Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2017-B-203 Pembrolizumab

Stand: November 2017

Gemeinsamer Bundesausschuss

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Pembrolizumab **[Pembrolizumab in Kombination mit Pemetrexed und Carboplatin zur Erstlinientherapie des NSCLC ohne EGFR- oder ALK-Mutation]**	
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

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Pembrolizumab **[Pembrolizumab in Kombination mit Pemetrexed und Carboplatin zur Erstlinientherapie des NSCLC ohne EGFR- oder ALK-Mutation]**	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	**Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:** • Crizotinib (ROS1-positives NSCLC): Beschluss vom 16. März 2017 • Pembrolizumab (Monotherapie; 1. Linie NSCLC): Beschluss vom 03. August 2017 • Dabrafenib (NSCLC mit BRAF-V600-Mutation): Beschluss vom 19. Oktober 2017 • Trametinib (NSCLC mit BRAF-V600-Mutation): Beschluss vom 19. Oktober 2017 **Richtlinien:** Carboplatin: Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie - Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten - (Stand: 8. Juni 2016): Arzneimittel, die unter Beachtung der dazu gegebenen Hinweise in nicht zugelassenen Anwendungsgebieten (Off-Label-Use) verordnungsfähig sind: • Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCL) – Kombinationstherapie Richtlinie Methoden Krankenhausbehandlung (Stand: 7. Mai 2016); Ausgeschlossene Methoden (§ 4): • Protonentherapie beim inoperablen nicht-kleinzelligen Lungenkarzinom des UICC Stadiums IV • Protonentherapie bei Hirnmetastasen • Protonentherapie bei Lebermetastasen
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:	
Pembrolizumab	Zugelassenes Anwendungsgebiet: KEYTRUDA ist in Kombination mit Pemetrexed und Platin-Chemotherapie zur Erstlinienbehandlung des metastasierenden nichtplattenepithelialen NSCLC ohne EGFR- oder ALK-positive Tumormutationen bei Erwachsenen angezeigt
Chemotherapien:	
Carboplatin L01XA02 (generisch)	Off-Label-Indikation für Carboplatin: Kombinationstherapie des fortgeschrittenen NSCLC (palliativ)
Cisplatin L01XA01 (generisch)	Cisplatin wird angewendet zur Behandlung des: fortgeschrittenen oder metastasierten nichtkleinzelligen Bronchialkarzinoms. Cisplatin kann als Mono- oder Kombinationstherapie angewendet werden. (Cisplatin Teva® 1 mg / ml Konzentrat)
Docetaxel L01CD02 (generisch)	Nicht-kleinzelliges Bronchialkarzinom: Docetaxel ist in Kombination mit Cisplatin zur Behandlung von Patienten mit nicht resezierbarem, lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Bronchialkarzinom ohne vorausgegangene Chemotherapie angezeigt. (Docetaxel-ratiopharm® 20 mg/ml Konzentrat)
Etoposid L01CB01 (generisch)	Etoposid ist in Kombination mit anderen antineoplastisch wirksamen Arzneimitteln bei der Behandlung folgender bösartiger Neubildungen angezeigt: Palliative Therapie des fortgeschrittenen nicht-kleinzelligen Bronchialkarzinoms bei Patienten in gutem Allgemeinzustand (Etopophos® 100 mg/1000 mg)
Gemcitabin	Gemcitabin ist in Kombination mit Cisplatin als Erstlinientherapie von Patienten mit lokal fortgeschrittenem oder metastasiertem

L01BC05 (generisch)	nichtkleinzelligen Bronchialkarzinom (NSCLC) angezeigt. Eine Gemcitabin-Monotherapie kann bei älteren Patienten oder solchen mit einem Performance Status 2 in Betracht gezogen werden. (Gemcitabin Kabi 38 mg/ml Konzentrat)
Ifosfamid L01AA06 (Holoxan®)	Nicht-kleinzellige Bronchialkarzinome: Zur Einzel- oder Kombinationschemotherapie von Patienten mit inoperablen oder metastasierten Tumoren. (Holoxan®)
Mitomycin L01DC03 (generisch)	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Bei intravenöser Gabe ist es in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei folgenden metastasierenden Tumoren wirksam: […] nicht-kleinzelliges Bronchialkarzinom […]. (Mitomycin Teva® 1 mg/ml)
Paclitaxel L01CD01 (generisch)	Fortgeschrittenes nicht-kleinzelliges Bronchialkarzinom (NSCLC): Paclitaxel ist, in Kombination mit Cisplatin, zur Behandlung des nicht-kleinzelligen Bronchialkarzinoms bei Patienten angezeigt, für die potentiell kurative chirurgische Maßnahmen und/oder eine Strahlentherapie nicht in Frage kommen. (Paclitaxel-GRY® 6 mg/ml Konzentrat)
Paclitaxel Nanopartikel L01CD01 Abraxane®	Abraxane ist in Kombination mit Carboplatin indiziert für die Erstlinienbehandlung des nicht-kleinzelligen Bronchialkarzinoms bei erwachsenen Patienten, bei denen keine potentiell kurative Operation und/oder Strahlentherapie möglich ist. (Abraxane® 5 mg/ml)
Pemetrexed L01BA04 (Alimta®)	Alimta ist in Kombination mit Cisplatin angezeigt zur first-line Therapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie. Alimta in Monotherapie ist angezeigt für die Erhaltungstherapie bei lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie bei Patienten, deren Erkrankung nach einer platinbasierten Chemotherapie nicht unmittelbar fortgeschritten ist. (Alimta®)
Vindesin L01CA03 (Eldesine®)	Kombinationschemotherapie: Lokal fortgeschrittenes oder metastasiertes nicht-kleinzelliges Bronchialkarzinom (Stadium IIIB, IV).
Vinorelbin L01CA04 (generisch)	Behandlung des nicht kleinzelligen Bronchialkarzinoms (Stadium 3 oder 4). (Vinorelbin onkovis 10 mg/ml Konzentrat)

Proteinkinase-Inhibitoren:	
Crizotinib L01XE16 (Xalkori®)	Xalkori wird angewendet bei Erwachsenen zur Erstlinienbehandlung des Anaplastische-Lymphom-Kinase(ALK)-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, NSCLC). Xalkori wird angewendet bei Erwachsenen zur Behandlung des ROS1-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, NSCLC).
Dabrafenib L01XE23 (Tafinlar®)	Dabrafenib in Kombination mit Trametinib ist angezeigt zur Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligen Lungenkarzinom mit einer BRAF-V600-Mutation.
Trametinib L01XE25 (Mekinist®)	Trametinib in Kombination mit Dabrafenib ist angezeigt zur Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligen Lungenkarzinom mit einer BRAF-V600-Mutation.
Antikörper:	
Pembrolizumab L01XC18 (Keytruda®)	Keytruda ist als Monotherapie zur Erstlinienbehandlung des metastasierenden nicht-kleinzelligen Lungenkarzinoms (NSCLC) mit PD-L1 exprimierenden Tumoren (Tumor Proportion Score [TPS] ≥ 50 %) ohne EGFR oder ALK-positive Tumormutationen bei Erwachsenen angezeigt.
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.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

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

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *nicht kleinzelligem Lungenkarzinom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 09.10.2017 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1233 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 32 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Erstlinientherapie bei Patienten mit metastasierendem nicht-plattenepithelialen NSCLC ohne EGFR oder ALK positive Mutation in Kombination mit Pemetrexed und Carboplatin

Hinweis:

In die Evidenzsynopse nicht eingeschlossen wurden Publikationen mit

- der Intervention „(Chemo-)Radiotherapie“.

Abkürzungen:

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

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

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

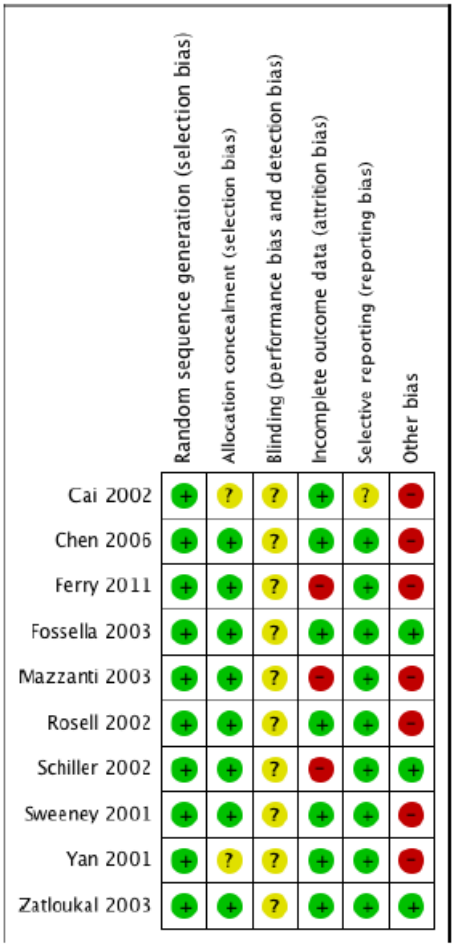
G-BA Beschlüsse

G-BA, 2017 [9]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Pembrolizumab (neues Anwendungsgebiet: Erstlinienbehandlung, nicht kleinzelliges Lungenkarzinom)	Neues Anwendungsgebiet (laut Zulassung vom 27.01.2017): KEYTRUDA ist als Monotherapie zur Erstlinienbehandlung des metastasierenden nicht-kleinzelligen Lungenkarzinoms (NSCLC) mit PD-L1 exprimierenden Tumoren (Tumor Proportion Score [TPS] ≥ 50 %) ohne EGFR oder ALK-positive Tumormutationen bei Erwachsenen angezeigt. **Zweckmäßige Vergleichstherapie:** Patienten mit ECOG-Performance-Status 0, 1 oder 2: • Cisplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin oder Gemcitabin oder Docetaxel oder Paclitaxel oder Pemetrexed) unter Beachtung des Zulassungsstatus *oder* • Carboplatin in Kombination mit einem Drittgenerationszytostatikum (nur für Patienten mit erhöhtem Risiko für Cisplatin-induzierte Nebenwirkungen im Rahmen einer Kombinationstherapie; vgl. Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie) *oder* • Carboplatin in Kombination mit nab-Paclitaxel Patienten mit ECOG-Performance-Status 2: • alternativ zur Platin-basierten Kombinationsbehandlung: eine Monotherapie mit Gemcitabin oder Vinorelbin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie):** Hinweis auf einen beträchtlichen Zusatznutzen.
G-BA, 2017 [8]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Crizotinib (neues Anwendungsgebiet: ROS1-positives, fortgeschrittenes nicht kleinzelliges Lungenkarzinom)	Zugelassenes Anwendungsgebiet (laut Zulassung vom 25.08.2016): XALKORI wird angewendet bei Erwachsenen zur Behandlung des ROS1-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, NSCLC) 1) nicht vorbehandelte Patienten mit ROS1-positivem, fortgeschrittenem nicht kleinzelligem Lungenkarzinom (NSCLC) Zweckmäßige Vergleichstherapie: - Patienten mit ECOG-Performance-Status 0, 1 oder 2: Cisplatin in Kombination mit oder Carboplatin in Kombination mit einem Drittgenerationszytostatikum (nur für Patienten mit erhöhtem Risiko für Cisplatin-induzierte Nebenwirkungen im Rahmen einer Kombinationstherapie; vgl. Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie) - Patienten mit ECOG-Performance-Status 2: alternativ zur platinbasierten Kombinationsbehandlung: Monotherapie mit Gemcitabin oder Vinorelbin Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Cisplatin Kombination mit Pemetrexed oder Carboplatin in Kombination mit Pemetrexed: Ein Zusatznutzen ist nicht belegt. **Studienergebnisse nach Endpunkten:** 1) nicht vorbehandelte Patienten mit ROS1-positivem, fortgeschrittenem nicht kleinzelligem Lungenkarzinom (NSCLC): Es liegen keine validen Daten

IQWiG, 2017 [12]. Crizotinib (nicht kleinzelliges Lungenkarzinom) – Nutzenbewertung gemäß § 35a SGB V	vor.

Cochrane Reviews

De Castria TB et al., 2013 [6]. Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer	**1. Fragestellung** To assess the efficacy and safety of carboplatin-based chemotherapy when compared with cisplatin-based chemotherapy, both in combination with a third-generation drug, in people with advanced NSCLC. To compare quality of life in people with advanced NSCLC receiving chemotherapy with cisplatin and carboplatin combined with a third-generation drug.
	2. Methodik **Population:** people with advanced NSCLC **Interventionen und Komparatoren:** regimens with cisplatin or carboplatin in combination with a third-generation drug (i.e. docetaxel, paclitaxel, vinorelbine, gemcitabine or irinotecan) • Cisplatin plus gemcitabine versus carboplatin plus gemcitabine. • Cisplatin plus docetaxel versus carboplatin plus docetaxel. • Cisplatin plus paclitaxel versus carboplatin plus paclitaxel. • Cisplatin plus vinorelbine versus carboplatin plus vinorelbine. • Cisplatin plus irinotecan versus carboplatin plus irinotecan. We included trials comparing these compounds for any number of cycles or treatment schedules. **Endpunkte:** <u>Primär</u>: • Overall survival • One-year survival rate • QoL • Drug toxicities (according to the National Cancer Institute Common Toxicity Criteria v2.0) <u>Sekundär</u>: Objective response rate, classified according to the Response Evaluation Criteria in Solid Tumors (RECIST) (Eisenhauer 2009). **Suchzeitraum:** 1966 bis 03/2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 10 (5017), nur RCTs **Qualitätsbewertung der Studien:** Cochrane risk of bias' tool
	3. Ergebnisdarstellung



OS: There was no difference between carboplatin based and cisplatin-based chemotherapy in overall survival (hazard ratio (HR) 1.00; 95% confidence interval (CI) 0.51 to 1.97, I^2 =0%) and one-year survival rate (risk ratio (RR) 0.98; 95% CI 0.88 to 1.09, I^2 = 24%).

ORR: Cisplatin had higher response rates when we performed an overall analysis (RR 0.88; 95% CI 0.79 to 0.99, I^2 = 3%), but trials using paclitaxel or gemcitabine plus a platin in both arms had equivalent response rates (paclitaxel: RR 0.89; 95% CI 0.74 to 1.07, I^2 = 0%; gemcitabine: RR 0.92; 95% CI 0.73 to 1.16, I^2 = 34%).

Adverse events: Cisplatin caused more nausea or vomiting, or both (RR 0.46; 95% CI 0.32 to 0.67, I2 = 53%) and carboplatin caused more thrombocytopenia (RR 2.00; 95% CI 1.37 to 2.91, I2 = 21%) and neurotoxicity (RR 1.55; 95% CI 1.06 to 2.27, I^2 = 0%). There was no difference in the incidence of grade III/IV anaemia (RR 1.06; 95% CI 0.79 to 1.43, I2 = 20%), neutropenia (RR 0.96; 95% CI 0.85 to 1.08, I^2 = 49%), alopecia (RR 1.11; 95% CI 0.73 to 1.68, I2 = 0%) or renal toxicity (RR 0.52; 95% CI 0.19 to 1.45, I^2 = 3%).

QoL: Two trials performed a quality of life analysis; however, they used different methods of measurement so we could not perform a meta-analysis.

4. **Fazit der Autoren:** The initial treatment of people with advanced NSCLC is palliative, and carboplatin can be a treatment option. It has a similar effect on survival but a different toxicity profile when compared with cisplatin. Therefore,

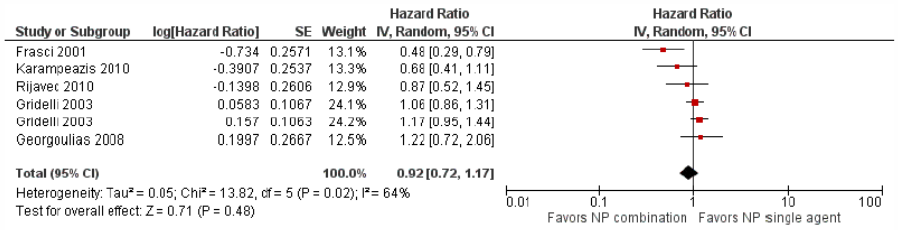
	the choice of the platin compound should take into account the expected toxicity profile and the person's comorbidities. In addition, when used with either paclitaxel or gemcitabine, the drugs had an equivalent response rate. 5. **Hinweis der FBMed** Der Mutationsstatus wurde in diesem CR nicht untersucht.

Santos FN et al., 2015 [22]. Chemotherapy for advanced non-small cell lung cancer in the elderly population (Review)	**1. Fragestellung** To assess the effectiveness and safety of different cytotoxic chemotherapy regimens for previously untreated elderly patients with advanced (stage IIIB and IV) NSCLC. To also assess the impact of cytotoxic chemotherapy on quality of life.
	2. Methodik **Population:** patients 70 years of age and older with previously untreated and histologically confirmed NSCLC, with metastatic disease and/or pleural effusion (stage IIIB or IV). **Interventionen und Komparatoren:** We classified chemotherapy regimens into three categories. • Non-platinum monotherapy. • Non-platinum combination therapy. • Platinum combination therapy. We considered trials comparing these compounds, whatever the numbers. Categories were compared according to the following. • Non-platinum monotherapy versus non-platinum combination therapy. • Non-platinum therapy (given as a single agent or in combination) versus platinum combination therapy. **Endpunkte:** <u>Primär</u>: • Overall survival • QoL <u>Sekundär</u>: • One-year survival rate (1yOS). • Progression-free survival (PFS). • Objective response rate (ORR), classified according to Response Evaluation Criteria in Solid Tumors (RECIST), World Healh Organization (WHO) criteria, or individual study criteria. • Serious adverse events (grade 3 or above, according to WHO or National Cancer Institute Common Toxicity Criteria (NCI-CTC)) **Suchzeitraum:**

	• Cochrane CENTRAL; latest issue • MEDLINE (via OVID) (from 1966 to 31 October 2014) • EMBASE (via Elsevier) (from 1974 to 31 October 2014) • Latin American Caribbean Health Sciences Literature (LILACS) (from 1982 to 31 October 2014) • Handsearch (from 1990 to 31 October 2014). **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 51 (13,103), nur RCTs **Qualitätsbewertung der Studien:** Cochrane risk of bias' tool
	3. Ergebnisdarstellung  **Non-platinum single-agent versus non-platinum combination therapy**

OS: The meta-analysis of five RCTs involving 1294 participants showed no differences in OS between treatment strategies (hazard ratio (HR) 1.01, 95% confidence interval (CI) 0.89 to 1.15) and significant heterogeneity among trials (I2 = 64%). As a result of the presence of heterogeneity, we performed an analysis using a random-effects model with no impact on effects of the intervention (HR 0.92, 95% CI 0.72 to 1.17)

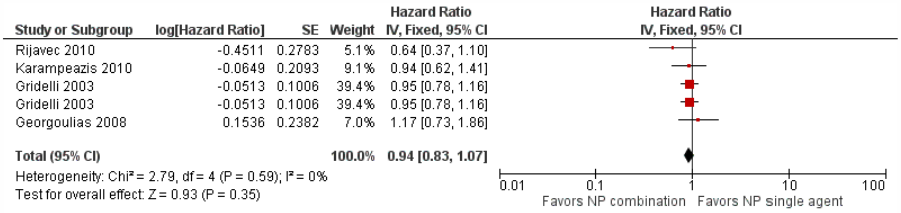
Figure 4. Forest plot of comparison: 1 Non-platinum single agent vs non-platinum combination, outcome: 1.1 Overall survival (OS).Gridelli 2003 was designed for a separate comparison of each single-agent arm (V arm and G arm) vs the combination arm (VG arm). Therefore, each entry for this trial represents one comparison (V vs VG and G vs VG arm).



QoL: Only two RCTs included quality of life (QoL) assessment in the trial design. We were not able to performameta-analysis because of the paucity of available data.

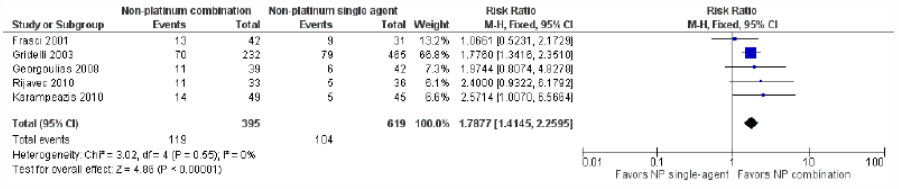
PFS: The meta-analysis of four RCTs involving 942 participants showed no impact on the PFS of non-platinum combination over nonplatinum single-agent therapy (HR 0.94, 95% CI 0.83 to 1.07) with low heterogeneity among trials (I2 = 0%)

Figure 5. Forest plot of comparison: 1 Non-platinum single-agent vs non-platinum combination, outcome: 1.3 Progression-free survival.



ORR: The meta-analysis including 1014 participants assessed from five RCTs showed statistically significant improvement in response rate (RR 1.79, 95% CI 1.41 to 2.26; I2 = 0%) with no heterogeneity among trials (I2 = 0%)

Figure 6. Forest plot of comparison: 1 Non-platinum single agent vs non-platinum combination, outcome: 1.6 Overall response rate (ORR).



Toxicity:

Grade 3 or higher hematological adverse events

We found no significant differences in risk of anemia (RR 1.18, 95% CI 0.57 to 2.40; participants = 1064; five studies; I2 = 0%), neutropenia (RR 1.19, 95%CI 0.93 to 1.54; participants = 1064; five studies; I2 = 24%), febrile neutropenia (RR 0.34, 95% CI 0.04 to 3.20; participants = 995; four studies; I2 = 0%), or thrombocytopenia (RR 1.58, 95% CI 0.82 to 3.04; participants = 995; four studies; I2 = 0%).

Grade 3 or higher non-hematological adverse events

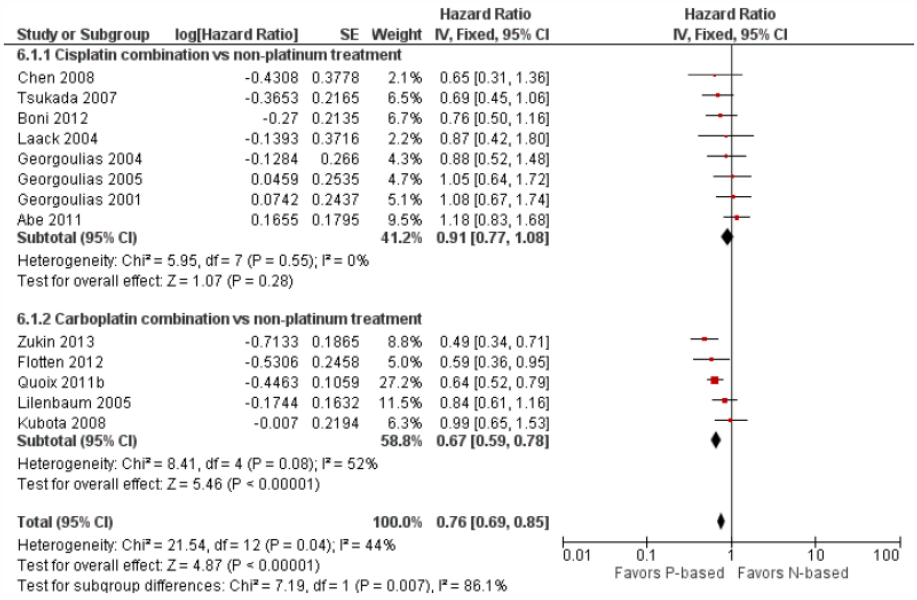
We found no significant differences in risk of fatigue (RR 1.16, 95%CI 0.69 to 1.96; participants = 995; four studies; I2 = 0%) or emesis (RR 1.73, 95% CI 0.68 to 4.43; participants = 995; four studies; I2 = 0%). For diarrhea, constipation, and mucositis, few grade 3 or 4 events were observed in all included trials

Non-platinum therapy versus platinum combination therapy

The meta-analysis of 13 RCTs involving 1705 elderly participants showed improvement in OS in favor of platinum combination treatment (HR 0.76, 95% CI 0.69 to 0.85), with moderate heterogeneity observed among trials (I2 = 44%)

Exploratory analysis by platinum agent showed improvement in OS for carboplatin combination treatment (HR 0.67, 95% CI 0.59 to 0.78) and no significant differences for cisplatin combination treatment (HR 0.91, 95% CI 0.77 to 1.08) over non-platinum therapy. Differences between subgroups reached statistical significance (Chi2= 7.16; P value = 0.007; I2 = 86%), suggesting greater benefit of carboplatin over cisplatin regimens when compared with non-platinum therapy.

Figure 7. Forest plot of comparison: 3 Overall survival analysis for platinum combination by cisplatin or carboplatin combination, outcome: 3.1 Overall survival by platinum agent.

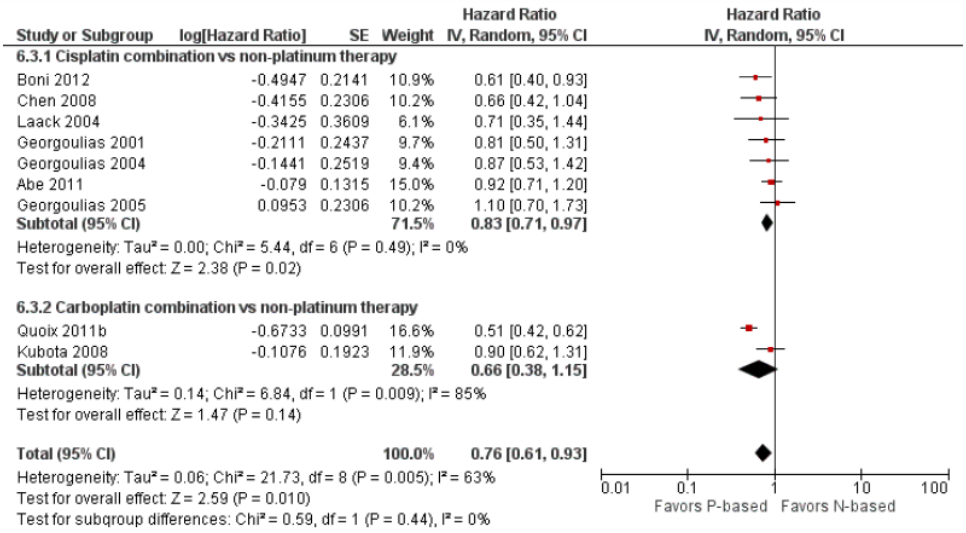


QoL: Only five RCTs included QoL assessment. However, we were not able to

performameta-analysis of these data because of the paucity of data provided.

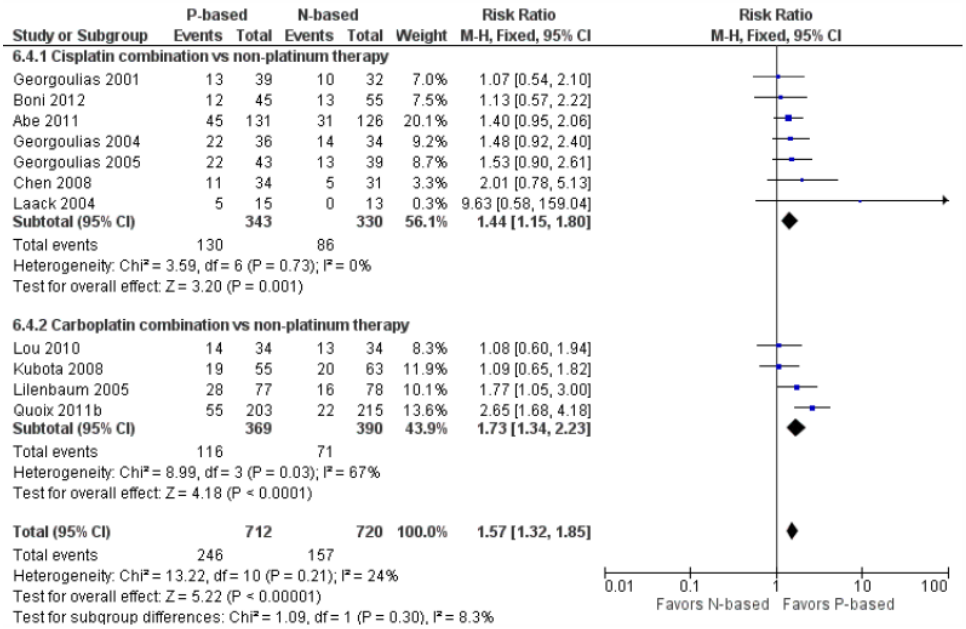
PFS: The meta-analysis of nine RCTs with 1273 elderly participants showed significant improvement in PFS in favor of platinum combination over non-platinum therapy (HR 0.70, 95% CI 0.63 to 0.79). In light of the presence of significant heterogeneity (I2 = 63%), we performed an analysis using a random-effects model, while maintaining a significant difference in PFS in favor of platinum combination (HR 0.76, 95% CI 0.61 to 0.93)

Figure 8. Forest plot of comparison: 3 Outcome analysis for platinum combination by cisplatin or carboplatin combination, outcome: 3.3 Progression-free survival by platinum agent.



ORR: The meta-analysis from 11 RCTs with 1432 elderly participants showed benefit in RR in favor of platinum combination over nonplatinum regimens with low heterogeneity among trials (RR 1.57, 95% CI 1.32 to 1.85; I2 = 24%)

Figure 9. Forest plot of comparison: 3 Outcome analysis for platinum combination by cisplatin or carboplatin combination, outcome: 3.4 Objective response rate by platinum agent.

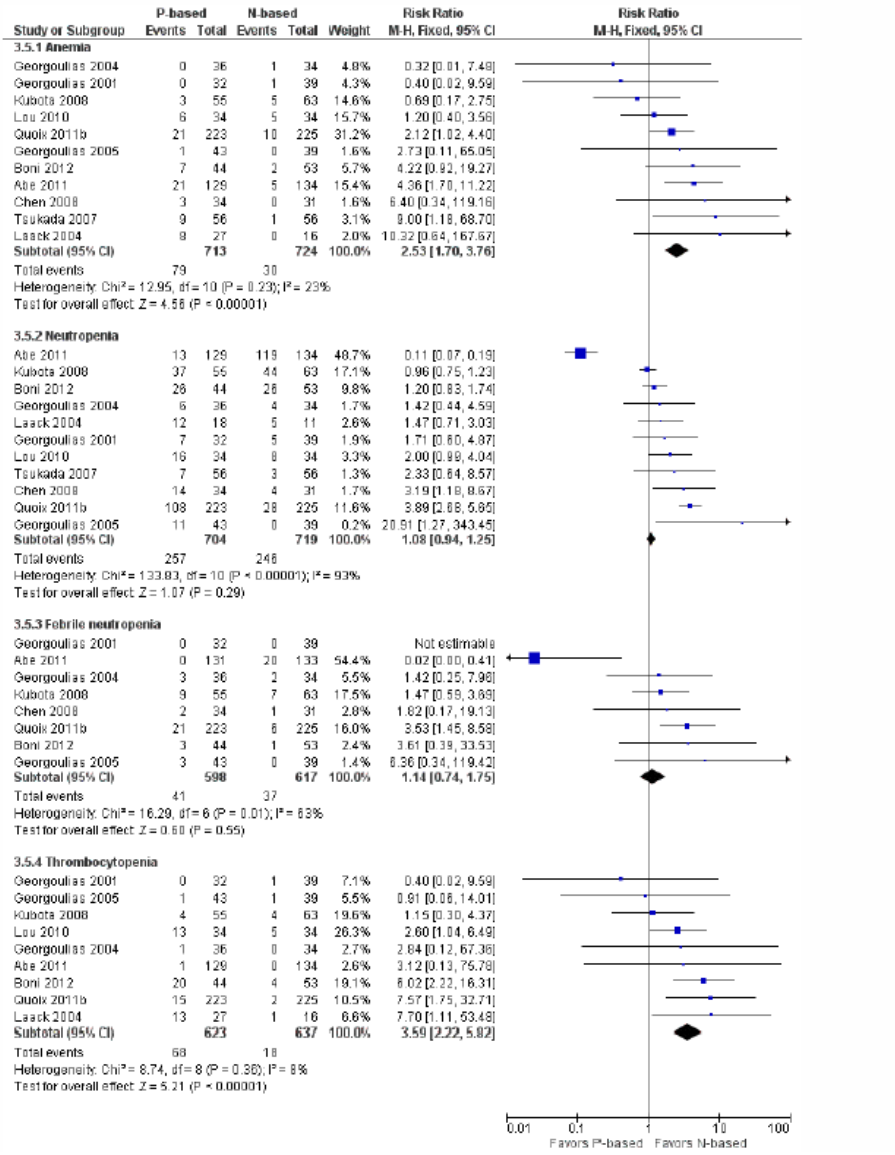


Toxicity:

Hematological grade 3 or higher adverse events

Using a fixed-effect model, we found greater risk of anemia (RR 2.53, 95% CI 1.70 to 3.76; participants = 1437; 11 studies; I2 = 23%) and thrombocytopenia (RR 3.59, 95% CI 2.22 to 5.82; participants = 1260; nine studies; I2 = 8%) for platinum combinations. We found no statistically significant differences in risks of neutropenia (RR 1.08, 95%CI 0.94 to 1.25; participants = 1423; 12 studies; I2 = 93%) and febrile neutropenia (RR 1.14, 95% CI 0.74 to 1.75; participants = 1215; eight studies; I2 = 63%), and results for both were associated with high heterogeneity among trials

Figure 10. Forest plot of comparison: 4 Non-platinum vs platinum combination therapy, outcome: 4.6 Grade 3 or higher hematological toxicity for platinum therapies.



Non-hematological grade 3 or higher adverse events

We found higher risk of fatigue (RR 1.56, 95% CI 1.02 to 2.38; participants =

	1150; seven studies; I2 = 0%), emesis (RR3.64, 95% CI 1.82 to 7.29), and peripheral neuropathy (RR 7.02, 95% CI 2.42 to 20.41; participants = 776; five studies; I2 = 0%) associated with platinum combination treatment. We found no statistically significant differences in the incidence of diarrhea (RR 1.75, 95% CI 0.91 to 3.38; participants = 1075; seven studies; I2 = 21%) and mucositis (RR 0.93, 95% CI 0.33 to 2.67; participants = 740; five studies; I2 = 0%)
	4. **Fazit der Autoren:** Our assessment of treatment effect supports the use of platinum combination for fit elderly patients with advanced NSCLC, with advantages for survival (number needed to treat for an additional beneficial outcome (NNTB) for 1yOS 12.6, 95% CI 7.8 to 34.5) and response rate (NNTB for ORR 8.0, 95% CI 5.0 to 14.3). Nonetheless, such treatment is also associated with greater risk of grade 3 or 4 hematological (number needed to treat for an additional harmful outcome (NNTH) for anemia 15.6, 95% CI 8.7 to 34.5; NNTH for thrombocytopenia 13.7, 95% CI 7.4 to 28.6) and non-hematological adverse events (NNTH for peripheral neuropathy 32.3, 95% CI 10.1 to 142.9). Exploratory analysis also suggests that carboplatin combinations should be preferred over cisplatin combinations; however, this finding should be interpreted with caution, as it was not based on a direct comparison between cisplatin and carboplatin combinations. For patients who are not candidates for platinum treatment (unfit), our findings suggest an increase in response rate in favor of non-platinum doublets, with similar efficacy for survival. Unfortunately, we also found scarce evidence on the impact of different treatment regimens on quality of life, challenging the process of decision making. 5. **Hinweis der FBMed** Der Mutationsstatus wurde in diesem CR nicht untersucht.

Systematische Reviews

Lai XX et al., 2016 [14].

Risk of adverse events with bevacizumab addition to therapy in advanced non-small-cell lung cancer: a meta-analysis of randomized controlled trials

1. Fragestellung

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor ligand, has shown survival benefits in the treatment of many types of malignant tumors, including non-small-cell lung cancer (NSCLC). We conducted this systematic review and meta-analysis to investigate the risk of the most clinically relevant adverse events related to bevacizumab in advanced NSCLC.

2. Methodik

Population: advanced NSCLC

Intervention/ Komparator: treatment with or without bevacizumab in addition to concurrent chemotherapy and/or biological agent

Endpunkt: AEs classified as grade ≥ 3 by the National Cancer nstitute – Common Toxicity Criteria (CTAE)

Suchzeitraum (Aktualität der Recherche): 2004 - 01/2014

Anzahl eingeschlossene Studien/Patienten (Gesamt): 9 (3745)

Qualitätsbewertung der Studien: Jadad scale

3. Ergebnisdarstellung

Three trials were double-blinded, randomized, placebo-controlled trials and had a Jadad score of 5. The other six trials had a Jadad score of 3.

Table 1 Baseline characteristics of nine trials included for analysis

Name of clinical trial	Author/year	Phase	Line of treatment	No of patients	Treatment regimens	Median age, y	Median PFS, m
NR	Johnson et al/2004	II	First line	99	Bevacizumab 2.5 mg/kg/wk + PTX + CBP	NR	4.3
					Bevacizumab 5 mg/kg/wk + PTX + CBP	NR	7.4
					PTX + CBP	NR	4.2
NR	Sandler et al/2006	III	First line	878	Bevacizumab 5 mg/kg/wk + PTX + CBP	NR	6.2
					PTX + CBP	NR	4.5
AVAil	Reck et al/2009	III	First line	1,043	Bevacizumab 5 mg/kg/wk + GEM + DDP	59	6.7
					Bevacizumab 2.5 mg/kg/wk + GEM + DDP	57	6.5
					Placebo + GEM + DDP	59	6.1
BeTa	Herbst et al/2011	III	Second line	636	Bevacizumab 5 mg/kg/wk + erlotinib	64.8	3.4
					Placebo + erlotinib	65	1.7
JO19907	Niho et al/2012	II	First line	180	Bevacizumab 5 mg/kg/wk + PTX + CBP	61	6.9
					PTX + CBP	60	5.9
JO25567	Seto et al/2014	II	First line	154	Bevacizumab 5 mg/kg/wk + erlotinib	67	16
					Placebo + erlotinib	67	9.7
ERACLE	Galetta et al/2015	III	First line	118	Bevacizumab 5 mg/kg/wk + PEM + DDP maintenance with bevacizumab	62	8.3
					PEM + DDP maintenance with PEM	60	8.1
BEYOND	Zhou et al/2015	III	First line	276	Bevacizumab 5 mg/kg/wk + PTX + CBP	57	9.2
					PTX + CBP	56	6.5
PRONOUNCE	Zinner et al/2015	III	First line	361	Bevacizumab 5 mg/kg/wk + PEM + DDP maintenance with bevacizumab	65.4	5.49
					PEM + DDP maintenance with PEM	65.8	4.44

Abbreviations: y, year; PFS, progression-free survival; m, month; NR, not reported; wk, week; PTX, paclitaxel; CBP, carboplatin; GEM, gemcitabine; DDP, cisplatin; PEM, pemetrexed.

No observed heterogeneity for VTEs, GI perforation, hypertension,

	proteinuria, hemorrhagic events, or fatal AEs was found except for ATEs (I^2=78.3%, P=0.003; Table 2). We thus used the random-effects model to pool the risk of ATEs related to bevacizumab. **Table 2** Relative risk of adverse outcomes for clinical trials included in the meta-analysis **Adverse outcome (grade ≥3)** | **Trials (n)** | **No of patients (n)** | | **Incidence, % (95%)** | | I^2 | **Relative risk (95%)** | ***P*-value** | | **Bevacizumab, events/total** | **Controls, events/total** | **Bevacizumab** | **Controls** | | | | ATEs | 4 | 32/1,079 | 16/877 | 2.6 (0.8%–7.9%) | 1.0 (0.2%–5.6%) | 78.3 | 2.83 (0.32–25.45) | 0.35 VTEs | 7 | 58/1,919 | 30/1,470 | 1.6 (0.5%–4.5%) | 1.8 (0.6%–5.6%) | 14.0 | 0.98 (0.64–1.51) | 0.92 GI perforation | 2 | 2/799 | 2/461 | 0.3 (0.1%–1.5%) | 0.6 (0.2%–1.9%) | 30.9 | 0.60 (0.09–4.10) | 0.60 Hypertension | 8 | 162/1,870 | 22/1,428 | 8.2 (3.5%–17.8%) | 1.7 (0.7%–4.2%) | 0 | 5.34 (3.49–8.16) | <0.001 Proteinuria | 6 | 32/1,491 | 0/1,083 | 2.5 (1.2%–5.3%) | 0 | 0 | 7.55 (2.26–25.22) | 0.001 Hemorrhagic events | 9 | 72/2,051 | 17/1,607 | 3.6 (2.5%–5.0%) | 1.4 (0.9%–2.2%) | 0 | 2.61 (1.57–4.35) | <0.001 Fatal adverse events | 8 | 89/1,977 | 51/1,530 | 4.6 (3.1%–6.7%) | 2.5 (1.2%–5.2%) | 43.9 | 1.21 (0.85–1.73) | 0.29 **Note:** I^2≥50% suggests high heterogeneity across studies. **Abbreviations:** ATEs, arterial thromboembolic events; VTEs, venous thromboembolic events; GI, gastrointestinal. Summary RRs showed a statistically significant bevacizumab-associated increased risk in three of the adverse outcomes studied: proteinuria (RR =7.55), hypertension (RR =5.34), and hemorrhagic events (RR =2.61). No statistically significant differences were found for gastrointestinal perforation (P=0.60), arterial and venous thromboembolic events (P=0.35 and P=0.92, respectively), or fatal events (P=0.29).
	4. Anmerkungen/Fazit der Autoren The addition of bevacizumab to therapy in advanced NSCLC did significantly increase the risk of proteinuria, hypertension, and hemorrhagic events but not arterial/venous thromboembolic events, gastrointestinal perforation, or fatal adverse events. **5. Hinweise der FBMed** • Eine der eingeschlossenen Primärstudien untersuchte Patienten in der 2. Linie, alle anderen bezogen sich auf die 1. Linie. • Der EGFR- oder ALK-Mutationsstatus der Patienten ist nicht untersucht/ dargestellt.
He X, Wang J, Li Y, 2015 [11]. Efficacy and safety of docetaxel for advanced non-small-cell lung cancer: a meta-analysis of Phase III randomized controlled trials	**1. Fragestellung** Several clinical trials have performed risk–benefit analyses comparing docetaxel and pemetrexed or docetaxel and vinca alkaloid, but the efficacy and safety remain uncertain. The aim was to conduct a meta-analysis to compare the efficacy and safety of docetaxel and pemetrexed or docetaxel and vinca alkaloid for non-small-cell lung cancer.
	2. Methodik Population: advanced NSCLC Intervention: docetaxel Komparator: pemetrexed or vinca alkaloid

Endpunkte: overall response rate (ORR), median survival time, progression-free survival (PFS), disease control rate, and toxicities
Suchzeitraum (Aktualität der Recherche): bis 24.1.2015
Anzahl eingeschlossene Studien/Patienten (Gesamt): 7 (2080)
Qualitätsbewertung der Studien: Jadad scoring system

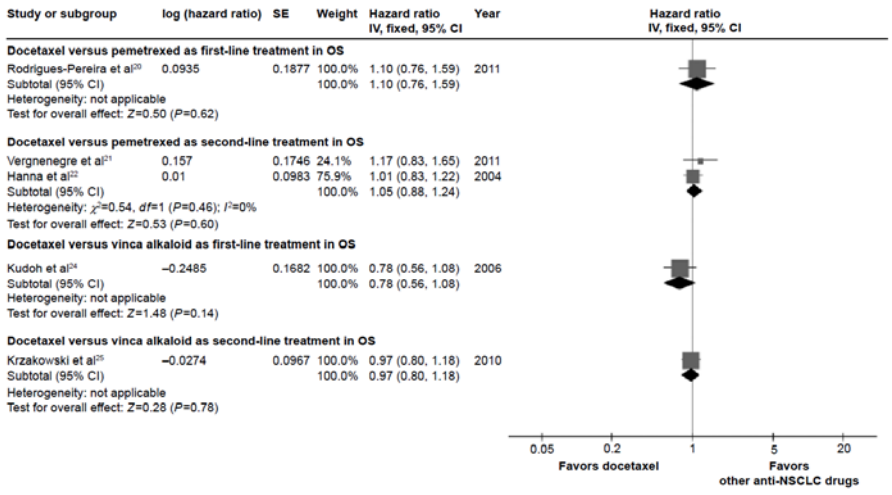
3. Ergebnisdarstellung

Table I Characteristics of the seven eligible Phase III randomized trials in this meta-analysis

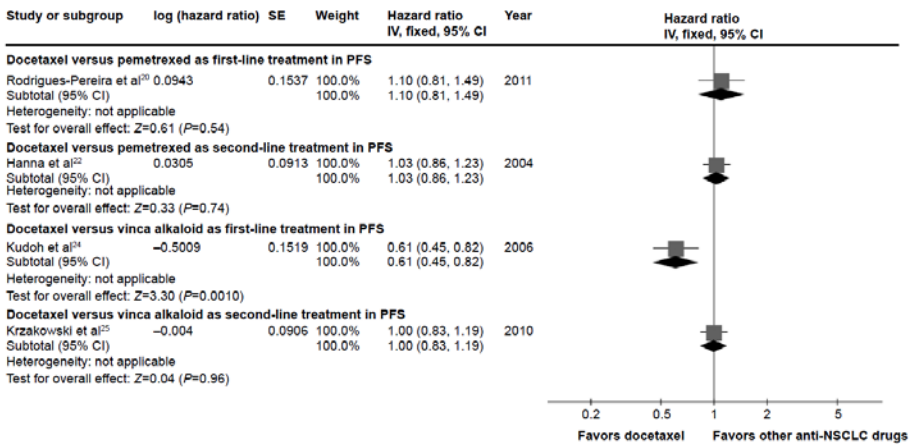
Study	Study region	Intervention	Number	Median age (years)	Male (%)	Stage	Outcome	Jadad score
Rodrigues-Pereira et al[20]	Argentina	Doc (75 mg/m²) + Carb	105	58.9	47.6	Stage IIIB/IV	SWT, OS, PFS	3
		Pem (500 mg/m²) + Carb	106	60.1	60.4			
Karampeazis et al[23]	Greece	Doc (38 mg/m²)	66	75.5	92.4	Stage IIIB/IV	OS, ORR, TTP, Toxl	4
		Vin (25 mg/m²)	64	77	93.8			
Vergnenegre et al[21]	France	Doc (75 mg/m²)	75	64	85.3	Stage IIIB/IV	OS, PFS, ORR, Toxl	3
		Pem (500 mg/m²)	75	62	82.7			
Krzakowski et al[25]	France	Doc (75 mg/m²)	275	60	75.3	Stage III/IV	PFS, ORR, OS	4
		Vfl (320 mg/m²)	262	61.9	75			
Kudoh et al[24]	Japan	Doc (60 mg/m²)	88	76	77.5	Stage IIIB/IV	OS, PFS, ORR, Toxl	3
		Vin (25 mg/m²)	91	76	74.7			
Hanna et al[22]	United States	Doc (75 mg/m²)	288	57	75.3	Stage III/IV	OS, PFS, ORR, Toxl	3
		Pem (500 mg/m²)	283	59	68.6			
Kubota et al[26]	Japan	Doc (60 mg/m²) + Cis	151	63	64.2	Stage IV	OS, ORR, Toxl	3
		Vds (3 mg/m²) + Cis	151	64	68.2			

Abbreviations: Doc, docetaxel; Carb, carboplatin; Pem, pemetrexed; Vin, vinorelbine; Vfl, vinflunine; Vds, vindesine; Cis, cisplatin; SWT, survival without grade 3 or 4 toxicity; OS, overall survival; PFS, progression-free survival; ORR, overall response rate; TTP, time to tumor progression; Toxl, toxicity indexes.

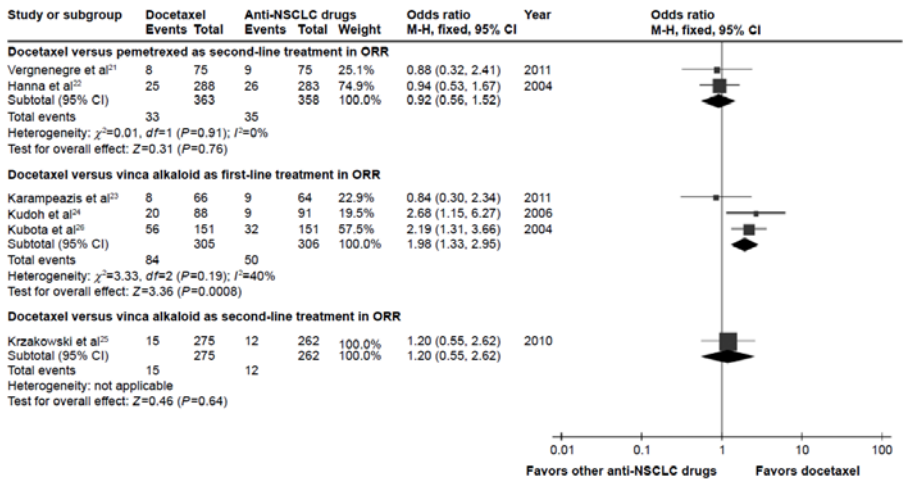
OS



PFS



ORR



AE

Table 2 Comparison of grade 3/4 toxicity between docetaxel and pemetrexed as first-line treatment

Grade 3/4 toxicity symptom	Docetaxel	Pemetrexed	OR (95% CI)	*P*-value
Hematologic events				
Neutropenia	68/105	35/106	3.73 (2.11, 6.59)	<0.00001
Anemia	2/105	13/106	0.14 (0.03, 0.63)	0.01
Thrombocytopenia	3/105	10/106	0.28 (0.08, 1.06)	0.06
Leukopenia	42/105	17/106	3.49 (1.82, 6.68)	0.0002
Febrile neutropenia	9/105	0/106	20.97 (1.20, 365.10)	0.04
Non-hematologic events				
Diarrhea	4/105	1/106	4.16 (0.46, 37.84)	0.21
Nausea	1/105	1/106	1.01 (0.06, 16.36)	0.99
Vomiting	0/105	1/106	0.33 (0.01, 8.28)	0.50

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 4 Comparison of grade 3/4 toxicity between docetaxel and vinca alkaloid as first-line treatment

Grade 3/4 toxicity symptom	Docetaxel	Vinca alkaloid	Heterogeneity		OR (95% CI)	*P*-value
			P-value	I^2		
Hematologic events						
Neutropenia	165/305	171/306	0.0001	89%	0.67 (0.19, 2.32)	0.53
Anemia	18/305	44/306	0.97	0%	0.37 (0.20, 0.65)	0.0007
Thrombocytopenia	1/305	0/306	–	–	3.02 (0.12, 74.72)	0.50
Leukopenia	120/239	149/242	0.003	89%	0.71 (0.23, 2.22)	0.56
Febrile neutropenia	12/154	11/155	0.91	0%	1.14 (0.48, 2.71)	0.77
Non-hematologic events						
Diarrhea	19/305	3/306	0.83	0%	5.94 (1.88, 18.73)	0.002
Nausea	23/305	15/306	0.72	0%	1.59 (0.82, 3.10)	0.17
Vomiting	13/305	8/306	0.31	4%	1.64 (0.68, 3.97)	0.27

Abbreviations: CI, confidence interval; OR, odds ratio.

	4. Anmerkungen/Fazit der Autoren Docetaxel leads to a better result than vinca alkaloid in effectiveness and safety on patients with advanced non-small-cell lung cancer as first-line therapy. […] However, the differences in efficacy and safety between docetaxel and pemetrexed are not obvious. Further clinical study with more details, such as sex, age, histology, and so on, should be considered for illustrating the differences between these two drugs.

Xiao HQ et al., 2016 [31]. Efficacy of pemetrexed plus platinum doublet chemotherapy as first-line treatment for advanced nonsquamous non-small-cell-lung cancer: a systematic review and meta-analysis	1. Fragestellung To assess the efficacy of pemetrexed plus platinum doublet chemotherapy as first-line treatment for advanced nonsquamous non-small-cell lung cancer (NSCLC) through a trial-level meta-analysis.
	2. Methodik Population: chemotherapy-naïve advanced nonsquamous NSCLC patients Intervention: pemetrexed plus platinum doublet chemotherapy Komparator: platinum plus other first-line chemotherapy Endpunkte: ORR, PFS; OS Suchzeitraum (Aktualität der Recherche): Systematische Literaturrecherche zwischen 1990 und 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): A total of 2,551 patients with advanced nonsquamous NSCLC from 10 trials Heterogenität: To measure overall heterogeneity across the included cohorts, we calculated the I2 statistic, with I2>50% indicating high heterogeneity. Qualitätsbewertung der Studien: Mittels Jadad scale.
	3. Ergebnisdarstellung Qualität der Studien: Four of the included trials did not mention the blinding of allocation clearly in the randomization process and thus had Jadad scores of 3.

Table 1 Baseline characteristics of ten trials included for meta-analysis

Source	Country	Chemotherapy regimen	Patients enrolled	Median age (years)	Median OS (months)	Median PFS (months)	ORR (%)
Scagliotti et al[8]	Multicenter	Pemetrexed + cisplatin	618	NR	11.8	5.3	NR
		Gemcitabine + cisplatin	614	NR	10.4	4.7	NR
Gronberg et al[10]	Multicenter	Pemetrexed + carboplatin	162	64	7.8	NR	NR
		Gemcitabine + carboplatin	167	66	7.5	NR	NR
Rodrigues-Pereira et al[20]	Multicenter	Pemetrexed + carboplatin	106	60.1	14.9	5.8	36
		Docetaxel + carboplatin	105	58.9	14.7	6	NR
Kim et al[14]	Japan	Pemetrexed + carboplatin	49	63	24.3	7.9	51
Kawano et al[15]	Japan	Pemetrexed + cisplatin	50	60	22.2	4.3	44.00
Zhang et al[21]	People's Republic of China	Pemetrexed + platinum	105	54	16.69	NR	NR
		Gemcitabine + platinum	100	55	16.66	NR	NR
Belani et al[16]	USA	Pemetrexed + cisplatin	57	59	15.9	7.1	26
Kanazawa et al[17]	Japan	Pemetrexed + carboplatin	41	63	16.2	4.7	37
Yu et al[18]	People's Republic of China	Pemetrexed + platinum	59	54.9	20.8	7	28
Paz-Ares et al[19]	Multicenter	Pemetrexed + cisplatin	318	60	11.5	5.6	32.08

Abbreviations: OS, overall survival; PFS, progression-free survival; ORR, objective response rate; NR, not reported.

- Overall, a total of 1,565 patients with advanced nonsquamous NSCLC receiving PPC and 986 with other platinum-based doublet chemotherapy were included; the pooled median PFS and OS were 5.7 and 16.05 months, respectively.
- A total of 680 patients from seven trials receiving PPC as first-line chemotherapy were included for ORR analysis. The pooled overall response rate was 37.8% (95% CI: 31.7%–44.3%). There was significant heterogeneity between the trials ($I2$=56.9%, P=0.031), and the pooled overall response was performed using a random-effects model.

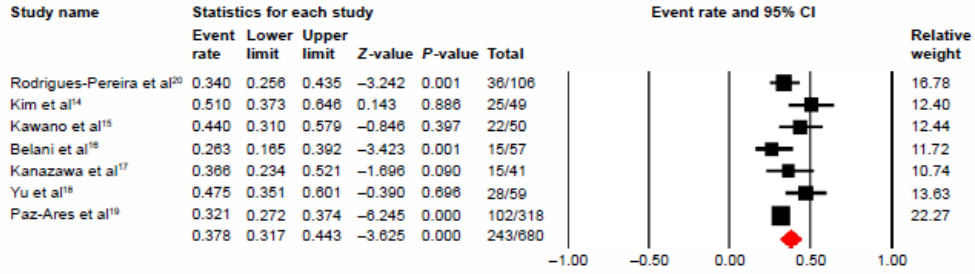


Figure 2 Random-effects model of ORR (95% CI) for pemetrexed plus platinum doublet chemotherapy.

Abbreviations: CI, confidence interval; ORR, objective response rate.

- All of the four RCTs reported OS data. The pooled results demonstrated that PPC significantly improved OS in comparison with other platinum-based doublet chemotherapy treatments (0.86, 95% CI: 0.77–0.97, P=0.01) using a fixed-effects model ($I2$=0%, P=0.65).

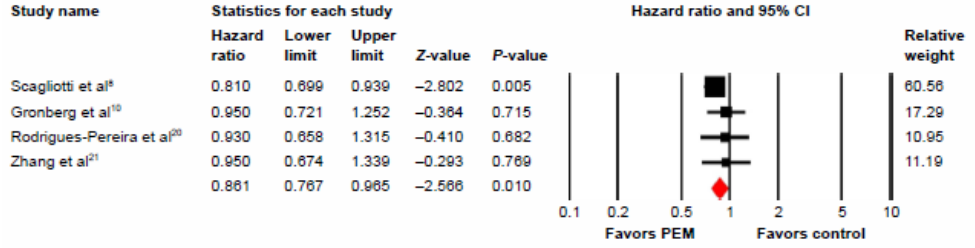


Figure 3 Fixed-effects model of HR (95% CI) of OS associated with PEM plus platinum versus other platinum-based chemotherapy.

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; PEM, pemetrexed.

	• Two of four RCTs reported PFS data. The pooled hazard ratio for PFS demonstrated that PPC tends to improve PFS by giving HR 0.90(not significant), compared with other platinum-based doublet chemotherapy in advanced nonsquamous NSCLC patients. There was no significant heterogeneity between trials (*I*2=0%, *P*=0.95), and the pooled HR for PFS was performed by using fixed-effects model.
	4. Fazit der Autoren • In conclusion, pemetrexed plus platinum doublet regimen is an efficacious treatment for advanced nonsquamous NSCLC patients. Our findings support the use of pemetrexed plus platinum doublet regimens as first-line treatment in advanced nonsquamous NSCLC patients because of its potential survival benefits. Further investigation of this regimen as first-line treatment in nonsquamous NSCLC patients is still warranted. • Der Mutationsstatus der Patienten in beiden Publikationen ist nicht dargestellt. Es ist daher nicht bekannt ob und in welchem Umfang Patienten mit einer EGFR oder ALK positive Mutation in den zugrunde liegenden Studien eingeschlossen wurden.

Pilkington G, et. al., 2015 [19]. A systematic review of the clinical effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer <u>Siehe auch</u>: **Brown T et al., 2013 [4].** Clinical effectiveness and cost-	**1. Fragestellung** Our aim was to evaluate the clinical effectiveness of chemotherapy treatments currently licensed in Europe and recommended by the National Institute for Health and Care Excellence (NICE) for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). Our review is unique in its focus on theefficacy of first-line treatments in the subpopulations of NSCLC patients, specifically patients with squamous disease, patients with non-squamous disease, and patients who are EGFR M+.
	2. Methodik **Population:** patients with locally advanced or metastatic NSCLC **Intervention:** first-line chemotherapy treatments. treatments had to be currently licensed for use in Europe and recommended by NICE **Komparator:** first-line chemotherapy treatments. treatments had to be currently licensed for use in Europe and recommended by NICE **Endpunkte:** OS, PFS, time to progression (TTP) **Suchzeitraum:** 2001-2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 23 RCTs **Qualitätsbewertung der Studien:** All RCTs were assessed for methodological quality using criteria based on the Centre for Reviews and Dissemination guidance for undertaking reviews in healthcare **Heterogenitätsuntersuchungen:** Statistical heterogeneity was assessed by

effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: a systematic review and economic evaluation	considering the χ2 test for heterogeneity with a 10% level of significance, and the I2 statistic with a value of 50% representing moderate heterogeneity

3. Ergebnisdarstellung

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

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

Baselinecharakteristika

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

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

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

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

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

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

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

NSCLC population with non-squamous disease

OS (20 RCTs)

- 9553 randomly assigned patients and 7608 deaths
- For patients with non-squamous disease, there is evidence that pemetrexed+platinum increases OS compared with gemcitabine+platinum (MA: HR 0.85, 95% CI 0.73 to 1.00; MTC-1: HR 0.85, 95% CI 0.74 to 0.98)
- There is no evidence to conclude that there is any statistically significant difference between any of the other chemotherapy treatments in terms of increasing OS for patients with nonsquamous disease.
- The MTC analysis shows a statistically significant difference between paclitaxel+platinum and docetaxel+platinum (HR 0.79, 95% CI 0.66 to 0.93), but the results of MA were not statistically significant.

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

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

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

Table 4 Top 10 adverse events by chemotherapy regimen

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

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

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

Der NICE Bericht von Brown et al. 2013 ist die Langversion zu Pilkington et al. 2015.

Sun L et al.,

1. Fragestellung:

2015 [28]. Efficacy and safety of chemotherapy or tyrosine kinase inhibitors combined with bevacizumab versus chemotherapy or tyrosine kinase inhibitors alone in the treatment of non-small cell lung cancer: a systematic review and meta-analysis Siehe auch **Sheng L et al., 2016 [25].** Targeted drugs for unselected patients with advanced non-small-cell lung cancer: a network meta-analysis	To evaluate the efficacy an;d safety of chemotherapy or tyrosine kinase inhibitors combined with bevacizumab versus chemotherapy or tyrosine kinase inhibitors alone in the treatment of non-small cell lung cancer (NSCLC)
	2. Methodik Population: advanced stage IIIB/IV or recurrent NSCLC with ECOG performance status of 0–2 or Karnofsky performance score 60 Intervention: chemotherapy or EGFR-TKIs plus bevacizumab; first-line or secondline treatment Komparator: chemotherapy or EGFR-TKIs; first-line or secondline treatment Endpunkte: PFS, OS, ORR, AE grade ≥3 Suchzeitraum: bis 1.Oktober 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 9 RCTs (n= 3547); 7 RCTs first-line (n=2,528) Qualitätsbewertung der Studien: Cochrane Collaboration risk of bias tool und Publikaionsbias Heterogenitätsuntersuchungen: Cochran Q statistic andinconsistency index (I2 statistic). If the P value was <0.10, I2>50 % or the Q statistic indicated significant heterogeneity, the reason for the heterogeneity was examined using the random-effects model (DerSimonian–Laird method). Otherwise, the fixed-effects model (Mantel– Haenszel method) was used.
	3. Ergebnisdarstellung Among these studies, there were seven first-line studies including 2,528 cases and two second-line studies including 756 cases; two studies compared the combination of bevacizumab and EGFR-TKIs with EGFR-TKIs alone, and seven compared combination treatment with bevacizumab and chemotherapy to chemotherapy alone. Characteristics of the included studies:

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

PCb paclitaxel-carboplatin, GCis gemcitabine-cisplatin, DCb docetaxel-carboplatin, Bev bevacizumab, Erl erlotinib, CT chemotherapy with docetaxel or pemetrexed, Ade. adenocarcinoma, LCC large cell carcinoma, SCC squamous cell carcinoma, BAC bronchioloalveolar carcinoma

Kein Publikationsbias

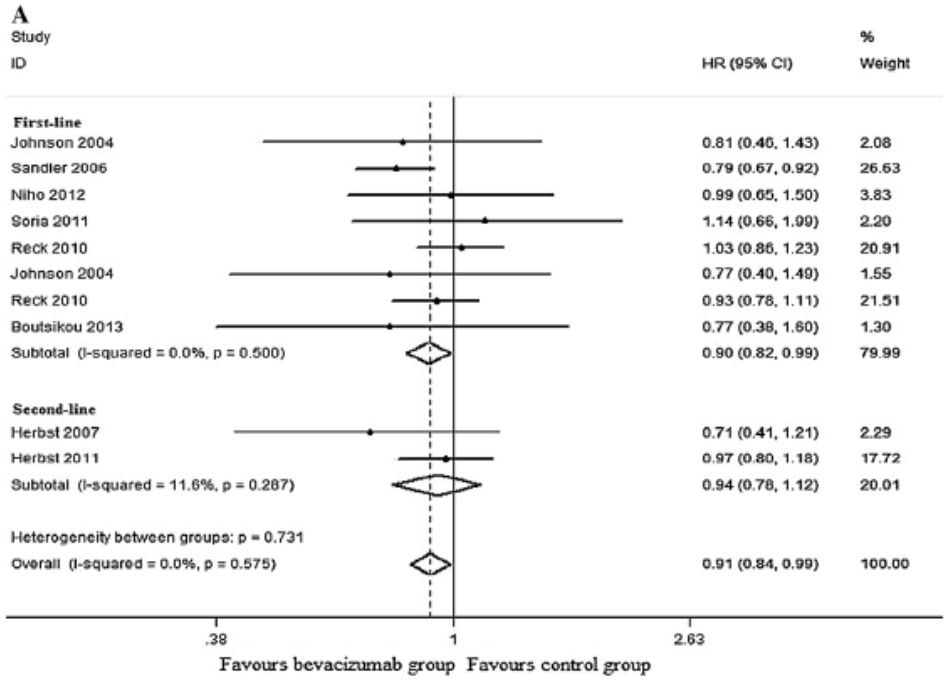
There was slight heterogeneity in the pooled analysis of ORR between different treatment protocols and different lines, and a random-effects model was used for final analysis. There was no significant heterogeneity in the analysis of other indexes, and a fixed-effects model was used.

Unterscheidung nach Therapielinie:

Forest plots comparing bevacizumab combined with chemotherapy or TKI to chemotherapy or TKI alone in first- and second-line treatments. The Chi-squared test showed no significant heterogeneity between the trials. The fixed-effects model was used

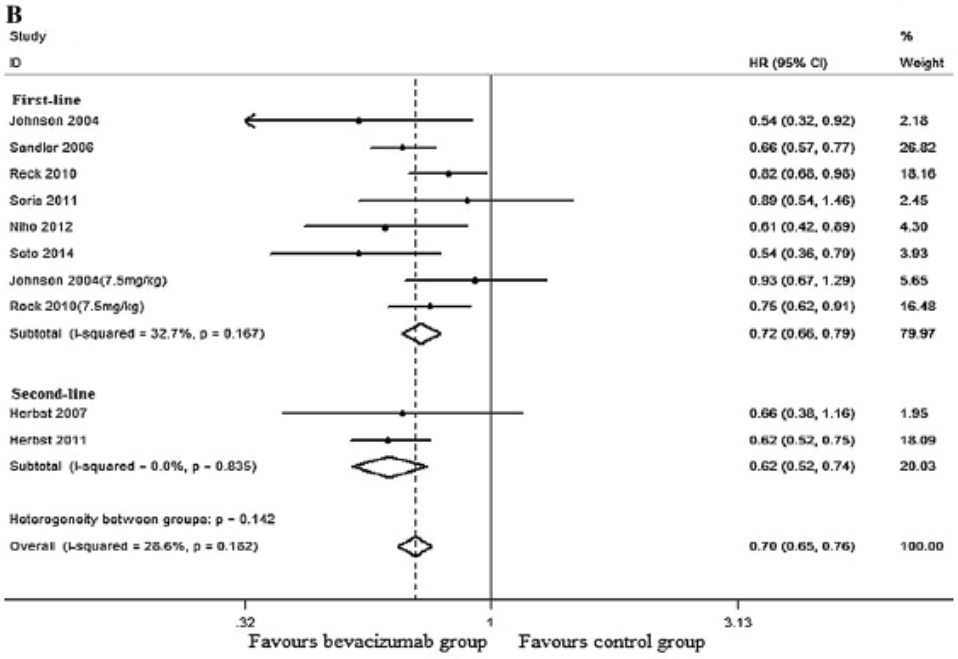
HR for OS:

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



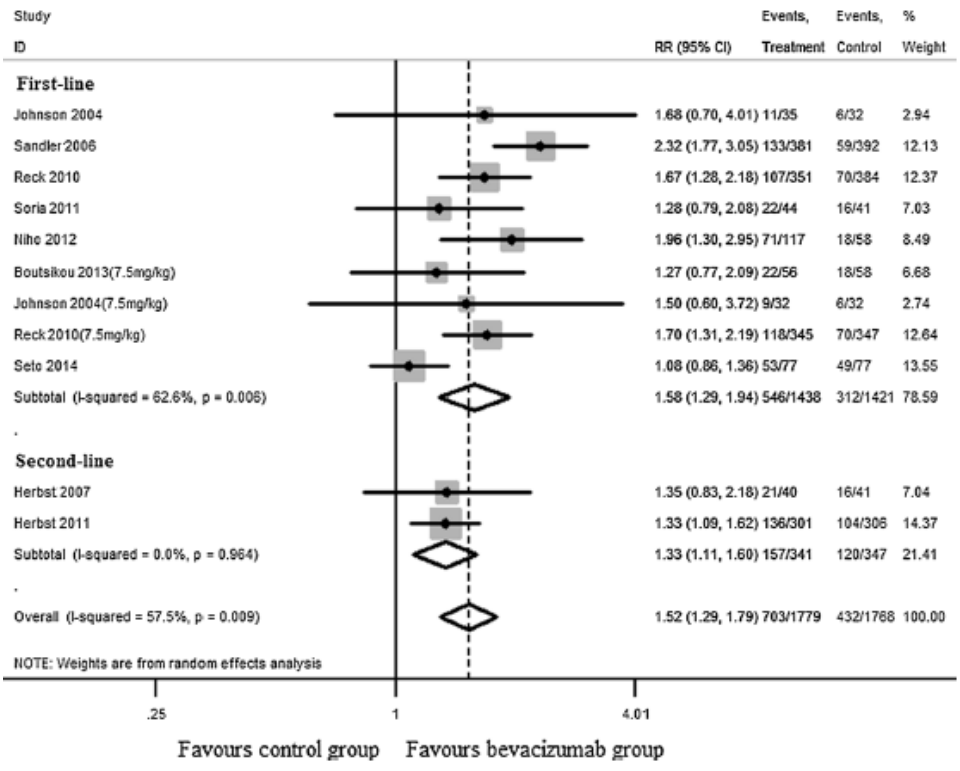
HR for PFS

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



RR for ORR

stat. signifikanter Vorteil für die Kombination mit Bevacizumab in der Erstlinie (RR 1.58, 95 % CI 1.28–1.95, P<0.001).



4. Anmerkungen/Fazit der Autoren

The addition of bevacizumab to chemotherapy or erlotinib can significantly improve PFS and ORR in the first- and second-line treatment of advanced NSCLC, with an acceptable and tolerated risk of bleeding events, hypertension, proteinuria, and rash. Bevacizumab plus chemotherapy can also provide an OS benefit

5. Hinweis der FBMed:

- Aufgrund des vorliegenden Anwendungsgebietes sind nur die Auswertungen der First-Line von Relevanz
- In die Auswertungen zu den Endpunkten PFS, RR, für die First-Line Behandlung ging mit der Studie von Seto 2014 eine Kombination von Erlotinib in die Auswertung mit ein.
- Bevacizumab plus Chemotherapie vs Chemotherapie wurde im Rahmen einer Netzwerkmetaanalyse ebenfalls von **Sheng et al. 2016** untersucht. Dabei untersuchten die Autoren ORR sowie safety, schlossen jedoch nur fünf von sechs der in **Sun et al. 2015** zugrundeliegenden Studien ein. Ein Grund für diese Diskrepanz ist nicht ersichtlich. Die Schlussfolgerung war dennoch vergleichbar: In summary, our study suggested that the use of bevacizumab in combination with chemotherapy in the treatment of unselected patients with advanced NSCLC may offer a greater ORR

Mörth C et al., 2014 [17].	**1. Fragestellung** The purpose of this study was to compare the efficacy and tolerability of first-line

Single-agent versus combination chemotherapy as first-line treatment for patients with advanced non-small cell lung cancer and performance status 2: a literature-based meta-analysis of randomized studies Siehe auch: **Luo et al., 2015 [15].** Comparing single-agent with doublet chemotherapy in first-line treatment of advanced non-small cell lung cancer with performance status 2: a meta-analysis	treatment with combination versus single agent chemotherapy in patients with advanced non-small cell lung cancer (NSCLC) and performance status (PS) 2
	2. Methodik **Population:** advanced NCSLC mit PS 2 **Intervention:** combination chemotherapy **Komparator:** single agent chemotherapy **Endpunkte:** OS, PFS, ORR **Suchzeitraum:** Bis 07/2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 12 (1114) **Qualitätsbewertung der Studien:** Cochrane's risk of bias tool; Publication bias was assessed with the construction of contour enhanced funnel plots. **Heterogenitätsuntersuchungen:** I^2
	3. Ergebnisdarstellung **MÖRTH et al.** **Table 1** Characteristics of eligible trials. Author [trial name] (ref) / Study phase / Treatment arms / Dose and schedule of chemotherapy / PS analysis / No of patients Kosmidis [8] / II / Gemcitabine / 1250 mg/m² day 1 + 14, q4w / Dedicated to PS 2 / 47 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 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 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 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 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 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 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 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 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 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 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 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 heterogeneity was observed **OS (11 Studien, 1114 Patienten):** • significant improvement in OS in favor of combination treatment compared with single-agent chemotherapy (HR:0.79, 95% CI: 0.71–0.88, p-value <

0.001)

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

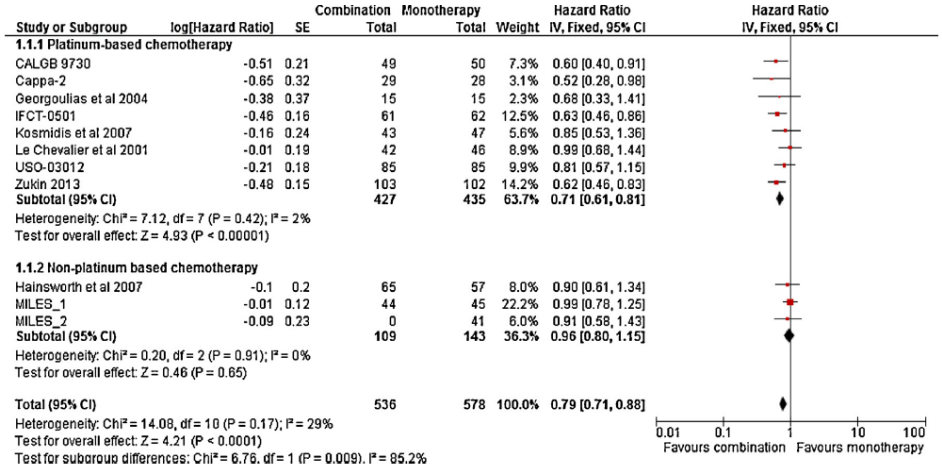


Fig. 2. Forest plot for overall survival (with subgroup analysis based on the administration of platinum-based or non-platinum based chemotherapy in combination arms).The size of the squares indicates the weight of the study. Error bars represent 95% confidence intervals (CIs). The diamond indicates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

PFS (5 Studien, 522 Patienten)

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

ORR (8 Studien, 822 Patienten)

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

grades III and IV toxicity (4 Studien)

Due to lack of adequate data, we could not perform meta-analysis on the incidence of other toxicities.

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

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

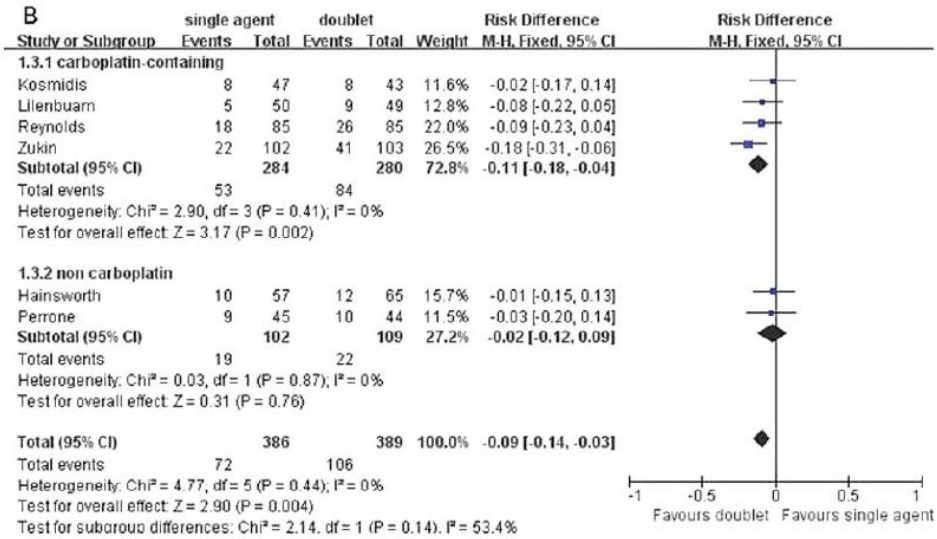
Abbreviations: No: number; OR: odds ratio; CI: confidence interval.

Luo et al.

Mortalität:

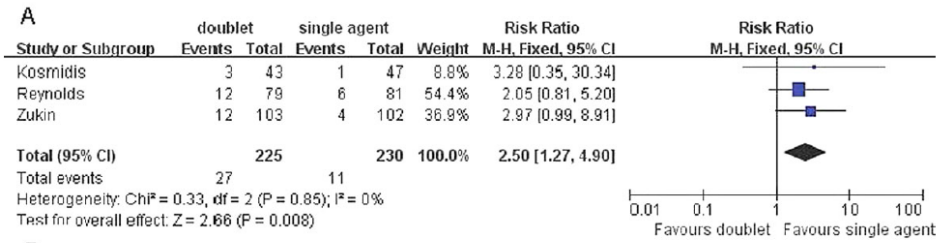
Für OS vergleichbare Ergebnisse wie Mörth et al.

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



Toxizität:

A



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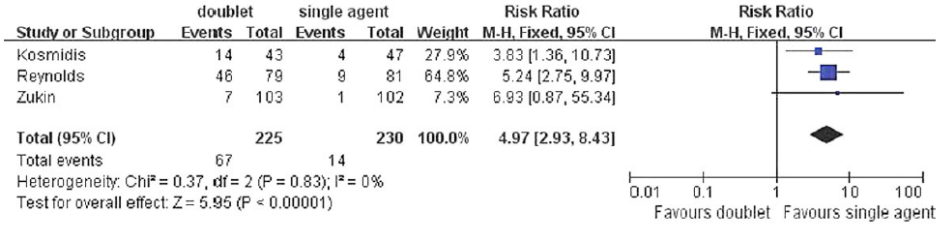

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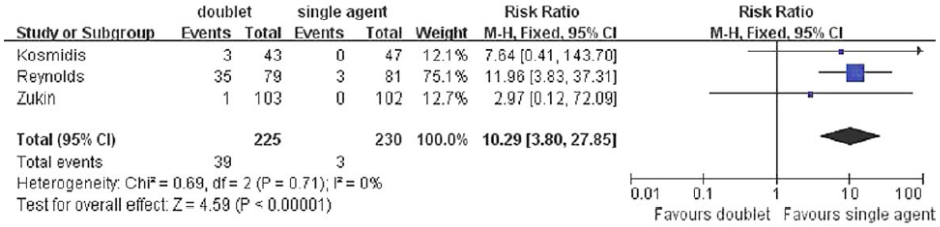


4. Fazit der Autoren

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

This meta-analysis provides evidence supporting the use of combination chemotherapy in patients with NSCLC and PS 2. However, the patients should be informed about the higher risk for toxicity with the combination chemotherapy and the final treatment strategy should be individualized

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

Hinweise durch FB Med

Die Ergebnisse von Luo et al. sind mit den Ergebnissen von Mörth et al. vergleichbar. Alle in Luo eingeschlossenen Studien (insgesamt 6) wurden auch in Mörth eingeschlossen, jedoch wurden in Mörth noch 6 weitere Studien eingeschlossen. Diese Diskrepanz lässt sich weder durch den Suchzeitraum noch durch andere Parameter erklären. Luo fand, ohne dies explizit in den Ein- und

	Ausschlussgründen zu nennen, ausschließlich Studien zu Carboplatin, während bei Mörth auch Studien zu Cisplatin eingeschlossen wurden. Luo untersuchte neben OS auch Ansprechen und die 1-Jahres Überlebensrate. • Der Mutationsstatus der Patienten in den beiden Publikationen ist nicht dargestellt. Es ist daher nicht bekannt ob und in welchem Umfang Patienten mit einer EGFR oder ALK positive Mutation in den zugrunde liegenden Studien eingeschlossen wurden.
Shen G 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	• Fragestellung To compare the VC and DC regimens in the first‐line treatment of advanced NSCLC.
	• Methodik **Population:** 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) **Endpunkt**: 1- and 2‐year survival rate, ORR, Toxicity **Suchzeitraum**: Bis Mai 2013 **Anzahl eingeschlossene Studien/Patienten:** 9 RCTs mit 1886 Patienten **Qualitätsbewertung der Studien:** Jaded Score **Heterogenitätsuntersuchungen**: The heterogeneity of the studies was also assessed and P<0.1 was defined as heterogenous. If the test indicated heterogeneity across studies, the random effects model (Der Simonian and Laird) was selected. Otherwise, we used the fixed effects model (Mantel-Haenszel) to analyze two treatment groups.
	• Ergebnisdarstellung 7 trials were phase II and the remaining were phase III RCTs. Randomization was stated in all trials; however, only 5 described the detailed methods of randomization. None of the trials were double‐blind and all trials reported withdrawals and drop‐outs. Overall, 1,886 patients were randomized to receive VC or DC chemotherapy (950 and 936 patients, respectively)

Table I. Baseline characteristics of the 9 trials comparing VC with DC in the treatment of advanced non-small-cell lung cancer.

Patient no.	Treatment regimen	Mean age (years)	Disease stage (%IIIB/IV)	Quality scores	Year (refs.)
404	Vin 25 mg/m² d1, 8, 15 and 22 + cispl 100 mg/m² d1[a]	61	33/67	3	2003 (11)
408	Doc 75 mg/m² d1 + cispl 75 mg/m² d1	61	33/67		
118	Vin 30 mg/m² d1, 8 + cispl 100 mg/m² d1	57	0/100	3	2005 (15)
115	Doc 75 mg/m² d1 + cispl 100 mg/m² d1	58	0/100		
33	Vin 25 mg/m² d1, 8 + cispl 20 mg/m² d1-3	56	46/54	2	2006 (16)
26	Doc 37.5 mg/m² d1, 8 + cispl 20 mg/m² d1-3	55	27/73		
48	Vin 25 mg/m² d1, 8 + cispl 60 mg/m² d1	65	17/83	3	2007 (17)
46	Doc 160 mg/m² d1 + cispl 60 mg/m² d1	60	20/80		
45	Vin 30 mg/m² d1, 8 + cispl 25 mg/m² d1-3	51	58/42	3	2007 (18)
42	Doc 75 mg/m² d1 + cispl 30 mg/m² d1-3	47	60/40		
33	Vin 25 mg/m² d1, 8 + cispl 75 mg/m² d1	-	55/45	2	2007 (19)
34	Doc 75 mg/m² d1 + cispl 75 mg/m² d1	-	59/41		
35	Vin 25 mg/m² d1, 8 + cispl 27 mg/m² d1-3	62	63/37	2	2007 (20)
32	Doc 37.5 mg/m² d1, 8 + cispl 27 mg/m² d1-3	61	63/37		
190	Vin 30 mg/m² d 1iv, 80 mg/m² d8 oral + cispl 80 mg/m² d1	59	20/80	3	2009 (21)
191	Doc 75 mg/m² d1 + cispl 75 mg/m² d1	62	15/85		
44	Vin 30 mg/m² d1, 8 + cispl 80 mg/m² d1	62	20/80	2	2009 (22)
42	Doc 75 mg/m² d1 + cispl 75 mg/m² d1	61	19/81		

[a]28 days per cycle; the remaining, 21 days per cycle. Vin, vinorelbin; doc, docetaxel; cispl, cisplatin; VC, vinorelbine plus cisplatin; DC, docetaxel plus cisplatin; yrs, years; d, day; iv, intravenous.

ORR (9 RTCs):

The intention‐to‐treat analysis demonstrated that the overall response rate of the VC group was 28.11% and that of the DC group was 33.65%. The patients receiving DC therapy exhibited a significantly higher response rate (RR=0.83, 95% CI: 0.73‐0.95 and P<0.05). There was no heterogeneity between the compared groups (χ2=5.71; P=0.68; I2=0%).

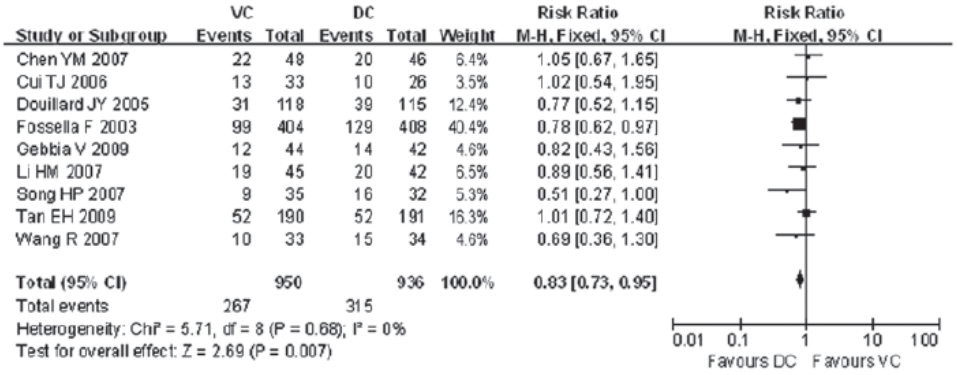


Figure 1. The overall response rate analysis of vinorelbine plus cisplatin (VC) or docetaxel plus cisplatin (DC) for advanced non-small-cell lung cancer (NSCLC). The fixed effects model was applied. Relative risk (RR) ratio and 95% confidence interval (CI) for each study are also plotted on the graph.

1- and 2‐year survival rate (7 RTCs):

The 1‐year survival rates of the VC and DC group were comparable (RR=0.90, 95% CI: 0.81‐1.01 and P=0.07) and there was no heterogeneity (χ2=2.08; P=0.91; I2=0%). Furthermore, as shown in, patients treated with the DC regimen benefited from a significant reduction in the risk of mortality within the first 2 years (RR=0.65, 95% CI: 0.50‐0.84 and P=0.001), as shown in the 2‐year survival analysis of 4 trials.

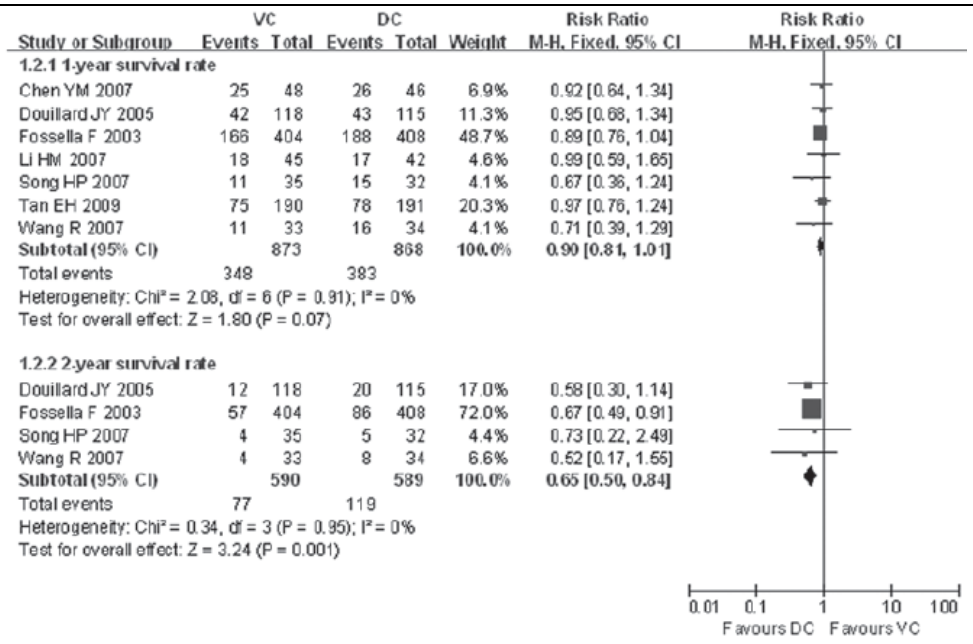


Figure 2. The 1-and 2-year survival analysis of vinorelbine plus cisplatin (VC) or docetaxel plus cisplatin (DC) for advanced non-small-cell lung cancer (NSCLC). The fixed effects model was applied. Relative risk (RR) ratio and 95% confidence interval (CI) for each study are also plotted on the graph.

Toxicity (9 RTCs)

The adverse effects of chemotherapy were described as number of cases experiencing grade 3/4 toxicity. The most frequently reported toxicities included leucopenia, neutropenia, thrombocytopenia, anemia, nausea and vomiting and diarrhea. VC chemotherapy was more frequently associated with grade 3/4 leucopenia, anemia and vomiting (OR=1.26, 95% CI: 1.02‑1.54 and P<0.05; OR=3.40; 95% CI: 2.42‑4.76 and P<0.05; and OR=1.58, 95% CI: 1.14‑2.20 and P<0.05, respectively), whereas patients receiving DC chemotherapy were more prone to grade 3/4 diarrhea (OR=0.31, 95% CI: 0.18‑0.55 and P<0.0001). However, the incidence of neutropenia, thrombocytopenia and nausea were not significantly different between the two groups (OR=1.46, 95% CI: 0.93‑2.29 and P=0.10; OR=1.69, 95% CI: 0.97‑2.96 and P=0.06; and OR=0.94; 95% CI: 0.37‑2.38 and P=0.90, respectively).

Table II. Summary of grade 3/4 toxicities in VC and DC for advanced non-small-cell lung cancer.

		No. of cases		Test of homogeneity			
Toxicity	No. of studies	VC	DC	I^2 (%)	P-value	OR (95% CI)	P-value
Leucopenia	8	338/822	298/817	21	0.26	1.26 (1.02, 1.54)[a]	0.03
Neutropenia	6	561/829	524/830	65	0.01	1.46 (0.93, 2.29)[b]	0.10
Thrombocytopenia	8	33/907	19/898	0	0.88	1.69 (0.97, 2.96)[a]	0.06
Anemia	6	146/686	51/683	48	0.09	3.40 (2.42, 4.76)[a]	<0.0001
Nausea	4	88/752	72/758	77	0.004	0.94 (0.37, 2.38)[b]	0.90
Vomiting	6	99/831	66/832	47	0.10	1.58 (1.14, 2.20)[a]	0.006
Diarrhea	6	15/829	49/826	0	0.71	0.31 (0.18, 0.55)[a]	<0.0001

[a]Fixed effects model. [b]Random effects model. VC, vinorelbine plus cisplatin ; DC, docetaxel plus cisplatin; OR, odds ratio; CI, confidence interval.

- Anmerkungen/Fazit der Autoren

We observed that patients receiving DC therapy exhibited higher response and 2‑year survival rates compared to those who received VC therapy;

	however there was no significant difference in the 1‐year survival rate between the VC and DC groups. Since second‐line treatment may affect survival, the unbalanced post‐study treatment may have had an impact on the survival analysis of our study. In conclusion, this meta-analysis revealed that DC therapy exhibited a marginally better response rate and 2-year survival rate and a milder toxicity profile compared to VC. Therefore, the former may be the better choice for patients with advanced NSCLC. However, these results need to be interpreted with caution, as the outcome of these meta-analyses on the basis of summary data derived from the literature may be affected by several biases. **Hinweise durch FB Med** Der Mutationsstatus der Patienten in den beiden Publikationen ist nicht dargestellt. Es ist daher nicht bekannt ob und in welchem Umfang Patienten mit einer EGFR oder ALK positive Mutation in den zugrunde liegenden Studien eingeschlossen wurden.
Cui J et al., 2013 [5]. The Efficacy of Bevacizumab Compared with Other Targeted Drugs for Patients with Advanced NSCLC: A Meta-Analysis from 30 Randomized Controlled Clinical Trials	**1. Fragestellung** The extent of the benefit of bevacizumab combined with chemotherapy in the treatment of advanced nonsmall- cell lung cancer (NSCLC) is still unclear. We performed this meta-analysis to compare the efficacy of bevacizumab with other commonly used targeted drugs for different patients with advanced NSCLC.
	2. Methodik **Population**: patients with confirmed stage IIIB, stage IV or recurrent NSCLC based on historical or cytological evidence, 1. und 2. Linie **Intervention**: bevacizumab (15 mg/kg) with chemotherapy **Komparator**: standard chemotherapy alone **Endpunkt**: OS, ORR, PFS **Methode**: systematic review and meta-analysis of RCTs (placebo-controlled or other types of superiority trial as well as noninferiorityv trial) **Suchzeitraum**: 1999 to 2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 30 (k.A.) **Qualitätsbewertung der Primärstudien:** Jadad Score
	3. Ergebnisdarstellung ***Erste Linie (chemotherapy-naıve patients)*** the pooled OR of response rate was 2.741(95%CI: 2.046, 3.672), the pooled HR for disease progression was 0.645 (95%CI: 0.561, 0.743), the pooled HR for death was 0.790 (95%CI: 0.674, 0.926), respectively **2. Linie** adjusted HR for previously-treated patients was 0.680 (95%CI: 0.492, 0.942) EGFR-Status

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

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

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

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

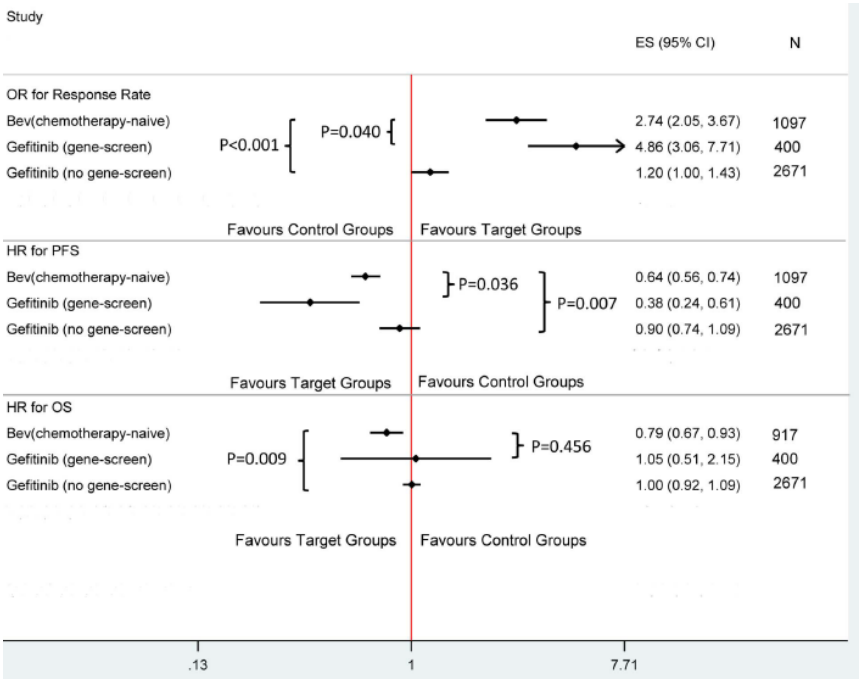


Fig. 3 Response rate, PFS, OS of Bevacizumab versus Gefitinib in NSCLC patients with different EGFR status.

4. Fazit der Autoren:

Our meta-analyses showed that compared to other commonly used targeted drugs, chemotherapy with bevacizumab significantly improved patients'

	response rate, PFS and OS. In addition, bevacizumab provided significantly higher OR_{ORR}, lower HR_{PFS}, and lower HR_{OS} among chemotherapy-naıve patients, and lower HR_{PFS} among previous treated patients. It was also found that in EGFRmutated patients, gefitinib significantly improved OR_{ORR} and reduces HR_{PFS}. However, in general patients with EGFR status untested, bevacizumab showed a clear benefit in OR_{ORR}, HR_{PFS}, as well as HR_{OS}, compared with gefitinib. 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.
Jiang J et al., 2013 [13]. Paclitaxel plus platinum or gemcitabine plus platinum in first-line treatment of advanced non-small-cell lung cancer: results from 6 randomized controlled trials	**1. Fragestellung** The goal of this study was to compare the efficacy and toxicity of paclitaxel plus platinum (TP) regimens with GP regimens in patients with untreated advanced NSCLC by a meta-analysis of randomized controlled trials.
	2. Methodik **Population:** patients must be cytologically or pathologically confirmed with NSCLC and in clinical stage III–IV; patients must be chemotherapynaı¨ve **Intervention:** paclitaxel plus cisplatin or carboplatin (TP) **Komparator:** gemcitabine plus cisplatin or carboplatin (GP) **Endpunkt:** numbers of patients who had overall response (complete response plus partial response), disease control rate (overall response plus stable disease), chemotherapy regimens, and 1-year survival Toxicity data such as numbers of patients experiencing grade 3 or 4 nausea or vomiting, sensory neuropathy, fatigue, anemia, neutropenia and thrombocytopenia were extracted. **Suchzeitraum:** bis 05/2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 6 (2793) **Qualitätsbewertung der Studien:** Jadad
	3. Ergebnisdarstellung

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

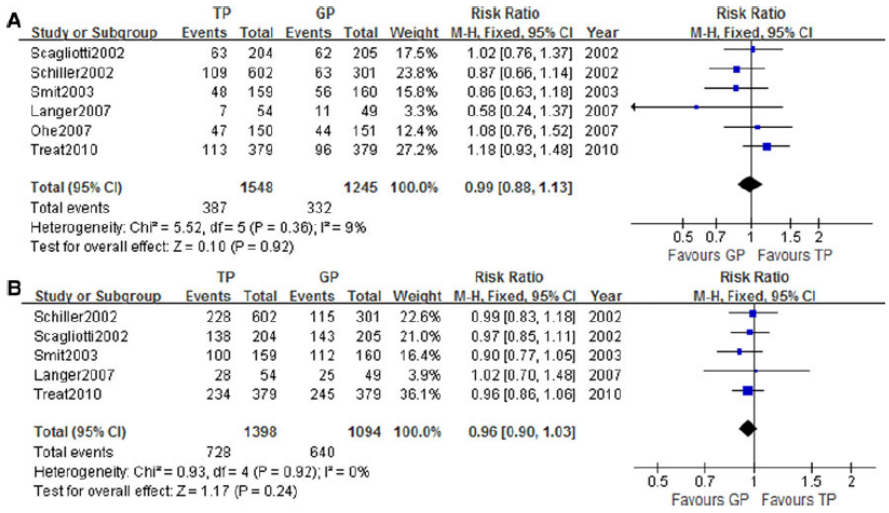
Study ID [references]	Regimens	*n*(ITT)	*n*(t)	Male (%)	PS 0–1 (%)	Median age (years)	SCC (%)	IV or recurrent (%)	MST (95 % CI) (months)
Scagliotti2002 [19]	G 1250 mg/m^2 d1,8 + P 75 mg/m^2 d1	205	205	81.0	95	63	33.0	81.0	9.8 (8.6–11.2)
	T 225 mg/m2 d1 + C AUC 6.0 d1	204	201	76.0	92	62	32.0	82.0	10.0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

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

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

OR

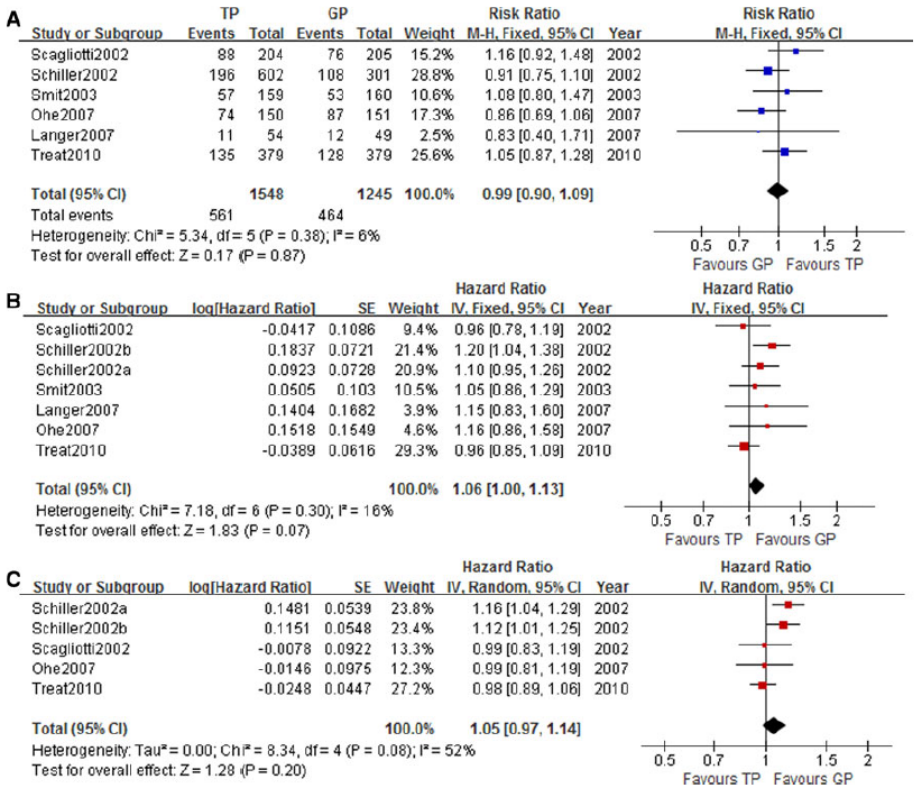
Fig. 2 Response analyses. a The pooled RR for overall response showed no difference between the GP and TP groups (RR = 0.99, 95 % CI = 0.88–1.13, p = 0.92). b The pooled RR for disease control rate also showed no difference between the GP and TP groups (RR = 0.96, 95 % CI = 0.90–1.03, p = 0.24)



OS

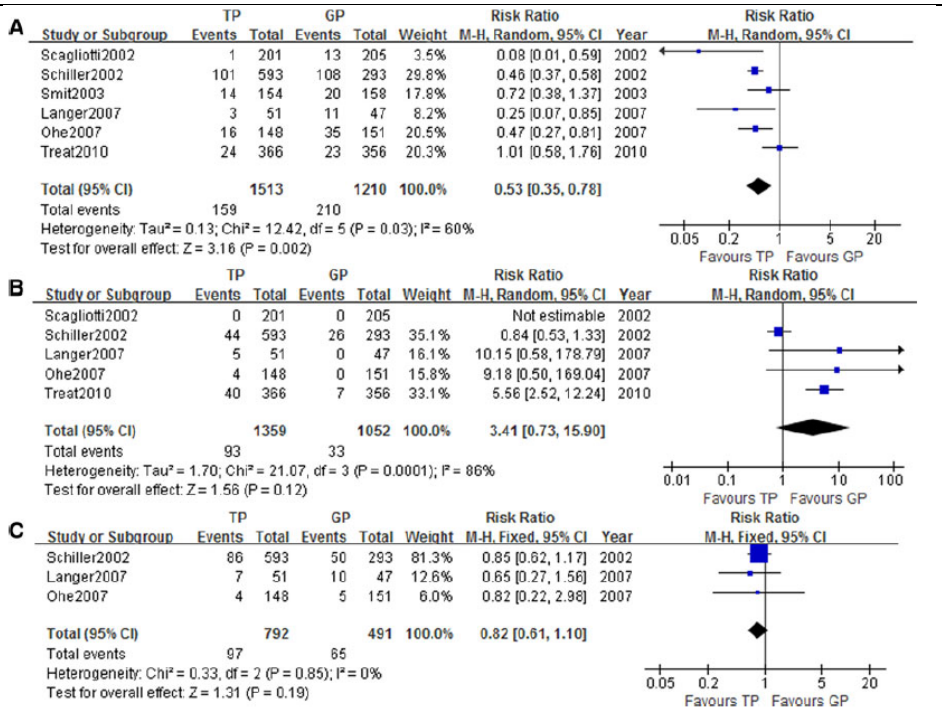
Survival analyses. a The pooled RR for 1-year survival showed no difference between the GP and TP groups (RR = 0.99, 95 % CI = 0.90–1.09, p = 0.87). b The pooled HR for overall survival showed no difference between the TP and GP regimens (HR = 1.06, 95 % CI = 1.00–1.13, p = 0.07). c The pooled HR for time-to-disease progression showed no difference between the TP and GP regimens (HR = 1.05, 95 % CI = 0.97–1.14, p = 0.20). In Schiller2002a, log HR and variance of paclitaxel plus cisplatin arm versus gemcitabine plus cisplatin arm was estimated from overall survival or time-to-disease progression Kaplan–Meier curves of Schiller2002 trial; in Schiller2002b, log HR and variance of paclitaxel

plus carboplatin arm versus gemcitabine plus cisplatin arm was estimated from overall survival or time-to-disease progression Kaplan–Meier curves of Schiller2002 trial.



AEs

Fig. 4 Grade 3–4 non-hematological toxicity analyses. a Grade 3–4 nausea or vomiting was less frequent in the TP than the GP group (RR = 0.53, 95 % CI = 0.35–0.78, p = 0.002). b Grade 3–4 sensory neuropathy was comparable between the TP and GP arms. c Grade 3–4 fatigue was also comparable between the TP and GP arms

	 **4. Fazit der Autoren** Our meta-analysis showed that 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.
Soria JC et al., 2013 [27]. Systematic Review and meta-analysis 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	**1. Fragestellung** To further assess the efficacy (in terms of OS and PFS) and toxicity of bevacizumab used in combination with platinum-based chemotherapy, compared with chemotherapy alone, in the first-line treatment of patients with advanced NSCLC
	2. Methodik **Population:** patients with inoperable locally advanced (stage IIIB), recurrent or metastatic NSCLC **Intervention:** first-line bevacizumab plus platinum-based chemotherapy **Komparator:** chemotherapy alone (platinum-based) without bevacizumab **Endpunkte:** OS, PFS **Suchzeitraum:**

bis 04/ 2009

Anzahl eingeschlossene Studien/Patienten (Gesamt):

4 Phase II und III Studien (2 194)

Qualitätsbewertung der Studien:

The quality of trials and the risk of bias were assessed by considering randomisation methods, stratification factors, blinding, follow-up and intention-to-treat analysis.

Heterogenitätsuntersuchungen:

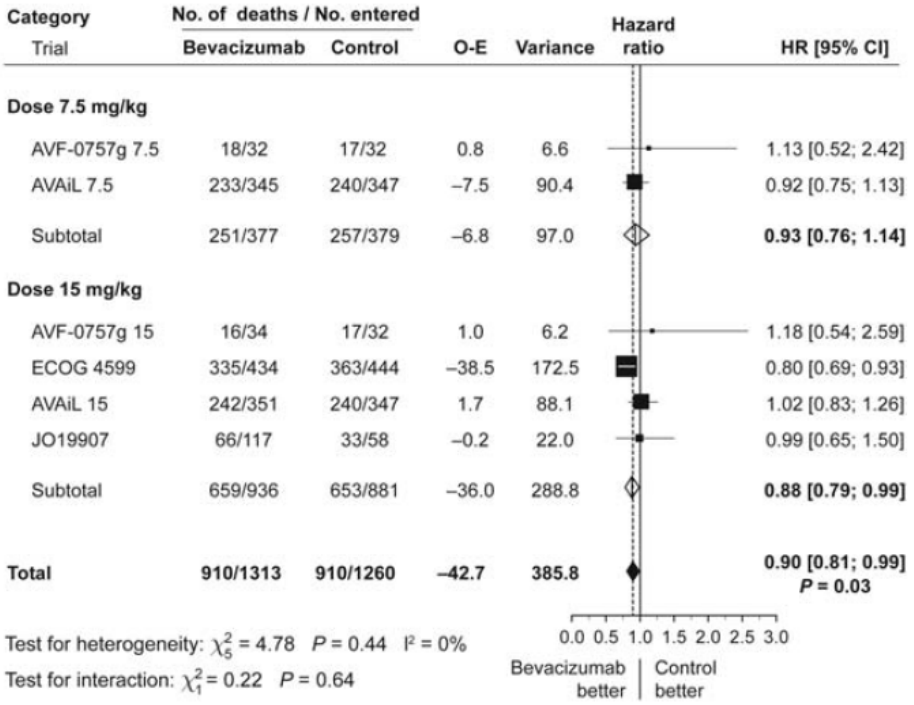
Random-effect models were used in cases of significant and unexplained heterogeneity. The chi-squared heterogeneity test was used to test for gross statistical heterogeneity between the trials. The I2 statistic (0%–100%) was used to assess the proportion of variability in the results that was attributable to heterogeneity between the trials

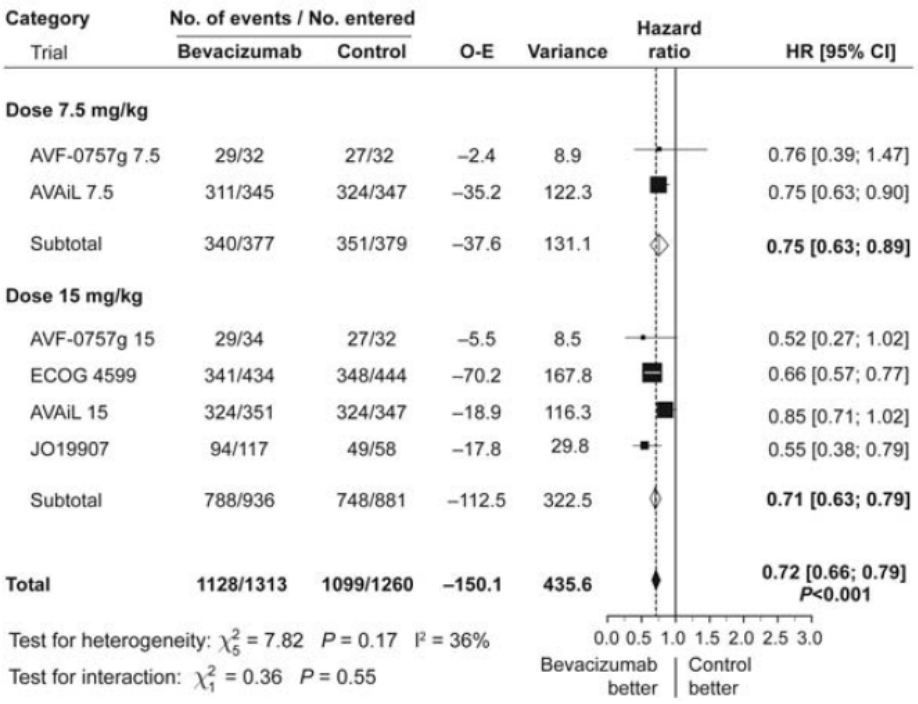
3. Ergebnisdarstellung

Trial	Design, main inclusion/exclusion criteria, primary end point	Treatment arms[a]	*N* analysed /randomly assigned patients
AVF-0757g [24]	Design: open-label, parallel-group, multicentre, blinded assessment phase II Inclusion critera: histologically confirmed stage IIIB (with pleural effusion), stage IV or recurrent NSCLC; ECOG PS ≤2; life expectancy ≥3 months; no previous chemotherapy, biological therapy or radiotherapy. Exclusions included: CNS metastasis, therapeutic anticoagulation, uncontrolled hypertension Primary end point: PFS Tumour assessment: every three cycles (i.e. 9 weeks) for the first six cycles and every four cycles (12 weeks) thereafter	Bevacizumab 7.5 mg/kg + carboplatin + paclitaxel Bevacizumab 15 mg/kg + carboplatin + paclitaxel Carboplatin + paclitaxel	32/32 34/35 32/32
ECOG 4599 [21]	Design: open-label, parallel-group, multicentre, phase III Inclusion criteria: histologically or cytologically confirmed, predominantly non-squamous stage IIIB (with pleural effusion), stage IV or recurrent NSCLC; ECOG PS 0–1; no previous chemotherapy. Exclusions included: haemoptysis (≥2.5 ml per episode), tumours invading or abutting major blood vessels, CNS metastasis, therapeutic anticoagulation, uncontrolled hypertension Primary end point: OS Tumour assessment: every two cycles (i.e. every 6 weeks) for 24 weeks and then every three cycles thereafter	Bevacizumab 15 mg/kg + carboplatin + paclitaxel Carboplatin + paclitaxel	434/434 444/444
AVAiL [22]	Design: double-blind, parallel-group, multicentre, international, phase III Inclusion criteria: histologically or cytologically confirmed, stage IIIB (with supraventricular lymph node metastasis, or malignant pleural or pericardial effusion), stage IV or recurrent non-squamous NSCLC; ECOG PS 0–1; no previous chemotherapy. Exclusions included: haemoptysis (≥2·5 ml per episode), CNS metastasis, therapeutic anticoagulation, uncontrolled hypertension Primary end point: PFS Tumour assessment: every three cycles	Bevacizumab 7.5 mg/kg + cisplatin + gemcitabine Bevacizumab 15 mg/kg + cisplatin + gemcitabine Cisplatin + gemcitabine + placebo (low or high dose)	345/345 351/351 347/347
JO19907 [31]	Design: open-label, parallel-group, multicentre, phase II Inclusion criteria: previously untreated stage IIIB (with pleural and/or pericardial effusion and/or pleural dissemination), IV or recurrent non-squamous NSCLC; ECOG PS 0–1. Exclusions included haemoptysis and CNS metastasis, uncontrolled hypertension Primary end point: PFS Tumour assessment: every 6 weeks for the first 18 weeks and every 9 weeks thereafter	Bevacizumab 15 mg/kg + carboplatin + paclitaxel Carboplatin + paclitaxel	117/121 58/59

aDoses: carboplatin, dosed to a target area under the curve of 6 mg/ml/min; paclitaxel, 200 mg/m2; cisplatin, 80 mg/m2; gemcitabine, 1250 mg/m2. In all trials, treatment was administered in 3-week cycles for up to six cycles, or until disease progression or unacceptable toxicity. Patients who completed six cycles of bevacizumab-containing therapy in ECOG 4599, AVAiL and JO19907 then received bevacizumab monotherapy until disease progression or unacceptable toxicity. In AVF-0757g, non-progressing patients randomly assigned to bevacizumab could receive up to 18 doses of bevacizumab following the initial six cycles. Patients in the control arms were permitted to receive bevacizumab (15 mg/kg) on disease progression.
bExperimental arm.
CNS, central nervous system; NSCLC, non-small-cell lung cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status; OS, overall survival; PFS, progression-free survival.

All trials used central randomisation stratified using between one and four factors (Table 2). Only one trial was doubleblind. For the main end point of this study,

	OS, an objective end point, the absence of blinding was not a problem. The proportion of randomly assigned patients excluded from the analysis by trial ranged from 0% to <3% and overall was 0.3%. Follow-up was good without clear imbalance between arms. **Overall survival (4 trials, 2.194 patients):** statistically significant difference in favor of bevacizumab plus chemotherapy, compared with chemotherapy alone, with HR of 0.90 (95% CI 0.81, 0.99; p = 0.03, I^2=0%). No significant difference between the two Bevacizumab doses (7.5 mg, 15 mg).  **PFS (4 trials, 2.194 patients):** statistically significant difference in favor of bevacizumab plus chemotherapy, compared with chemotherapy alone HR of 0.72 (95% CI 0.66, 0.79; P < 0.001).

	 **Toxicity**: Bevacizumab significantly increased the risk of grade ≥3 events of proteinuria (OR 4.81; 95% CI 2.28, 10.1), hypertension (OR 3.69; 95% CI 2.49, 5.47), haemorrhagic events (OR 2.67; 95% CI 1.63, 4.39), neutropenia (OR 1.53; 95% CI 1.25, 1.87) and febrile neutropenia (OR 1.72; 95% CI 1.01, 2.95), compared with chemotherapy alone
	4. Fazit der Autoren The effect on OS was greater in adenocarcinoma, compared with other histological types, while that on OS and PFS was greater in patients with a loss in body weight of ≤5%, compared with >5%. In conclusion, this meta-analysis of randomised studies indicates that bevacizumab significantly prolonged OS and PFS when added to standard platinum-based chemotherapy as first-line therapy in patients with advanced NSCLC, with no unexpected toxicity patterns being evident. **Hinweis der FB-Med:** Der Mutationsstatus der Patienten in der Publikation ist nicht dargestellt. Es ist daher nicht bekannt ob und in welchem Umfang Patienten mit einer EGFR oder ALK positive Mutation in den zugrunde liegenden Studien eingeschlossen wurden.

Qi WX et al., 2012 [20]. Doublet versus single cytotoxic	**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

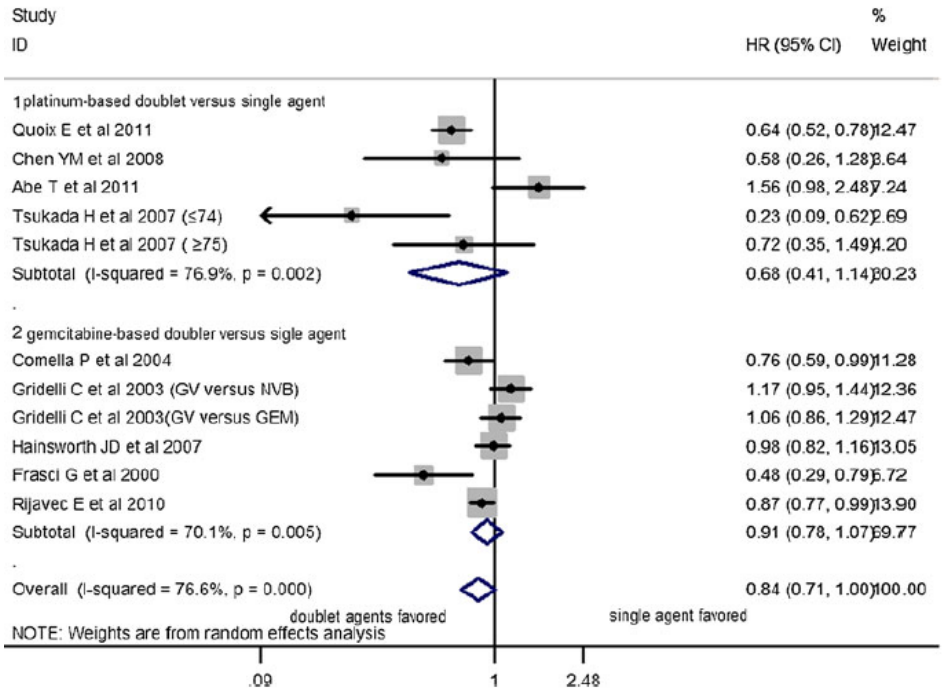
agent as first-line treatment for elderly patients with advanced non-small-cell lung cancer: a systematic review and meta-analysis Siehe auch **Wang S et al. 2015 [29].** Meta-analysis comparing doublet and single cytotoxic agent therapy as first-line treatment in elderly patients with advanced nonsmall-cell lung cancer Siehe auch **Xu CA et.al., 2013 [32].** Doublets versus single-agent therapy as first-line therapy for elderly patients with advanced non-small cell lung cancer? A systematic review of randomised controlled trials	cancer (NSCLC). **2. Methodik** **Population:** elderly (older than 65 years) patients with advanced non-small-cell lung cancer. First-line **Interventionen:** doublet cytotoxic agents **Komparator:** single third-generation cytotoxic agent **Endpunkte:** OS, TTP, ORR, Toxicity **Suchzeitraum:** 1980-2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 10 (n= 2 510) **Qualitätsbewertung der Studien:** Jadad **Heterogenitätsuntersuchungen:** Between-study heterogeneity was estimated using the v2-based Q statistic. Heterogeneity was considered statistically significant when $p_{heterogeneity} < 0.05$ or I2>50 %. If heterogeneity existed, data were analyzed using a random-effects model. In the absence of heterogeneity, a fixed-effects model was used. **3. Ergebnisdarstellung** There was no placebo-controlled double-blinded trial. Alle Studien wurden mit Jadad 2-3 bewertet. Kein Publikationsbias

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

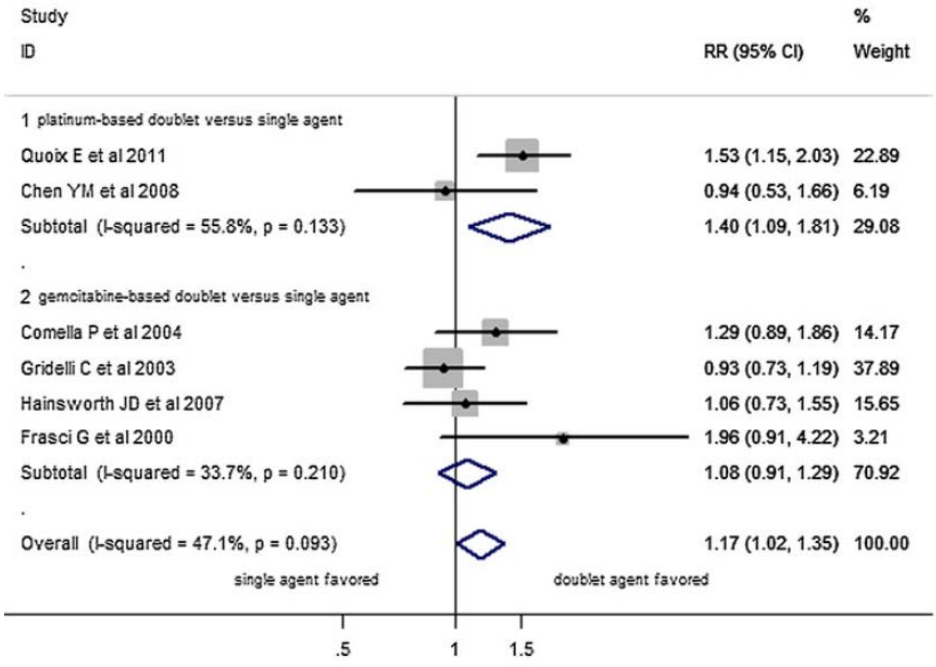
CBP carboplatin, NVB vinorelbine, PTX paclitaxel, DDP cisplatin, GEM gemcitabine, TXT docetaxel, PFS progression-free survival, TTP time to progression, OS overall survival, NA not available

Mortalität (9 Studien)

- no statistically significant difference, HR of 0.84 (95% CI = 0.71–1.00, p = 0.053, I^2=76.6%)
- we did a subgroup analysis based on chemotherapy regimens and found that OS was not significantly improved by platinum-based doublet (HR = 0.68, 95 % CI = 0.41–1.14, p = 0.143) or by gemcitabine-based doublet (HR = 0.91, 95 % CI = 0.78–1.07, p = 0.26)
- Stat. signifikanter Vorteil für Kombinationstherapie vs. Monotherapie für 1-Jahres Überleben (RR = 1.17, 95 % CI = 1.02–1.35, p = 0.03; I^2=47,7)



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



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

	TTP (3 trials): statistically significant difference in favor of doublet therapy (HR = 0.76, 95 % CI = 0.60–0.96, p=0,022, I^2=72.2%). **ORR (10 trials):** statistically significant difference in favor of doublet therapy (RR = 1.54, 95 % CI = 1.36–1.73, p = 0.0001, I^2=0) **Toxizität** More incidences of grade 3 or 4 anemia, thrombocytopenia, and neurotoxicity were observed with doublet therapy. With respect to the risk of grade 3 or 4 neutropenia and nonhematologic toxicities such as diarrhea, fatigue, nausea, and vomiting, equivalent frequencies were found between the two groups
	4. Fazit der Autoren: Our meta-analysis showed that doublet therapy was superior to single-agent therapy as first-line treatment for elderly patients with advanced NSCLC in terms of OS, TTP, ORR, and 1-year SR, but more hematologic toxicities and neurotoxicity were observed with doublet therapy. Due to significant heterogeneity between randomized trials, we performed a subgroup analysis based on different chemotherapy regimens. Similar results were found in platinum-based doublet therapy, although the OS benefit with doublet therapy was not significant. Furthermore, gemcitabine-based doublet significantly increased ORR compared with single agent, but it did not translate into an increase in survival benefit. Platinum-based doublet therapy might be considered as first-line treatment for older patients to improve efficacy, but the optimal drug dosage and treatment schedule should be investigated in future prospective clinical trials. Gemcitabine-based doublet therapy could be considered for elderly patients who were not suitable for platinum-based chemotherapy due to its tendency to improve OS and 1-year SR. **5. Hinweise durch FB Med** • Alle in **Xu et al.** untersuchten Studien sind auch in **Qi et al.** enthalten. Zusätzlich wurden drei weitere Studien bei Qi et al. betrachtet. Die Gründe für diesen Unterschied sind nicht transparent. Die Ergebnisse der Reviews sind vergleichbar • **Wang et al.** führte 2015 eine weitere, aktuelle Metaanalyse mit vergleichbarer Fragestellung durch. In diese wurde jedoch nur eine weitere Studie im Vergleich zu Qi et al. mehr eingeschlossen. Darüber hinaus sind die Ergebnisse und Schlussfolgerungen vergleichbar • Der Mutationsstatus der Patienten in beiden Publikationen ist nicht dargestellt. Es ist daher nicht bekannt ob und in welchem Umfang Patienten mit einer EGFR oder ALK positive Mutation in den zugrunde liegenden Studien eingeschlossen wurden.

Leitlinien

Ellis PM et al., 2016 [7]. Cancer Care Ontario (CCO) Systemic Treatment for Patients with Advanced Non-Small Cell Lung Cancer. Guideline 7-10 Version 3	**Fragestellung/Zielsetzung** The guideline objective is to determine the most effective systemic treatment options in terms of overall survival, quality of life, and response in the management of advanced non-small cell lung cancer (NSCLC). **Methodik** The recent guideline by ASCO was used as the base for the recommendations. The Working Group considered the guideline to be of high quality because the rigour of development domain, which assesses the methodological quality of the guideline, was well above 50%. ASCO-guideline: Masters GA, Temin S, Azzoli CG, Giaccone G, Baker S, Brahmer JR, et al. Systemic Therapy for Stage IV Non–Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015. THE PROGRAM IN EVIDENCE-BASED CARE The PEBC is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC's mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control. The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province. The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC. BACKGROUND FOR GUIDELINE The original version of this guidance document was released by CCO's PEBC in 2009 and a second version was released in February 2010. In November 2012, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert reviewed and interpreted the new eligible evidence and proposed the existing recommendations were to be updated. The new data from the PEBC update contradicted the recommendation to stop treatment after four to six cycles, which needed to be tempered with new maintenance study data. Also, there was a need to reference first-line EGFR TKIs in mutation carriers. Therefore, the Lung Cancer Disease Site Group (DSG) decided to update the 2010 recommendations on first-line systemic chemotherapy in the treatment of advanced NSCLC.

	GUIDELINE DEVELOPERS This guideline was developed by the Systemic Treatment for Advanced NSCLC GDG (Appendix 1), which was convened at the request of the Lung Cancer DSG. The project was led by a small Working Group of the Systemic Treatment for Advanced NSCLC GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The PEBC uses the AGREE II framework as a methodological strategy for guideline development. The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the PEBC Document Assessment and Review Protocol. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the PEBC Handbook and the PEBC Methods Handbook. Systematisches Review Literturrecherche bis 02/2016
	First-Line Treatment for Patients: ☐Without an epidermal growth factor receptor (EGFR)-sensitizing mutation or ALK gene rearrangement, and Eastern Cooperative Oncology Group performance status (PS) 0 to 1 (or appropriate PS 2), a variety of combination cytotoxic chemotherapies are recommended. Platinum-based doublets are preferred, along with early concurrent palliative care and symptom management. Based on tumour histology (ie, squamous vs. non-squamous), there are some variations. ☐Adding bevacizumab to carboplatin plus paclitaxel is recommended if there are no contraindications. An alternative treatment strategy for patients who are eligible for carboplatin, paclitaxel, and bevacizumab would include cisplatin or carboplatin plus pemetrexed and maintenance pemetrexed. ☐With PS 2: combination or single-agent chemotherapy or palliative care alone may be used. ☐With sensitizing EGFR mutations: afatinib, erlotinib, or gefitinib is recommended. ☐With ALK gene rearrangements: crizotinib is recommended. ☐With ROS1 rearrangement: crizotinib is recommended. ☐With large-cell neuroendocrine carcinoma: platinum plus etoposide or the same treatment as other patients with non-squamous carcinoma may be administered.

	☐First-line cytotoxic chemotherapy should be stopped at disease progression or after four cycles in patients with nonresponsive stable disease. ☐With stable disease or response after four to six cycles of a platinum-based chemotherapy: pemetrexed (in patients with non-squamous cell carcinoma [NSCC]) or EGFR tyrosine kinase inhibitors (TKIs) are options for maintenance therapy. **Clinical Question A2: What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with NSCC, negative or unknown EGFR-sensitizing mutation and ALK gene rearrangement status, and PS 0 to 1 or possibly PS 2?** For patients who have the characteristics described in Clinical Question A2 and who have non-squamous histology, the following options are acceptable: ☐☐Cisplatin-based combinations ☐☐Cisplatin plus docetaxel ☐☐Cisplatin plus paclitaxel ☐☐Cisplatin plus pemetrexed ☐☐Cisplatin plus vinorelbine ☐☐Cisplatin plus gemcitabine ☐☐Carboplatin-based combinations ☐☐Carboplatin plus albumin-bound (nab) ☐paclitaxel ☐☐Carboplatin plus paclitaxel ☐☐Carboplatin plus pemetrexed ☐☐Carboplatin plus docetaxel ☐☐Carboplatin plus gemcitabine ☐☐Nonplatinum doublets **Clinical Question A2.a** **What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with negative or unknown *EGFR*/*ALK* status, NSCC, and no contraindications to bevacizumab?** For patients receiving carboplatin plus paclitaxel, the addition of bevacizumab 15 mg/kg once every three weeks is recommended, except for patients with SCC histologic type, clinically significant hemoptysis, a *known bleeding disorder,* inadequate organ function, Eastern Cooperative Oncology Group PS > 1, clinically significant cardiovascular disease, or medically uncontrolled hypertension. *Caution should be exercised in patients with brain metastases.* Bevacizumab may be continued, as tolerated, until disease progression. *An alternative treatment strategy for patients who are eligible for carboplatin, paclitaxel, and bevacizumab would include cisplatin or carboplatin plus*

	pemetrexed and maintenance pemetrexed. There is insufficient evidence (for or against) to recommend pemetrexed in combination with bevacizumab plus carboplatin for patients who do not have contraindications to bevacizumab. **Clinical Question A2.b** **What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with PS 2, NSCC, and negative or unknown *EGFR*-sensitizing mutation and *ALK* gene rearrangement status?** In the context of shared decision making, combination therapy, single-agent chemotherapy, or palliative therapy alone may be used for patients in this population with PS 2. **Clinical Question A3** **What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with SCC, negative or unknown EGFR-sensitizing mutation and ALK gene rearrangement status, and PS 0 to 1 or possibly PS 2?** Patients with the characteristics listed in Clinical Question A3 and with SCC histology should be offered the following options: ● Cisplatin-based combinations ● Cisplatin plus docetaxel ● Cisplatin plus gemcitabine ● Cisplatin plus paclitaxel ● Cisplatin plus vinorelbine ● Carboplatin-based combinations ● Carboplatin plus gemcitabine ● Carboplatin plus paclitaxel ● Carboplatin plus nab-paclitaxel ● Carboplatin plus docetaxel ● Nonplatinum doublets **Clinical Question A3.a** **What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with negative or unknown EGFR/ALK status, SCC, and PS 2?** In the context of shared decision making, combination chemotherapy, single-agent chemotherapy, or palliative therapy alone may be used for patients with the characteristics described in Clinical Question A3.a.
Hanna N et al., 2017 [10].	**Fragestellung/Zielsetzung** Provide evidence-based recommendations updating the 2015 ASCO guideline on systemic therapy for patients with stage IV non–small-cell lung cancer

American Society of Clinical Oncology (ASCO)

Systemic Therapy for Stage IV Non–Small-Cell Lung Cancer:

American Society of Clinical Oncology Clinical Practice Guideline Update

(NSCLC).
Guideline Question
What systemic therapy treatment options should be offered to patients with stage IV NSCLC, depending on the subtype of the patient's cancer?

Methodik

Grundlage des Leitlinie-Updates

The ASCO NSCLC Expert Panel made recommendations based on a systematic review of randomized controlled trials from February 2014 to December 2016 plus the Cancer Care Ontario Program in Evidence-Based Care's update of a previous ASCO search.

Fourteen randomized controlled trials provide the evidence base; earlier phase trials also informed recommendation development.

This update includes nine phase III randomized controlled trials (RCTs),4,6-13 four phase II RCTs,14-17 one phase II/III RCT,5 and six nonrandomized studies on systemic therapy18-23 (five of the studies were found by Cancer Care Ontario [CCO]23a). The current guideline has updated the systematic review of new and updated evidence, including results of literature searches regarding afatinib, alectinib, avelumab, atezolizumab, crizotinib, dabrafenib, durvalumab, erlotinib, everolimus, ipilimumab, necitumumab, nivolumab, osimertinib, pembrolizumab, ramucirumab, rociletinib, trametinib, tremelimumab, continuation maintenance, and switch maintenance.

LoE/GoR analog ASCO

LoE

Rating for Strength of Evidence	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits *v* harms) and that further research is very unlikely to change either the magnitude or direction of this net effect.
Intermediate	Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.

GoR

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Detailed information about the methods used to develop this guideline update is available in theMethodology Supplement at www.asco. org/lung-cancer-guidelines, including an overview (eg, panel composition, development process, and revision dates); literature search and data extraction; the recommendation development process (GLIDES and BRIDGE-Wiz); and quality assessment.

Freitext/Empfehlungen/Hinweise

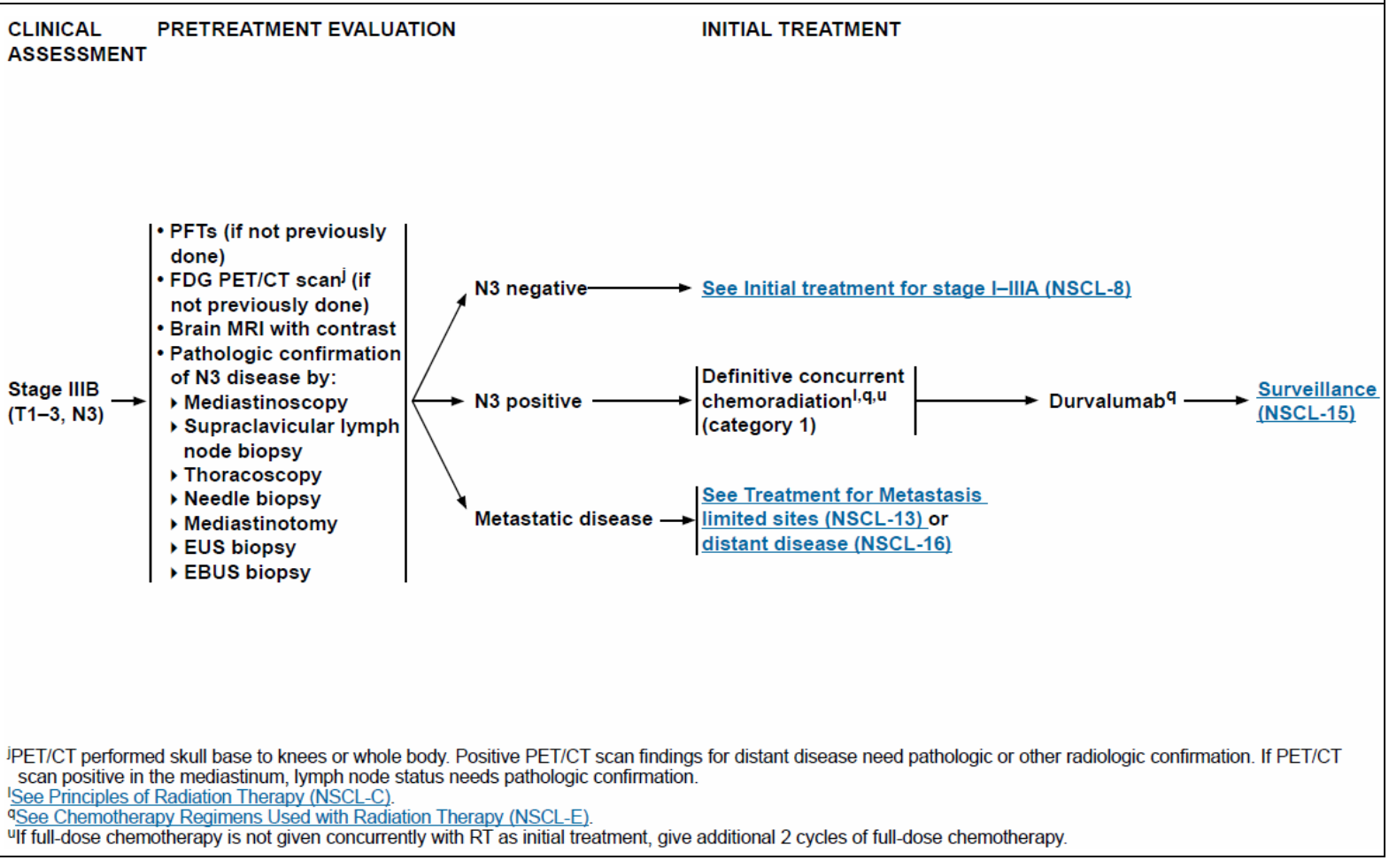
First-Line Treatment for Patients

Patients with non–squamous cell carcinoma without a tumor EGFR-sensitizing mutation or ALK or ROS1 gene rearrangement and with a performance status (PS) of 0 or 1 (and appropriate PS of 2):

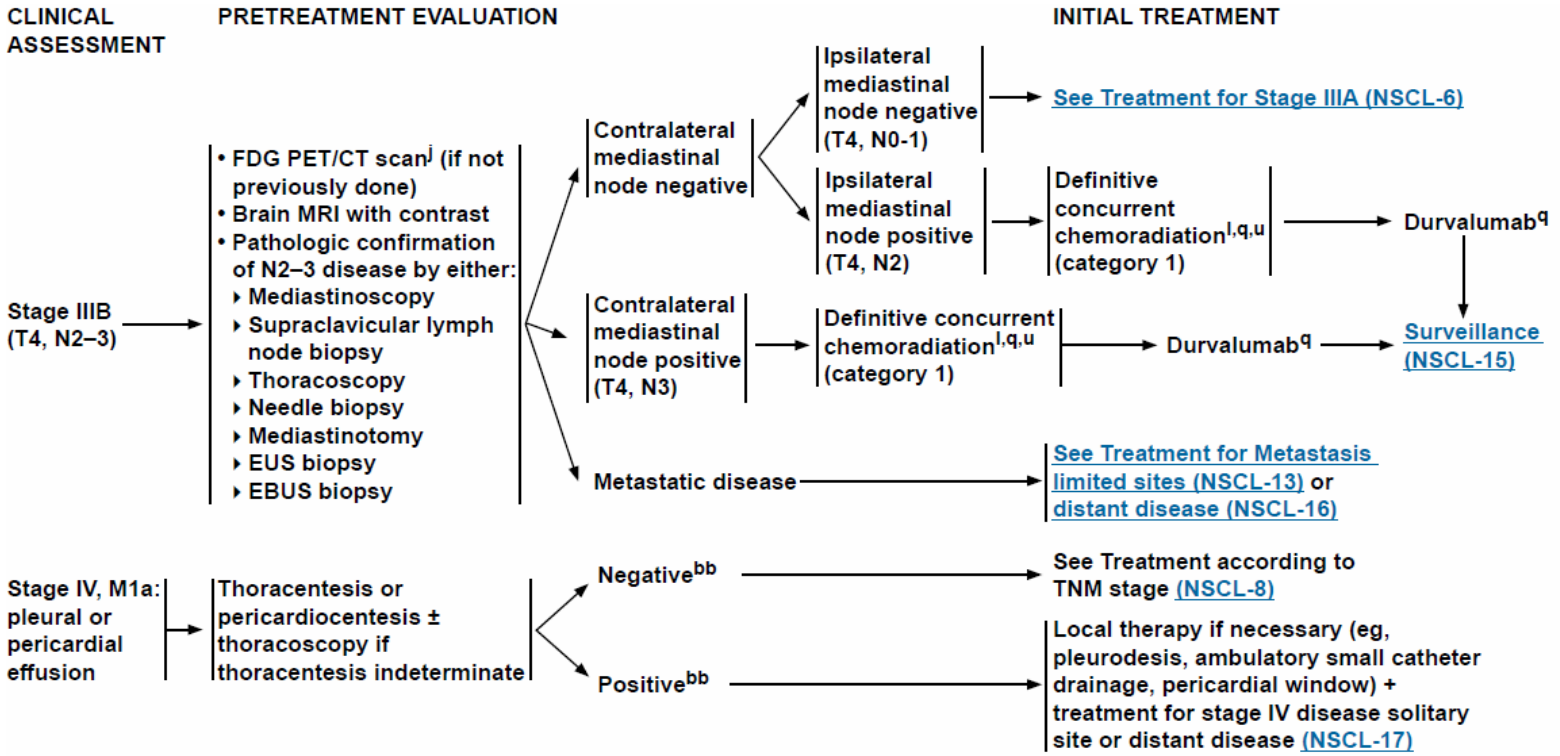
- With high PD-L1 expression (tumor proportion score [TPS] ≥ 50%) and no contraindications, single-agent pembrolizumab is recommended (Evidence quality: high; Strength of recommendation: strong).
- With low PD-L1 expression (TPS ≤ 50%), a variety of combination cytotoxic chemotherapies (with or without bevacizumab if patients are receiving carboplatin and paclitaxel) are recommended (Platinum based [Evidence quality: high; Strength of recommendation: strong]; Non–platinum based [Evidence quality: intermediate; Strength of recommendation: weak]).
- There is insufficient evidence to recommend bevacizumab in combination with pemetrexed plus carboplatin.
- Other checkpoint inhibitors, combination checkpoint inhibitors, or immune checkpoint therapy with chemotherapy are not recommended.
- With PS of 2, combination or single-agent therapy or palliative care alone may be used (chemotherapy [Evidence quality: intermediate; Strength of recommendation: weak]; palliative care [Evidence quality: intermediate;

	Strength of recommendation: strong]). With ROS1 rearrangement, crizotinib is recommended (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

National Comprehensive Cancer Network, 2017 [18]. Non-Small Cell Lung Cancer, Vers. 09.2017	Fragestellung/Zielsetzung: Diagnose, Pathologie, Staging, Therapie des NSCLC
	Methodik Grundlage der Leitlinie: Update der LL von 2016, Systematik der Literatursuche und -bewertung nicht vollständig transparent dargestellt, Diskussion der Literatur und Empfehlungen im Expertenpanel, Interessenkonflikte unklar Literatursuche: in PubMed zwischen 07/2015 und 07/2016 GoR, LoE: Alle Empfehlungen entsprechen der Kategorie 2A, sofern nicht explizit anders spezifiziert. **NCCN Categories of Evidence and Consensus** **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. **Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. **All recommendations are category 2A unless otherwise noted.**
	Empfehlungen **STAGE IIIB (T1-3, N3)**



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



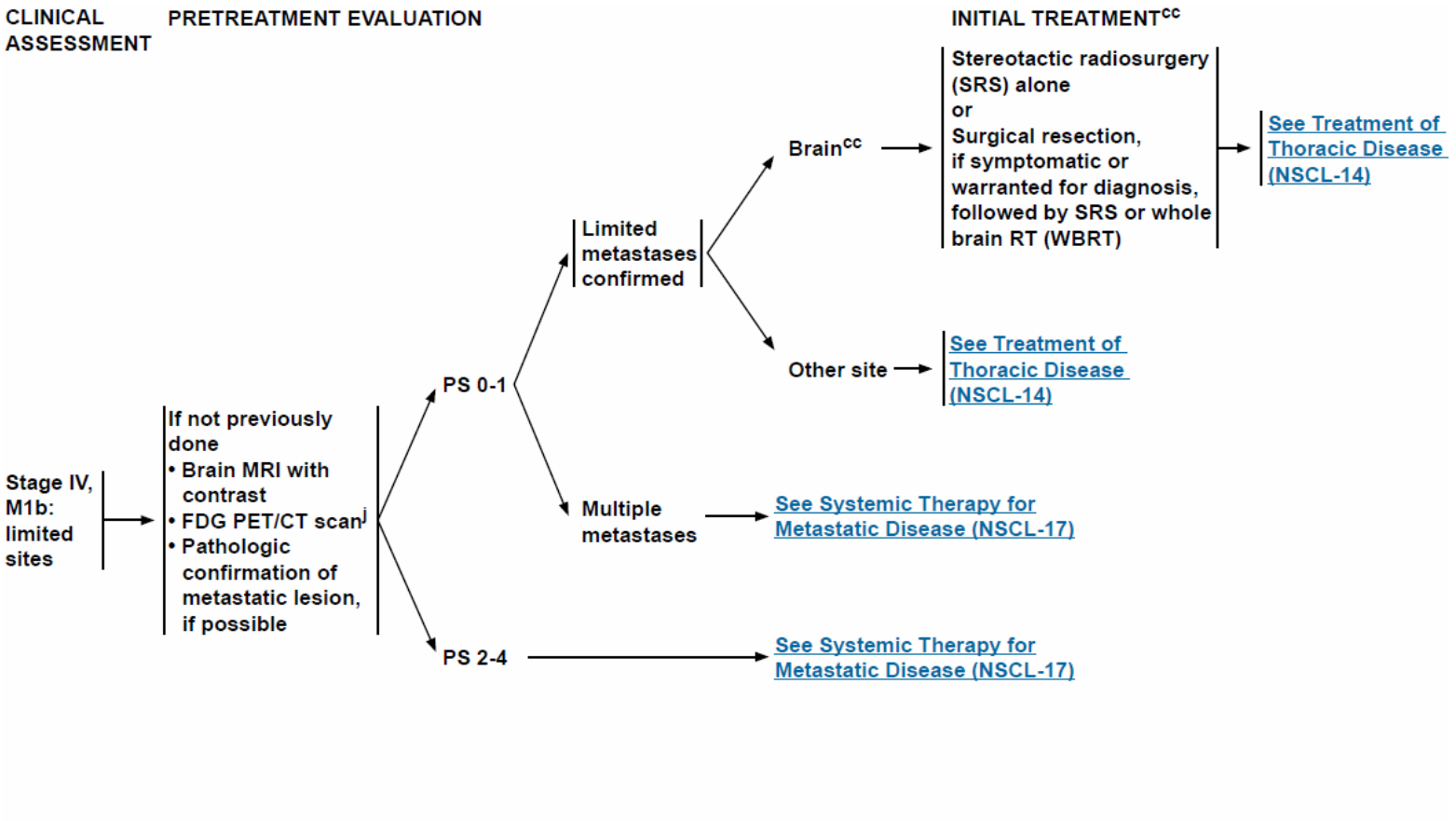
[j]PET/CT performed skull base to knees or whole body. Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

[l]See Principles of Radiation Therapy (NSCL-C).

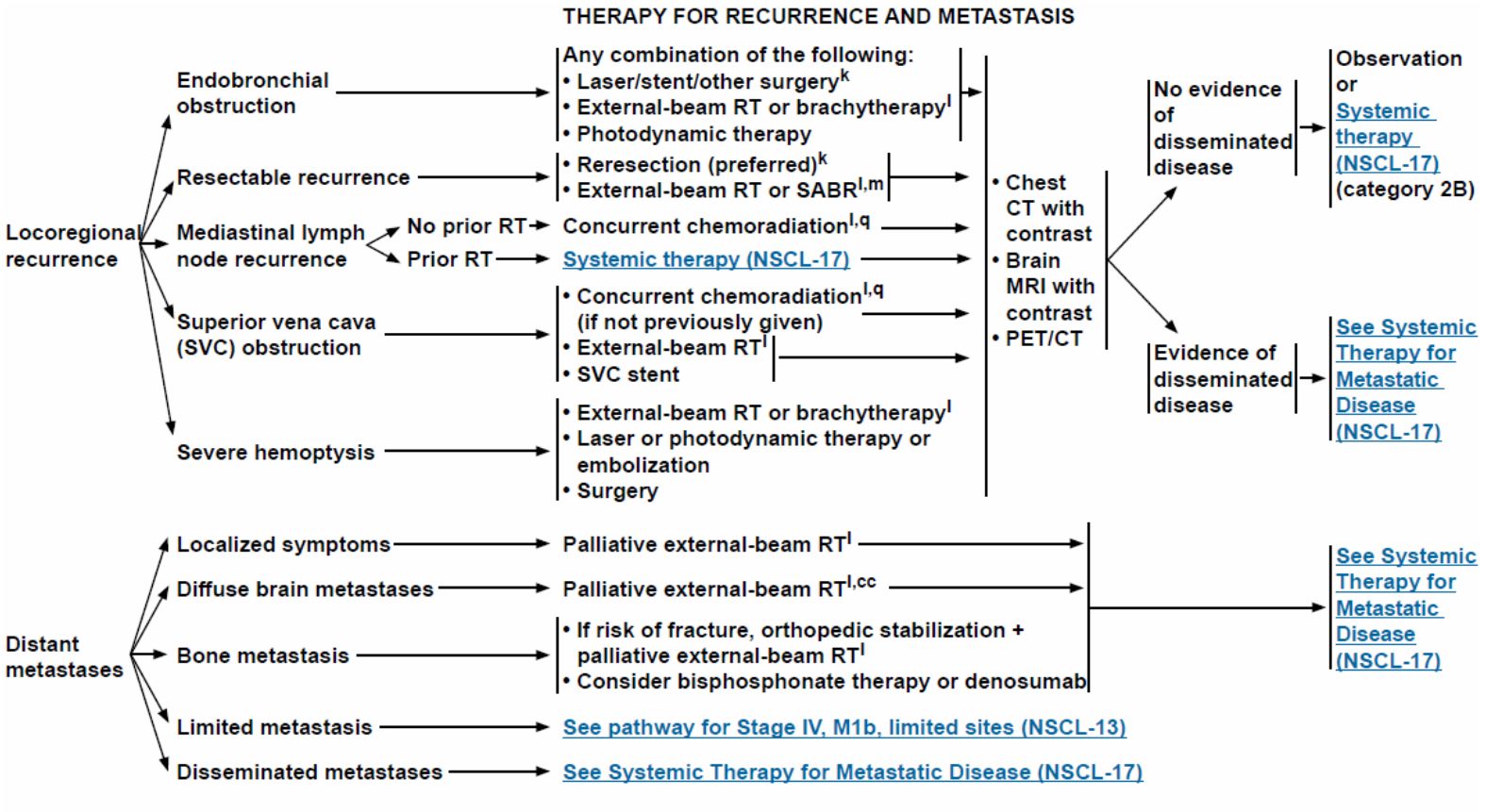
[q]See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

[u]If full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 2 cycles of full-dose chemotherapy.

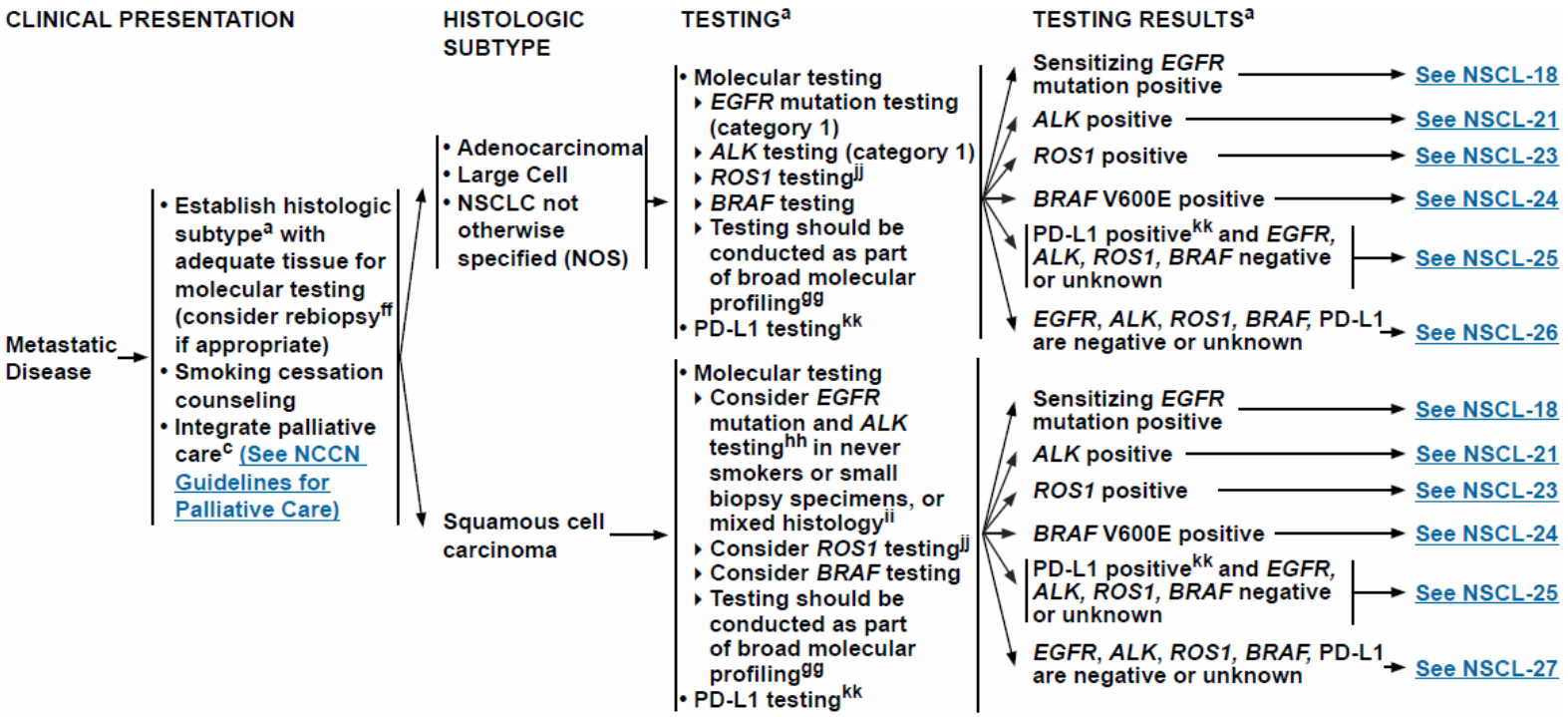
[bb]While most pleural effusions associated with lung cancer are due to tumor, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor and fluid is non-bloody and not an exudate. When these elements and clinical judgment dictate that the effusion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



[j]PET/CT performed skull base to knees or whole body. Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation.
[cc]See NCCN Guidelines for Central Nervous System Cancers.



[k] See Principles of Surgical Therapy (NSCL-B).
[l] See Principles of Radiation Therapy (NSCL-C).
[m] Interventional radiology ablation is an option for selected patients.
[q] See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).
[cc] See NCCN Guidelines for Central Nervous System Cancers.



[a] See Principles of Pathologic Review (NSCL-A).

[c] Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742.

[ff] If repeat biopsy is not feasible, plasma biopsy should be considered.

[gg] The NCCN NSCLC Guidelines Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).

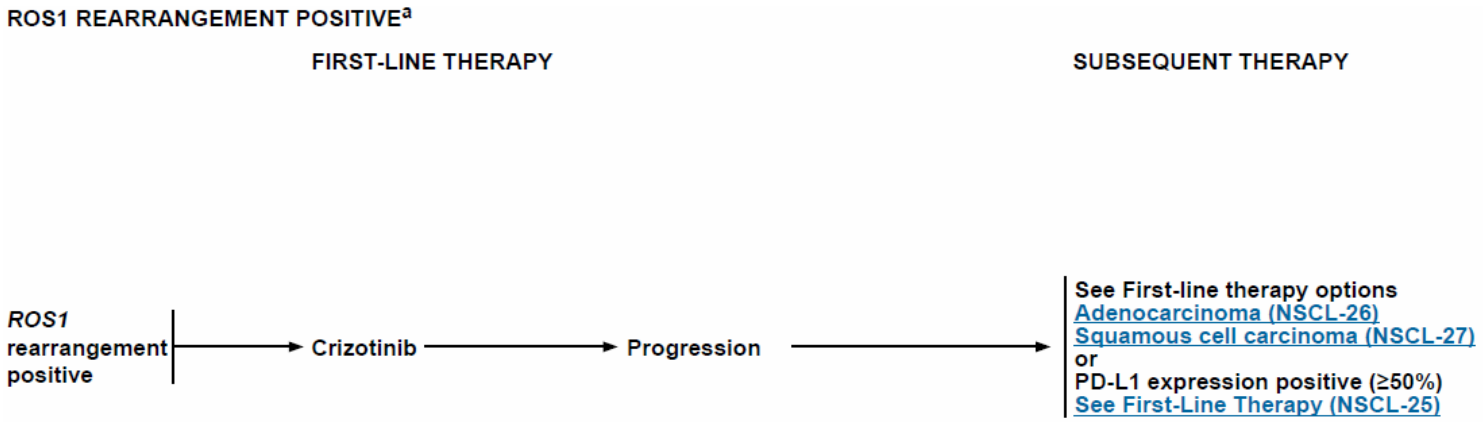
[hh] In patients with squamous cell carcinoma, the observed incidence of *EGFR* mutations is 2.7% with a confidence that the true incidence of mutations is less than 3.6%. This frequency of *EGFR* mutations does not justify routine testing of all tumor specimens. Forbes SA, Bharma G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). Curr Protoc Hum Genet 2008;chapter 10:unit 10.11.

[ii] Paik PK, Varghese AM, Sima CS, et al. Response to erlotinib in patients with *EGFR* mutant advanced non-small cell lung cancers with a squamous or squamous-like component. Mol Cancer Ther 2012;11:2535-2540.

[jj] Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in ROS1-rearranged non-small cell lung cancer. N Engl J Med 2014;371:1963-1971.

[kk] PD-L1 expression levels of ≥50% are a positive test result for first-line pembrolizumab therapy.

ROS1 REARRANGEMENT POSITIVE[a]



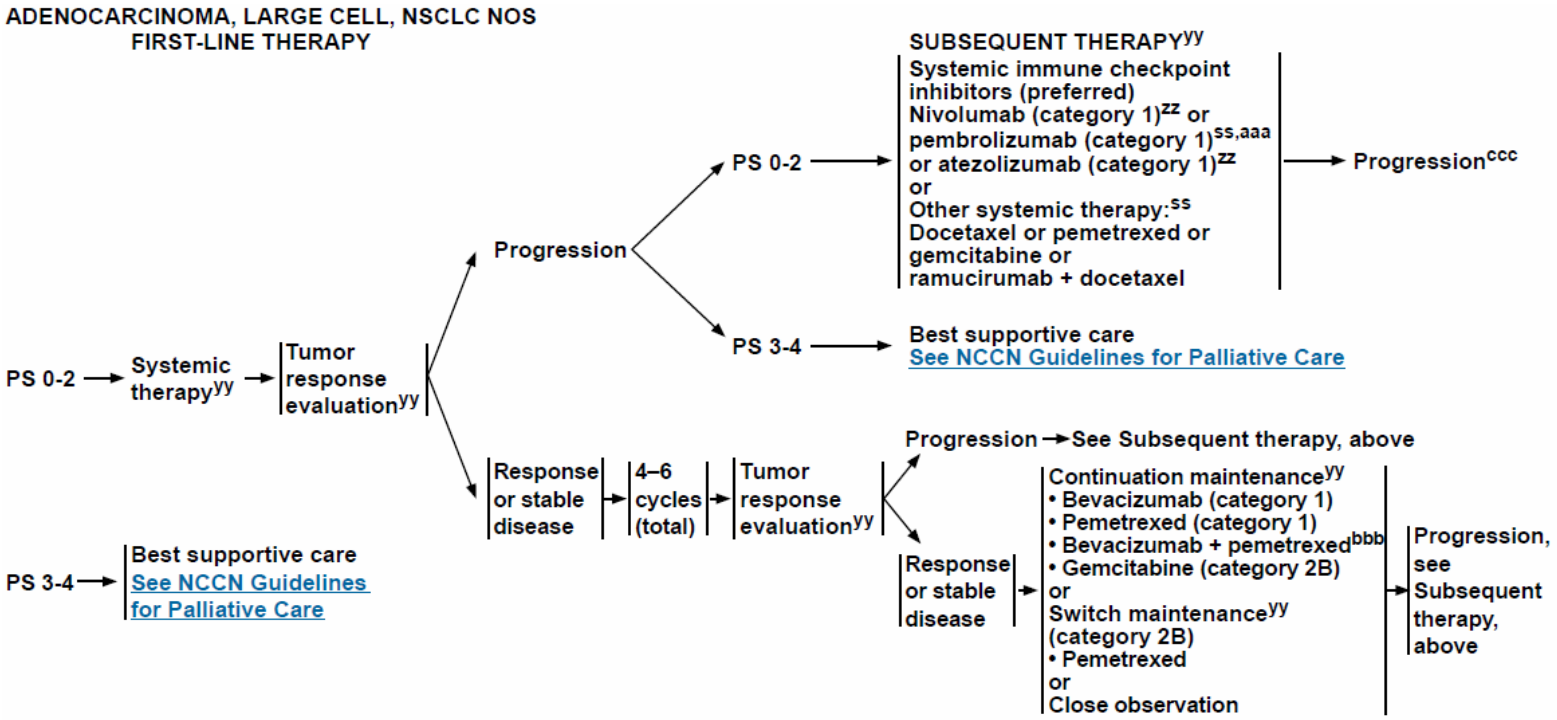
[a]See Principles of Pathologic Review (NSCL-A).

PD-L1 EXPRESSION POSITIVE[a]

FIRST-LINE THERAPY			SUBSEQUENT THERAPY
PD-L1 expression positive (≥50%) and *EGFR, ALK, ROS1, BRAF* negative or unknown	→ Pembrolizumab[xx] (category 1)	→ Progression	→ See First-line therapy options for Adenocarcinoma (NSCL-26) or Squamous cell carcinoma (NSCL-27)

[a] See Principles of Pathologic Review (NSCL-A).

[xx] Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. N Engl J Med 2016;375:1823-1833.



[ss]If not previously given.
[yy]See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[zz]If pembrolizumab not previously given.
[aaa]Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression levels ≥1%, as determined by an FDA-approved test.
[bbb]If bevacizumab was used with a first-line pemetrexed/platinum chemotherapy regimen.
[ccc]If not already given, options for PS 0-2 include (nivolumab, pembrolizumab, or atezolizumab), docetaxel (category 2B), pemetrexed (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include best supportive care. Options for further progression are best supportive care or clinical trial.

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (1 OF 4)

ADVANCED DISEASE:

- The drug regimen with the highest likelihood of benefit with toxicity deemed acceptable to both the physician and the patient should be given as initial therapy for advanced lung cancer.
- Stage, weight loss, performance status, and gender predict survival.
- Platinum-based chemotherapy prolongs survival, improves symptom control, and yields superior quality of life compared to best supportive care.
- Histology of NSCLC is important in the selection of systemic therapy.
- New agent/platinum combinations have generated a plateau in overall response rate (≈ 25%–35%), time to progression (4–6 mo), median survival (8–10 mo), 1-year survival rate (30%–40%), and 2-year survival rate (10%–15%) in fit patients.
- Unfit patients of any age (performance status 3–4) do not benefit from cytotoxic treatment, except erlotinib, afatinib, gefitinib, or osimertinib for *EGFR* mutation-positive and crizotinib, ceritinib, or alectinib for *ALK*-positive tumors of nonsquamous NSCLC or NSCLC NOS.

First-line Therapy

- There is superior efficacy and reduced toxicity for cisplatin/pemetrexed in patients with nonsquamous histology, in comparison to cisplatin/gemcitabine.
- There is superior efficacy for cisplatin/gemcitabine in patients with squamous histology, in comparison to cisplatin/pemetrexed.
- Two drug regimens are preferred; a third cytotoxic drug increases response rate but not survival. Single-agent therapy may be appropriate in select patients.
- Response assessment after 2 cycles, then every 2–4 cycles with CT of known sites of disease with or without contrast or when clinically indicated.

Maintenance Therapy

- Continuation maintenance refers to the use of at least one of the agents given in first line, beyond 4–6 cycles, in the absence of disease progression. Switch maintenance refers to the initiation of a different agent, not included as part of the first-line regimen, in the absence of disease progression, after 4–6 cycles of initial therapy.

Subsequent Therapy

- Response assessment with CT of known sites of disease with or without contrast every 6–12 weeks.

See First-line Systemic Therapy Options for Adenocarcinoma, Large cell, NSCLC NOS on NSCL-F (2 of 4)

See First-line Systemic Therapy Options for Squamous Cell Carcinoma on NSCL-F (3 of 4)

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

First-line Systemic Therapy Options

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

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

Adenocarcinoma, Large Cell, NSCLC NOS (PS 2)

- Albumin-bound paclitaxel[17]
- Carboplatin/albumin-bound paclitaxel[18,19]
- Carboplatin/docetaxel[5]
- Carboplatin/etoposide[6,7]
- Carboplatin/gemcitabine[8]
- Carboplatin/paclitaxel[9]
- Carboplatin/pemetrexed[10]
- Docetaxel[20,21]
- Gemcitabine[22-24]
- Gemcitabine/docetaxel[14]
- Gemcitabine/vinorelbine[15]
- Paclitaxel[25-27]
- Pemetrexed[28]

†Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or for patients where the standard premedications (ie, dexamethasone, H2 blockers, H1 blockers) are contraindicated.
*Bevacizumab should be given until progression.
**Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.
***Criteria for treatment with bevacizumab: non-squamous NSCLC, and no recent history of hemoptysis. Bevacizumab should not be given as a single agent, unless as maintenance if initially used with chemotherapy.
¶If pembrolizumab not previously given.

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

First-line Systemic Therapy Options

Squamous Cell Carcinoma (PS 0-1)

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

Squamous Cell Carcinoma (PS 2)

- Albumin-bound paclitaxel[17]
- Carboplatin/albumin-bound paclitaxel[18,19]
- Carboplatin/docetaxel[5]
- Carboplatin/etoposide[6,7]
- Carboplatin/gemcitabine[8]
- Carboplatin/paclitaxel[9]
- Docetaxel[20,21]
- Gemcitabine[22-24]
- Gemcitabine/docetaxel[14]
- Gemcitabine/vinorelbine[15]
- Paclitaxel[25-27]

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

††Cisplatin/gemcitabine/necitumumab in the first-line setting and erlotinib or afatinib in the second-line setting are not used at NCCN institutions for these indications related to the efficacy and safety of these agents compared to the efficacy and safety of other available agents.

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

[1]Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small cell lung cancer. N Engl J Med 2006;355:2542-2550.

[2]Patel JD, Socinski MA, Garon EB, et al. Pointbreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small cell lung cancer. J Clin Oncol 2013;31:4349-4357.

[3]Barlesi F, Scherpereel A, Rittmeywr A, et al. Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced nonsquamous non-small cell lung cancer: AVAPERL. J Clin Oncol 2013;31:3004-3011.

[4]Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small cell lung cancer: final results of a phase III trial. J Clin Oncol 2012:30:2055-2062.

[5]Fossella F, Periera JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol 2003;21(16):3016-3024.

[6]Klastersky J, Sculier JP, Lacroix H, et al. A randomized study comparing cisplatin or carboplatin with etoposide in patients with advanced non-small cell lung cancer: European Organization for Research and Treatment of Cancer Protocol 07861. J Clin Oncol 1990;8:1556-1562.

[7]Frasci G, Comella P, Panza N, eta l. Carboplatin-oral etoposide personalized dosing in elderly non-small cell lung cancer patients. Gruppo Oncologico Cooperativo Sud-Italia. Eur J Cancer 1998;34:1710-1714.

[8]Danson S, Middleton MR, O'Byrne KJ, et al. Phase III trial of gemcitabine and carboplatin versus mitomycin, ifosfamide, and cisplatin or mitomycin, vinblastine, and ciplatin in patients with advanced non-small cell lung carcinoma. Cancer 2003;98:542-553.

[9]Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol 2007;18:317-323.

[10]Scagliotti GV, Kortsik C, Dark GG, et al. Pemetrexed combined with oxaliplatin or carboplatin as first-line treatment in advanced non-small cell lung cancer: a multicenter, randomized, phase II trial. Clin Cancer Res 2005;11:690-696.

[11]Cardenal F, Lopez-Cabrerizo MP, Anton A, et al. Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small cell lung cancer. J Clin Oncol 1999;17:12-18.

[12]Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage NSCLC. J Clin Oncol 2008;26:3543-3551.

[13]Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. N Engl J Med 2002;346:92-98.

[14]Pujol JL, Breton JL, Gervais R, et al. Gemcitabine-docetaxel versus cisplatin-vinorelbine in advanced or metastatic non-small-cell lung cancer: a phase III study addressing the case for cisplatin. Ann Oncol 2005;16:602-610.

[15]Tan EH, Szczesna A, Krzakowski M, et al. Randomized study of vinorelbine--gemcitabine versus vinorelbine--carboplatin in patients with advanced non-small cell lung cancer. Lung Cancer 2005;49:233-240.

[16]Langer CJ, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. The Lancet Oncology. 2016;17:1497-1508.

[17]Green M, Manikhas G, Orlov S, et al. Abraxane®, a novel Cremophor® -free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. Ann Oncol 2006;17:1263-1268.

[18]Rizvi N, Riely G, Azzoli, C, et al. Phase I/II Trial of Weekly Intravenous 130-nm Albumin-Bound Paclitaxel As Initial Chemotherapy in Patients With Stage IV Non–Small-Cell Lung Cancer. J Clin Oncol 2008;26:639-643.

[19]Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small cell lung cancer: final results of a phase III trial. J Clin Oncol 2012:30:2055-2062.

[20]Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000;18:2354-2362.

[21]Fidias PM, Dakhil SR, Lyss AP, et al. Phase III study of immmediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small cell lung cancer. J Clin Oncol 2009;27:591-598.

[22]Zatloukal P, Kanitz E, Magyar P, et al Gemcitabine in locally advanced and metastatic non-small cell lung cancer: the Central European phase II study. Lung Cancer 1998;22:243-250.

[23]Sederholm C, Hillerdal G, Lamberg K, et al. Phase III trial of gemcitabine plus carboplatin versus single agent gemcitabine in the treatment of locally advanced or metastatic non-small cell lung cancer: the Swedish Lung Cancer Study group. J Clin Oncol 2005;23:8380-8288.

[24]Perol M, Chouaid C, Perol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small celll lung cancer. J Clin Oncol 2012;30:3516-3524.

[25]Lilenbaum RC, Herndon JE, List MA, et al. Single-agent versus combination chemotherapy in advanced non-small cell lung cancer: the cancer and leukemia group B (study 9730). J Clin Oncol 2005;23:190-196.

[26]Ceresoli GL, Gregorc V, Cordio S, et al. Phase II study of weekly paclitaxel as second-line therapy in patients wit h advanced non-small cell lung cancer. Lung Cancer 2004;44:231-239.

[27]Yasuda K, Igishi T, Kawasaki Y, et al. Phase II study of weekly paclitaxel in patients with non-small cell lung cancer who have failed previous treatments. Oncology 2004;66:347-352.

[28]Hanna NH, Sheperd FA, Fossella FV, et al. Randomized phase III study of pemetrexed versus docetaxel in patients with non-small cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589-1597.

Australian Government Cancer Council Australia, 2015 [3]. Clinical practice guidelines for the treatment of lung cancer	Fragestellung/Zielsetzung: What is the optimal first-line chemotherapy regimen in patients with stage IV inoperable NSCLC? Is carboplatin based chemotherapy as effective as cisplatin based chemotherapy for treatment of stage IV inoperable NSCLC? Which new agent or platinum combination regimen is best for treatment of stage IV inoperable NSCLC? Is monotherapy with new third generation (3G) agents as effective as platinum combination therapy for treatment of stage IV inoperable NSCLC? Are three chemotherapy agents better than two chemotherapy agents for treatment of stage IV inoperable NSCLC? Are non-platinum doublet chemotherapy regimens as effective as platinum doublet regimens for treatment of stage IV inoperable NSCLC? Is chemotherapy with a biologic or targeted therapy superior to chemotherapy alone in unselected patients for treatment of stage IV inoperable NSCLC? What is the optimal chemotherapy regimen for overall quality of life for patients in the treatment of stage IV inoperable NSCLC? What is the optimal second-line therapy in patients with stage IV inoperable NSCLC? What is the optimal third-line therapy in unselected patients with stage IV inoperable NSCLC? What is the optimal systemic therapy regimen for patients with poor performance status for treatment of stage IV inoperable NSCLC? What is the optimal systemic therapy regimen in selected patients for treatment of stage IV inoperable NSCLC?
	Methodik Grundlage der Leitlinie: Systematischer Review und Konsensusprozess über Empfehlungen. Alle Aussagen sind mit Literaturstellen (Meta-Analysen oder RCTs) belegt. Suchzeitraum: bis 2015 <u>LoE:</u>

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation	All or none	All or none	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: • Non-randomised, experimental trial • Cohort study • Case-control study • Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: • Non-randomised, experimental trial • Cohort study • Case-control study
III-3	A comparative study without concurrent controls: • Historical control study • Two or more single arm study • Interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: • Historical control study • Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

GoR:

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

Empfehlungen

Stage III inoperable

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

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

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

✓ Practice point?

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

✓ Practice point?

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

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

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

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

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

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

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

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

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

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

✓ Practice point?

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

Stage IV inoperable

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

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

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

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

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

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

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

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

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

✓ Practice point?

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

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

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

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

✓ Practice point?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1

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

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

✓ Practice point?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

✓ Practice point?

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

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

Last reviewed December 2015

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

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

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

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

✓ Practice point?

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

Masters GA et al., 2015 [16]. Systemic Therapy for	Diese Leitlinie wurde von Ellis PM, Vella ET, Ung YT, and the Lung Cancer Disease Site Group. 2016 bewertet und adaptiert (siehe oben).

Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update	
Alberta Provincial Thoracic Tumour Team, 2013 [1]. Non-small cell lung cancer - stage III. Alberta Health Services	**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
	Methodik Grundlage der Leitlinie: - systematic literature search, evidence tables, AGREE used for retrieved guidelines, working group reviewed currency and acceptability of all relevant literature, then circulated a draft of the updated guideline to entire provincial tumour team for final feedback and approval - Population: NSCLC, adult patients over the age of 18 years - Suchzeitraum: bis 2013 LoE / GoR: no use of formal rating schemes for describing the strength of the recommendations, rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations Sonstige methodische Hinweise Kein formaler Konsensusprozess beschrieben; Auswahl und Bewertung der Literatur nicht beschrieben; no direct industry involvement in the development or dissemination of this guideline authors have not been remunerated for their contributions
	Empfehlungen

	When is palliation recommended, and what are the recommended palliative treatment options for patients with inoperable stage III non-small cell lung cancer? **Palliative Treatment for Inoperable Disease** 12. In patients where lung reserve precludes radical radiotherapy, palliative chemotherapy and/or palliative radiotherapy are recommended. 13. Palliative chemotherapy options include: - 1st line: platinum-based doublets - 2nd line: docetaxel, erlotinib or pemetrexed 14. For symptomatic patients with poor performance status (ECOG>2) and/or significant weight loss (usually defined as >10% in previous 3 months), radiotherapy for symptom palliation is recommended. Dose-fractionation schedule options include: - 20Gy in 5 fractions or 30Gy in 10 fractions - Single fractions of radiotherapy less than 10Gy may be appropriate in some clinical circumstances such as poor performance status or patient travel distance. - Split course radiation can also be used in select cases.
Alberta Provincial Thoracic Tumour Team, 2013 [2]. Non-small cell lung cancer - stage IV. Alberta Health Services	**Fragestellungen** 1. What is the recommended first-line therapy for patients with stage IV non-small cell lung cancer (NSCLC)? 2. What is the role for EGFR tyrosine kinase inhibitors in first-line treatment of patients with stage IV NSCLC? 3. What is the optimal second-line therapy for patients with stage IV NSCLC? 4. What is the role of palliative radiotherapy in the management of patients with stage IV NSCLC?
	Methodik Grundlage der Leitlinie: - systematic literature search, evidence tables, AGREE used for retrieved guidelines, working group reviewed currency and acceptability of all relevant literature, then circulated a draft of the updated guideline to entire provincial tumour team for final feedback and approval - Population: NSCLC, adult patients over the age of 18 years - Suchzeitraum: bis 2013 LoE / GoR: no use of formal rating schemes for describing the strength of the recommendations, rather describes, in conventional and explicit language, the

	type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations Sonstige methodische Hinweise Kein formaler Konsensusprozess beschrieben; Auswahl und Bewertung der Literatur nicht beschrieben; no direct industry involvement in the development or dissemination of this guideline authors have not been remunerated for their contributions
	Empfehlungen 3. Combination chemotherapy consisting of a platinum-based doublet is the standard of care for first-line treatment of advanced NSCLC (except for EGFR-positive patients; see recommendation 6 below). The combination of three chemotherapeutic agents for the first-line treatment of advanced NSCLC is not routinely recommended based on current evidence. 5. Acceptable alternatives to combination chemotherapy include non-platinum doublets or monotherapy: - For patients with a borderline performance status (PS=2), single-agent chemotherapy with vinorelbine, gemcitabine, paclitaxel, docetaxel or pemetrexed (for non-squamous cell carcinoma patients only) is recommended over best supportive care alone. - For elderly patients who cannot tolerate a platinum-based combination, single-agent chemotherapy with vinorelbine, gemcitabine, docetaxel, or pemetrexed (for non-squamous cell carcinoma patients only) is associated with improved survival and quality of life when compared to best supportive care alone. However, elderly patients with a good performance status (PS=0-1) should receive combination chemotherapy with a platinum-based doublet. 6. First-line monotherapy with the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib is recommended for patients with EGFR mutation-positive NSCLC. 7. Testing for EGFR mutations should take place for all eligible patients with advanced NSCLC and adenocarcinoma (including adenosquamous) histology who are being considered for first-line therapy with gefitinib, irrespective of their gender, ethnicity, and smoking status. 8. Second-line or subsequent chemotherapy options for advanced NSCLC include single-agent docetaxel or erlotinib for patients with squamous cell carcinoma histology, or single agent treatment with a drug that has not been previously used. 9. Crizotinib has been approved for second-line treatment of patients who are positive for ALK-rearrangements from the pan-Canadian Oncology Drug Review (pCODR) and has also been approved for provincial coverage in Alberta.

	10. Testing for ALK mutations should take place for all eligible patients with advanced NSCLC and adenocarcinoma (including adenosquamous) histology who are being considered for second line therapy with crizotinib. 11. Palliative radiotherapy is recommended for relief of specific symptoms and prophylactic prevention of symptom development.
Scottish Intercollegiate Guidelines Network (SIGN) 2014 [23] Management of lung cancer. A national clinical guideline	Fragestellung/Zielsetzung The guideline covers all aspects of the management of patients with small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), and provides information for discussion with patients and carers. 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
	Methodik Grundlage der Leitlinie: systematische Recherche und Bewertung der Literatur, Entwicklung durch multidisziplinäre Gruppe von praktizierenden klinischen ExpertInnen, Expertenreview, öffentliche Konsultation Suchzeitraum: 2005 - 2012 LoE/GoR:

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

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

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

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

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

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

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

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

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

No particular combination of these agents in regimens with platinum

	has been shown to be more effective. **(LoE 1+)** 225. Schiller JH, et al. Comparison of four chemotherapy regimens for advanced nonsmall- cell lung cancer. N Engl J Med 2002;346(2):92-8. Standard treatment is in four cycles, and exceptionally six cycles. Continuing beyond four cycles may increase progression-free survival but at the expense of an increase in toxicity and worse quality of life without any significant gain in survival. **(LoE 1+/1++)** 226. Goffin J, et al. First-line systemic chemotherapy in the treatment of advanced non-small cell lung cancer: A systematic review. J Thorac Oncol 2010;5(2):260-74. 227. Lima JP, et al. Optimal duration of first-line chemotherapy for advanced non-small cell lung cancer: a systematic review with meta-analysis. Eur J Cancer 2009;45(4):601-7. In patients who have advanced disease and a performance status <2 at the time of diagnosis of NSCLC, first line treatment should be offered according to histology. Patients with non-squamous histology demonstrated a superior survival when treated with cisplatin and pemetrexed compared with cisplatin and gemcitabine (hazard ratio (HR) 0.84, 95% CI 0.74 to 0.96, p=0.011). Patients with squamous histology do not benefit from pemetrexed/platinum combination. **(LoE 1+)** 228. Scagliotti GV, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapynaive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26(21):3541-51. 229. Scagliotti GV, et al. Survival without toxicity for cisplatin plus pemetrexed versus cisplatin plus gemcitabine in chemonaïve patients with advanced non-small cell lung cancer: a risk-benefit analysis of a large phase III study. Eur J Cancer 2009;45(13):2298-303. In patients with adenocarcinoma, overall survival was statistically superior for cisplatin/pemetrexed versus cisplatin/gemcitabine (n=847; 12.6 *v* 10.9 months). **(LoE 1+)** Siehe 228 <u>Recommendations</u> • 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)
Ramnath N et al., 2013 [21] Treatment of stage III non-	Fragestellung/Zielsetzung To update the published clinical trials since the last American College of Chest Physicians guidelines to make treatment recommendations for this controversial subset of patients

small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines	Methodik Grundlage der Leitlinie: Update der Leitlinie von 2007, Repräsentatives Gremium, systematische Suche, Auswahl und Bewertung der Literatur, iterative Konsensusprozesse, externes Reviewboard, Erklärungen zu möglichen Interessenkonflikten liegen vor und wurden bei der Erstellung der Leitlinie berücksichtigt Suchzeitraum: Systematische Recherche bis Dezember 2011 LoE/GoR: ACCP Grading System **Table 1—*Strength of the Recommendations Grading System*** Grade of Recommendation | Benefit vs Risk and Burdens | Methodologic Strength of Supporting Evidence | Implications Strong recommendation, high-quality evidence (1A) | Benefits clearly outweigh risk and burdens or vice versa | Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies | Recommendation can apply to most patients in most circumstances. 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 . Sonstige methodische Hinweise • Unklar ob die Population des AWG von Pembrolizumab hier adressiert ist
	Freitext/Empfehlungen/Hinweise **2.0 Infiltrative Stage III (N2,3) Non-small Cell Lung Cancer** Multiple phase 3 trials using platinum-based chemotherapy have confirmed improved survival for patients treated with chemotherapy plus radiotherapy compared with radiotherapy alone (Fig 1).

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

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

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

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

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

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

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

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

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

19 . Miller T , et al . A randomized trial of chemotherapy and radiotherapy for stage III non-small cell lung cancer . Cancer Ther . 1998 ; 1 : 229 - 236 .

20 . Trovò MG , et al. Radiotherapy versus radiotherapy enhanced by cisplatin in stage III non-small cell lung cancer. Int J Radiat Oncol Biol Phys . 1992 ;24(3):573-574.

21 . Jeremic B, et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily carboplatin/etoposide for stage III non-smallcell lung cancer: a randomized study . J Clin Oncol . 1996; 14 (4): 1065 - 1070 .

22 . Jeremic B , et al . Randomized trial of hyperfractionated radiation therapy with or without concurrent chemotherapy for stage III non-small-cell lung cancer . J Clin Oncol . 1995 ; 13 (2): 452 - 458 .

23 . Blanke C, et al. Phase III trial of thoracic irradiation with or without cisplatin for locally advanced unresectable non-small-cell lung cancer: a Hoosier Oncology Group protocol . J Clin

	Oncol . 1995 ; 13 (6): 1425 - 1429. Two meta-analyses reviewing >50 trials confirmed the survival benefit of combined platinum-based chemotherapy with radiotherapy over radiotherapy alone in locally advanced, unresectable NSCLC. [24,25] 24 . Marino P, et al. Randomized trials of radiotherapy alone versus combined chemotherapy and radiotherapy in stages IIIa and IIIb nonsmall cell lung cancer. A meta-analysis . Cancer . 1995 ; 76 (4): 593 - 601 . 25 . Pritchard RS , Anthony SP . Chemotherapy plus radiotherapy compared with radiotherapy alone in the treatment of locally advanced, unresectable, non-small-cell lung cancer. A metaanalysis . Ann Intern Med . 1996 ; 125 (9): 723 - 729 . <u>2.3 Recommendations</u> 2.3.1. In patients with infi ltrative stage III (N2,3) NSCLC and performance status 0-1 being considered for curative-intent treatment, radiotherapy alone is not recommended (Grade 1A) . 2.3.2. In patients with infi ltrative stage III (N2,3) NSCLC and performance status 0-1 being considered for curative-intent treatment, combination platinum-based chemotherapy and radiotherapy (60-66 Gy) are recommended (Grade 1A) . Remark: Dose escalation of radiotherapy is not recommended (except in a clinical trial). Remark: For patients with stage III NSCLC, once daily thoracic radiotherapy plus platinum-based doublet chemotherapy is recommended. 2.3.6. In patients with infiltrative stage III (N2,3) NSCLC and performance status 2 or those with substantial weight loss (>10%), concurrent chemoradiotherapy is suggested but with careful consideration of the potential risks and benefits (Grade 2C). Remark: Patient-related and tumor-related factors can influence the balance of risks vs benefits; patient preferences should also play a significant role. 2.3.8. In patients with symptomatic infiltrative stage III (N2,3) NSCLC and either performance status 3-4, comorbidities, or disease too extensive to treat with curative intent, palliative radiotherapy is recommended. The fractionation pattern should be chosen based on the physician's judgment and patient's needs (Grade 1C).
Socinski MA et al., 2013 [26]. Treatment of stage IV non-small cell lung cancer:	Fragestellung/Zielsetzung (relevante Auswahl) PICO 1: Should the choice of first-line chemotherapy be based on histology in patients with advanced stage IV NSCLC? PICO 3: Is bevacizumab with chemotherapy safer for patients with advanced stage IV NSCLC and treated brain metastases, anticoagulation, or a poor PS than chemotherapy alone? 7. Is doublet chemotherapy more effective than single-agent chemotherapy for

Diagnosis and management of lung cancer. 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines	patients >70 years of age with advanced stage IV NSCLC? 8. Is doublet chemotherapy more effective than single-agent chemotherapy for patients with a PS of 2 with advanced stage IV NSCLC?
	Methodik (Siehe auch Ramnath N et al., 2013 [21]) Grundlage der Leitlinie: Update der Leitlinie von 2007, Repräsentatives Gremium, systematische Suche, Auswahl und Bewertung der Literatur, iterative Konsensusprozesse, externes Reviewboard, Erklärungen zu möglichen Interessenkonflikten liegen vor und wurden bei der Erstellung der Leitlinie berücksichtigt Suchzeitraum: Systematische Recherche bis Dezember 2011 LoE/GoR: ACCP Grading System **Table 1—*Strength of the Recommendations Grading System*** Grade of Recommendation / Benefit vs Risk and Burdens / Methodologic Strength of Supporting Evidence / Implications Strong recommendation, high-quality evidence (1A) / Benefits clearly outweigh risk and burdens or vice versa / Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies / Recommendation can apply to most patients in most circumstances. 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 .
	Freitext/Empfehlungen/Hinweise **2.0 General Approach to Patients** **2.1 Recommendations (Adapted From First and Second Editions)** [3,4] 2.1.1. In patients with a good PS (ie, ECOG level 0 or 1) and stage IV NSCLC, a platinum-based chemotherapy regimen is recommended based on the survival advantage and improvement in QOL over 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)

3 .Socinski MA , Morris DE , Masters GA , Lilenbaum R ; American College of Chest Physicians . Chemotherapeutic management of stage IV non-small cell lung cancer. Chest . 2003 ; 123 (suppl 1): 226S - 243S .

4 .Socinski MA , Crowell R , Hensing TE , et al . Treatment of non-small cell lung cancer, stage IV: ACCP evidence-based clinical practice guidelines (2nd edition). Chest .2007 ; 132(suppl 3):277S-289S.

3.0 First-Line Chemotherapy

3.1 Histology-Based Chemotherapy Selection

In 2006, the antiangiogenesis agent bevacizumab was approved by the US Food and Drug Administration (FDA) for use with carboplatin and paclitaxel chemotherapy only in patients with nonsquamous cell advanced NSCLC. The landmark ECOG 4599 trial, which established the use of bevacizumab, had excluded patients with squamous cell carcinoma because a phase 2 study had found a higher incidence of grade 4/5 hemoptysis in patients with squamous cell histology. [10,11]

In 2008, pemetrexed was approved by the FDA as a first-line therapy combined with cisplatin for patients with nonsquamous cell advanced chemonaïve NSCLC. This approval came after publication of the results of a large randomized first-line trial comparing the standard combination of cisplatin and gemcitabine with cisplatin and pemetrexed.[12] Although neither regimen appeared superior overall, nonsquamous cell histology predicted a survival benefit with the pemetrexed containing regimen (n = 1,000; hazard ratio [HR] 0.81; 95% CI 0.7-0.94; P = .005)

10 . Sandler A , et al . Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer . N Engl J Med . 2006 ; 355 (24): 2542 - 2550 .

11. Johnson DH , Fehrenbacher L , Novotny WF , et al . Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic nonsmall- cell lung cancer . J Clin Oncol . 2004; 22(11): 2184- 2191 .

12 . Scagliotti GV , et al . Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advancedstage non-small-cell lung cancer . J Clin Oncol . 2008 ;26 (21): 3543 - 3551 .

3.1.1 Recommendation

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.

3.3 Use of Vascular Endothelial Growth Factor Inhibitors

	In summary, based on both prospective and retrospective analyses, the use of bevacizumab in patients with stage IV NSCLC with treated and controlled brain metastases who retain an ECOG PS of 0 to 1 is safe. No recommendations can be given regarding the safety of bevacizumab either in patients with an ECOG PS of 2 or in those requiring anticoagulation. This is based on the fact that the data that exist are either retrospective or observational. 10 . Sandler A , et al . Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer . N Engl J Med . 2006 ; 355 (24): 2542 - 2550 . 40 . Socinski MA , et al . Safety of bevacizumab in patients with non-small-cell lung cancer and brain metastases . J Clin Oncol . 2009 ; 27 (31): 5255 - 5261 . 41 . Wozniak AJ , et al . Clinical outcomes (CO) for special populations of patients (pts) with advanced non-small cell lung cancer (NSCLC): Results from ARIES, a bevacizumab (BV) observational cohort study (OCS) [abstract] . J Clin Oncol . 2010 ; 28 (15s)(suppl):abstr7618. 42 . Besse B, et al. Bevacizumab safety in patients with central nervous system metastases . Clin Cancer Res . 2010 ; 16 (1): 269 - 278 . 43 . Reck M , et al . Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as fi rst-line therapy for nonsquamous non-small-cell lung cancer: AVAil . J Clin Oncol . 2009 ; 27 (8): 1227 - 1234 . 44 . Crinò L , et al . Safety and effi cacy of fi rst-line bevacizumab-based therapy in advanced nonsquamous non-small-cell lung cancer (SAiL, MO19390): a phase 4 study . Lancet Oncol . 2010 ; 11 (8): 733 - 740 . 45 . Hardy-Bessard AC , et al . Safety and efficacy of bevacizumab combined with taxanes in the fi rst-line treatment of metastatic breast cancer: ATHENA study-France [in French] . Bull Cancer . 2012 ; 99 (6): 609 - 618 . 46 . Miller VA , et al. A randomized, double-blind, placebo-controlled, phase IIIb trial (ATLAS) comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemotherapy with B for fi rstline treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol. 2009 27 (18s)(suppl):abstrLBA8002. 47 . Carden CP , et al. What is the risk of intracranial bleeding during anti-VEGF therapy? Neurooncol . 2008 ; 10 (4): 624 - 630 . 48 . Leighl NB , et al. Bleeding events in bevacizumab-treated cancer patients who received full-dose anticoagulation and remained on study . Br J Cancer . 2011 ; 104 (3): 413 - 418 . 49 . Griesinger F , et al. Safety of fi rst-line bevacizumab- based therapy with concomitant cardiovascular or anticoagulation medication in advanced or recurrent nonsquamous non-small cell lung cancer (NSCLC) in MO19390 (SAiL) [abstract] . J Clin Oncol . 2008 ; 26 (suppl)8049. 3.3.1.1. Bevacizumab improves survival combined with carboplatin and paclitaxel in a clinically selected subset of patients with stage IV NSCLC and good PS (nonsquamous histology, lack of brain metastases, and no hemoptysis). In these patients, addition of bevacizumab to carboplatin and paclitaxel is recommended **(Grade 1A)** . 3.3.1.2. In patients with stage IV non-squamous NSCLC and treated, stable brain metastases, who are otherwise candidates for bevacizumab therapy, the addition of bevacizumab to firstline, platinum-based chemotherapy is a safe therapeutic option **(Grade 2B)** . Remark: No recommendation can be given about the use of bevacizumab in patients receiving therapeutic anticoagulation or with an ECOG PS of 2. *6.0 Treatment of Patients With Poor PS* In summary, patients with a PS of 2 are a heterogeneous group, and poor PS may be related to NSCLC or may be caused by underlying comorbidities. An RCT of double-agent compared with single-agent chemotherapy demonstrated

	an improvement in PFS and OS. Chemotherapy treatment improves HRQOL in patients with a PS of 2; data are insufficient to determine if single-or double-agent chemotherapy provides greater HRQOL benefit. Currently, there are insufficient data to recommend routine use of bevacizumab in patients with a PS of 2. 111 . Stanley KE . Prognostic factors for survival in patients with inoperable lung cancer . J Natl Cancer Inst . 1980 ; 65 (1): 25 - 32 . 112 . Ruckdeschel JC , Finkelstein DM , Ettinger DS , et al . A randomized trial of the four most active regimens for metastatic non-small-cell lung cancer . J Clin Oncol . 1986 ; 4 (1): 14 - 22 . 113 . Albain KS , Crowley JJ , LeBlanc M , Livingston RB . Survival determinants in extensive-stage non-small-cell lung cancer: the Southwest Oncology Group experience . J Clin Oncol . 1991 ; 9 (9): 1618 - 1626 . 114 . Paesmans M , Sculier JP , Libert P , et al ; The European Lung Cancer Working Party . Prognostic factors for survival in advanced non-small-cell lung cancer: univariate and multivariate analyses including recursive partitioning and amalgamation algorithms in 1,052 patients . J Clin Oncol . 1995 ; 13 (5): 1221 - 1230 . 115 . Sweeney CJ , Zhu J , Sandler AB , et al . Outcome of patients with a performance status of 2 in Eastern Cooperative Oncology Group Study E1594: a Phase II trial in patients with metastatic nonsmall cell lung carcinoma . Cancer . 2001 ; 92 (10): 2639 - 2647 . 116 . Lilenbaum RC , Herndon JE II , List MA , et al . Single-agent versus combination chemotherapy in advanced non-smallcell lung cancer: the cancer and leukemia group B (study 9730) . J Clin Oncol . 2005 ; 23 (1): 190 - 196 . 117 . Stinchcombe TE , Choi J , Schell MJ , et al . Carboplatin-based chemotherapy in patients with advanced non-small cell lung cancer and a poor performance status . Lung Cancer . 2006 ; 51 (2): 237 - 243 . 118 . Langer CJ , O'Byrne KJ , Socinski MA , et al . Phase III trial comparing paclitaxel poliglumex (CT-2103, PPX) in combination with carboplatin versus standard paclitaxel and carboplatin in the treatment of PS 2 patients with chemotherapy- naïve advanced non-small cell lung cancer . J Thorac Oncol . 2008 ; 3 (6): 623 - 630 . 119 . O'Brien ME , Socinski MA , Popovich AY , et al . Randomized phase III trial comparing single-agent paclitaxel Poliglumex (CT-2103, PPX) with single-agent gemcitabine or vinorelbine for the treatment of PS 2 patients with chemotherapynaïve advanced non-small cell lung cancer . J Thorac Oncol . 2008 ; 3 (7): 728 - 734 . 120 . Lilenbaum R , Villafl or VM , Langer C , et al . Single-agent versus combination chemotherapy in patients with advanced non-small cell lung cancer and a performance status of 2: prognostic factors and treatment selection based on two large randomized clinical trials . J Thorac Oncol . 2009; 4(7): 869- 874. 121 . Reynolds C, Obasaju C, Schell MJ, et al. Randomized phase III trial of gemcitabine-based chemotherapy with in situ RRM1 and ERCC1 protein levels for response prediction in nonsmall-cell lung cancer . J Clin Oncol . 2009; 27(34): 5808- 5815. 122 . Lilenbaum R , Zukin M , Pereira JR , et al . A randomized phase III trial of single-agent pemetrexed (P) versus carboplatin and pemetrexed (CP) in patients with advanced non- small cell lung cancer (NSCLC) and performance status (PS) of 2 [abstract 7506] . J Clin Oncol . 2012 ; 30 :7506. 123 . Billingham LJ , Cullen MH . The benefi ts of chemotherapy in patient subgroups with unresectable non-small-cell lung cancer . Ann Oncol . 2001 ; 12 (12): 1671 - 1675 . 124 . Hickish TF , Smith IE , O'Brien ME , Ashley S , Middleton G . Clinical benefi t from palliative chemotherapy in non-smallcell lung cancer extends to the elderly and those with poor prognostic factors . Br J Cancer . 1998 ; 78 (1): 28 - 33 . 6.2 Recommendation 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) .

Wauters I et al., 2013 [30]

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

Fragestellung/Zielsetzung

This study aims to develop a clinical practice guideline (CPG) on lung cancer. The CPG will cover a broad range of topics: staging, treatment of non-small cell lung cancer, treatment of small cell lung cancer and followup. The specific clinical questions (paragraph 2.3) were the result of a scoping review of existing guidelines and consecutive discussion within the external expert group.

Methodik

Grundlage der Leitlinie:

- The present clinical practice guideline (CPG) was developed by adapting (inter)national CPGs to the Belgian context. In general, and whenever necessary, included guidelines were updated with more recent evidence. In summary, recent evidence-based guidelines of high quality were searched and summarized and served, together with more recent evidence, as basis to formulate the recommendations.
  Based on the retrieved evidence, draft recommendations were prepared by KCE experts, and sent for review to the external experts group selected by the College of Oncology. The evidence and the recommendations were discussed during meetings between KCE experts and the group of external experts.
- Suchzeitraum:
  OVID Medline, the National Guideline Clearinghouse (guideline.gov) and Guidelines International Network (www.g-i-n.net) were searched for both national and international CPGs from 2009 to 20 February 2012.
  The update search for peer-reviewed articles included a search in OVID Medline, EMBASE, CENTRAL and the Cochrane Database of Systematic Reviews. Searches were run between April, 2012 and January, 2013.

LoE

Table 1 – Levels of evidence according to the GRADE system

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

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

GoR

Nach GRADE (strong, weak recommendation)

Freitext/Empfehlungen/Hinweise

Treatment of locally advanced NSCLC (stage cIIIA-cIIIB)

5.2.1. Combined chemo-radiotherapy

Update: One recent RCT by Atagi et al.[104] compared radiotherapy with or without daily low-dose carboplatin in elderly patients (older than 70 years old) with NSCLC. Improved OS and PFS with the combination therapy were confirmed. Median overall survival was 22.4 months in the chemoradiotherapy group and 16.9 months in the radiotherapy group respectively. We updated the Cochrane review with this; the result is reported in following table

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
Overall survival	11	1807	Hazard Ratio (IV, Random, 95% CI)	0.71 [0.64, 0.79]
Treatment related deaths	15	2269	Risk Ratio (IV, Random, 95% CI)	0.70 [0.41, 1.20]
Acute pneumonitis	10	1373	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.48, 1.04]
Oesophagitis	18	2421	Risk Ratio (M-H, Random, 95% CI)	1.64 [1.22, 2.21]
Neutropenia	8	1031	Risk Ratio (M-H, Random, 95% CI)	5.24 [3.50, 7.83]
Anemia grade 3 to 4	6	1016	Risk Ratio (M-H, Random, 95% CI)	5.31 [1.86, 15.13]

3. NICE NCCfC-. The diagnosis and treatment of lung cancer (update). In: National Collaborating Centre for Cancer, cardiff, Wales; 2011.

7. Landelijke werkgroep longtumoren IKNL. Niet-kleincellig longcarcinoom - Landelijke richtlijn, Versie 2.0. In. 2.0 ed; 2011.

104. Atagi S, Kawahara M, Yokoyama A, Okamoto H, Yamamoto N, Ohe Y, et al. Thoracic radiotherapy with or without daily low-dose carboplatin in elderly patients with non-small-cell lung cancer: a randomised, controlled, phase 3 trial by the Japan Clinical Oncology Group (JCOG0301). Lancet Oncol. 2012;13(7):671-8.

The recommendation to consider chemoradiotherapy for patients with inoperable stage III NSCLC is based on moderate level of evidence. The evidence on the effect on survival is counterbalanced by evidence on its increased toxicity and the evidence is considered moderate because of inconsistency, with a number of studies and subgroup analysis in the Cochrane review showing no effect

Treatment of stage cIII NSCLC

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

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

Treatment of metastatic (stage cIV) and recurrent NSCLC

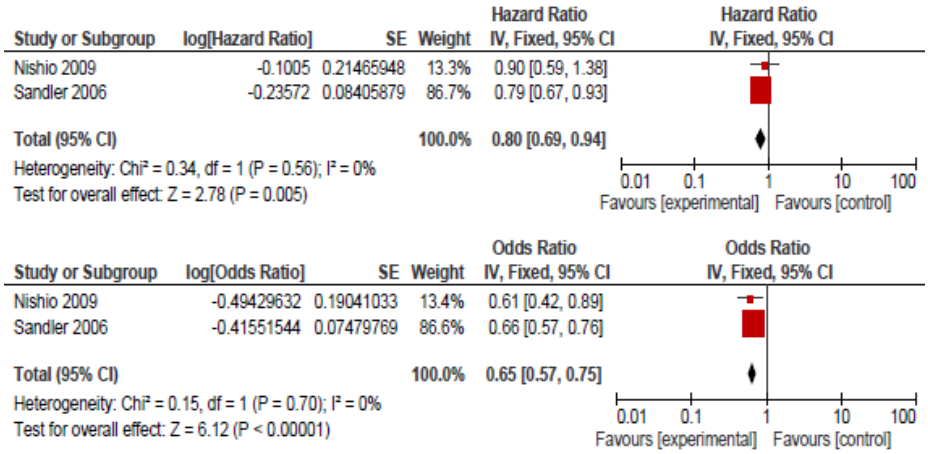
	5.3.2. What is the most effective first-line chemotherapy? 5.3.2.2. Platinum vs. non platinum containing regimens The ASCO guideline[4] of 2011 recommends a combination of two cytotoxic drugs for first line therapy in patients with a PS of 0 or 1. Platinum combinations are preferred over non-platinum combinations because they are superior in terms of response rate and marginally superior in OS. Meta-analyses (MAs) were published comparing platinum- with non– platinum containing regimens. The number of participants in the MAs ranged from 23 512 to 7633 patients, and the number of participants in the individual RCTs ranged from 28 117 to 1725 patients. The toxicities reported were higher with platinum agents. AEs specific to platinum include nephrotoxicity and GI problems. Twelve individual trials showed statistically significantly higher hematologic toxicities in platinum treatment arms, and seven trials showed significantly higher non-hematologic toxicities in platinum arms. The Dutch guideline[7] also recommends platinum based regimens if tolerated by the patient, based on a meta-analysis showing a better tumour response (OR 1.62, 95 %CI 1.46 – 1.80) and a better 1-year survival (34 % vs. 29 %; OR 1.21, 95% CI 1.09– 1.35). 5.3.2.3. Cisplatin vs. Carboplatin The ASCO guideline4 considers the choice of either cisplatin or carboplatin acceptable. 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 is more likely to cause thrombocytopenia. This recommendation is based on a lack of consistent superiority of either agent in terms of OS, toxicity or quality of life across the literature. The Dutch guideline[7] on the contrary recommends cisplatin as a first choice combined with a third generation agents for non-squamous NSCLC based on a meta-analysis showing that carboplatin was associated with 12% higher relative hazard of death (HR: 1,12; 95%CI: 1,01-1,23) in the subgroup of non-squamous NSCLC although the effect is comparable when considering all (HR: 1,07; 95%CI: 0,99-1,15). 5.3.2.4. Which doublet therapy? The ASCO guideline4 considers the choice of either cisplatin or carboplatin acceptable. Drugs that may be combined with platinum include the thirdgeneration cytotoxic drugs docetaxel, gemcitabine, irinotecan, paclitaxel, pemetrexed, and vinorelbine. The Dutch guideline7 also considered the evidence insufficient to recommend a specific schedule bud does not recommend the combination

pemetrexed/cisplatin for patients with squamous NSCLC based on the data above. Third generation cytotoxic agents are superior to second generation, based on a Cochrane review.

5.3.2.5. Addition of Bevacizumab to doublet chemotherapy.

We found two systematic reviews on the subject, with a slightly different focus. Botrel et al 2011[121] pooled 4 trials, comprising 2200 patients. The appropriateness of these pooling can be questioned given the heterogeneity of the interventions, studies using the doublet carboplatin plus paclitaxel and the doublet cisplatin and gemcitabine are pooled here, resulting in considerable heterogeneity, which is subsequently treated with a random effects model. We excluded the second systematic review of Lima et al 2011 [122] because also studies including second line patients were pooled here.

Because we considered the pooling of Botrel et al. not justified we pooled the 2 studies on the addition of bevacizumab ourselves, details are given in appendix 5.3.2.5. The pooled estimate of the overall survival was 0.80 (95 % CI 0.69 to 0.94) and the pooled odds ratio for the response rate 0.65 (95 % CI 0.57 to 0.75).



121. Botrel TE, Clark O, Clark L, Paladini L, Faleiros E, Pegoretti B. Efficacy of bevacizumab (Bev) plus chemotherapy (CT) compared to CT alone in previously untreated locally advanced or metastatic non-small cell lung cancer (NSCLC): systematic review and metaanalysis. Lung Cancer. 2011;74(1):89-97.

122. Lima AB, Macedo LT, Sasse AD. Addition of bevacizumab to chemotherapy in advanced non-small cell lung cancer: a systematic review and meta-analysis. PLoS ONE. 2011;6(8):e22681.

Other considerations: The guideline development group decided not to make a recommendation on bevacizumab as it is neither registered nor reimbursed in Belgium for this indication.

Treatment of metastatic (stage cIV) and recurrent NSCLC

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

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

Anmerkung:

Für Bevacizumab wird keine Recommendation ausgesprochen, da es in Belgien nicht registriert ist/vergütet wird

Gemeinsamer Bundesausschuss

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 25.09.2017

#	Suchfrage
1	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees
2	(((non next small) or nonsmall) next cell next lung):ti,ab,kw
3	(tumor* or tumour* or carcinoma* or adenocarcinoma* or neoplasm* or sarcoma* or cancer*):ti,ab,kw
4	advanced:ti,ab,kw or metastat*:ti,ab,kw or metastas*:ti,ab,kw or recurren*:ti,ab,kw or relaps*:ti,ab,kw
5	#2 and #3 and #4
6	nsclc*:ti,ab,kw
7	#1 or #5 or #6
8	#7 from 2012 to 2017

SR, HTAs in Medline (PubMed) am 25.09.2017

#	Suchfrage
1	Carcinoma, Non-Small-Cell Lung[mh]
2	(((non[tiab]) AND small[tiab]) OR nonsmall[tiab]) AND cell[tiab]) AND lung[tiab]
3	(((((((tumor[Tiab]) OR tumors[Tiab]) OR tumour*[Tiab]) OR carcinoma*[Tiab]) OR adenocarcinoma*[Tiab]) OR neoplasm*[tiab]) OR sarcoma*[Tiab]) OR cancer*[Tiab]
4	(#2 AND #3) OR #1
5	(#4) AND ((((advanced[Tiab]) OR metastat*[Tiab]) OR metastas*[Tiab]) OR recurren*[Tiab] or relaps*[tiab])
6	(#5) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Tiab] OR studies[Tiab] OR database*[Tiab] OR literature[Tiab] OR publication*[Tiab] OR Medline[Tiab] OR Embase[Tiab] OR Cochrane[Tiab] OR Pubmed[Tiab])) AND systematic*[Tiab] AND (search*[Tiab] OR research*[Tiab]))) OR ((((((((((HTA[Tiab]) OR technology assessment*[Tiab]) OR technology report*[Tiab]) OR (systematic*[Tiab] AND review*[Tiab])) OR (systematic*[Tiab] AND overview*[Tiab])) OR meta-analy*[Tiab]) OR (meta[Tiab] AND analyz*[Tiab])) OR (meta[Tiab] AND analys*[Tiab])) OR (meta[Tiab] AND analyt*[Tiab]))) OR (((review*[Tiab]) OR overview*[Tiab]) AND ((evidence[Tiab]) AND based[Tiab]))))
7	((#6) AND ("2012/09/01"[PDAT] : "2017/09/30"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 25.09.2017

#	Suchfrage
1	Carcinoma, Non-Small-Cell Lung[mh]
2	Lung Neoplasms/*therapy/drug therapy
3	Medical Oncology/methods/*standards
4	(((non[tiab]) AND small[tiab]) OR nonsmall[tiab]) AND cell[tiab]) AND lung[tiab]
5	(((((((tumor[Tiab]) OR tumors[Tiab]) OR tumour*[Tiab]) OR carcinoma*[Tiab]) OR adenocarcinoma*[Tiab]) OR neoplasm*[Tiab]) OR sarcoma*[Tiab]) OR cancer*[Tiab]
6	lung[ti] AND #5
7	(#4 AND #5) OR #6
8	#1 OR #2 OR #3 OR #7

9	(#8) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[Title])*
10	(((#9) AND ("2012/09/01"[PDAT] : "2017/09/30"[PDAT])) NOT (animals[MeSH:noexp] NOT ((Humans[mh] AND animals[MeSH:noexp]) NOT ("The Cochrane database of systematic reviews"[Journal]))

Literatur

1. **Alberta Provincial Thoracic Tumour Team.** Non-small cell lung cancer stage III [online]. Edmonton (CAN): Alberta Health Services (AHS); 2012. [Zugriff: 26.09.2017]. (Clinical practice guideline; Band LU-003). URL: http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-lu003-nlscs-stage3.pdf.

2. **Alberta Provincial Thoracic Tumour Team.** Non-small cell lung cancer stage IV [online]. Edmonton (CAN): Alberta Health Services (AHS); 2013. [Zugriff: 26.09.2017]. (Clinical practice guideline; Band LU-004, vers. 06). URL: http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-lu004-nsclc-stage4.pdf.

3. **Australian Government Cancer Council Australia.** Clinical practice guidelines for the treatment of lung cancer [online]. 08.2017. Sydney (AUS): Cancer Council Australia; 2017. [Zugriff: 26.09.2017]. URL: http://wiki.cancer.org.au/australia/Guidelines:Lung_cancer, http://wiki.cancer.org.au/australiawiki/index.php?title=Guidelines:Lung_cancer/Treatment/Non_small-cell/Summary_of_recommendations&printable=yes.

4. **Brown T, Pilkington G, Bagust A, Boland A, Oyee J, Tudur-Smith C, et al.** Clinical effectiveness and cost-effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: a systematic review and economic evaluation [online]. 1-278. 2013. [Zugriff: 31]. (Health Technology Assessment). URL: PM:23886301.

5. **Cui J, Cai X, Zhu M, Liu T, Zhao N.** The efficacy of bevacizumab compared with other targeted drugs for patients with advanced NSCLC: a meta-analysis from 30 randomized controlled clinical trials. PLoS One 2013;8(4):e62038.

6. **De Castria TB, Da Silva EM, Gois AF, Riera R.** Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer. Cochrane Database of Systematic Reviews [online]. 2013(8):Cd009256. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009256.pub2/abstract.

7. **Ellis PM, Vella ET, Ung YT, and the Lung Cancer Disease Site Group.** Systemic Treatment for Patients with Advanced Non-Small Cell Lung Cancer [online]. 11.2016. Toronto (CAN): Cancer Care Ontario (CCO); 2016. [Zugriff: 26.09.2017]. (Evidence-Based Series; Band 7-10, Vers. 3). URL: https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=366077.

8. **Gemeinsamer Bundesausschuss (G-BA).** Beschluss über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Crizotinib (neues Anwendungsgebiet: ROS1-positives, fortgeschrittenes nicht kleinzelliges Lungenkarzinom) vom 16.03.2017 [online]. Berlin (GER): G-BA; 2017. [Zugriff: 26.09.2017]. URL: https://www.g-ba.de/informationen/beschluesse/2879/.

9. **Gemeinsamer Bundesausschuss (G-BA).** Beschluss über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Pembrolizumab (neues Anwendungsgebiet: Erstlinienbehandlung, nicht kleinzelliges Lungenkarzinom) vom 03.08.2017 [online]. Berlin (GER): G-BA; 2017. [Zugriff: 26.09.2017]. URL: https://www.g-ba.de/informationen/beschluesse/3033/.

10. **Hanna N, Johnson D, Temin S, Baker S, Jr., Brahmer J, Ellis PM, et al.** Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2017:JCO2017746065.

11. **He X, Wang J, Li Y.** Efficacy and safety of docetaxel for advanced non-small-cell lung cancer: a meta-analysis of Phase III randomized controlled trials. Onco Targets Ther 2015;8:2023-2031.

12. **Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG).** Crizotinib (nicht kleinzelliges Lungenkarzinom) - Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A16-59 [online]. Köln (GER): IQWIG; 2017. [Zugriff: 26.09.2017]. (IQWiG-Berichte; Band 472). URL: https://www.g-ba.de/downloads/92-975-1711/Nutzenbewertung-IQWiG_Crizotinib-2016-10-01-D-261.pdf.

13. **Jiang J, Liang X, Zhou X, Huang R, Chu Z, Zhan Q.** Paclitaxel plus platinum or gemcitabine plus platinum in first-line treatment of advanced non-small-cell lung cancer: results from 6 randomized controlled trials. Int J Clin Oncol 2013;18(6):1005-1013.

14. **Lai XX, Xu RA, Yu-Ping L, Yang H.** Risk of adverse events with bevacizumab addition to therapy in advanced non-small-cell lung cancer: a meta-analysis of randomized controlled trials. Onco Targets Ther 2016;9:2421-2428.

15. **Luo L, Hu Q, Jiang JX, Yang X, Dinglin XX, Lin X, et al.** Comparing single-agent with doublet chemotherapy in first-line treatment of advanced non-small cell lung cancer with performance status 2: a meta-analysis. Asia Pac J Clin Oncol 2015;11(3):253-261.

16. **Masters GA, Temin S, Azzoli CG, Giaccone G, Baker S, Jr., Brahmer JR, et al.** Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2015;33(30):3488-3515.

17. **Mörth C, Valachis A.** Single-agent versus combination chemotherapy as first-line treatment for patients with advanced non-small cell lung cancer and performance status 2: a literature-based meta-analysis of randomized studies. Lung Cancer 2014;84(3):209-214.

18. **National Comprehensive Cancer Network.** Non-Small Cell Lung Cancer, Vers. 09.2017 [online]. Fort Washington (USA): NCCN; 2017. [Zugriff: 26.09.2017]. URL: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

19. **Pilkington G, Boland A, Brown T, Oyee J, Bagust A, Dickson R.** A systematic review of the clinical effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer. Thorax 2015;70(4):359-367.

20. **Qi WX, Tang LN, He AN, Shen Z, Lin F, Yao Y.** Doublet versus single cytotoxic agent as first-line treatment for elderly patients with advanced non-small-cell lung cancer: a systematic review and meta-analysis. Lung 2012;190(5):477-485.

21. **Ramnath N, Dilling TJ, Harris LJ, Kim AW, Michaud GC, Balekian AA, et al.** 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. Chest 2013;143(5 Suppl):e314S-e340S.

22. **Santos FN, de CTB, Cruz MR, Riera R.** Chemotherapy for advanced non-small cell lung cancer in the elderly population. Cochrane Database of Systematic Reviews [online]. 2015(10):Cd010463. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010463.pub2/abstract.

23. **Scottish Intercollegiate Guidelines Network (SIGN).** Management of lung cancer. A national clinical guideline [online]. 02.2014. Edinburgh (GBR): SIGN; 2014. [Zugriff: 26.09.2017]. (SIGN publication; Band 137). URL: http://www.sign.ac.uk/pdf/SIGN137.pdf.

24. **Shen G, Bian G, Yu H, Gao M, Kang D, Shen G, et al.** 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. Mol Clin Oncol 2014;2(1):146-150.

25. **Sheng M, Zhao Y, Wang F, Li S, Wang X, Shou T, et al.** Targeted drugs for unselected patients with advanced non-small-cell lung cancer: a network meta-analysis. J Thorac Dis 2016;8(1):98-115.

26. **Socinski MA, Evans T, Gettinger S, Hensing TA, Sequist LV, Ireland B, et al.** Treatment of stage IV non-small cell lung cancer: Diagnosis and management of lung cancer. 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl):e341S-e368S.

27. **Soria JC, Mauguen A, Reck M, Sandler AB, Saijo N, Johnson DH, et al.** Systematic review and meta-analysis 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. Ann Oncol 2013;24(1):20-30.

28. **Sun L, Ma JT, Zhang SL, Zou HW, Han CB.** Efficacy and safety of chemotherapy or tyrosine kinase inhibitors combined with bevacizumab versus chemotherapy or tyrosine kinase inhibitors alone in the treatment of non-small cell lung cancer: a systematic review and meta-analysis. Med Oncol 2015;32(2):473.

29. **Wang S, Wang Q, Tian J, Zhou Z, Jiao L, Fu Y, et al.** Meta-analysis comparing doublet and single cytotoxic agent therapy as first-line treatment in elderly patients with advanced nonsmall-cell lung cancer. J Int Med Res 2015;43(6):727-737.

30. **Wauters I, Robays J, Verleye L, Holdt Henningsen K, Hulstaert F, Berghmans T, et al.** Non-small cell and small cell lung cancer: diagnosis, treatment and follow-up [online]. Brüssel (BEL): Belgian Health Care Knowledge Centre; 2013. [Zugriff: 26.09.2017]. (KCE Report; Band 206). URL: https://kce.fgov.be/sites/default/files/page_documents/KCE_206_lung_cancer.pdf.

31. **Xiao HQ, Tian RH, Zhang ZH, Du KQ, Ni YM.** Efficacy of pemetrexed plus platinum doublet chemotherapy as first-line treatment for advanced nonsquamous non-small-cell-lung cancer: a systematic review and meta-analysis. Onco Targets Ther 2016;9:1471-1476.

32. **Xu CA, Chang ZY, Wang XJ, Qi HY.** Doublets versus single-agent therapy as first-line therapy for elderly patients with advanced non-small cell lung cancer? A systematic review of randomised controlled trials. Int J Clin Pract 2013;67(11):1118-1127.

Anlage

Table 3-2. Modifications to ASCO's recommendations (Ellis PM, et al. 2016 [7]).

Clinical questions	ASCO recommendations	Modifications	Modification rationale	Implementation considerations
A2: What is the most effective first-line therapy for patients with stage IV NSCLC with non-SCC (NSCC), negative or unknown *EGFR*-sensitizing mutation and *ALK* gene rearrangement status, and PS 0 to 1 or possibly PS 2?	**Recommendation A2** For patients who have the characteristics described in Clinical Question A2 and who have non-squamous histology, the following options are acceptable: ● Cisplatin-based combinations ● Cisplatin plus docetaxel ● Cisplatin plus paclitaxel ● Cisplatin plus pemetrexed ● Cisplatin plus vinorelbine ● Carboplatin-based combinations ● Carboplatin plus albumin-bound (nab)–paclitaxel ● Carboplatin plus	Add another option: Cisplatin or carboplatin in combination with gemcitabine	The evidence for platinum-based chemotherapy plus gemcitabine that was included in ASCO's review was conflicting [1]. Scagliotti et al. [6] found inferior efficacy with cisplatin plus gemcitabine compared with cisplatin plus pemetrexed for patients with NSCC and Gronberg et al. [7] found no difference in efficacy	Nonplatinum doublets will be a funding gap for Ontario.

Quellen:

1. Masters GA, Temin S, Azzoli CG, Giaccone G, Baker S, Brahmer JR, et al. Systemic Therapy for Stage IV Non–Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015.
6. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008;26(21):3543-51.
7. Gronberg BH, Bremnes RM, Flotten O, Amundsen T, Brunsvig PF, Hjelde HH, et al. Phase III study by the Norwegian lung cancer study group: pemetrexed plus carboplatin compared with gemcitabine plus carboplatin as first-line chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol. 2009;27(19):3217-24.

Clinical questions	ASCO recommendations	Modifications	Modification rationale	Implementation considerations
A2.a: What is the most effective first-line therapy for patients with stage IV NSCLC with negative or unknown *EGFR*/*ALK* status, NSCC, and no contraindications to bevacizumab?	**Recommendation A2.a.1** For patients receiving carboplatin plus paclitaxel, the Update Committee recommends the addition of bevacizumab 15 mg/kg once every 3 weeks, except for patients with SCC histologic type, clinically significant hemoptysis, inadequate organ function, Eastern Cooperative Oncology Group PS > 1, clinically significant cardiovascular disease, or medically uncontrolled hypertension. Bevacizumab may be continued, as tolerated, until disease progression.	Reword: For patients receiving carboplatin plus paclitaxel, the addition of bevacizumab 15 mg/kg once every 3 weeks is recommended, except for patients with SCC histologic type, clinically significant hemoptysis, a *known bleeding disorder,* inadequate organ function, Eastern Cooperative Oncology Group PS > 1, clinically significant cardiovascular disease, or medically uncontrolled hypertension. *Caution should be exercised in patients with brain metastases.* Bevacizumab may be continued, as tolerated, until disease progression. *An alternative treatment strategy for patients who are eligible for carboplatin, paclitaxel and bevacizumab would include cisplatin or carboplatin plus pemetrexed and maintenance pemetrexed.* Qualifying statement: An alternative treatment strategy for patients who are eligible for carboplatin, paclitaxel, and bevacizumab would include cisplatin plus pemetrexed and maintenance pemetrexed.	The addition of any known bleeding disorder as a contraindication was added since patients with hemorrhagic disorders were excluded [8]. Furthermore, low-quality data from one study suggested that bevacizumab may be effective in patients with brain metastases [9]; therefore, caution was recommended when prescribing bevacizumab to patients with brain metastases. A more recent trial published after the search cut-off date of the ASCO review, found that carboplatin plus paclitaxel and bevacizumab and maintenance bevacizuamb compared with carboplatin plus pemetrexed and maintenance pemetrexed had similar PFS and grade IV toxicity [10].	There is no funding for bevacizumab in Ontario.

Clinical questions	ASCO recommendations	Modifications	Modification rationale	Implementation considerations
Quellen: 8. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006;355(24):2542-50. 9. De Braganca KC, Janjigian YY, Azzoli CG, Kris MG, Pietanza MC, Nolan CP, et al. Efficacy and safety of bevacizumab in active brain metastases from non-small cell lung cancer. J Neurooncol. 2010;100(3):443-7. 10. Zinner RG, Obasaju CK, Spigel DR, Weaver RW, Beck JT, Waterhouse DM, et al. PRONOUNCE: randomized, open-label, phase III study of first-line pemetrexed + carboplatin followed by maintenance pemetrexed versus paclitaxel + carboplatin + bevacizumab followed by maintenance bevacizumab in patients ith advanced nonsquamous non-small-cell lung cancer. J Thorac Oncol. 2015;10(1):134-42.				

Abbreviations: ASCO, American Society of Clinical Oncology; CI, confidence interval; EGFR, epidermal growth factor receptor; NSCC, non-squamous cell carcinoma; NSCLC, non-small cell lung cancer; PEBC, Program in Evidence-Based Care; PFS, progression-free survival; PS, performance status; SCC, squamous cell carcinoma; TKI, tyrosine kinase inhibitors