Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2014-B-092 Necitumumab

Stand: Oktober 2014

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Necitumumab in Kombination mit Gemcitabin und Cisplatin zur Therapie von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem, den epidermalen Wachstumsfaktor-Rezeptor (EGFR) exprimierenden, plattenepithelialen, nicht-kleinzelligen Lungenkarzinom, wenn diese bislang keine Chemotherapie für dieses Stadium der Erkrankung erhalten haben	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	*Nicht angezeigt.*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschluss vom 8. Mai 2014 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Afatinib Richtlinie Methoden Krankenhausbehandlung (Stand: 26. Juni 2014); Ausgeschlossene Methoden (§ 4): Protonentherapie beim inoperablen nicht-kleinzelligen Lungenkarzinom des UICC Stadiums IV […] Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie - Verordnungsfähigkeit von zugelassenen Arznei-mitteln in nicht zugelassenen Anwendungsgebieten (Stand: 30. Juli 2014): Off-Label-Indikation für Carboplatin: Kombinationstherapie des fortgeschrittenen NSCLC (palliativ)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche.*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff ATC-Code Handelsname	**Anwendungsgebiet** (Text aus Fachinformation)
Zu prüfendes Arzneimittel:	
Necitumumab	**in Kombination mit Gemcitabin und Cisplatin zur Therapie von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem, den epidermalen Wachstumsfaktor-Rezeptor (EGFR) exprimierenden, plattenepithelialen, nicht-kleinzelligen Lungenkarzinom, wenn diese bislang keine Chemotherapie für dieses Stadium der Erkrankung erhalten haben**
Chemotherapien:	
Carboplatin L01XA02 (generisch)	Off-Label-Indikation für Carboplatin: Kombinationstherapie des fortgeschrittenen NSCLC (palliativ)
Cisplatin L01XA01 (generisch)	Cisplatin wird angewendet zur Behandlung des: fortgeschrittenen oder metastasierten nichtkleinzelligen Bronchialkarzinoms. (FI Cisplatin-HAEMATO, 06-2012)
Docetaxel L01CD02 (generisch)	Nicht-kleinzelliges Bronchialkarzinom: […] Docetaxel ist in Kombination mit Cisplatin zur Behandlung von Patienten mit nicht resezierbarem, lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Bronchialkarzinom ohne vorausgegangene Chemotherapie angezeigt. (FI Docetaxel-ratiopharm®, 05-2013)
Etoposid L01CB01 (generisch)	Kombinationstherapie folgender Malignome: Palliative Therapie des fortgeschrittenen NSCLC bei Patienten mit gutem Allgemeinzustand (Karnofsky-Index >80%). (FI Riboposid®, 02-2014)
Gemcitabin L01BC05 (generisch)	Gemcitabin ist in Kombination mit Cisplatin als Erstlinientherapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nichtkleinzelligen Bronchialkarzinom (NSCLC) angezeigt. Eine Gemcitabin-Monotherapie kann bei älteren Patienten oder solchen mit einem Performance Status 2 in Betracht gezogen werden. (FI Gemcitabin Kabi, 05-2013)
Ifosfamid L01AA06 (Holoxan®)	Nicht-kleinzellige Bronchialkarzinome: Zur Einzel- oder Kombinationschemotherapie von Patienten mit inoperablen oder metastasierten Tumoren. (FI Holoxan®, 11-2008)
Mitomycin L01DC03 (generisch)	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Bei intravenöser Gabe ist es in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei folgenden metastasierenden Tumoren wirksam: […] nicht-kleinzelliges Bronchialkarzinom […]. (FI Mitomycin 2 medac, 03-2014)
Paclitaxel	Fortgeschrittenes nicht-kleinzelliges Bronchialkarzinom (NSCLC):

L01CD01 (generisch)	Paclitaxel ist, in Kombination mit Cisplatin, zur Behandlung des nicht-kleinzelligen Bronchialkarzinoms bei Patienten angezeigt, für die potentiell kurative chirurgische Maßnahmen und/oder eine Strahlentherapie nicht in Frage kommen. (FI Paclitaxel Hospira, 01-2014)
Vindesin L01CA03 (Eldesine®)	Kombinationschemotherapie: Lokal fortgeschrittenes oder metastasiertes nicht-kleinzelliges Bronchialkarzinom (Stadium IIIB, IV). (Lauer Taxe, 02-2014)
Vinorelbin L01CA04 (generisch)	Vinorelbin ist angezeigt zur Behandlung: des nicht kleinzelligen Bronchialkarzinoms (Stadium 3 oder 4). (FI Bendarelbin, 01-2013)
Proteinkinase-Inhibitoren:	
Afatinib L01XE13 (Giotrif®)	Giotrif® als Monotherapie wird angewendet zur Behandlung von EGFR-TKI-naiven erwachsenen Patienten mit lokal fortgeschrittenem und/oder metastasiertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit aktivierenden EGFR-Mutationen. (FI Giotrif®, 09-2013)
Erlotinib L01XE03 (Tarceva®)	Tarceva® ist zur First-Line-Behandlung bei Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit aktivierenden EGFR-Mutationen angezeigt. […] Bei Patienten mit epidermalen Wachstumsfaktor-Rezeptor-(EGFR)-IHC-negativen Tumoren konnten weder ein Überlebensvorteil noch andere klinisch relevante Wirkungen durch die Behandlung gezeigt werden. (FI Tarceva®, 12-2013)
Gefitinib L01XE02 (Iressa®)	Iressa® ist angezeigt zur Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Lungenkarzinom (NSCLC) mit aktivierenden Mutationen der EGFR-TK. (FI Iressa®, 04-2014)

Quellen: AMIS-Datenbank, Lauer-Taxe, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2014-B-092 Necitumumab

Datum: 07.10.2014

Recherche und Synopse der Evidenz zur Bestimmung der zVT:

Indikation für die Recherche:

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

Berücksichtigte Wirkstoffe/Therapien:

in: „Übersicht zVT, Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet“

Methodische Anmerkungen:

- Die Systematischen Reviews sind in alphabetischer Reihenfolge aufgeführt.
- Variationen in den Therapieregimen (z.B. Therapiedauern und zeitliche Abfolgen, Therapiezyklen, Therapiewechsel und ihre Bedingungen, …) wurden nicht berücksichtigt.
- Publikationen zur Radiochemotherapie wurden nicht eingeschlossen. Ebenso hier nicht berücksichtigt ist die Protonentherapie (vgl. G-BA, 2011**:** Protonentherapie beim Nichtkleinzelligen Lungenkarzinom (NSCLC). Abschlussbericht). Beratungsverfahren nach § 137c SGB V (Krankenhausbehandlung 13. Januar 2011. Protokollnotiz: Beratungen hierzu sollen 2015 wieder aufgenommen werden)

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation ***„fortgeschrittenes nicht-kleinzelliges Lungenkarzinom“*** durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am ***23.07.2014*** abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, TRIP. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien (z.B. NICE, SIGN). Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab **621** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden **261** Quellen eingeschlossen. Insgesamt ergab dies **44** Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

ACCP	American College of Chest Physicians
AE	Unerwünschte Ereignisse (adverse events)
AIOT	Italian Associatlon of Thoracic Oncology
ALK	Anaplastic Lymphoma Kinase
AM	Arzneimittel
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
Bev	Bevacizumab
BSC	Best supportive care
CARB	Carboplatin
CI	Konfidenzintervall
CIS	Cisplatin
CR	Complete response
CT	Chemotherapie
DAHTA	Deutsche Agentur für Health Technology Assessment
DCR	disease control rate
DGHO-Onkopedia	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie
DGP	Gesellschaft für Pneumologie und Beatmungsmedizin
DOC	Docetaxel
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for QLQ Research and Treatment of Cancer Quality of Life Questionnaire
EGFR	Epidermal Growth Factor Receptor
FACT-L	Functional assessment of cancer-lung (questionnaire)
FEM	Fixed effects model
G-BA	Gemeinsamer Bundesausschuss
GEF/GFT	Gefintinib
GEM	Gemcitabin
GoR	Grade of Recommendation
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard ratio
HRQoL	Gesundheitsbezogene Lebensqualität (health related quality of life)
ILD	interstitial lung disease
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
k.A.	keine Angabe
KRAS	Kirsten rat sarcoma viral oncogene homolog
LoE	Level of Evidence
M+	mutation positive (EGFR)
n	number
N.A	not available
NCCN	National Comprehensive Cancer Network
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NNT	Number needed to treat
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
PFS	Progressionsfreies Überleben (progression free survival)
PLAT	Platinhaltige Chemotherapeutika
PR	Partial response
PS	Performance status
QoL	Lebensqualität (quality of life)
RCT	Randomized controlled trial
REM	Random effects model
RR	Risk ratio
SACT	systemic anticancer therapy
SR	Systematisches Review
TA	Technology Assessment
TKI	Tyrosinkinsaseinhibitor
TNM	Tumor-Node-Metastasis (Klassifikationssystem)
TOI	Trial outcome index
TRIP	Turn Research into Practice Database
TTP	Time to Progression
UICC	Union for International Cancer Control
VNB	Vinorelbin
WHO	World Health Organisation
WT	Wild type

IQWiG Berichte/ G-BA Beschlüsse

G-BA, 2014: Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Afatinib [12]	**Beginn des Verfahrens:** 15.11.2013 **Veröffentlichung der Nutzenbewertung und Beginn des schriftlichen Stellungnahmeverfahrens:** 17.02.2014 **Fristende zur Abgabe einer schriftlichen Stellungnahme:** 10.03.2014 **Beschlussfassung:** 08.05.2014 **Verfahrensstatus:** Verfahren abgeschlossen **Zugelassenes Anwendungsgebiet** Giotrif® als Monotherapie wird angewendet zur Behandlung von EGFR-TKI-naiven erwachsenen Patienten mit lokal fortgeschrittenem und/oder metastasiertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit aktivierenden EGFR-Mutationen. **Zweckmäßige Vergleichstherapie:** 1) Noch nicht vorbehandelte Patienten mit ECOG-Performance-Status 0 oder 1: - Gefitinib oder Erlotinib *oder* - Cisplatin in Kombination mit einem Drittgenerationszytostatikum (Vinorelbin, Gemcitabin, Docetaxel, Paclitaxel, Pemetrexed) unter Beachtung des jeweils zugelassenen Anwendungsgebietes Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Cisplatin in Kombination mit Pemetrexed: a) Patientengruppe mit EGFR-Mutation Del19: Hinweis für einen beträchtlichen Zusatznutzen b) Patientengruppe mit EGFR-Mutation L858R: Anhaltspunkt für einen geringen Zusatznutzen c) Patientengruppe mit anderen EGFR-Mutationen: Hinweis für einen geringeren Nutzen 2) Noch nicht vorbehandelte Patienten mit ECOG-Performance-Status 2: **Zweckmäßige Vergleichstherapie:** - Gefitinib oder Erlotinib *oder* - Gemcitabin Ausmaß und Wahrscheinlichkeit des Zusatznutzens: Ein Zusatznutzen ist nicht belegt.
IQWiG, 2014: Afatinib - Nutzenbewertung gemäß § 35a SGB V [19]	Ziel der vorliegenden Nutzenbewertung ist die Bewertung des Zusatznutzens von Afatinib bei Epidermal Growth Factor Receptor-Tyrosinkinase-Inhibitor (EGFR-TKI)-naiven erwachsenen Patienten mit lokal fortgeschrittenem und / oder metastasiertem nichtkleinzelligem Lungenkarzinom (NSCLC) mit aktivierenden EGFR-Mutationen. **Mortalität** Für das Gesamtüberleben zeigte sich ein Beleg für eine

	Effektmodifikation durch die EGFR-Mutation der Patienten, sodass Aussagen nur auf Basis der entsprechenden Subgruppen-ergebnisse sinnvoll sind. Für Patienten mit einer Del19-Mutation ergab sich ein Hinweis auf einen Zusatznutzen von Afatinib im Vergleich zu Cisplatin + Pemetrexed. Für Patienten mit einer L858R-Mutation ergab die Behandlung mit Afatinib keinen statistisch signifikanten Unterschied zwischen den Behandlungsgruppen. Für Patienten mit anderen Mutationen (nicht-Del19 und nicht-L858R) zeigte sich für das Gesamtüberleben ein Hinweis auf einen geringeren Nutzen von Afatinib. **Morbidität** Die Morbidität der Patienten wurde mit den Symptomskalen der krankheitsspezifischen Fragebögen EORTC QLQ-C30 und EORTC QLQ-LC13 erhoben. Ausgewertet wurden die Rate der Patienten mit klinisch relevanter Verbesserung und die Zeit bis zur Verschlechterung der Symptome. Anhaltspunkte für einen Zusatznutzen von Afatinib zeigten sich für die Symptome Dyspnoe, Übelkeit und Erbrechen, Husten (beide Auswertungen), Fatigue und Haarausfall. Für Schmerzen in der Brust (Zeit bis zur Verschlechterung) und Schmerzen in Arm oder Schulter (Verbesserung) wurden zwar Effekte beobachtet, diese waren jedoch nicht mehr als geringfügig, sodass sich daraus kein Zusatznutzen für Afatinib ableiten ließ. Für die Symptome Diarrhö (beide Auswertungen), Mundschmerzen und Schluckbeschwerden (Zeit bis zur Verschlechterung) zeigte sich jeweils ein Anhaltspunkt für einen geringeren Nutzen. Bei den Symptomskalen Schmerzen, Schmerzen (andere als Brust oder Arm / Schulter) Schlaflosigkeit, Appetitverlust, Verstopfung, Bluthusten, sowie periphere Neuropathie zeigte sich kein statistisch signifikanter Unterschied zwischen den Behandlungsgruppen. Die beschriebenen Effekte zeigten sich aufgrund von Effektmodifikationen zum Teil nur in einzelnen Subgruppen. Dies wurde bei der abschließenden Aussage zum Zusatznutzen entsprechend berücksichtigt. **Gesundheitsbezogene Lebensqualität** Die gesundheitsbezogene Lebensqualität wurde mit den Funktionsskalen des Fragebogens EORTC QLQ-C30 erhoben. Ausgewertet wurden die Rate der Patienten mit klinisch relevanter Verbesserung und die Zeit bis zur Verschlechterung der Symptome. Für die Endpunkte körperliche Funktion, Rollenfunktion und globaler Gesundheitsstatus lagen Hinweise auf Effektmodifikationen durch den Faktor Alter, im Falle der körperlichen Funktion außerdem durch den EGFR-Mutationsstatus vor. Bezüglich der körperlichen Funktion und der Rollenfunktion ergab sich bei Patienten < 65 Jahren für beide Auswertungen jeweils ein Anhaltspunkt für einen Zusatznutzen von Afatinib. In der Rollenfunktion zeigte sich bei Patienten ≥ 65 Jahren für die Verbesserung der Funktion hingegen ein Anhaltspunkt für einen geringeren Nutzen von Afatinib. Für Patienten mit Del19-Mutation ergab sich hinsichtlich der körperlichen Funktion für beide Auswertungen ein Anhaltspunkt für einen Zusatznutzen von Afatinib; für L858R und andere Mutationen ergaben sich keine statistisch signifikanten Unterschiede zwischen den Behandlungsgruppen. Bei den Endpunkten emotionale Funktion und kognitive Funktion zeigte

sich jeweils kein statistisch signifikanter Unterschied zwischen den Behandlungsgruppen.
Für die gesundheitsbezogene Lebensqualität gemessen mit dem EQ-5D lagen keine Ergebnisse für die einzelnen Skalen des Fragebogens vor. Die VAS-Daten wurden nicht herangezogen, da zu diesen vom pU keine Subgruppenergebnisse vorgelegt wurden, obwohl sich bei der Erhebung der gesundheitsbezogenen Lebensqualität mittels EORTC QLQ-C30 relevante Effektmodifikationen zeigten.

Nebenwirkungen
Die zwischen den Studienarmen deutlich unterschiedliche Beobachtungsdauer ermöglicht auf Grundlage der vorliegenden Daten keine quantitative Bewertung eines möglichen Schadens von Afatinib gegenüber der zweckmäßigen Vergleichstherapie. Es waren ausschließlich qualitative Aussagen auf Basis der naiven Proportionen möglich. Auf dieser Grundlage ergab sich in der Gesamtschau der Nebenwirkungen weder ein Vorteil noch ein Nachteil von Afatinib gegenüber der zweckmäßigen Vergleichstherapie. Ein größerer oder geringerer Schaden von Afatinib im Vergleich zu Cisplatin + Pemetrexed ist damit insgesamt nicht belegt.

Patientengruppen, zweckmäßige Vergleichstherapien und Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Afatinib für TKI-naive erwachsene Patienten mit lokal fortgeschrittenem und / oder metastasiertem nichtkleinzelligem Lungenkarzinom mit aktivierenden EGFR-Mutationen

Therapielinie	Patientengruppe	Zweckmäßige Vergleichstherapie[a]	Subgruppe	Ausmaß und Wahrscheinlichkeit des Zusatznutzens
nicht vorbehandelte Patienten	ECOG-PS 0-1	Gefitinib oder Erlotinib oder **Cisplatin +** (Vinorelbin, Gemcitabin, Docetaxel, Paclitaxel oder **Pemetrexed**)	EGFR-Mutation Del19	Hinweis auf erheblichen Zusatznutzen
			EGFR-Mutation L858R, Alter < 65	Anhaltspunkt für geringen Zusatznutzen
			Alter ≥ 65	Zusatznutzen nicht belegt
			andere[b] EGFR-Mutationen	Hinweis auf geringeren Nutzen
	ECOG-PS 2	Gefitinib oder Erlotinib oder **Gemcitabin**	Zusatznutzen nicht belegt	
mit einer oder mehreren Chemotherapie(n) vorbehandelte Patienten		Erlotinib oder Gefitinib	Zusatznutzen nicht belegt	

a: Dargestellt ist jeweils die vom G-BA festgelegte zweckmäßige Vergleichstherapie. In den Fällen, in denen der pU aufgrund der Festlegung der zweckmäßigen Vergleichstherapie durch den G-BA aus mehreren Alternativen eine Vergleichstherapie auswählen kann, ist die entsprechende Auswahl des pU fett markiert.
b: nicht L858R, nicht Del19-Mutation
ECOG-PS: Eastern Cooperative Oncology Group Performance Status

G-BA, 2014 Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Afatinib [14]	**Anwendungsgebiet:** EGFR-TKI-naive erwachsenen Patienten mit lokal fortgeschrittenem und/oder metastasiertem nicht-kleinzelligen Lungen-karzinom (NSCLC) mit aktivierenden EGFR-Mutationen <u>2.1 Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie - Begründung auf Basis der Kriterien nach 5. Kapitel § 6 Absatz 3 VerfO:</u> zu 4. Für das vorliegende Anwendungsgebiet wird davon ausgegangen, dass sich die Patienten mit NSCLC im Krankheitsstadium III B bis IV befinden (Stadieneinteilung nach IASLC, UICC), ohne Indikation zur kurativen Resektion, Strahlenbehandlung bzw. Radiochemotherapie. Die Behandlung erfolgt symptomorientiert palliativ sowie in Abhängigkeit von Krankheitsverlauf, Allgemeinzustand, Erfolg und Verträglichkeit der Erstlinientherapie, Begleiterkrankungen, Tumorhistologie, EGFR-Status und Therapiewunsch des Patienten. Tumore mit aktivierenden Mutationen des EGFR weisen in der Regel eine nicht-plattenepitheliale Histologie auf und sind in der Regel ALK-negativ. … Die Nutzenbewertung zu Afatinib beruht auf den vorliegenden Ergebnissen der Studie LUX-Lung 3, die zum Zeitpunkt der Einreichung des Dossiers zur Nutzenbewertung noch nicht abgeschlossen war. Die im Studienprotokoll geplante finale Auswertung des Gesamtüberlebens liegt noch nicht vor. Auch im Hinblick auf die in einer Interimsanalyse beobachteten Unterschiede im Gesamtüberleben in Abhängigkeit vom EGFR-Mutationsstatus bestehen weiterhin Unsicherheiten. Auf Basis der finalen Analyse zum Gesamtüberleben ist eine höhere Aussagesicherheit für die Ergebnisse zum Gesamtüberleben zu erwarten. Auch wird erwartet, dass weitere, differenzierte Ergebnisse im Hinblick auf die heterogene Gruppe der Patienten mit anderen EGFR-Mutationen vorgelegt werden.
G-BA, 2014: Tragende Gründe zum 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) [13]	**Eckpunkte der Entscheidung** Die Firma Sun Pharmaceuticals Germany GmbH hat nachträglich zur Beschlussfassung des G-BA vom 21. November 2006 über die Umsetzung der Empfehlung der Expertengruppe Off-Label zu „Carboplatin-haltigen Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie“ die Anerkennung des bestimmungsgemäßen Gebrauchs nach § 84 AMG ihrer Carboplatin-haltigen Arzneimittel zur Anwendung bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie erklärt. Die Änderung der Arzneimittel-Richtlinie in Bezug auf die Wiedergabe der Zustimmungen pharmazeutischer Unternehmer zum Off-Label-Use Carboplatin-haltiger Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie dient daher der Veröffentlichung der zustimmenden Erklärung des betroffenen pharmazeutischen Unternehmers Sun Pharmaceuticals Germany GmbH gemäß § 35c Abs. 1 Satz 7 SGB V.

de Castria TB, 2013: Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer [5]	**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:** Overall survival, One-year survival rate, QoL, Drug toxicities (according to the National Cancer Institute Common Toxicity Criteria v2.0), Objective response rate, classified according to the Response Evaluation Criteria in Solid Tumors (RECIST) **Suchzeitraum:** 1966 bis 03/2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 10 (5017), nur RCTs **Qualitätsbewertung der Studien:** Risk of bias' tool created by The Cochrane Collaboration: Alle Studien wiesen eine mittlere bis gute Qualität auf **Heterogenitätsuntersuchungen:** durchgeführt (siehe Punkt 3.): geringe Heterogenitäten
	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 event:** Cisplatin caused more nausea or vomiting, or both (RR 0.46; 95% CI 0.32 to 0.67, I2 = 53%) and carboplatin caused more thrombocytopenia (RR 2.00; 95% CI 1.37 to 2.91, I2 = 21%) and neurotoxicity (RR 1.55; 95% CI 1.06 to 2.27, I^2 = 0%). There was no difference in the incidence of grade III/IV anaemia (RR 1.06; 95% CI 0.79 to 1.43, I2 = 20%), neutropenia (RR 0.96; 95% CI 0.85 to 1.08, I^2 = 49%), alopecia (RR 1.11; 95% CI 0.73 to 1.68, I2 = 0%) or renal toxicity (RR 0.52; 95% CI 0.19 to 1.45, I^2 =

	3%). ***QoL:*** Two trials performed a quality of life analysis; however, they used different methods of measurement so we could not perform a meta-analysis.
	4. Anmerkungen/Fazit der Autoren The initial treatment of people with advanced NSCLC is palliative, and carboplatin can be a treatment option. It has a similar effect on survival but a different toxicity profile when compared with cisplatin. Therefore, the choice of the platin compound should take into account the expected toxicity profile and the person's comorbidities. In addition, when used with either paclitaxel or gemcitabine, the drugs had an equivalent response rate. **5. Anmerkungen der FBMed** Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt

In Planung/ Durchführung:

- First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer (Protocol 2013)
- Chemotherapy for non-small cell lung cancer in the elderly population (Protocol 2013)
- Chemotherapy with cetuximab versus chemotherapy alone for chemotherapy-naive advanced non-small cell lung cancer (Protocol 2012)

Bria E et al., 2011: Outcome of advanced NSCLC patients harboring sensitizing EGFR mutations randomized to EGFR tyrosine kinase inhibitors or chemotherapy as first-line treatment: a meta-analysis [1]	**1. Fragestellung** to quantify the magnitude of benefit with upfront **EGFR TKI** in EGFR-M+ patients **2. Methodik** **Population**: previously untreated patients with advanced/metastatic NSCLC **Interventionen**: Gefitinib, erlotinib **Komparator**: chemotherapy **Endpunkt**: PFS, OS, ORR, toxicity **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: bis 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 5 (n=2 035). 4 trials gefitinib, 3 trials erlotinib **3. Ergebnisdarstellung** **Overall survival**: no statistically significant difference **PFS**: statistically significant difference in favor of EGFR TKI (HR 0.45, 95% CI 0.36–0.58, P < 0.0001, significant heterogeneity) **ORR**: statistically significant difference in favor of EGFR TKI (HR 2.08, 95% CI 1.75–2.46, P < 0.0001) **Toxicity**: Only two of the prospective RCTs reported toxicity data for the EGFR-M+ population: grades 3–4 neutropenia was significantly lower in patients receiving EGFR TKI (RR 0.012, 95% CI 0.002–0.059, P < 0.0001), without significant heterogeneity. **4. Anmerkungen/Fazit der Autoren** This meta-analysis provides a cumulative estimate of the magnitude of benefit obtained with EGFR TKI (gefitinib and erlotinib) when used as front-line treatment in advanced, EGFR-M+, NSCLC patients. In this setting, EGFR TKI provide an unusually large PFS benefit when compared with cytotoxic chemotherapy, with an absolute reduction in the risk of progression of 22%–30%. Similarly an advantage is achieved in terms of ORR, taking into consideration that patients often derive a clinically significant symptomatic benefit from tumor shrinkage. **5. Hinweise der FBMed** Dem Review von Bria et al. liegen bis auf 1 RCT die gleichen Studien zu Grunde wie bei Petrelli et al. (2012) und Gao et al. (2011). Die Ergebnisse fallen vergleichbar bei den drei Reviews aus. Es wurde keine getrennte Auswertung für Plattenepithelkarzinom

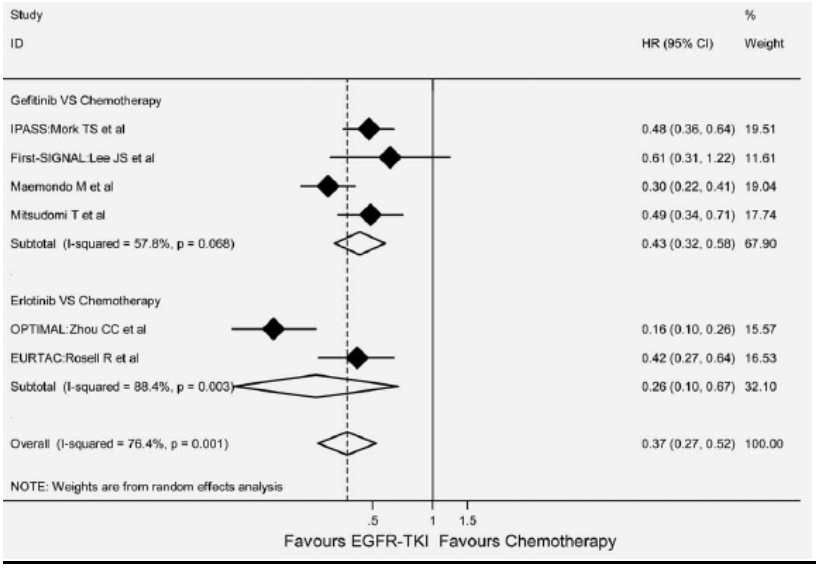
	durchgeführt. EGFR Mutationen treten gehäuft bei Adenokarzinomen auf
Chen P et al., 2011: EGFR-targeted therapies combined with chemotherapy for treating advanced non-small-cell lung cancer: a meta-analysis [4]	**1. Fragestellung** to systematically evaluate **EGFR targeted therapies** plus chemotherapy for advanced NSCLC **2. Methodik** **Population**: adults (aged 18 or older) with advanced NSCLC. Patients previously exposed to EGFR-directed agents or radiotherapy were excluded (alle first-line) **Intervention**: EGFR targeted therapies plus platinum-based doublet chemotherapy **Komparator**: platinum-based doublet chemotherapy **Endpunkt**: OS, PFS, ORR **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: up to 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 10 (n= 5936) **3. Ergebnisdarstellung** Niedermolekulare TKIs+Chemotherapie vs. Chemotherapie (basierend auf 6 Studien mit 3918 Patienten, 3 trials mit Erlotinib, 2, trials mit Gefitinib, 1 trial mit Vandetanib): **Overall survival:** Kein stat. signifikanter Unterschied zwischen den Gruppen **PFS:** stat. signifikanter Vorteil unter der Kombinationstherapie (HR=0.87, 95% KI: 0.76–0.99, p=0.030 bei gleichzeitig hoher Heterogenität I^2=68,2%) **ORR**: stat. signifikanter Vorteil unter der Kombinationstherapie (RR 1.10 95% CI, 1.00–1.20). **4. Anmerkungen/Fazit der Autoren** Small-molecule TKIs plus PBDC lead to a slightly additive efficacy compared with PBDC alone **5. Hinweise der FBMed** Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt. EGFR Mutationen treten gehäuft bei Adenokarzinomen auf
Des Guetz G et al., 2012: Comparison of the efficacy and safety of single-agent and doublet chemotherap	**1. Fragestellung** To compare efficacy (1-Year Overall Survival or OS and Overall Response Rate or ORR) and safety of **doublet vs single-agent chemotherapy** among elderly patients aged 70 years or more. To assess the comparative efficacy and side effects of regimens including platinum derivates or not. **2. Methodik** **Population**: elderly patients (70 years or older) treated for metastatic or

y in advanced non-small cell lung cancer in the elderly: A meta-analysis [7]	advanced NSCLC (stage IV and IIIB) **Intervention**: doublet-agent chemotherapy **Komparator**: single-agent chemotherapy **Endpunkt**: OS, ORR, toxicity **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: up to 2012 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 10 (n= 2605) **Qualitätsbewertung der Primärstudien:** k.A. **3. Ergebnisdarstellung** ***Overall survival:*** • Overall effect: no statistically significant difference • Platinum-based therapy (5 trials): no statistically significant difference • Non-platinum-based therapy (5 trials): no statistically significant difference • Docetaxel (5 trials): no statistically significant difference • Paclitaxel (3 trials): statistically significant difference in favor of doublet therapy (HR 0.76; 0.60–0.97; random effect model) ***Response rate:*** • Overall effect: statistically significant difference in favor of doublet therapy (HR 1.51; 1.22–1.86; p < 0.001; random effect model) • Platinum-based therapy (4 trials): no statistically significant difference • Non-platinum-based therapy (5 trials): statistically significant difference in favor of doublet therapy (HR 1.36, 95% CI: 1.11–1.67; p = 0.003; fixed effect model) • Docetaxel (5 trials): statistically significant difference in favor of doublet therapy (HR 1.40; 1.07–1.83; fixed effect model) • Paclitaxel (3 trials): statistically significant difference in favor of doublet therapy ORR (HR 2.32; 1.71–3.15; fixed effect model) ***Toxicity:*** All grade nausea/vomiting was similar for doublets and single agents, whereas neutropenia, thrombocytopenia and anemia were significantly more frequent for doublets compared with single agents (HRs 1.26, 1.15–1.39, fixed effect model; 1.75, CI 1.11–2.77 random effect model; 1.33, CI 1.17–1.52 fixed effect model respectively; all p inferior to 0.001). **4. Anmerkungen/Fazit der Autoren** Platinum-based doublets represent the gold standard of chemotherapy of NSCLC. Our MA does not firmly confirm the superiority of platinum-based doublets among elderly patients. The great majority of studies used carboplatin, which seems preferable since it is devoid of renal toxicity. The benefit to-risk ratio of doublets in advanced NSCLC might be more favorable than that of single agents, at least for doublets including platinum derivates and in elderly patients with good performance status. Doublets not including platinum derivates showed an increased toxicity without improving survival and should therefore be avoided in elderly patients with good

	performance status. **5. Hinweise durch FB Med** Keine Information über Therapielinie. 839 Patienten hatten ein Plattenepithelkarzinom. Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt.
Gao et al., 2009: A meta-analysis of platinum plus gemcitabine or vinorelbine in the treatment of advanced non-small-cell lung cancer [9]	**1. Fragestellung** To compare the **gemcitabine plus platinum** with **vinorelbine plus platinum** regimens in first-line treatment of advanced NSCLC. **2. Methodik** **Population**: Patients must be pathologically confirmed of NSCLC and in clinical III–IV stage. First-line **Intervention**: gemcitabine plus platinum **Komparator**: vinorelbine plus platinum **Endpunkt**: ORR, 1-year survival, toxicity **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: 1996 bis 2008 **Anzahl eingeschlossene Studien/Patienten**: 9 (n= 2 186) **Qualitätsbewertung der Primärstudien:** mittels Jadad. Alle mittlere Qualität, da keine Angabe über Durchführung der Randomisierung **3. Ergebnisdarstellung** **Survival (9 trials, 2186 patients):** no statistically significant difference In subgroup analysis of seven trials containing gemcitabine or vinorelbine plus cisplatin, the results showed that there was also no statistically significant difference between the two groups **Response (8 trials):** no statistically significant difference **Toxicity (9 trials):** Vinorelbine plus platinum chemotherapy led to more frequent grade 3 or 4 neutropenia, nephrotoxicity, constipation and phlebitis (OR, 0.37; 95%CI, 0.26–0.52; p < 0.00001;OR, 0.38; 95%CI, 0.25–0.57; p < 0.00001;OR, 0.50; 95%CI, 0.27–0.92; p = 0.03 and OR, 0.13; 95%CI, 0.05–0.32; p < 0.00001, respectively), while gemcitabine plus platinum chemotherapy inclined to developing more grade 3 or 4 thrombocytopenia (OR, 11.37; 95%CI, 4.56–28.38; p < 0.00001). **4. Anmerkungen/Fazit der Autoren** These meta-analyses showed that there was no significant difference between platinum plus gemcitabine or vinorelbine. And the similar results were found in sub-analysis in which gemcitabine and vinorelbine was compared when in combination with cisplatin. Gemcitabine plus platinum chemotherapy had an equal overall response rate and survival advantage in comparison with vinorelbine plus platinum

	regimens and the toxicity profiles might play an important role in the decision to choose gemcitabine-based regimens or vinorelbine-based regimens. In conclusion, the gemcitabine plus platinum regimens may be the better choice for the patients whose thrombocytopenia could be taken care, especially for the elder or the people with poor conditions, on the other hand, the vinorelbine plus platinum regimens should be more suitable for the patients who would be apt to bleed or be supersensitive to TPO or IL-11. **5. Hinweise der FBMed** Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt.
Gao H et al., 2011: Efficacy of erlotinib in patients with advanced non-small cell lung cancer: a pooled analysis of randomized trials [11]	**1. Fragestellung** to assess the efficacy and safety of **erlotinib** in patients with advanced NSCLC **2. Methodik** **Population**: advanced NSCLC **Intervention**: erlotinib alone or based combination therapy **Komparator**: other agent or based combination regimen **Endpunkt**: OS, PFS, ORR, toxicity **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: 1997 bis 2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 14 (n= 7974) **Qualitätsbewertung der Primärstudien:** mittels Jadad. Keine Angabe über Qualität der einzelnen Studien. **3. Ergebnisdarstellung** ***First-line therapy (5 trials)*** **Overall survival (4 trials)**: no statistically significant difference between erlotinib-based regimens and other regimens. Significant heterogeneity • The subgroup analysis showed a similar OS compared with placebo (HR: 1.02; 95% CI: 0.92–1.13; P=0.73) • a decreased OS compared with chemotherapy (HR: 1.39; 95% CI: 0.99–1.94; P=0.05) • and a similar OS compared with placebo as maintenance therapy (HR: 0.87; 95% CI: 0.68–1.11; P=0.22) **PFS (3 trials)**: no statistically significant difference between erlotinib-based regimens and other regimens. Significant heterogeneity • The pooled estimate showed a similar PFS when compared with placebo (HR: 0.93; 95% CI: 0.85–1.01; P=0.09) • a decreased PFS compared with chemotherapy (HR: 1.55; 95% CI: 1.24–1.93; P<0.01) • but a prolonged PFS compared with placebo as maintenance therapy (HR: 0.71; 95% CI: 0.60–0.83; P<0.01). **Response rate (9 trials, 5.404 patients):** no statistically significant difference

	between erlotinib-based regimens and other regimens. Significant heterogeneity • The subgroup analysis showed a similar ORR comparing with placebo (OR: 0.90; 95% CI: 0.74–1.09; P=0.29) • or chemotherapy (OR: 0.33; 95% CI: 0.64–17.36; P=0.15) • but an increased ORR comparing with placebo as maintenance therapy (OR: 0.47; 95% CI: 0.31–0.70; P<0.01). ***Toxicity**:* All 14 trials including 7261 patients provided results of adverse events. Reported toxicities were analyzed in only 12 trials except for the targeted drugs containing trials. Grade 3/4 diarrhea (OR: 4.87; 95% CI: 3.19–7.44; P<0.01), rash (OR: 28.94; 95% CI: 14.28–58.66; P<0.01), and anemia (OR: 1.39; 95% CI: 1.06–1.82; P=0.02) were significantly prominent in the erlotinib-based regimens. **4. Anmerkungen/Fazit der Autoren** Our findings demonstrate that erlotinib-based regimens significantly increase ORR and improve PFS as a first-line maintenance therapy or as a second/third-line therapy compared with placebo. Thus, the use of erlotinib may be a new effective therapy in treating advanced NSCLC as first-line maintenance therapy or second/third-line therapy compared with best supportive care. **5. Hinweise der FBMed** Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt.
Gao G et al, 2011: Epidermal growth factor receptor-tyrosine kinase inhibitor therapy is effective as first-line treatment of advanced non-small-cell lung cancer with mutated EGFR: a meta-analysis from six phase III randomized	**1. Fragestellung** Gefitinib and erlotinib are two similar small molecules of selective and reversible epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), which have been approved for second-line or third-line indication in previously treated advanced Non-small-cell lung cancer (NSCLC) patients. The results of comparing the **EGFR-TKI** with standard **platinum-based** doublet chemotherapy as the first-line treatment in advanced NSCLC patients with activated EGFR mutation were still controversial. Ameta-analysis was performed to derive a more precise estimation of these regimens. **2. Methodik** **Population**: patients >18 years, pathologically proven NSCLC with EGFR mutation-positive, clinical IIIB‑IV stage, previously untreated **Intervention**: EGFR-TKI, first-line **Komparator**: platinum-based doublet chemotherapy **Endpunkt**: PFS, OS, ORR **Methode**: systematic review mit RCTs **Suchzeitraum**: 1966 bis 06/2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 6 (1021) **Qualitätsbewertung der Primärstudien:** All included studies, regardless of whether they were published or not, were assessed for internal validity parameters, with particular emphasis on randomization, masking of

controlled trials [10]	patients and clinicians, concealment of allocation, documentation of dropouts and withdrawals and intent-to-treat (ITT) analysis **Heterogenitätsuntersuchung:** Ist erfolgt (I^2) **3. Ergebnisdarstellung** ***PFS:*** The patients receiving EGFR-TKI as front-line therapy had a significantly longer progression-free survival (PFS) than patients treated with chemotherapy [median PFS was 9.5 versus 5.9 months; hazard ratio (HR) 5 0.37; 95% confidence intervals (CI) 5 0.27–0.52; p < 0.001].  Meta-analysis of PFS among patients receiving EGFR-TKI or Chemotherapy. The pooled HR showed that EGFR-TKI could prolong PFS in patients with previously untreated NSCLC with mutated EGFR (p < 0.001). Subgroup-analysis and sensitivity analysis of Gefitinib vs. Chemotherapy and Erlotinib vs. Chemotherapy also revealed the same conclusion (p < 0.001 and p = 0.005, respectively). ***OS:*** The overall survival (OS) was numerically longer in the patients received EGFR-TKI than patients treated by chemotherapy, although the difference did not reach a statistical significance (median OS was 30.5 vs. 23.6 months; HR= 0.94; 95% CI 5 0.77–1.15; p= 0.57). ***ORR:*** The overall response rate (ORR) of EGFR-TKI was 66.60%, whereas the ORR of chemotherapy regimen was 30.62%, which was also a statistically significant favor for EGFR-TKI [relative risk (RR) = 5.68; 95% CI = 3.17–10.18; p < 0.001]. **4. Anmerkungen/Fazit der Autoren** Comparing with first-line chemotherapy, treatment of EGFR-TKI achieved a statistical significantly longer PFS, higher ORR and numerically longer OS in the advanced NSCLC patients harboring activated EGFR mutations, thus, it should be the first choice in the previously untreated NSCLC patients with activated EGFR mutation. **5. Hinweise der FBMed** Nebenwirkungsprofile nicht untersucht Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt. Der Großteil der eingeschlossenen

	Patienten hatte ein Adenokarzinom (siehe 1. Tabelle in der Ergebnisdarstellung). EGFR Mutationen treten gehäuft bei Adenokarzinomen auf
Goffin J et al., 2010: First-line systemic chemotherapy in the treatment of advanced non-small cell lung cancer: a systematic review [15]	**1. Fragestellung** Evidence for first-line treatment in NSCLC **2. Methodik** **Population**: patients with IIIB or IV NSCLC **Intervention**: chemotherapy (mono and doublet, platinum and non-platinum). First-line **Komparator**: k.A. **Endpunkt**: OS, QoL, ORR, toxicity **Methode**: systematic review of evidence based guidelines, systematic reviews and RCTs **Suchzeitraum**: up to 2007 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 2 evidence based guidelinies, 10 systematic reviews, 46 RCTs **Qualitätsbewertung der Primärstudien:** Overview Quality Assessment Questionnaire **3. Ergebnisdarstellung** <u>Does Doublet Chemotherapy Consisting of a Platinum Agent Plus a New Agent Improve Outcomes Compared with Doublets Using Older Agents?</u> Meta-analysis by Baggstrom et al. considered third generation, platinum-based regimens compared with second generation, platinum-based regimens. In a subgroup analysis of six trials (n = 1998) examining only doublet regimens, a 1 -year survival rate risk difference of 6% (95% confidence interval [CI], 2 to 10%) was found in favor of doublet chemotherapy regimens containing platinum and a new agent. Toxicity data were not examined. Five additional trials not included in the meta-analysis of Baggstrom et al. compared new doublet therapies with older regimens. Only one trial, comparing docetaxel plus cisplatin with vindesine plus cisplatin found superior survival with a newer agent. This trial also found superior QOL in the physical domain for the docetaxel-containing arm. <u>Does Doublet Chemotherapy Consisting of a Platinum Agent Plus a New Agent Improve Outcomes Compared with a New Single Agent Alone or to a Platinum Agent Alone?</u> A literature-based meta-analysis of randomized trials by Hotta et al. compared a doublet of platinum plus a new agent with a new agent alone in previously untreated patients with ECOG performance status of 0-2. Included were eight trials involving 2374 patients. Platinum-based doublets improved survival (HR, 0.87; 95% CI, 0.80- 0.94; p < 0.001) and produced a higher response rate (odds ratio [OR]. 2.32: 95% Cl. 1.68 -3.20) compared with new single-agent therapy. Platinum-based regimens increased myelosuppression, nephrotoxicity and nausea and vomiting but not treatment-related mortality.

	<u>Which Doublet Chemotherapy Regimen Consisting of a Platinum Agent Plus a New Agent is most Effective in Improving Clinical Outcomes?</u> Le Chevalier el al. tested the efficacy of gemcitabine plus platinum combinations versus any other platinum-based regimen and survival outcomes. A subgroup analysis of six trials (n = 2481) with a platinum-based third-generation comparator found a trend toward superior survival with gemcitabine-based regimens and improved progression-free survival (HR, 0.89: 95% CI, 0.82-0.96; p value not reported). However, the gemcitabine arms of two studies were counted more than once in the meta-analysis to allow comparison with more than one non-gemcitabine arm, and without weighting. Toxicity was not compared. The second meta-analysis, by Douillard et al. included seven trials (n = 3271) that compared docetaxel containing regimens with vinca-alkaloid regimens. The comparison for overall survival favored docetaxel (HR, 0.89; 95% CI, 0.82-0.96; p = 0.004), as did the subgroup analysis of three trials (n = 1762) comparing platinum-based docetaxel doublets (HR, 0.87; 95% CI, 0.79-0.96; p value not reported). <u>Does Doublet Chemotherapy Consisting of a Platinum Agent Plus a New Agent Improve Outcomes Compared with Non-platinum Combination Chemotherapy Including a New Agent?</u> A meta-analysis of II phase III RCTs by Pujol et al. assessed 4602 patients treated with a platinum-based new doublet or a combination of new non-platinum agents. Platinum-based regimens had a 2.9% absolute reduction in the risk of death at 1 year (OR, 0.88; 95% CI, 0.78-0.99; p = 0.044). Although the data were statistically heterogeneous, response rates appeared higher with platinum combinations. Toxicity was also more severe with platinum combinations, with significantly worse myelosuppression and gastrointestinal toxicity and trends to worse rates of febrile neutropenia and toxic death. The meta-analysis of D'Addario et al., which included 14 trials (n = 3307), did not find a survival benefit with platinum-based agents over non-platinum chemotherapy regimens (OR, 1.11; 95% CI, 0.0.96-1.28; p = 0.17). Compared with the meta-analysis by Pujol et al., the meta-analysis by D' Addaria et al. included trials conducted as early as 1983 (whereas Pujol et al. included trials published in 2002 and onward), included phase II studies, and included platinum combinations using three drugs. There is little trial overlap between the meta-analyses (ie, four trials). The meta-analysis by Pujol et al. is more representative of new agents. <u>Are New Doublets Containing Cisplatin more Effective than Doublets Containing Carboplatin?</u> The meta-analysis by Jiang et al. showed higher overall response rates with cisplatin-based regimens in two subgroup analyses; platinum plus new drugs (eight trials) and platinum plus the same drug (nine trials) (relative risk [RR], 0.87; 95% CI, 0.78-0.97; p = 0.01 and RR, 0.79; 95% CI, 0.70-0.89; p = 0.0001, respectively). However, these findings did not translate into significant improvements in 1-year survival among the regimens containing any new agent (n = 4364, seven trials) (RR, 0.98; 95% CI, 0.90-1.07; p = 0.66) or the same agent (n = 3752, six trials) (RR, 0.91; 95% CI, 0.82-1.01; p = 0.07). Two other meta-analyses limited inclusion to trials that combined the same

	non-platinum agent in the cisplatin and carboplatin arms but used different analytic methods. In a subgroup analysis of five trials (n = 2251), Hotta el al. showed that new platinum-based combination regimens containing cisplatin offered superior survival compared with carboplatin plus the same new agent (HR. 1.106: 1 95% Cl. 1.005-1.218; p = 0.039). The objective response rate to cisplatin-based regimens was significantly higher than that of carboplatin-based chemotherapy (OR. 1.38: 95% Cl. 1.14-1.67: p = 0.001), in the same subgroup of trials but using individual patient data. Is a Single New Agent Superior to Single-Agent or Doublet Therapy lncluding Older Agents? The 2007 meta-analysis by Baggstrom et al. considered four trials (n = 871) that compared new monotherapy with a second-generation, platinum-based combination regimen. The single agents used were vinorelbine, gemcitabine, and irinotecan, whereas the control arms consisted of cisplatin plus either vindesine or etoposide. Despite an apparent decrease in response rates with new single agents (absolute risk difference estimate for response -6%, 95% Cl -11 to 0%), 1-year survival did not differ (risk difference 3%, 95% Cl -3 to 10%). Which Single New Agent is Most Effective? Three RCTs, all focused on patients 70 years or older, compared new single-agent chemotherapies. The agents investigated included gemcitabine, vinorelbine, paclitaxel, and docetaxel. No study found a significant survival benefit. Kudoh et al. reported improved response rate with docetaxel over vinorelbine (22.7 versus 9.9, p = 0.019) and an improvement in the overall symptom score (but not global QOL score) in favor of docetaxel. Gridelli et al. found no differences in QOL scores. ln general, toxicity was similar between study arms, apart from alopecia. **4. Anmerkungen/Fazit der Autoren** Despite the plethora of new drug combinations studied, data continue to support the use of a platinum agent plus a new agent as the reference standard. This combination seems to have a slight survival advantage over pairs of new agents, although at a cost of additional toxicity. Among new platinum doublets, no particular combination seems to have demonstrated satisfactory or consistent superiority and any may be chosen. There does seem to be a slight response and survival advantage to cisplatin combinations over carboplatin combinations, although the toxicity profile favors the latter. Both conventional cytotoxic agents and EGFR TKl's have been added to doublet chemotherapy, but neither has improved survival. Conversely, in a population carefully chosen to optimize safety, the addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor, may improve survival. Although it is reasonable to use Bevacizumab in combination with paclitaxel and carboplatin in the trial specified population (ie, good performance status [ECOG 0-1], no brain metastasis, no dominant squamous cell histology or hemoptysis, and no history of bleeding diathesis or coagulopathy), data are presently insufficient to recommend that Bevacizumab be used in the general treatment of incurable NSCLC, based

	on the lack of a confirmatory trial, the toxicity of the treatment, and its cost. The evidence demonstrates that a new single agent improves survival compared with BSC, although not by more than a median of 2 months. When the use of a platinum agent plus a new agent is considered standard, the use of a single agent may be considered for some patients, including patients aged 70 years or older, patients who have a performance status of two, or patients for whom platinum therapy might be contraindicated. Single new agents also seem comparable in terms of survival with older combinations of a platinum and nonplatinum agent, although they also offer better outcomes when they are combined with a platinum agent. Combinations of new agents are not consistently superior to single agents, although these trials are relatively few and limited to the elderly and poor performance status population.
Grossi et al., 2009: Impact of third-generation drugs on the activity of first-line chemotherapy in advanced non-small cell lung cancer: a meta-analytical approach [16]	**1. Fragestellung** To assess the relative impact of different **third-generation drugs** on the activity of first-line chemotherapy in advanced non-small cell lung cancer by considering both response and progressive disease (PD) rates as outcome measures. **2. Methodik** **Population**: pathologically proven advanced NSCLC, no previous treatment for metastatic disease **Intervention**: two-drug regimen containing at least one third-generation agent. Platinum (defined as cisplatin or carboplatin) and nonplatinum combinations were allowed. Third-generation drugs were defined as gemcitabine, vinorelbine, docetaxel, and paclitaxel. **Komparator**: Doublet regimen free of a third generation agent **Endpunkt**: Response rate, disease progression **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: 1980 bis 2007 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 45 (n= k.A.) **Qualitätsbewertung der eingeschlossenen Studien:** k.A. **3. Ergebnisdarstellung** **Overall response** (45 trials, 11.231 patients): no statistically significant difference for gemcitabine-, docetaxel-, vinorelbine-, or paclitaxel-containing arms with the corresponding control groups **Disease progression** • Gemcitabine (23 trials, 6.681 patients): statistically significant difference in favor of gemcitabine (OR 0.86, 95% CI, 0.77– 0.95; p=0.005) • Paclitaxel (16 trials, 5.536 patients): statistically significant difference in favor of paclitaxel-free regimens (OR, 1.22; 95% CI, 1.09 –1.37; p=0.0008) • Docetaxel (12 trials, 4.642 patients): no statistically significant difference • Vinorelbine (23 trials, 6.048 patients): no statistically significant difference

	4. Anmerkungen/Fazit der Autoren Different third-generation regimens provide comparable response rates in chemotherapy-naïve patients with advanced NSCLC. Paclitaxel-based third-generation regimens are associated with a significantly higher risk for immediate progression, whereas gemcitabine-containing regimens may provide superior disease control. Given the impact of first-line chemotherapy on the natural history of the disease, the influence of disease control on treatment-free survival, and the recent evidence of a strong correlation between nonprogression and OS, these data should be considered when new studies are designed comparing standard with innovative regimens or combining them with novel compounds. In view of the results of a cisplatin versus carboplatin meta-analysis, one could object that the apparent superiority of gemcitabine over paclitaxel might be a result of the usual association of the two agents with cisplatin versus carboplatin, respectively. **5. Hinweise der FBMed** Qualität der aufgenommenen Studien nicht untersucht. Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt.
Haaland B, 2014: Meta-analysis of first-line therapies in advanced non-small-cell lung cancer harboring EGFR-activating mutations [17]	**1. Fragestellung** This meta-analysis compares gefitinib, erlotinib, afatinib, and chemotherapy. **2. Methodik** **Population:** advanced non–small-cell lung cancer **Intervention:** gefitinib, erlotinib, or afatinib; first-line therapy **Komparator:** chemotherapy **Endpunkte:** PFS, ORR,OS, AEs **Suchzeitraum:** “last five years” (nicht spezifiziert) **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 11 (Gesamtzahl k.A.; Range [42; 251]). Nur: randomized phase 3 clinical trials **Qualitätsbewertung der Studien:** k.A. **Heterogenitätsuntersuchungen:** I^2 statistics and predictive intervals (PIs) **3. Ergebnisdarstellung** **PFS** Hazard ratio meta-estimates • gefitinib versus chemotherapy 0.44 (95% confidence interval [CI] 0.31–0.63; 95% PI, 0.22–0.88), • erlotinib versus chemotherapy 0.25 (95% CI, 0.15–0.42; 95% PI, 0.11–0.55), • afatinib versus chemotherapy 0.44 (95% CI, 0.26–0.75; 95% PI, 0.20–0.98), • erlotinib versus gefitinib 0.57 (95% CI, 0.30–1.08; 95% PI, 0.24–1.36), • afatinib versus gefitinib 1.01 (95% CI, 0.53–1.92; 95% PI, 0.41–2.42),

	• erlotinib versus afatinib 0.56 (95% CI, 0.27–1.18; 95% PI, 0.22–1.46). Results for overall response rate and disease control rate were similar. **OS:** There was no evidence that gefitinib, erlotinib, or afatinib improved overall survival compared with chemotherapy **4. Anmerkungen/Fazit der Autoren** Gefitinib, erlotinib, and afatinib out-performed chemotherapy in terms of progression-free survival, overall response rate, and disease control rate. Differences among gefitinib, erlotinib, and afatinib were not statistically significant. **5. Hinweise der FBMed** Qualität der aufgenommenen Studien nicht untersucht Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt. EGFR Mutationen treten gehäuft beim Adenokarzinom auf
Jiang J et al., 2013: Paclitaxel plus platinum or gemcitabine plus platinum in first-line treatment of advanced non-small-cell lung cancer: results from 6 randomized controlled trials [21]	**1. Fragestellung** to compare the efficacy and toxicity of **paclitaxel plus platinum** (TP) with **gemcitabine plus platinum** (GP) in untreated advanced non-small-cell lung cancer by a meta-analysis. **2. Methodik** **Population**: patients must be cytologically or pathologically confirmed of NSCLC and in clinical III–IV stage, patients must be chemotherapy-naive **Intervention**: paclitaxel plus platinum (TP) **Komparator**: gemcitabine plus platinum (GP) **Endpunkt**: efficacy, toxicity **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: bis 2010 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 6 (n=2.793) **Qualitätsbewertung**: Jadad. Alle eingeschlossenen Studien hatte mittlere Qualität, da keine Studie doppelt verblindet war **3. Ergebnisdarstellung** **1-Jahres-Überleben (6 trials):** no statistically significant difference (RR = 0.99, 95% CI = 0.90–1.09, p = 0.87; I^2=6%) **Gesamtüberleben (6 trials)**: no statistically significant difference (RR = 1.06, 95% CI = 1.00–1.13, p = 0.07; I^2=16%) **Response (6 trials)**: no statistically significant difference (RR = 0.99, 95 % CI = 0.88–1.13, p = 0.92, I^2=9%) **Toxicity:** Grade 3–4 nausea or vomiting was less frequent in the TP than the GP group (10.5 vs. 17.4 %, RR = 0.53, 95 % CI = 0.35–0.78, p = 0.002). Grade 3–4 sensory neuropathy and fatigue were comparable between the TP and GP arms. Grade 3–4 anemia (8.8 vs. 22.4 %, RR = 0.37, 95 % CI =

	0.30–0.45, p<0.00001) and thrombocytopenia (8.8 vs. 47.8 %, RR = 0.20, 95 % CI = 0.14–0.27, p<0.00001) were less frequent in the TP than the GP group. **4. Anmerkungen/Fazit der Autoren** As there were no double-blind trials, the highest quality scores of the 6 trials according to Jadad's method were 3, and all 6 trials scored 3 Paclitaxel plus platinum had similar efficacy and less toxicity compared with gemcitabine plus platinum in first-line treatment of advanced non-small-cell lung cancer. **5. Hinweise der FBMed** Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt.
Jiang J et al., 2013: Non-platinum doublets were as effective as platinum-based doublets for chemotherapy-naive advanced non-small-cell lung cancer in the era of third-generation agents [20]	**1. Fragestellung** The aim was to compare the efficacy between doublets of third-generation agents (non-platinum) and doublets of platinum plus a third-generation agent (platinum-based) for chemotherapy-naıve advanced non-smallcell lung cancer (NSCLC). **2. Methodik** **Population:** cytologically or pathologically confirmed of NSCLC and in clinical III–IV stage and chemotherapy-naıve **Intervention:** non-platinum doublets (two-third generation agents combination) **Komparator:** platinum-based doublets (cisplatin or carboplatin combined with a thirdgeneration agent) **Endpunkte:** Primär: OS, sekundär; PFS, RR; toxicity **Suchzeitraum:** 2000 bis 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 16 (Gesamtzahl k.A.) **Qualitätsbewertung der Studien:** assessed with the components recommended by the Cochrane Collaboration **Heterogenitätsuntersuchungen:** Cochran Q statistic Kein Hinweis auf Publikationsbias (Begg's funnel plot) **3. Ergebnisdarstellung** ***OS:*** pooled HR = 1.03, 95 % CI = 0.98–1.08, p = 0.29 ***RR:*** Pooled RR = 0.99, 95 % CI = 0.90–1.08, p = 0.24 ***PFS:*** pooled HR : platinum-based doublets might have an advantage in PFS compared with non-platinum doublets (HR = 1.06, 95 % CI = 1.01–1.12, p = 0.03). ***Toxicity*** • The Grade 3–4 nausea or vomiting, anemia, neutropenia,

	thrombocytopenia, alopecia, and hearing loss of **vinorelbine plus gemcitabine** may be less frequent than platinum-based doublets, while grade 3–4 constipation of vinorelbine plus gemcitabine may be more frequent than platinum-based doublets. • The grade 3–4 toxicity of **vinorelbine plus paclitaxel** may be comparable with platinum-based doublets excepted for neutropenia and allergy, which might be more frequent in **vinorelbine plus paclitaxel** group. • **Gemcitabine plus paclitaxel** was more tolerable than platinum-based doublets on the whole according to anemia, neutropenia, thrombocytopenia except grade 3–4 peripheral neuropathy and alopecia. • **Gemcitabine plus carboplatin** caused especially more grade 3–4 anemia, neutropenia, thrombocytopenia and hemorrhage than gemcitabine plus paclitaxel. • **Gemcitabine plus docetaxel** caused less nausea or vomiting, diarrhea, anemia and neutropenia, but more lung toxicity than platinum-based doublets. • **Vinorelbine plus cisplatin** may cause more grade 3–4 peripheral neuropathy than gemcitabine plus docetaxel. **4. Anmerkungen/Fazit der Autoren** Non-platinum doublets were as effective as platinum-based doublets with different toxicity profile for chemotherapy-naı¨ve advanced NSCLC in the era of third generation agents. **5. Hinweise der FBMed** Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt.
Lee JK et al., 2014: Epidermal growth factor receptor tyrosine kinase inhibitors vs conventional chemotherapy in non-small cell lung cancer harboring wild-type epidermal growth factor receptor: a meta-analysis [24]	**1. Fragestellung** Current guidelines recommend both epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and cytotoxic chemotherapy drugs as standard treatment options for patients with wild-type (WT) EGFR who were previously treated for non–small cell lung cancer (NSCLC). However, it is not clear that EGFR TKIs are as efficacious as chemotherapy in patients with WT EGFR. **2. Methodik** **Population:** Patients with advanced NSCLC, defined as inoperable locally advanced (stage IIIB) or metastatic or recurrent disease (stage IV) **Intervention:** first-generation EGFR TKI (erlotinib and gefitinib) **Komparator:** chemotherapy **Endpunkte:** OS, OR, PFS **Suchzeitraum:** Bis 12/2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 11 (1605) **Qualitätsbewertung der Studien:** Risk of bias assessment (supplement). Alle Studien waren open-label. Randomisierung und Verblindung bei den meisten Studien adäquat **Heterogenitätsuntersuchungen:** I^2

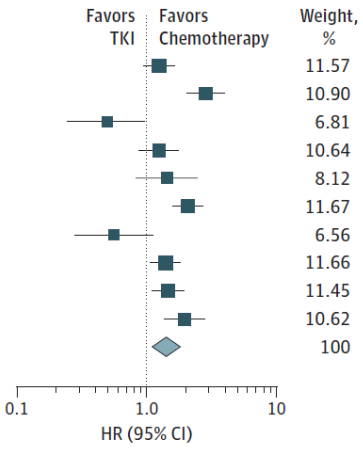
3. Ergebnisdarstellung

PFS

- significantly longer PFS with chemotherapy than with TKI in the patients with WT EGFR (HR, 1.41; 95% CI, 1.10-1.81);
- a significant statistical heterogeneity was noted in this analysis (I^2 = 79.1%)
- Für PFS in der Subgruppenanalyse kein statistisch signifikanter Unterschied für TKI vs. Placebo in der Erstlinie

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

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



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

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

OS: No statistically significant difference. HR for TKI (1.08; 95% CI, 0.96-1.22)

4. Anmerkungen/Fazit der Autoren

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

Limitierungen:

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

	5. Hinweise der FBMed Der Großteil der Studien hatten Patienten in der Zweit- oder Drittlinie eingeschlossen. Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt. EGFR Mutationen treten gehäuft beim Adenokarzinom auf
Ku GY et al., 2011: Gefitinib vs. chemotherapy as first-line therapy in advanced non-small cell lung cancer: meta-analysis of phase III trials [22]	**1. Fragestellung** To perform a meta-analysis of the most updated results of these studies to better quantify the toxicities and clinical benefits of gefitinib over chemotherapy. **2. Methodik** **Population:** advanced (stage IIIB/IV) NSCLC **Intervention:** gefitinib **Komparator:** chemotherapy **Endpunkte:** PFS, OS, ORR, toxicity **Suchzeitraum:** k.A. **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 5 (1617) **Qualitätsbewertung der Studien:** k.A. **Heterogenitätsuntersuchungen:** k.A. **3. Ergebnisdarstellung** ***PFS:*** While median PFS was not different compared to the chemotherapy group (5.7 vs. 5.8 months), the 12-month PFS rate was 25% vs. 7% respectively (hazard ratio for progression 0.74, $p < 0.001$). ***OS:*** No statistically significant difference. Hazard ratio 1.64, $p = 0.211$ ***QoL:*** QoL was analyzed in both the IPASS and first-SIGNAL studies. In the IPASS study, QoL was analyzed using the FACT-L, TOI and LCS instruments. The gefitinib group had better QoL and nominal symptom reduction compared to the chemotherapy group, with odds ratios (p values) for the respective measures of 1.34 (0.01), 1.78 (<0.001) and 1.13 (0.30). ***Toxicity:*** Representative toxicities include fatigue, which was significantly more common in the chemotherapy arms. In the North-East Japan, West Japan and IPASS studies, the cumulative incidence of fatigue of any grade in the gefitinib arms was 18% (148 of 808) vs. 46% (363 of 790) in the chemotherapy arms (odds ratio 0.24, $p < 10−15$). Nausea was also more common in the chemotherapy arms of the North-East Japan and IPASS trials, where 51% (344 of 677) of the patients experienced any grade nausea vs. 17% (116 of 694) in the gefitinib arms (odds ratio 0.19, $p < 10^{-15}$). Patients receiving chemotherapy also experienced significantly more myelosuppression. As an example, the incidence of all-grade and grade ≥ 3 neutropenia was much less common in the gefitinib arms (7% vs. 84% and 3% vs. 69%, respectively). Across the studies, the odds ratio for grade ≥ 3 neutropenia for gefitinib vs. chemotherapy was 0.01 ($p < 10^{-15}$). **4. Anmerkungen/Fazit der Autoren** The results of our metaanalysis confirm the results of the individual trials:

	initial gefitinib is associated with a higher ORR and PFS as well as superior toxicity and QoL profiles as compared to chemotherapy. These benefits are seen in Asian patients who are selected by clinicopathologic characteristics associated with the presence of an EGFR mutation but are even more pronounced in patients with known EGFR mutations. In these studies, there was no OS benefit for upfront gefitinib over chemotherapy, quite possibly because most patients treated initially with chemotherapy received and benefited from an EGFR TKI at progression. **5. Hinweise der FBMed** Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt.
Lee CK et al., 2013: Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis [23]	**1. Fragestellung** We examined the impact of **EGFR–tyrosine kinase inhibitors** (TKIs) on progression-free survival (PFS) and overall survival (OS) in advanced NSCLC patients with and without EGFR mutations. **2. Methodik** **Population**: advanced NSCLC patients with and without EGFR mutations **Intervention**: of EGFR-TKIs monotherapy, EGFR-TKIs and chemotherapy **Komparator**: chemotherapy, placebo, best supportive care **Endpunkt**: PFS, OS **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: 2004 bis 2012 **Qualitätsbewertung der Studien:** k.A. **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 23 (n=14 570) **3. Ergebnisdarstellung** <u>First-line therapy (13 trials)</u> **Overall survival:** no statistically significant difference between EGFR-TKI-based therapy and other therapy. Neither for EGFRmut+ patients (11 trials) nor for EGFRmut- patients (6 trials). **PFS:** • EGFRmut+ patients (12 trials): statistically significant difference in favor of EGFR-TKI-based therapy (HR = 0.43; 95% CI = 0.38 to 0.49; p < 0.001) • EGFRmut- patients (7 trials): no statistically significant difference • Sensitivity analysis (EGFR-TKIs combined with chemotherapy vs. chemotherapy alone): statistically significant difference in favor of EGFR-TKI-based therapy (EGFRmut+: HR = 0.54, 95% CI = 0.30 to 0.95, p = 0.04; EGFRmut–: HR = 0.82, 95% CI = 0.68 to 0.98, p = 0.03 • Sensitivity analysis (EGFR-TKIs monotherapy vs. chemotherapy): statistically significant difference in favor of EGFR-TKI-based therapy in EGFRmut+ subgroup (HR = 0.42; 95% CI = 0.37 to 0.48; p < 0.001). Increased risk in the EGFRmut- subgroup (HR = 1.56; 95% CI = 1.36 to

	1.80; p < 0.001) **4. Anmerkungen/Fazit der Autoren** Treatment with EGFR-TKIs statistically significantly delays disease progression in EGFRmut+ patients but has no demonstrable impact on OS. These findings support assessment of EGFR mutation status before initiation of EGFR-TKIs treatment and indicate that EGFR-TKIs should be considered as front-line therapy in EGFRmut+ patients with advanced NSCLC. **5. Hinweise der FBMed** Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt. EGFR Mutationen treten gehäuft beim Adenokarzinom auf
Li C et al., 2010: Gemcitabine plus paclitaxel versus carboplatin plus either gemcitabine or paclitaxel in advanced non-small-cell lung cancer: a literature-based meta-analysis [25]	**1. Fragestellung** To compare the activity, efficacy, and toxicity of **gemcitabine plus paclitaxel** versus **carboplatin plus either gemcitabine or paclitaxel** in patients with untreated advanced NSCLC. **2. Methodik** **Population:** Patients were confirmed pathologically to have NSCLC and to be in clinical stage III or IV. **Intervention**: gemcitabine plus paclitaxel **Komparator**: carboplatin plus either gemcitabine or paclitaxel **Endpunkt**: survival, ORR, toxicity **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: up to 2009 **Qualitätsbewertung der Studien:** k.A. **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 4 (n=2.186) **3. Ergebnisdarstellung** **Survival**: no statistically significant difference **ORR**: statistically significant difference in favor of gemcitabine plus paclitaxel (OR = 1.20; 95% CI = 1.02–1.42; p = 0.03, I^2=0%) **Toxicity**: Grade 3–4 nausea and vomiting are similar, while significant decreases in grade 3–4 neutropenia, anemia, and thrombocytopenia were observed with the gemcitabine and paclitaxel combination **4. Anmerkungen/Fazit der Autoren** We conclude that adding carboplatin to either gemcitabine or paclitaxel would increase the prevalence of hematologic side effects while not improving on the treatment response of gemcitabine plus paclitaxel. **5. Hinweise durch FB Med**

	Keine Hinweise zur Qualitätsbewertung der eingeschlossenen Studien, keine Angaben zu Interessenskonflikten. Keine Information über Therapielinie in den eingeschlossenen Studien. Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt.
Liang W et al., 2014: Network meta-analysis of erlotinib, gefitinib, afatinib and icotinib in patients with advanced non-small-cell lung cancer harboring EGFR mutations [26]	**1. Fragestellung** Several EGFR-tyrosine kinase inhibitors (EGFR-TKIs) including erlotinib, gefitinib, afatinib and icotinib are currently available as treatment for patients with advanced non-small-cell lung cancer (NSCLC) who harbor EGFR mutations. However, no head to head trials between these TKIs in mutated populations have been reported, which provides room for indirect and integrated comparisons. Thus, in the current study, we sought to provide some useful information about comparison between these four agents through integrating and indirect methods, expecting this message will be helpful for physicians and patients in decision-making. **2. Methodik** **a)** pair-wise meta-analyses with a randomeffects model to synthesize studies comparing the same pair of treatments **b)** random-effects network within a Bayesian framework using Markov chain Monte Carlo methods (translated binary outcomes of survival analysis and binary outcomes of ORR within studies and specified the relations among the ORs across studies making different comparisons as previously reported **Population:** patients with advanced NSCLC that presents activating EGFR mutations advanced NSCLC: defined as stage III or IV disease that was not feasible to surgical treatment or radiotherapy **Intervention:** one TKI (including erlotinib, gefitinib, afatinib and icotinib), first-line or second-line **Komparator:** • one TKI (including erlotinib, gefitinib, afatinib and icotinib) or • standard chemotherapy (defined as platinum-based third generation doublets for first-line treatments or pemetrxed/ doctaxel for second-line treatments). Since the dominant histological type of patients with EGFR mutation was nonsquamous carcinoma in which pemetrexed were proved to yield superior efficacy compared with other third-generation chemotherapy agents, we also included studies that compared pemetrexed-based regimen with pemetrexed-free regimen in order to optimize the network. **Endpunkte:** ORR, OS, PFS **Suchzeitraum:** Bis 03/2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 12 (1821) Nur phase III RCTs **Qualitätsbewertung der Studien:** QUORUM and the Cochrane Collaboration guidelines. Ergebnis der Qualitätsbewertung nicht berichtet **Heterogenitätsuntersuchungen:** inconsistency statistic (I^2) **3. Ergebnisdarstellung** 12 phase III RCTs that compared elotinib, gefitinib, icotinib, afatinib or chemotherapy in chemo-naıve or previously treated advanced NSCLC

patients. Davon 8 RCTs mit den AM als first-line Therapie

Pooled weighted outcomes

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

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

- pooled ORR and PFS of EGFR-TKIs were significant higher than standard chemotherapy
- TKIs yielded higher 1-year PFS than standard chemotherapy
- No difference in 1- and 2-year OS

Network Meta-Analyses for Efficacy and Toxicities

erlotinib, gefitinib, icotinib and afatinib shared equivalent efficacy in all outcome measures by showing no significant differences in ORs while all TKIs were better than chemotherapy (assessment of icotinib was not available neither in comparison of OS data nor in network 2). Coherence between direct and indirect comparisons based on networks was confirmed.

We selected rash and diarrhea, which are the most common TKIspecific toxicities, as the representative of treatment-related toxicities. Patients who received afatinib experienced more severe diarrhea compared with the other three TKIs. In terms of rash, afatinib is significant severer than gefitinib while no other significant difference was observed among the rest comparisons.

Afatinib and erlotinib had significant more grade 3 to 4 diarrhea or diarrhea compare with gefitinib and icotinib.

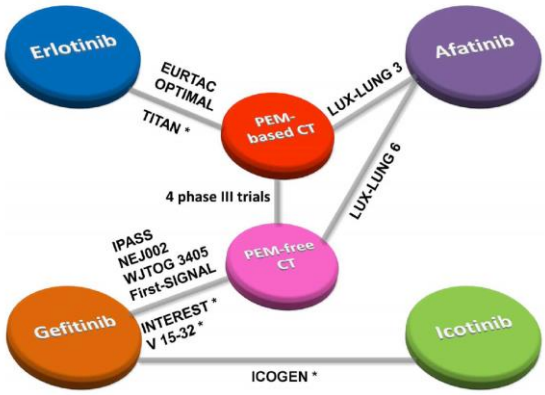


Figure 3. Network established for multiple treatment comparisons. Solid lines between drugs represented the existence of direct comparisons. PEM, pemetrexed; * Second-line studies

According to network 2 (1st-line studies only), the cumulative probabilities of being the most efficacious treatments were (ORR, 1-year PFS, 1-year OS, 2-year OS):

	• erlotinib (61%, 61%, 15%, 19%), • gefitinib (2%, 10%, 7%, 19%), • afatinib (36%, 29%, 30%, 27%), • whereas outcomes of icotinib were not assessable **4. Anmerkungen/Fazit der Autoren** In conclusion, this network meta-analysis indicated that erlotinib, gefitinib, afatinib and icotinib shared equivalent efficacy but presented different efficacy-toxicity pattern for EGFR-mutated patients according to current evidences. **Limitations:** • OS data in mutant population of ICOGEN were not available hence we could not evaluate the survival benefits of icotinib • comparisons in terms of OS were onfounded by subsequent treatments • performance of icotinib in first-line setting was not available could not assess some important molecular markers including T790M status in the population which might have effects on the efficacy of TKIs and cause bias • established networks lacked sufficient direct comparisons between TKIs **5. Hinweise der FBMed** Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt. Die meisten Patienten hatten kein Plattenepithelkarzinom.
Mörth C et al., 2014: 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 [27]	**1. Fragestellung** The purpose of this study was to compare the efficacy and tolerability of first-line treatment with combination versus single agent chemotherapy in patients with advanced non-small cell lung cancer (NSCLC) and performance status (PS) 2. **2. Methodik** **Population:** advanced NCSLC mit PS 2 **Intervention:** combination chemotherapy **Komparator:** single agent chemotherapy **Endpunkte:** Primär: OS; sekundär: PFS, ORR **Suchzeitraum:** Bis 07/213 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 12 (1114) **Qualitätsbewertung der Studien:** Cochrane's risk of bias tool. Adäquate Randomisierung bei allen eingeschlossenen Studien. Keine Studie war doppelt verblindet durchgeführt **Heterogenitätsuntersuchungen:** Durchgeführt (I^2) **3. Ergebnisdarstellung** ***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 dedicatedto PS 2 and HR: 0.83, 95% CI: 0.72–0.96 for studies with subgroupanalysis, p-value for subgroup difference = 0.30)
- improvement inOS was more pronounced in trials with platinum-based combina-tion versus single-agent therapy (HR: 0.71, 95% CI: 0.61–0.81) whileno difference was observed in studies with non-platinum basedcombination (HR: 0.96, 95% CI: 0.80–1.15) (p-value for subgroupdifference = 0.009) (Fig. 2)
- no statistical heterogeneitywas observed

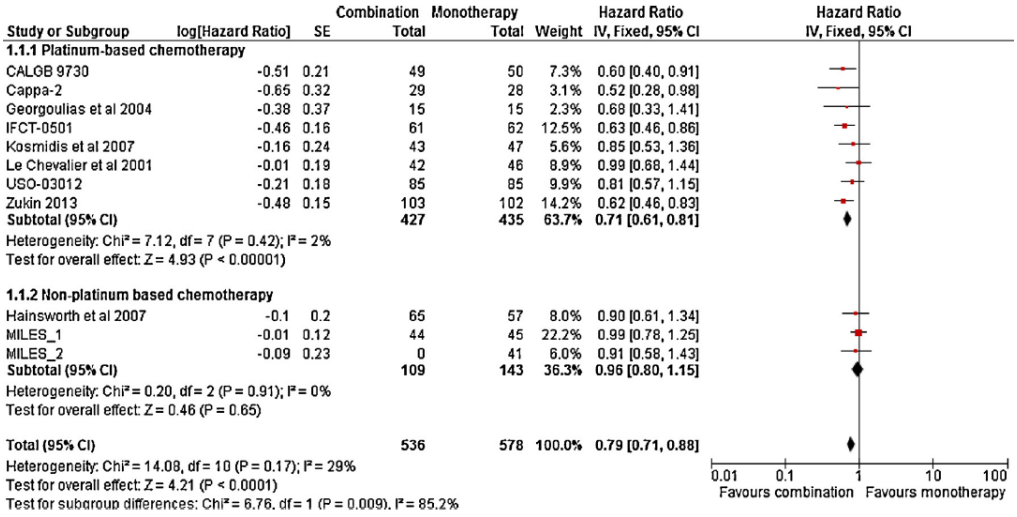


Fig. 2. Forest plot for overall survival (with subgroup analysis based on the administration of platinum-based or non-platinum based chemotherapy in combination arms).The size of the squares indicates the weight of the study. Error bars represent 95% confidence intervals (CIs). The diamond indicates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

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

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

PFS *(5 Studien, 522 Patienten):* combination chemotherapy resulted in statisticallysignificant 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 chemother-apy 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

	couldnot perform meta-analysis on the incidence of other toxicities. **4. Anmerkungen/Fazit der Autoren** This meta-analysis provides evidence supporting the use of combination chemotherapy in patients with NSCLC and PS 2. However, the patients should be informed about the higher risk for toxicity with the combination chemotherapy and the final treatment strategy should be individualized **Limits:** unable to investigate whether the survival benefit with combination chemotherapy is similar on different histological subtypesof lung cancer **5. Hinweise der FBMed** Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt.
NICE, 2013: Clinical effectiveness and cost-effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: a systematic review and economic evaluation [2]	**1. Fragestellung** To evaluate the clinical effectiveness and cost-effectiveness of first-line chemotherapy currently licensed in Europe and recommended by NICE, for adult patients with locally advanced or metastatic nonsmall cell lung cancer (NSCLC). 2. **Methodik** **Population:** locally advanced or metastatic NSCLC **Intervention:** chemotherapy drug regimens that are currently licensed in Europe and are recommended by NICE in a monotherapy or in combination, first line **Komparator:** platinum (PLAT) drug **Endpunkte:** Overall survival (OS), OS at 1 and 2 years, progression-free survival (PFS), time to progression (TTP), tumour overall response rate, quality of life (QoL) and adverse events (AEs). **Suchzeitraum:** 1990 bis 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 23 (11 428); nur RCTs und SRs **3. Ergebnisdarstellung** ***OS.*** Among NSCLC patients with squamous disease, there were no statistically significant differences between any of the four chemotherapy regimens (DOC + PLAT, GEM + PLAT, PAX + PLAT, VNB + PLAT) in terms of increasing OS. However, both the direct and indirect evidence suggests a potential non-statistically significant advantage in terms of OS for GEM + PLAT [direct meta-analysis 1: hazard ratio (HR) = 1.08; 95% confidence interval (CI) 0.98 to 1.20] and for DOC + PLAT (direct meta-analysis 1: HR = 0.89; 95% CI 0.78 to 1.00; mixed-treatment comparison 1, HR = 0.92; 95% CI 0.81 to 1.03) compared with VNB + PLAT. Analyses of 1- and 2-year survival support this conclusion. For patients with non-squamous NSCLC there is borderline statistically significant evidence to

	suggest that PEM + PLAT increases OS compared with GEM + PLAT (direct meta-analysis 1, HR = 0.85; 95% CI 0.73 to 1.00). However, there is no statistically significant evidence to suggest that PEM + PLAT compared with GEM + PLAT increases PFS (mixed-treatment comparison 1, HR = 0.85; 95% CI 0.74 to 0.98). Among patients with EGFR M+ status, OS was not statistically significantly different in those treated with GEF and those receiving PAX + PLAT or in those treated with GEF compared with those treatedwith DOC + PLAT. ***PFS.*** There was a statistically significant improvement in PFS among those patients treated with GEF compared with those treated with DOC + PLAT or PAX + PLAT. However, there was significant quantitative heterogeneity between the two trials comparing GEF with PAX + PLAT, which requires further exploration. It remains unknown whether or not the clinical effectiveness of PEM + PLAT is superior to that of GEF monotherapy for patients with non-squamous disease. The relative clinical effectiveness of PEM + PLAT in patients who are EGFR M+ is unknown. ***QoL*** (insgesamt 12 Studien). Seven trials reported no significant difference in QoL and four trials reported some significant differences between treatment groups. A lack of reporting of QoL data is a feature of the great majority of trials assessing outcomes of treatment for patients with NSCLC. This, despite its relevance to patients and clinicians, is a major shortcoming of lung cancer research. Measuring QoL outcomes in patients with advanced NSCLC is difficult mainly because of the severity of symptoms, the side effects of chemotherapy and early deaths associated with NSCLC. However, the British Thoracic Oncology Group Trial 2 has shown that it is feasible to collect QoL data in patients with performance status (PS) 0–2, stage IIIB/IV NSCLC disease within a clinical trial setting. A number of instruments/tools that measure QoL were employed in the included trials. The EORTC QLQ-C30 and the lung cancer-specific module QLQ-LC13 were used in five trials, the LCSS by three trials, and the FACT-L32 questionnaire by three trials. Four reported some significant differences between treatment groups for QoL; however, in one of these trials,3 results after two cycles of chemotherapy favoured the PAX + CARB arm over the VNB + CIS arm, and results after four cycles favoured the VNB + CIS arm. In one trial, significantly more patients in the GEF group than in the PAX + CARB group had a clinically relevant improvement in QoL, as assessed by scores on the FACT-L questionnaire (odds ratio = 1.34; 95% CI 1.06 to 1.69; $p = 0.01$) and by scores on the Trial Outcome Index (TOI) (which is the sum of the physical well-being, functional well-being and lung cancer subscale scores of FACT-L; odds ratio = 1.78; 95% CI 1.40 to 2.26; $p < 0.001$). ***AEs.*** Across all the chemotherapy arms of the included trials, the most common AEs were neutropenia, anaemia and leucopenia. Rates of haematological AEs were similar for all the chemotherapy drugs with the exception of GEF, which appears to be associated with a significantly lower evere AE rate than some of the other drugs. The trials often varied in the way that AEs were defined, measured and reported.

	<u>Patienten mit Plattenepithelkarzinom</u> The PLAT-based doublets of DOC, GEM, PAX and VNB had relatively more data points for all outcomes than the newer PEM + PLAT regimen and GEF monotherapy. In general, there was consistency between the results of the direct meta-analyses and the mixed-treatment comparison analyses, and very good consistency across individual trials in the within-group comparisons. ***OS:*** The evidence related to outcomes for patients with squamous disease demonstrates that there are no statistically significant differences in OS between any of the four third-generation chemotherapy treatments (DOC + PLAT, GEM + PLAT, PAX + PLAT or VNB + PLAT). However, both the direct and indirect evidence suggest a potential advantage in terms of OS for GEM + PLAT (direct meta-analysis 1, HR = 1.08; 95% CI 0.98 to 1.20) and for DOC + PLAT (direct meta-analysis 1, HR = 0.89; 95% CI 0.78 to 1.00; mixed treatment comparison 1, HR = 0.92; 95% CI 0.81 to 1.03) compared with VNB + PLAT, although this advantage is not statistically significant. Analyses of 1- and 2-year survival support this conclusion. **PFS:** Only seven trials were included in the PFS analysis and the majority of these trials used slightly different definitions of PFS. There was no evidence of any significant difference in PFS for GEM + PLAT compared with VNB + PLAT. There was insufficient evidence to conclude whether or not there were any statistically significant differences in PFS between the other third-generation chemotherapy comparators. **<u>EGFR-positive Patienten</u>** ***OS:*** For patients with EGFR M+ status, there is no statistically significant difference in OS between GEF compared with PAX + PLAT and between GEF compared with DOC + PLAT. There is evidence of a statistically significant improvement in PFS with GEF compared with DOC + PLAT. ***PFS:*** Although there is also evidence of a statistically significant improvement in PFS with GEF compared with PAX + PLAT the significant heterogeneity between trials means the PFS results should be viewed with caution. **4. Anmerkungen/ Fazit der Autoren** The mix of patient population is now expected to be taken into consideration at the time of trial design as demonstrated in the PEM and GEF trials. Making comparisons across the six available first-line chemotherapy treatments is therefore limited by the comparability of the treatment populations in the published trials. • there were few trials with fully reported methods and the definitions of the health outcomes used often differed between trials • very few trials reported QoL data; AEs from the different trials were difficult to compare; QoL: variety of instruments/tools • CARB and CIS were treated as being similarly effective in the clinical analyses; and owing to the large volumes of data available for patients with lung cancer, • the methods employed in the review do not always match the methods stated in the original protocol

NIHR, 2011: Clinical and cost effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: a systematic review and economic evaluation. Health, Technology Assessment [18]	**1. Fragestellung** To evaluate the clinical effectiveness and cost-effectiveness of first-line **chemotherapy** currently licensed in Europe and recommended by NICE, for adult patients with locally advanced or metastatic nonsmall cell lung cancer (NSCLC). **2. Methodik** **Population**: Chemotherapy-naive adult patients with locally advanced or metastatic NSCLC **Intervention**: Any first-line chemotherapy treatment currently licensed in Europe and approved by NICE including: • PLAT-based chemotherapy (CARB or CIS) in combination with DOC, GEM, PAX or VNB • PEM + CIS • Single-agent therapy – GEF **Komparator**: Any first-line chemotherapy treatment currently licensed in Europe and approved by NICE for the first-line treatment of patients with locally advanced and metastatic NSCLC **Endpunkt**: OS, PFS, TTP, ORR, AE, HRQoL **Suchzeitraum**: 2000-2009 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 23 RCTs (n=11.428) **3. Ergebnisdarstellung** <u>Non-small cell lung cancer patients with squamous disease (18 RCTs, 7.382 patients):</u> **Overall survival:** Kein statistisch signifikanter Unterschied zwischen: • Gemcitabine plus platinum compared with paclitaxel plus platinum • Gemcitabine plus platinum compared with docetaxel plus platinum • Vinorelbine plus platinum compared with paclitaxel plus platinum • Vinorelbine plus platinum compared with docetaxel plus platinum • Paclitaxel plus platinum compared with docetaxel plus platinum **PFS:** statistisch signifikanter Zusammenhang zwischen: • Vinorelbine plus platinum compared with paclitaxel plus platinum (1 RCT, 140 patients): statistically significant suggesting an advantage for VNB + CIS (HR = 1.52; 95% CI 1.06 to 2.17) kein statistisch signifikanter Zusammenhang zwischen: • Gemcitabine plus platinum compared with vinorelbine plus platinum • Gemcitabine plus platinum compared with paclitaxel plus platinum • Gemcitabine plus platinum compared with docetaxel plus platinum • Vinorelbine plus platinum compared with docetaxel plus platinum <u>Epidermal growth factor receptor mutation-positive population.</u>

	Overall survival: Kein statistisch signifikanter Unterschied zwischen: • Paclitaxel plus platinum compared with gefitinib • Docetaxel plus platinum compared with gefitinib • Paclitaxel plus platinum compared with docetaxel plus platinum **PFS:** statistisch signifikanter Zusammenhang zwischen: • Paclitaxel plus platinum compared with gefitinib (2 RCTs, 491 patients) (HR = 0.38; 95% CI 0.24 to 0.60, I^2=78,8%) • Docetaxel plus platinum compared with gefitinib (1 RCT, HR = 0.49; 95% CI 0.33 to 0.73) kein statistisch signifikanter Zusammenhang zwischen: • Paclitaxel plus platinum compared with docetaxel plus platinum **4. Anmerkungen/Fazit der Autoren** Overall, the quality of the included RCTs was poorer than expected – there were few trials with fully reported methods and the definitions of the health outcomes used often differed between trials. In addition, it is generally agreed that RCTs typically include patients who are generally fitter and younger than patients receiving treatment in routine clinical practice and that outcomes from RCTs are not always of the same magnitude as those gained from routine care. Caution is therefore required when interpreting and comparing the results of these trials, in particular the results generated through meta-analysis and mixed-treatment comparison. The evidence related to outcomes for patients with squamous disease demonstrates that there are no statistically significant differences in OS between any of the four third-generation chemotherapy treatments (DOC + PLAT, GEM + PLAT, PAX + PLAT or VNB + PLAT). However, both the direct and indirect evidence suggest a potential advantage in terms of OS for GEM + PLAT (direct meta-analysis 1, HR = 1.08; 95% CI 0.98 to 1.20) and for DOC + PLAT (direct meta-analysis 1, HR = 0.89; 95% CI 0.78 to 1.00; mixedtreatment comparison 1, HR = 0.92; 95% CI 0.81 to 1.03) compared with VNB + PLAT, although this advantage is not statistically significant. Analyses of 1- and 2-year survival support this conclusion.
Ouyang PY et al., 2013: Combination of EGFR-TKIs and Chemotherapy as First-Line Therapy for Advanced NSCLC: A Meta-Analysis [28]	**1. Fragestellung** Controversy continues regarding the role of the addition of EGFR–TKIs in patients receiving chemotherapy. Therefore, we conducted this meta-analysis to comprehensively estimate the treatment effect of the combined regimen on PFS and overall survival (OS) based on characteristics of patients. **2. Methodik** **Population:** chemotherapy-naıve patients with advanced NSCLC **Intervention:** Chemotherapy, first-line treatment **Komparator:** EGFR–TKI monotherapy or the combined regimen of EGFR– TKI and chemotherapy **Endpunkte:** PFS, OS **Suchzeitraum:** Nur: prospective randomized controlled trials (phase II or

	III) **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 8 (4585) **Qualitätsbewertung der Studien:** examined the randomization procedure, estimation of sample size, blinding, loss to follow-up, dropout and if the intention-to-treat analysis. Insgesamt hohe Qualität **Heterogenitätsuntersuchungen:** Chi-square test and I^2 statistic **Publication Bias**: Begg's test and Egger's test **3. Ergebnisdarstellung** ***Unselected Patients (4 Studien)*** • ***PFS:*** Significant PFS benefit was observed from the combined regimen of TKIs and chemotherapy (HR= 0.81, 95% CI 0.69–0.95, P = 0.01; Figure 2a) based on random-effects model, due to significant heterogeneity (Chi2 = 35.17, P<0.001; I^2 = 80%). • ***OS:*** no evidence of improvement in OS with the combined regimen (HR= 1.01, 95% CI 0.93–1.08, P = 0.87, fixed-effects model ***Selected Patients by EGFR-Mutation Status (4 Studien)*** • ***PFS***: combined regimen was superior over chemotherapy or TKIs monotherapy with a significant improvement in PFS (HR= 0.48, 95% CI 0.28–0.83, P = 0.009); combined regimen also showed significant PFS benefit in the EGFR-mutation negative cohort, compared with chemotherapy or TKIs monotherapy (HR =0.84, 95% CI 0.72–0.98, p= 0.02) • ***OS:*** combined regimen marginally enhanced OS of EGFR-mutation positive patients (HR =0.67, 95% CI 0.44–1.00, P = 0.05), but not EGFR-mutation negative patients (HR =0.91, 95% CI 0.77–1.08, p= 0.27) **4. Anmerkungen/Fazit der Autoren** In conclusion, on the basis of this meta-analysis, combination of EGFR–TKIs and chemotherapy leads to PFS benefit as first-line treatment for advanced NSCLC, regardless of EGFR-mutation status, but has no demonstrable impact on OS. And there is a larger magnitude of PFS benefit for Asian patients, with sequential administration of EGFR–TKIs and chemotherapy. EGFR-mutation status is still a predictive biomarker of benefit with the combined regimen, for a larger magnitude of improvement in EGFR-mutation positive patients. This strategy deserved to be considered in the future although it is not approved for advanced NSCLC at the moment. **5. Hinweise der FBMed** Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt.
Pan G et al., 2013: Comparison	**1. Fragestellung** This study aims to assess the efficacy and safety of doublettargeted agents

of the efficacy and safety of single-agent erlotinib and doublet molecular targeted agents based on erlotinib in advanced non-small cell lung cancer (NSCLC): a systematic review and meta-analysis [29]	based on erlotinib in patients with advanced NSCLC. **2. Methodik** **Population:** Adult patients with advanced NSCLC **Intervention:** doublets (erlotinib plus another targeted drugs) **Komparator:** erlotinib **Endpunkte:** OS, ORR,DCR (disease control rate), side effects **Suchzeitraum:** Bis 11/2012, nur RCTs **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 5 (2100 Patienten) **Qualitätsbewertung der Studien:** Cochrane risk of bias. Insgesamt gute Qualität der Studien **Heterogenitätsuntersuchungen:** I^2 **3. Ergebnisdarstellung** mean age 63; 1,224 men and 876 women; 118 stage IIIB and 1,180 stage IV; 441 squamous cell cancers, 1,287 adenocarcinomas, and 372 other pathological types Effects: fixed effect models ***OS:*** One-year OS did not significantly improve with doublets compared with single erlotinib (HR 1.06, 95 % CI 0.95–1.18, p=0.26; fixed effect model) ***ORR:*** ORR were significantly superior with doublets (HR 1.49, 95%CI 1.13–1.98, p<0.05; ***DCR (disease control rate):*** HR 1.25, 95%CI 1.12–1.39, p<0.05) ***Side effects/ AEs:*** All grades of the most frequent side effects such as rash, anemia, diarrhea, anorexia, and fatigue were similar for two groups (HR 1.25, 95 % CI 0.99–1.58; 0.98, 95 % CI 0.78–1.24; 1.43, 95%CI 0.97–2.11; 1.18, 95%CI 0.84–1.65; 1.23, 95 % CI 0.86–1.77, respectively; random effect model). The grade ≥3 toxicity was not significantly different (HR 1.40, 95 % CI 0.97–2.01; random effect model). Some adverse events (e.g., alopecia, dyspnea, dry skin, hypertension, bleeding complications, stomatitis, interstitial lung disease, and thrombocytopenia) could not be analyzed precisely due to their low incidence. **4. Anmerkungen/Fazit der Autoren** The results of this systematic review suggest that patients with advanced NSCLC might benefit from doublet-targeted therapy based on erlotinib compared to erlotinib alone. However, an individual patient data systematic review and meta-analysis are needed to give us a more reliable assessment of the size of benefits and to explore whether doublet therapy may be more or less effective for particular types of patients. **5. Hinweise der FBMed** Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt.

Petrelli et al., 2012: Efficacy of EGFR tyrosine kinase inhibitors in patients with EGFR-mutated non-small-cell lung cancer: a meta-analysis of 13 randomized trials [30]	**1. Fragestellung** To evaluate the benefit of **EGFR TKIs** in EGFR-mutated NSCLCs. Eligible studies included published randomized controlled trials in which erlotinib or gefitinib (alone or with chemotherapy) were compared with standard therapy **2. Methodik** **Population**: Patienten mit fortgeschrittenem/metastasiertem NSCLC und EGFR-Mutation, die entweder in der Erstlinie oder in späteren Behandlungslinien mit Erlotinib oder Gefitinib behandelt wurden **Intervention**: TKIs (allein oder + Chemotherapie) **Komparator**: Chemotherapie ohne TKI **Endpunkt**: OS, PFS, ORR **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: bis 2011 **Qualitätsbewertung der Studien:** **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 13 (n= 10 433) **3. Ergebnisdarstellung** 8 first line trials **Response rate** (7 trials, 994 patients, 3 trials erlotinib, 4 trials gefitinib): statistically significant difference in favor of EGFR TKI (RR, 2.09 [1.82, 2.39]; p=0.04; fixed-effects model) **OS: no** statistically significant difference **4. Anmerkungen/Fazit der Autoren** In conclusion, NSCLCs harboring EGFR mutations derive greater benefit from erlotinib or gefitinib than from chemotherapy, either in first-line or subsequent lines of therapy. These agents double the chance of an objective response and reduce the risk of progression by about 70 % but do not increase OS. **5. Hinweise durch FB Med** • Keine Beschreibung zur Evaluation der Qualität der eingeschlossenen Studien. • Daten zu OS und PFS liegen für first und second line nicht getrennt vor. • Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt. Die meisten Patienten hatten kein Plattenepithelkarzinom
Qi WX et al., 2012: Doublet versus single cytotoxic agent as first-line treatment	**1. Fragestellung** to perform a systematic review and meta-analysis of all randomized controlled trials that compared the efficacy of **doublet versus single third-generation cytotoxic agent** as first-line treatment for elderly patients with advanced non-small-cell lung cancer (NSCLC). **2. Methodik**

for elderly patients with advanced non-small-cell lung cancer: a systematic review and meta-analysis [31]	**Population**: elderly (older than 65 years) patients with advanced non-small-cell lung cancer. First-line **Interventionen**: doublet cytotoxic agents **Komparator**: single third-generation cytotoxic agent **Endpunkte**: OS, TTP, ORR, Toxicity **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: 1980-2011 **Qualitätsbewertung der Studien:** Jadad. Keine Studie doppeltverblindet. Insgesamt mittlere Qualität auf Jadad Skala **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 10 (n= 2 510) **3. Ergebnisdarstellung** **Overall survival (9 trials):** no statistically significant difference, HR of 0.84 (95% CI = 0.71–1.00, p = 0.053, I^2=76.6%) **1-year survival** (6 trials statistically significant difference in favor of doublet therapy (RR = 1.17, 95 % CI = 1.02–1.35, p = 0.03, I^2=47.1%) **TTP (3 trials):** statistically significant difference in favor of doublet therapy (HR = 0.76, 95 % CI = 0.60–0.96, p=0,022, I^2=72.2%). **ORR (10 trials):** statistically significant difference in favor of doublet therapy (RR = 1.54, 95 % CI = 1.36–1.73, p = 0.0001, I^2=0) **Toxicity**: More incidences of grade 3 or 4 anemia, thrombocytopenia, and neurotoxicity were observed with doublet therapy. With respect to the risk of grade 3 or 4 neutropenia and nonhematologic toxicities such as diarrhea, fatigue, nausea, and vomiting, equivalent frequencies were found between the two groups **4. Anmerkungen/Fazit der Autoren** Our meta-analysis showed that doublet therapy was superior to single-agent therapy as first-line treatment for elderly patients with advanced NSCLC in terms of OS, TTP, ORR, and 1-year SR, but more hematologic toxicities and neurotoxicity were observed with doublet therapy. Due to significant heterogeneity between randomized trials, we performed a subgroup analysis based on different chemotherapy regimens. Similar results were found in platinum-based doublet therapy, although the OS benefit with doublet therapy was not significant. Furthermore, gemcitabine-based doublet significantly increased ORR compared with single agent, but it did not translate into an increase in survival benefit. Platinum-based doublet therapy might be considered as first-line treatment for older patients to improve efficacy, but the optimal drug dosage and treatment schedule should be investigated in future prospective clinical trials. Gemcitabine-based doublet therapy could be considered for elderly patients who were not suitable for platinum-based chemotherapy due to its tendency to improve OS and 1-year SR. **5. Hinweise durch FB Med** Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt.
Russo A et	**1. Fragestellung**

al., 2009: Gemcitabine-based doublets versus single-agent therapy for elderly patients with advanced nonsmall cell lung cancer: a Literature-based Meta-analysis [33]	To assess the efficacy and tolerability of **gemcitabine-based doublets** compared with **single-agent chemotherapy** for elderly patients with NSCLC **2. Methodik** **Population**: elderly patients with stage IIIB/IV NSCLCs (individuals ages 65 through 79 years). First-line **Intervention**: gemcitabine-based doublets **Komparator**: third generation single-agent chemotherapy (vinorelbine, docetaxel, and paclitaxel) **Endpunkt**: Survival, ORR, toxicity **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: 1966-2008 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 4 (n= 1.436) **3. Ergebnisdarstellung** **1-year survival**: no statistically significant difference (OR, 0.78; 95% CI, 0.57-1.06 [p=0.169]) **Overall response**: statistically significant difference in favor of doublets (OR, 0.65; 95% CI, 0.51-0.82 [p <0 .001]). **Toxicity**: gemcitabine-based doublets were associated with increases in thrombocytopenia (OR, 1.76; 95% CI, 1.12-2.76 [p=0.014]), but not in grade 3 or 4 hematologic or nonhematologic toxicities **4. Anmerkungen/Fazit der Autoren** Gemcitabine-based doublets appeared to be effective and feasible compared with single agents in the treatment of elderly patients with advanced NSCLC who were not suitable for full-dose, platinum-based chemotherapy **5. Hinweise durch FB Med** Keine Beschreibung zur Evaluation der Qualität der eingeschlossenen Studien. Keine Angaben zu Interessenskonflikten. Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt.
Shen et al., 2014: Comparison between cisplatin plus vinorelbine and cisplatin plus docetaxel in the treatment of advanced non-small-cel	**1. Fragestellung** To compare the VC and DC regimens in the first-line treatment of advanced NSCLC **2. Methodik** **Population:** The patients involved were required to have pathological or cytological confirmation of advanced (stage IIIB/IV) NSCLC, with a performance status of 0-2 on the World Health Organization (WHO) scale, or a Karnofsky performance status of ≥80%. **Intervention:** cisplatin plus vinorelbine (VC) **Komparator:** cisplatin plus docetaxel (DC) **Endpunkte:** 1‑year survival rate , 2‑year survival rate , safety

l lung cancer: A meta-analysis of randomized controlled trials [35]	**Suchzeitraum:** bis Mai 2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 9 RCTs (1 886) **Qualitätsbewertung der Studien:** Jadad Score. Alle Studien mit mittlerer Qualität im Jadad Score **Heterogenitätsuntersuchungen:** Wurden durchgeführt **3. Ergebnisdarstellung** Patients receiving DC therapy exhibited a significantly higher response rate [relative risk (RR)=0.83, 95% CI: 0.73‐0.95 and P=0.007] and 2‐year survival rate (RR=0.65, 95% CI: 0.50‐0.84 and P=0.001). However, the 1‐year survival rate for the two cisplatin‐based regimens were comparable (RR=0.90, 95% CI: 0.81‐1.01 and P=0.07). Patients receiving the VC regimen more frequently developed grade 3¼4 leucopenia, anemia and vomiting, whereas those receiving DC chemotherapy were more prone to grade 3¼4 diarrhea. The incidence of grade 3¼4 neutropenia, thrombocytopenia and nausea were similar between the two arms. In conclusion, our study indicated that DC is superior to the VC regimen in terms of tumor response rate, 2‐year survival rate and safety for the first‐line treatment of advanced NSCLC. **4. Anmerkungen/Fazit der Autoren** In conclusion, our study indicated that DC is superior to the VC regimen in terms of tumor response rate, 2-year survival rate and safety for the first-line treatment of advanced NSCLC. **Limits:** Our study was limited by the number and quality of the available RCTs. Although it may be difficult for phase II studies to produce reliable survival data, no significant heterogeneity was observed in the response rate or in the 1- and 2-year survival rates among the trials included in the analysis. This result of the 2-year survival analysis supports the decision to include all randomized phase II or III trials with prospectively recorded 2-year survival data. Furthermore, the survival data at 2 years of follow-up and some adverse effects were lacking in several trials, which may have led to a biased estimate. **5. Hinweise durch FB Med** Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt.
Shi L et al., 2014: Risk of interstitial lung disease with gefitinib and erlotinib in advanced non-small cell lung cancer: A systematic	**1. Fragestellung** We performed a systematic review and meta-analysis to determine the incidence and the relative risk (RR) associated with the use of gefitinib and erlotinib. **2. Methodik** **Population:** Patients with advanced NSCLC, assigned to treatment with gefitinib or erlotinib **Intervention:** Gefitinib oder Erlotinib **Komparator:** Platinbasierte Chemotherapie, Pemetrexed, Docetaxel, Paclitaxel, Vinorelbin oder Placebo **Endpunkte:** Overall incidence of interstitial lung disease (ILD) **Suchzeitraum:** Januar 2000 bis Oktober 2012

review and meta-analysis of clinical trials [36]	**Anzahl eingeschlossene Studien/Patienten (Gesamt):** 29 RCTs (15 618). 17 Studien in der Erstlinie **Qualitätsbewertung der Studien:** Jadad Score. Mittlere Studienqualität **3. Ergebnisdarstellung** The overall incidence for all-grade ILD events was 1.2% (95% CI, 0.9–1.6%) among patients receiving gefitinib and erlotinib, with a mortality of 22.8% (95% CI, 14.6–31.0%). Compared with controls, the RR of all-grade ILD events associated with gefitinib and erlotinib was 1.53 (95% CI, 1.13–2.08; P = 0.006) using a fixed effects model. The RR of fatal ILD events associated with EGFR TKIs treatment was 1.96 (95% CI, 1.03–3.72, P = 0.041) compared with control patients. The analysis was also stratified for drug type, study location, treatment arm, and treatment line, but no significant differences in RRs were observed. **4. Anmerkungen/Fazit der Autoren** Treatment with EGFR TKIs gefitinib and erlotinib is associated with a significant increase in the risk of developing both all-grade and fatal ILD events in advanced NSCLC. **Limits:** The National Cancer Institute's common toxicity criteria grading system for ILD has its own limitations. No term specific for ILD is listed in NCI CTCAE v2.0 or v3.0. Also, the majority of trials included in this analysis reported ILD events in combined grades (all-grade, or high-grade), we cannot distinguish cases in each grade. ILD is not a single disease, but encompasses many different pathological diseases. There were no uniform diagnostic criteria of ILD in various studies, also, the trials included in the analysis were performed at various centers, and the ability to detect ILD events might vary among these institutions, which could result in a bias of reported incidence rates. The incidence of ILD events showed significant heterogeneity among the included studies. This might reflect differences in trial designs, sample sizes, concomitant chemotherapy, and many other factors among these studies. Despite these differences, the RRs reported by all of these studies showed remarkable homogeneity. In addition, calculation using the random-effects model for overall incidence estimation might minimize the problem. The study might have a potential observation time bias because EGFR TKIs groups might have longer follow-up time than controls owing to the prolonged PFS that is often associated with the use of EGFR TKIs. However, most ILD events did not occur evenly over time, but in the early phase (first 4 weeks) of EGFR TKIs treatment . This is a meta-analysis at the study level, data were abstracted from published clinical trial results, and individual patient information was not available. Therefore, subgroup analyses according to possible risk factors for the development of ILD, including preexisting pulmonary fibrosis, age, performance status, gender, smoking history, lung cancer histology, and the mutational status of EGFR, are not possible in this analysis. **5. Hinweise durch FB Med** Es wurde keine getrennte Auswertung für Plattenepithelkarzinom

	durchgeführt.
Wang F et al., 2011: Gefitinib Compared with Systemic Chemotherapy as First-line Treatment for Chemotherapy-naive Patients with Advanced Non-small Cell Lung Cancer: A Meta-analysis of Randomised Controlled Trials [38]	**1. Fragestellung** To define the efficacy of gefitinib in chemotherapy-naive patients with advanced non-small cell lung cancer. **2. Methodik** **Population**: Chemotherapy-naive patients with NSCLC **Intervention:** Gefitinib therapy as first-line **Komparator:** Conventional therapy **Endpunkt:** PFS, OS **Methode:** systematic review and meta-analysis of RCTs **Suchzeitraum:** up to 2011 **Qualitätsbewertung der Studien:** (1) generation of allocation concealment, (2) description of drop-outs, (3) masking of randomisation, intervention, outcome assessment, (4) intention-to-treat analyses, (5) final analysis reported. Each criterion was rated as yes, no or unclear. Keine Ergebnisdarstellung der Qualitätsbewertung **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 7 (n= 4656) **3. Ergebnisdarstellung** <u>Gefitinib monotherapy</u> **OS** • Patients with lung adenocarcinoma: statistically significant difference in favor of gefitinib monotherapy compared to chemotherapy. HR 0.89 (0.81, 0.99); p = 0.03 • EGFR mutant treated with gefitinib monotherapy: no statistically significant difference • Combination of conventional chemotherapy with gefitinib: no statistically significant difference **PFS** • EGFR mutant treated with gefitinib monotherapy: statistically significant difference in favor of gefitinib monotherapy compared to chemotherapy HR 0.43 (0.32, 0.58) (p < 0.001) • Patients with lung adenocarcinoma: statistically significant difference in favor of gefitinib monotherapy compared to chemotherapy HR 0.71 (0.60, 0.83) (p < 0.001) • Patients without EGFR mutant: statistically significant difference in favor of chemotherapy compared to gefitinib monotherapy. HR 2.16 (1.17, 3.99) p = 0.01 • Patients with lung non- adenocarcinoma: no statistically significant difference **4. Anmerkungen/Fazit der Autoren** First-line treatment with gefitinib conferred prolonged progression-free

	survival than treatment with systemic chemotherapy in a molecularly or histologically defined population of patients with non-small cell lung cancer, and improved survival in the subgroup of patients with lung adenocarcinoma. **5. Hinweise durch FB Med** Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt.
Xiao Y-Y et al., 2013: Chemotherapy plus multitargeted antiangiogenic tyrosine kinase inhibitors or chemotherapy alone in advanced NSCLC: a meta-analysis of randomized controlled trials [39]	**1. Fragestellung** to compare the efficacy and toxicity of chemotherapy plus multitargeted antiangiogenic TKI with chemotherapy alone in patients with advanced NSCLC **2. Methodik** **Population:** Patients with advanced NSCLC (Erst- und Zweitlinientherapie) **Intervention**: Chemotherapy plus multitargeted antiangiogenic TKI vs. **Komparator**: chemotherapy alone **Endpunkte**: PFS (primary endpoint), ORR, OS, toxic effects (secondary endpoints) **Eingeschlossene Studien (Patienten):**6 (3 337) Zeitlinientherapie: 3 Studien (2 052) (jeweils mit 5 Punkten JADAD-Score bewertet) **Qualitätsbwertung der Studien:** Jadad Scale. Five of the included randomised controlled trials reported final analyses, one reported an interim analysis, one only reported an abstract. Only two studies were blind. All studies reported intention-to-treat analyses, but a description of drop-outs was reported in published ones. **3. Ergebnisse:** **PFS:** A significant difference between between the chemotherapy plus multitargeted antiangiogenic TKI and chemotherapy alone groups (HR 0.83, 95 % CI 0.76–0.90). Chemotherapy plus multitargeted antiangiogenic TKI significantly increased PFS. There was no significant heterogeneity (p= 0.288). No significant difference for non-adenocarcinoma. **OS:** No significant difference between the chemotherapy plus multitargeted antiangiogenic TKI and chemotherapy alone groups with no significant heterogeneity. **ORR:** Chemotherapy plus multitargeted antiangiogenic TKI significantly improved the ORR (RR 1.71, 95 % CI1.43–2.05). However, there was significant heterogeneity (p= 0.013). <u>Toxic effects</u>: • The risks of rash, diarrhea, and hypertension were higher in patients receiving chemotherapy plus multitargeted antiangiogenic TKI than in those receiving chemotherapy alone (OR2.78, 95 % CI 2.37–3.26; OR1.92, 95 % CI1.65–2.24; OR2.90, 95 % CI2.19–3.84, respectively). • The risks of nausea and vomiting were higher in patients receiving

	chemotherapy alone than in those receiving chemotherapy plus multitargeted antiangiogenic TKI (OR0.71, 95 % CI0.60–0.83; OR0.75, 95 % CI0.61–0.92, respectively). • The risk of hemorrhage, fatigue, cough, constipation, anorexia and alopecia were comparable between two groups (OR1.27, 95 % CI 0.98–1.56; OR0.95, 95 % CI0.82–1.11; OR1.08, 95 % CI 0.87–1.34; OR0.95, 95 % CI0.78–1.17; OR1.12, 95 % CI 0.95–1.33; OR0.91, 95 % CI0.75–1.11, respectively). **4. Fazit der Autoren:** Therapy consisting of chemotherapy plus multitargeted antiangiogenic TKI was found to have specific advantages over chemotherapy alone in terms of PFS and ORR. The toxicity was comparable between the two therapies. Therefore, chemotherapy plus multitargeted antiangiogenic TKI may be a safe and valid therapeutic option for patients with advanced NSCLC.' • Inclusion in our meta-analysis if the chemotherapy plus multitargeted antiangiogenic TKI was compared with chemotherapy alone in first-line or second-line treatment of advanced NSCLC. • only 56 % of included patients in second-line studies had Adenocarcinoma • clinical IIIB–IV stages; phase II and III RCTs included • Publication bias was not found
Xu C et al., 2012: Can EGFR-TKIs be used in first line treatment for advanced non-small cell lung cancer based on selection according to clinical factors? – A literature-based meta-analysis [40]	**1. Fragestellung** We aimed to determine whether patients could be treated with **TKIs** based on clinical factors in the first-line setting **2. Methodik** **Population**: IIIB/IV or post-operational recurrent NSCLC (including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma) patients. First-line **Intervention**: gefitinib, erlotinib monotherapy **Komparator**: chemotherapy (mono or doublet) **Endpunkt**: OS, PFS, ORR **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: bis 2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 10 (n=3.045) **Qualitätsbewertung der Primärstudien:** k.A. **3. Ergebnisdarstellung** Unselected trials: Four studies of randomized NSCLC patients were based on no particular patient criteria in the first-line setting. Among them, three used gemcitabine, vinorelbine, or paclitaxel plus carboplatin. Selected trials: Two trials selected East Asian patients using the clinical factors of gender and smoking history. Both trials used gefitinib as the treatment arm; the control arm was paclitaxel plus carboplatin in 1 trial and gemcitabine plus cisplatin in the other. EGFRmut+ trials: Five trials chose patients with an EGFR mutation who were

	randomized for treatment with TKI or chemotherapy. <u>First line – unselected patients</u> • **Overall survival**: statistically significant difference in favor of chemotherapy. HR 1.35 [95% CI, 1.13–1.61] • **PFS**: statistically significant difference in favor of chemotherapy. HR 1.29 [95% CI, 1.00–1.66] • **Response rate**: statistically significant difference in favor of chemotherapy. RR 3.52 [95% CI, 2.41–5.15] <u>First line – selected patients</u> • **Overall survival**: no statistically significant difference. HR 0.92 [95% CI, 0.79–1.07] • **PFS**: statistically significant difference in favor of TKI therapy. HR 0.83 [95% CI, 0.74–0.93] • **Response rate**: statistically significant difference in favor of TKI therapy. RR 0.64 [95% CI, 0.52–0.79] <u>First line – EGFRmut+ patients</u> • **Overall survival**: no statistically significant difference. HR 1.00 [95% CI, 0.79–1.27] • **PFS**: statistically significant difference in favor of TKI therapy. HR 0.36 [95% CI, 0.31–0.43] • **Response rate**: statistically significant difference in favor of TKI therapy. RR 0.47 [95% CI, 0.41–0.55] **4. Anmerkungen/Fazit der Autoren** Our meta-analysis indicates that among NSCLC patients, advanced NSCLC patients with EGFR gene mutations would benefit most from TKI treatment, especially in the first-line setting. Nevertheless, EGFR-TKI treatment is justified for patients with unknown EGFR status, those who cannot tolerate chemotherapy owing to advanced age or who have poor performance status, and those with other medical conditions, when selected according to clinical factors. **5. Hinweise durch FB Med** Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt.
Yang X et al., 2014: The efficacy and safety of EGFR inhibitor monotherapy in non-small cell lung	**1. Fragestellung** Efficacy of (EFGR-TKIs: gefitinib or erlotinib) monotherapy in previously treated non-small-cell lung cancer (NSCLC) **2. Methodik** **Population:** advanced NSCLC **Intervention:** gefitinib or erlotinib

cancer: a systematic review [41]	**Komparator:** placebo or BSC **Endpunkte:** PFS and OS **Suchzeitraum:** December 2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 14/8 970 (3 front-line, 2 second-line, 9 maintenance) **Qualitätsbewertung der Studien:** scrutinized – no further information **Heterogenitätsuntersuchungen:** χ2 test, I2 statistic used, values of 50 % regarded as representing low heterogeneity, FEM with Mantel-Haenszel method used, once the results were homogeneous; otherwise, random-effect model with DerSimonian and Laird method adopted, sensitivity analysis was also conducted to examine the impact of the overall results from this study **„Publication bias“:** plotting the HRs against their standard errors, Begg-adjusted rank correlation test and Egger regression asymmetry test performed **3. Ergebnisdarstellung** OS • HR (EGFR-TKIs mono vs. placebo) 0,88, 95 % KI 0,82 – 0,96, I^2 = 50.5% - significantly increased • patients with EGFR mutation positive had more pronounced benefit • second-line therapy group: HR 0,80; 95 % KI 0,63 – 1,01; I^2 = 74,6%, p = 0,047 • EGFR-mutation patients: HR 0,987; 95 % KI 0,881 – 1,105; I^2 = 12,8%, p = 0,330 PFS • HR (EGFR-TKIs) 0,71, 95 % KI 0,63 – 0,81, I2 = 81,2% • patients with EGFR mutation positive had more pronounced benefit • Subgruppe mit ausschließlich first-line Studien zeigte keinen statistisch signifikanten Unterschied adverse reactions (EGFR TKIs vs. placebo) • diarrhea (OR) 3,635; 95 % KI 2,377 to 5,557 • rashes (OR) 5,664; 95 % KI 8,869 to 27,665 • anorexia (OR) 1,555; 95 % KI 1,060 to 2,283 • anemia (OR) 1,481; 95 % KI 1,114 to 1,969 **4. Anmerkungen/Fazit der Autoren** The results show that monotherapy therapy with EFGR-TKIs produce a significant OS and PFS benefit for patients with NSCLC compared with placebo or BSC, especially for the patients who had adenocarcinomas, non-smokers and patients with EGFR gene mutations. **5. Hinweise durch FB Med** Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt.

Yu Y et al., 2012: Non-platinum regimens of gemcitabine plus docetaxel versus platinum-based regimens in first-line treatment of advanced non-small cell lung cancer: a meta-analysis on 9 randomized controlled trials [42]	**1. Fragestellung** The aim was to compare the efficacy and toxicity of **gemcitabine plus docetaxel (GD)** with **platinum-based regimens** in patients with untreated advanced non-small cell lung cancer (NSCLC). **2. Methodik** **Population**: cytologically or pathologically confirmed of NSCLC and in clinical Ill-IV stage and patients must be chemotherapy naive **Intervention**: gemcitabine plus docetaxel (GD regimens) **Komparator**: cisplatin or carboplatin combined with a cytotoxic drug (platinum-based regimens) **Endpunkt**: OS, TTP, ORR, toxicity **Methode**: systematic review and meta-analysis of RCTs **Suchzeitraum**: up to 2011 **Qualitätsbewertung der Studien**: Cochrane risk of bias tool. Mittlere bis gute Qualität **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 9 (n=2.658) **3. Ergebnisdarstellung** **Overall survival (9 trials, 2658 patients):** no statistically significant difference, no heterogeneity **TTP (5 trials):** statistically significant difference in favor of platinum-based regimens (HR = 1.12, 95% CI= 1.02-1.24, p = 0.02) **Response rate (8 trials):** statistically significant difference in favor of platinum-based regimens (RR = 0.86, 95% CI= 0.74-D.99, p = 0.03) **Toxicity**: GD induced less grade 3-4 nausea/vomiting, anemia, neutropenia and febrile neutropenia (RR = 0.36, 95% Cl = 0. 15-0.86, p = 0.02; RR = 0.35, 95% CI = 0.23-0.53, p = 0.00; RR = 0.68, 95% Cl = 0.52-0.88, p = 0.003; RR = 0.53, 95% Cl = 0.34-0.82, p = 0.004. respectively). **4. Anmerkungen/Fazit der Autoren** In our meta-analysis, we found that the efficacy was comparable between GD regimens and platinum-based regimens according to overall survival and 1-year survival. Although platinum-based regimen had an advantage in TTP and ORR, the advantage was lost when the two trials used sequential regimens were removed. **5. Hinweise durch FB Med** Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt. Die meisten Patienten hatten Adenokarzinom
Zhang JW et al., 2014: The impact of both platinum-based	**1. Fragestellung** To understand the impact of PBC and EGFR-TKIs on NSCLC prognosis, we evaluated the association between the receipt of both regimens and overall survival (OS) evaluate the association between the receipt of both regimens and overall survival (OS)

chemotherapy and EGFR-TKIs on overall survival of advanced non—small cell lung cancer [43]	**2. Methodik** **Population:** advanced NSCLC **Interventionen:** • platinum-based doublet chemotherapy (PBC) • epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) **Komparator:** Placebo **Endpunkte:** OS **Suchzeitraum:** 2001 bis 02/2012 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 15 (11456) Nur: prospective, randomized, controlled phase III clinical trials (und: the percentage of patients treated with both PBC and EGFR-TKIs was available in the trial and OS was reported) **Qualitätsbewertung der Studien:** k.A **Heterogenitätsuntersuchungen:** k.A. **3. Ergebnisdarstellung** The OS was positively correlated with the percentage of patients treated with both PBC and EGFR-TKIs ($r = 0.797$, $P < 0.001$). The correlation was obvious in the trials in Asian populations ($r = 0.936$, $P < 0.001$) but was not statistically significant in the trials in predominantly Caucasian populations ($r = 0.116$, $P = 0.588$). **4. Anmerkungen/Fazit der Autoren** These results suggest that treatment with PBC and EGFR-TKIs may provide a survival benefit to patients with advanced NSCLC, highlighting the importance of having both modalities available for therapy. **5. Hinweise durch FB Med** Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt.
Zhong N et al., 2013: Chemotherapy Plus Best Supportive Care versus Best Supportive Care in Patients with Non-Small Cell Lung Cancer: A Meta-Analysis of Randomized Controlled Trials [44]	**1. Fragestellung** We performed a systematic review and meta-analysis to evaluate the effects of chemotherapy plus BSC versus BSC alone on survival of patients with NSCLC. **2. Methodik** **Population:** patients with NSCLC (Stage III/IV or advanced) **Intervention:** chemotherapy and BSC **Komparator:** BSC alone **Endpunkte:** OS or treatment-related mortality **Suchzeitraum:** Nicht angegeben **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 16 RCTs (4 135) **Qualitätsbewertung der Studien:** The quality of the trials was also assessed by pre-defined criteria using Jadad score. Gute bis mittlere Qualität der Studien **Heterogenitätsuntersuchungen:** Durchgeführt (Sensitivitätsanalysen)

	3. Ergebnisdarstellung **Ergebnisse zum Overall Survival:** Von den 16 Studien konnten aus 13 Studien Ergebnisse zum OS ermittelt werden. Hier zeigte sich ein statistisch signifikanter Vorteil für die Kombination aus Chemotherapie plus BSC versus BSC allein (HR, 0.76; 95%CI, 0.69–0.84; P<0.001) bei geringer Heterogenität (I^2=24%, p=0,201). **Ergebnisse zu Nebenwirkungen/Unerwünschten Ereignissen:** Overall, we noted that treatment with chemotherapy plus BSC were associated with significant increase in the risks of neutropenia (RR, 31.01; 95%CI, 10.71–89.75; P<0.001, I^2=0%), leukopenia (RR, 11.49; 95%CI, 3.50–37.69; P<0.001, I^2=14%), anemia (RR, 3.85; 95%CI, 1.58–9.38; P=0.003, I^2=12%), infection (RR, 2,10; 95%CI, 1,04–4.25; P=0.04, I^2=10%), nausea/vomiting (RR, 3.82; 95%CI, 1.31–11.14; P=0.01, I^2=47%), alopecia (RR, 15.84; 95%CI, 1,05–239.49; P00.05, I^2=80%), and ankle swelling (RR, 2,64; 95%CI, 1.61–4.33; P<0.001, I^2=0%). No other significant differences were identified between the effects of chemotherapy plus BSC and BSC alone. **4. Anmerkungen/Fazit der Autoren** Chemotherapy plus BSC increased the OS and reduced the 6-month, 12-month, and 2-year mortality of NSCLC patients. Since nearly all the trials in our study included patients with stage III/IV disease or advanced NSCLC, the conclusions should be applicable only to patients with advanced or metastatic NSCLC. **Limits:** First, inherent assumptions were made for all meta-analyses, because the analyses used pooled data,either published or provided by the individual study; individual patient data or original data were unavailable, which did not allow us to perform more detailed analyses and to obtain more comprehensive results. Second, treatments given in those trials included second generation, third generation, and the fourth generation chemotherapy regiments, which prevented us from exploring the association between the type of chemotherapy and survival outcomes. Third, heterogeneity among the trials is another limitation of our study. We applied a random-effect model that took possible heterogeneity into consideration and performed subgroup analyses based on several important factors to further explore the source of heterogeneity. Fourth, data on progression-free survival were rarely available in these trials; therefore, no conclusions could be drawn. **5. Hinweise der FBMed** Kein Suchzeitraum angegeben. Es wird nicht dargestellt, welche Interventionen unter BSC subsummiert waren. Es wurde keine getrennte Auswertung für Plattenepithelkarzinom durchgeführt.

Scottish Intercollegiate Guidelines Network (SIGN), 2014: Management of lung cancer [34]	**1. Fragestellung** The guideline covers all aspects of the management of patients with small cell lung cancer (SCLC) and nonsmall cell lung cancer (NSCLC), and provides information for discussion with patients and carers.
	2. Methodik ***Grundlage der Leitlinie:*** systematische Recherche und Bewertung der Literatur, Entwicklung durch multidisziplinäre Gruppe von praktizierenden klinischen ExpertInnen, Expertenreview, öffentliche Konsultation ***Suchzeitraum:*** 2005 - 2012 ***LoE/GoR:*** Vgl. *Anlage 1* dieser Synopse
	Empfehlungen ***First line treatment*** <u>First line therapy for patients with stage IIIB and IV NSCLC</u> Results from a meta-analysis and systematic review demonstrate the benefit of SACT for patients with advanced non-small cell lung cancer (absolute improvement in survival of 9% at 12 months versus control). **(LoE 1++)** Burdett S, Stephens R, Stewart L, Tierney J, Auperin A, Le Chevalier T, et al. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: A systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. J Clin Oncol 2008;26(28):4617-25. Four randomised trials of single agent SACT (gemcitabine, paclitaxel, docetaxel and vinorelbine) versus best supportive care (including radiotherapy) in patients with advanced NSCLC reveal a trend to improved quality of life with increased survival in three of the four studies. **(LoE 1+)** Anderson H, Hopwood P, Stephens RJ, Thatcher N, Cottier B, Nicholson M, et al. Gemcitabine plus best supportive care (BSC) vs BSC in inoperable non-small cell lung cancer - a randomised trial with quality of life as the primary outcome. UK NSCLC Gemcitabine Group. Non-Small Cell Lung Cancer. . Br J Cancer 2000;83(4):447-53. Ranson M, Davidson N, Nicolson M, Falk S, Carmichael J, Lopez P, et al. Randomized trial of paclitaxel plus supportive care versus supportive care for patients with advanced non-small-cell lung cancer. J Natl Cancer Inst 2000;92(13):1074-80. Roszkowski K, Pluzanska A, Krzakowski M, Smith AP, Saigi E, Aasebo U, et al. A multicenter, randomized, phase III study of docetaxel plus best supportive care versus best supportive care in chemotherapynaive patients with metastatic or non-resectable localized non-small cell lung cancer (NSCLC). Lung Cancer 2000;27(3):145-57. Gridelli C. The ELVIS trial: a phase III study of single-agent vinorelbine as first-line treatment in elderly patients with advanced non-small cell lung cancer. Elderly Lung Cancer Vinorelbine Italian Study. Oncologist 2001;6(Suppl 1):4-7. No particular combination of these agents in regimens with platinum has been shown to be more effective. **(LoE 1+)** Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced nonsmall- cell lung cancer. N Engl J Med 2002;346(2):92-8. In patients who have advanced disease and a performance status <2 at the time of diagnosis of NSCLC, first line treatment should be offered according to histology. Patients with non-squamous histology demonstrated a superior survival when treated with cisplatin and pemetrexed compared with cisplatin and

	gemcitabine (hazard ratio (HR) 0.84, 95% CI 0.74 to 0.96, p=0.011). Patients with squamous histology do not benefit from pemetrexed/platinum combination. **(LoE 1+)** Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapynaive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26(21):3541-51. Scagliotti GV, Park K, Patil S, Rolski J, Goksel T, Martins R, et al. Survival without toxicity for cisplatin plus pemetrexed versus cisplatin plus gemcitabine in chemonaïve patients with advanced non-small cell lung cancer: a risk-benefit analysis of a large phase III study. Eur J Cancer 2009;45(13):2298-303. EGFR tyrosine kinase inhibitors (TKIs) are effective as first line treatment of advanced NSCLC in patients with sensitising *EGFR* mutations. The optimum treatment is orally delivered single agent therapy. TKIs significantly increased progression-free survival (PFS) (HR 0.45, 95% CI 0.36 to 0.58, P<0.0001) over SACT.230 In a European trial, the median PFS was 9.4 months in the erlotinib (TKI) group and 5.2 months in the doublet SACT group, (HR 0.42, 95% CI 0.27 to 0.64), p<0.0001. **(LoE 1+)** Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13(3):239-46. <u>Recommendations</u> • First line single agent tyrosine kinase inhibitors should be offered to patients with advanced NSCLC who have a sensitising *EGFR* mutation. Adding combination systemic anticancer therapy to a TKI confers no benefit and should not be used. (A) • Patients who have advanced disease, are performance status 0-1, have predominantly nonsquamous NSCLC and are *EGFR* mutation negative should be offered combination systemic anticancer therapy with cisplatin and pemetrexed. (A) • All other patients with NSCLC should be offered combination systemic anticancer therapy with cisplatin/carboplatin and a third generation agent (docetaxel, gemcitabine, paclitaxel or vinorelbine). (A)
Ramnath et al., 2013: Treatment of Stage III Non-small Cell Lung Cancer [32]	Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines **1. Fragestellung** updates the published clinical trials since the last American College of Chest Physicians guidelines to make treatment recommendations for this controversial subset of patients
	2. Methodik Siehe *Socinski et al., 2013*
	Infiltrative Stage III (N2,3) Non-small Cell Lung Cancer In patients with infiltrative stage III (N2,3) non-small cell lung cancer (NSCLC) and performance status 0-1 being considered for curative-intent treatment, radiotherapy alone is not recommended **(Grade 1A**) . 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 IIIB NSCLC, once daily thoracic radiotherapy plus platinum-based doublet chemotherapy is recommended. In patients with infiltrative stage III (N2,3) NSCLC, performance status 0-1, and minimal weight loss being considered for curative-intent treatment, concurrent chemoradiotherapy is recommended over sequential chemoradiotherapy (**Grade 1A**) .
Socinski et al., 2013: Treatment of Stage IV Non-small Cell Lung Cancer [37]	Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines **1. Fragestellung** to update the previous edition of the American College of Chest Physicians Lung Cancer Guidelines Stage IV non-small cell lung cancer (NSCLC) is a treatable, but not curable, clinical entity in patients given the diagnosis at a time when their performance status (PS) remains good.
	1. **Methodik** A writing committee was assembled and approved according to ACCP policies as described in the methodology article of the lung cancer guidelines. **Suchzeitraum:**bis 12/2011 **LoE und GoR** **Table 1—*Strength of the Recommendations Grading System*** See table below ***Literatursuche:***

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.

	focused primarily on randomized trials, selected metaanalyses, practice guidelines, and reviews. In addition, phase 2 controlled studies that provided relevant information (eg, for toxicity or particular patient subgroups) were included.
	2. **Empfehlungen** ***General Approach*** 2.1.1. In patients with a good performance status (PS) (ie, Eastern Cooperative Oncology Group [ECOG] level 0 or 1) and stage IV non-small cell lung cancer (NSCLC), a platinum-based chemotherapy regimen is recommended based on the survival advantage and improvement in quality of life (QOL) over best supportive care (BSC) **.(Grade 1A)** Remark: Patients may be treated with several chemotherapy regimens (carboplatin and cisplatin are acceptable, and can be combined with paclitaxel, docetaxel, gemcitabine, pemetrexed or vinorelbine) 2.2.2. In patients with stage IV NSCLC and a good PS, two-drug combination chemotherapy is recommended. The addition of a third cytotoxic chemotherapeutic agent is not recommended because it provides no survival benefit and may be harmful. **(Grade 1A)** ***First Line Treatment*** 3.1.1.1. In patients receiving palliative chemotherapy for stage IV NSCLC, it is recommended that the choice of chemotherapy is guided by the histologic type of NSCLC **(Grade 1B).** *Remark:* The use of pemetrexed (either alone or in combination) should be limited to patients with nonsquamous NSCLC. *Remark:* Squamous histology has not been identified as predictive of better response to any particular chemotherapy agent. 3.2.1.1. In patients with known epidermal growth factor receptor (EGFR) mutations and stage IV NSCLC, first-line therapy with an EGFR tyrosine kinase inhibitor (gefitinib or erlotinib) is recommended based on superior response rates, progression-free survival and toxicity profiles compared with platinum-based doublets **(Grade 1A)** . 3.3.1.1. Bevacizumab improves survival combined with carboplatin and paclitaxel in a clinically selected subset of patients with stage IV NSCLC and good PS (nonsquamous histology, lack of brain metastases, and no hemoptysis). In these patients, addition of bevacizumab to carboplatin and paclitaxel is recommended **(Grade 1A)** . 3.3.1.2. In patients with stage IV non-squamous NSCLC and treated, stable brain metastases, who are otherwise candidates for bevacizumab therapy, the addition of bevacizumab to firstline, platinum-based chemotherapy is a safe therapeutic option **(Grade 2B)** . *Remark* : No recommendation can be given about the use of bevacizumab in patients receiving therapeutic anticoagulation or with an ECOG PS of 2.
Ellis PM et al., 2014: Use of the	A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO) **1. Fragestellungen**

Epidermal Growth Factor Receptor Inhibitors Gefitinib (Iressa®), Erlotinib (Tarceva®), Afatinib, Dacomitinib or Icotinib in the Treatment of Non–Small-Cell Lung Cancer: A Clinical Practice Guideline[3]	In patients with advanced non–small-cell lung cancer (NSCLC) who have not received any chemotherapy (chemo-naive), is first-line therapy with the epidermal growth factor receptor (EGFR) inhibitors gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib superior to platinum-based chemotherapy for clinical meaningful outcomes (overall survival, progression-free survival (PFS), response rate and quality of life)? What are the toxicities associated with gefitinib (Iressa®), erlotinib (Tarceva®), afatinib, dacomitinib or icotinib?
	Empfehlungen First-line therapy with an EGFR tyrosine kinase inhibitor (TKI) is not recommended in unselected (patients who have not undergone mutation testing) or clinically selected populations of patients. Available data would suggest that first-line EGFR TKI is inferior to platinum-based chemotherapy in this group of NSCLC patients. The use of clinical characteristics such as Asian ethnicity, female sex, adenocarcinoma histology and light/never smoking status is not recommended to select patients for first-line EGFR TKI therapy, as this strategy does not reliably select patients who have mutations. *Key Evidence:* Twenty-six randomized first-line studies in unselected and clinically selected populations were used to formulate this recommendation. The results of these trials showed no benefit for the use of an EGFR inhibitor in unselected and clinically selected patients In patients with EGFR mutation-positive NSCLC, first-line therapy with an EGFR TKI such as gefitinib, erlotinib or afatinib is the preferred treatment compared to platinum-based therapies. There is no evidence to support one EGFR TKI over another, so the decision about which EGFR TKI to use should take into consideration the expected toxicity of the drug as well as the cost. EGFR TKI therapy is associated with higher response rates, longer PFS and improved quality of life. *Qualifying Statement:* There is no clear difference in overall survival. Many patients in these trials randomized to platinum-doublet chemotherapy, crossed over to an EGFR TKI as subsequent therapy. The likely effect of this cross-over is to dilute any survival difference between the groups, making comparison of overall survival less informative. *Key Evidence:* Seven randomized trials and two meta-analyses comprised the evidence base. The trials and meta-analyses based on data from these trials showed that PFS was prolonged in molecularly selected patients when an EGFR was used as first-line treatment. • Six trials were included in the initial meta-analysis that showed a hazard ratio (HR) of 0.35 (95% confidence interval (CI), 0.28-0.45; p<0.00001). • A second meta-analysis done on PFS that included subsets of EGFR-positive patients from first-line trials had similar results with an HR of 0.38 (95% CI, 0.31-0.44; p<0.00001).

	All seven trials showed a decrease in adverse effects with an EGFR inhibitor compared to chemotherapy. **Toxicity** The most common toxicities from EGFR inhibitors were diarrhea and rash. Fatigue was also noted to be more prevalent with EGFR inhibitors. Rarer adverse events include interstitial lung disease (ILD). The newer TKIs (icotinib, dacomitinib and afatinib) were noted to have greater incidence of diarrhea, dermatitis and hepatotoxicity. ***Key Evidence*** Two randomized phase II trials , each involving more than 200 patients randomized to either 250 mg or 500 mg of gefitinib daily, identified that grade 3 or 4 toxicity was higher with the higher dose gefitinib. Interstitial lung disease-type events occurred in only one of the two trials, and only with 500 mg/day gefitinib (1% of patients) . • One study comparing dacomitinib to erlotinib identified a greater predilection to diarrhea, dermatitis and paronychia with dacomitinib . • One study comparing icotinib to gefitinib identified a greater incidence of elevated liver transaminases with gefitinib (12.6% vs 8%).
de Marinis F et al., 2011: Treatment of advanced non-small-cell-lung cancer: Italian Association of Thoracic Oncology (AIOT) clinical practice guidelines [6]	**1. Fragestellung** AIOT (Italian Associatlon of Thoracic Oncology) produces up-to-date, cllnlcal practice guidellnes for the management of lung cancer in ltaly. Guidelines were developed by answerlog clinical relevant questions. Here we report only major cllnical issues concerning the management of advanced non-small cell lung cancer (NSCLC). Here we report only eight clinical questions regarding the management of advanced non-small-cell lung cancer (NSCLC) which have been subsequently updated for this manuscrlpt on December 2010.
	2. Methodik Systematische Literatursuche und formaler Konsensusprozess ***Suchzeitraum:*** 2004 bis 2009 ***LoE, GoR*** **Table 1** Level of evidence and strength of recommendation. Level of evidence | | Strength of recommendation Ia | Evidence from systematic reviews and meta-analysis of randomized controlled trials | A Ib | Evidence from at least one randomized controlled trial | IIa | Evidence from at least one controlled study without randomization | B IIb | Evidence from at least one other type of quasi-experimental study | III | Evidence from observational studies | IV | Evidence from expert committee reports or experts | C
	3. Empfehlungen Platinum-based (cisplatin or carboplatin) chemotherapy is the standard treatment for adult patients with advanced NSCLC, with good peformance status

(PS 0-1). Chemotherapy should be stopped at disease pragression or after 4 cycles in patients who do not obtain an objective response, and continued for maximum 6 cycles in patients achieving an objective response. Treatment options are different according to tumour histotype (squamous versus non squamous).

A. Treatment options for patients with squamous tumour

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

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

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

3.2.1. Recommendations

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

3.3.1. Recommendations

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

3.4.1. Recommendations

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

3.5.1. Recommendations

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

- In elderly patients (older than 70years), with EGFR mutation positive advanced NSCLC, gefitinib ls the recommended treatment. (**LoE lA, GoR A)**

3.6.1. Recommendations

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

3.7.1. Recommendations

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

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

3.8.1. Recommendations

- In patients wlth advanced NSCLC and EGFR mutation negative or unknown status, with progressive disease after first-line treatment chemotherapy (docetaxel or pemetrexed ln non-squamous histology) or erlotinlb should be offered. There are no concluslve data to help the choice between chemotherapy and erlotinib. (**LoE IB, GoR A)**
-

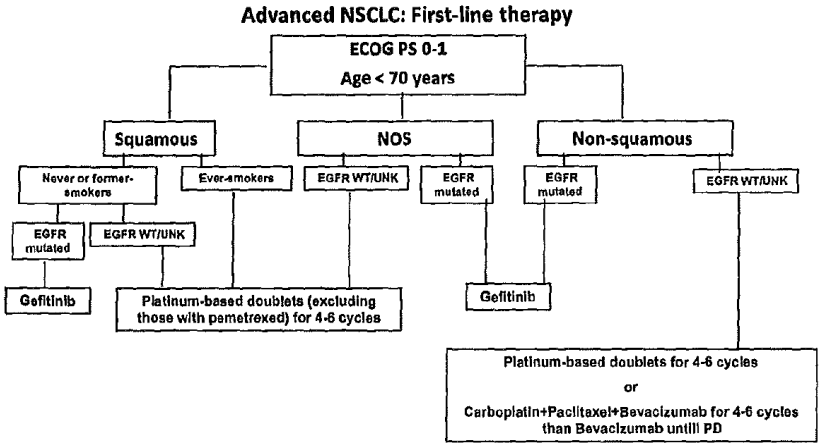


Fig. 1. Suggested algorithm for first-line treatment of advanced non-small-cell lung cancer (ECOG PS: Eastern Cooperative Oncology Group performance status; NOS: not otherwise specified; EGFR: epidermal growth factor receptor; WT: wild type; and UNK: unknown).

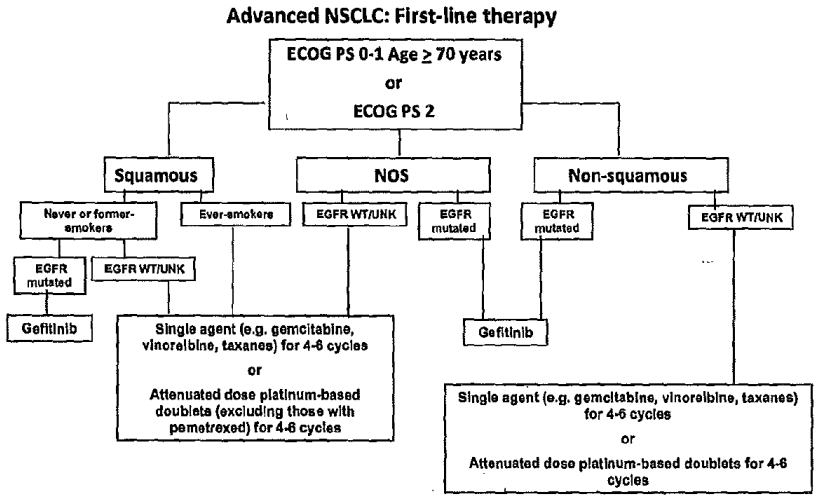


Fig. 2. Suggested algorithm for first-line treatment of advanced non-small-cell lung cancer in special patients population (ECOG PS: Eastern Cooperative Oncology Group performance status; NOS: not otherwise specified; EGFR: epidermal growth factor receptor; WT: wild type; and UNK: unknown).

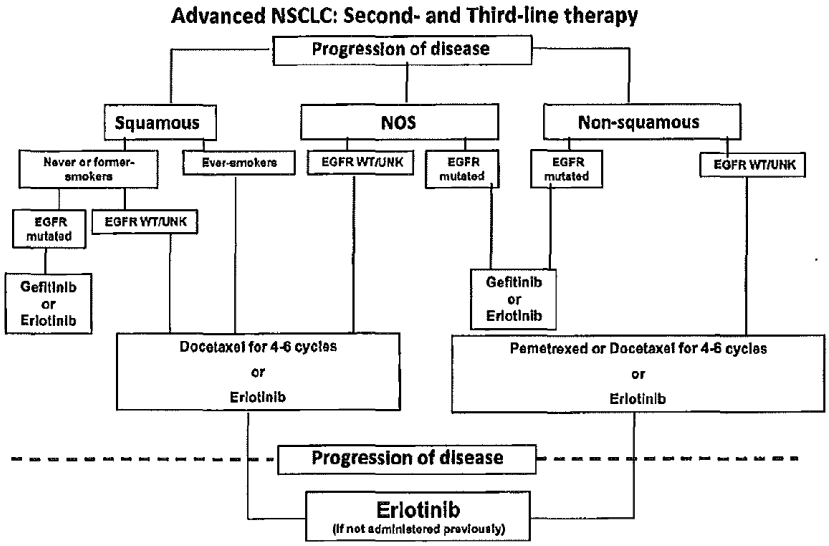


Fig. 3. Suggested algorithm for second- and third-line treatment of advanced non-small-cell lung cancer (NOS: not otherwise specified; EGFR: epidermal growth factor receptor; WT: wild type; and UNK: unknown).

DGP, 2010:

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

Fragestellung

Ziel der vorliegenden Leitlinie ist die Verbesserung der Prognose und der Lebensqualität von Patienten mit Lungenkarzinomen durch Optimierung des Einsatzes der derzeitigen diagnostischen und therapeutischen Möglichkeiten in einem interdisziplinären Ansatz. Außerdem soll durch die Empfehlung präventiver Maßnahmen die Häufigkeit des Lungenkarzinoms reduziert werden.

Methodik

Grundlage der Leitlinie: systematische Recherche, formale Konsensusprozesse

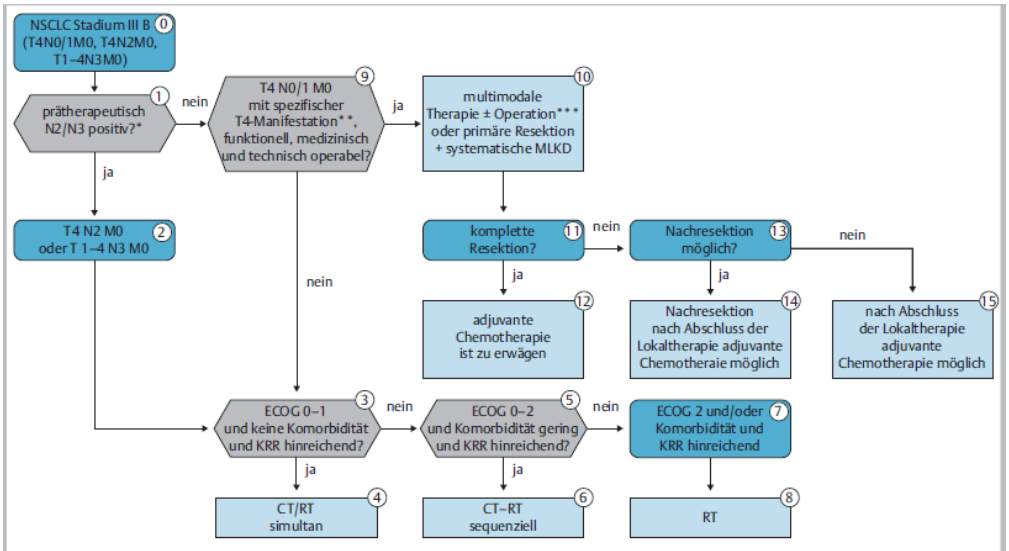
Suchzeitraum: bis 06/2006

Der nachfolgende Zeitraum bis zur Veröffentlichung der Leitlinie wurde hinsichtlich relevanter Publikationen von den Arbeitsgruppen beobachtet. Relevante Literatur aus diesem Zeitraum wurde dann in der Leitlinie berücksichtigt, wenn es sich um Studien mit hoher Evidenzstärke

Beatmungsmedizin und der Deutschen Krebsgesellschaft [8]	(Evidenzgrad 1–2) oder Leitlinien handelte und sich neue Aspekte ergaben. ***LoE, GoR:*** **Tab. 1** Beziehung zwischen Evidenz- und Empfehlungsgrad (modifiziert nach Oxford Center for Evidence-based Medicine 2001 und AWMF). **Evidenzgrad** / **Evidenz Therapeutische Studien** / **Diagnostische Studien** / **Konsensus Modifizierende Kriterien für Empfehlungsgrad** / **Empfehlungsgrad** 1a: syst. Review von randomisierten kontrollierten klinischen Studien / syst. Review validierende Kohortenstudien 1b: individ. randomisierte kontrollierte Studie (enges Konfidenzintervall) / validierende Kohortenstudie mit guten Referenzstandards 1c: Alle-oder-keiner-Prinzip / absolute Spezifität zum Einschluss oder absolute Sensitivität zum Ausschluss der Diagnose 2a: systematische Review von Kohortenstudien / syst. Review von explorativen Kohortenstudien 2b: individ. Kohortenstudie, randomisierte kontr. Studie geringerer Qualität / exploratorische Kohortenstudie mit guten Referenzstandards 2c: Outome-Research-Studie 3a: syst. Review Fall-Kontroll-Studien / syst. Review von nichtkonsekutiven Studien 3b: individ. Fall-Kontroll-Studie / nicht-konsekutive Studien 4: Fallserie, Kohortenstudien und Fallkontrollstudien geringerer Qualität / Fall-Kontroll-Studie, schlechter oder nicht-unabhängiger Referenzstandard 5: Expertenmeinung ohne explizite kritische Bewertung, physiolog. Modelle etc. / Expertenmeinung ohne explizite kritische Bewertung, physiolog. Modelle etc. Konsensus Modifizierende Kriterien für Empfehlungsgrad: – ethische Aspekte; – Patienten-Präferenzen; – klin. Relevanz, integr. Outcome; – klinisch bedeutsame Abweichung von Studiensituation; – Studien: Konsistenz, Effektstärke; – Nutzen, Risiken, Nebenwirkungen; – Anwendbarkeit  Empfehlungsgrad: A starke Empfehlung; B mittelstarke Empfehlung; C schwache Empfehlung; D fehlende oder inkonsistente Studien, Empfehlung aufgrund von Expertenmeinung ***Sonstige methodische Hinweise:*** • Rechercheende liegt lange zurück (8 Jahre) • LoE und GoR nicht direkt verknüpft • Nach Prüfverfahren keine Interessenkonflikte festgestellt • Keine Angaben zur Notwendigkeit von der Bestimmung von Markern vor Behandlung mit Gefitinib, Erlotinib • Evidenztabellen (nur online) nicht verfügbar
	Empfehlungen: **Zusammenfassende Empfehlungen zur Therapie im Stadium III** • Die TNM-Stadienzusammenfassung in IIIA und IIIB unterschied technisch resektable – jedoch prognostisch ungünstige – Tumorausbreitungen im Stadium IIIA von in der Regel technisch inoperablen Erkrankungsausdehnungen (Stadium IIIB). Weiterentwicklungen in Staging, Operationstechnik und multimodalen Ansätzen haben die Grenzen dieser Einteilung für therapeutische Entscheidungen gezeigt. Eine optimale Behandlungswahl für den einzelnen Patienten erfordert vor Therapiebeginn die interdisziplinäre Diskussion und Festlegung (zumindest Beteiligung von Pneumologie, Onkologie, Thoraxchirurgie, Radioonkologie und diagnostischer Radiologie) (**Empfehlungsgrad D**). • Die Unterscheidung von Subgruppen speziell im Stadium IIIA (N2) ist für Therapiewahl und Prognose von großer Bedeutung (**Empfehlungsgrad B**). • Ein Beginn der Chemotherapie nach Abschluss der Wundheilung innerhalb von 60 Tagen nach Resektion wird empfohlen (**Empfehlungsgrad D**). • Bei Patienten mit bedeutsamer Komorbidität aufgrund der vorangegangenen Resektion oder vorbestehender Erkrankungen wird empfohlen, die adjuvante Chemotherapie in einem interdisziplinär ausgerichteten Behandlungskontext mit entsprechender Erfahrung in der Durchführung von multimodalen Therapien durchführen zu lassen (**Empfehlungsgrad D**).

	• Für Patienten mit mediastinalem Lymphknotenbefall im Stadium IIIA1 bzw. IIIA2 sollte zusätzlich zur adjuvanten Chemotherapie die Indikation zur postoperativen Mediastinalbestrahlung geprüft werden (**Empfehlungsgrad B**). • Die Bestrahlung sollte bis spätestens 4 Wochen nach Abschluss der adjuvanten Chemotherapie beginnen und eine Dosis von 50–60 Gy nach CT-gestützter 3-dimensionaler Bestrahlungsplanung umfassen. Komorbiditäten müssen bei diesem Vorschlag ausreichend berücksichtigt werden (**Empfehlungsgrad B**). • Patienten im Stadium IIIA3 sollten präferenziell im Rahmen von Studien zur weiteren Definition des Therapiealgorithmus behandelt werden (**Empfehlungsgrad D**). • Außerhalb von Studien können Patienten im Stadium IIIA3 und technisch resektabler Tumorausdehnung individuell mit einem Induktionsprotokoll (Induktionschemotherapie oder Induktionschemostrahlentherapie) behandelt und anschließend operiert werden (**Empfehlungsgrad** B). Grundsätzlich erfordern solche Behandlungsansätze zur sicheren Indikationsstellung vor Therapiebeginn eine interdisziplinäre Diskussion und Festlegung (zumindest Beteiligung von Pneumologie, Onkologie, Thoraxchirurgie Radioonkologie und diagnostischer Radiologie). Präoperativ soll die Indikation zur Resektion im interdisziplinären Kontext gleichermaßen überprüft werden. Die Durchführung sollte an Zentren mit entsprechender Erfahrung und hinreichendem Behandlungsvolumen erfolgen. • In der Subgruppe T4N0/1 des Stadiums IIIB ist die primäre Operation bzw. die Integration der Operation in das Gesamtbehandlungskonzept bei medizinischer und funktioneller Operabilität in folgenden Fällen möglich: Karinabefall, resektabler Trachealbefall, resektabler Befall des Atrium, Infiltration der V. cava oder der Pulmonalarterie, ipsilobäre Metastase im tumortragenden Lungenlappen (**Empfehlungsgrad** B). • Nach Operation und R0-Resektion sollte im Stadium IIIA3 bei alleiniger Induktionschemotherapie eine mediastinale Radiotherapie erfolgen. Bei Induktionschemostrahlentherapieprotokollen sollte nach R0-Resektion keineweitere postoperative Radiotherapie durchgeführt werden (**Empfehlungsgrad B**). • Patienten im Stadium IIIA3 – insbesondere bei multiplem N2-Befall – können gleichermaßen mit einer Kombination aus Strahlentherapie und Chemotherapie (definitive Chemo-/ Radiotherapie) behandelt werden (**Empfehlungsgrad A**). • Patienten im Stadium IIIA4/IIIB sollten – wenn Allgemeinzustand und Tumorausdehnung dies zulassen – eine Kombination aus Strahlentherapie und Chemotherapie erhalten (**Empfehlungsgrad A**). • Für selektionierte Patienten im Stadium IIIA4/IIIB kann im begründeten Ausnahmefall ein multimodaler Behandlungsansatz unter Integration der Operation (möglichst nur in Studien) erfolgen (**Empfehlungsgrad D**). • Im direkten Vergleich ist bei geeigneten Patienten die simultane Radio-/Chemotherapie der sequenziellen überlegen. Bei der Patientenselektion ist auf Komorbiditätsspektrum und Allgemeinzustand zu achten (**Empfehlungsgrad A**). • Die Sequenz von Chemotherapie gefolgt von definitiver Strahlentherapie kann im Vergleich zur alleinigen Strahlentherapie sowohl medianes Überleben als auch 5-Jahres-Überlebensraten signifikant verbessern (**Empfehlungsgrad B**).

- Für die sequenzielle und simultane Chemostrahlentherapie sollten cisplatinbasierte Chemotherapieprotokolle gewählt werden (Kombinationspartner bei simultaner Therapie in der Regel Etoposid oder Vincaalkaloid) (**Empfehlungsgrad B**).
- Sowohl bei der sequenziellen als auch simultanen Behandlung werden typischerweise zwei Zyklen einer voll-dosierten cisplatinhaltigen Kombinationschemotherapie (Zyklusintervall 3–4Wochen) appliziert (**Empfehlungsgrad B**).
- Angesichts des hohen systemischen Rezidivrisikos nach definitiver Chemostrahlentherapie kann im Einzelfall eine konsolidierende platinbasierte Kombinationschemotherapie aufgrund der im historischen Vergleich vielversprechenden Daten im Vergleichsarm einer großen randomisierten Phase-IIIStudie (INT 0139) durchgeführtwerden (**Empfehlungsgrad D**).
- Im Vergleich zur alleinigen simultanen Chemo-/Radiotherapie ist der Stellenwert einer zusätzlichen konsolidierenden Chemotherapie in randomisierten Studien bisher allerdings nicht gegenüber Beobachtung belegt. Die zusätzliche Konsolidierung in Form der Monotherapie mit einem Taxan nach stattgehabter Radio-/Chemotherapie führt sogar zu deutlicher **und inakzeptabler Toxizität und wird nicht empfohlen (Empfehlungsgrad** A).
- Die Strahlentherapie sollte typischerweise eine Dosis zwischen 60 und 66 Gy bei einmal-täglicher Fraktionierung haben (**Empfehlungsgrad A**). Die Zeitdauer hängt von der Einzelfraktionierung ab und liegt typischerweise bei 6–7 Wochen (Empfehlungsgrad B). Eine Unterbrechung der Strahlentherapie sollte vermieden werden (**Empfehlungsgrad C**). […]



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

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

Stadium IV/IIIB (ohne Indikation zur definitiven Radiatio)

- Die Lebenszeit von Patienten im Stadium IIIB/IV ist begrenzt (Median 8–12 Monate). Von vornherein sollte in dieser Situation ein stabiler und

	zuverlässiger Betreuungskontext hergestellt werden. Dafür sollte auch der unmittelbare Zugang zu einem entsprechend ausgerichteten interdisziplinären Betreuungskontext ermöglicht werden (**Empfehlungsgrad D**). • Neben der medizinischen Behandlung sollten im Rahmen des Aufklärungsgesprächs bzw. im fortlaufenden Gesprächskontakt die Möglichkeiten zur Rehabilitation, psychoonkologischen Unterstützung, Sozialberatung bzw. Unterstützung durch Selbsthilfegruppen angesprochen werden (**Empfehlungsgrad D**). • Im Stadium IIIB/IV sollte zunächst geprüft werden, ob eine Erkrankungsmanifestation einer zeitnahen Intervention bedarf. Diese sollte dann rasch und vor Einleitung einer systemischen Therapie erfolgen. Der Zugang zu diesen Techniken und Verfahren muss für alle Patienten zeitnah gewährleistet sein (**Empfehlungsgrad D**). • Bei Vorstellung in einem interdisziplinären Zentrum (Pneumologie; Radioonkologie; Thoraxchirurgie; Onkologie; diagnostische Radiologie; Ernährungsberatung und -therapie; psychologische Beratung und Betreuung; Sozialdienst; Palliativmedizin; im Bedarfsfall Tumororthopädie und Neurochirurgie) sollte eine zeitnahe Entscheidungsfindung und –umsetzung (interdisziplinäre Tumorkonferenz; Dokumentation der Therapiefestlegung) gewährleistet sein (**Empfehlungsgrad D**). Diskussionspunkte: Für die **rezeptor- und ligandenspezifische Therapie** ist es notwendig, in Zukunft prädiktive Parameter zu entwickeln, die vorhersagen, welche Gruppen von Patienten von der Therapie am ehesten profitieren. Ebenfalls ist eine Verbesserung der Therapieergebnisse zum jetzigen Zeitpunkt mit den vorhandenen Substanzen am ehesten von pharmakogenomischen Ansätzen zu erwarten, die in prospektiven klinischen Studien mit standardisierten und validierten Nachweisverfahren erhoben werden sollten. **Empfehlungen** • Bei Patienten im Stadium IIIB/IV in gutem Allgemeinzustand (ECOG 0,1) sollte eine cisplatinbasierte Kombinationschemotherapie zur Verbesserung der Überlebenszeit, der Krankheitskontrolle und der Lebensqualität durchgeführt werden (**Empfehlungsgrad A**). • Bei relevanter Komorbidität (Herzinsuffizienz; Niereninsuffizienz) kann Carboplatin statt Cisplatin eingesetzt werden. Alternativ kann dann auch eine platinfreie Kombination mit Drittgenerationszytostatika eingesetzt werden (**Empfehlungsgrad B**). • In der Erstlinienchemotherapie sollten 4 (–6) Zyklen gegeben werden. Es gibt derzeit keine konsistenten Daten, die im Hinblick auf die Überlebenszeit in der Erstlinienbehandlung eine Erhaltungschemotherapie unterstützen (**Empfehlungsgrad B**). • Patienten in reduziertem Allgemeinzustand (ECOG 2) bzw. mit Kontraindikationen gegen eine platinbasierte Kombinationschemotherapie im Stadium IIIB/IV können eine Monotherapie mit einem Drittgenerationszytostatikum (z. B. Vinorelbin, Gemcitabin) erhalten (**Empfehlungsgrad A**). • Bei Patienten im Stadium IIIB/IV (ECOG 0,1) mit Nicht-Plattenepithelkarzinom führt die Behandlung mit Bevacizumab zusätzlich zur platinbasierten Kombinationschemotherapie zu einer signifikanten

	Verbesserung der Remissionsrate und der medianen Überlebenszeit bzw. des medianen progressionsfreien Überlebens. Bei selektionierten Patienten im Stadium IIIB/IV mit Nicht- Plattenepithelkarzinom und gutem Allgemeinzustand (ECOG 0,1) kann daher – unter Berücksichtigung der Kontraindikationen – Bevacizumab in der Erstlinienbehandlung zusätzlich zur platinbasierten Kombinationschemotherapie eingesetzt werden (**Empfehlungsgrad B**). • Die weitere Charakterisierung von Patientensubgruppen, die am besten profitieren, ist wünschenswert (**Empfehlungsgrad D**). • Bei Patienten > 70 Jahre kann die therapieassozierte Toxizität und Letalität unter Bevacizumab bedeutsam sein. Daher sollte bei älteren Patienten die Indikation besonders streng unter kritischer Würdigung der Komorbidität gestellt werden (**Empfehlungsgrad B**). • Auch unter einer laufenden Therapie müssen regelmäßige Kontrollen erfolgen, um eine die Lebensqualität kompromittierende Symptomatik frühzeitig zu erkennen und zu behandeln (**Empfehlungsgrad B**). • Unter einer laufenden Therapie sollten die Kontrolluntersuchungen in der Regel in 6-wöchigen Intervallen erfolgen. Nach abgeschlossener Therapie erfolgen Kontrollen nach klinischer Erfordernis, die Kontrollintervalle liegen in der Regel bei 6–12Wochen (**Empfehlungsgrad D**). • Bei Patienten im Stadium IIIB/IV führt die Behandlung mit Cetuximab zusätzlich zur platinbasierten Kombinationschemotherapie zu einer statistisch signifikanten Verbesserung der Remissionsrate und der medianen Überlebenszeit. Bei Patienten im Stadium IIIB/IV kann Cetuximab in der Erstlinienbehandlung zusätzlich zur platinbasierten Kombinationschemotherapie eingesetzt werden (**Empfehlungsgrad B**). • Die weitere Charakterisierung von Patientensubgruppen, die am besten profitieren, sollte erfolgen (**Empfehlungsgrad D**). Zum Zeitpunkt der Publikation der Leitlinie ist Cetuximab nicht zur Therapie des nicht-kleinzelligen Lungenkarzinoms zugelassen. • Bei Patienten mit aktivierenden Mutationen des EGF-Rezeptors (insbesondere del. 19; exon 21 L858R) ist Gefitinib im Hinblick auf Remissionsrate und progressionsfreies Überleben in der Erstlinienbehandlung einer Chemotherapie signifikant überlegen (**Empfehlungsgrad B**). Gefitinib ist daraufhin bei positivem Mutationsstatus des EGF-Rezeptors in allen Therapielinien als eine mögliche Behandlungsoption zugelassen worden. In der zulassungsrelevanten Studie erfolgte die Analyse des Mutationsstatus bei Patienten mit einem Adenokarzinom und minimalem Nikotinkonsum (94 % Nieraucher).

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews) am 21.07.2014

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

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

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

MEDLINE (PubMed) am 21.07.2014

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

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

MEDLINE (PubMed) nach Leitlinien am 21.07.2014

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

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

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

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

Literatur

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