Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2018-B-110 Atezolizumab

Stand: Juni 2018

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Atezolizumab **[zur Erstlinienbehandlung des metastasierten NSCLCs mit nicht-plattenepithelialer Histologie]**	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	*Nicht angezeigt*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	**Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:** • Crizotinib (ROS1-positives NSCLC): Beschluss vom 16. März 2017 • Pembrolizumab (PD-L1 Expression: TPS ≥ 50 %): 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:** Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie - Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (Off-Label-Use): • Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie *(Beschluss vom 10. April 2018 über die Einleitung eines Stellungnahmeverfahrens - Carboplatin bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie, Aktualisierung)*
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:	
Atezolizumab Tecentriq®	Geplantes Anwendungsgebiet: Tecentriq wird in Kombination mit Bevacizumab, Paclitaxel und Carboplatin bei erwachsenen Patienten zur Erstlinienbehandlung des metastasierten nicht-kleinzelligen Lungenkarzinoms (NSCLC) mit nicht-plattenepithelialer Histologie angewendet. Patienten mit aktivierenden EGFR-Mutationen oder ALK-positiven Tumormutationen sollten, wenn klinisch indiziert, vor der Therapie mit Tecentriq bereits eine auf diese Mutationen zielgerichtete Therapie erhalten haben.
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)
Gemcitabin L01BC05 generisch	Gemcitabin ist in Kombination mit Cisplatin als Erstlinientherapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nichtkleinzelligen Bronchialkarzinom (NSCLC) angezeigt. Eine Gemcitabin-Monotherapie kann bei älteren Patienten oder solchen mit einem Performance Status 2 in Betracht gezogen werden. (Gemcitabin Kabi 38 mg/ml Konzentrat)
Ifosfamid L01AA06 Holoxan®	Nicht-kleinzellige Bronchialkarzinome: Zur Einzel- oder Kombinationschemotherapie von Patienten mit inoperablen oder metastasierten Tumoren.

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.
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.
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 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:	
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.
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.

Quellen: AMIS-Datenbank, Fachinformationen

Abteilung Fachberatung Medizin

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

Vorgang: 2018-B-110 (Atezolizumab)

Auftrag von:	Abt. AM
bearbeitet von:	Abt. FB Med
Datum:	30.05.2018

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 *metastasiertes nicht-kleinzelliges Lungenkarzinom (NSCLC)* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 13.03.2018 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 1314 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 30 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Zur Erstlinienbehandlung von Erwachsenen mit metastasierten nicht-kleinzelligen Lungenkarzinoms (ohne EGFR- ALK- und ROS1-spezifische TKI-Therapien)

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
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
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

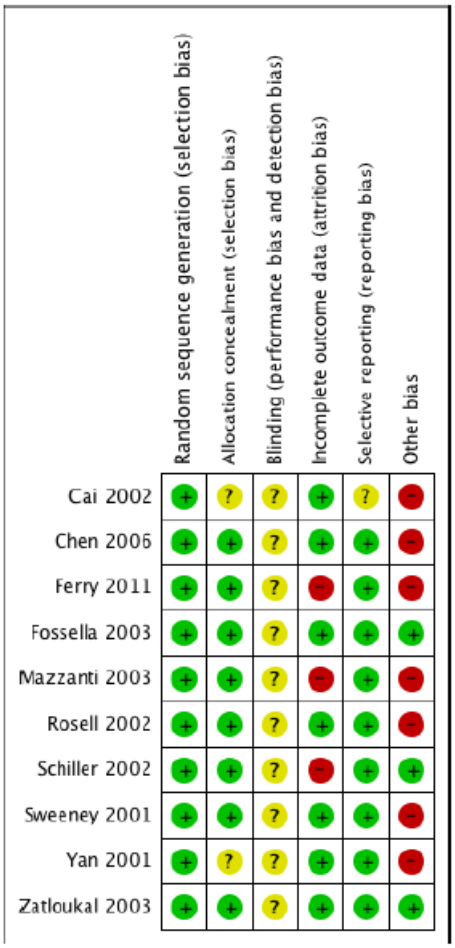
G-BA, 2017 [8]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Pembrolizumab (neues Anwendungsgebiet: Erstlinienbehandlung, nicht kleinzelliges Lungenkarzinom) Vom 03. August 2017	<u>Neues Anwendungsgebiet (laut Zulassung vom 27.01.2017):</u> 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:** <u>Patienten mit ECOG-Performance-Status 0, 1 oder 2:</u> • 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 <u>Patienten mit ECOG-Performance-Status 2:</u> • 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 [6]. 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) Vom 16. März 2017	<u>Zugelassenes Anwendungsgebiet (laut Zulassung vom 25.08.2016):</u> 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) <u>Zweckmäßige Vergleichstherapie:</u> - 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 <u>Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Cisplatin Kombination mit Pemetrexed oder Carboplatin in Kombination mit Pemetrexed</u>: Ein Zusatznutzen ist nicht belegt.

Siehe auch: **IQWiG, 2017 [12]**	
G-BA, 2017 [7]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzen-bewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Dabrafenib (neues Anwendungsgebiet: nicht-kleinzelliges Lungenkarzinom). Vom 19. Oktober 2017	Neues Anwendungsgebiet (laut Zulassung vom 29. März 2017): „Dabrafenib (Tafinlar®) in Kombination mit Trametinib ist angezeigt zur Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligen Lungenkarzinom mit einer BRAF-V600-Mutation." **1) Patienten ohne Vorbehandlung:** 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 Arz-neimittel-Richtlinie) oder Carboplatin in Kombination mit nab-Paclitaxel • Patienten mit ECOG-Performance-Status 2: alternativ zur platinbasierten Kombinationsbehandlung: eine Monotherapie mit Gemcitabin oder Vinorelbin Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie: Ein Zusatznutzen ist nicht belegt.
G-BA, 2017 [9]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzen-bewertung von Arzneimitteln mit neuen Wirk-stoffen nach § 35a SGB V – Trametinib (neues Anwendungsgebiet: nicht-kleinzelliges Lungenkarzinom). Vom 19. Oktober 2017	**Neues Anwendungsgebiet (laut Zulassung vom 27. März 2017):** „Trametinib (Mekinist®) in Kombination mit Dabrafenib ist angezeigt zur Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligen Lungenkarzinom mit einer BRAF-V600-Mutation." 1) Patienten ohne Vorbehandlung: **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 Arz-neimittel-Richtlinie) *oder* − Carboplatin in Kombination mit nab-Paclitaxel • Patienten mit ECOG-Performance-Status 2: − alternativ zur platinbasierten Kombinationsbehandlung: eine Monotherapie mit Gemcitabin oder Vinorelbin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt.

G-BA, 2014 [5]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage VI - Off-Label-Use Teil A Ziffer III. Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie, Zustimmung eines pharmazeutischen Unternehmers. letzte Änderung in Kraft getreten am: 07.12.2017	(…) III. Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCL) – Kombinationstherapie 1. Hinweise zur Anwendung von Carboplatin gemäß § 30 Abs. 1 a) Nicht zugelassenes Anwendungsgebiet (Off-Label-Indikation): Fortgeschrittenes nicht-kleinzelliges Bronchialkarzinom (NSCL) - Kombinationstherapie b) Behandlungsziel: palliativ c) Folgende Wirkstoffe sind für die Indikation fortgeschrittenes nicht-kleinzelliges Bronchialkarzinom (NSCL) -Kombinationstherapie zugelassen: − Cisplatin − Docetaxel − Erlotinib − Etoposid − Gemcitabin − Ifosfamid − Mitomycin − Paclitaxel − Pemetrexed − Vindesin − Vinorelbin d) Spezielle Patientengruppe: Patienten mit einem erhöhten Risiko für cisplatininduzierte Nebenwirkungen im Rahmen einer Kombinationstherapie (z. B. vorbestehende Neuropathie oder relevante Hörschädigung, besondere Neigung zu Übelkeit, Niereninsuffizienz, Herzinsuffizienz) e) Patienten, die nicht behandelt werden sollten: − Patienten, für die zugelassene Behandlungen in Frage kommen − Monotherapie (…)

Cochrane Reviews

De Castria TB et al., 2013 [3]. 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.

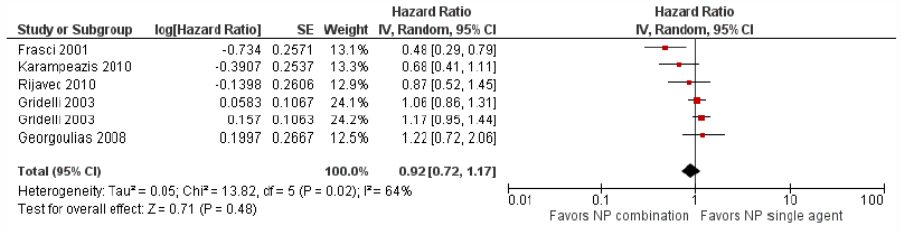
4. **Fazit der Autoren:** The initial treatment of people with advanced NSCLC is palliative, and carboplatin can be a treatment option. It has a similar effect on survival but a different toxicity profile when compared with cisplatin.

	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. Kommentar zum Review** • Der Mutationsstatus wurde in diesem CR nicht untersucht.
Santos FN et al., 2015 [20]. Chemotherapy for advanced non-small cell lung cancer in the elderly population	**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)

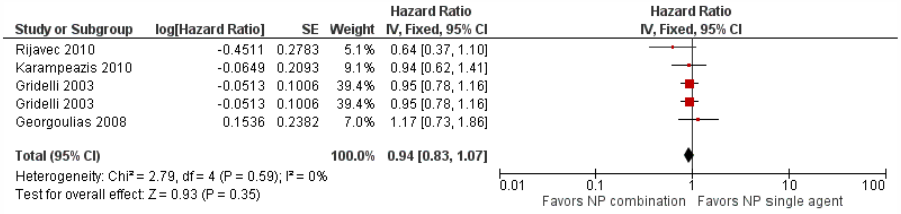
Figure 4. Forest plot of comparison: 1 Non-platinum single agent vs non-platinum combination, outcome: 1.1 Overall survival (OS).Gridelli 2003 was designed for a separate comparison of each single-agent arm (V arm and G arm) vs the combination arm (VG arm). Therefore, each entry for this trial represents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

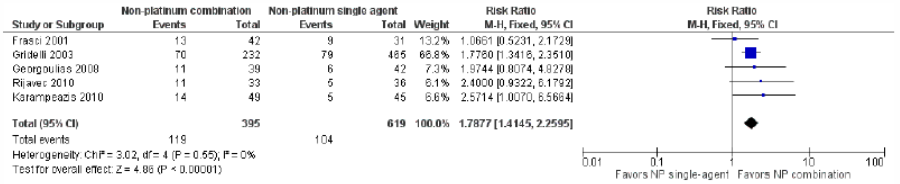
PFS: The meta-analysis of four RCTs involving 942 participants showed no impact on the PFS of non-platinum combination over nonplatinum single-agent therapy (HR 0.94, 95% CI 0.83 to 1.07) with low heterogeneity among trials (I2 = 0%)

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

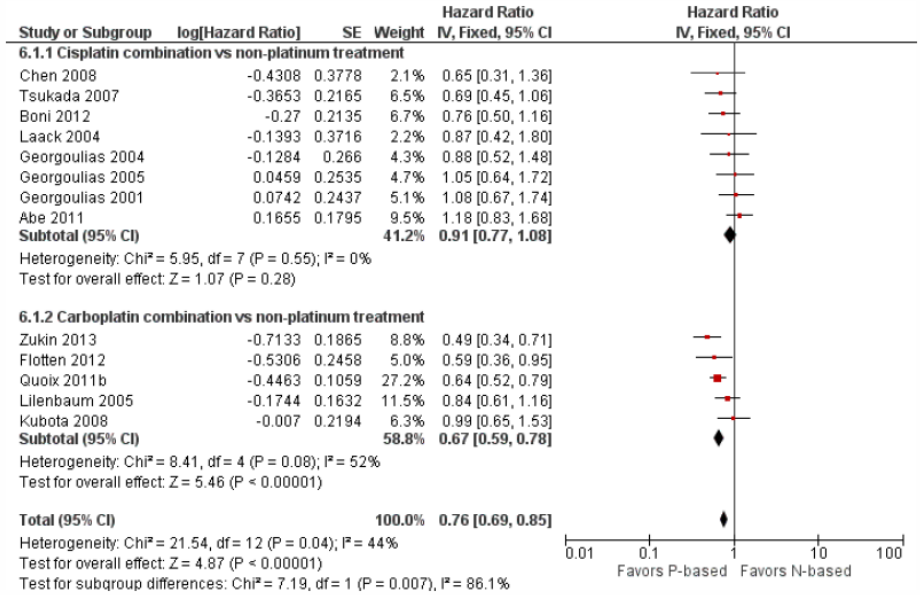
We found no significant differences in risk of fatigue (RR 1.16, 95%CI 0.69 to 1.96; participants = 995; four studies; I2 = 0%) or emesis (RR 1.73, 95% CI 0.68 to 4.43; participants = 995; four studies; I2 = 0%). For diarrhea, constipation, and mucositis, few grade 3 or 4 events were observed in all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

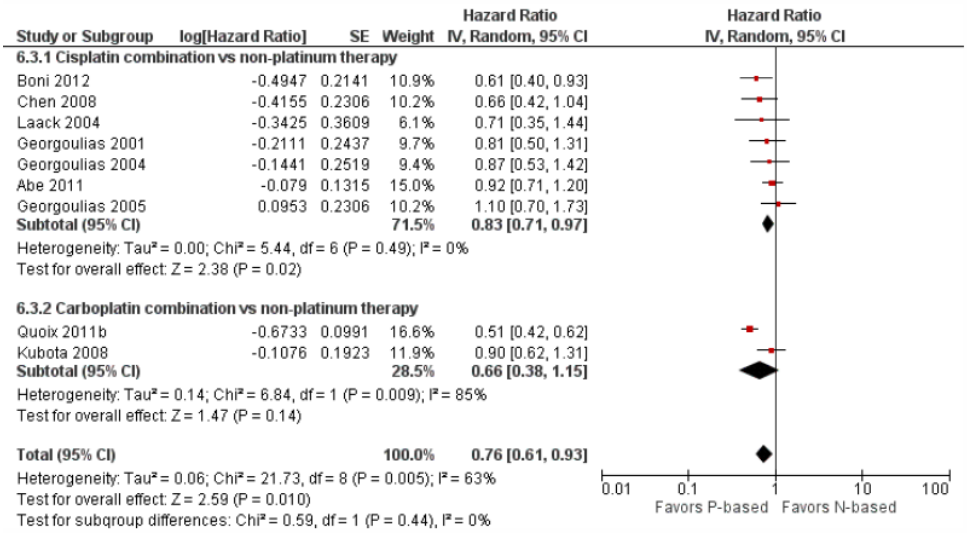


QoL: Only five RCTs included QoL assessment. However, we were not able to performameta-analysis of these data because of the paucity of data provided.

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-

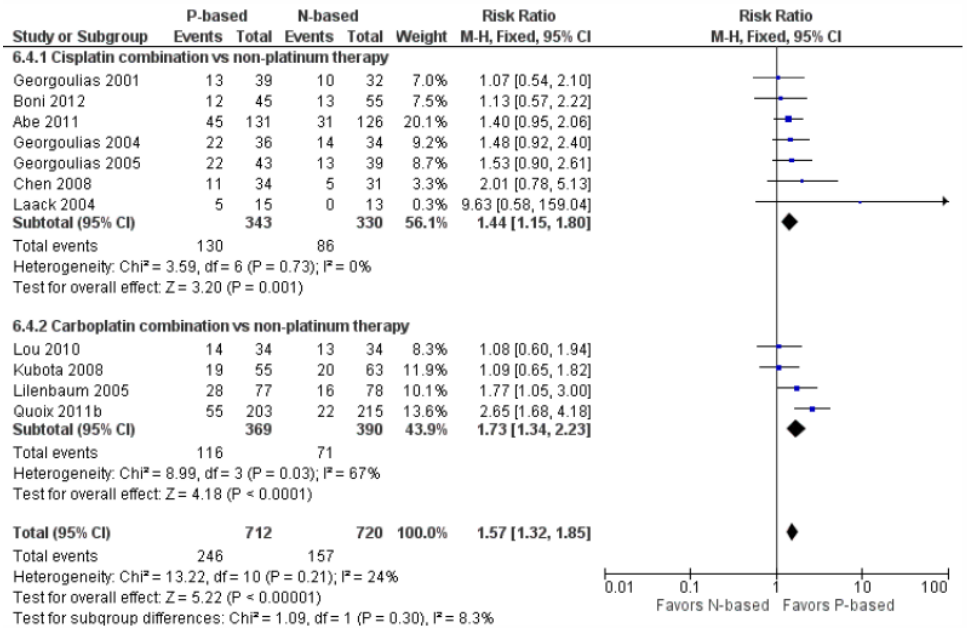
effects model, while maintaining a significant difference in PFS in favor of platinum combination (HR 0.76, 95% CI 0.61 to 0.93)

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.



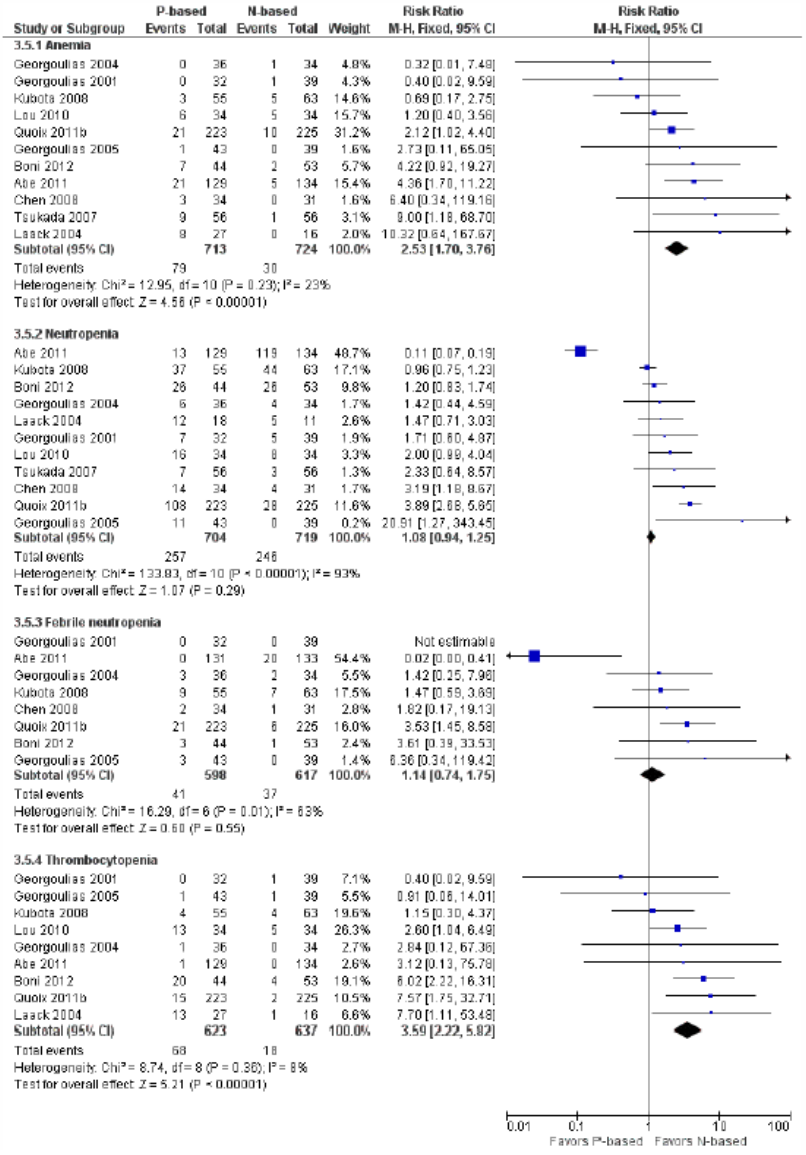
Toxicity:

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

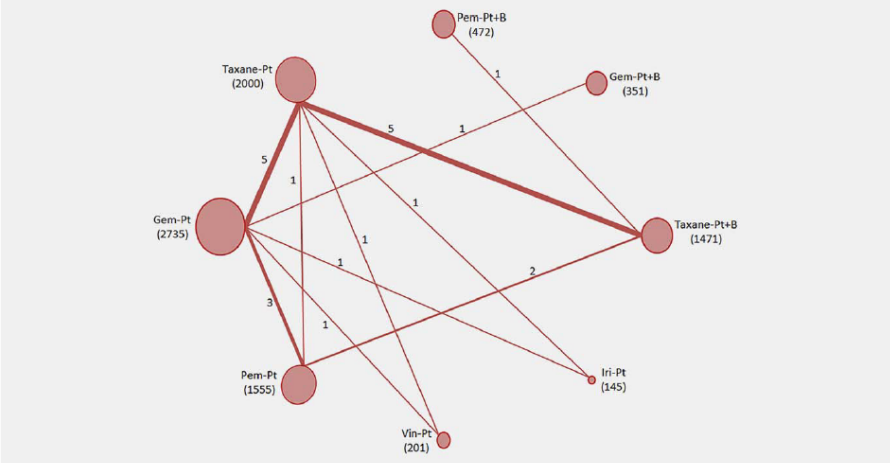
We found higher risk of fatigue (RR 1.56, 95% CI 1.02 to 2.38; participants = 1150; seven studies; I2 = 0%), emesis (RR3.64, 95% CI 1.82 to 7.29), and peripheral neuropathy (RR 7.02, 95% CI 2.42 to 20.41; participants = 776; five studies; I2 = 0%) associated with platinum combination treatment. We found 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. Kommentar zum Review** • Der Mutationsstatus wurde in diesem CR nicht untersucht.

Systematische Reviews

Zhao S et al., 2018 [30]. Bevacizumab in combination with different platinum-based doublets in the first-line treatment for advanced nonsquamous non-small-cell lung cancer: A network meta-analysis	**1. Fragestellung** to estimate the relative efficacy and tolerability of bevacizumab in combination with different platinumbased doublets in the first-line treatment for advanced nonsquamous non-small cell lung cancer (NS-NSCLC), attempting to identify the most and least preferable regimen to be used with bevacizumab for this population.
	2. Methodik Bayesian network meta-analysis Population: advanced NS-NSCLC patients (first-line setting) Intervention/Komparator: least two of the following treatments → platinumbased doublets with and without bevacizumab for untreated advanced NS-NSCLC were classified into six categories, taxane–platinum chemotherapy (Taxane–Pt), gemcitabine–platinum chemotherapy (Gem–Pt), pemetrexed–platinum chemotherapy (Pem–Pt), taxane–platinum plus bevacizumab (Taxane–Pt1B), gemcitabine–platinum plus bevacizumab (Gem–Pt1B) and pemetrexed–platinum plus bevacizumab (Pem–Pt1B) Endpunkte: OS, PFS, SAE Recherche: PubMed, EMBASE, Cochrane Central Register of Controlled Trials databases and ClinicalTrials.gov until the end of June 2017 Anzahl eingeschlossene Studien/Patienten (Gesamt): Data of 8,548 patients from 18 randomized controlled trials (RCTs) receiving six treatments, including taxane–platinum (Taxane–Pt), gemcitabine–platinum (Gem–Pt), pemetrexed–platinum (Pem–Pt), taxane–platinum1bevacizumab (Taxane–Pt1B), gemcitabine–platinum1bevacizumab (Gem–Pt1B) and pemetrexed–platinum1bevacizumab (Pem–Pt1B), were incorporated into the analyses Qualitätsbewertung der Studien: Cochrane risk of bias tool
	3. Ergebnisdarstellung <u>Qualität der Studien</u>: As for the risks of bias, one trial (Boutsikou et al.33) was rated with high overall risk of bias, as it had three rated with an unclear risk of bias. Among the remaining trials, eleven trials had two items and three trials had one item rated with unclear risk of bias. • Direct and indirect evidence of overall survival (OS) and progression-free survival (PFS) were synthesized at the hazard ratio (HR) scale and evidence of objective response rate (ORR) and serious adverse events (SAE) were synthesized at the odds ratio (OR) scale. • Taxane–Pt1B showed significant advantages in OS (HR=0.79, $p < 0.001$), PFS (HR=0.54, $p < 0.001$) and ORR (OR=2.7, $p < 0.001$) over Taxane–Pt with comparable tolerability (OR53.1, p=0.08). • Gem–Pt1B showed no OS benefit compared to any other treatment.

	• No significant differences were detected between Pem–Pt1B and Pem–Pt in four outcomes. • In terms of the benefit-risk ratio, Pem–Pt and Taxane–Pt1B were ranked the first and second, respectively.  Figure 2. Network of all eligible trials assessing the six treatments in the first-line setting for advanced NS-NSCLC established for the Bayesian network meta-analysis. The size of the nodes is proportional to the number of patients (in parentheses) randomized to receive the treatment. The width of the lines is proportional to the number of trials (beside the line) comparing the connected treatments (nodes). Taxane–Pt + B, taxane–platinum plus bevacizumab; Gem–Pt + B, gemcitabine–platinum plus bevacizumab; Pem-Pt + B, pemetrexed–platinum plus bevacizumab; Taxane–Pt, taxane–platinum chemotherapy; Gem–Pt, gemcitabine–platinum chemotherapy; Pem–Pt, pemetrexed–platinum chemotherapy; Vin–Pt, vinorelbine–platinum chemotherapy; Iri–Pt, irinotecan–platinum chemotherapy. [Color figure can be viewed at
	4. Fazit der Autoren: In conclusion, in the first-line treatment for advanced NS-NSCLC, Taxane–Pt and Gem–Pt are the most and least preferable regimens to be used with bevacizumab, respectively. Adding bevacizumab to Pem–Pt remains unjustified because it fails to improve efficacy or tolerability. In terms of the benefit-risk ratio, Pem–Pt and Taxane–Pt1B are the best and second-best treatment for this population.
Lai XX et al., 2016 [13]. 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

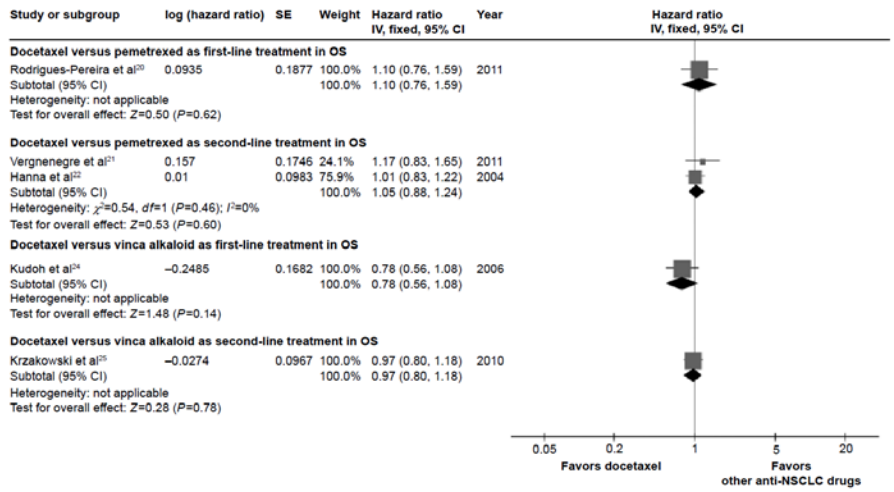
The addition of bevacizumab to therapy in advanced NSCLC did significantly increase the risk of proteinuria, hypertension, and hemorrhagic events but not arterial/venous thromboembolic events, gastrointestinal perforation, or fatal adverse events.

	5. Kommentar zum Review • 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 et al., 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 1** Characteristics of the seven eligible Phase III randomized trials in this meta-analysis

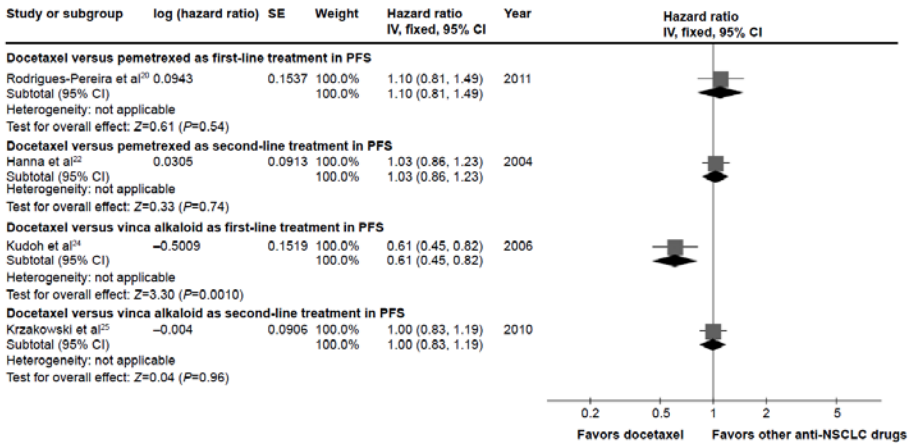
Study	Study region	Intervention	Number	Median age (years)	Male (%)	Stage	Outcome	Jadad score
Rodrigues-Pereira et al[20]	Argentina	Doc (75 mg/m²) + Carb	105	58.9	47.6	Stage IIIB/IV	SWT, OS, PFS	3
		Pem (500 mg/m²) + Carb	106	60.1	60.4			
Karampeazis et al[23]	Greece	Doc (38 mg/m²)	66	75.5	92.4	Stage 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.

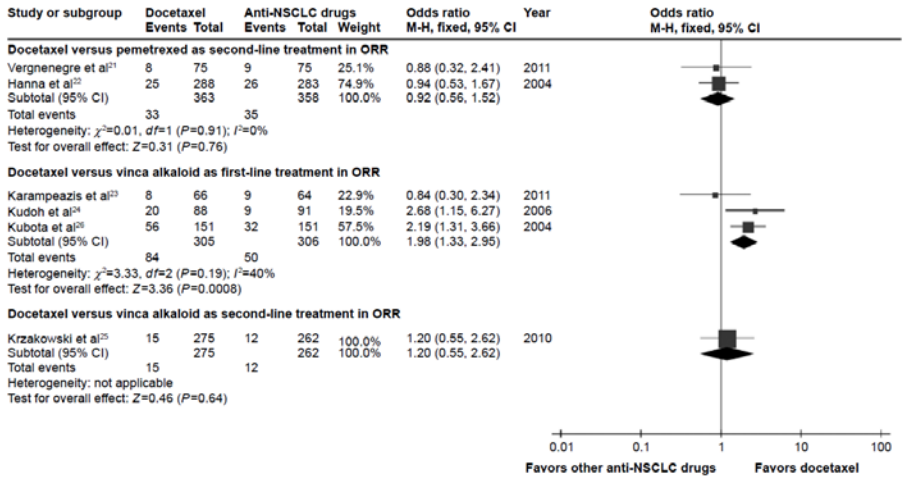
OS


Study or subgroup
log (hazard ratio)
SE
Weight
Hazard ratio IV, fixed, 95% CI
Year
Hazard ratio IV, fixed, 95% CI
Docetaxel versus pemetrexed as first-line treatment in OS
Rodrigues-Pereira et al[20] 0.0935 0.1877 100.0% 1.10 (0.76, 1.59) 2011
Subtotal (95% CI) 100.0% 1.10 (0.76, 1.59)
Heterogeneity: not applicable
Test for overall effect: Z=0.50 (P=0.62)
Docetaxel versus pemetrexed as second-line treatment in OS
Vergnenegre et al[21] 0.157 0.1746 24.1% 1.17 (0.83, 1.65) 2011
Hanna et al[22] 0.01 0.0983 75.9% 1.01 (0.83, 1.22) 2004
Subtotal (95% CI) 100.0% 1.05 (0.88, 1.24)
Heterogeneity: χ²=0.54, df=1 (P=0.46); I²=0%
Test for overall effect: Z=0.53 (P=0.60)
Docetaxel versus vinca alkaloid as first-line treatment in OS
Kudoh et al[24] −0.2485 0.1682 100.0% 0.78 (0.56, 1.08) 2006
Subtotal (95% CI) 100.0% 0.78 (0.56, 1.08)
Heterogeneity: not applicable
Test for overall effect: Z=1.48 (P=0.14)
Docetaxel versus vinca alkaloid as second-line treatment in OS
Krzakowski et al[25] −0.0274 0.0967 100.0% 0.97 (0.80, 1.18) 2010
Subtotal (95% CI) 100.0% 0.97 (0.80, 1.18)
Heterogeneity: not applicable
Test for overall effect: Z=0.28 (P=0.78)
0.05
0.2
1
5
20
Favors docetaxel
Favors other anti-NSCLC drugs

PFS


Study or subgroup
log (hazard ratio)
SE
Weight
Hazard ratio IV, fixed, 95% CI
Year
Hazard ratio IV, fixed, 95% CI
Docetaxel versus pemetrexed as first-line treatment in PFS
Rodrigues-Pereira et al[20] 0.0943 0.1537 100.0% 1.10 (0.81, 1.49) 2011
Subtotal (95% CI) 100.0% 1.10 (0.81, 1.49)
Heterogeneity: not applicable
Test for overall effect: Z=0.61 (P=0.54)
Docetaxel versus pemetrexed as second-line treatment in PFS
Hanna et al[22] 0.0305 0.0913 100.0% 1.03 (0.86, 1.23) 2004
Subtotal (95% CI) 100.0% 1.03 (0.86, 1.23)
Heterogeneity: not applicable
Test for overall effect: Z=0.33 (P=0.74)
Docetaxel versus vinca alkaloid as first-line treatment in PFS
Kudoh et al[24] −0.5009 0.1519 100.0% 0.61 (0.45, 0.82) 2006
Subtotal (95% CI) 100.0% 0.61 (0.45, 0.82)
Heterogeneity: not applicable
Test for overall effect: Z=3.30 (P=0.0010)
Docetaxel versus vinca alkaloid as second-line treatment in PFS
Krzakowski et al[25] −0.004 0.0906 100.0% 1.00 (0.83, 1.19) 2010
Subtotal (95% CI) 100.0% 1.00 (0.83, 1.19)
Heterogeneity: not applicable
Test for overall effect: Z=0.04 (P=0.96)
0.2
0.5
1
2
5
Favors docetaxel
Favors other anti-NSCLC drugs

ORR


Study or subgroup
Docetaxel Events Total
Anti-NSCLC drugs Events Total Weight
Odds ratio M-H, fixed, 95% CI
Year
Odds ratio M-H, fixed, 95% CI
Docetaxel versus pemetrexed as second-line treatment in ORR
Vergnenegre et al[21] 8 75 9 75 25.1% 0.88 (0.32, 2.41) 2011
Hanna et al[22] 25 288 26 283 74.9% 0.94 (0.53, 1.67) 2004
Subtotal (95% CI) 363 358 100.0% 0.92 (0.56, 1.52)
Total events 33 35
Heterogeneity: χ²=0.01, df=1 (P=0.91); I²=0%
Test for overall effect: Z=0.31 (P=0.76)
Docetaxel versus vinca alkaloid as first-line treatment in ORR
Karampeazis et al[23] 8 66 9 64 22.9% 0.84 (0.30, 2.34) 2011
Kudoh et al[24] 20 88 9 91 19.5% 2.68 (1.15, 6.27) 2006
Kubota et al[26] 56 151 32 151 57.5% 2.19 (1.31, 3.66) 2004
Subtotal (95% CI) 305 306 100.0% 1.98 (1.33, 2.95)
Total events 84 50
Heterogeneity: χ²=3.33, df=2 (P=0.19); I²=40%
Test for overall effect: Z=3.36 (P=0.0008)
Docetaxel versus vinca alkaloid as second-line treatment in ORR
Krzakowski et al[25] 15 275 12 262 100.0% 1.20 (0.55, 2.62) 2010
Subtotal (95% CI) 275 262 100.0% 1.20 (0.55, 2.62)
Total events 15 12
Heterogeneity: not applicable
Test for overall effect: Z=0.46 (P=0.64)
0.01
0.1
1
10
100
Favors other anti-NSCLC drugs
Favors docetaxel

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 [28].

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.

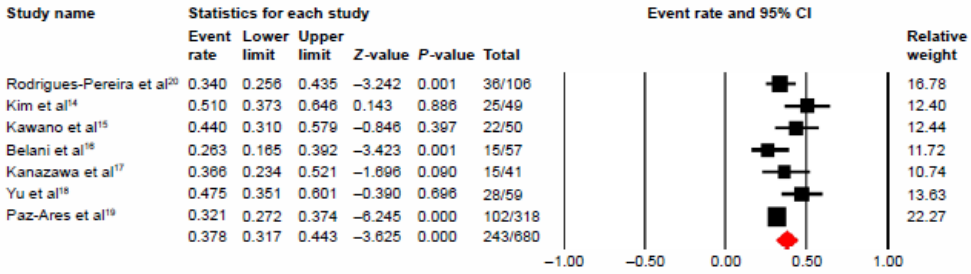


Figure 2 Random-effects model of ORR (95% CI) for pemetrexed plus platinum doublet chemotherapy.

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).

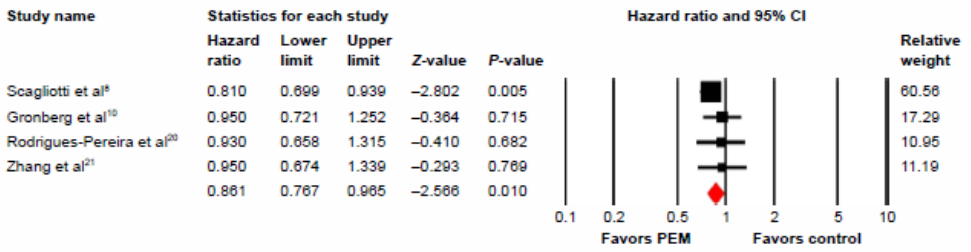


	Figure 3 Fixed-effects model of HR (95% CI) of OS associated with PEM plus platinum versus other platinum-based chemotherapy. **Abbreviations:** CI, confidence interval; HR, hazard ratio; OS, overall survival; PEM, pemetrexed. • Two of four RCTs reported PFS data. The pooled hazard ratio for PFS demonstrated 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 (I2=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. **5. Kommentar zum Review:** • 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.
Sun L et al., 2015 [25]. 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	**1. Fragestellung:** 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

review and meta-analysis

Siehe auch:
Sheng M et al., 2016 [23].

Targeted drugs for unselected patients with advanced non-small-cell lung cancer: a network meta-analysis

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.

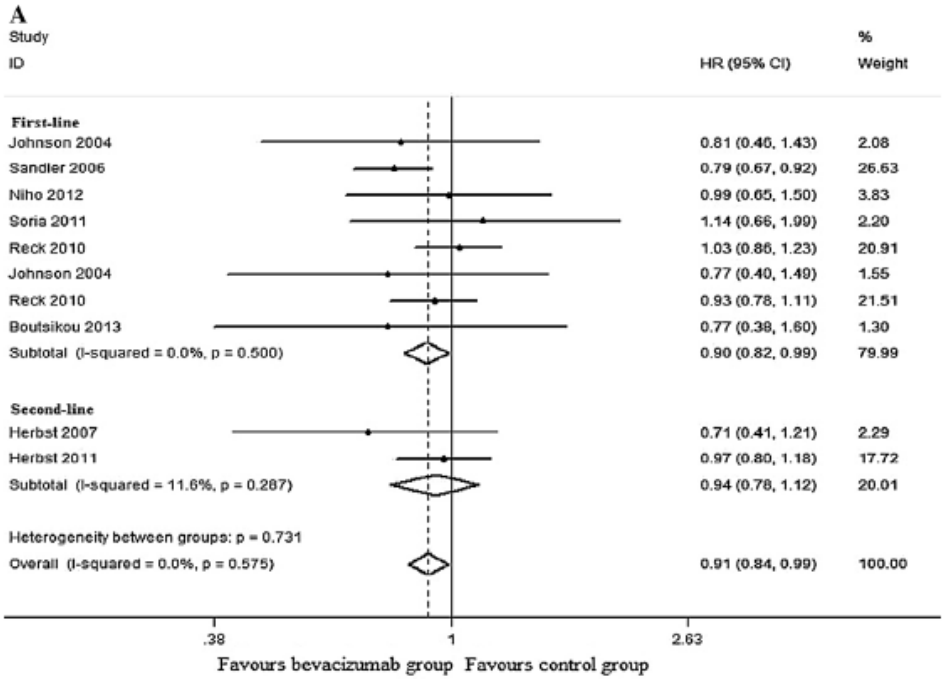
Unterscheidung nach Therapielinie:

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

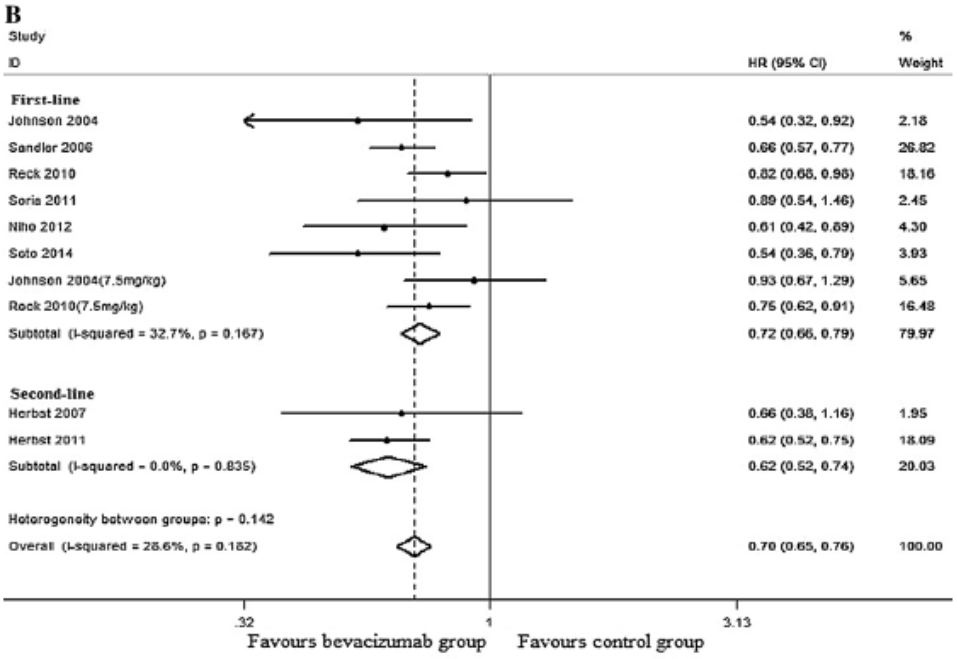
HR for OS:

(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, keine Heterogenität).



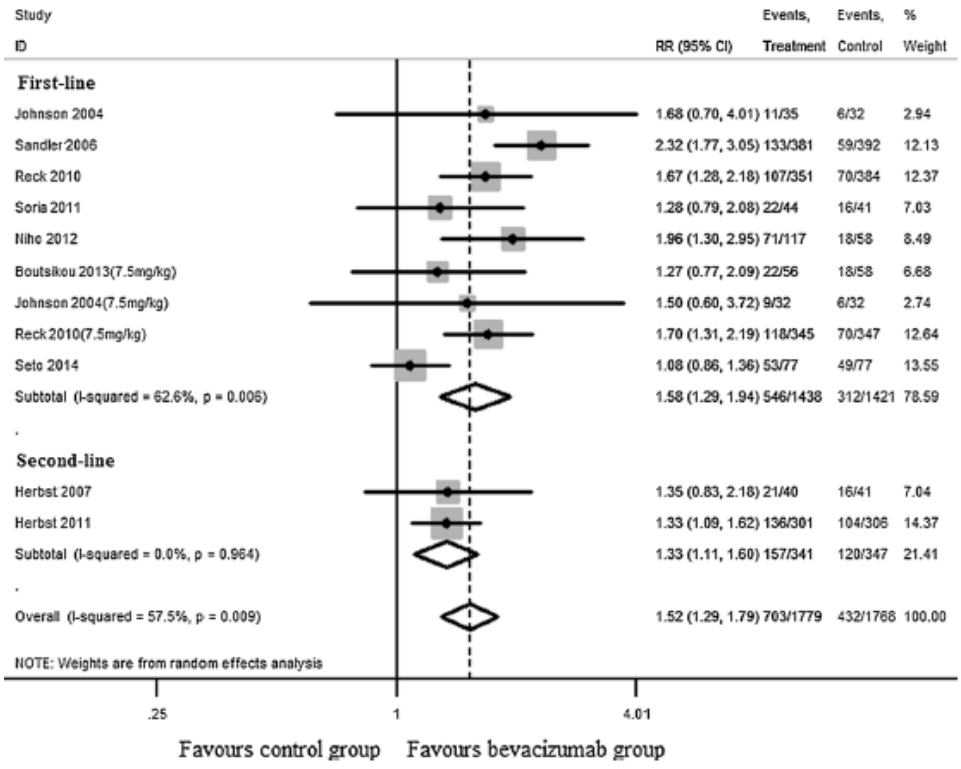
HR for PFS

(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. **Kommentar zum Review**

- 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

1. Fragestellung

Mörth C et al., 2014 [17]. Single-agent versus combination chemotherapy as first-line treatment for patients with advanced non-small cell lung cancer and performance status 2: a literature-based meta-analysis of randomized studies <u>Siehe auch:</u> **Luo L et al., 2015 [15].**	The purpose of this study was to compare the efficacy and tolerability of first-line treatment with combination versus single agent chemotherapy in patients with advanced non-small cell lung cancer (NSCLC) and performance status (PS) 2
	2. Methodik **Population:** advanced NCSLC mit PS 2 **Intervention:** combination chemotherapy **Komparator:** single agent chemotherapy **Endpunkte:** OS, PFS, ORR **Suchzeitraum:** Bis 07/2013 **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 **<u>MÖRTH et al.</u>** **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)

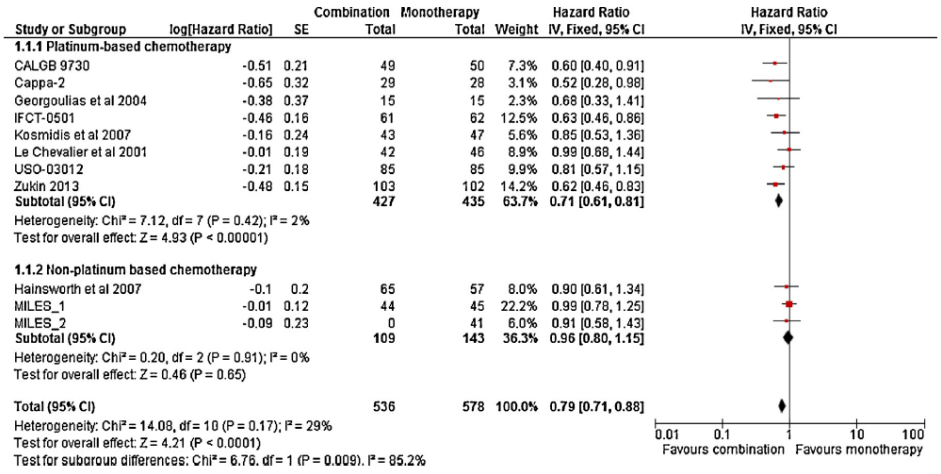


Fig. 2. Forest plot for overall survival (with subgroup analysis based on the administration of platinum-based or non-platinum based chemotherapy in combination arms).The size of the squares indicates the weight of the study. Error bars represent 95% confidence intervals (CIs). The diamond indicates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

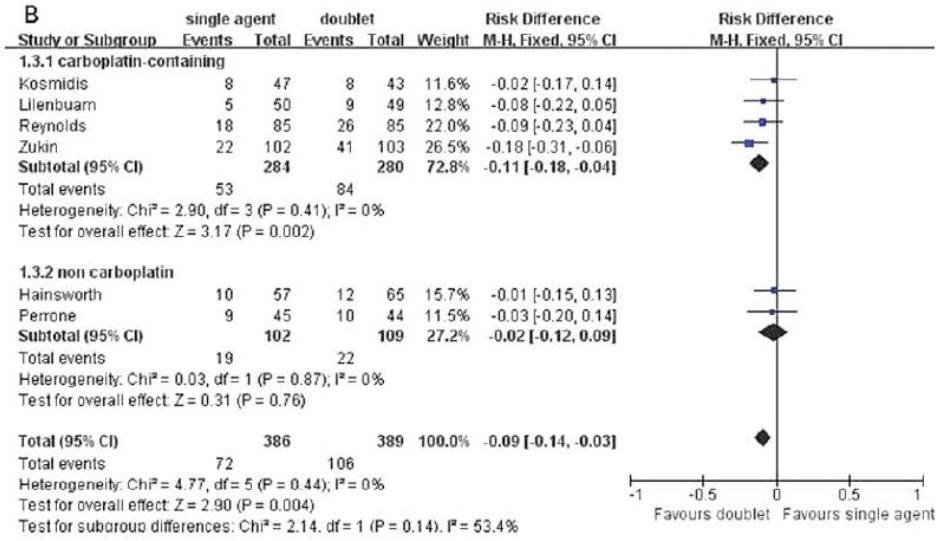
Abbreviations: No: number; OR: odds ratio; CI: confidence interval.

Luo et al.

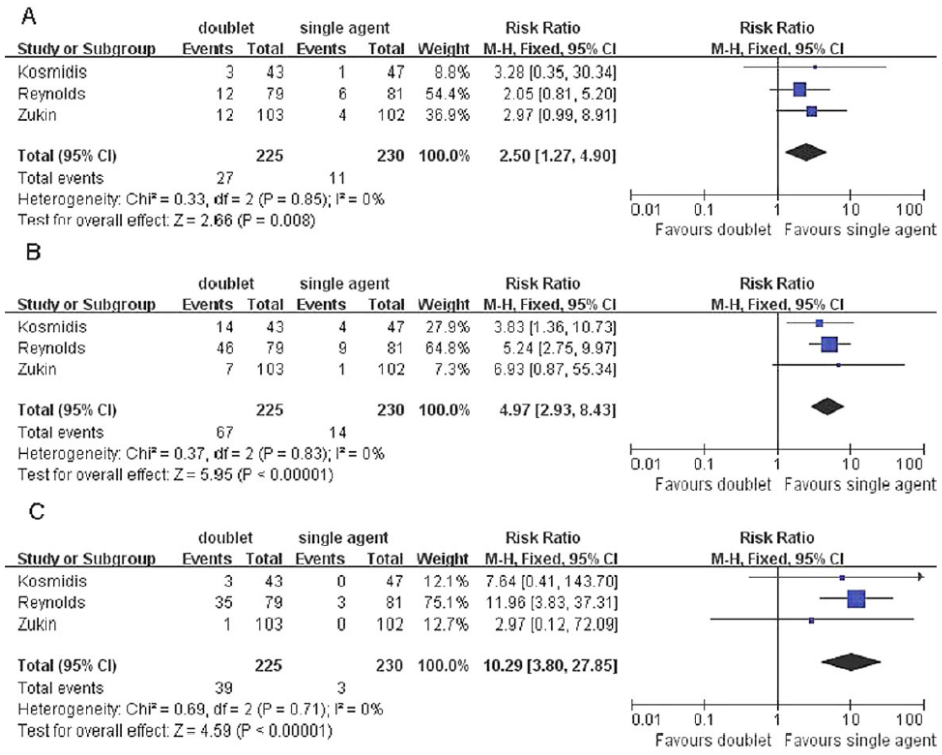
Mortalität:

Für OS vergleichbare Ergebnisse wie Mörth et al.

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



Toxizität:



4. Fazit der Autoren

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

	This meta-analysis provides evidence supporting the use of combination chemotherapy in patients with NSCLC and PS 2. However, the patients should be informed about the higher risk for toxicity with the combination chemotherapy and the final treatment strategy should be individualized **Luo et al.:** In conclusion, the results from our meta-analysis imply that carboplatin-containing doublet chemotherapy may well be superior to non-carboplatin containing treatment. Additional prospective clinical trials are warranted to evaluate treatment combinations. **5. Kommentar zum Review** • 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 [22]. Comparison between cisplatin plus vinorelbine and cisplatin plus docetaxel in the treatment of advanced non-small-cell lung cancer: A meta-analysis of randomized controlled trials	**1. Fragestellung** To compare the VC and DC regimens in the first-line treatment of advanced NSCLC.
	2. Methodik **Population:** 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.

3. 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 ($\chi 2=5.71$; P=0.68; I2=0%).

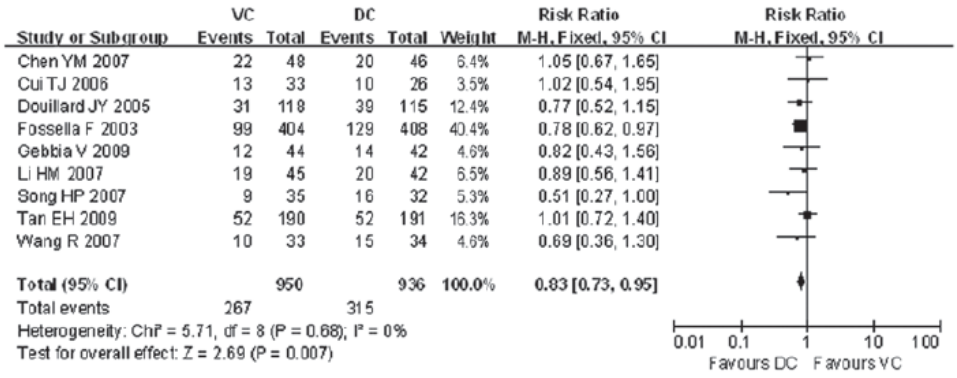


Figure 1. The overall response rate analysis of vinorelbine plus cisplatin (VC) or docetaxel plus cisplatin (DC) for advanced non-small-cell lung cancer (NSCLC). The fixed effects model was applied. Relative risk (RR) ratio and 95% confidence interval (CI) for each study are also plotted on the graph.

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 ($\chi 2$=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.

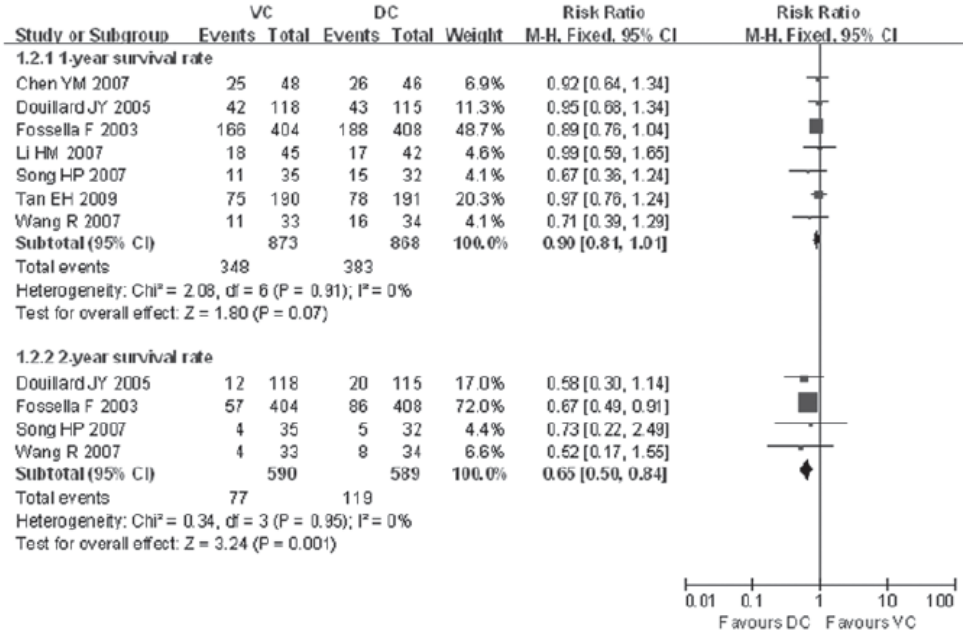


Figure 2. The 1-and 2-year survival analysis of vinorelbine plus cisplatin (VC) or docetaxel plus cisplatin (DC) for advanced non-small-cell lung cancer (NSCLC). The fixed effects model was applied. Relative risk (RR) ratio and 95% confidence interval (CI) for each study are also plotted on the graph.

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.

Toxicity	No. of studies	No. of cases		Test of homogeneity		OR (95% CI)	P-value
		VC	DC	I^2 (%)	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.

4. 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.

5. Kommentar zum Review

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.

Wang S et al., 2015 [26]

Meta-analysis comparing doublet and single cytotoxic agent therapy as first-line treatment in elderly patients with advanced nonsmall-cell lung cancer

1. Fragestellung

To perform a systematic review and meta-analysis comparing doublet versus single agent therapy in elderly patients with advanced nonsmall-cell lung cancer (NSCLC).

2. Methodik

Population: Patients diagnosed with advanced NSCLC that was previously untreated (involving patients aged >65 years)

Interventionen / Komparator: comparisons between doublets and single agents as first-line treatment, using **a third-generation cytotoxic drug**

Endpunkte: OS, TTP, ORR, Toxicity

Suchzeitraum: PubMed and Cochrane databases, and American Society of Clinical Oncology,World Congress of Lung Cancer, and European Society of Medical Oncology abstracts were searched to September 2012

Siehe auch: **Xu et al. 2013 [29]**	**Anzahl eingeschlossene Studien/Patienten (Gesamt):** 11 studies (13 randomized trials; n=2782) **Qualitätsbewertung der Studien:** Jadad
	3. Ergebnisdarstellung Qualität der Studien: 7 Studien hatten einen Jadad Score von 3; 2 Studien hatten einen Jadad Score von 2. • Doublet therapy was associated with significantly increased OS (hazard ratio [HR] 0.89, 95% confidence interval [CI] 0.83, 0.95), 1-year SR (risk ratio [RR] 1.15, 95% CI 1.04, 1.28), and ORR (RR 1.39, 95% CI 1.39, 1.86) versus singleagents. • Chemotherapy regimen-based subgroup analyses favoured platinum-based doublet therapy for OS (RR 0.71, 95% CI 0.60, 0.84), 1-year SR (RR 1.28, 95% CI 1.11, 1.47), and ORR (RR 1.88, 95% CI 1.49, 2.38). • Race-based subgroup analyses revealed increased benefit from doublet therapy in Asian populations for ORR (RR 1.70, 95% CI 1.29, 2.23) but not increased survival benefit. • Higher incidences of grade 3/4 anaemia (RR 2.23, 95% CI 1.61, 3.09), thrombocytopenia (RR 2.47, 95% CI 1.17, 5.20), and fatigue (RR 1.36, 95% CI 1.06, 1.74) were observed with doublet versus single-agent therapy.
	4. Fazit der Autoren: Doublet therapy was associated with significantly increased OS, 1-year SR and ORR compared with single agent therapy. Race may be considered when choosing doublet versus singleagent therapy as first-line treatment of NSCLC in elderly patients. **5. Kommentar zum Review** • Der Mutationsstatus der Patienten 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

Leitlinienprogramm Onkologie, 2018 [14]. **Deutsche Krebsgesellschaft (DKG)** Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms. (S3-Leitlinie; Langversion 1.0)	Fragestellung/Zielsetzung: Therapieempfehlungen des Lungenkarzinoms
	Methodik <u>Grundlage der Leitlinie</u> Da im Rahmen der Aktualisierung 2013-2018 nicht die komplette Leitlinie aktualisiert werden konnte, sondern lediglich priorisierte Kapitel (siehe Kapitel 2.1) enthält diese Leitlinienversion zwei verschiedene Graduierungsschemata. Bei den Empfehlungen der Version 2010 kam das in Tabelle 5 aufgeführte Schema zur Anwendung. Hierbei werden vier Empfehlungsgrade (A-D) unterschieden. Bei den im Rahmen der Aktualisierung 2013-2018 konsentierten Empfehlungen kamen die in Tabelle 6 aufgeführten, in den OL-Leitlinien etablierten, Empfehlungsstärken zur Anwendung. Diese spiegeln sich auch in den Formulierungen der Empfehlungen wider. Erläuterungen zur Festlegung der Empfehlungsstärken können dem Leitlinienreport entnommen werden. Die Methodik des Leitlinienprogramms Onkologie sieht eine Vergabe von Empfehlungs-graden durch die Leitlinien-Autoren im Rahmen eines formalen Konsensusverfahrens vor. Dementsprechend wurden durch die AWMF moderierte, nominale Gruppenpro-zesse bzw. strukturierte Konsensuskonferenzen durchgeführt [1]. Im Rahmen dieser Prozesse wurden die Empfehlungen von den stimmberechtigten Mandatsträgern (siehe Kapitel 1.9) formal abgestimmt. Die Ergebnisse der jeweiligen Abstimmungen (Kon-sensstärke) sind entsprechend den Kategorien in Tabelle 7 den Empfehlungen zugeordnet. <u>LoE/GoR</u> **Ersterstellung Leitlinie (2006-2010)** Bei der Ersterstellung Leitlinie (2006-2010) wurde für die Graduierung der Evidenz das in Tabelle 3 aufgeführte System des Oxford Centre for Evidence-based Medicine in der Version von 2001verwendet. Die in den Empfehlungen aus 2010 aufgeführten Level of Evidence beziehen sich auf dieses Schema.

Tabelle 3: Oxford Centre for Evidence-based Medicine Levels of Evidence (Mai 2001), übersetzte Version von Gabriele Schlömer, FR Gesundheit, Universität Hamburg

Level	Therapie/Prävention, Ätiologie/ Nebenwirkungen	Prognose	Diagnose	Differential Diagnose/ Symptom Prävalenz-studie	Ökonomische - und Entscheidungsanalyse
1a	**Systematischer Review (SR)** (mit Homogenität von Randomisiert-kontrollierten Studien (RCTs)	**SR** (mit Homogenität§) der eingeschlossenen Kohortenstudien; Klinische Entscheidungsfindung (CDR†) validiert in verschiedenen Populationen	**SR** (mit Homogenität§) der Level 1 diagnostischen Studien; CDR† mit 1b Studien von verschiedenen klinischen Zentren	**SR** (mit Homogenität§) von prospektiven Kohortenstudien	**SR** (mit Homogenität§) von Level 1 ökonomischen Studien
1b	**Einzelner RCT** (mit engem Konfidenzintervall‡)	**Einzelne Kohortenstudie** mit > 80% Nachbeobachtungsrate; CDR† validiert in einer einzelnen Population	**Validierungs-** Kohortenstudie** mit gutem††† Referenzstandard; oder getesteter CDR† in einem klinischem Zentrum	**Prospektive Kohortenstudie** mit guter Nachbeobachtungsrate††††	**Analyse basiert auf** klinisch sinnvollen Kosten oder Alternativen; systematische(r) Review(s) der Evidenz; und Einbeziehung einer Sensitivitätsanalyse
1c	**Alle oder keiner** §	**Alle oder keiner** Fallserie	**Absolute SpPins und SnNouts**††	**Alle oder keiner** Fallserie	**Absolute ökonomische Kosten-Nutzen-Analyse** ††††
2a	**SR** (mit Homogenität§) **der Kohortenstudien**	**SR** (mit Homogenität§) von entweder **retrospektiven Kohortenstudien** oder unbehandelten Kontrollgruppen in RCTs	**SR** (mit Homogenität§) von Level >2 **diagnostischen Studien**	**SR** (mit Homogenität§) von 2b und besseren Studien	**SR** (mit Homogenität§) von Level >2 ökonomischen Studien

2b	**Einzelne Kohorten Studie** (eingeschlossen RCT mit schlechter Qualität; z.B. <80% Nachbeobachtungsrate)	**Retrospektive Kohortenstudie** oder Nachbeobachtungsrate von unbehandelten Kontrollpatienten in einem RCT; Ableitung einer CDR† oder lediglich validiert bei einem Teil der Stichprobe§§§	**Explorative** Kohortenstudie** mit gutem††† Referenzstandard; CDR† nach Derivation oder lediglich validiert bei einem Teil der Stichprobe§§§ oder Basisdaten	**Retrospektive Kohortenstudie**, oder geringe Nachbeobachtungsrate	Analyse basiert auf klinisch sinnvollen Kosten oder Alternativen; begrenzte(r) Review der Evidenz, oder einzelne Studie; und Einschluss multi-variabler Sensitivitätsanalyse
2c	**Ergebnisforschung; Ökologische Studien**	**Ergebnisforschung**		**Ökologische Studien**	Audit oder Ergebnisforschung
3a	SR (mit Homogenität*) von **Fall-Kontroll-Studien**		SR (mit Homogenität*) von 3b und besseren Studien	SR (mit Homogenität*) von 3b und besseren Studien	SR (mit Homogenität*) von 3b und besseren Studien
3b	**Einzelne Fall-Kontroll Studie**		**Nicht-konsekutive Studie**; oder ohne Konsistenz der angewendeten Referenzstandards	**Nicht-konsekutive Kohortenstudie** oder sehr limitierte Population	Analyse basiert auf limitierte Alternativen oder Kosten, qualitativ schlechte Berechnung der Daten, aber Einschluss der Sensitivitätsanalyse mit klinisch relevanten Variationen.
4	**Fall-Serie** (und qualitative schlechte Kohorten- und Fall-Kontroll-Studien)	**Fall-Serie** (und qualitative schlechte prognostische Kohortenstudien)	**Fall-Kontrolle Studie**, schlechte oder nicht unabhängige Referenzstandards	**Fall-Serie** oder veralteter Referenzstandard	Analyse ohne Sensitivitätsanalyse
5	**Expertenmeinung** ohne kritische Analyse oder basiert auf physiologischer oder experimenteller Forschung oder "Grundprinzipien"	**Expertenmeinung** ohne kritischer Analyse oder basiert auf physiologischer oder experimenteller Forschung oder "Grundprinzipien"	**Expertenmeinung** ohne kritische Analyse oder basiert auf physiologischer oder experimenteller Forschung oder "Grundprinzipien"	**Expertenmeinung** ohne kritische Analyse oder basiert auf physiologischer oder experimenteller Forschung oder "Grundprinzipien"	Expertenmeinung ohne kritische Analyse oder basiert auf ökonomischer Theorie oder "Grundprinzipien"

Legende:

* = Mit Homogenität meinen wir einen systematischen Review ohne bedeutender Varianz (Heterogenität) in bezug auf die Richtung und die Varianz der Ergebnisse zwischen einzelnen Studien. Nicht alle systematischen Reviews mit statistisch signifikanter Heterogenität müssen zwingend besorgniserregend sein und nicht alle besorgniserregenden Heterogenitäten müssen statistisch signifikant sein. Wie oben erwähnt sollten Studien mit besorgniserregender Heterogenität mit einem "–" am Ende des gewünschten Grades versehen werden.

† = Clinical Decision Rule (CDR) = Klinische Entscheidungsfindung. (Dies sind Algorithmen oder Punktesysteme, die zu einer prognostischen Schätzung oder einer diagnostischen Kategorie führen.)

‡ = Siehe Anmerkung #2 als Hilfe zum Verständnis, Eingruppieren und Gebrauch von Studien mit breiten Konfidenzintervallen.

§ = Trifft zu, wenn alle Patienten starben, bevor die Therapie verfügbar war und nach Einführung der Therapie einige überleben; oder wenn einige Patienten starben, bevor die Therapie verfügbar war und keiner nach Einführung der Therapie stirbt.

§§ = Mit qualitativ schlechten Kohortenstudien meinen wir jene, die die Vergleichsgruppe nicht klar definiert hat und/oder die Exposition und Ergebnisse nicht in der gleichen objektiven Art und Weise (verblindet) in den beiden Gruppen (exponiert und nicht-exponiert) gemessen hat und/oder keine angemessenen Störfaktoren identifiziert und kontrolliert hat und/oder keine angemessene Nachbeobachtungsrate hatte.
Mit qualitativ schlechten Fall-Kontrolle Studien meinen wir jene, die keine definierte Vergleichsgruppe hat und/oder die Exposition und Ergebnisse nicht in der gleichen objektiven Art und Weise (verblindet) in den beiden Gruppen (Fälle und Kontrollen) gemessen hat und/oder keine angemessenen Störfaktoren identifiziert und kontrolliert hat.

§§§ =Eine Validierung bei einem Teil der Stichprobe wird erreicht, wenn alle Informationen ein einem Zweig gesammelt werden und dieser dann künstlich in Derivations- und Validierungsgruppe geteilt wird.

†† = Eine "Absolute SpPin" ist ein diagnostisches Ergebnis dessen Spezifität so hoch ist, so dass ein Positives Ergebnis die Diagnose einschließt. Ein "Absolute SnNout" ist ein diagnostisches Ergebnis, dessen Sensitivität so hoch ist, so dass das Negative Ergebnis die Diagnose ausschließt.

‡‡ = Gut, besser und schlecht bezieht sich auf den Vergleich zwischen Behandlungen im Sinne ihrer klinischen Risiken und Nutzen.

††† = Gute Referenzstandards sind unabhängig vom Test und werden blind oder objektiv an allen Patienten angewandt. Schlechte Referenzstandards werden zufällig angewandt, sind aber dennoch vom Test unabhängig. Der Gebrauch nicht unabhängiger Referenzstandards (wenn der Test in der Referenz eingeschlossen ist oder wenn das Testen die Referenz beeinflusst) impliziert eine Level 4 Studie.

†††† = Behandlungen mit hohem Nutzen sind ebenso gut, aber günstiger oder besser bei gleichen oder geringeren Kosten. Behandlungen mit geringem Nutzen sind ebenso gut, aber teurer oder schlechter bei gleichen oder höheren Kosten.

** = Validierungsstudien testen die Qualität eines spezifischen diagnostischen Tests, basierend auf der vorher entwickelten Evidenz. Eine explorative Studie sammelt Informationen und untersucht alle Daten (z.B. mit einer Regressionsanalyse) um herauszufinden, welche Faktoren signifikant sind.

*** = Mit qualitativ schlechten prognostischen Kohortenstudien meinen wir solche, in denen die Stichprobenauswahl verzerrt ist und diejenigen Patienten bevorzugt, die bereits das Ergebnis haben oder die Messung der Ergebnisse in weniger als <80% der Studienpopulation durchgeführt wurde oder das Ergebnis durch nicht verblindete nicht objektive Art und Weise gemessen wurde oder keine Korrigierung der Störfaktoren stattfand.

**** = Eine gute Nachbeobachtungsrate in einer Differentialdiagnosestudie ist >80%, mit angemessener Zeit für das Auftreten alternativer Diagnosen (z.B. 1-6 Monate akute, 1 - 5 Jahre chronische)

Erste Aktualisierung der Leitlinie (2013-2018)

Bei der ersten Aktualisierung der Leitlinie (2013-2018) das System des Oxford Centre for Evidence-based Medicine System in der Version von 2009 verwendet (siehe Tabelle 4). Die in den Empfehlungen aus 2018 aufgeführten Level of Evidence beziehen sich auf dieses Schema.

Tabelle 4: Schema der Evidenzgraduierung nach Oxford (Version März 2009)

Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity) of RCTs	SR (with homogeneity) inception cohort studies; CDR validated in different populations	SR (with homogeneity) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centers	SR (with homogeneity) of prospective cohort studies	SR (with homogeneity) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval)	Individual inception cohort study with > 80 % follow-up; CDR validated in a single population	Validating cohort study with good reference standards; or CDR tested within one clinical centre	Prospective cohort study with good follow-up	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
2a	SR (with homogeneity) of cohort studies	SR (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity) of Level >2 diagnostic studies	SR (with homogeneity) of Level 2b and better studies	SR (with homogeneity) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80 % follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR or validated on split-sample only	Exploratory cohort study with good reference standards; CDR after derivation, or validated only on split-sample or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity) of case-control studies		SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study; or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations
4	Case-series (and poor quality cohort and case-control studies)	Case-series (and poor quality prognostic cohort studies)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Tabelle 5: Beziehung zwischen Evidenz- und Empfehlungsgrad für Empfehlungen 2010 (modifiziert nach Oxford Center for Evidence-based Medicine 2001 und AWMF)

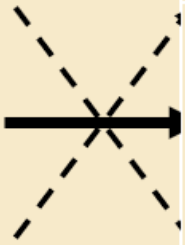
Evidenzgrad	Evidenz		Konsensus	Empfehlungsgrad	
	Therapeutische Studien	Diagnostische Studien	Modifizierende Kriterien für Empfehlungsgrad		
1a	Syst. Review von randomisierten kontrollierten klinischen Studien	Syst. Review validierende Kohortenstudien	Ethische Aspekte Patienten-Präferenzen Klin. Relevanz, integr. Outcome Klinisch bedeutsame Abweichung von Studiensituation	A	Starke Empfehlung
1b	Individ. randomisierte kontrollierte Studie (enges Konfidenzintervall)	Validierende Kohortenstudie mit guten Referenz-standards			
1c	Alle-oder-keiner-Prinzip	Absolute Spezifität zum Einschluss oder absolute Sensitivität zum Ausschluss der Diagnose			
2a	Systematische Review von Kohortenstudien	Syst. Review von explorativen Kohortenstudien	 Studien: Konsistenz, Effektstärke Nutzen, Risiken, Nebenwirkungen Anwendbarkeit	B	Mittelstarke Empfehlung
2b	Individ. Kohortenstudie, randomisierte kontr. Studie geringerer Qualität	Exploratorische Kohortenstudie mit guten Referenz-standards			
2c	Outome-Research-Studie				
3a	Syst. Review Fall-Kontroll-Studien	Syst. Review von nicht-konsekutiven Studien			
3b	Individ. Fall-Kontroll-Studie	Nicht-konsekutive Studien			
4	Fallserie, Kohortenstudien und Fallkontrollstudien geringerer Qualität	Fall-Kontroll-Studie, schlechter oder nicht-unabhängiger Referenzstandard		C	Schwache Empfehlung
5	Expertenmeinung ohne explizite kritische Bewertung, physiolog. Modelle etc.	Expertenmeinung ohne explizite kritische Bewertung, physiolog. Modelle etc.		D	Fehlende oder inkonsistente Studien, Empfehlung aufgrund von Experten-meinung

Tabelle 6: Schema der Empfehlungsgraduierung für Empfehlungen 2018

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll
B	Empfehlung	sollte
0	Empfehlung offen	kann

Tabelle 7: Konsensusstärke

Konsenstärke	Prozentuale Zustimmung
Starker Konsens	> 95 % der Stimmberechtigten
Konsens	> 75 – 95 % der Stimmberechtigten
Mehrheitliche Zustimmung	50 – 75 % der Stimmberechtigten
Dissens	< 50 % der Stimmberechtigten

Sonstige methodische Hinweise

Die methodische Vorgehensweise bei der Ersterstellung der Leitlinie ist im Leitlinienre-port aus dem Jahr 2010 dargelegt.

Das methodische Vorgehen bei der ersten Aktualsierung der Leitlinie im Rahmen des Leitlinienprogramms Onkologie ist Gegenstand eines separaten Leitlinienreports.

Beide Dokumente sind im Internet z. B. auf den Seiten des Leitlinienprogramms Onko-logie (http://leitlinienprogramm-onkologie.de/Lungenkarzinom.98.0.html) und den Seiten der AWMF (http://www.awmf.org/) frei verfügbar.

Empfehlungen

Systemtherapie (Erstlinie) bei Patienten ohne Mutationsnachweis

8.6.2.1. **Patienten mit PD-L1-Expression von ≥50 %**

8.66.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad **B**	Bei Therapie-naiven Patienten im Stadium IV, welche keine therapierbaren Mutationen (z.B. EGFR, EML4-ALK, ROS1) aufweisen, und welche in Gewebeproben eine PD-L1-Expression von ≥50 % der Tumorzellen aufweisen, sollte Pembrolizumab (200 mg i.v. alle 3 Wochen) als Erstlinientherapie angeboten werden.	
Level of Evidence **1b**	Literatur : [773]	
	Konsensstärke:	

8.6.2.2. **Patienten mit PD-L1-Expression von <50 % und ECOG 0-1**

8.67.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad **A**	Bei Patienten im Stadium IV (neu: IV B) in gutem Allgemeinzustand (ECOG 0-1) soll eine platinbasierte Kombinationschemotherapie angeboten werden, vorzugsweise mit Cisplatin.	
Level of Evidence **1a**	Literatur: [774-783]	
	Konsensstärke: 100 %	

8.68.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad **A**	In der Erstlinienchemotherapie sollen 4-6 Zyklen gegeben werden.	
Level of Evidence **1a**	Literatur : [784][660][659]	
	Konsensstärke: 80%	

8.69.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad **0**	Als Alternative zu einer cisplatinhaltigen 2xKombination kann eine additive Gabe von Bevacizumab zu Carboplatin/Paclitaxel mit anschließender Erhaltungstherapie mit Bevacizumab bei geeigneten Patienten mit einem nicht-plattenepithelialen NSCLC unter Ausschluss von relevanten Komborbiditäten, die mit einer erhöhten Toxizität von Bevacizumab assoziiert sind, erwogen werden.	
Level of Evidence **1b**	Literatur : [770, 787-791]	
	Konsensstärke: 96 %	

8.70.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad 0	Bei Patienten mit Plattenepithelkarzinom und einer EGFR-Expression größer 1% in der immunhistochemischen Untersuchung (IHC) kann als Erstlinientherapie Cisplatin/Gemcitabin in Kombination mit Necitumumab angeboten werden. Nach der Erstlinientherapie kann bei fehlendem Krankheitsprogress und bei guter Verträglichkeit der Therapie eine Erhaltungstherapie mit Necitumumab angeboten werden.	
Level of Evidence 1b	Literatur : [798-800]	
	Konsensstärke: 96 %	

Patienten mit PD-L1-Expression von <50 % und ECOG 2

8.71.	Evidenzbasiertes Statement	2018
Level of Evidence 1a	Auch beim NSCLC ECOG 2 sind die Therapieziele der palliativen (nicht kurativen) Therapie (ohne therapierbare Mutationen/Translokationen) Symptomlinderung, Verbesserung oder Erhalt der Lebensqualität, Tumoransprechen und Überlebensverlängerung). Diese Therapieziele können mit einer palliativen Chemotherapie, zusätzlich zu best supportive care erreicht werden.	
	Quellen :[804, 805]	
	Konsensstärke: 100 %	

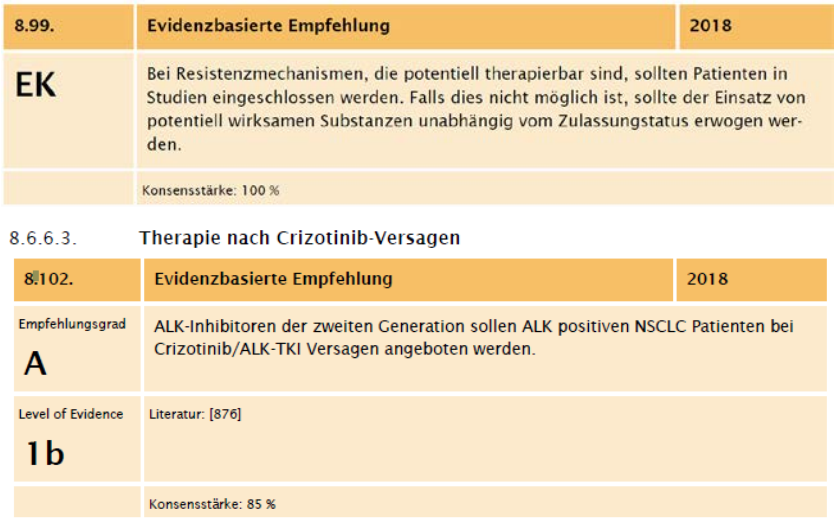
8.72.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad A	Bei Patienten mit ECOG 2 ohne wesentliche Komorbiditäten sollen platinbasierte Kombinationen, z.B. Carbo/Pacli oder Carbo/Pem angeboten werden.	
Level of Evidence 1a	Quellen : :[804]	
	Konsensstärke: 100 %	

8.73.	Konsensbasierte Empfehlung	2018
EK	Bei Patienten mit ECOG 2 mit Komorbiditäten, bei denen die Komorbiditäten eine platinhaltige Kombinationstherapie nicht erlauben, kann eine Monotherapie angeboten werden.	
	Konsensstärke: 100 %	

Resistenzmechanismen und Zweitlinientherapie bei EGFR mutierten Patienten

8.97.	Evidenzbasierte Empfehlung	2018
Empfehlungsgrad A	Bei Nachweis einer erworbenen EGFR-TKI-Resistenz durch Akquisition einer EGFR-T790M-Mutation soll eine T790M spezifische Substanz angeboten werden.	
Level of Evidence 1b	Literatur: [863, 870]	
	Konsensstärke: 100 %	

8.98.	Konsensbasierte Empfehlung	2018
Empfehlungsgrad EK	Bei fehlendem Nachweis einer erworbenen EGFR-T790M-Mutation und fehlendem Nachweis von weiteren therapierbaren genetischen Alterationen sollte analog zur Erstlinientherapie - Wildtyp vorgegangen werden.	
	Konsensstärke: 96 %	

	 8.99. | Evidenzbasierte Empfehlung | 2018 EK | Bei Resistenzmechanismen, die potentiell therapierbar sind, sollten Patienten in Studien eingeschlossen werden. Falls dies nicht möglich ist, sollte der Einsatz von potentiell wirksamen Substanzen unabhängig vom Zulassungstatus erwogen werden. Konsensstärke: 100 % 8.6.6.3. Therapie nach Crizotinib-Versagen 8.102. | Evidenzbasierte Empfehlung | 2018 Empfehlungsgrad A | ALK-Inhibitoren der zweiten Generation sollen ALK positiven NSCLC Patienten bei Crizotinib/ALK-TKI Versagen angeboten werden. Level of Evidence 1b | Literatur: [876] Konsensstärke: 85 %
Ellis PM et al., 2016 [4]. Cancer Care Ontario (CCO) Systemic Treatment for Patients with Advanced Non-Small Cell Lung Cancer. Guideline 7-10 Version 3 <u>Siehe auch:</u> **Masters GA et al., 2015 [16].**	**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 squamous cell carcinoma (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. Second-Line Treatment for Patients: • With sensitizing EGFR mutations who did not respond to a first-line EGFR TKI: combination cytotoxic chemotherapy as listed in under first-line treatment or a third-generation EGFR TKI such as osimertinib in patients shown to have a T790M mutation is recommended for those with NSCC.

	• With sensitizing EGFR mutations who received a first-line EGFR TKI and experienced disease progression after an initial response: may be switched to chemotherapy or a third-generation EGFR TKI such as osimertinib in patients shown to have a T790M mutation as second-line therapy. • With ALK rearrangement and progression after first-line crizotinib: chemotherapy or ceritinib may be offered. **Clinical Question B1** **What is the most effective second-line therapy for patients with stage IIIB/IV NSCLC with negative or unknown EGFR/ALK status and NSCC?** For patients with advanced NSCLC, NSCC, negative or unknown EGFR/ALK status, and adequate PS, when disease has progressed during or after first-line platinum-based therapy, nivolumab (in all patients with NSCLC) or pembrolizumab (in patients with PD-L1-positive tumours) is preferred, if either is available, over docetaxel, erlotinib, gefitinib, or pemetrexed as second-line therapy. **Clinical Question B2** **What is the most effective second-line therapy for patients with stage IIIB/IV NSCLC with negative or unknown EGFR/ALK status and SCC?** For patients with advanced NSCLC, SCC, negative or unknown EGFR/ALK status, and adequate PS, when disease has progressed during or after first-line platinum-based therapy, nivolumab (in all patients with NSCLC) or pembrolizumab (in patients with PD-L1-positive tumours) is preferred, if either is available, over docetaxel, erlotinib, or gefitinib as second-line therapy. **Clinical Question B3.a** **What is the most effective second-line therapy for patients with stage IIIB/IV NSCLC with a sensitizing EGFR mutation who received a first-line EGFR TKI and experienced disease progression?** For patients with a sensitizing EGFR mutation who did not respond to a first-line EGFR TKI, combination cytotoxic chemotherapy (Recommendation A2) or a third-generation EGFR TKI such as osimertinib in patients shown to have a T790M mutation is recommended, following the first-line recommendations for patients with NSCC. **Clinical Question B3.b** **What is the most effective second-line therapy for patients with stage IIIB/IV NSCLC with a sensitizing EGFR mutation who received a first-line EGFR TKI and experienced disease progression after an initial response?** Patients who received an EGFR TKI in the first-line setting, had an initial response, and subsequently experienced disease progression may be switched to chemotherapy or a third-generation EGFR TKI such as osimertinib in patients shown to have a T790M mutation as second-line therapy. There is insufficient evidence to recommend the use of other EGFR TKIs, such as afatinib, in previously treated patients, as available data do not demonstrate any improvement in overall survival.

	Clinical Question B4 **What is the most effective second-line therapy for patients with stage IIIB/IV NSCLC with ALK rearrangement with progression after first-line crizotinib?** Patients whose tumours have ALK rearrangements and who received crizotinib in the first-line setting may be offered the option of chemotherapy (after first-line recommendations for patients with NSCC [see Recommendation A2]) or ceritinib in the second-line setting. **Clinical Question B5** **What is the optimal second-line treatment for elderly patients with stage IIIB/IV NSCLC?** The evidence does not support the selection of a specific second-line chemotherapy drug or combination based on age alone. As stated in Recommendation A8, age alone is not a contraindication to chemotherapy for NSCLC. **Clinical Question C** **Is there a role for third-line therapy or beyond in the treatment of stage IIIB/IV NSCLC?** When disease progresses during or after second-line chemotherapy, treatment with erlotinib may be recommended as third-line therapy for patients with a PS of 0 to 3 who have not received prior erlotinib or gefitinib. Docetaxel, erlotinib, gefitinib, or pemetrexed may be used in patients with stage IIIB/IV NSCLC with negative or unknown EGFR/ALK status and NSCC after progression on nivolumab or pembrolizumab, although data are limited. Docetaxel, erlotinib, or gefitinib may be used in patients with stage IIIB/IV NSCLC with negative or unknown EGFR/ALK status and SCC after progression on nivolumab or pembrolizumab, although data are limited.
Hanna N et al., 2017 [10]. **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	**Fragestellung/Zielsetzung** Provide evidence-based recommendations updating the 2015 ASCO guideline on systemic therapy for patients with stage IV non–small-cell lung cancer (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 <u>Grundlage des Leitlinie-Updates</u> 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]). Patients with squamous cell carcinoma without a tumor EGFR-sensitizing mutation or ALK or ROS1 gene rearrangement and with a PS of 0 or 1 (and appropriate PS of 2): • With high PD-L1 expression (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 are recommended (Platinum based [Evidence quality: high; Strength of recommendation: strong]; Non–platinum based [Evidence quality: low; Strength of recommendation: weak]). • 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 squamous NSCLC treated with cisplatin and gemcitabine, the Panel neither recommends for nor recommends against the addition of necitumumab to chemotherapy. With sensitizing EGFR mutations, afatinib, erlotinib, or gefitinib is recommended (Evidence quality: high; Strength of recommendation: strong for each). With ALK gene rearrangements, crizotinib is recommended (Evidence quality: intermediate; Strength of recommendation: moderate). With ROS1 rearrangement, crizotinib is recommended (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak). *Second-Line Treatment for Patients* With sensitizing EGFR mutations: • In patients with disease progression after first-line therapy with an EGFR tyrosine kinase inhibitor (TKI) and the presence of the T790M resistance mutation, osimertinib is recommended (Evidence quality: high; Strength of recommendation: strong). • If T790M mutation is not present, a platinum doublet is recommended (Type: informal consensus; Evidence quality: low; Strength of recommendation: strong). • In patients who received an EGFR-TKI in the first-line setting, had an initial response, and subsequently experienced slow or minimal disease progression at isolated sites, EGFR-TKI with local therapy to the isolated sites is an option (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: weak). With ROS1 rearrangement: • In patients who have not received prior crizotinib, crizotinib is recommended (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate). • In patients who have received prior crizotinib, platinum-based therapy in the second line with or without bevacizumab is recommended (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).
National Comprehensive Cancer Network, 2018 [18]. Non-Small Cell Lung Cancer, Vers. 03.2018 (February 21, 2018)	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.

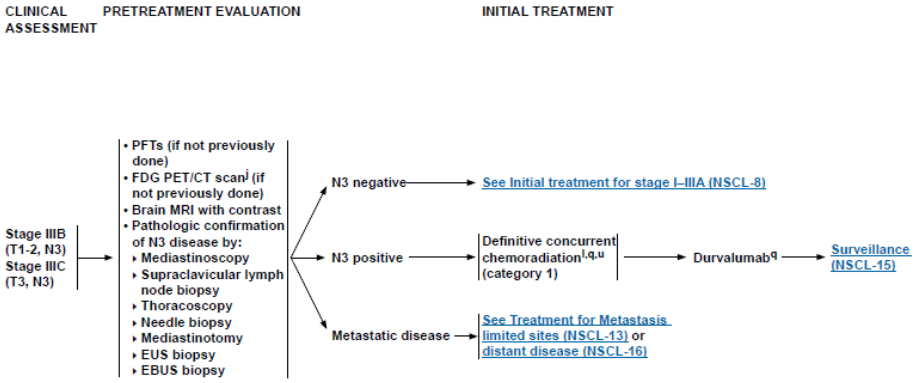
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

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.

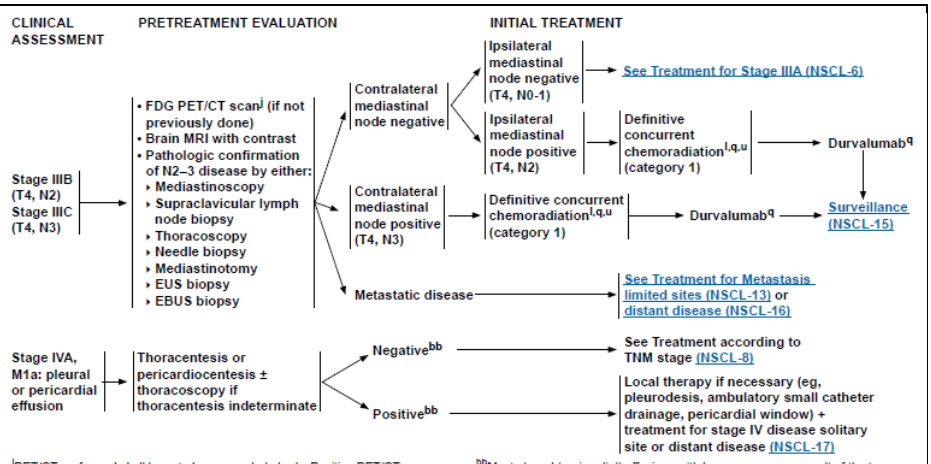
Empfehlungen



[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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

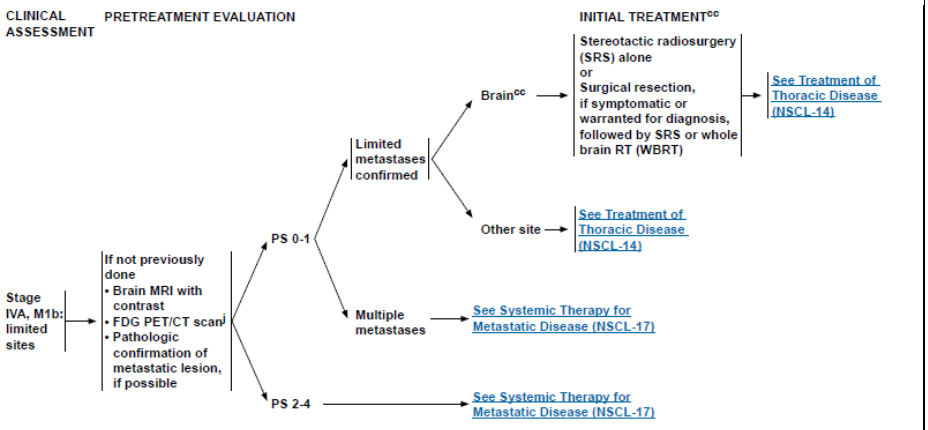
NSCL-11



[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.

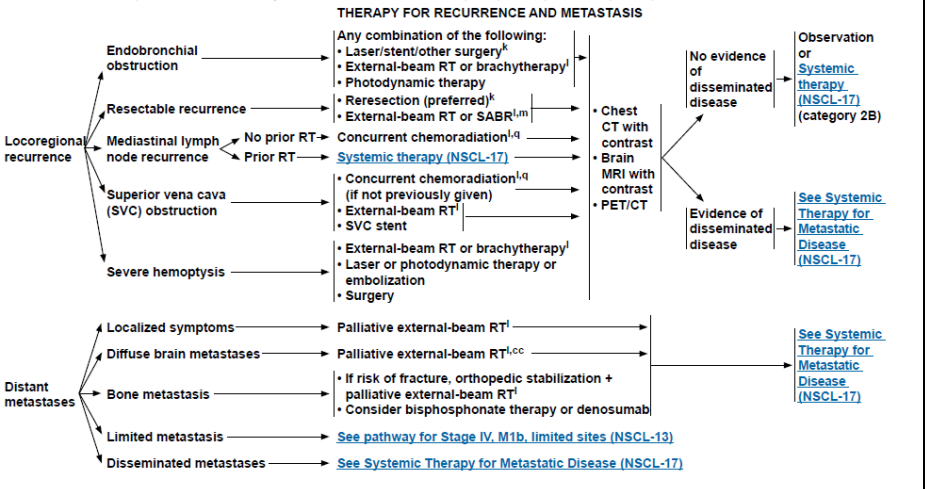
[bb]Most pleural (pericardial) effusions with lung cancer are a result of the tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and fluid is non-bloody and not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



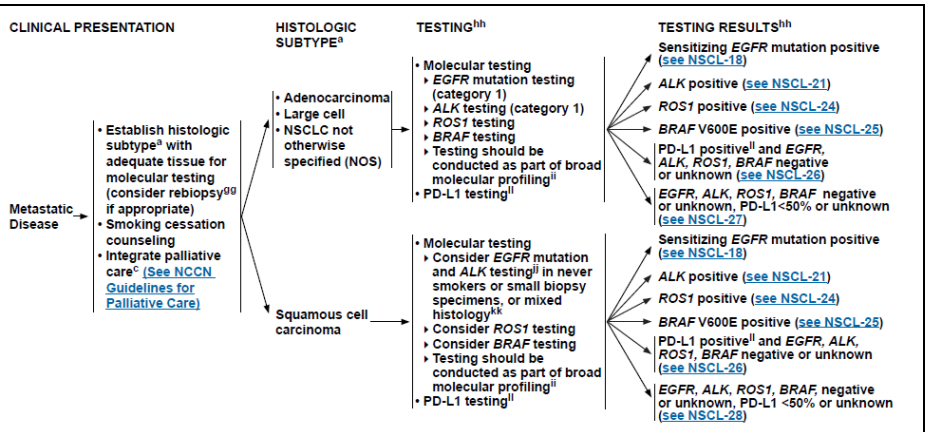
[j]PET/CT performed skull base to knees or whole body. Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation.
[cc]See NCCN Guidelines for Central Nervous System Cancers.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



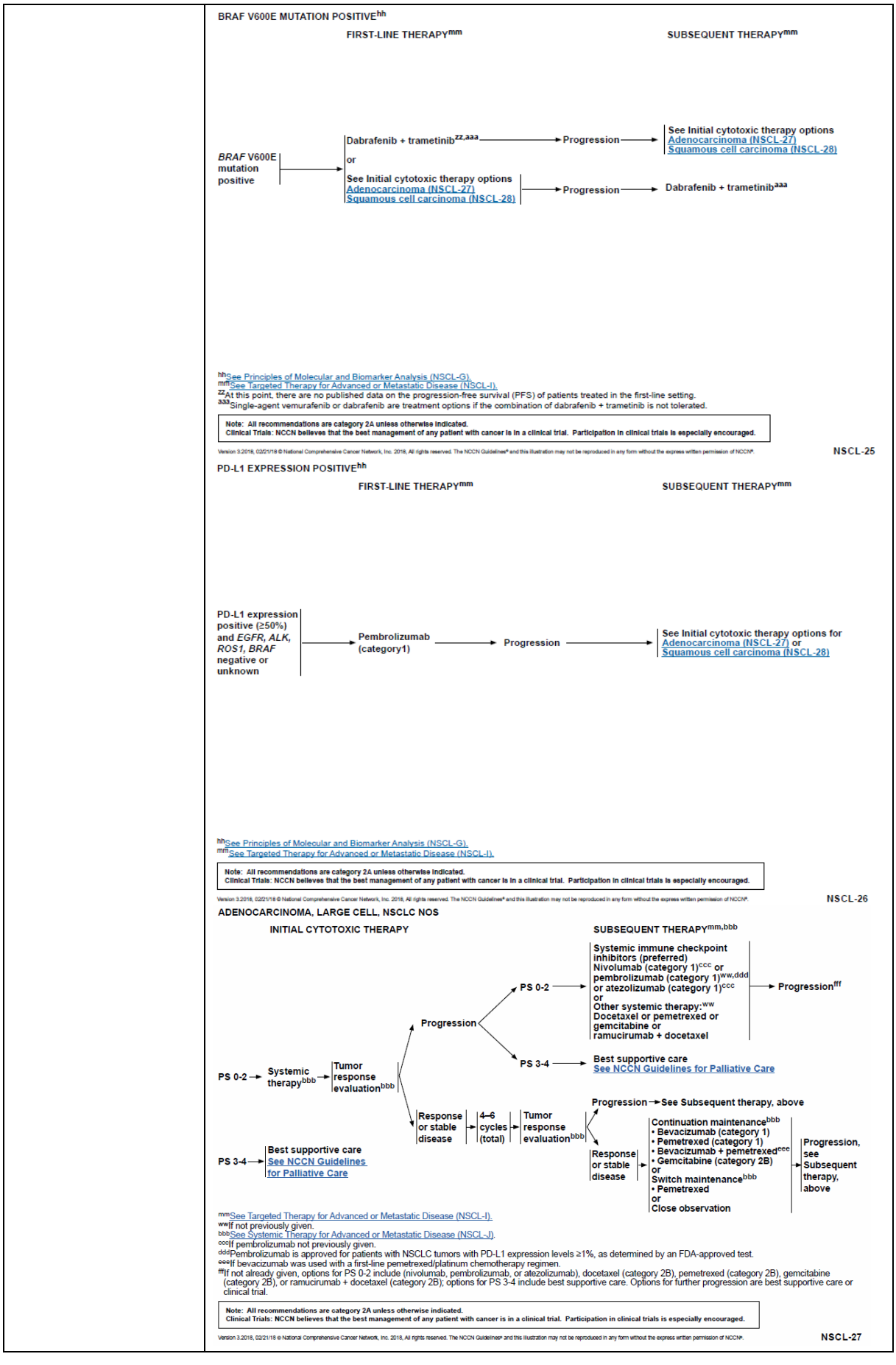
[a]See Principles of Pathologic Review (NSCL-A).
[c]Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742.
[gg]If repeat biopsy is not feasible, plasma biopsy should be considered.
[hh]See Principles of Molecular and Biomarker Analysis (NSCL-G).
[ii]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).
[jj]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 (COSMIC). Curr Protoc Hum Genet 2008;chapter 10:unit 10.11.
[kk]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.
[ll]PD-L1 expression levels of ≥50% are a positive test result for first-line pembrolizumab therapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ROS1 REARRANGEMENT POSITIVE[hh]

[hh]See Principles of Molecular and Biomarker Analysis (NSCL-G).
[mm]See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
[nn]For performance status 0-4.
[tt]The data in the second-line setting suggest that immunotherapy is less effective, irrespective of PD-L1 expression, in tumors with an actionable mutation.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.


BRAF V600E MUTATION POSITIVE[hh]
FIRST-LINE THERAPY[mm]
SUBSEQUENT THERAPY[mm]
BRAF V600E mutation positive
Dabrafenib + trametinib[zz,aaa]
Progression
See Initial cytotoxic therapy options
Adenocarcinoma (NSCL-27)
Squamous cell carcinoma (NSCL-28)
or
See Initial cytotoxic therapy options
Adenocarcinoma (NSCL-27)
Squamous cell carcinoma (NSCL-28)
Progression
Dabrafenib + trametinib[aaa]
[hh]See Principles of Molecular and Biomarker Analysis (NSCL-G).
[mm]See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
[zz]At this point, there are no published data on the progression-free survival (PFS) of patients treated in the first-line setting.
[aaa]Single-agent vemurafenib or dabrafenib are treatment options if the combination of dabrafenib + trametinib is not tolerated.
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
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NSCL-25
PD-L1 EXPRESSION POSITIVE[hh]
FIRST-LINE THERAPY[mm]
SUBSEQUENT THERAPY[mm]
PD-L1 expression positive (≥50%) and EGFR, ALK, ROS1, BRAF negative or unknown
Pembrolizumab (category1)
Progression
See Initial cytotoxic therapy options for
Adenocarcinoma (NSCL-27) or
Squamous cell carcinoma (NSCL-28)
[hh]See Principles of Molecular and Biomarker Analysis (NSCL-G).
[mm]See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
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NSCL-26
ADENOCARCINOMA, LARGE CELL, NSCLC NOS
INITIAL CYTOTOXIC THERAPY
SUBSEQUENT THERAPY[mm,bbb]
PS 0-2
Systemic therapy[bbb]
Tumor response evaluation[bbb]
Progression
PS 0-2
Systemic immune checkpoint inhibitors (preferred)
Nivolumab (category 1)[ccc] or
pembrolizumab (category 1)[ww,ddd]
or atezolizumab (category 1)[ccc]
or
Other systemic therapy:[ww]
Docetaxel or pemetrexed or
gemcitabine or
ramucirumab + docetaxel
Progression[fff]
PS 3-4
Best supportive care
See NCCN Guidelines for Palliative Care
Response or stable disease
4–6 cycles (total)
Tumor response evaluation[bbb]
Progression
See Subsequent therapy, above
Response or stable disease
Continuation maintenance[bbb]
• Bevacizumab (category 1)
• Pemetrexed (category 1)
• Bevacizumab + pemetrexed[eee]
• Gemcitabine (category 2B)
or
Switch maintenance[bbb]
• Pemetrexed
or
Close observation
Progression, see Subsequent therapy, above
PS 3-4
Best supportive care
See NCCN Guidelines for Palliative Care
[mm]See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
[ww]If not previously given.
[bbb]See Systemic Therapy for Advanced or Metastatic Disease (NSCL-J).
[ccc]If pembrolizumab not previously given.
[ddd]Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression levels ≥1%, as determined by an FDA-approved test.
[eee]If bevacizumab was used with a first-line pemetrexed/platinum chemotherapy regimen.
[fff]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.
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
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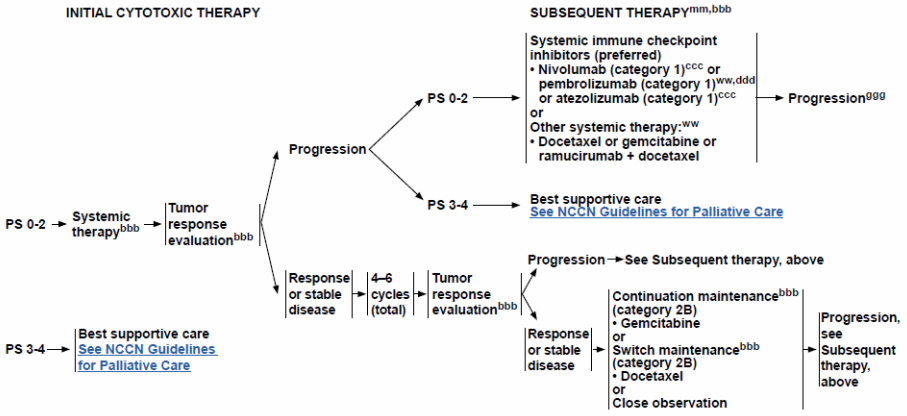
NSCL-27

SQUAMOUS CELL CARCINOMA



[mm]See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
[ww]If not previously given.
[bbb]See Systemic Therapy for Advanced or Metastatic Disease (NSCL-J).
[ccc]If pembrolizumab not previously given.
[ddd]Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression levels ≥1%, as determined by an FDA-approved test.
[ggg]If not already given, options for PS 0-2 include (nivolumab, pembrolizumab, or atezolizumab), docetaxel (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include best supportive care. Options for further progression are best supportive care or clinical trial.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (2 of 4)[*,]**

Initial Cytotoxic 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.
**Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.
†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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (3 of 4)[*,,§]**

Initial Cytotoxic 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.
**Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.
§Cisplatin/gemcitabine/necitumumab in the first-line setting and afatinib in the second-line setting are not used at NCCN Member Institutions for these indications related to the efficacy and safety of these agents compared to the efficacy and safety of other available agents.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Second-line and Beyond (Subsequent) Systemic Therapy

Second-Line and Beyond (Subsequent) Systemic Therapy

The phrase *subsequent* therapy was recently substituted for the terms *second-line, third-line, and beyond* systemic therapy, because the line of therapy may vary depending on previous treatment with targeted agents. Subsequent systemic therapy regimens for patients who have disease progression during or after first-line therapy are described in the NSCLC algorithm and depend on the specific genetic alteration, the histologic subtype, and whether the patient has symptoms (see the NCCN Guidelines for NSCLC).[877-886] The NCCN Panel recommends response assessment of known sites of disease with CT (with contrast) every 6 to 12 weeks in patients receiving subsequent therapy. Note that traditional RECIST response criteria (1.1) are used to assess response for most types of systemic therapy, but different response criteria may be useful for assessing response in patients receiving immunotherapy.[192,810,812,887,888]

The NCCN Panel recommends immune checkpoint inhibitors as preferred agents for subsequent therapy in patients with metastatic NSCLC based on improved survival rates, longer duration of response, and fewer adverse events when compared with cytotoxic chemotherapy (see *Nivolumab, Pembrolizumab,* and *Atezolizumab* in this Discussion).[261,264,694] Human immune-checkpoint–inhibitor antibodies inhibit the PD-1 receptor or PD-L1, which improves antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T cells.[261-263] The NCCN Panel recommends nivolumab (category 1) as subsequent therapy for patients with metastatic nonsquamous or squamous NSCLC based on phase 3 randomized trials (CheckMate 017 and CheckMate 057) and FDA approvals.[261,674] The NCCN Panel recommends pembrolizumab (category 1) as subsequent therapy for patients with metastatic nonsquamous or squamous NSCLC and PD-L1 expression based on a phase 2/3 randomized trial (KEYNOTE-010) trial, KEYNOTE-001 trial, and FDA approval.[271,688] The NCCN Panel also recommends atezolizumab (category 1) as subsequent therapy for patients with metastatic nonsquamous or squamous NSCLC based on a

	phase 3 randomized trial (OAK), data from a phase 2 trial (POPLAR), and FDA approval.[267,693,694] The NCCN Panel recommends osimertinib (category 1) as subsequent therapy for patients with metastatic *EGFR* T790M-positive NSCLC who have progressed on erlotinib, gefitinib, or afatinib therapy based on recent data and on the FDA approval (see *Osimertinib* in this Discussion).[195,199] For patients with sensitizing *EGFR* mutations who progress during or after first-line erlotinib, afatinib, or gefitinib, recommended subsequent therapy depends on whether the progression is asymptomatic or symptomatic and includes: 1) considering local therapy; 2) continuing erlotinib, afatinib, or gefitinib; 3) taking osimertinib; or 4) taking a first-line systemic therapy regimen for nonsquamous NSCLC (such as cisplatin/pemetrexed). The NCCN Panel also recommends osimertinib (category 1) for patients with T790M who have brain metastases and have progressed on erlotinib, afatinib, or gefitinib.[195,639-641] Data suggest that an afatinib/cetuximab regimen may be useful for patients who have progressed after receiving erlotinib, afatinib, or gefitinib and after chemotherapy.[889] Patients with T790M-positive and T790M-negative tumors had a similar response rate to an afatinib/cetuximab regimen (32% vs. 25%; *P* = .341). The NCCN Panel recommends (category 2A) considering an afatinib/cetuximab regimen for patients who have progressed after receiving erlotinib, afatinib, or gefitinib and chemotherapy based on these data. The NCCN Panel recently added a new subsequent therapy algorithm for patients with advanced NSCLC and sensitizing *EGFR* mutations who progress during or after first-line therapy with osimertinib. Recommended subsequent therapy depends on whether the progression is asymptomatic or symptomatic and includes: 1) considering local therapy; and/or 2) continuing osimertinib or switching to a first-line systemic therapy regimen for nonsquamous NSCLC (such

as cisplatin/pemetrexed). There are no data to support using erlotinib, gefitinib, or afatinib after progression on osimertinib.

Among patients with sensitizing EFGR mutations, no improvement in overall survival has been noted in the phase 3 trials assessing subsequent therapy with pembrolizumab, nivolumab, or atezolizumab compared to docetaxel, but there were not enough patients with these mutations to determine whether there were statistically significant differences (see next paragraph).[261,271,272,694] Immunotherapy was not worse than chemotherapy and was better tolerated. In the phase 3 trials for pembrolizumab, nivolumab, or atezolizumab versus docetaxel as subsequent therapy for patients with metastatic NSCLC, subset analyses were done in patients with *EGFR* mutations to determine the best subsequent therapy.[261,271,694] The HRs for overall survival do not favor docetaxel over nivolumab (HR, 1.18; CI, 0.69–2.0), pembrolizumab (HR, 0.88; CI, 0.45–1.7), or atezolizumab (HR, 1.24; CI, 0.7–2.2); the CIs for the HRs are wide probably because there were so few patients with *EGFR* mutations. The HRs for PFS do favor docetaxel for patients with *EGFR* mutations when compared with either pembrolizumab (HR, 1.79; CI, 0.94–3.42) or nivolumab (HR, 1.46; CI, 0.90–2.37). But again, the CIs are wide. The evidence is weak for recommending docetaxel, pembrolizumab, nivolumab, or atezolizumab as subsequent therapy for patients with *EGFR* mutations. Data suggest that patients with *EGFR* mutations or *ALK* rearrangements have a low response rate to PD-1 or PD-L1 inhibitors when compared with patients without these genetic alterations (response rate, 3.6% vs. 23%, respectively).[272] For the 2018 update (Version 1), the NCCN Panel deleted the recommendation for pembrolizumab as subsequent therapy for patients with PD-L1 expression of 50% or more and genetic alterations such as *EGFR* mutations or ROS1 rearrangements.

	For patients with *ALK* rearrangements who progress during or after first-line targeted therapy, recommended subsequent therapy also depends on whether the progression is asymptomatic or symptomatic and includes: 1) considering local therapy; 2) continuing alectinib, crizotinib, or ceritinib; 3) taking ceritinib (if not previously given); 4) taking alectinib (if not previously given); 5) taking brigatinib; or 6) taking a first-line systemic therapy regimen for nonsquamous NSCLC. After further progression on subsequent targeted therapy, first-line combination chemotherapy options for NSCLC are recommended for patients with PS of 0 to 1 such as carboplatin/paclitaxel.[136,890] Other chemotherapy options are also recommended for patients with PS 2, such as docetaxel (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC). Note that immune checkpoint inhibitors are not recommended as subsequent therapy for patients with *ALK* rearrangements. Patients with ALK-positive NSCLC and very high PD-L1 expression do not respond to pembrolizumab.[272] In addition, those with *MET* exon 14 mutations and high PD-L1 expression also do not respond to immunotherapy.[891] Most patients with NSCLC do not have *ALK* rearrangements, *ROS1* rearrangements, *BRAF* V600E mutations, or sensitizing *EGFR* mutations. For patients with all histologic subtypes and PS of 0 to 2 but without these genetic alterations who have disease progression during or after initial cytotoxic therapy, recommended subsequent systemic therapy options include immunotherapy (nivolumab [category 1], pembrolizumab [category 1] if not previously given, or atezolizumab [category 1]) or chemotherapy (docetaxel with or without ramucirumab, or gemcitabine if not already given; pemetrexed is recommended for patients with nonsquamous NSCLC). The NCCN Panel recommends immune checkpoint inhibitors—nivolumab, pembrolizumab, and atezolizumab—as preferred options for subsequent therapy for all

	survival, 7.9 months [95% CI, 7.2–8.7] vs. 6.8 months [95% CI, 5.9–7.8]; HR, 0.81 [95% CI, 0.69–0.95], *P* = .0077); however, almost 60% of patients in each arm had grade 3 or higher adverse events. In contrast, the median overall survival was 9.2 months with nivolumab compared with 6.0 months for docetaxel for patients with squamous cell NSCLC.[264] In addition, only 7% of patients receiving nivolumab had grade 3 or higher adverse events. Erlotinib and afatinib are not recommended as second-line therapy for squamous cell carcinoma based on a phase 3 randomized trial showing low response rates; they are less efficacious and safe compared to other available options.[632] Doublet chemotherapy options used for initial cytotoxic therapy are recommended for patients with metastatic NSCLC (eg, carboplatin/paclitaxel) and genetic alterations who progress with symptomatic systemic multiple lesions after first-line targeted therapy.[235] Recent data (IMPRESS) indicate that chemotherapy should be used alone and not be combined with EGFR inhibitors such as gefitinib in patients who have progressed on gefitinib.[896] Erlotinib, gefitinib, afatinib, or osimertinib may be continued in patients with sensitizing *EGFR* mutations who have progressed after first-line therapy, depending on the type of progression.[176,842,871,872] Osimertinib is recommended for patients with T790M whose disease becomes resistant to erlotinib, afatinib, or gefitinib.[199] Afatinib/cetuximab may be considered for patients with sensitizing *EGFR* mutations who have progressed after erlotinib, gefitinib, or afatinib and after doublet chemotherapy.[889] Ceritinib, alectinib, or brigatinib are recommended in patients with *ALK*-positive NSCLC who have progressed after first-line therapy with crizotinib or for patients who are intolerant to crizotinib.[134,234,242] Flare phenomenon may occur in some patients who discontinue ALK inhibitors. If disease flare occurs, then ALK inhibitors should be restarted.[869,897] Subsequent therapy is recommended after second disease progression in patients with advanced NSCLC and a PS of 0 to 2 if the following agents have not already been given: 1) immune checkpoint inhibitors including nivolumab, pembrolizumab, and atezolizumab (all are category 2A); 2) docetaxel with or without ramucirumab (category 2B for both); 3) gemcitabine (category 2B); or 4) pemetrexed (nonsquamous only) (category 2B).[878,894,898,899]
Australian Government Cancer Council Australia, 2017 [2]. Clinical practice guidelines for the treatment of lung cancer	Fragestellung/Zielsetzung: What is the optimal first-line chemotherapy regimen in patients with stage IV inoperable NSCLC? Is carboplatin based chemotherapy as effective as cisplatin based chemotherapy for treatment of stage IV inoperable NSCLC? Which new agent or platinum combination regimen is best for treatment of stage IV inoperable NSCLC? Is monotherapy with new third generation (3G) agents as effective as platinum combination therapy for treatment of stage IV inoperable NSCLC? Are three chemotherapy agents better than two chemotherapy agents for treatment of stage IV inoperable NSCLC? Are non-platinum doublet chemotherapy regimens as effective as platinum doublet

regimens for treatment of stage IV inoperable NSCLC? Is chemotherapy with a biologic or targeted therapy superior to chemotherapy alone in unselected patients for treatment of stage IV inoperable NSCLC? What is the optimal chemotherapy regimen for overall quality of life for patients in the treatment of stage IV inoperable NSCLC? What is the optimal second-line therapy in patients with stage IV inoperable NSCLC? What is the optimal third-line therapy in unselected patients with stage IV inoperable NSCLC? What is the optimal systemic therapy regimen for patients with poor performance status for treatment of stage IV inoperable NSCLC? What is the optimal systemic therapy regimen in selected patients for treatment of stage IV inoperable NSCLC?

Methodik

Grundlage der Leitlinie:
Systematischer Review und Konsensusprozess über Empfehlungen. Alle Aussagen sind mit Literaturstellen (Meta-Analysen oder RCTs) belegt.
Suchzeitraum: bis 2015
LoE:

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

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

GoR

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

Empfehlungen

Stage III inoperable

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

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

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

✓ Practice point?

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

✓ Practice point?

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

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

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

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

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

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

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

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

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

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

✓ Practice point?

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

Stage IV inoperable

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

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

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

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

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

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

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

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

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

✓ Practice point?

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

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

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

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

✓ Practice point?

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

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

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

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

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

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

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

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

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

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.

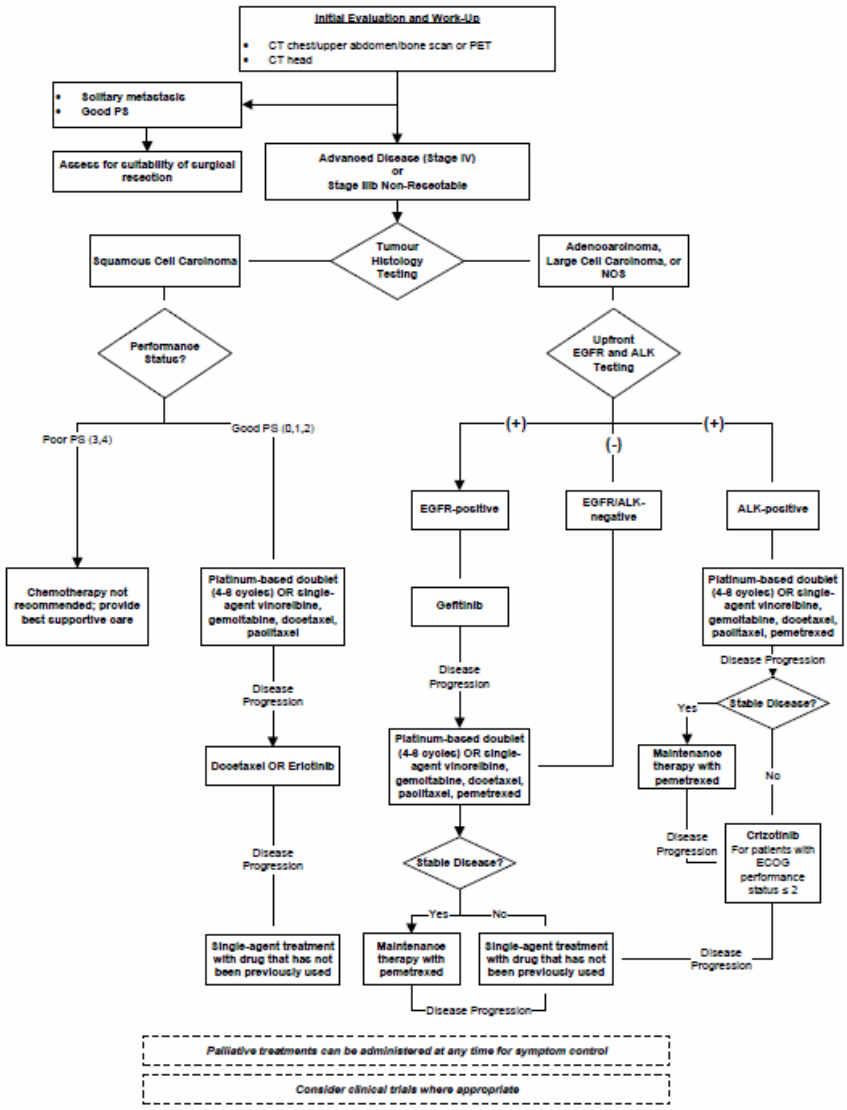
Last reviewed December 2015

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

	<table><tr><th>Evidence summary</th><th>Level</th><th>References</th></tr><tr><td>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</td><td>II</td><td>[5]</td></tr></table> <table><tr><th>+ Evidence-based recommendation?</th><th>Grade</th></tr><tr><td>Where EGFR mutation status is negative or unknown, patients should be treated with standard chemotherapy. Last reviewed December 2015</td><td>B</td></tr></table> <table><tr><th>✓ Practice point?</th></tr><tr><td>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</td></tr></table>
Alberta Provincial Thoracic Tumour Team, 2013 [1]. 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. TREATMENT ALGORITHM 
Scottish Intercollegiate Guidelines Network (SIGN), 2014 [21]. 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 [19]. 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 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
	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

Empfehlungen

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 [24]. Treatment of stage IV non-small cell lung cancer: Diagnosis and management of lung cancer. 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines	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 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 [19]) 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 . <u>3.1.1 Recommendation</u> 3.1.1.1. In patients receiving palliative chemotherapy for stage IV NSCLC, it is recommended that the choice of chemotherapy is guided by the histologic type of NSCLC (Grade 1B). Remark: The use of pemetrexed (either alone or in combination) should be limited to patients with nonsquamous NSCLC. Remark: Squamous histology has not been identified as predictive of better response to any particular chemotherapy agent. *3.3 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 [27]. 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)

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).

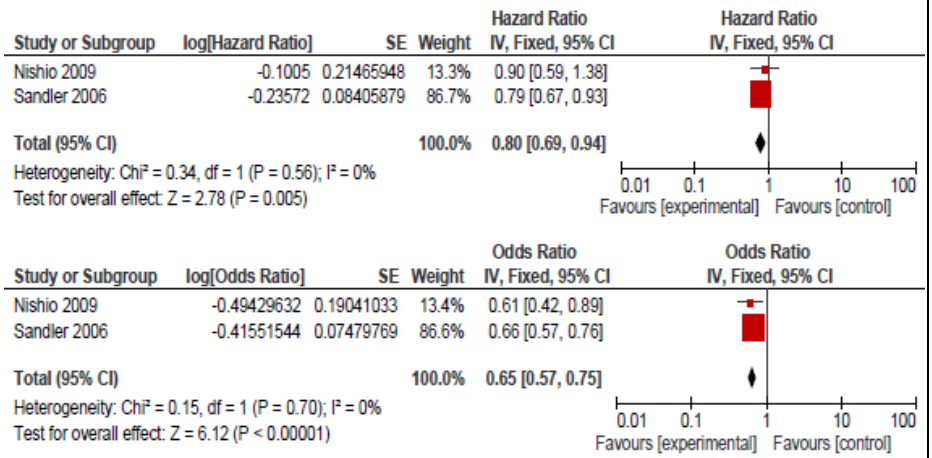
5.3.2.4. Which doublet therapy?

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.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 13.03.2018

#	Suchfrage
1	[mh “Carcinoma, Non-Small-Cell Lung”]
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 2013 to 2018

SR, HTAs in Medline (PubMed) am 13.03.2018

#	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 ("2013/03/01"[PDAT] : "3000"[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 13.03.2018

#	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 ("2013/03/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT ((Humans[mh] AND animals[MeSH:noexp]) NOT ("The Cochrane database of systematic reviews"[Journal])))

Literatur

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Anlage

Table 3-2. Modifications to ASCO's recommendations (Ellis PM, et al. 2016 [4]).

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.

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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
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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