Patienten mit nicht resezierbarem, lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Bronchialkarzinom ohne vorausgegangene Chemotherapie angezeigt. (FI Docetaxel-ratiopharm®, 05-2013)
Etoposid L01CB01 (generisch)	Kombinationstherapie folgender Malignome: Palliative Therapie des fortgeschrittenen NSCLC bei Patienten mit gutem Allgemeinzustand (Karnofsky-Index >80%). (FI Riboposid®, 02-2014)
Gemcitabin L01BC05 (generisch)	Gemcitabin ist in Kombination mit Cisplatin als Erstlinientherapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Bronchialkarzinom (NSCLC) angezeigt. Eine Gemcitabin-Monotherapie kann bei älteren Patienten oder solchen mit einem Performance Status 2 in Betracht gezogen werden. (FI Gemcitabin Kabi, 05-2013)
Ifosfamid L01AA06 (Holoxan®)	Nicht-kleinzellige Bronchialkarzinome: Zur Einzel- oder Kombinationschemotherapie von Patienten mit inoperablen oder metastasierten Tumoren. (FI Holoxan®, 11-2008)
Mitomycin L01DC03 (generisch)	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Bei intravenöser Gabe ist es in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei folgenden metastasierenden Tumoren wirksam: […] nicht-kleinzelliges Bronchialkarzinom […]. (FI Mitomycin 2 medac, 03-2014)
Paclitaxel L01CD01 (generisch)	Fortgeschrittenes nicht-kleinzelliges Bronchialkarzinom (NSCLC): Paclitaxel ist, in Kombination mit Cisplatin, zur Behandlung des nicht-kleinzelligen Bronchialkarzinoms bei Patienten angezeigt, für die potentiell kurative chirurgische Maßnahmen und/oder eine Strahlentherapie nicht in Frage kommen. (FI Paclitaxel Hospira, 01-2014)
Pemetrexed L01BA04 (Alimta®)	ALIMTA ist in Kombination mit Cisplatin angezeigt zur first-line Therapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie. (FI Alimta®, 11-2012)

Vindesin L01CA03 (Eldesine®)	Kombinationschemotherapie: Lokal fortgeschrittenes oder metastasiertes nicht-kleinzelliges Bronchialkarzinom (Stadium IIIB, IV). (Lauer Taxe, 02-2014)
Vinorelbin L01CA04 (generisch)	Vinorelbin ist angezeigt zur Behandlung: des nicht kleinzelligen Bronchialkarzinoms (Stadium 3 oder 4). (FI Bendarelbin, 10-2013)
Antikörper	
Bevacizumab L01XC07 (Avastin®)	Bevacizumab wird zusätzlich zu einer platinhaltigen Chemotherapie zur First-Line-Behandlung von erwachsenen Patienten mit inoperablem fortgeschrittenem, metastasiertem oder rezidivierendem nicht kleinzelligem Bronchialkarzinom, außer bei vorwiegender Plattenepithel-Histologie, angewendet. (FI Avastin®, 11-2014)

Quellen: AMIS-Datenbank, Lauer-Taxe, Fachinformationen

Gemeinsamer Bundesausschuss

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

Indikation für die Recherche: 5

Berücksichtigte Wirkstoffe/Therapien: 5

Systematische Recherche: 5

Detaillierte Darstellung der Recherchestrategie: 101

Literatur 104

Anlage 1: Levels of Evidence and Grades of Recommendation, aus: *SIGN 2014* 108

Anlage 2: Summary of Recommendations aus: Azzoli et. al 2010 109

Indikation für die Recherche:

Erstlinientherapie bei Erwachsenen mit Anaplastische-Lymphom-Kinase (ALK)-positivem, fortgeschrittenem, nicht-kleinzelligem Bronchialkarzinom (NSCLC).

Berücksichtigte Wirkstoffe/Therapien:

Siehe Tabelle „II. Zugelassene Arzneimittel im Anwendungsgebiet“

- Die Systematischen Reviews sind in alphabetischer Reihenfolge aufgeführt.
- Variationen in den Therapieregimen (z.B. Therapiedauern und zeitliche Abfolgen, Therapiezyklen, Therapiewechsel und ihre Bedingungen, …) wurden nicht berücksichtigt.

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation **„fortgeschrittenes nicht-kleinzelliges Lungenkarzinom“** durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 23.07.2014 abgeschlossen.

Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, TRIP. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien (z.B. NICE, SIGN). Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab **618** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden **261** Quellen eingeschlossen. Insgesamt ergab dies **42** Quellen, die in die synoptische Evidenzübersicht aufgenommen wurden.

Abkürzungen

ACCP	American College of Chest Physicians
AE	Unerwünschte Ereignisse (adverse events)
AIOT	Italian Associatlon of Thoracic Oncology
ALK	Anaplastic Lymphoma Kinase
AM	Arzneimittel
AP	pemetrexed + cisplatin
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
CECOG	Central European Cooperative Oncology Group
CG	clinical gudeline
CI	Konfidenzintervall
CIS	Cisplatin
CT	Chemotherapie
DAHTA	Deutsche Agentur für Health Technology Assessment
DART	Documentation and Appraisal Review Tool
DCR	disease control rate
DGP	Gesellschaft für Pneumologie und Beatmungsmedizin
DC	Docetaxel
DOC	Docetaxel
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for QLQ Research and Treatment of Cancer Quality of Life Questionnaire
EGFR	Epidermal Growth Factor Receptor
ESMO	European Society for Medical Oncology
FACT-L	Functional assessment of cancer-lung (questionnaire)
G-BA	Gemeinsamer Bundesausschuss
GEF/GFT	Gefintinib
GEM	Gemcitabin
GIN	Guidelines International Network
GN	gemcitabine + vinorelbine
GoR	Grade of Recommendation
GP	gemcitabine + cisplatin

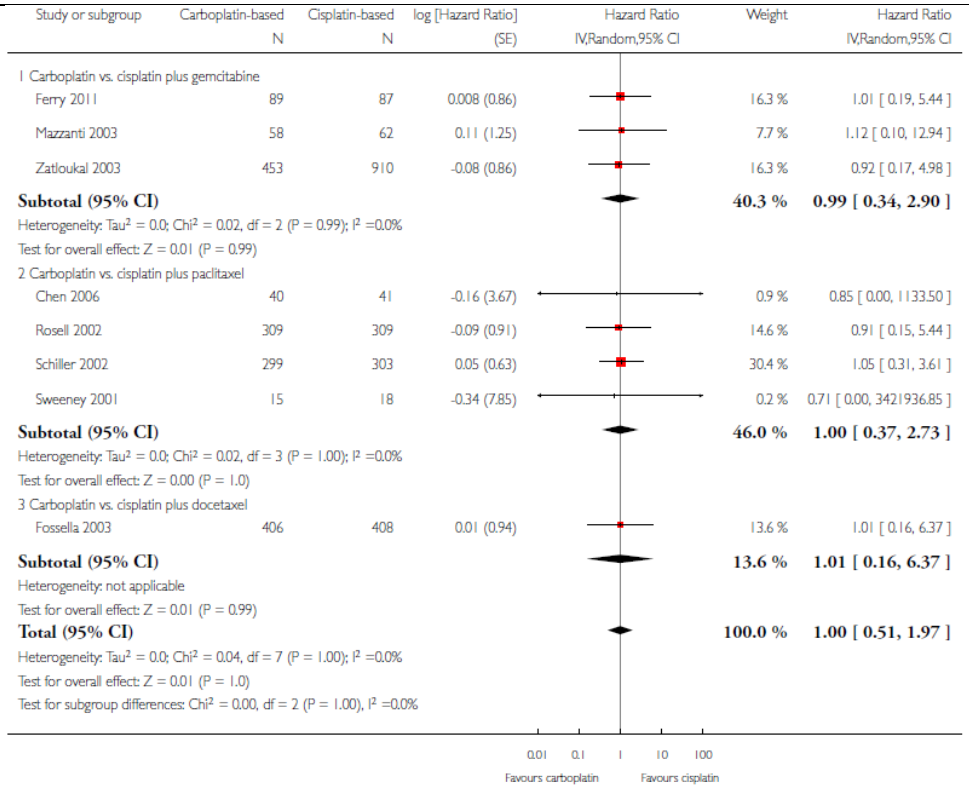
HR	Hazard ratio
HRQoL	Gesundheitsbezogene Lebensqualität (health related quality of life)
ILD	interstitial lung disease
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
k.A.	keine Angabe
LoE	Level of Evidence
Mat	matuzumab
mut	Mutation
M+	mutation positive (EGFR)
n	number
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NIHR HSC	National Institute for Health Research Horizon Scanning Centre
NNT	Number needed to treat
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
PEM	Pemetrexed
PFS	Progressionsfreies Überleben (progression free survival)
PLAT	Platinhaltige Chemotherapeutika
PS	Performance status
QOL	Quality of life
RCT	Randomized controlled trial
RR	Relatives Risiko, “risk ratio”
RT	Radiotherapie
SACT	systemic anticancer therapy
SR	Systematisches Review
TKI	Tyrosinkinsaseinhibitor
TNM	Tumor-Node-Metastasis (Klassifikationssystem)
TOI	Trial outcome index
TRIP	Turn Research into Practice Database
TTP	Time to Progression
VNB	Vinorelbin
vs.	versus
WHO	World Health Organisation
WT	Wild type

IQWiG Berichte/G-BA Beschlüsse

G-BA, 2014 [1] Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage VI-Off-Label-Use Teil A Ziffer III. Carboplatinhaltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) - Kombinationstherapie, Zustimmung eines pharmazeutischen Unternehmers	**Eckpunkte der Entscheidung** Die Firma Sun Pharmaceuticals Germany GmbH hat nachträglich zur Beschlussfassung des G-BA vom 21. November 2006 über die Umsetzung der Empfehlung der Expertengruppe Off-Label zu „Carboplatinhaltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie“ die Anerkennung des bestimmungsgemäßen Gebrauchs nach § 84 AMG ihrer carboplatinhaltigen Arzneimittel zur Anwendung bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie erklärt. Die Änderung der Arzneimittel-Richtlinie in Bezug auf die Wiedergabe der Zustimmungen pharmazeutischer Unternehmer zum Off-Label-Use carboplatinhhaltiger Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie dient daher der Veröffentlichung der zustimmenden Erklärung des betroffenen pharmazeutischen Unternehmers Sun Pharmaceuticals Germany GmbH gemäß § 35c Abs. 1 Satz 7 SGB V.

de Castria TB, 2013 [2] Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer	**1. Fragestellung** To assess the efficacy and safety of carboplatin-based chemotherapy when compared with cisplatin-based chemotherapy, both in combination with a third-generation drug, in people with advanced NSCLC. To compare quality of life in people with advanced NSCLC receiving chemotherapy with cisplatin and carboplatin combined with a third-generation drug.
	2. Methodik ***Population:*** people with advanced NSCLC ***Interventionen und Komparatoren:*** regimens with cisplatin or carboplatin in combination with a third-generation drug (i.e. docetaxel, paclitaxel, vinorelbine, gemcitabine or irinotecan) • Cisplatin plus gemcitabine versus carboplatin plus gemcitabine. • Cisplatin plus docetaxel versus carboplatin plus docetaxel. • Cisplatin plus paclitaxel versus carboplatin plus paclitaxel. • Cisplatin plus vinorelbine versus carboplatin plus vinorelbine. • Cisplatin plus irinotecan versus carboplatin plus irinotecan. We included trials comparing these compounds for any number of cycles or treatment schedules. ***Endpunkte*:** <u>Primär</u>: • Overall survival. • One-year survival rate. • QoL. • Drug toxicities (according to the National Cancer Institute Common Toxicity Criteria v2.0) <u>Sekundär</u>: Objective response rate, classified according to the Response Evaluation Criteria in Solid Tumors (RECIST) (Eisenhauer 2009). ***Suchzeitraum:*** 1966 bis 03/2013 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 10 (5017), nur RCTs ***Qualitätsbewertung der Studien:***

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



4. Anmerkungen/Fazit der Autoren

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

5. Hinweise durch FB Med:

- *Irinotecan nicht zugelassen in Deutschland*

Systematische Reviews

Azim HA et al., 2009 [3] Third generation triplet cytotoxic chemotherapy in advanced non-small cell lung cancer: a systematic overview	**1. Fragestellung** to compare the relative efficacy of third generation **triplet therapy** with that of standard **double therapy** in the treatment of advanced NSCLC.
	2. Methodik **Population**: treatment-naïve patients with pathologically proven advanced NSCLC **Intervention**: third generation triplet therapy (vinorelbine, paclitaxel, gemcitabine and docetaxel) **Komparator**: double therapy (platinum and/or third generation cytotoxic drugs) **Endpunkte**: Respone, OS, toxicity **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: k.A. **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 6 (n=2.117) **Qualitätserwertung der eingeschlossenen Primärstudien:** k.A.

3. Ergebnisdarstellung

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

Author	Therapy	n
Comella et al. [17]	Cisplatin 50 mg/m² + gemcitabine 1000 mg/m² + vinorelbine 25 mg/m² on days 1, 8 repeated every 3 weeks	60
	Cisplatin 100 mg/m² on day 1 + gemcitabine 1000 mg/m² on days 1, 8, 15 repeated every 4 weeks	60
	Cisplatin 120 mg/m² on day 1, 29 and then every 6 weeks + vinorelbine 30 mg/m² weekly for 10 weeks	60
Comella et al. [18]	Cisplatin 50 mg/m² + gemcitabine 1000 mg/m² + paclitaxel 125 mg/m² on days 1, 8 repeated every 3 weeks for 5 cycles	114
	Cisplatin 50 mg/m² + gemcitabine 1000 mg/m² + vinorelbine 25 mg/m² on days 1, 8 repeated every 3 weeks for 5 cycles	117
	Cisplatin 100 mg/m² on day 1 + gemcitabine 1000 mg/m² on days 1, 8, 15 repeated every 4 weeks for 5 cycles	112
Alberola et al. [19]	Cisplatin 100 mg/m² on day 1 + gemcitabine 1000 mg/m² on day 1, 8 + vinorelbine 25 mg/m² on day 1, 8 every 21 days	188
	Cisplatin 100 mg/m² on day 1 + gemcitabine 1250 mg/m² on day 1, 8 repeated every 21 days	182
	Gemcitabine 1000 mg/m² on day 1, 8 + vinorelbine 30 mg/m² on day 1, 8 for three cycles followed by vinorelbine 30 mg/m² on day 1, 8 + ifosfamide 3000 mg/m² on day 1	187
Laack et al. [20]	Gemcitabine 1000 mg/m² + vinorelbine 25 mg/m² on days 1, 8 + cisplatin 75 mg/m² on day 2 repeated every 3 weeks	144
	Gemcitabine 1000 mg/m² + vinorelbine 25 mg/m² on days 1, 8 repeated every 3 weeks	143
Paccagnella et al. [21]	Carboplatin AUC 6 + paclitaxel 200 mg/m² on day 1 + gemcitabine 1000 mg/m² on days 1 and 8 repeated every 3 weeks for at least 6 cycles	163
	Carboplatin AUC 6 + paclitaxel 200 mg/m² on day 1 repeated every 3 weeks for at least 6 cycles	156
Comella et al. [22]	Gemcitabine 1000 mg/m² + vinorelbine 25 mg/m² on days 1, 8 repeated every 3 weeks	110
	Gemcitabine 1000 mg/m² + paclitaxel 125 mg/m² on days 1, 8 repeated every 3 weeks	107
	Gemcitabine 1000 mg/m² + vinorelbine 25 mg/m² + cisplatin 50 mg/m² on days 1, 8 repeated every 3 weeks	109
	Gemcitabine 1000 mg/m² + paclitaxel 125 mg/m² + cisplatin 50 mg/m² on days 1, 8 repeated every 3 weeks	107

Survival (6 trials, 1.921 patients):

no statistically significant difference

Response (6 trials):

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

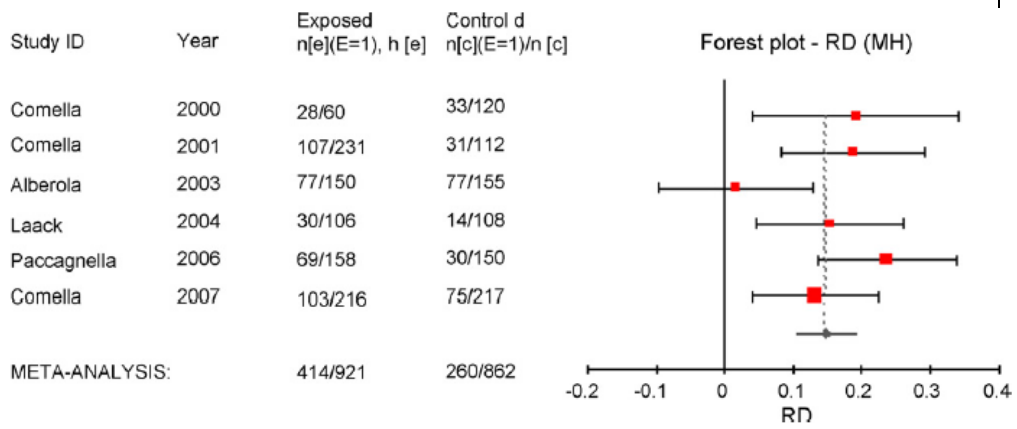


Fig. 2. Response rates.

Toxicity:

Patients who were randomized to receive triplet chemotherapy had significantly more grade III/IV toxicity in terms of myelosuppression, neurological toxicity and diarrhea. However the incidence of oral mucositis, renal dysfunction, nausea and vomiting were not significantly different between the two groups.

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

et al. (2011) [5]

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

3. Ergebnisdarstellung

Table 1
Characteristics of included studies.

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

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

Overall survival:

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

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

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

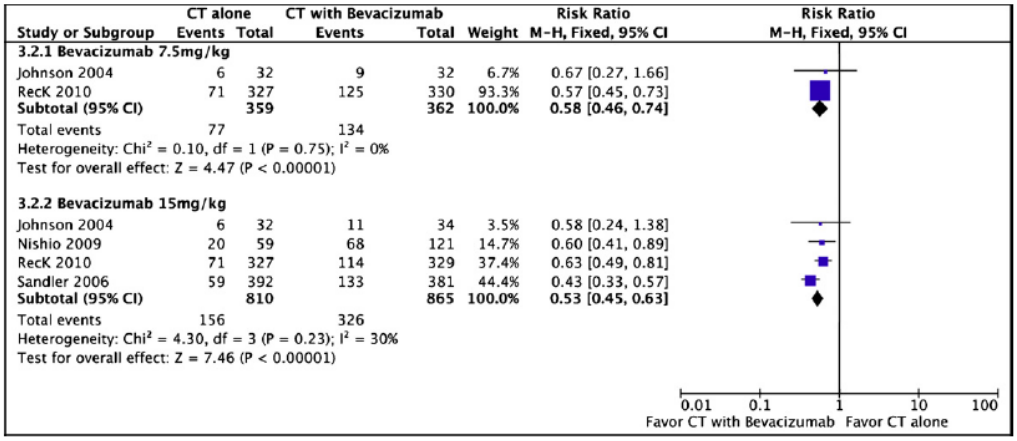


Fig. 2. comparative effect in objective response rates of CT with Bev versus CT alone. Abbreviations: CT – chemotheraphy. Observation: Sandler et al.: only patients with a measurable lesion are assessed

***Toxicity**:*

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

4. Anmerkungen/Fazit der Autoren

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

Chen P et al, 2011 [6] EGFR-	**1. Fragestellung** to systematically evaluate **EGFR targeted therapies** plus chemotherapy for advanced NSCLC

targeted therapies combined with chemotherapy for treating advanced non-small-cell lung cancer: a meta-analysis	**2. Methodik** **Population**: adults (aged 18 or older) with advanced NSCLC. Patients previously exposed to EGFR-directed agents or radiotherapy were excluded (alle first-line) **Intervention**: EGFR targeted therapies plus platinum-based doublet chemotherapy **Komparator**: platinum-based doublet chemotherapy **Endpunkt**: OS, PFS, ORR **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: up to 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 10 (n = 5 936)
	3. Ergebnisdarstellung Table 1 Characteristics of randomized clinical trials reviewed in the meta-analysis Study | Number of patients | Mean age (years) | Year of study | Center | Median OS (month) | First-line treatment | EGFR-targeted therapies used | Chemotherapy used | Jadad score Gatzemeier [12] | 1,159 | 60/59.1 | 2007 | multicenter | 9.9/10.2 | Yes | Erlotinib | Gemcitabine, Cisplatin | 5 Herbst [9] | 1,079 | 62.7/62..6 | 2005 | multicenter | 10.6/10.5 | Yes | Erlotinib | Paclitaxel, Carboplatin | 3 Mok [20] | 154 | 57.5/57 | 2009 | multicenter | 6.8/5.1 | Yes | Erlotinib | Gemcitabine, Cisplatin or Carboplatin | 3 Roy S. Herbst [14] | 690 | 61/63 | 2004 | multicenter | 9.8/9.9 | Yes | Gefitinib | Paclitaxel, Carboplatin | 5 Giaccone [13] | 728 | 59/61 | 2004 | multicenter | 9.9/10.9 | Yes | Gefitinib | Gemcitabine, Cisplatin | 5 Heymach [15] | 108 | 60/59 | 2008 | unclear | 10.2/12.6 | Yes | vandetanib | Paclitaxel, Carboplatin | 4 Pirker [17] | 1,125 | 59/60 | 2009 | multicenter | 11.3/10.1 | Yes | Cetuximab | Cisplatin, Vinorelbine | 3 Butts [19] | 131 | 66/64 | 2007 | multicenter | 11.9/9.26 | Yes | Cetuximab | Gemcitabine, Cisplatin or Carboplatin | 2 Rosell [18] | 86 | 58/57 | 2008 | multicenter | 8.3/7.3 | Yes | Cetuximab | Vinorelbine, Cisplatin | 3 Lynch [16] | 676 | 64/65 | 2010 | multicenter | 9.69/8.38 | Yes | Cetuximab | Paclitaxel or Docetaxel, Carboplatin | 4 Niedermolekulare TKIs+Chemotherapie vs. Chemotherapie (basierend auf 6 Studien mit 3918 Patienten, 3 trials mit Erlotinib, 2, trials mit Gefitinib, 1 trial mit Vandetanib): **Overall survival:** Kein stat. signifikanter Unterschied zwischen den Gruppen

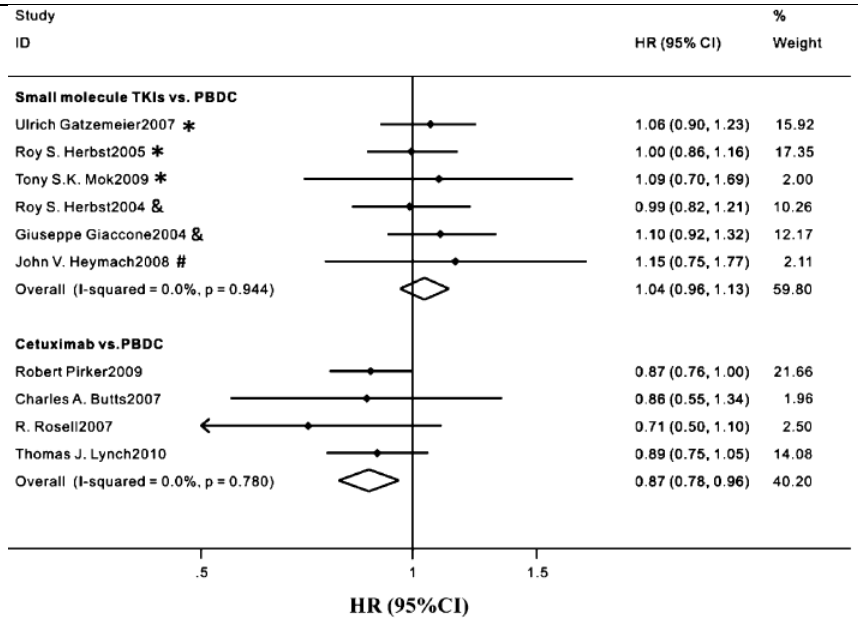


Fig. 2 Overall survival of epidermal growth factor receptor (EGFR)-targeted combination therapies vs. platinum-based doublet chemotherapy (PBDC). *Erlotinib administered, & gefitinib administered, # vandetanib administered, HR hazard ratio, 95% CI 95% confidence interval, HR<1 numerically longer survival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

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

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

4. Anmerkungen/Fazit der Autoren

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

5. Hinweise durch FB Med:

- *Erlotinib, Gefitinib, nur bei nachgewiesener EGFR-Mutation zugelassen*
- *Vandetanib, Cetuximab nicht zugelassen in Deutschland*

Cui J, et al. 2013 [7]

The Efficacy of Bevacizumab Compared with

1. Fragestellung

The extent of the benefit of bevacizumab combined with chemotherapy in the treatment of advanced non-small cell lung cancer (NSCLC) is still unclear. We performed this meta-analysis to compare the efficacy of bevacizumab with other commonly used targeted drugs for different patients with advanced NSCLC.

Other Targeted Drugs for Patients with Advanced NSCLC: A Meta-Analysis from 30 Randomized Controlled Clinical Trials	**2. Methodik** ***Population***: patients with confirmed stage IIIB, stage IV or recurrent NSCLC based on historical or cytological evidence ***Intervention***: bevacizumab (15 mg/kg) with chemotherapy ***Komparator***: standard chemotherapy alone, 1. und 2. Linie ***Endpunkt***: OS, ORR, PFS ***Methode***: systematic review and meta-analysis of RCTs (placebo-controlled or other types of superiority trial as well as noninferiorityv trial) ***Suchzeitraum***: 1999 to 2011 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 30 (k.A.) ***Qualitätsbewertung der Primärstudien:*** Jadad Score
	3. Ergebnisdarstellung ***1. Linie (chemotherapy-naive patients)*** • the pooled OR of response rate was 2.741(95%CI: 2.046, 3.672), • the pooled HR for disease progression was 0.645 (95%CI: 0.561, 0.743), • the pooled HR for death was 0.790 (95%CI: 0.674, 0.926), respectively

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

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

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

	4. Fazit der Autoren Our meta-analyses showed that compared to other commonly used targeted drugs, chemotherapy with bevacizumab significantly improved patients' response rate, PFS and OS. In addition, bevacizumab provided significantly higher OR_{ORR}, lower HRPFS, and lower HR_{OS} among chemotherapy-naı¨ve patients. … However, in general patients with EGFR status untested, bevacizumab showed a clear benefit in OR_{ORR}, $HR_{PF}S$, as well as HR_{OS}, compared with gefitinib. **Limitierungen** • Our study included clinical trials with only slightly different enrollment criteria and patient demographics. However patient characteristics (age, gender, ECOG performance status) were found not to be balanced between groups in a small number of trials. Such patient level difference may lead to heterogeneity in the meta-analysis. • Inconsistency of chemotherapies of the control group did exist in this analysis, which could not be eliminated due to the study background. • Finally, the clinical trials collected in this study show high heterogeneity.
Gao et al, 2009 [8] A meta-analysis of platinum plus gemcitabine or vinorelbine in the treatment of advanced non-small-cell lung cancer	**1. Fragestellung** To compare the **gemcitabine plus platinum** with **vinorelbine plus platinum** regimens in first-line treatment of advanced NSCLC.
	2. Methodik ***Population****:* Patients must be pathologically confirmed of NSCLC and in clinical III–IV stage. First-line ***Intervention****:* gemcitabine plus platinum ***Komparator****:* vinorelbine plus platinum ***Endpunkt****:* ORR, 1-year survival, toxicity ***Methode****:* systematic review and meta-analysis of RCTs ***Suchzeitraum***: 1996 bis 2008 ***Anzahl eingeschlossene Studien/Patienten*** *:* 9 (n=2 186)

3. Ergebnisdarstellung

Survival (9 trials, 2 186 patients): no statistically significant difference

In subgroup analysis of seven trials containing gemcitabine or vinorelbine plus cisplatin, the results showed that there was also no statistically significant difference between the two groups

Response (8 trials): no statistically significant difference

Toxicity (9 trials): Vinorelbine plus platinum chemotherapy led to more frequent grade 3 or 4 neutropenia, nephrotoxicity, constipation and phlebitis (OR, 0.37; 95%CI, 0.26–0.52; p < 0.00001;OR, 0.38; 95%CI, 0.25–0.57; p < 0.00001;OR, 0.50; 95%CI, 0.27–0.92; p = 0.03 and OR, 0.13; 95%CI, 0.05–0.32; p < 0.00001, respectively), while gemcitabine plus platinum chemotherapy inclined to developing more grade 3 or 4 thrombocytopenia (OR, 11.37; 95%CI, 4.56–28.38; p < 0.00001).

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

First author	Quality scores	Group	*n*	Eligible for evaluation	PS 0-1 (%)	Stage IV (%)	Mean age	Male (%)	CR + PR	1-year OS (%)
Martoni [18]	2	GEM1200 mg/m² d1,8 + DDP75 mg/m² d1	143	135	100[d]	56.0	63	81.5	36	44
		NVB25 mg/m² d1,8 + DDP75 mg/m² d1	143	137	100[d]	65.0	62	75.9	44	40
Vokes [19]	2	GEM1250 mg/m² d1,8 + DDP80 mg/m² d1[a]	62	62	100	0[e]	62	66.0	42	68
		NVB25 mg/m² d1,8 + DDP80 mg/m² d1[b]	55	55	100	0[e]	58	76.0	38	65
Scagliotti [20]	2	GEM1250 mg/m² d1,8 + DDP75 mg/m² d1	205	205	95	81.0	63	81.0	62	37
		NVB25 mg/m²/wk + DDP100 mg/m² d1[c]	203	201	92	81.o	63	78.0	61	37
Liu [21]	2	GEM1000 mg/m² d1,8 + DDP30 mg/m² d1	83	83	100	59.0	59	62.7	36	31
		NVB25 mg/m² d1,8 + DDP30 mg/m² d1	99	97	100	60.6	56	54.5	41	35
Helbekkmo [22]	2	GEM1000 mg/m² d1,8 + CBP4 AUC d1	222	214	71	72.0	67	64.0	–	30
		NVB25 mg/m² d1,8 + CBP4 AUC d1	222	218	72	70.0	67	59.0	–	28
Comella [23]	2	GEM1000 mg/m² d1,8,15 + DDP100 mg/m² d1[c]	70	60	100	60.0	60	90.0	18	40
		NVB30 mg/m²/wk + DDP120 mg/m² d1[c]	68	60	100	56.7	61	93.3	15	34
Thomas [24]	2	GEM1250 mg/m² d1,8 + CBP 6AUC d1	51	48	86.3	86.3	60	82.4	10	47
		NVB30 mg/m²/wk + DDP80 mg/m² d1	49	42	87.8	95.9	56	83.7	14	47
Gebbia [25]	2	GEM1400 mg/m² d1,8 + DDP100 mg/m² d8[c]	138	138	81	54.0	60	78.0	46	20
		NVB25 mg/m² d1,8 + DDP100 mg/m² d1[c]	140	140	83	53.0	63	76.0	62	24
Ohe [26]	2	GEM1000 mg/m² d,1,8 + DDP80 mg/m² d1	151	146	100	79.5	61	69.2	44	60
		NVB25 mg/m² d,1,8 + DDP80 mg/m² d1	150	145	100	82.1	61	69.7	48	48

PS: Zubrod-ECOG-WHO; 1y OS: 1-year survival; DDP: cisplatin; CBP: carboplatin; CR: complete response; PR: partial response.
[a] Gemcitabine 1250 mg/m² on days 1, 8, 22, and 29 and 600 mg/m² on days 43, 50, 64, and 71.
[b] Vinorelbine 25 mg/m² on days 1, 8, 15, 22, and 29 and 15 mg/m² on days 43, 50, 64, and 71.
[c] Twenty-eight days every cycle, the rest 21 days every cycle.
[d] Karnofsky ≥ 70.
[e] Stage III = 100%.

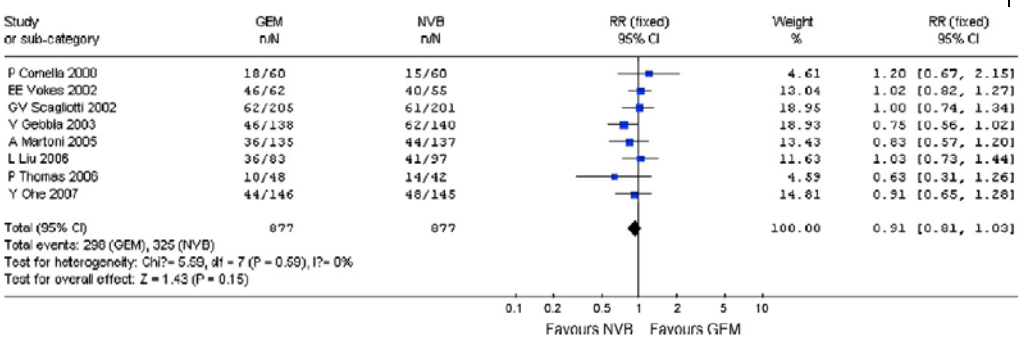
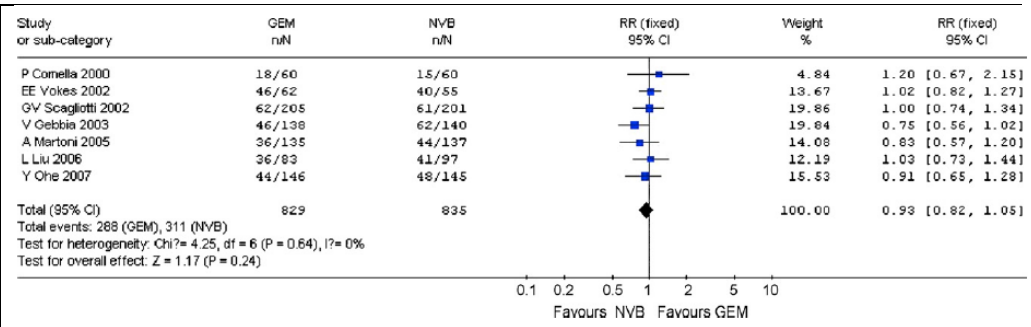


Fig. 2. The overall response rate analysis of platinum plus gemcitabine or vinorelbine for advanced NSCLC.

	 Fig. 3. The sub-analysis of overall response rate of cisplatin plus gemcitabine or vinorelbine for advanced NSCLC.
	4. Anmerkungen/Fazit der Autoren These meta-analyses showed that there was no significant difference between platinum plus gemcitabine or vinorelbine. And the similar results were found in sub-analysis in which gemcitabine and vinorelbine was compared when in combination with cisplatin. Gemcitabine plus platinum chemotherapy had an equal overall response rate and survival advantage in comparison with vinorelbine plus platinum regimens and the toxicity profiles might play an important role in the decision to choose gemcitabine-based regimens or vinorelbine-based regimens. In conclusion, the gemcitabine plus platinum regimens may be the better choice for the patients whose thrombocytopenia could be taken care, especially for the elder or the people with poor conditions, on the other hand, the vinorelbine plus platinum regimens should be more suitable for the patients who would be apt to bleed or be supersensitive to TPO or IL-11.
Goffin J et al, 2010 [9] First-line systemic chemotherapy in the treatment of advanced non-small cell lung cancer: a systematic review	**1. Fragestellung** Evidence for first-line treatment in NSCLC
	2. Methodik **Population**: patients with IIIB or IV NSCLC **Intervention**: chemotherapy (mono and doublet, platinum and non-platinum). First-line **Komparator**: k.A. **Endpunkt**: OS, QoL, ORR, toxicity **Methode**: systematic review of evidence based guidelines, systematic reviews and RCTs **Suchzeitraum**: up to 2007 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 2 evidence based guidelinies, 10 systematic reviews, 46 RCTs

	3. Ergebnisdarstellung Does Doublet Chemotherapy Consisting of a Platinum Agent Plus a New Agent Improve Outcomes Compared with Doublets Using Older Agents? Meta-analysis by Baggstrom et al. considered third generation, platinum-based regimens compared with second generation, platinum-based regimens. In a subgroup analysis of six trials (n = 1998) examining only doublet regimens, a 1 -year survival rate risk difference of 6% (95% confidence interval [CI], 2 to 10%) was found in favor of doublet chemotherapy regimens containing platinum and a new agent. Toxicity data were not examined. Five additional trials not included in the meta-analysis of Baggstrom et al. compared new doublet therapies with older regimens. Only one trial, comparing docetaxel plus cisplatin with vindesine plus cisplatin found superior survival with a newer agent. This trial also found superior QOL in the physical domain for the docetaxel-containing arm. Does Doublet Chemotherapy Consisting of a Platinum Agent Plus a New Agent Improve Outcomes Compared with a New Single Agent Alone or to a Platinum Agent Alone? A literature-based meta-analysis of randomized trials by Hotta et al. compared a doublet of platinum plus a new agent with a new agent alone in previously untreated patients with ECOG performance status of 0-2. Included were eight trials involving 2374 patients. Platinum-based doublets improved survival (HR, 0.87; 95% CI, 0.80- 0.94; p < 0.001) and produced a higher response rate (odds ratio [OR]. 2.32: 95% Cl. 1.68 -3.20) compared with new single-agent therapy. Platinum-based regimens increased myelosuppression, nephrotoxicity and nausea and vomiting but not treatment-related mortality. Which Doublet Chemotherapy Regimen Consisting of a Platinum Agent Plus a New Agent is most Effective in Improving Clinical Outcomes? Le Chevalier el al. tested the efficacy of gemcitabine plus platinum combinations versus any other platinum-based regimen and survival outcomes. A subgroup analysis of six trials (n = 2481) with a platinum-based third-generation comparator found a trend toward superior survival with gemcitabine-based regimens and improved progression-free survival (HR, 0.89: 95% CI, 0.82-0.96; p value not reported). However, the gemcitabine arms of two studies were counted more than once in the meta-analysis to allow comparison with more than one non-gemcitabine arm, and without weighting. Toxicity was not compared. The second meta-analysis, by Douillard et al. included seven trials (n = 3271) that compared docetaxel containing regimens with vinca-alkaloid regimens. The comparison for overall survival favored docetaxel (HR, 0.89; 95% Cl, 0.82-0.96; p = 0.004), as did the subgroup analysis of three trials (n = 1762) comparing platinum-based docetaxel doublets (HR, 0.87; 95% CI,

Grossi et al, 2009 [10] Impact of third-generation drugs on the activity of first-line chemotherapy in advanced non-small cell lung cancer: a meta-analytical approach	**1. Fragestellung** To assess the relative impact of different **third-generation drugs** on the activity of first-line chemotherapy in advanced non-small cell lung cancer by considering both response and progressive disease (PD) rates as outcome measures.
	2. Methodik **Population**: pathologically proven advanced NSCLC, no previous treatment for metastatic disease **Intervention**: two-drug regimen containing at least one third-generation agent. Platinum (defined as cisplatin or carboplatin) and nonplatinum combinations were allowed. Third-generation drugs were defined as gemcitabine, vinorelbine, docetaxel, and paclitaxel. **Komparator**: Doublet regimen free of a third generation agent **Endpunkt**: Response rate, disease progression **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: 1980 bis 2007 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 45 (n= k.A.) **Qualitätsbewertung der eingeschlossenen Studien:** k.A.
	3. Ergebnisdarstellung **Overall response** (45 trials, 11.231 patients): no statistically significant difference for gemcitabine-, docetaxel-, vinorelbine-, or paclitaxel-containing arms with the corresponding control groups **Disease progression** • Gemcitabine (23 trials, 6.681 patients): statistically significant difference in favor of gemcitabine (OR 0.86, 95% CI, 0.77– 0.95; p=0.005) • Paclitaxel (16 trials, 5.536 patients): statistically significant difference in favor of paclitaxel-free regimens (OR, 1.22; 95% CI, 1.09 –1.37; p=0.0008) • Docetaxel (12 trials, 4.642 patients): no statistically significant difference • Vinorelbine (23 trials, 6.048 patients): no statistically significant difference

	4. Anmerkungen/Fazit der Autoren Different third-generation regimens provide comparable response rates in chemotherapy-naïve patients with advanced NSCLC. Paclitaxel-based third-generation regimens are associated with a significantly higher risk for immediate progression, whereas gemcitabine-containing regimens may provide superior disease control. Given the impact of first-line chemotherapy on the natural history of the disease, the influence of disease control on treatment-free survival, and the recent evidence of a strong correlation between non-progression and OS, these data should be considered when new studies are designed comparing standard with innovative regimens or combining them with novel compounds. In view of the results of a cisplatin versus carboplatin meta-analysis, one could object that the apparent superiority of gemcitabine over paclitaxel might be a result of the usual association of the two agents with cisplatin versus carboplatin, respectively.
Ibrahim EM, 2010 [11] Frontline gefitinib in advanced non-small cell lung cancer: Meta-analysis of published randomized trials	**1. Fragestellung** The inconsistent results and the lack published meta-analysis that systematically examined the overall efficacy of **gefitinib** in the frontline setting in patients with advanced non-small cell lung cancer (NSCLC), have prompted the current meta-analysis.
	2. Methodik **Population**: Chemotherapy naïve patients with locally advanced or metastatic **Intervention**: gefitinib-based therapy (GBT) **Komparator**: placebo or none after initial chemoradiation or chemotherapy induction **Endpunkt**: OS, PFS, ORR, QoL **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: k.A. **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 7 (n=4 585)

	3. Ergebnisdarstellung 4 trials compared gefitinib plus chemotherapy vs. chemotherapy alone, 2 trials compared gefitinib alone vs. chemotherapy, 1 trial compared gefitinib plus best supportive care (BSC) vs. BSC alone **Overall survival**: no statistically significant difference. Statistically significant OS survival for GBT was not demonstrated regardless of tumor histology (adenocarcinoma vs. non-adenocarcinoma), or EGFR mutation status **PFS:** no statistically significant difference between GBT and control regardless of trials designs (HR = 0.97, 95% CI: 0.78–1.20, p = 0.78), neither was any PFS advantage was found among patients with mutant or wild EGFR **Response rate**: no statistically significant difference Quality of life (3 trials): statistically significant difference in favor of GBT. FACT-L questionnaire (OR = 1.38; 95% CI: 1.06‑1.79; p = 0.02) TOI questionnaire (OR = 1.87; 95% CI: 1.13‑3.09; p = 0.02). Rates of reduction in symptoms, as assessed on the basis of the LCS scores, were similar in patients who received GBT and those randomized to the control groups (OR = 1.14; 95% CI: 0.92‑1.42; p = 0.24).
	• **Anmerkungen/Fazit der Autoren** GBT cannot be recommended for the management of patients with advanced NSCLC in the first-line setting as compared with other standard interventions in unselected patient population. The significant improvement in QOL shown with GFT would be offset by the involved cost and the potential side effects known to be associated with the use of gefitinib. • ***Hinweise durch FB Med*** • *Keine Beschreibung zur Evaluation der Qualität der eingeschlossenen Studien* • *keine Angabe zum Suchzeitraum, keine doppelte Datenextraktion* • *Gefitinib nur bei nachgewiesener EGFR-Mutation zugelassen*
Jiang J et al, 2013 [12]: Paclitaxel plus platinum or gemcitabine plus platinum in first-line treatment of advanced non-small-cell lung cancer: results	**1. Fragestellung** to compare the efficacy and toxicity of **paclitaxel plus platinum** (TP) with **gemcitabine plus platinum** (GP) in untreated advanced non-small-cell lung cancer by a meta-analysis.
	2. Methodik **Population**: patients must be cytologically or pathologically confirmed of NSCLC and in clinical III–IV stage, patients must be chemotherapy-naive **Intervention**: paclitaxel plus platinum (TP) **Komparator**: gemcitabine plus platinum (GP) **Endpunkt**: efficacy, toxicity

from 6 randomized controlled trials	**Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: bis 2010 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 6 (n=2 793)
	3. Ergebnisdarstellung **1-Jahres-Überleben (6 trials):** no statistically significant difference (RR = 0.99, 95% CI = 0.90–1.09, p = 0.87; I^2=6%) **Gesamtüberleben (6 trials)**: no statistically significant difference (RR = 1.06, 95% CI = 1.00–1.13, p = 0.07; I^2=16%) **Response (6 trials)**: no statistically significant difference (RR = 0.99, 95 % CI = 0.88–1.13, p = 0.92, I^2=9%) **Toxicity:** Grade 3–4 nausea or vomiting was less frequent in the TP than the GP group (10.5 vs. 17.4 %, RR = 0.53, 95 % CI = 0.35–0.78, p = 0.002). Grade 3–4 sensory neuropathy and fatigue were comparable between the TP and GP arms. Grade 3–4 anemia (8.8 vs. 22.4 %, RR = 0.37, 95 % CI = 0.30–0.45, p<0.00001) and thrombocytopenia (8.8 vs. 47.8 %, RR = 0.20, 95 % CI = 0.14–0.27, p<0.00001) were less frequent in the TP than the GP group.
	4. Anmerkungen/Fazit der Autoren As there were no double-blind trials, the highest quality scores of the 6 trials according to Jadad's method were 3, and all 6 trials scored 3 Paclitaxel plus platinum had similar efficacy and less toxicity compared with gemcitabine plus platinum in first-line treatment of advanced non-small-cell lung cancer.
Jiang J et al, 2013 [13] Non-platinum doublets were as effective as	**1. Fragestellung** The aim was to compare the efficacy between doublets of third-generation agents (non-platinum) and doublets of platinum plus a third-generation agent (platinum-based) for chemotherapy-naı¨ve advanced non-small cell lung cancer (NSCLC).

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

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

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

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

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

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

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

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

[d] number of the patients in both group

[e] performance status over 80 according to Karnofsky

[f] performance status over 70 according to Karnofsky

[g] Non-adenocarcinoma

OS

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

RR

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

PFS

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

Toxicity

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

	anemia and neutropenia, but more lung toxicity than platinum-based doublets. • **Vinorelbine plus cisplatin** may cause more grade 3–4 peripheral neuropathy than gemcitabine plus docetaxel. Kein Hinweis auf Publikationsbias (Begg's funnel plot)
	4. Anmerkungen/Fazit der Autoren Non-platinum doublets were as effective as platinum-based doublets with different toxicity profile for chemotherapy-naı¨ve advanced NSCLC in the era of third generation agents.
Ku GY et al, 2011 [14] Gefitinib vs. chemotherapy as first-line therapy in advanced non-small cell lung cancer: meta-analysis of phase III trials	**1. Fragestellung** To perform a meta-analysis of the most updated results of these studies to better quantify the toxicities and clinical benefits of gefitinib over chemotherapy.
	2. Methodik ***Population:*** advanced (stage IIIB/IV) NSCLC ***Intervention:*** gefitinib ***Komparator:*** chemotherapy ***Endpunkte*:** PFS, OS, ORR, toxicity ***Suchzeitraum:*** k.A. ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** *5 (1617)* ***Qualitätsbewertung der Studien:*** *k.A.* ***Heterogenitätsuntersuchungen:*** k.A.

3. Ergebnisdarstellung

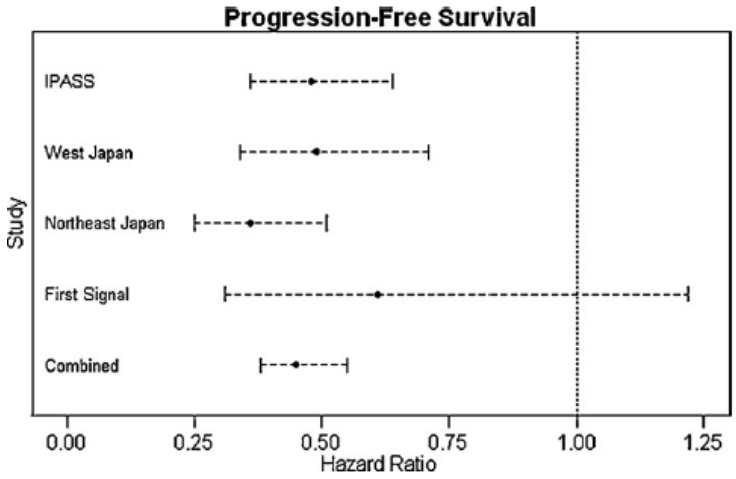
Table 1
Patient demographics.

Characteristic	Gefitinib ($n = 809$)*	Chemotherapy ($n = 808$)*
Sex		
Male	194 (24%)	194 (24%)
Female	615 (76%)	614 (76%)
Smoking history		
Never	707 (87%)	692 (86%)
Former/current	102 (13%)	116 (14%)
ECOG/WHO performance status		
0	267 (33%)	270 (33%)
1	480 (59%)	471 (58%)
2	62 (8%)	67 (8%)
Stage		
IIIB	175 (22%)	174 (22%)
IV/recurrent	634 (78%)	633 (78%)
Unknown	0	1 (0%)

ECOG/WHO, Eastern Cooperative Oncology Group/World Health Organization.
* Complete demographic data are available only for the North-East Japan, West Japan and IPASS studies.

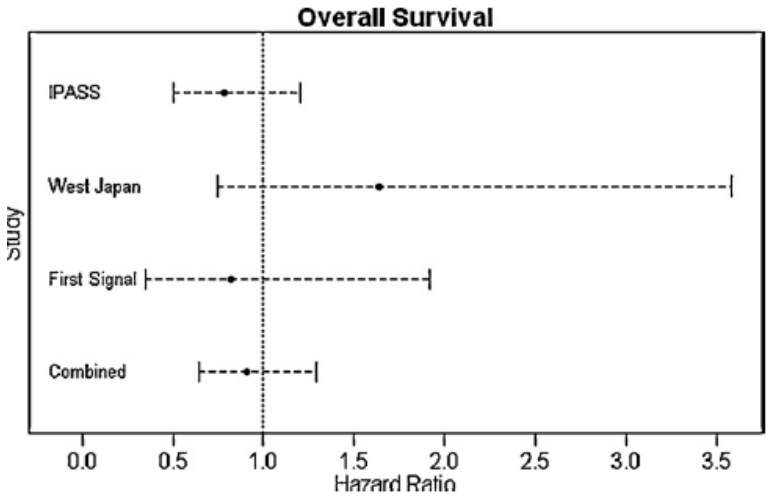
PFS

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



OS

hazard ratio 1.64, p = 0.211



	QoL QoL was analyzed in both the IPASS and first-SIGNAL studies. In the IPASS study, QoL was analyzed using the FACT-L, TOI and LCS instruments. The gefitinib group had better QoL and nominal symptom reduction compared to the chemotherapy group, with odds ratios (p values) for the respective measures of 1.34 (0.01), 1.78 (<0.001) and 1.13 (0.30). ***Toxicity*** Representative toxicities include fatigue, which was significantly more common in the chemotherapy arms. In the North-East Japan, West Japan and IPASS studies, the cumulative incidence of fatigue of any grade in the gefitinib arms was 18% (148 of 808) vs. 46% (363 of 790) in the chemotherapy arms (odds ratio 0.24, $p < 10–15$). Nausea was also more common in the chemotherapy arms of the North-East Japan and IPASS trials, where 51% (344 of 677) of the patients experienced any grade nausea vs. 17% (116 of 694) in the gefitinib arms (odds ratio 0.19, $p < 10^{-15}$). Patients receiving chemotherapy also experienced significantly more myelosuppression. As an example, the incidence of all-grade and grade ≥3 neutropenia was much less common in the gefitinib arms (7% vs. 84% and 3% vs. 69%, respectively). Across the studies, the odds ratio for grade ≥3 neutropenia for gefitinib vs. chemotherapy was 0.01 ($p < 10^{-15}$).
	4. Anmerkungen/Fazit der Autoren The results of our meta-analysis confirm the results of the individual trials: initial gefitinib is associated with a higher ORR and PFS as well as superior toxicity and QoL profiles as compared to chemotherapy. These benefits are seen in Asian patients who are selected by clinicopathologic characteristics associated with the presence of an EGFR mutation but are even more pronounced in patients with known EGFR mutations. In these studies, there was no OS benefit for upfront gefitinib over chemotherapy, quite possibly because most patients treated initially with chemotherapy received and benefited from an EGFR TKI at progression. ***5. Hinweise durch FB Med*** • *Gefitinib nur bei nachgewiesener EGFR-Mutation zugelassen*
Lee CK, et al. 2013 [15] Impact of EGFR inhibitor	**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.

in non-small cell lung cancer on progression-free and overall survival: a meta-analysis	**2. Methodik** ***Population****:* advanced NSCLC patients with and without EGFR mutations ***Intervention****:* of EGFR-TKIs monotherapy, EGFR-TKIs and chemotherapy ***Komparator****:* chemotherapy, placebo, best supportive care **Endpunkt**: PFS, OS ***Methode****:* systematic review and meta-analysis of RCTs ***Suchzeitraum****:* 2004 bis 2012 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 23 (n=14 570) ***Bewertung der Studienqualität der Primärstudien:*** k.A.
	3. Ergebnisdarstellung <u>First-line therapy (13 trials)</u> **Overall survival:** no statistically significant difference between EGFR-TKI-based therapy and other therapy. Neither for EGFRmut+ patients (11 trials) nor for EGFRmut- patients (6 trials). **PFS:** • EGFRmut+ patients (12 trials): statistically significant difference in favor of EGFR-TKI-based therapy (HR = 0.43; 95% CI = 0.38 to 0.49; p < 0.001) • EGFRmut- patients (7 trials): no statistically significant difference • Sensitivity analysis (EGFR-TKIs combined with chemotherapy vs. chemotherapy alone): statistically significant difference in favor of EGFR-TKI-based therapy (EGFRmut+: HR = 0.54, 95% CI = 0.30 to 0.95, p = 0.04; EGFRmut–: HR = 0.82, 95% CI = 0.68 to 0.98, p = 0.03 • Sensitivity analysis (EGFR-TKIs monotherapy vs. chemotherapy): statistically significant difference in favor of EGFR-TKI-based therapy in EGFRmut+ subgroup (HR = 0.42; 95% CI = 0.37 to 0.48; p < 0.001). Increased risk in the EGFRmut- subgroup (HR = 1.56; 95% CI = 1.36 to 1.80; p < 0.001)

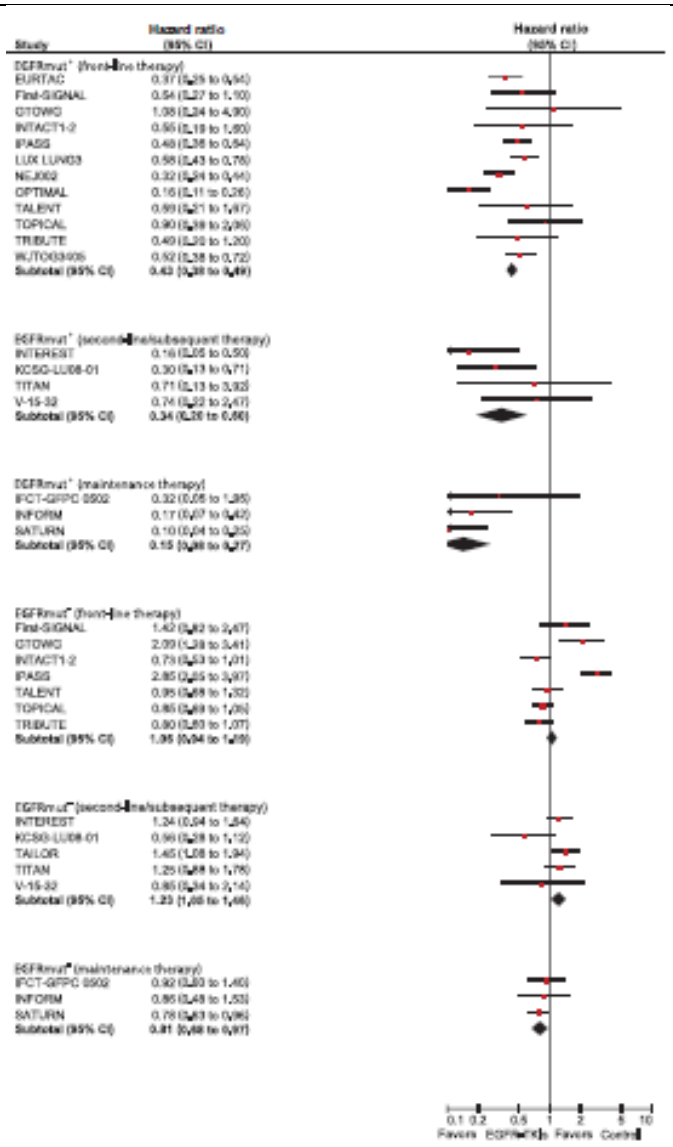


Figure 2. Forest plot of hazard ratios comparing progression-free survival in subgroups of epidermal growth factor receptor (EGFR) mutation–positive (EGFRmut+) and EGFR mutation–negative (EGFRmut-) patients who received EGFR–tyrosine kinase inhibitors (TKIs) vs control.

4. Anmerkungen/Fazit der Autoren

Treatment with EGFR-TKIs statistically significantly delays disease progression in EGFRmut+ patients but has no demonstrable impact on OS. These findings support assessment of EGFR mutation status before initiation of EGFR-TKIs treatment and indicate that EGFR-TKIs should be considered as front-line therapy in EGFRmut+ patients with advanced NSCLC.

Lee JK et al, 2014 [16]

Epidermal

1. Fragestellung

To determine the association between first-generation EGFR TKI vs chemotherapy and survival in advanced NSCLC patients with WT EGFR.

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	**2. Methodik** ***Population:*** advanced NSCLC with wild type (WT) EGFR ***Intervention:*** EGFR TKI ***Komparator:*** conventional chemotherapy ***Endpunkte:*** primary - progression-free survival (PFS), secondary - objective response rate, overall survival ***Suchzeitraum:*** through December 2013 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 11/1 605 (7 studies on second line treatment or later) ***Qualitätsbewertung der Studien:*** not mentioned ***Heterogenitätsuntersuchungen*:** χ 2 statistic used, I2 statistic also calculated, predefined subgroup analyses performed: line of treatment (first vs second or later), experimental drug (erlotinib vs gefitinib), ethnicity (Asiandominant vs white-dominant trials), and EGFR mutation analysis method (direct sequencing only vs more sensitive platforms; eg, fragment length analysis, amplificationrefractory mutation system, and mass spectrometric genotyping) ***„Publication bias“:*** funnel plot method together with the Egger test for asymmetry to assess the possibility of publication bias
	3. Ergebnisdarstellung • among patients with WT EGFR tumors, chemotherapy associated with improvement of PFS, compared with TKI (HR for TKI, 1.41; 95%CI, 1.10-1.81) • No statistically significant subgroup difference was identified in terms of line of treatment (first-line vs. second- or later-line), experimental drug, dominant ethnicity, or EGFR mutation analysis method • association of chemotherapy with improvement in PFS also significant in second- or later-line trials (HR, 1.34; 95%CI, 1.09-1.65) • association of chemotherapy with improvement in PFS <u>not significant</u> in first-line trials (4 trials, HR, 1.53; 95%CI, 0.87-2.69, favors CT) • objective response rate higher with chemotherapy (92/549, 16.8%, vs

	39/540, 7.2%, for TKI; relative risk for TKI, 1.11; 95%CI, 1.02-1.21) • no statistically significant difference observed with respect to overall survival (HR for TKI, 1.08; 95%CI, 0.96-1.22)
	4. Anmerkungen/Fazit der Autoren Among patients with advanced NSCLC harboring WT EGFR, conventional chemotherapy, compared with first-generation EGFR TKI, was associated with improvement in PFS but not overall survival. ***5. Hinweise durch FB Med*** • *EGFR-TKIs nur bei nachgewiesener EGFR-Mutation zugelassen*
Lima AB, 2011 [5] Addition of bevacizumab to chemotherapy in advanced non-small cell lung cancer: a systematic review and meta-analysis	**1. Fragestellung** As the results of clinical trials were not completely consistent, and none of them was large enough to accurately interpret the efficacy and safety of bevacizumab in combination with chemotherapy, the aim of this meta-analysis was to evaluate and to quantify the effectiveness and safety of bevacizumab in patients with advanced NSCLC.
	2. Methodik ***Population:*** patients with advanced NSCLC ***Intervention:*** Chemotherapy with bevacizumab ***Komparator:*** Chemotherapy without bevacizumab ***Endpunkte*:** OS, PFS, ***Suchzeitraum:*** Bis 12/2010 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 5 (2252) ; nur RCTs with a parallel design ***Qualitätsbewertung der Studien:*** ja, Publication bias: Egger's test ***Heterogenitätsuntersuchungen:*** I^2
	3. Ergebnisdarstellung

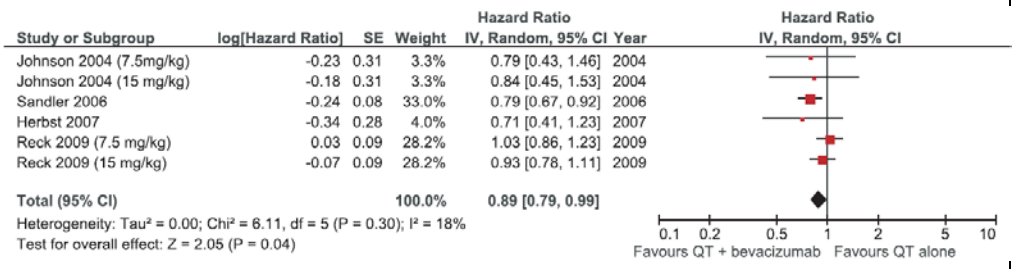
Author/year	Study/arm	Patients enrolled	Setting	Primary endpoint	ECOG 0, 1(%)	Histology	Maintenance of bevacizumab (maximum cycles)	Crossover permitted
Johnson 2004	TP	32	1st line	PFS	93.7	NSCLC	Yes (18)	Yes
	TP+Bev (7.5)	32			96.8			
	TP+Bev (15)	35			88.5			
Sandler 2006	TP	444	1st line	OS	100	Non-squamous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

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

all of them using platinum-based chemotherapy regimens

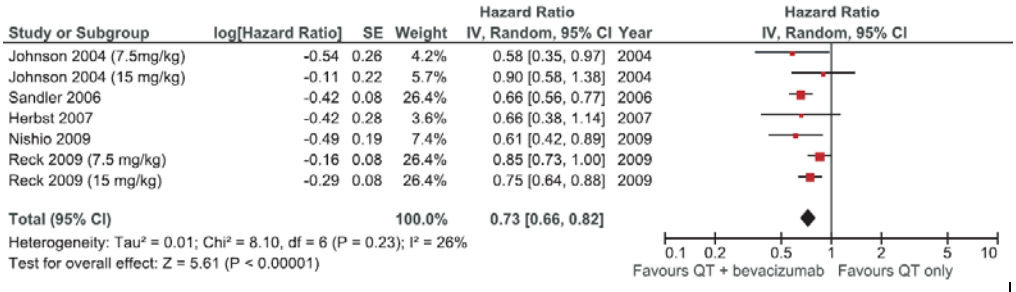
OS

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



PFS

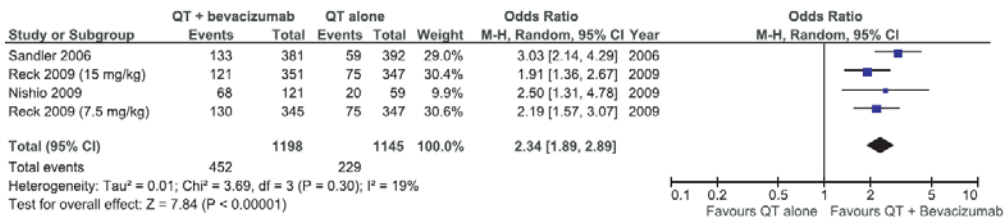
addition of bevacizumab to chemotherapy resulted in longer PFS (HR 0.73; 95% CI 0.66 to 0.82; p,0.00001)



ORR

addition of bevacizumab to chemotherapy resulted in higher response rates (OR 2.34; 95% CI 1.89 to 2.89; p,0.00001)

high heterogeneity between trials (I2 =53%; p =0.06)

	 ***Toxicity*** Some of the more clinically relevant grade 3/4 AEs increased by the addition of bevacizumab to chemotherapy were hypertension [OR, 5.51 (3.17–9.55), p,0.00001], bleeding events [OR 3.16 (1.82–5.48); p,0.0001] and febrile neutropenia [OR 2.12 (1.19–3.81), p = 0.01] …
	4. Anmerkungen/Fazit der Autoren The addition of bevacizumab to chemotherapy in patients with advanced NSCLC prolongs OS, PFS and RR. Considering the toxicities added, and the small absolute benefits found, bevacizumab plus platinum-based chemotherapy can be considered an option in selected patients with advanced NSCLC. However, risks and benefits should be discussed with patients before decision making. **5. Hinweise durch FB Med** • *eine Studie in Zweitlinientherapiesituation eingeschlossen*
Mörth C et al, 2014 [17] Single-agent versus combination	• **Fragestellung** The purpose of this study was to compare the efficacy and tolerability of first-line treatment with combination versus single agent chemotherapy in patients with advanced non-small cell lung cancer (NSCLC) and performance status (PS) 2.

chemotherapy as first-line treatment for patients with advanced non-small cell lung cancer and performance status 2: a literature-based meta-analysis of randomized studies	• **Methodik** ***Population:*** advanced NCSLC mit PS 2 ***Intervention:*** combination chemotherapy ***Komparator:*** single agent chemotherapy ***Endpunkte*:** Primär: OS; sekundär: PFS, ORR ***Suchzeitraum:*** Bis 07/213 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 12 (1114) ***Qualitätsbewertung der Studien:*** Cochrane's risk of bias tool ***Heterogenitätsuntersuchungen:*** Durchgeführt (I^2)

- **Ergebnisdarstellung**

Table 1
Characteristics of eligible trials.

Author [trial name] (ref)	Study phase	Treatment arms	Dose and schedule of chemotherapy	PS analysis	No of patients	Outcomes
Kosmidis [8]	II	Gemcitabine	1250 mg/m² day 1 + 14, q4w	Dedicated to PS 2	47	OS, PFS, ORR, Toxicity
		Carboplatin-Gemcitabine	3 AUC – 1250 mg/m² day 1 + 14, q4w		43	
Morabito [CAPPA-2] [9]	III	Gemcitabine	1200 mg/m² day 1 + 8, q3w	Dedicated to PS 2	28	OS, PFS, ORR, Toxicity
		Cisplatin-Gemcitabine	60–1200 mg/m2 day 1 + 8, q3w		29	
Reynolds [USO-03012] [10]	III	Gemcitabine	1250 mg/m² day 1+ 8, q3w	Dedicated to PS 2	85	OS, PFS, ORR, Toxicity
		Carboplatin-Gemcitabine	5 AUC – 1000 mg/m² day 1 + 8, q3w		85	
Zukin [11]	III	Pemetrexed	500 mg/m² day 1, q3w	Dedicated to PS 2	102	OS, PFS, ORR, Toxicity
		Carboplatin-Pemetrexed	5 AUC – 500 mg/m² day 1, q3w		103	
Comella [SICOG 9909] [14]	III	Gemcitabine	1200 mg/m² day 1 + 8 + 15, q4w	Subset analysis	19	ORR
		Paclitaxel	100 mg/m² day 1 + 8 + 15, q4w		22	
		Gemcitabine-Paclitaxel	1000 mg/m²–80 mg/m2 day 1 + 8, q3w		15	
		Gemcitabine-Vinorelbine	1000 mg/m²–25 mg/m² day 1 + 8, q3w		21	
Georgoulias [15]	III	Docetaxel	100 mg/m² day 1, q3w	Subset analysis	15	OS, ORR
		Cisplatin-Docetaxel	80 mg/m² day 2–100 mg/m² day 1, q3w		15	
Hainsworth [16]	III	Docetaxel	36 mg/m2 day 1 + 8 + 15, q4w	Subset analysis	57	OS
		Docetaxel-Gemcitabine	30 mg/m²–800 mg/m² day 1 + 8 + 15, q4w		65	
Le Chevalier [17]	III	Vinorelbine	30 mg/m² weekly	Subset analysis	46	OS
		Cisplatin-Vinorelbine	120 mg/m² day 1 + 29 -> q6w, 30 mg/m² weekly		42	
		Cisplatin-Vindesine	120 mg/m² day 1 + 29 -> q6w, 3 mg/m² weekly for 6 wk -> q2w		33	
Lilenbaum [CALGB 9730] [18]	III	Paclitaxel	225 mg/m² day 1, q3w	Subset analysis	50	OS, ORR
		Carboplatin-Paclitaxel	6 AUC–225 mg/m2 day 1, q3w		49	
Perrone [MILES] [19]	III	Vinorelbine	30 mg/m² day 1 + 8, q3w	Subset analysis	45	OS, ORR
		Gemcitabine	1200 mg/m² day 1 + 8, q3w		41	
		Vinorelbine-Gemcitabine	25–1000 mg/m² day 1 + 8, q3w		44	
Quoix [IFCT-0501] [20]	III	Gemcitabine or Vinorelbine	1150 mg/m² day 1 + 8, q3w or 25 mg/m² day 1 + 8, q3w	Subset analysis	62	OS
		Carboplatin-Paclitaxel	6 AUC day 1–90 mg/m² day 1 + 8 + 15, q4w		61	
Sederholm [21]	III	Gemcitabine	1250 mg/m² day 1 + 8, q3w	Subset analysis	20	OS (not adequate data for meta-analysis)
		Carboplatin-Gemcitabine	5 AUC day 1–1250 mg/m² day 1 + 8, q3w		24	

Abbreviations: ref: reference; PS: performance status; No: number; q4w: every 4 weeks; q3w: every 3 weeks; OS: overall survival; PFS: progression-free survival; ORR: objective response rate.

no statistical heterogeneitywas observed

OS (11 Studien, 1114 Patienten):

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

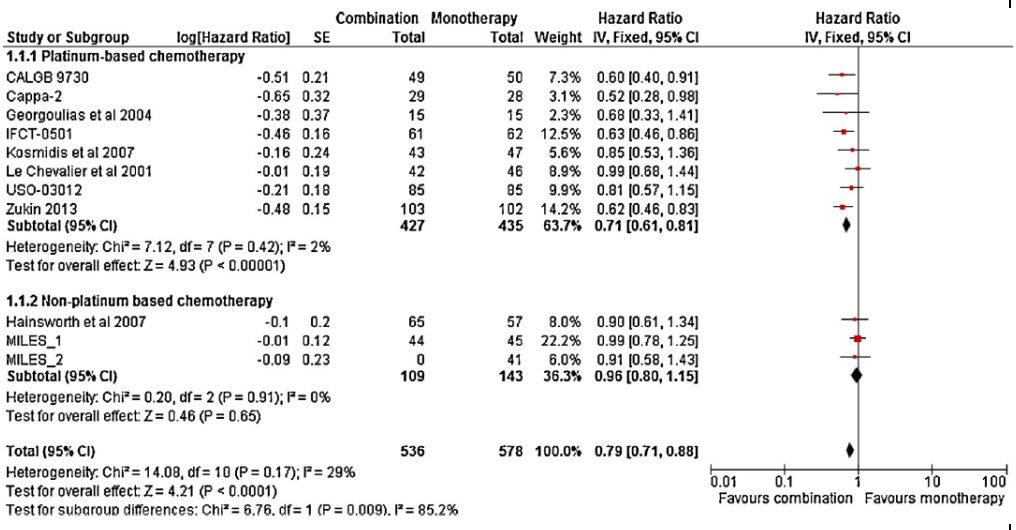


Fig. 2. Forest plot for overall survival (with subgroup analysis based on the administration of

	platinum-based or non-platinum based chemotherapy in combination arms).The size of the squares indicates the weight of the study. Error bars represent 95% confidence intervals (CIs). The diamond indicates the summary hazard ratio. Values lowerthan one indicate survival advantage of combination chemotherapy. **Table 2** Meta-analyses of grade III–IV adverse events. Toxicity grade III–IV | No of studies | No of patients analyzed | Pooled OR (95% CI) | *p*-Value Hematologic Anemia | 4 | 519 | 3.12 (1.55–6.27) | 0.001 Trombocytopenia | 4 | 519 | 12.81 (4.65–33.10) | <0.001 Neutropenia | 4 | 519 | 7.91 (3.97–15.78) | <0.001 Non-hematologic Febrile neutropenia | 3 | 432 | 0.32 (0.05–2.06) | 0.23 Fatigue | 3 | 349 | 0.75 (0.40–1.40) | 0.36 Nausea | 3 | 432 | 1.21 (0.05–29.34) | 0.91 ***PFS** (5 Studien, 522 Patienten)* combination chemotherapy resulted in statistically significant longer PFS compared with single agent chemotherapy(HR: 0.61, 95% CI: 0.45–0.84, p-value = 0.002) ***ORR** (8 Studien, 822 Patienten)* was higher in patients that received combination chemotherapy compared with those received single agent (OR: 2.20, 95% CI:1.42–3.39, p-value < 0.001) ***grades III and IV toxicity** (4 Studien)* Due to lack of adequate data, we could not perform meta-analysis on the incidence of other toxicities.
	• **Anmerkungen/Fazit der Autoren** This meta-analysis provides evidence supporting the use of combination chemotherapy in patients with NSCLC and PS 2. However, the patients should be informed about the higher risk for toxicity with the combination chemotherapy and the final treatment strategy should be individualized **Limits:** • unable to investigate whether the survival benefit with combination chemotherapy is similar on different histological subtypesof lung cancer
NICE, 2013 [18] Clinical effectiveness	**1. Fragestellung** To evaluate the clinical effectiveness and cost-effectiveness of first-line chemotherapy currently licensed in Europe and recommended by NICE, for adult patients with locally advanced or metastatic nonsmall cell lung cancer (NSCLC).

and cost-effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: a systematic review and economic evaluation	2. **Methodik** **Population** locally advanced or metastatic NSCLC **Intervention:** chemotherapy drug regimens that are currently licensed in Europe and are recommended by NICE in a monotherapy or in combination, first line **Komparator:** platinum (PLAT) drug **Endpunkte:** Overall survival (OS), OS at 1 and 2 years, progression-free survival (PFS), time to progression (TTP), tumour overall response rate, quality of life (QoL) and adverse events (AEs). **Methode:** Systmatisches Review mit Metaanalyse und Netzwerkmetaanalyse **Suchzeitraum:** 1990 bis 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 23 (11 428); nur RCTs und SRs
	3. Ergebnisdarstellung ***OS*** Among NSCLC patients with squamous disease, there were no statistically significant differences between any of the four chemotherapy regimens (DOC + PLAT, GEM + PLAT, PAX + PLAT, VNB + PLAT) in terms of increasing OS. However, both the direct and indirect evidence suggests a potential non-statistically significant advantage in terms of OS for GEM + PLAT [direct meta-analysis 1: hazard ratio (HR) = 1.08; 95% confidence interval (CI) 0.98 to 1.20] and for DOC + PLAT (direct meta-analysis 1: HR = 0.89; 95% CI 0.78 to 1.00; mixed-treatment comparison 1, HR = 0.92; 95% CI 0.81 to 1.03) compared with VNB + PLAT. Analyses of 1- and 2-year survival support this conclusion. For patients with non-squamous NSCLC there is borderline statistically significant evidence to suggest that PEM + PLAT increases OS compared with GEM + PLAT (direct meta-analysis 1, HR = 0.85; 95% CI 0.73 to 1.00). However, there is no statistically significant evidence to suggest that PEM + PLAT compared with GEM + PLAT increases PFS (mixed-treatment comparison 1, HR = 0.85; 95% CI 0.74 to 0.98). Among patients with EGFR M+ status, OS was not statistically significantly different in those treated with GEF and those receiving PAX + PLAT or in those treated with GEF compared with those treatedwith DOC + PLAT. ***PFS*** There was a statistically significant improvement in PFS among those patients treated with GEF compared with those treated with DOC + PLAT or PAX + PLAT. However, there was significant quantitative heterogeneity between the two trials comparing GEF with PAX + PLAT, which requires further exploration. It remains unknown whether or not the clinical effectiveness of PEM + PLAT is superior to that of GEF monotherapy for patients with non-squamous disease. The relative clinical effectiveness of PEM + PLAT in patients who are EGFR M+ is unknown. ***QoL*** (insgesamt 12 Studien) Seven trials reported no significant difference in QoL and four trials reported

some significant differences between treatment groups. A lack of reporting of QoL data is a feature of the great majority of trials assessing outcomes of treatment for patients with NSCLC. This, despite its relevance to patients and clinicians, is a major shortcoming of lung cancer research. Measuring QoL outcomes in patients with advanced NSCLC is difficult mainly because of the severity of symptoms, the side effects of chemotherapy and early deaths associated with NSCLC. However, the British Thoracic Oncology Group Trial 2 has shown that it is feasible to collect QoL data in patients with performance status (PS) 0–2, stage IIIB/IV NSCLC disease within a clinical trial setting.

A number of instruments/tools that measure QoL were employed in the included trials. The EORTC QLQ-C30 and the lung cancer-specific module QLQ-LC13 were used in five trials, the LCSS by three trials, and the FACT-L32 questionnaire by three trials.
Four reported some significant differences between treatment groups for QoL; however, in one of these trials,3 results after two cycles of chemotherapy favoured the PAX + CARB arm over the VNB + CIS arm, and results after four cycles favoured the VNB + CIS arm. In one trial, significantly more patients in the GEF group than in the PAX + CARB group had a clinically relevant improvement in QoL, as assessed by scores on the FACT-L questionnaire (odds ratio = 1.34; 95% CI 1.06 to 1.69; $p = 0.01$) and by scores on the Trial Outcome Index (TOI) (which is the sum of the physical well-being, functional well-being and lung cancer subscale scores of FACT-L; odds ratio = 1.78; 95% CI 1.40 to 2.26; $p < 0.001$).

AEs
Across all the chemotherapy arms of the included trials, the most common AEs were neutropenia, anaemia and leucopenia. Rates of haematological AEs were similar for all the chemotherapy drugs with the exception of GEF, which appears to be associated with a significantly lower evere AE rate than some of the other drugs. The trials often varied in the way that AEs were defined, measured and reported.

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

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

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

	Mixed-treatment comparison – direct and indirect comparisons - Vergleiche für verschiedene Patientengruppen (aus Platzgründen hier nicht dargestellt) ***Squamöse NSCLC*** The PLAT-based doublets of DOC, GEM, PAX and VNB had relatively more data points for all outcomes than the newer PEM + PLAT regimen and GEF monotherapy. In general, there was consistency between the results of the direct meta-analyses and the mixed-treatment comparison analyses, and very good consistency across individual trials in the within-group comparisons. • ***OS*** The evidence related to outcomes for patients with squamous disease demonstrates that there are no statistically significant differences in OS between any of the four third-generation chemotherapy treatments (DOC + PLAT, GEM + PLAT, PAX + PLAT or VNB + PLAT). However, both the direct and indirect evidence suggest a potential advantage in terms of OS for GEM + PLAT (direct meta-analysis 1, HR = 1.08; 95% CI 0.98 to 1.20) and for DOC + PLAT (direct meta-analysis 1, HR = 0.89; 95% CI 0.78 to 1.00; mixed treatment comparison 1, HR = 0.92; 95% CI 0.81 to 1.03) compared with VNB + PLAT, although this advantage is not statistically significant. Analyses of 1- and 2-year survival support this conclusion. • **PFS** Only seven trials were included in the PFS analysis and the majority of these trials used slightly different definitions of PFS. There was no evidence of any significant difference in PFS for GEM + PLAT compared with VNB + PLAT. There was insufficient evidence to conclude whether or not there were any statistically significant differences in PFS between the other third-generation chemotherapy comparators. ***EGFR-positive*** • ***OS*** For patients with EGFR M+ status, there is no statistically significant difference in OS between GEF compared with PAX + PLAT and between GEF compared with DOC + PLAT. There is evidence of a statistically significant improvement in PFS with GEF compared with DOC + PLAT. • ***PFS*** Although there is also evidence of a statistically significant improvement in PFS with GEF compared with PAX + PLAT the significant heterogeneity between trials means the PFS results should be viewed with caution.

	4. Anmerkungen/ Fazit der Autoren The mix of patient population is now expected to be taken into consideration at the time of trial design as demonstrated in the PEM and GEF trials. Making comparisons across the six available first-line chemotherapy treatments is therefore limited by the comparability of the treatment populations in the published trials. • there were few trials with fully reported methods and the definitions of the health outcomes used often differed between trials • very few trials reported QoL data; AEs from the different trials were difficult to compare; QoL: variety of instruments/tools • CARB and CIS were treated as being similarly effective in the clinical analyses; and owing to the large volumes of data available for patients with lung cancer, • the methods employed in the review do not always match the methods stated in the original protocol
NIHR, 2011 [19] Clinical and cost effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: a systematic review and economic evaluation. Health, Technology Assessment	**1. Fragestellung** To evaluate the clinical effectiveness and cost-effectiveness of first-line **chemotherapy** currently licensed in Europe and recommended by NICE, for adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).
	2. Methodik **Population**: Chemotherapy-naive adult patients with locally advanced or metastatic NSCLC **Intervention**: Any first-line chemotherapy treatment currently licensed in Europe and approved by NICE including: • PLAT-based chemotherapy (CARB or CIS) in combination with DOC, GEM, PAX or VNB • PEM + CIS • Single-agent therapy – GEF **Komparator**: Any first-line chemotherapy treatment currently licensed in Europe and approved by NICE for the first-line treatment of patients with locally advanced and metastatic NSCLC **Endpunkt**: OS, PFS, TTP, ORR, AE, HRQoL **Methode**: Systematic review an meta-analysis of RCTs and systematic reviews **Suchzeitraum**: 2000-2009 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 23 RCTs (n=11 428)

	3. Ergebnisdarstellung Non-small cell lung cancer patients with squamous disease (18 RCTs, 7.382 patients): **Overall survival:** Kein statistisch signifikanter Unterschied zwischen: • Gemcitabine plus platinum compared with paclitaxel plus platinum • Gemcitabine plus platinum compared with docetaxel plus platinum • Vinorelbine plus platinum compared with paclitaxel plus platinum • Vinorelbine plus platinum compared with docetaxel plus platinum • Paclitaxel plus platinum compared with docetaxel plus platinum **PFS:** statistisch signifikanter Zusammenhang zwischen: • Vinorelbine plus platinum compared with paclitaxel plus platinum (1 RCT, 140 patients): statistically significant suggesting an advantage for VNB + CIS (HR = 1.52; 95% CI 1.06 to 2.17) kein statistisch signifikanter Zusammenhang zwischen: • Gemcitabine plus platinum compared with vinorelbine plus platinum • Gemcitabine plus platinum compared with paclitaxel plus platinum • Gemcitabine plus platinum compared with docetaxel plus platinum • Vinorelbine plus platinum compared with docetaxel plus platinum Population 2: non-small cell lung cancer patients with non-squamous disease (20 RCTs, 9553 patients). **Overall survival:** Kein statistisch signifikanter Unterschied zwischen: • Gemcitabine plus platinum compared with pemetrexed plus platinum • Vinorelbine plus platinum compared with pemetrexed plus platinum • Paclitaxel plus platinum compared with pemetrexed plus platinum • Docetaxel plus platinum compared with pemetrexed plus platinum **PFS:** kein statistisch signifikanter Zusammenhang zwischen: • Gemcitabine plus platinum compared with pemetrexed plus platinum • Vinorelbine plus platinum compared with pemetrexed plus platinum • Paclitaxel plus platinum compared with pemetrexed plus platinum • Docetaxel plus platinum compared with pemetrexed plus platinum Epidermal growth factor receptor mutation-positive population. **Overall survival:** Kein statistisch signifikanter Unterschied zwischen: • Paclitaxel plus platinum compared with gefitinib • Docetaxel plus platinum compared with gefitinib • Paclitaxel plus platinum compared with docetaxel plus platinum

	PFS: statistisch signifikanter Zusammenhang zwischen: • Paclitaxel plus platinum compared with gefitinib (2 RCTs, 491 patients) (HR = 0.38; 95% CI 0.24 to 0.60, I^2=78,8%) • Docetaxel plus platinum compared with gefitinib (1 RCT, HR = 0.49; 95% CI 0.33 to 0.73) kein statistisch signifikanter Zusammenhang zwischen: • Paclitaxel plus platinum compared with docetaxel plus platinum
	4. Anmerkungen/Fazit der Autoren Overall, the quality of the included RCTs was poorer than expected – there were few trials with fully reported methods and the definitions of the health outcomes used often differed between trials. In addition, it is generally agreed that RCTs typically include patients who are generally fitter and younger than patients receiving treatment in routine clinical practice and that outcomes from RCTs are not always of the same magnitude as those gained from routine care. Caution is therefore required when interpreting and comparing the results of these trials, in particular the results generated through meta-analysis and mixed-treatment comparison. The evidence related to outcomes for patients with squamous disease demonstrates that there are no statistically significant differences in OS between any of the four third-generation chemotherapy treatments (DOC + PLAT, GEM + PLAT, PAX + PLAT or VNB + PLAT). However, both the direct and indirect evidence suggest a potential advantage in terms of OS for GEM + PLAT (direct meta-analysis 1, HR = 1.08; 95% CI 0.98 to 1.20) and for DOC + PLAT (direct meta-analysis 1, HR = 0.89; 95% CI 0.78 to 1.00; mixedtreatment comparison 1, HR = 0.92; 95% CI 0.81 to 1.03) compared with VNB + PLAT, although this advantage is not statistically significant. Analyses of 1- and 2-year survival support this conclusion.
Ouyang PY et al, 2013 [20] Combination of EGFR-TKIs and Chemotherapy as First-Line Therapy for Advanced NSCLC: A Meta-Analysis	**1. Fragestellung** Controversy continues regarding the role of the addition of EGFR–TKIs in patients receiving chemotherapy. Therefore, we conducted this meta-analysis to comprehensively estimate the treatment effect of the combined regimen on PFS and overall survival (OS) based on characteristics of patients.
	2. Methodik ***Population:*** chemotherapy-naive patients with advanced NSCLC ***Intervention:*** Chemotherapy, first-line treatment ***Komparator:*** EGFR–TKI monotherapy or the combined regimen of EGFR– TKI and

chemotherapy

***Endpunkte*:**

PFS, OS

Suchzeitraum:

Nur: prospective randomized controlled trials (phase II or III)

Anzahl eingeschlossene Studien/Patienten (Gesamt):

8 (4585)

Qualitätsbewertung der Studien:

examined the randomization procedure, estimation of sample size, blinding, loss to follow-up, dropout and if the intention-to-treat analysis

Heterogenitätsuntersuchungen:

Chi-square test and I^2 statistic

Publication ias: Begg's test and Egger's test

3. Ergebnisdarstellung

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

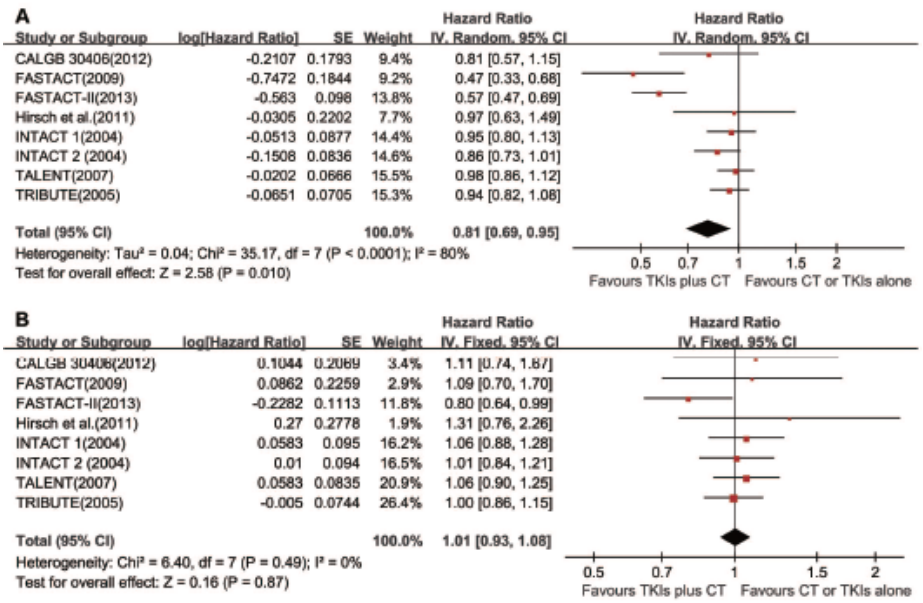
Trials(year)	TKIs	chemotherapy (dose*cycles)	Patients analyzed	Median age (range)	Female	Race (% Asian)	Never/light smoker	EGFR mutation positive
FASTACT(2009) [13]	E[†]	DDP(75 mg/m^2,d1)/CBP(AUC = 5,d1)+GBM1250(mg/m^2,d1,8),q4w*6	76vs78	57.5(33–79) vs57.0(27–79)	22vs24	93vs95	24vs28	2vs5
FASTACT-II (2013) [14]	E[†]	DDP(75 mg/m^2,d1)/CBP(AUC = 5,d1)+GBM1250(mg/m^2,d1,8),q4w*6	226vs225	59.0(31–96)vs57.3(37–88)	94vs85	100vs100	112vs107	49vs48
INTACT 1(2004) [7] [17]	G[‡]	DDP(80 mg/m^2,d1)+GEM(1250 mg/m^{2}d1,8),q3w*6	365vs363	59(34–83)vs61(33–81)	85vs101	1.6vs0.8	NA	23vs9[&]
INTACT 2(2004) [8] [17]	G[‡]	CBP(AUC = 6)+TAX(225 mg/m^2),q3w*6	345vs345	61(27–86)vs63(31–85)	146vs133	NA	NA	
TALENT(2007) [9]	E	DDP(80 mg/m^2,d1)+GEM(1250 mg/m^{2}d1,8),q3w*6	580vs579	61(26–82)vs60(28–84)	125vs142	3vs4	8vs10	NA
TRIBUTE(2005) [10] [18]	E	CBP(AUC = 6)+TAX(200 mg/m^2),q3w*6	539vs540	63(24–84)vs63(26–84)	217vs207	3.9vs2.4	72vs44	15vs14
CALGB30406(2012) [12]	E	CBP(AUC = 6)+TAX(200 mg/m^2),q3w*6	100vs81	60(34–81)vs58(32–78)	58vs49	8vs6	100vs81	33vs33
Hirsch et al.2011 [11]	E	CBP(AUC = 6)+TAX(200 mg/m^2),q3w*4	71vs72	NA	31vs44	6vs12	NA	6vs9

Note: TKIs = tyrosine kinase inhibitors, PS = performance status, E = erlotinib, G = gefitinib, DDP = dsplatin, CBP = carboplatin, AUC = area under the curve, GEM = gemcitabine, q4w = every four weeks, vs = the combined regimen versus chemotherapy or TKIs monotherapy, NA = not available, TAX = paclitaxel.
[†]Sequential administration of erlotinib following gemcitabine/platinum chemotherapy, rather than concurrent administration as the other trials.
[‡]Only included patients treated with gefitinib 250 mg/d.
[&]Data from trials INTACT 1and 2 together.
doi:10.1371/journal.pone.0079000.t001

Unselected Patients (4 Studien)

- ***PFS:*** Significant PFS benefit was observed from the combined regimen of TKIs and chemotherapy (HR= 0.81, 95% CI 0.69–0.95, P = 0.01; Figure 2a) based on random-effects model, due to significant heterogeneity (Chi^2 = 35.17, P<0.001; I^2 = 80%).
- ***OS:*** no evidence of improvement in OS with the combined regimen (HR= 1.01, 95% CI 0.93–1.08, P = 0.87, fixed-effects model

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

	 **4. Anmerkungen/Fazit der Autoren** In conclusion, on the basis of this meta-analysis, combination of EGFR–TKIs and chemotherapy leads to PFS benefit as first-line treatment for advanced NSCLC, regardless of EGFR-mutation status, but has no demonstrable impact on OS. And there is a larger magnitude of PFS benefit for Asian patients, with sequential administration of EGFR–TKIs and chemotherapy. EGFR-mutation status is still a predictive biomarker of benefit with the combined regimen, for a larger magnitude of improvement in EGFR-mutation positive patients. This strategy deserved to be considered in the future although it is not approved for advanced NSCLC at the moment. ***5. Hinweise durch FB Med:*** • *EGFR-TKIs nur bei nachgewiesener EGFR-Mutation zugelassen*
Perez-Moreno MA et al, 2014 [21] Systematic review of efficacy and	**1. Fragestellung** • to evaluate the efficacy and safety of pemetrexed therapy in adult patients with advanced stage NSCLC. Specific objectives were to evaluate the efficacy of pemetrexed in NSCLC in each of the approved indications first-line induction, maintenance and second-line), according to histology (squamous/epidermoid adenocarcima or large cell) and to assess safety according to concomitant therapy administered.

safety of pemetrexed in non-small-cell-lung cancer	**2. Methodik** ***Population:*** NSCLC, Population: age 18 years or older patients ***Intervention:*** *pemetrexed* ***Komparator:*** *Other available therapies* ***Endpunkte*:** Nicht vorab spezifiziert ***Suchzeitraum:*** 04/ 2004 is 04/ 2012 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 5 (3541), nur RCTs ***Qualitätsbewertung der Studien:*** specific assessment scales, Critical Appraisal Skills Program (CASP) adapted for CASP Spain
	3. Ergebnisdarstellung Eingeschlossene RCTs in Metaanalyse: nur first line, Studienqualität moderate bis high In first-line induction, treatment with pemetrexed associated with a platinum was similar in terms of efficacy to other alternative chemotherapy regimens, except in patients with non-squamous histology, in whom survival was higher in the experimental group. In maintenance treatment, greater efficacy was seen with pemetrexed in patients with nonsquamous histology. In second-line treatment, there were no significant differences in terms of efficacy and safety for pemetrexed treatment versus other chemotherapy options. The most frequent adverse reactions were: hematological, gastrointestinal and neurological. All were significantly less frequent with pemetrexed versus other alternative therapies, except for liver toxicity.

Table 5 Efficacy results of PMX in NSCLC

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

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

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

* Patients with Complete response + Partial responsel + stable disease

Disease control (6 weeks)

4. Anmerkungen/Fazit der Autoren

Due to the high degree of uncertainty as to its efficacy in certain subgroups of patients, including conflicting data; to its recent incorporation, and therefore lack of safety data in the medium and long term, and the high budgetary impact of its incorporation into health systems, it seems reasonable to optimize its use, identifying those patients who may benefit most.

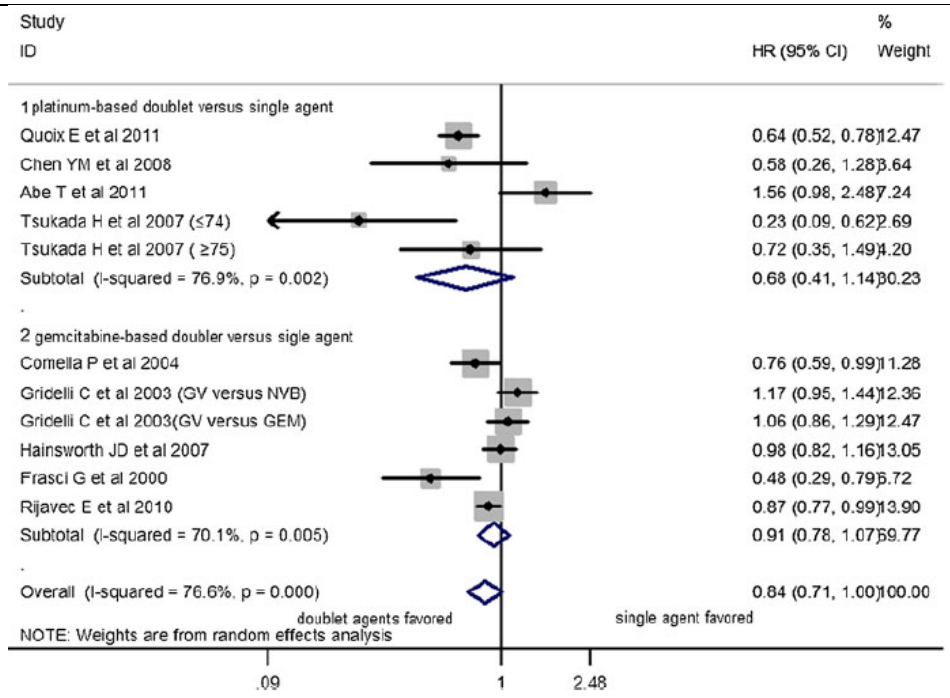
Qi WX et al, 2012 [22]

Doublet versus single cytotoxic agent

1. Fragestellung

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

as first-line treatment for elderly patients with advanced non-small-cell lung cancer: a systematic review and meta-analysis	**2. Methodik** ***Population**:* elderly (older than 65 years) patients with advanced non-small-cell lung cancer. First-line **Interventionen**: doublet cytotoxic agents ***Komparator**:* single third-generation cytotoxic agent ***Endpunkte**:* OS, TTP, ORR, Toxicity ***Methode**:* systematic review and meta-analysis of RCTs ***Suchzeitraum**:* 1980-2011 ***Anzahl eingeschlossene Studien/Patienten** (Gesamt):* 10 (n= 2 510)
	3. Ergebnisdarstellung Table 1 Baseline characteristics of the eight trials comparing doublet with single agent for elderly patients with advanced NSCLC References | Years | Patient age | Chemotherapy regimens | No. of patients | Median TTP (months) | Median PFS (months) | Median OS (months) | 1-year SR (%) | Jadi score Quoix et al. [18] (IFCT-0501) | 2011 | ≥70 | CBP AUC = 6 d1 + PTX 90 mg/m², d1,8,15 iv q.4.w. | 225 | NA | 6.0 | 10.3 | 44.5 | 3 NVB 25 mg/m², d1,8 ivq.3.w. or GEM 1,150 mg/m², d1,8 iv q.3.w. | 226 | NA | 2.8 | 6.2 | 25.4 Chen et al. [19] | 2008 | ≥70 | NVB 22.5 mg/m² iv, d1,8 + DDP 50 mg/m² iv d1 q.3.w. | 34 | 5.2 | NA | 11.3 | 47.2 | 3 NVB 25 mg/m², d1,8 iv q.3.w. | 31 | 3.1 | NA | 12 | 50.9 Comella et al. [20] | 2004 | ≥70 or poor performance status | GEM 1,000 mg/m² iv, d1,8 + NVB 25 mg/m²,d1,8 iv q.3.w. | 68 | NA | NA | 9.7 | 32 % | 3 GEM 1,000 mg/m² iv, d1,8 + PTX 80 mg/m² iv, d1,8 q.3.w. | 65 | NA | NA | 9.4 | 44 % GEM 1,200 mg/m²iv, d1,8,15 q.4.w. | 68 | NA | NA | 5.1 | 29 % PTX 100 mg/m² iv, d1,8,15 q.4.w. | 63 | NA | NA | 6.4 | 25 % Gridelli et al. [7] (MILES) | 2003 | ≥70 | GEM 1,000 mg/m² iv, d1,8 + NVB 25 mg/m² iv, d1,8 q.3.w. | 232 | 19 weeks | NA | 30 weeks | 30 | 3 GEM 1,200 mg/m² iv, d1,8 q.3.w. | 233 | 17 weeks | NA | 28 weeks | 28 GEM 1,000 mg/m² iv, d1,8 + NVB 25 mg/m² iv, d1,8 q.3.w. | 232 | 19 weeks | NA | 30 weeks | 30 NVB 30 mg/m² iv, d1,8q.3.w. | 233 | 18 weeks | NA | 36 weeks | 38 Hainsworth et al. [21] | 2007 | >65 or poor performance status | GEM 800 mg/m² iv, d1,8,15 + TXT 30 mg/m² iv, d1,8,15 q.4.w. | 174 | 4.8 | NA | 5.5 | 26 % | 3 TXT 36 mg/m² iv, d1,8,15 q.4.w. | 171 | 2.9 | NA | 5.1 | 24 % Frasci et al. [22] | 2000 | ≥70 | GEM 1,200 mg/m² iv, d1,8 + NVB 30 mg/m² iv, d1,8 q.3.w. | 60 | NA | NA | 29 weeks | 30 % | 3 NVB 30 mg/m² iv, d1,8 q.3.w. | 60 | NA | NA | 18 weeks | 13 % Rijavec et al. [23] | 2010 | ≥70 | TXT 35 mg/m² iv, d1,8,15 + GEM 800 mg/m² iv, d1,8,15 q.4.w. | 36 | 3.9 | NA | 7.2 | NA | 2 TXT 35 mg/m² iv, d1,8,15q4.w. | 33 | 7.4 | NA | 7.9 | NA Kampeanis et al. [24] | 2010 | ≥70 | TXT 30 mg/m² iv, d1,8 + GEM 900 mg/m² iv, d1,8 q.3.w. | 49 | 3.17 | NA | 15.9 | NA | 2 GEM 1,200 mg/m² iv, d1,8 q.3.w. | 47 | 2.53 | NA | 12.2 | NA Tsukada et al. [25] | 2007 | ≥70 | TXT 20 mg/m² iv, d1,8,15 + DDP 25 mg/m² iv, d1,8,15 q.4.w. | 63 | NA | NA | NA | NA | 2 TXT 25 mg/m² iv, d1,8,15 q.4.w. | 63 | NA | NA | NA | NA Abe et al. [26] | 2011 | ≥70 | TXT 20 mg/m² iv, d1,8,15 + DDP 25 mg/m² iv, d1,8,15 q.4.w. | 139 | NA | NA | 13.3 | NA | 2 TXT 60 mg/m² iv, d1 q.3.w. | 137 | NA | NA | 17.3 | NA *CBP* carboplatin, *NVB* vinorelbine, *PTX* paditaxel, *DDP* cisplatin, *GEM* gemcitabine, *TXT* docetaxel, *PFS* progression-free survival, *TTP* time to progression, *OS* overall survival, *NA* not available **Overall survival (9 trials):** no statistically significant difference, HR of 0.84 (95% CI = 0.71–1.00, p = 0.053, I^2=76.6%)



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

TTP (3 trials):

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

ORR (10 trials):

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

Toxicity:

More incidences of grade 3 or 4 anemia, thrombocytopenia, and neurotoxicity were observed with doublet therapy. With respect to the risk of grade 3 or 4 neutropenia and nonhematologic toxicities such as diarrhea, fatigue, nausea, and vomiting, equivalent frequencies were found between the two groups

	4. Anmerkungen/Fazit der Autoren Our meta-analysis showed that doublet therapy was superior to single-agent therapy as first-line treatment for elderly patients with advanced NSCLC in terms of OS, TTP, ORR, and 1-year SR, but more hematologic toxicities and neurotoxicity were observed with doublet therapy. Due to significant heterogeneity between randomized trials, we performed a subgroup analysis based on different chemotherapy regimens. Similar results were found in platinum-based doublet therapy, although the OS benefit with doublet therapy was not significant. Furthermore, gemcitabine-based doublet significantly increased ORR compared with single agent, but it did not translate into an increase in survival benefit. Platinum-based doublet therapy might be considered as first-line treatment for older patients to improve efficacy, but the optimal drug dosage and treatment schedule should be investigated in future prospective clinical trials. Gemcitabine-based doublet therapy could be considered for elderly patients who were not suitable for platinum-based chemotherapy due to its tendency to improve OS and 1-year SR.
Russo A et al, 2009 [23] Gemcitabine-based doublets versus single-agent therapy for elderly patients with advanced nonsmall cell lung cancer: a Literature-based Meta-analysis	**1. Fragestellung** To assess the efficacy and tolerability of **gemcitabine-based doublets** compared with **single-agent chemotherapy** for elderly patients with NSCLC
	2. Methodik **Population**: elderly patients with stage IIIB/IV NSCLCs (individuals ages 65 through 79 years). First-line **Intervention**: gemcitabine-based doublets **Komparator**: third generation single-agent chemotherapy (vinorelbine, docetaxel, and paclitaxel) **Endpunkt**: Survival, ORR, toxicity **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: 1966-2008 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 4 (n= 1.436)
	3. Ergebnisdarstellung **1-year survival**: no statistically significant difference (OR, 0.78; 95% CI, 0.57-1.06 [p=0.169]) **Overall response**: statistically significant difference in favor of doublets (OR, 0.65; 95% CI, 0.51-0.82 [p <0 .001]). **Toxicity**: gemcitabine-based doublets were associated with increases in thrombocytopenia (OR, 1.76; 95% CI, 1.12-2.76 [p=0.014]), but not in grade 3 or 4 hematologic or nonhematologic toxicities

	4. Anmerkungen/Fazit der Autoren Gemcitabine-based doublets appeared to be effective and feasible compared with single agents in the treatment of elderly patients with advanced NSCLC who were not suitable for full-dose, platinum-based chemotherapy ***5. Hinweise durch FB Med*** • *Keine Beschreibung zur Evaluation der Qualität der eingeschlossenen Studien* • *Keine Angaben zu Interessenskonflikten*
Shen et al, 2014 [24] Comparison between cisplatin plus vinorelbine and cisplatin plus docetaxel in the treatment of advanced non-small-cell lung cancer: A meta-analysis of randomized controlled trials	**1. Fragestellung** To compare the VC and DC regimens in the first-line treatment of advanced NSCLC
	2. Methodik ***Population*:** The patients involved were required to have pathological or cytological confirmation of advanced (stage IIIB/IV) NSCLC, with a performance status of 0-2 on the World Health Organization (WHO) scale, or a Karnofsky performance status of ≥80%. ***Intervention*:** cisplatin plus vinorelbine (VC) ***Komparator*:** cisplatin plus docetaxel (DC) ***Endpunkte*:** 1‑year survival rate , 2‑year survival rate , safety ***Suchzeitraum*:** bis Mai 2013 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 9 RCTs (1 886) ***Qualitätsbewertung der Studien:*** Jadad Score **Heterogenitätsuntersuchungen:** Wurden durchgeführt

	3. Ergebnisdarstellung Patients receiving DC therapy exhibited a significantly higher response rate [relative risk (RR)=0.83, 95% CI: 0.73‑0.95 and P=0.007] and 2‑year survival rate (RR=0.65, 95% CI: 0.50‑0.84 and P=0.001). However, the 1‑year survival rate for the two cisplatin‑based regimens were comparable (RR=0.90, 95% CI: 0.81‑1.01 and P=0.07). Patients receiving the VC regimen more frequently developed grade 3¼4 leucopenia, anemia and vomiting, whereas those receiving DC chemotherapy were more prone to grade 3¼4 diarrhea. The incidence of grade 3¼4 neutropenia, thrombocytopenia and nausea were similar between the two arms. In conclusion, our study indicated that DC is superior to the VC regimen in terms of tumor response rate, 2‑year survival rate and safety for the first‑line treatment of advanced NSCLC.
	4. Anmerkungen/Fazit der Autoren In conclusion, our study indicated that DC is superior to the VC regimen in terms of tumor response rate, 2-year survival rate and safety for the first-line treatment of advanced NSCLC. **Limits:** Our study was limited by the number and quality of the available RCTs. Although it may be difficult for phase II studies to produce reliable survival data, no significant heterogeneity was observed in the response rate or in the 1- and 2-year survival rates among the trials included in the analysis. This result of the 2-year survival analysis supports the decision to include all randomized phase II or III trials with prospectively recorded 2-year survival data. Furthermore, the survival data at 2 years of follow-up and some adverse effects were lacking in several trials, which may have led to a biased estimate.
Soria JC et al, 2013 [25] Systematic Review and meta-analysis	**1. Fragestellung** To further assess the efficacy (in terms of OS and PFS) and toxicity of **bevacizumab** used in combination with platinum-based chemotherapy, compared with **chemotherapy** alone, in the first-line treatment of patients with advanced NSCLC

of randomised, phase II/III trials adding Bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer	**2. Methodik** **Population:** patients with inoperable locally advanced (stage IIIB), recurrent or metastatic NSCLC **Intervention:** first-line bevacizumab plus platinum-based chemotherapy **Komparator:** chemotherapy alone (platinum-based) without bevacizumab **Endpunkte:** OS, PFS **Suchzeitraum:** bis 04/ 2009 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 4 Phase II und III Studien (2 194) **Qualitätsbewertung der Studien:** The quality of trials and the risk of bias were assessed by considering randomisation methods, stratification factors, blinding, follow-up and intention-to-treat analysis. **Heterogenitätsuntersuchungen:** Wurde durchgeführt

3. Ergebnisdarstellung

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

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

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

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

Overall survival (4 trials, 2.194 patients):
statistically significant difference in favor of bevacizumab plus chemotherapy, compared with chemotherapy alone, with HR of 0.90 (95% CI 0.81, 0.99; p = 0.03, I^2=0%). No significant difference between the two Bevacizumab doses (7.5 mg, 15 mg).
PFS (4 trials, 2.194 patients):
statistically significant difference in favor of bevacizumab plus chemotherapy, compared with chemotherapy alone HR of 0.72 (95% CI 0.66, 0.79; P < 0.001).
Toxicity:
Bevacizumab significantly increased the risk of grade ≥3 events of proteinuria (OR 4.81; 95% CI 2.28, 10.1), hypertension (OR 3.69; 95% CI 2.49, 5.47), haemorrhagic events (OR 2.67; 95% CI 1.63, 4.39), neutropenia (OR 1.53; 95% CI 1.25, 1.87) and febrile neutropenia (OR 1.72; 95% CI 1.01, 2.95), compared with chemotherapy alone

	4. Anmerkungen/Fazit der Autoren The effect on OS was greater in adenocarcinoma, compared with other histological types, while that on OS and PFS was greater in patients with a loss in body weight of ≤5%, compared with >5%. In conclusion, this meta-analysis of randomised studies indicates that bevacizumab significantly prolonged OS and PFS when added to standard platinum-based chemotherapy as first-line therapy in patients with advanced NSCLC, with no unexpected toxicity patterns being evident. **Limits:** Our analysis is limited by its use of summary data rather than data from the individual patients from each trial.
Wang F et al, 2011 [26] Gefitinib Compared with Systemic Chemotherapy as First-line Treatment for Chemotherapy-naive Patients with Advanced Non-small Cell Lung Cancer: A Meta-analysis of Randomised Controlled Trials	**1. Fragestellung** To define the efficacy of gefitinib in chemotherapy-naive patients with advanced non-small cell lung cancer.
	2. Methodik ***Population***: Chemotherapy-naive patients with NSCLC ***Intervention:*** Gefitinib therapy as first-line ***Komparator:*** Conventional therapy ***Endpunkt:*** PFS, OS ***Methode:*** systematic review and meta-analysis of RCTs ***Suchzeitraum:*** up to 2011 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 7 (n=4 656)

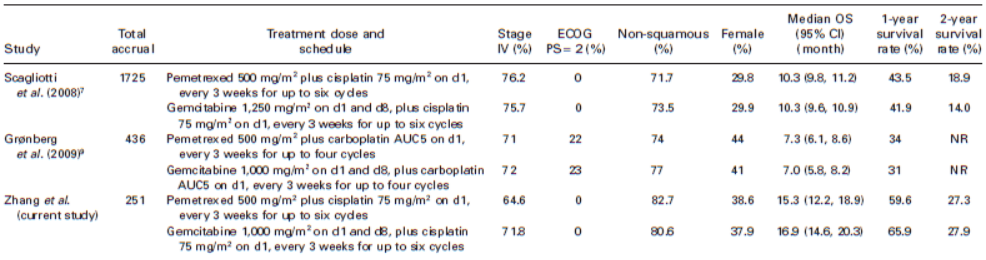
	3. Ergebnisdarstellung Gefitinib monotherapy versus platinum-doublet chemotherapy (4 Asian trials) Gefitinib combined with systemic chemotherapy (2 trials, most patients of with ethnicity) Gefitinib sequential therapy after chemotherapy (1 Asian trail) <u>OS</u> • Patients with lung adenocarcinoma: statistically significant difference in favor of gefitinib monotherapy compared to chemotherapy. HR 0.89 (0.81, 0.99); p = 0.03 • EGFR mutant treated with gefitinib monotherapy: no statistically significant difference • Combination of conventional chemotherapy with gefitinib: no statistically significant difference <u>PFS</u> • EGFR mutant treated with gefitinib monotherapy: statistically significant difference in favor of gefitinib monotherapy compared to chemotherapy HR 0.43 (0.32, 0.58) (p < 0.001) • Patients with lung adenocarcinoma: statistically significant difference in favor of gefitinib monotherapy compared to chemotherapy HR 0.71 (0.60, 0.83) (p < 0.001) • Patients without EGFR mutant: statistically significant difference in favor of chemotherapy compared to gefitinib monotherapy. HR 2.16 (1.17, 3.99) p = 0.01 • Patients with lung non-adenocarcinoma: no statistically significant difference
	4. Anmerkungen/Fazit der Autoren First-line treatment with gefitinib conferred prolonged progression-free survival than treatment with systemic chemotherapy in a molecularly or histologically defined population of patients with non-small cell lung cancer, and improved survival in the subgroup of patients with lung adenocarcinoma. ***5. Hinweise durch FB Med:*** • *EGFR-TKIs nur bei nachgewiesener EGFR-Mutation zugelassen*
Xu C et al, 2012 [27] Can EGFR-	**1. Fragestellung** We aimed to determine whether patients could be treated with **TKIs** based on clinical factors in the first-line setting

TKIs be used in first line treatment for advanced non-small cell lung cancer based on selection according to clinical factors? – A literature-based meta-analysis	**2. Methodik** ***Population**:* IIIB/IV or post-operational recurrent NSCLC (including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma) patients. First-line ***Intervention**:* gefitinib, erlotinib monotherapy ***Komparator**:* chemotherapy (mono or doublet) ***Endpunkt**:* OS, PFS, ORR ***Methode**:* systematic review and meta-analysis of RCTs ***Suchzeitraum**:* bis 2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 10 (n=3.045) **Qualitätsbewertung der Primärstudien:** k.A.
	3. Ergebnisdarstellung **Table 1 Characters of the eligible trials** Unselected trials: Four studies of randomized NSCLC patients were based on no particular patient criteria in the first-line setting. Among them, three used gemcitabine, vinorelbine, or paclitaxel plus carboplatin. First line – unselected patients • **Overall survival**: statistically significant difference in favor of chemotherapy. HR 1.35 [95% CI, 1.13–1.61] • **PFS**: statistically significant difference in favor of chemotherapy. HR 1.29 [95% CI, 1.00–1.66] • **Response rate**: statistically significant difference in favor of chemotherapy. RR 3.52 [95% CI, 2.41–5.15]
	4. Anmerkungen/Fazit der Autoren

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

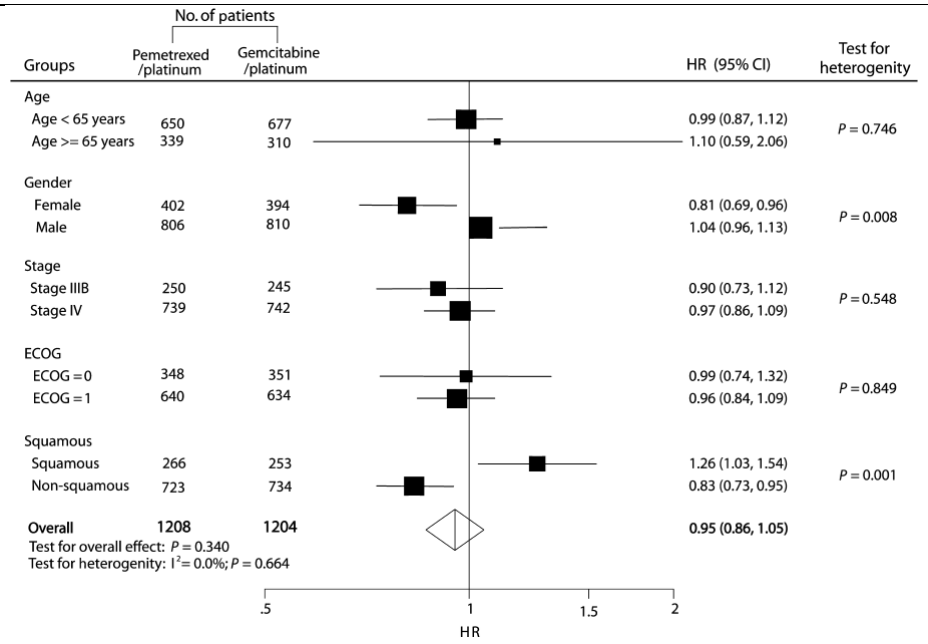
	Our meta-analysis indicates that among NSCLC patients, advanced NSCLC patients with EGFR gene mutations would benefit most from TKI treatment, especially in the first-line setting. Nevertheless, EGFR-TKI treatment is justified for patients with unknown EGFR status, those who cannot tolerate chemotherapy owing to advanced age or who have poor performance status, and those with other medical conditions, when selected according to clinical factors. ***6. Hinweise durch FB Med:*** • *EGFR-TKIs nur bei nachgewiesener EGFR-Mutation zugelassen*
Yu Y et al, 2012 [28] Non-platinum regimens of gemcitabine plus docetaxel versus platinum-based regimens in first-line treatment of advanced non-small cell lung cancer: a	**1. Fragestellung** The aim was to compare the efficacy and toxicity of **gemcitabine plus docetaxel (GD)** with **platinum-based regimens** in patients with untreated advanced non-small cell lung cancer (NSCLC).
	2. Methodik **Population**: cytologically or pathologically confirmed of NSCLC and in clinical Ill-IV stage and patients must be chemotherapy naive **Intervention**: gemcitabine plus docetaxel (GD regimens) **Komparator**: cisplatin or carboplatin combined with a cytotoxic drug (platinum-based regimens) **Endpunkt**: OS, TTP, ORR, toxicity **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: up to 2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 9 (n=2 658)

meta-analysis on 9 randomized controlled trials	**3. Ergebnisdarstellung** **Overall survival (9 trials, 2658 patients):** no statistically significant difference, no heterogeneity ***TTP (5 trials):*** statistically significant difference in favor of platinum-based regimens (HR = 1.12, 95% CI= 1.02-1.24, p = 0.02) ***Response rate (8 trials):*** statistically significant difference in favor of platinum-based regimens (RR = 0.86, 95% CI= 0.74-D.99, p = 0.03) ***Toxicity****:* GD induced less grade 3-4 nausea/vomiting, anemia, neutropenia and febrile neutropenia (RR = 0.36, 95% CI = 0. 15-0.86, p = 0.02; RR = 0.35, 95% CI = 0.23-0.53, p = 0.00; RR = 0.68, 95% CI = 0.52-0.88, p = 0.003; RR = 0.53, 95% CI = 0.34-0.82, p = 0.004. respectively). a Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio IV, Fixed, 95% CI | Year Georgoulias2001 0.00019996 0.10135436 16.8% 1.00 [0.82, 1.22] 2001 Georgoulias2005 -0.00618814 0.09191059 20.4% 0.99 [0.83, 1.19] 2005 Pujol2005 -0.10412747 0.12885312 10.4% 0.90 [0.70, 1.16] 2005 Katakami2006 0.19777472 0.22117603 3.5% 1.22 [0.79, 1.88] 2006 Binder2007 -0.01399402 0.18963025 4.8% 0.99 [0.68, 1.43] 2007 Rigas2008 0.02449031 0.07195241 33.3% 1.02 [0.89, 1.18] 2008 Novello2009b 0.5577347 0.22220667 3.5% 1.75 [1.13, 2.70] 2009 Novello2009a 0.34154842 0.23948491 3.0% 1.41 [0.88, 2.25] 2009 Rubio2009 0.07451164 0.1985865 4.4% 1.08 [0.73, 1.59] 2009 Total (95% CI) 100.0% 1.04 [0.96, 1.12] Heterogeneity: Chi² = 9.33, df = 8 (P = 0.32); I² = 14% Test for overall effect: Z = 0.85 (P = 0.39) Hazard Ratio IV, Fixed, 95% CI 0.2 0.5 1 2 5 Favours GD Favours Platinum-based Fig. 2 The efficacy meta -analysis between gemcitabine plus docetaxel (GO) and platinum-based regimens. a The pooled HR for overall did not display a difference between the two groups (HR = 1.04. 95% CI = 0.96-1.1 2. *p* = 0.39).
	4. Anmerkungen/Fazit der Autoren In our meta-analysis, we found that the efficacy was comparable between GD regimens and platinum-based regimens according to overall survival and 1-year survival. Although platinum-based regimen had an advantage in TTP and ORR, the advantage was lost when the two trials used sequential regimens were removed.
Zhang et al, 2012 [29] Pemetrexed plus platinum or gemcitabine plus platinum for advanced	**1. Fragestellung** To systematically evaluate **pemetrexed/platinum** as first line treatment for advanced NSCLC.
	2. Methodik ***Population****:* patients with stage IIIB or stage IV NSCLC. First-line

non-small cell lung cancer: final survival analysis from a multicentre randomized phase II trial in the East Asia region and a meta-analysis	***Intervention**:* pemetrexed/platinum ***Komparator**:* gemcitabine/platinum ***Endpunkte**:* OS, toxicity ***Methode***: systematic review and meta-analysis of RCTs ***Suchzeitraum***: up to 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 3 (n= 2 412)
	3. Ergebnisdarstellung **Table 4** Characteristics of the trials included in the meta-analysis  **Overall survival**: • Overall population: no statistically significant difference • Female population: statistically significant difference in favor of pemetrexed/platinum (HR 0.81; 95% CI 0.69–0.96, significant heterogeneity) • Non squamous cell lung cancer: statistically significant difference in favor of pemetrexed/platinum (HR 0.83; 95% CI 0.73–0.95, significant heterogeneity) • Squamous cell lung cancer:statistically significant difference in favor of gemcitabine/platinum (HR 1.26; 95% CI 1.03–1.54, significant heterogeneity)

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

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

	 Pooled treatment effect on overall survival within the major patient subgroups, as determined by meta-analysis. ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval. **Toxicity**: pemetrexed-platinum treatment was associated with significantly lower ORs for leukopenia (OR 0.43; 95% CI 0.29-0.65; p < 0.0001), thrombocytopenia (OR 0.28; 95% CI 0.21–0.37; p < 0.001) and neutropenia (OR 0.57; 95% CI 0.45–0.74; p < 0.001).
	4. Anmerkungen/Fazit der Autoren The meta-analysis confirmed that the histological subtype of lung cancer is an important predictor of treatment efficacy.
Zhang JW et al, 2014 [30] The impact of both platinum-based chemotherapy and EGFR-TKIs on overall survival of advanced non—small cell lung cancer	**1. Fragestellung** To understand the impact of PBC and EGFR-TKIs on NSCLC prognosis, we evaluated the association between the receipt of both regimens and overall survival (OS) evaluate the association between the receipt of both regimens and overall survival (OS)
	2. Methodik ***Population:*** *advanced NSCLC* ***Interventionen:*** • platinum-based doublet chemotherapy (PBC) • epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) ***Komparator:*** *Plazebo*

***Endpunkte*:**

OS

Suchzeitraum:

2001 bis 02/2012

Anzahl eingeschlossene Studien/Patienten (Gesamt):

15 (11 456)

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

Qualitätsbewertung der Studien:

k.A

Heterogenitätsuntersuchungen:

k.A.

3. Ergebnisdarstellung

Table 1. Characteristics of the trials included in the analysis

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

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

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

Caucasian populations (r = 0.116, P = 0.588).

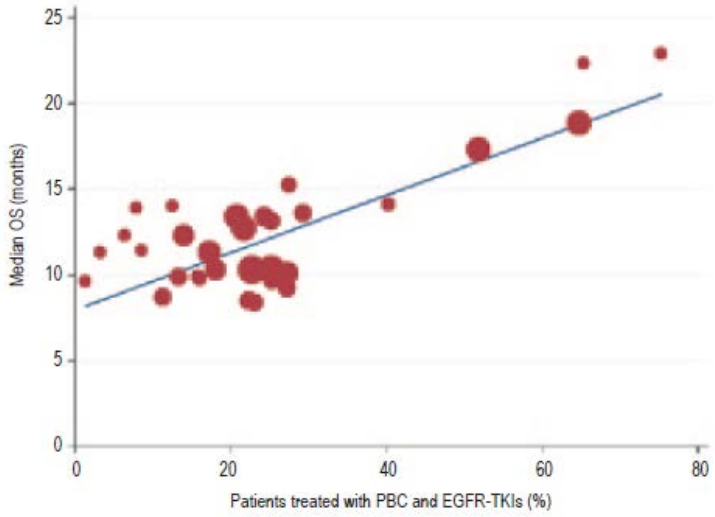


Figure 2. Linear regression curve showing positive correlation between the percentage of patients treated with both PBC and EGFR-TKIs during the course of treatment and the OS (r = 0.797, R2 = 0.636, P < 0.001) in all selected trials. Mathematic equation of regression (based on a weighted model): OS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

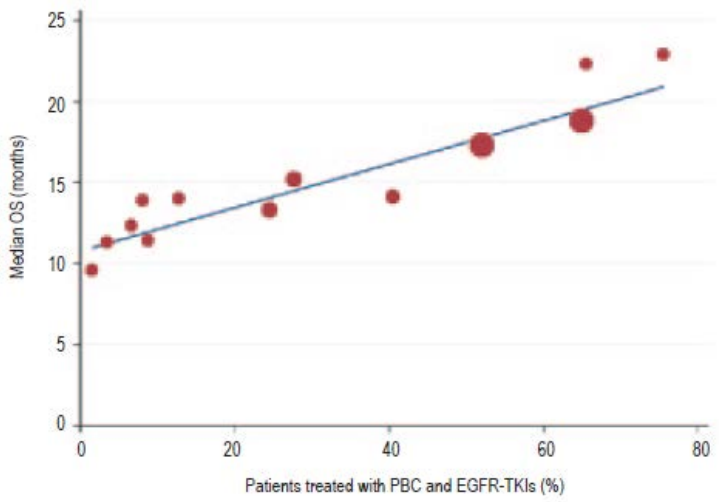


Figure 3. Linear regression curve showing positive correlation between the percentage of patients treated with both PBC and EGFR-TKIs during the course of treatment and the OS (r = 0.936, R2 = 0.876, P < 0.001) in Asian trials. Mathematic equation of regression (based on a weighted model): OS (months)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

4. Anmerkungen/Fazit der Autoren

	These results suggest that treatment with PBC and EGFR-TKIs may provide a survival benefit to patients with advanced NSCLC, highlighting the importance of having both modalities available for therapy.
Zhong N et al, 2013 [31] Chemotherapy Plus Best Supportive Care versus Best Supportive Care in Patients with Non-Small Cell Lung Cancer: A Meta-Analysis of Randomized Controlled Trials	**1. Fragestellung** We performed a systematic review and meta-analysis to evaluate the effects of chemotherapy plus BSC versus BSC alone on survival of patients with NSCLC.
	2. Methodik ***Population:*** patients with NSCLC (Stage III/IV or advanced) ***Intervention:*** chemotherapy and BSC ***Komparator:*** BSC alone ***Endpunkte*:** OS or treatment-related mortality ***Suchzeitraum:*** Nicht angegeben ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 16 RCTs (4 135) ***Qualitätsbewertung der Studien:*** The quality of the trials was also assessed by pre-defined criteria using Jadad score ***Heterogenitätsuntersuchungen:*** Durchgeführt (Sensitivitätsanalysen)

3. Ergebnisdarstellung

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

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

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

Ergebnisse zum Overall Survival:

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

Ergebnisse zu Nebenwirkungen/Unerwünschten Ereignissen:

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

	4. Anmerkungen/Fazit der Autoren Chemotherapy plus BSC increased the OS and reduced the 6-month, 12-month, and 2-year mortality of NSCLC patients. Since nearly all the trials in our study included patients with stage III/IV disease or advanced NSCLC, the conclusions should be applicable only to patients with advanced or metastatic NSCLC. **Limits:** First, inherent assumptions were made for all meta-analyses, because the analyses used pooled data,either published or provided by the individual study; individual patient data or original data were unavailable, which did not allow us to perform more detailed analyses and to obtain more comprehensive results. Second, treatments given in those trials included second generation, third generation, and the fourth generation chemotherapy regiments, which prevented us from exploring the association between the type of chemotherapy and survival outcomes. Third, heterogeneity among the trials is another limitation of our study. We applied a random-effect model that took possible heterogeneity into consideration and performed subgroup analyses based on several important factors to further explore the source of heterogeneity. Fourth, data on progression-free survival were rarely available in these trials; therefore, no conclusions could be drawn. ***5. Hinweise der FBMed*** • *Kein Suchzeitraum angegeben* • *Es wird nicht dargestellt, welche Interventionen unter BSC subsummiert waren*

Scottish Intercollegiate Guidelines Network (SIGN), 2014 [32] Management of lung cancer	**1. Fragestellung** 13. In patients with NSCLC (locally advanced or metastatic disease), what is the most effective first line systemic anticancer therapy (chemotherapy, targeted therapy, EGFR Inhibitors)? Outcomes: Overall survival, progression-free survival, toxicity, quality of life
	2. Methodik ***Grundlage der Leitlinie:*** systematische Recherche und Bewertung der Literatur, Entwicklung durch multidisziplinäre Gruppe von praktizierenden klinischen ExpertInnen, Expertenreview, öffentliche Konsultation ***Suchzeitraum:*** 2005 - 2012 ***LoE/GoR:*** Vgl. *Anlage 1* dieser Synopse ***Sonstige methodische Hinweise*** • *keine Empfehlung zur gesuchten Indikation* • *Hintergrundtext (siehe unten) ohne Quellenangaben*
	Empfehlungen ***First line treatment*** <u>Kernempfehlung</u> Systemische Therapie: First line single agent tyrosine kinase inhibitors should be offered to patients with advanced NSCLC who have a sensitising *EGFR* mutation. Adding combination systemic anticancer therapy to a TKI confers no benefit and should not be used. (A) <u>Molecular testing of predictive biomarkers in patients with NSCLC</u> … Other molecular abnormalities which may be tested for include anaplastic lymphoma kinase (ALK) gene rearrangement …. Drugs targeting these mutations are at various stages of development. <u>First line therapy for patients with stage IIIB and IV NSCLC</u> Results from a meta-analysis and systematic review demonstrate the benefit of SACT for patients with advanced non-small cell lung cancer (absolute improvement in survival of 9% at 12 months versus control). **(LoE 1++)** Burdett S, Stephens R, Stewart L, Tierney J, Auperin A, Le Chevalier T, et al. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: A systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. J Clin Oncol 2008;26(28):4617-25. Four randomised trials of single agent SACT (gemcitabine, paclitaxel,

docetaxel and vinorelbine) versus best supportive care (including radiotherapy) in patients with advanced NSCLC reveal a trend to improved quality of life with increased survival in three of the four studies. **(LoE 1+)**

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

Ranson M, Davidson N, Nicolson M, Falk S, Carmichael J, Lopez P, et al. Randomized trial of paclitaxel plus supportive care versus supportive care for patients with advanced non-small-cell lung cancer. J Natl Cancer Inst 2000;92(13):1074-80.

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

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

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

Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced nonsmall- cell lung cancer. N Engl J Med 2002;346(2):92-8.

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

Goffin J, Lacchetti C, Ellis PM, Ung YC, Evans WK. First-line systemic chemotherapy in the treatment of advanced non-small cell lung cancer: A systematic review. J Thorac Oncol 2010;5(2):260-74.

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

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

Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapynaive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26(21):3541-51.

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

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

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

EGFR tyrosine kinase inhibitors (TKIs) are effective as first line treatment of advanced NSCLC in patients with sensitising *EGFR* mutations. The optimum treatment is orally delivered single agent therapy. TKIs significantly increased progression-free survival (PFS) (HR 0.45, 95% CI 0.36 to 0.58, P<0.0001) over SACT.230 In a European trial, the median PFS was 9.4 months in the erlotinib (TKI) group and 5.2 months in the doublet SACT group, (HR 0.42,

	95% CI 0.27 to 0.64), p<0.0001. **(LoE 1+)** Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13(3):239-46. <u>Recommendations</u> • First line single agent tyrosine kinase inhibitors should be offered to patients with advanced NSCLC who have a sensitising *EGFR* mutation. Adding combination systemic anticancer therapy to a TKI confers no benefit and should not be used. (A) • Patients who have advanced disease, are performance status 0-1, have predominantly nonsquamous NSCLC and are *EGFR* mutation negative should be offered combination systemic anticancer therapy with cisplatin and pemetrexed. (A) • All other patients with NSCLC should be offered combination systemic anticancer therapy with cisplatin/carboplatin and a third generation agent (docetaxel, gemcitabine, paclitaxel or vinorelbine). (A) • Platinum doublet systemic anticancer therapy should be given in four cycles; it is not recommended that treatment extends beyond six cycles. (A)
Alberta Provincial Thoracic Tumour Team, 2013 [33] Non-small cell lung cancer stage IV	**Fragestellung** What is the recommended first-line therapy for patients with stage IV non-small cell lung cancer (NSCLC)? What is the role for EGFR tyrosine kinase inhibitors in first-line treatment of patients with stage IV NSCLC?
	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 RECOMMENDATIONS 1. Whenever possible, patients with advanced non-small cell lung cancer (NSCLC) should be considered for eligibility in ongoing clinical trials. 2. Patients with a solitary metastasis as the basis for stage IV disease with good performance status and otherwise resectable and limited thoracic disease may benefit from more aggressive management, including surgical intervention and/or stereotactic radiotherapy. 3. Combination chemotherapy consisting of a platinum-based doublet is the standard of care for first-line treatment of advanced NSCLC (except for EGFR-positive patients; see recommendation 6 below). The combination of three chemotherapeutic agents for the first-line treatment of advanced NSCLC is not routinely recommended based on current evidence. 4. Therapy should be continued for four cycles in most patients, and not more than six cycles in responding patients. 5. Acceptable alternatives to combination chemotherapy include non-platinum doublets or monotherapy: • For patients with a borderline performance status (PS=2), single-agent chemotherapy with vinorelbine, gemcitabine, paclitaxel, docetaxel or pemetrexed (for non-squamous cell carcinoma patients only) is recommended over best supportive care alone. • For elderly patients who cannot tolerate a platinum-based combination, single-agent chemotherapy with vinorelbine, gemcitabine, docetaxel, or pemetrexed (for non-squamous cell carcinoma patients only) is associated with improved survival and quality of life when compared to best supportive care alone. However, elderly patients with a good performance status (PS=0-1) should receive combination chemotherapy with a platinum-based doublet. 6. First-line monotherapy with the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib is recommended for patients with EGFR mutation-positive NSCLC. 7. Testing for EGFR mutations should take place for all eligible patients with advanced NSCLC and adenocarcinoma (including adenosquamous) histology who are being considered for first-line therapy with gefitinib, irrespective of their gender, ethnicity, and smoking status. **Treatments for ALK-Positive Rearrangements** EML4-ALK fusion gene is present in approximately two to seven percent of such tumours, and is mutually exclusive with K-Ras and EGFR mutations.

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

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

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

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

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

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

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

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

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

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

Recently, a phase II clinical trial by Kim et al (see above) and a phase III clinical trial by Shaw et al. investigated the efficacy and safety of crizotinib; building off the results from an earlier phase I, single-arm clinical trial by Camidge et al. In the study by Kim et al, published as an abstract at the ASCO 2012 conference, patients with ALK-positive NSCLC were given 250mg BID crizotinib in three-week cycles. An ORR of 53% and 12-week DCR of 85% was observed with a median PFS of 8.5 months. Significant improvements in post-treatment pain, cough, and global QoL were reported. In the phase III clinical trial conducted by Shaw et al, also published as an abstract, this time at the ESMO 2012 conference, crizotinib was compared to standard CT for advanced NSCLC. Like before, 250mg BID crizotinib was administered to 173 patients with another 174 patients receiving either 500mg/m2 PEM (57%) or 75mg/m2 docetaxel (41%). Crizotinib prolonged PFS to median of 7.7 months from 3 months for those treated with standard CT (HR 0.49, CI 0.37-0.64, p<0.0001). The ORR was significantly higher in

	those treated with crizotinib (65% vs. 20%; p<0.0001). The OS data were still not mature. As there was significant crossover from the standard CT group to the crizotinib group it is possible that OS results may not significantly differ. That said, however, the authors believe crizotinib should be the new standard of care for individuals with ALK-positive advanced NSCLC. **117.** Shaw AT, Kim DW, Nakagawa K, et al. Phase III study of crizotinib versus pemetrexed or docetaxel chemotherapy in patients with advanced ALK-positive non-small cell lung cancer (NSCLC) (PROFILE 1007). Paper presented at: Congress of the European Society for Medical Oncology 20122012. **118.** Camidge DR, Bang YJ, Kwak EL, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol. Oct 2012;13(10):1011-1019. As a result of these, and other promising results, the US FDA have approved crizotinib for patients with ALK-positive advanced or metastatic NSCLC. **119.** Kimura H, Nakajima T, Takeuchi K, et al. ALK fusion gene positive lung cancer and 3 cases treated with an inhibitor for ALK kinase activity. *Lung Cancer.* 2012;75(1):66-72. The results of these early trials are promising, and, along with other clinical trials currently underway, may strengthen support for the role of prospective genotyping in the selection of therapy for patients with advanced NSCLC. Indeed, guidelines from the National Comprehensive Cancer Network and the European Society for Medical Oncology now recommend ALK gene rearrangement testing to better treat those patients with advanced NSCLC who are ALK-positive.
Brodowicz T et al, 2012: Third CECOG consensus on the systemic treatment of non-small-cell lung cancer [34]	**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 systemic therapy for advanced disease - first-line therapy - platinum-based chemotherapy conclusions: 1 Platin-based doublets containing a third-generation cytotoxic drug is the treatment of choice in patients with advanced NSCLC, unless platinum is contraindicated [I,A]. 2 Cisplatin might be preferred in patients with good PS. 3 Nonsquamous histology is a prerequisite for pemetrexed efficacy [I,B]. 4 Cisplatin doses of <75–80 mg/m2 every 3–4 weeks are recommended [I,B]. 5 Chemotherapy should be given for four to six cycles but stopped at disease progression [II,B]. systemic therapy for advanced disease - first-line therapy - targeted therapies bevacizumab conclusions. The addition of bevacizumab to first-line chemotherapy (either carboplatin–paclitaxel or cisplatin–gemcitabine) of advanced nonsquamous NSCLC provides benefit in patients with good PS and age < 70 [I,B]. The dose of bevacizumab may be either 7.5 or 15 mg/kg every 3 weeks depending on the chemotherapeutic backbone. systemic therapy for advanced disease - first-line therapy - targeted therapies cetuximab conclusions. Despite these results, the US Food and Drug Administration label for cetuximab does not yet include NSCLC, and the EMA did not grant its use in this indication owing to modest benefits and associated toxicity. Nevertheless, addition of cetuximab to a platinum-based chemotherapy regimen is a treatment option in advanced NSCLC [I,B]. systemic therapy for advanced disease - first-line therapy - targeted therapies EGFR tyrosine kinase inhibitors conclusions. 1 It is strongly recommended to test for EGFR-activating mutations [I,A]. 2 In the absence of EGFR-activating mutations, chemotherapy remains the treatment of choice [I,A]. 3 In patients with EGFR-activating mutations, treatment with gefitinib is the preferred treatment option [I,A]. Eastern Cooperative Oncology Group PS of two. Available data support the use of single-agent chemotherapy in patients with Eastern Cooperative Oncology Group PS of two. However, data are still insufficient to make a recommendation for or against using a combination of two cytotoxic drugs for patients with PS of two.

	treatment in the elderly - conclusions: Single-agent therapy remains a reasonable option for unfit elderly patients [I,B], although clinical evidence does not support selection of a specific first line chemotherapy drug or combination based on age alone. However, the need for enhanced supportive care should be emphasized in this patient population. targeted treatment options … 3 Patients with EML4-ALK fusion tumors benefit from specific targeted therapy against EML4-ALK fusion. The role of routinely carried out EML4-ALK fusion testing for clinical practice is awaiting the results from ongoing clinical trials. EML4-ALK fusion: The fusion gene EML4-Anaplastic Lymphoma Kinase (ALK) was first reported in NSCLC only a few years ago. Soda M, Choi YL, Enomoto M et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007; 448(7153): 561–566. A clinical dose-escalation phase I study with an oral MET and ALK inhibitor PF-02341066 showed for NSCLC patients with tumors harboring an activating ALK gene fusion an objective RR of 64% and a disease control rate of 90%. Bang Y, KE , Shaw AT, Kwak EL. Clinical activity of the oral ALK inhibitor PF-02341066 in ALK-positive patients with non-small cell lung cancer (NSCLC). J Clin Oncol (Meeting Abstracts) 2010; 28: 3. Although the ALK fusion either with EML4 or with other fusion partners is relatively infrequent in NSCLC (4%–5%), there still is a substantial number of patients who might have a significant clinical benefit from this well-tolerated therapy. Choi YL, Soda M, Yamashita Y et al. EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors. N Engl J Med 2010; 363(18): 1734–1739.
Ramnath et al, 2013 [35] Treatment of Stage III Non-small Cell Lung Cancer	Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines **1. Fragestellung** updates the published clinical trials since the last American College of Chest Physicians guidelines to make treatment recommendations for this controversial subset of patients
	2. Methodik Siehe *Socinski et al., 2013*
	Infiltrative Stage III (N2,3) Non-small Cell Lung Cancer 2.3.1. In patients with infiltrative stage III (N2,3) non-small cell lung cancer (NSCLC) and performance status 0-1 being considered for curative-intent treatment, radiotherapy alone is not recommended **(Grade 1A**) .

	2.3.2. In patients with infiltrative stage III (N2,3) NSCLC and performance status 0-1 being considered for curative-intent treatment, combination platinum-based chemotherapy and radiotherapy (60-66 Gy) are recommended (**Grade 1A**) . *Remark:* Dose escalation of radiotherapy is not recommended (except in a clinical trial). *Remark:* For patients with stage IIIB NSCLC, once daily thoracic radiotherapy plus platinum-based doublet chemotherapy is recommended. 2.3.3. In patients with infiltrative stage III (N2,3) NSCLC, performance status 0-1, and minimal weight loss being considered for curative-intent treatment, concurrent chemoradiotherapy is recommended over sequential chemoradiotherapy (**Grade 1A**) . *Remark:* We cannot currently recommend for or against induction chemotherapy (ie, before) concurrent chemo-radiotherapy, and patients should be referred for clinical trials to answer this question. *Remark:* We cannot currently recommend for or against consolidation chemotherapy (ie, after) concurrent chemo-radiotherapy, and patients should be referred to clinical trials to answer this question. 2.3.4. In patients with infiltrative stage III (N2,3) NSCLC with a complete response after treatment with concurrent chemo-radiotherapy, we suggest that prophylactic cranial irradiation should not be given (outside of a clinical trial) (**Grade 2C**) . 2.3.5. In patients with infiltrative stage III (N2,3) NSCLC and performance status 0-1 being considered for curative-intent treatment, treatment with neoadjuvant (induction) chemotherapy or chemo-radiotherapy followed by surgery is not recommended (**Grade 1C**) . 2.3.6. In patients with infiltrative stage III (N2,3) NSCLC and performance status 2 or those with substantial weight loss (. 10%), concurrent chemo-radiotherapy is suggested but with careful consideration of the potential risks and benefits (**Grade 2C**) . *Remark:* Patient-related and tumor-related factors can influence the balance of risks vs benefi ts; patient preferences should also play a significant role. 2.3.7. In patients with infiltrative stage III (N2,3) NSCLC, performance status 0-1, and minimal weight loss being considered for curative-intent treatment, a platinum-based doublet chemotherapy is suggested (**Grade 2C**). *Remark* : An optimal agent to be combined with platinum cannot be defined; one should choose a regimen with an acceptable toxicity profile for the individual patient among several combinations that have demonstrated activity when used concurrently with radiation in stage III NSCLC. 2.3.8. In patients with symptomatic infiltrative stage III (N2,3) NSCLC and either performance status 3-4, comorbidities, or disease too extensive to treat with curative intent, palliative radiotherapy is recommended. The fractionation

	pattern should be chosen based on the physician's judgment and patient's needs (**Grade 1C**). ***Adjuvant Therapy*** 4.5.3. In patients with resected NSCLC (R0) who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging and who have good performance status, adjuvant platinum-based chemotherapy is recommended (**Grade 1A**) . *Remark* : We suggest this should typically involve a doublet regimen for 3 to 4 cycles initiated within 12 weeks. 4.5.4. In patients with R0 resected NSCLC who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging, sequential adjuvant radiotherapy is suggested when concern for a local recurrence is high (**Grade 2C**) . *Remark* : Adjuvant postoperative radiotherapy reduces the incidence of local recurrence, but it is unclear whether it improves survival. *Remark:* Adjuvant chemotherapy should be used initially followed by radiotherapy; concurrent chemo-radiotherapy is not recommended (except in a clinical trial). 4.5.5. In patients with NSCLC who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging and were incompletely resected (R1,2), combined postoperative concurrent chemotherapy and radiotherapy is suggested (**Grade 2C**) . *Remark:* Incomplete resection (R1,2) does not appear to confer a survival benefit over no resection.
Socinski et al, 2013 [36] 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**

General Approach

2.1.1. In patients with a good performance status (PS) (ie, Eastern Cooperative Oncology Group [ECOG] level 0 or 1) and stage IV non-small cell lung cancer (NSCLC), a platinum-based chemotherapy regimen is recommended based on the survival advantage and improvement in quality of life (QOL) over best supportive care (BSC) **.(Grade 1A)**

Remark: Patients may be treated with several chemotherapy regimens (carboplatin and cisplatin are acceptable, and can be combined with paclitaxel, docetaxel, gemcitabine, pemetrexed or vinorelbine)

2.2.2. In patients with stage IV NSCLC and a good PS, two-drug combination chemotherapy is recommended. The addition of a third cytotoxic chemotherapeutic agent is not recommended because it provides no survival

	benefit and may be harmful. **(Grade 1A)** ***First Line Treatment*** 3.1.1.1. In patients receiving palliative chemotherapy for stage IV NSCLC, it is recommended that the choice of chemotherapy is guided by the histologic type of NSCLC **(Grade 1B).** *Remark:* The use of pemetrexed (either alone or in combination) should be limited to patients with nonsquamous NSCLC. *Remark:* Squamous histology has not been identified as predictive of better response to any particular chemotherapy agent. 3.2.1.1. In patients with known epidermal growth factor receptor (EGFR) mutations and stage IV NSCLC, first-line therapy with an EGFR tyrosine kinase inhibitor (gefitinib or erlotinib) is recommended based on superior response rates, progression-free survival and toxicity profiles compared with platinum-based doublets **(Grade 1A)** . 3.3.1.1. Bevacizumab improves survival combined with carboplatin and paclitaxel in a clinically selected subset of patients with stage IV NSCLC and good PS (nonsquamous histology, lack of brain metastases, and no hemoptysis). In these patients, addition of bevacizumab to carboplatin and paclitaxel is recommended **(Grade 1A)** . 3.3.1.2. In patients with stage IV non-squamous NSCLC and treated, stable brain metastases, who are otherwise candidates for bevacizumab therapy, the addition of bevacizumab to firstline, platinum-based chemotherapy is a safe therapeutic option **(Grade 2B)** . *Remark* : No recommendation can be given about the use of bevacizumab in patients receiving therapeutic anticoagulation or with an ECOG PS of 2. ***Special Patient Populations and Considerations*** 5.1.1. In elderly patients (age > 69–79 years) with stage IV NSCLC who have good PS and limited co-morbidities, treatment with the two drug combination of monthly carboplatin and weekly paclitaxel is recommended **(Grade 1A)** . *Remark:* In patients with stage IV NSCLC who are 80 years or over, the benefi t of chemotherapy is unclear and should be decided based on individual circumstances. 6.2.1.For patients with stage IV NSCLC with a PS of 2 in whom the PS is caused by the cancer itself, double agent chemotherapy is suggested over single agent chemotherapy **(Grade 2B)** . 6.2.2. In patients with stage IV NSCLC who are an ECOG PS of 2 or greater, it is suggested not to add bevacizumab to chemotherapy outside of a clinical trial (Grade 2B) . 7.1.1. In patients with stage IV NSCLC early initiation of palliative care is suggested to improve both QOL and duration of survival **(Grade 2B)** .

Ellis PM et al., 2014 [37] 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	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)? 4. What are the toxicities associated with gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib?
	Empfehlungen ***Recommendation 1a*** First-line therapy with an EGFR tyrosine kinase inhibitor (TKI) is not recommended in unselected (patients who have not undergone mutation testing) or clinically selected populations of patients. Available data would suggest that first-line EGFR TKI is inferior to platinum-based chemotherapy in this group of NSCLC patients. The use of clinical characteristics such as Asian ethnicity, female sex, adenocarcinoma histology and light/never smoking status is not recommended to select patients for first-line EGFR TKI therapy, as this strategy does not reliably select patients who have mutations. *Key Evidence:* Twenty-six randomized first-line studies in unselected and clinically selected populations were used to formulate this recommendation. The results of these trials showed no benefit for the use of an EGFR inhibitor in unselected and clinically selected patients **Recommendation 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 [38] 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 [39] American Society of Clinical	**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

Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer	2003.2 The current version covers treatment with chemotherapy and biologic agents and molecular markers for stage IV NSCLC and reviews literature published from 2002 through May 2009.
	2. Methodik The recommendations in this guideline were developed primarily on the basis of statistically significant improvements in overall survival (OS) documented in prospective RCTs. Treatment strategies demonstrated to improve only progression-free survival (PFS) prompted greater scrutiny regarding issues such as toxicity and quality of life. ***Suchzeitraum:*** 2002 bis 07/2008 ***GoR, LoE*** Keine Angabe in der zusammenfassenden Darstellung (vgl. Anlage 3)
	3. Empfehlungen The recommendations are designated as follows: First-line therapy recommendations begin with A, second-line recommendations with B, third-line recommendations with C, and molecular analysis recommendations with D. **First-Line Chemotherapy** In this summary, the term chemotherapy refers to any anticancer drug, regardless of its mechanism of action (ie, cytotoxic and biologic drugs are included). **Recommendation A1.** Evidence supports the use of chemotherapy in patients with stage IV non–small-cell lung cancer with Eastern Cooperative Oncology Group (ECOG)/Zubrod PS 0, 1, and possibly 2. (Note: Stage IV as defined by the International Association for the Study of Lung Cancer Lung Cancer Staging Project, for the seventh edition of the TNM Classification of Malignant Tumors.) **Recommendation A2.** In patients with PS 0 or 1, evidence supports using a combination of two cytotoxic drugs for firstline therapy. Platinum combinations are preferred over nonplatinum combinations because they are superior in response rate, and marginally superior in OS. Nonplatinum therapy combinations are reasonable in patients who have contraindications to platinum therapy. Recommendations A8 and A9 address whether to add bevacizumab or cetuximab to first-line cytotoxic therapy. **Recommendation A3.** Available data support use of singleagent chemotherapy in patients with a PS of 2. Data are insufficient to make a recommendation for or against using a combination of two cytotoxic drugs in patients with a PS of 2. **Comment.** PS is the most important prognostic factor for patients with stage

	IV NSCLC; patients with a PS of 0 to 1 live longer than patients with a PS of 2, regardless of therapy. Use of single-agent vinorelbine, docetaxel, or paclitaxel has led to improved survival in phase III comparisons versus best supportive care in patients with a PS of 0 to 2. Because of concerns about toxicity and drug tolerance, patients with stage IV NSCLC and a PS of 2 are routinely excluded from prospective trials of novel **Recommendation A4.** The evidence does not support the selection of a specific first-line chemotherapy drug or combination based on age alone. **Comment.** Clinical trial data since the 2003 update reinforce the recommendation that age alone should not be used to select chemotherapy for patients with stage IV NSCLC. Older patients may experience more toxicity from cytotoxic chemotherapy than younger patients but may garner an equal amount of benefit. The guideline emphasizes that physiologic age and PS are more important in treatment selection. **Recommendation A5.** The choice of either cisplatin or carboplatin is acceptable. Drugs that may be combined with platinum include the third-generation cytotoxic drugs docetaxel, gemcitabine, irinotecan, paclitaxel, pemetrexed, and vinorelbine. The evidence suggests that cisplatin combinations have a higher response rate than carboplatin and may improve survival when combined with third-generation agents. Carboplatin is less likely to cause nausea, nephrotoxicity, and neurotoxicity than cisplatin but more likely to cause thrombocytopenia. **Comment.** Cisplatin is slightly more effective than carboplatin but also has more adverse effects. Therefore, either is acceptable, depending on the individual. **Recommendation A6.** In patients with stage IV NSCLC, first-line cytotoxic chemotherapy should be stopped at disease progression or after four cycles in patients whose disease is not responding to treatment. Two-drug cytotoxic combinations should be administered for no more than six cycles. For patients who have stable disease or who respond to first-line therapy, evidence does not support the continuation of cytotoxic chemotherapy until disease progression or the initiation of a different chemotherapy before disease progression. **Comment.** With the advent of drugs that improve survival for patients with progressive cancer after first-line chemotherapy (ie, second-line drugs), there is renewed interest in whether initiation of a non–cross-resistant drug immediately after completion of first-line therapy may improve survival. There have been some preliminary results on such a strategy, but until more mature data are presented showing a survival benefit, these results suggest that PFS, but not OS, may be improved either by continuing an effective chemotherapy beyond four cycles or by immediately initiating alternative chemotherapy. The improvement in PFS is tempered by an increase in adverse effects from additional cytotoxic chemotherapy. Special announcement:

	The FDA approved a new indication for pemetrexed for maintenance therapy in patients with advanced NSCLC on July 2, 2009, when this guideline went to press. The data supporting this change were recently presented and were outside the scope of the comprehensive data review for this guideline. The recommendation recommendation on maintenance therapy in this guideline will be updated pending consideration of recently published relevant data. **Recommendation A7.** In unselected patients, erlotinib or gefitinib should not be used in combination with cytotoxic chemotherapy as first-line therapy. In unselected patients, evidence is insufficient to recommend single-agent erlotinib or gefitinib as first-line therapy. The first-line use of gefitinib may be recommended for patients with activating *EGFR* mutations. If *EGFR* mutation status is negative or unknown, then cytotoxic chemotherapy is preferred (see Recommendation A2). **Comment.** There is no current evidence that adding an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor to cytotoxic chemotherapy as first-line treatment is beneficial. In addition, there is no current evidence that erlotinib monotherapy is beneficial in the first-line setting in unselected patients. There is evidence that first-line gefitinib monotherapy improves PFS and has less adverse events compared with carboplatin and paclitaxel in patients of Asian ethnicity who are former or light smokers or have never smoked. In a recent trial, patients with tumors with *EGFR* mutations receiving gefitinib experienced longer PFS, and those whose tumors lacked *EGFR* mutations had longer PFS with chemotherapy. The *EGFR* mutation status of most patients' tumors, however, is negative or unknown. Current evidence is insufficient to recommend the routine use of molecular markers to select systemic treatment for patients with metastatic NSCLC (Recommendation D1). In cases in which the *EGFR* mutation status is negative or unknown, cytotoxic chemotherapy is preferred. **Recommendation A8.** Based on the results of one large phase III RCT, the Update Committee recommends the addition of bevacizumab, 15 mg/kg every 3 weeks, to carboplatin/ paclitaxel, except for patients with squamous cell carcinoma histologic type, brain metastases, clinically significant hemoptysis, inadequate organ function, ECOG PS greater than 1, therapeutic anticoagulation, clinically significant cardiovascular disease, or medically uncontrolled hypertension. Bevacizumab may be continued, as tolerated, until disease progression. **Comment.** Because of bleeding events and deaths observed in earlier clinical trials using bevacizumab for NSCLC, use of this drug was restricted in phase III testing, which informed the list of exclusion criteria in the recommendation. A recent trial suggested that there may be differences in outcomes depending on which chemotherapy regimen is combined with bevacizumab and also suggested that a lower dose of bevacizumab may be as effective as a high dose; however, OS benefit has not yet been shown from combining bevacizumab with other cytotoxic chemotherapy regimens. The duration recommendation is based on the design of RCTs of

	bevacizumab. The optimal duration of bevacizumab beyond chemotherapy has not yet been determined. **Recommendation A9.** On the basis of the results of one large phase III RCT, clinicians may consider the addition of cetuximab to cisplatin/ vinorelbine in first-line therapy in patients with an EGFR-positive tumor as measured by immuno-histochemistry. Cetuximab may be continued, as tolerated, until disease progression. **Comment.** Eligibility for this phase III RCT required that all patients have their tumor tested for EGFR expression by immunohistochemistry and that at least one tumor cell stained positive. This trial showed a benefit in OS and response rate with the addition of cetuximab to this chemotherapy doublet. The OS benefit may not directly translate to all chemotherapy regimens. The duration recommendation is based on the design of RCTs on cetuximab. However, the optimal duration of treatment with cetuximab beyond chemotherapy is not known.
de Marinis F et al, 2011 [40] 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
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Ia	Evidence from systematic reviews and meta-analysis of randomized controlled trials	A
Ib	Evidence from at least one randomized controlled trial	
IIa	Evidence from at least one controlled study without randomization	B
IIb	Evidence from at least one other type of quasi-experimental study	
III	Evidence from observational studies	
IV	Evidence from expert committee reports or experts	C

3. Empfehlungen

Platinum-based (cisplatin or carboplatin) chemotherapy is the standard treatment for adult patients with advanced NSCLC, with good peformance status (PS 0-1). Chemotherapy should be stopped at disease pragression or after 4 cycles in patients who do not obtain an objective response, and continued for maximum 6 cycles in patients achieving an objective response. Treatment options are different according to tumour histotype (squamous versus non squamous).

A. Treatment options for patients with squamous tumour
Patients with advanced squamous NSCLC are eligible for firstline platinum-based doublets with a third-generation drug, with the exception of pemetrexed.

B. Treatment options for patients with non-squamous tumours
Patients with advanced non-squamous NSCLC are eligile for first-line platinum-based doublets with a third-generation drug, including pemetrexed. Bevacizumab in combination with carboplatin plus paclitaxel or cisplatin plus gemicitabine is a further option for patients considered eligible to this therapy. Carboplatin plus paclitaxel should be considered the chemotherapy backbone [or bevacizumab. (**LoE lA GoR A)**

3.2. Question 2, Cisplatin* or *carboplatin for first-line treatment?

Several randomized trials compared cisplatin- versus carboplatin-based chemotherapy in advanced NSCLC. Those trials were lncluded in two meta-analyses. The one based on individual patient data showed a statistically slgnificant increase in objective response rate with cisplatin. Difference in overall sutvival between the two drugs did not reach statistical significance, although carboplatin was associated with a statistically significant increase in mortallty ln patients with non-squamous tumours andin patients receiving third-generation regimens. As expected, cispiatin *was* associated with higher lncidence of nausea, vomiting and renal toxicity, whilst carboplatin was associated with higher incidence of thrombocytopenia. Based on these data, cispiatin-containing third-generation regimens represent the standard treatment for patients with advanced NSCLC.

3.2.1. Recommendations

- Third-generation cisplatin-based regimens are recommended for the treatment of advanced NSCLC patients, with PS 0-1 and without major co-morbidities. Where the use of cisplatin is contra-indicated third-generation carboplatin-based regimens are a valid therapeutic option. (**LoE lA, GoR A**)

3.3.1. Recommendations

- Gefitinib is recommended as first-line therapy of patients with EGFR mutat!on positive NSCLC EGFR analysfs is recommended, if adequate tumoursampie is available, espedaily in patients selected on the basis of clinical and/or pathological charaeteristics known to be assodated with higher frequency of EGFR mutation (never or former smokers, adenocardnoma). (**LoE IB, GoR A)**

3.4.1. Recommendations

- in patients with advanced non-squamoiis NSCLCwho have an

objective response or a stable disease after completing first-line treatment consisting of 4 cycles of platinum-based chemotherapy, notincluding pemetrexed, maintenance therapy wlth pemetrexed can be considered (if aliowed by reimbursement procedures) and discussed with patients. (**LoE B, GoR A**)

- in patients with a/1 histotypes advanced NSCLC who have stable disease after completing first-line chemotherapy consisting of 4 eycles of platinum-based chemotherapy, maintenance therapy w!th erlotinlb can be considered (if allowed by reimbursement procedures) and discussed with patients. (**LoE B, GoR A)**

3.5.1. Recommendations

- In elderly patients (older than 70 years) with advanced NSCLC, single-ogent treatment with a third-generation drug is the recommended optionfor clinlcal practice. (**LoE lA, GoR A)**
- In elderly patients (older than 70 years) with advanced NSCLC and PS 0-1, without major co-morbldities and with adequate organ function, platinum-based chemotherapy wlth attenuated doses of clsplatin or carboplatln can be considered. (**LoE B; GoR A)**
- In elderly patients (older than 70years), with EGFR mutation positive advanced NSCLC, gefitinib ls the recommended treatment. (**LoE lA, GoR A)**

3.6.1. Recommendations

- First-line chemotherapy is recommended in patients wlth advanced NSCLC and ECOG PS 2 because lt is associated with a significant benefit in overall survival and quality of life, compared to BSC alone. (**LoE lA, GoR A)**
- Single-agent thlrd-generation drug ls a reasonable option. Comblnation chemotherapy with carboplatin or low doses of cisplatln is a reasonable alternative. (**LoE 1/B, GoR B)**
- ln PS 2 patients, with EGFR mutationpositive advanced NSCLC, gefitlnib ls the recommended treatment. (**LoE lB, GoR A)**

3.7.1. Recommendations

In patients with advanced NSCLC, after failure of first-line treatment,

- single-agent treatment with docetaxel orpemetrexed (the latter limlted to non-squamous tumours) is recommended. **LoE lB, GoR A**
- In patients wlth advanced NSCLC, progressing after first-line treatment, combination chemotherapy is not recommended. **LoE lA, GoR A**

3.8.1. Recommendations

- In patients wlth advanced NSCLC and EGFR mutation negative or unknown status, with progressive disease after first-line treatment chemotherapy (docetaxel or pemetrexed ln non-squamous histology) or erlotinlb should be offered. There are no concluslve data to help the choice between chemotherapy and erlotinib. (**LoE IB, GoR A)**
- In patients with advanced NSCLC, with progressive disease after second-line treatment erlotinib is the drug of cholce, lf not administered prevlously, because is the only approved for use ln clinical practice as third-line treatment (**LoE IB, GoR A)**

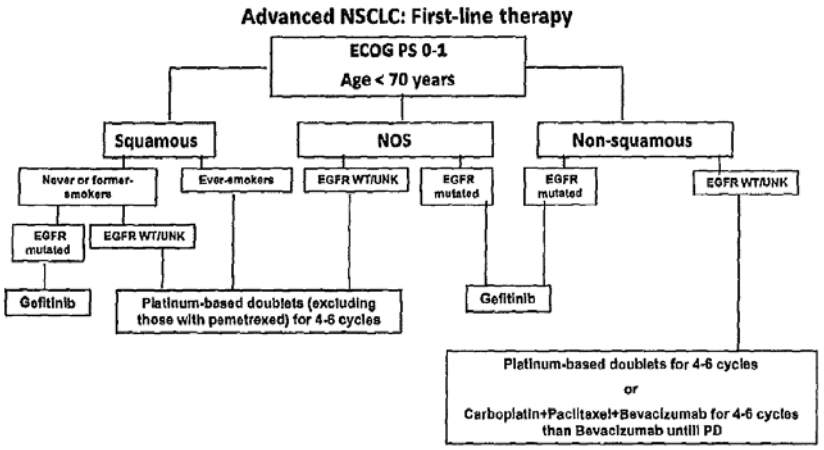


Fig. 1. Suggested algorithm for first-line treatment of advanced non-small-cell lung cancer (ECOG PS: Eastern Cooperative Oncology Group performance status; NOS: not otherwise specified; EGFR: epidermal growth factor receptor; WT: wild type; and UNK: unknown).

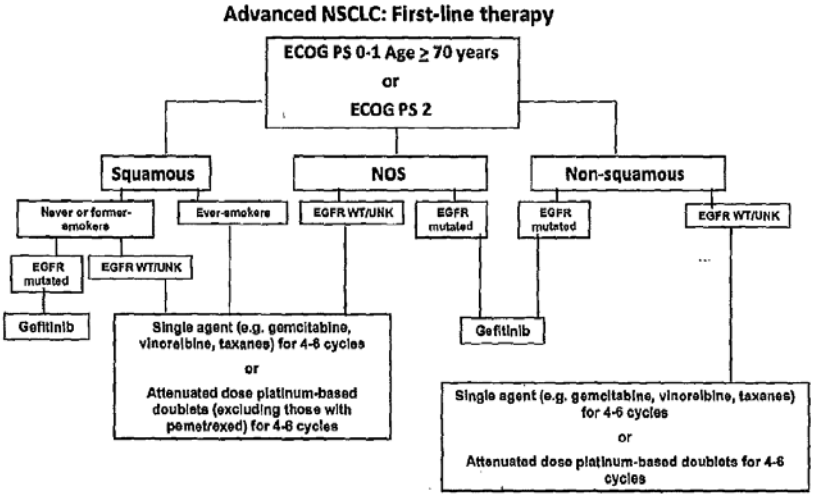


Fig. 2. Suggested algorithm for first-line treatment of advanced non-small-cell lung cancer in special patients population (ECOG PS: Eastern Cooperative Oncology Group performance status; NOS: not otherwise specified; EGFR: epidermal growth factor receptor; WT: wild type; and UNK: unknown).

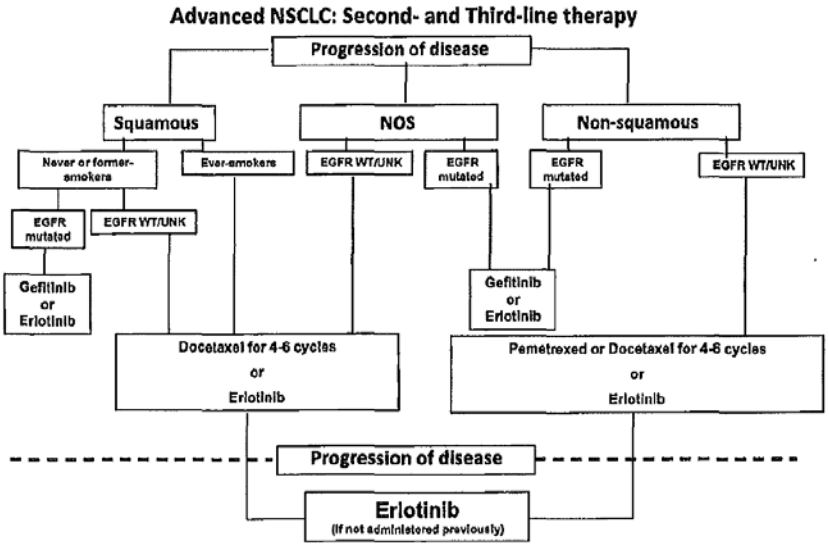


Fig. 3. Suggested algorithm for second- and third-line treatment of advanced non-small-cell lung cancer (NOS: not otherwise specified; EGFR: epidermal growth factor receptor; WT: wild type; and UNK: unknown).

DGP, 2010 [41]

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

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

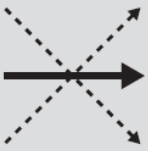
Suchzeitraum:

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.

LoE, GoR:

Tab. 1 Beziehung zwischen Evidenz- und Empfehlungsgrad (modifiziert nach Oxford Center for Evidence-based Medicine 2001 und AWMF).

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

Sonstige methodische Hinweise:

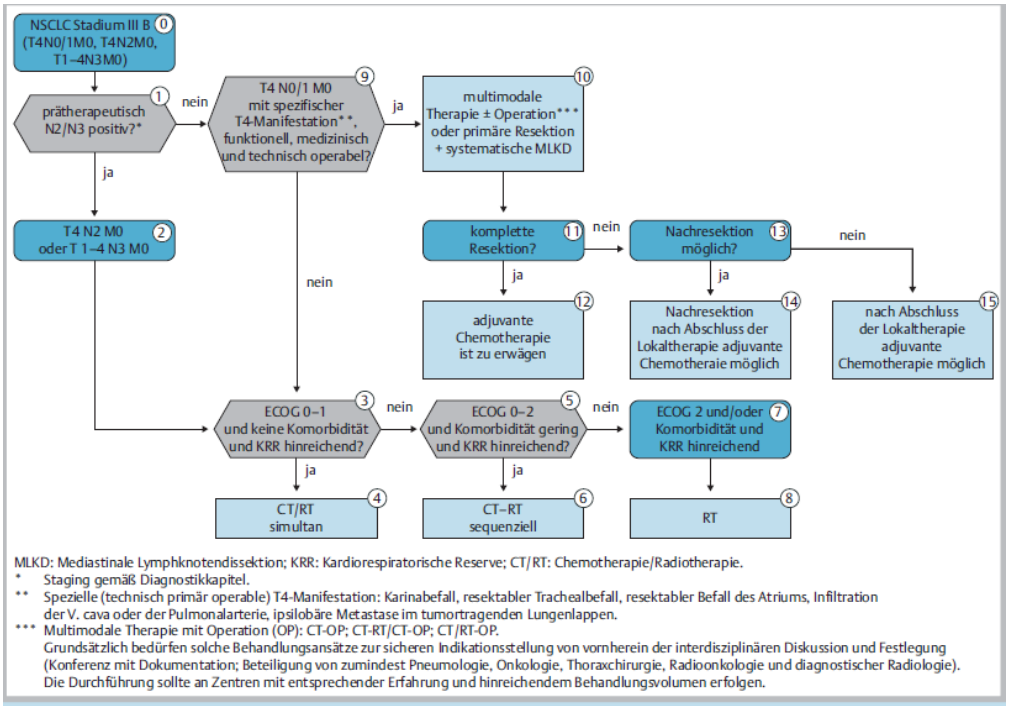
- Rechercheende liegt lange zurück (8 Jahre)
- LoE und GoR nicht direkt verknüpft
- Nach Prüfverfahren keine Interessenkonflikte festgestellt
- Keine Angaben zur Notwendigkeit von der Bestimmung von Markern vor Behandlung mit Gefitinib, Erlotinib
- Evidenztabellen (nur online) nicht verfügbar

Empfehlungen:

	Zusammenfassende Empfehlungen zur Therapie im Stadium III • Die TNM-Stadienzusammenfassung in IIIA und IIIB unterschied technisch resektable – jedoch prognostisch ungünstige – Tumorausbreitungen im Stadium IIIA von in der Regel technisch inoperablen Erkrankungsausdehnungen (Stadium IIIB). Weiterentwicklungen in Staging, Operationstechnik und multimodalen Ansätzen haben die Grenzen dieser Einteilung für therapeutische Entscheidungen gezeigt. Eine optimale Behandlungswahl für den einzelnen Patienten erfordert vor Therapiebeginn die interdisziplinäre Diskussion und Festlegung (zumindest Beteiligung von Pneumologie, Onkologie, Thoraxchirurgie, Radioonkologie und diagnostischer Radiologie) (**Empfehlungsgrad D**). • Die Unterscheidung von Subgruppen speziell im Stadium IIIA (N2) ist für Therapiewahl und Prognose von großer Bedeutung (**Empfehlungsgrad B**). • Eine adjuvante Chemotherapie wird im Stadium IIIA mit inzidentellem N2-Status (IIIA1 bzw. IIIA2) nach kompletter Resektion (R0) und systematischer Lymphknotendissektion empfohlen (**Empfehlungsgrad A**). • Ein Beginn der Chemotherapie nach Abschluss der Wundheilung innerhalb von 60 Tagen nach Resektion wird empfohlen (**Empfehlungsgrad D**). • In der adjuvanten Chemotherapie wird die Gabe einer cisplatinhaltigen Kombination über 4 Zyklen empfohlen (**Empfehlungsgrad** A). In der Mehrzahl der positiven Studien wurde eine Kombination mit Vinorelbin verwendet. • Bei Patienten mit bedeutsamer Komorbidität aufgrund der vorangegangenen Resektion oder vorbestehender Erkrankungen wird empfohlen, die adjuvante Chemotherapie in einem interdisziplinär ausgerichteten Behandlungskontext mit entsprechender Erfahrung in der Durchführung von multimodalen Therapien durchführen zu lassen (**Empfehlungsgrad D**). • Für Patienten mit mediastinalem Lymphknotenbefall im Stadium IIIA1 bzw. IIIA2 sollte zusätzlich zur adjuvanten Chemotherapie die Indikation zur postoperativen Mediastinalbestrahlung geprüft werden (**Empfehlungsgrad B**). • Die Bestrahlung sollte bis spätestens 4 Wochen nach Abschluss der adjuvanten Chemotherapie beginnen und eine Dosis von 50–60 Gy nach CT-gestützter 3-dimensionaler Bestrahlungsplanung umfassen. Komorbiditäten müssen bei diesem Vorschlag ausreichend berücksichtigt werden (**Empfehlungsgrad B**). • Patienten im Stadium IIIA3 sollten präferenziell im Rahmen von Studien zur weiteren Definition des Therapiealgorithmus behandelt werden (**Empfehlungsgrad D**). • Außerhalb von Studien können Patienten im Stadium IIIA3 und technisch resektabler Tumorausdehnung individuell mit einem Induktionsprotokoll (Induktionschemotherapie oder Induktionschemostrahlentherapie) behandelt und anschließend operiert werden (**Empfehlungsgrad** B). Grundsätzlich erfordern solche Behandlungsansätze zur sicheren Indikationsstellung vor Therapiebeginn eine interdisziplinäre Diskussion und Festlegung (zumindest Beteiligung von Pneumologie, Onkologie, Thoraxchirurgie Radioonkologie und diagnostischer Radiologie). Präoperativ soll die Indikation zur Resektion im interdisziplinären Kontext gleichermaßen überprüft werden. Die Durchführung sollte an Zentren mit

	entsprechender Erfahrung und hinreichendem Behandlungsvolumen erfolgen. • In der Subgruppe T4N0/1 des Stadiums IIIB ist die primäre Operation bzw. die Integration der Operation in das Gesamtbehandlungskonzept bei medizinischer und funktioneller Operabilität in folgenden Fällen möglich: Karinabefall, resektabler Trachealbefall, resektabler Befall des Atrium, Infiltration der V. cava oder der Pulmonalarterie, ipsilobäre Metastase im tumortragenden Lungenlappen (**Empfehlungsgrad** B). • Nach Operation und R0-Resektion sollte im Stadium IIIA3 bei alleiniger Induktionschemotherapie eine mediastinale Radiotherapie erfolgen. Bei Induktionschemostrahlentherapieprotokollen sollte nach R0-Resektion keineweitere postoperative Radiotherapie durchgeführt werden (**Empfehlungsgrad B**). • Patienten im Stadium IIIA3 – insbesondere bei multiplem N2-Befall – können gleichermaßen mit einer Kombination aus Strahlentherapie und Chemotherapie (definitive Chemo-/ Radiotherapie) behandelt werden (**Empfehlungsgrad A**). • Patienten im Stadium IIIA4/IIIB sollten – wenn Allgemeinzustand und Tumorausdehnung dies zulassen – eine Kombination aus Strahlentherapie und Chemotherapie erhalten (**Empfehlungsgrad A**). • Für selektionierte Patienten im Stadium IIIA4/IIIB kann im begründeten Ausnahmefall ein multimodaler Behandlungsansatz unter Integration der Operation (möglichst nur in Studien) erfolgen (**Empfehlungsgrad D**). • Im direkten Vergleich ist bei geeigneten Patienten die simultane Radio-/Chemotherapie der sequenziellen überlegen. Bei der Patientenselektion ist auf Komorbiditätsspektrum und Allgemeinzustand zu achten (**Empfehlungsgrad A**). • Die Sequenz von Chemotherapie gefolgt von definitiver Strahlentherapie kann im Vergleich zur alleinigen Strahlentherapie sowohl medianes Überleben als auch 5-Jahres-Überlebensraten signifikant verbessern (**Empfehlungsgrad B**). • Für die sequenzielle und simultane Chemostrahlentherapie sollten cisplatinbasierte Chemotherapieprotokolle gewählt werden (Kombinationspartner bei simultaner Therapie in der Regel Etoposid oder Vincaalkaloid) (**Empfehlungsgrad B**). • Sowohl bei der sequenziellen als auch simultanen Behandlung werden typischerweise zwei Zyklen einer voll-dosierten cisplatinhaltigen Kombinationschemotherapie (Zyklusintervall 3–4Wochen) appliziert (**Empfehlungsgrad B**). • Angesichts des hohen systemischen Rezidivrisikos nach definitiver Chemostrahlentherapie kann im Einzelfall eine konsolidierende platinbasierte Kombinationschemotherapie aufgrund der im historischen Vergleich vielversprechenden Daten im Vergleichsarm einer großen randomisierten Phase-IIIStudie (INT 0139) durchgeführtwerden (**Empfehlungsgrad D**). • Im Vergleich zur alleinigen simultanen Chemo-/Radiotherapie ist der Stellenwert einer zusätzlichen konsolidierenden Chemotherapie in randomisierten Studien bisher allerdings nicht gegenüber Beobachtung belegt. Die zusätzliche Konsolidierung in Form der Monotherapie mit einem Taxan nach stattgehabter Radio-/Chemotherapie führt sogar zu deutlicher **und inakzeptabler Toxizität und wird nicht empfohlen (Empfehlungsgrad** A). • Die Strahlentherapie sollte typischerweise eine Dosis zwischen 60 und 66 Gy bei einmal-täglicher Fraktionierung haben (**Empfehlungsgrad A**). Die

Zeitdauer hängt von der Einzelfraktionierung ab und liegt typischerweise bei 6–7 Wochen (Empfehlungsgrad B). Eine Unterbrechung der Strahlentherapie sollte vermieden werden (**Empfehlungsgrad C**). […]



MLKD: Mediastinale Lymphknotendissektion; KRR: Kardiorespiratorische Reserve; CT/RT: Chemotherapie/Radiotherapie.
* Staging gemäß Diagnostikkapitel.
** Spezielle (technisch primär operable) T4-Manifestation: Karinabefall, resektabler Trachealbefall, resektabler Befall des Atriums, Infiltration der V. cava oder der Pulmonalarterie, ipsilobäre Metastase im tumortragenden Lungenlappen.
*** Multimodale Therapie mit Operation (OP): CT-OP; CT-RT/CT-OP; CT/RT-OP.
Grundsätzlich bedürfen solche Behandlungsansätze zur sicheren Indikationsstellung von vornherein der interdisziplinären Diskussion und Festlegung (Konferenz mit Dokumentation; Beteiligung von zumindest Pneumologie, Onkologie, Thoraxchirurgie, Radioonkologie und diagnostischer Radiologie). Die Durchführung sollte an Zentren mit entsprechender Erfahrung und hinreichendem Behandlungsvolumen erfolgen.

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

Stadium IV/IIIB (ohne Indikation zur definitiven Radiatio)

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

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

	Kombinationschemotherapie eingesetzt werden (**Empfehlungsgrad B**). • Die weitere Charakterisierung von Patientensubgruppen, die am besten profitieren, sollte erfolgen (**Empfehlungsgrad D**). Zum Zeitpunkt der Publikation der Leitlinie ist Cetuximab nicht zur Therapie des nicht-kleinzelligen Lungenkarzinoms zugelassen. • Bei Patienten mit aktivierenden Mutationen des EGF-Rezeptors (insbesondere del. 19; exon 21 L858R) ist Gefitinib im Hinblick auf Remissionsrate und progressionsfreies Überleben in der Erstlinienbehandlung einer Chemotherapie signifikant überlegen (**Empfehlungsgrad B**). Gefitinib ist daraufhin bei positivem Mutationsstatus des EGF-Rezeptors in allen Therapielinien als eine mögliche Behandlungsoption zugelassen worden. In der zulassungsrelevanten Studie erfolgte die Analyse des Mutationsstatus bei Patienten mit einem Adenokarzinom und minimalem Nikotinkonsum (94 % Nieraucher).

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

NICE, 2009 [42] Pemetrexed for the first-line treatment of non-small-cell lung cancer	**The manufacturer's submission** In the submission the manufacturer compared pemetrexed plus cisplatin (pemetrexed/cisplatin) with gemcitabine plus cisplatin (gemcitabine/cisplatin). The manufacturer justified this choice of comparator with marketing data that suggest gemcitabine plus a platinum drug accounts for 80% of first-line NSCLC treatment, and the fact that according to a meta-analysis and clinical opinion cisplatin is the preferred platinum drug. The manufacturer identified gemcitabine plus carboplatin (gemcitabine/carboplatin) and docetaxel plus cisplatin (docetaxel/cisplatin) as additional comparators. The manufacturer stated that carboplatin is still commonly used in the UK because patients do not need the same hydration that is necessary with cisplatin. It also stated that docetaxel is used occasionally because it requires fewer infusions than gemcitabine. **Guidance** 1.1 Pemetrexed in combination with cisplatin is recommended as an option for the first-line treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) only if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma. 1.2 People who are currently being treated with pemetrexed for NSCLC but who do not meet the criteria in 1.1 should have the option to continue their therapy until they and their clinicians consider it appropriate to stop.

Primärstudien

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

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews) am 21.07.2014

Such-schritt	Suchfrage
#1	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees
#2	((non next small) or nonsmall) next cell next lung:ti,ab,kw
#3	tumor* or tumour* or carcinoma* or adenocarcinoma* or neoplasm* or sarcoma* or cancer*:ti,ab,kw
#4	#2 and #3
#5	nsclc*:ti,ab,kw (Word variations have been searched)
#6	#1 or #4 or #5
#7	#1 or #4 or #5 Publication Year from 2009 to 2014

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

Such-schritt	Suchfrage
#1	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees
#2	((non next small) or nonsmall) next cell next lung:ti,ab,kw)
#3	tumor* or tumour* or carcinoma* or adenocarcinoma* or neoplasm* or sarcoma* or cancer*:ti,ab,kw
#4	#2 and #3
#5	nsclc*:ti,ab,kw (Word variations have been searched)
#6	advanced or metastas* or metastat* or recurren* or ((3rd or third or 2nd or second) and line) or (stage next III*) or (stage next IV):ti,ab,kw
#7	(#4 or #5) and #6
#8	#1 or #7
#9	#1 or #7 Publication Year from 2009 to 2014

MEDLINE (PubMed) am 21.07.2014

Such-schritt	Suchfrage
#1	carcinoma, non small cell lung[MeSH Terms]
#2	((((((non[Title/Abstract]) AND small[Title/Abstract])) OR nonsmall[Title/Abstract])) AND cell[Title/Abstract]) AND lung[Title/Abstract]
#3	(((((((tumor*[Title/Abstract]) OR tumour*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract]) OR neoplasm*[Title/Abstract]) OR sarcoma*[Title/Abstract]) OR cancer*[Title/Abstract])
#4	(#2) AND #3
#5	nsclc*[Title/Abstract]
#6	(#4) OR #5

Such-schritt	Suchfrage
#7	((((((advanced[Title/Abstract]) OR metastas*[Title/Abstract]) OR metastat*[Title/Abstract]) OR recurren*[Title/Abstract])) OR ((((((3rd[Title/Abstract]) OR third[Title/Abstract]) OR 2nd[Title/Abstract]) OR second[Title/Abstract])) AND line[Title/Abstract])) OR ((stage III*[Title/Abstract]) OR stage IV[Title/Abstract])
#8	(#6) AND #7
#9	(#1) OR #8
#10	(#9) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
#11	(#9) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
#12	(#10) OR #11
#13	(#12) AND ("2009/07/01"[PDAT] : "2014/07/21"[PDAT])

MEDLINE (PubMed) nach Leitlinien am 21.07.2014

Such-schritt	Suchfrage
#1	carcinoma, non small cell lung[MeSH Terms]
#2	((((((non[Title/Abstract]) AND small[Title/Abstract])) OR nonsmall[Title/Abstract])) AND cell[Title/Abstract]) AND lung[Title/Abstract]
#3	(((((((tumor*[Title/Abstract]) OR tumour*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract]) OR neoplasm*[Title/Abstract]) OR sarcoma*[Title/Abstract]) OR cancer*[Title/Abstract])
#4	(#2) AND #3
#5	nsclc*[Title/Abstract]
#6	((#1) OR #4) OR #5
#7	(((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type])

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

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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: Summary of Recommendations aus: Azzoli et. al 2010

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).