Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2015-B-176 Alectinib

Stand: Januar 2016

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Alectinib **zur Behandlung des ALK-positiven lokal fortgeschrittenen oder metastasierten nicht-kleinzelligen Bronchialkarzinoms (NSCLC), nach einer Behandlung mit Crizotinib**	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	*Nicht angezeigt*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	• Afatinib: Beschluss vom 5. November 2015 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Ceritinib: Beschluss vom 17. Dezember 2015 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Crizotinib: Beschluss vom 2. Mai 2013 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Nintedanib : Beschluss vom 18. Juni 2015 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Nivolumab (nicht-kleinzelliges Lungenkarzinom): Beschluss vom 4. Februar 2016 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V • Carboplatin: Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie - Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten - (Stand: 30. Juni 2014): Arzneimittel, die unter Beachtung der dazu gegebenen Hinweise in nicht zugelassenen Anwendungsgebieten (Off-Label-Use) verordnungsfähig sind: Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCL) – Kombinationstherapie
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Beratungsanforderung/Fachinformation)
Zu prüfendes Arzneimittel:	
Alectinib N.N.	Geplantes Anwendungsgebiet: Alectinib wird angewendet zur Behandlung des Anaplastische-Lymphomkinase(ALK)-positiven lokal fortgeschrittenen oder metastasierten nicht-kleinzelligen Bronchialkarzinoms (NSCLC) bei erwachsenen Patienten, die progredient unter der Therapie mit Crizotinib sind oder die Crizotinib nicht vertragen 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.
Docetaxel L01CD02 (generisch)	Nicht-kleinzelliges Bronchialkarzinom: Docetaxel ist zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Bronchialkarzinom nach Versagen einer vorausgegangenen Chemotherapie angezeigt. Docetaxel ist in Kombination mit Cisplatin zur Behandlung von Patienten mit nicht resezierbarem, lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Bronchialkarzinom ohne vorausgegangene Chemotherapie angezeigt.
Etoposid L01CB01 (generisch)	Kombinationstherapie folgender Malignome: Palliative Therapie des fortgeschrittenen NSCLC bei Patienten mit gutem Allgemeinzustand (Karnofsky-Index >80%).
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.
Ifosfamid L01AA06 Holoxan®	Nicht-kleinzellige Bronchialkarzinome: Zur Einzel- oder Kombinationschemotherapie von Patienten mit inoperablen oder metastasierten Tumoren.
Mitomycin L01DC03 (generisch)	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Bei intravenöser Gabe ist es in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei folgenden metastasierenden Tumoren wirksam: […] nicht-kleinzelliges Bronchialkarzinom […].

Paclitaxel L01CD01 (generisch)	Fortgeschrittenes nicht-kleinzelliges Bronchialkarzinom (NSCLC): Paclitaxel ist, in Kombination mit Cisplatin, zur Behandlung des nicht-kleinzelligen Bronchialkarzinoms bei Patienten angezeigt, für die potentiell kurative chirurgische Maßnahmen und/oder eine Strahlentherapie nicht in Frage kommen.
Pemetrexed L01BA04 Alimta®	ALIMTA ist in Kombination mit Cisplatin angezeigt zur first-line Therapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie. ALIMTA in Monotherapie ist angezeigt für die Erhaltungstherapie bei lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie bei Patienten, deren Erkrankung nach einer platinbasierten Chemotherapie nicht unmittelbar fortgeschritten ist. ALIMTA in Monotherapie ist angezeigt zur Behandlung in Zweitlinientherapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie.
Vindesin L01CA03 Eldesine®	Kombinationschemotherapie: Lokal fortgeschrittenes oder metastasiertes nicht-kleinzelliges Bronchialkarzinom (Stadium IIIB, IV).
Vinorelbin L01CA04 (generisch)	Vinorelbin ist angezeigt zur Behandlung: des nicht kleinzelligen Bronchialkarzinoms (Stadium 3 oder 4).
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
Ceritinib L01XE28 Zykadia®	Zykadia wird angewendet bei erwachsenen Patienten zur Behandlung des fortgeschrittenen, Anaplastische-Lymphomkinase(ALK)-positiven, nicht-kleinzelligen Bronchialkarzinoms (NSCLC), die mit Crizotinib vorbehandelt wurden.
Crizotinib L01XE16 Xalkori®	XALKORI wird angewendet bei Erwachsenen zur Erstlinienbehandlung des Anaplastische-Lymphom-Kinase(ALK)-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, NSCLC). XALKORI wird angewendet bei Erwachsenen zur Behandlung des vorbehandelten Anaplastische-Lymphom-Kinase(ALK)-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, NSCLC).
Erlotinib L01XE03 Tarceva®	Nicht-kleinzelliges Lungenkarzinom (NSCLC): Tarceva ist zur First-Line-Behandlung bei Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit aktivierenden EGFR-Mutationen angezeigt. Tarceva ist auch als Monotherapie zur Erhaltungsbehandlung bei Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC angezeigt, deren Krankheitszustand nach 4 Behandlungszyklen einer platinbasierten First-Line-Standardchemotherapie unverändert ist. Tarceva ist auch zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC angezeigt, bei denen mindestens eine vorausgegangene Chemotherapie versagt hat. Beim Verschreiben von Tarceva sollten Faktoren, die im Zusammenhang mit einer verlängerten Überlebenszeit stehen, berücksichtigt werden. Bei Patienten mit epidermalen Wachstumsfaktor-Rezeptor-(EGFR)-IHC-negativen Tumoren konnten weder ein Überlebensvorteil noch andere

	klinisch relevante Wirkungen durch die Behandlung gezeigt werden (siehe Abschnitt 5.1).
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.
Nintedanib L01XE31 Vargatef®	Vargatef wird angewendet in Kombination mit Docetaxel zur Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem, metastasiertem oder lokal rezidiviertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit Adenokarzinom-Histologie nach Erstlinienchemotherapie.
Antikörper	
Bevacizumab L01XC07 Avastin®	Bevacizumab wird zusätzlich zu einer platinhaltigen Chemotherapie zur First-Line-Behandlung von erwachsenen Patienten mit inoperablem fortgeschrittenem, metastasiertem oder rezidivierendem nicht kleinzelligem Bronchialkarzinom, außer bei vorwiegender Plattenepithel-Histologie, angewendet.
Nivolumab L01XC17 Opdivo®	OPDIVO ist zur Behandlung des lokal fortgeschrittenen oder metastasierten nichtkleinzelligen Lungenkarzinoms (NSCLC) mit plattenepithelialer Histologie nach vorheriger Chemotherapie bei Erwachsenen indiziert.

Quellen: AMIS-Datenbank, Fachinformationen

Abteilung Fachberatung Medizin

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

Vorgang: 2015-B-176 Alectinib

Datum: 19.01.2016

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

Inhalt

Indikation für die Recherche:

„Alectinib wird angewendet zur Behandlung des Anaplastische-Lymphomkinase(ALK)-positiven lokal fortgeschrittenen oder metastasierten nicht-kleinzelligen Bronchialkarzinoms (NSCLC) bei erwachsenen Patienten, die progredient unter der Therapie mit Crizotinib sind oder die Crizotinib nicht vertragen haben."

Berücksichtigte Wirkstoffe/Therapien:

siehe Tabelle „II. Zugelassene Arzneimittel im Anwendungsgebiet."

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation *„nicht-kleinzelligem Lungenkarzinom (NSCLC)"* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 17.12.2015 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects,

Health Technology Assessment Database), MEDLINE (PubMed), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, TRIP.
Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien (z.B. NICE, SIGN). Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 732 Quellen, die anschließend in einem zweistufigen Screening Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 21 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CCO	Cancer Care Ontario
DAHTA	Deutsche Agentur für Health Technology Assessment
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG Berichte/ G-BA Beschlüsse

G-BA, 2015 [10]. **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 – Ceritinib** vom 17. Dezember 2015	**Anwendungsgebiet:** Zykadia wird angewendet bei erwachsenen Patienten zur Behandlung des fortgeschrittenen, Anaplastische-Lymphomkinase(ALK)-positiven, nicht-kleinzelligen Bronchialkarzinoms (NSCLC), die mit Crizotinib vorbehandelt wurden. **Zweckmäßige Vergleichstherapie:** 1) Patienten, für die eine Behandlung mit Docetaxel oder Pemetrexed infrage kommt: Docetaxel oder Pemetrexed **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber der Chemotherapie mit Docetaxel oder PEM: Ein Zusatznutzen ist *nicht* belegt. **Zweckmäßige Vergleichstherapie:** 2) Patienten, für die eine Behandlung mit Docetaxel oder Pemetrexed nichtinfrage kommt: Best-Supportive-Care (BSC) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber BSC: Ein Zusatznutzen ist *nicht belegt.*
G-BA, 2015 [11]. **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 – Nintedanib** vom 18. Juni 2015	**Anwendungsgebiet:** Nintedanib (Vargatef®) wird angewendet in Kombination mit Docetaxel zur Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem, metastasiertem oder lokal rezidiviertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit Adenokarzinom-Histologie nach Erstlinienchemotherapie. **Zweckmäßige Vergleichstherapie:** - Eine Chemotherapie mit Docetaxel oder Pemetrexed oder - Gefitinib oder Erlotinib (nur für Patienten mit aktivierenden EGFR-Mutationen) oder - Crizotinib (nur für Patienten mit aktivierenden ALK-Mutationen) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer Chemotherapie mit Docetaxel:** Hinweis für einen geringen Zusatznutzen
G-BA, 2014 [8]. **Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage VI - Off-Label-Use Teil A Ziffer III. Carboplatinhaltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – Kombinationstherapie,**	Der Gemeinsame Bundesausschuss hat in seiner Sitzung am 17. Juli 2014 beschlossen, die Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (Arzneimittel-Richtlinie) in der Fassung vom 18. Dezember 2008 / 22. Januar 2009 (BAnz. Nr. 49a vom 31. März 2009), zuletzt geändert am 19. Juni 2014 (BAnz AT 09.09.2014 B2), wie folgt zu ändern: I. Die Ziffer III. der Anlage VI Teil A zur Arzneimittel-Richtlinie wird unter Nr. 1 Buchstabe j „Zustimmung des pharmazeutischen Unternehmers“ wie folgt geändert: Im zweiten Absatz wird nach der Angabe „Stada Arzneimittel AG“ die Angabe „Sun Pharmaceuticals Germany GmbH“ eingefügt. II. Die Änderungen treten am Tag nach ihrer Veröffentlichung im

Zustimmung eines pharmazeutischen Unternehmers	Bundesanzeiger in Kraft. Die Tragenden Gründe zu diesem Beschluss werden auf den Internetseiten des Gemeinsamen Bundesausschusses unter www.g-ba.de veröffentlicht. Eckpunkte der Entscheidung (Anmerkung: aus den Tragenden Gründen zum Beschluss [9]) Die Firma Sun Pharmaceuticals Germany GmbH hat ... 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.
G-BA, 2013 [7]. **Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Crizotinib** vom 2. Mai 2013	**Anwendungsgebiet:** Zur Behandlung des vorbehandelten Anaplastische-Lymphom-Kinase (ALK)-positiven, fortgeschrittenen nicht kleinzelligen Bronchialkarzinoms (non small cell lung cancer, NSCLC). **Zweckmäßige Vergleichstherapie:** a) Patienten, bei denen eine Chemotherapie angezeigt ist: Docetaxel oder PEM zur Behandlung von Patienten, bei denen eine Chemotherapie angezeigt ist (dies können insbesondere Patienten mit ECOG-PS 0, 1 und gegebenenfalls 2 sein). **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber der Chemotherapie mit Docetaxel oder PEM: Anhaltspunkt für einen *beträchtlichen* Zusatznutzen. **Zweckmäßige Vergleichstherapie:** b) Patienten, bei denen eine Chemotherapie nicht angezeigt ist: BSC zur Behandlung von Patienten, bei denen eine Chemotherapie nicht angezeigt ist (dies können insbesondere Patienten mit ECOG-PS 4, 3 und gegebenenfalls 2 sein). **Ausmaß und Wahrscheinlichkeit des Zusatznutzens** gegenüber BSC: Ein Zusatznutzen ist *nicht belegt.*
GBA, 2011 [6]. **Protonentherapie beim Nichtkleinzelligen Lungenkarzinom (NSCLC) Abschlussbericht. Beratungsverfahren nach § 137c SGB V (Krankenhausbehandlung)**	Der Gemeinsame Bundesausschuss hat in seiner Sitzung am 21. Oktober 2010 beschlossen, die Richt-linie zu Untersuchungs- und Behandlungsmethoden im Krankenhaus (Richtlinie Methoden Kranken-hausbehandlung) in der Fassung vom 21. März 2006 (BAnz. 2006, S. 4466), zuletzt geändert am 18. Februar 2010 (BAnz. 2010, S. 1784), wie folgt zu ändern: I. In § 4 („Ausgeschlossene Methoden“) werden nach Nummer 3.7 folgende Nummern angefügt: „3.8 Protonentherapie beim operablen nicht-kleinzelligen Lungenkarzinom 3.9 Protonentherapie beim inoperablen nicht-kleinzelligen Lungenkarzinom des UICC Stadiums IV“ II. In Anlage II „Methoden, deren Bewertungsverfahren ausgesetzt sind“ wird nach Nummer 2.2 folgende Nummer 2.3 angefügt: „2.3 Protonentherapie beim inoperablen nicht-kleinzelligen

	Lungenkarzinom der UICC Stadien I bis III Beschluss gültig bis 31. Dezember 2015“

Cochrane Reviews

Zur Fragestellung wurden keine relevanten Cochrane Reviews identifiziert.

Systematische Reviews

Vale CL et al., 2015 [18].

Should Tyrosine Kinase Inhibitors Be Considered for Advanced Non-Small-Cell Lung Cancer Patients With Wild Type EGFR? Two Systematic Reviews and Meta-Analyses of Randomized Trials

1. Fragestellung

We assessed the effect of TKIs as second-line therapy and maintenance therapy after first-line chemotherapy in two systematic reviews and meta-analyses, focusing on patients without EGFR mutations.

2. Methodik

Population: advanced NSCLC irrespective of sex, age, histology, ethnicity, smoking history, or EGFR mutational status. Patients should not have received previous TKIs

Interventionen und Komparatoren: TKI (erlotinib or gefitinib) vs. chemotherapy

***Endpunkte*:** PFS, OS

Suchzeitraum: bis 2012

Anzahl eingeschlossene Studien/Patienten (Gesamt):

Second line: 14 (4388) Maintenance: 6 (2697)

Qualitätsbewertung der Studien: The risk of bias of individual trials was assessed with a low risk of bias being desirable for sequence generation, allocation concealment, and completeness of outcome data reporting. Trials in the maintenance setting should have also been at low risk of bias for blinding.

Heterogenitätsuntersuchungen: I^2

3. Ergebnisdarstellung

Tyrosine Kinase Inhibitor Versus Chemotherapy in the Second-Line Setting

- No trials were judged to be at high risk for any of the domains assessed
- Results based on 14 remaining eligible trials (4 388 patients, 98% of total randomized)
- Trials compared TKIs with either docetaxel or pemetrexed chemotherapy and were conducted between 2003 and 2012.
- Randomized patients had good performance status (0-2) and median age ranged from 54.5 to 67.5 years (range, 20-88 years).
- Most were men and either current or former smokers.
- One trial included considerably more women (85%) and only neversmokers.
- Three trials randomized patients with wild type EGFR exclusively (8, 9, 37 siehe unten).
- Five trials evaluated EGFR mutation status using a range of methods (including DAKO EGFR Pharma DX and Eppendorf Piezo-electric microdissector).
- Mutation status was not evaluated in 5 trials.
- Twelve trials (3 963 patients, 90% of total) reported PFS and 14 trials (4 355 patients, 99% of total) reported OS.

Trial and Patient Characteristics (Based on All Randomized Patients, Trials of Second-Line Treatment):

Trial/	TKI vs. Control	Patients With	EGFR	EGFR Wild

Patient n		Known EGFR Status (% of Total Randomized)	Mutation, n (% of Total With Known Status)	Type, n (% of Total With Known Status)
SIGN[26]/ 141	Gefitinib vs. Docetaxel	NR	NR	NR
V-15-32[27]/ 489 (387a)	Gefitinib vs. Docetaxel	57 (12)	31 (55)	26 (45)
Herbst et al[28]/ 79	Erlotinib vs. Docetaxel or pemetrexed with bevacizumab	30 (38)	1 (3)	29 (97)
INTEREST[29]/ 1466 (1316a)	Gefitinib vs. Docetaxel	267 (18)	38 (14)	229 (86)
ISTANA[30]/ 161	Gefitinib vs. Docetaxel	NR	NR	NR
Li et al[36]/ 98	Gefitinib vs. Docetaxel	NR	NR	NR
TITAN[31]/ 424	Erlotinib vs. Docetaxel or pemetrexed	160 (38)	11 (7)	149 (93)
HORG[32]/ 332	Erlotinib vs. Pemetrexed	NR	NR	NR
CTONG 0806 [9,b]/ 157	Gefitinib vs. Pemetrexed	157 (100)	Only WT patients	157 (100)
TAILOR[8,b]/ 219	Erlotinib vs. Docetaxel	219 (100)	Only WT patients	219 (100)
KCSG-LU08-01[33]/ 135	Gefitinib vs. Pemetrexed	71 (53)	33 (46)	38 (54)
PROSE[34]/ 263	Erlotinib vs. Docetaxel or pemetrexed	177 (67)	14 (8)	163 (92)
DELTA[35]/ 301	Erlotinib vs. Docetaxel	255	51 (20)	199 (78)
Li et al[37,b]/ 123	Erlotinib Pemetrexed	123 (100)	Only WT patients	123 (100)
Total	**N=4388 (4136)**	**1516 (35)**	**179 (12)**	**1332 (88)**

Abbreviations: ATLAS = Avastin Tarceva Lung Adenocarcinoma Study; CTONG = Chinese Thoracic Oncology Group; DELTA = Docetaxel and Erlotinib Lung Cancer Trial; EGFR =epidermal growth factor receptor; EORTC = European Organisation for Research and Treatment of Cancer; HORG = Hellenic Oncology Research Group; IFCT-GFPC = Partenariat Intergroupe Francophone de Cancérologie Thoracique-Groupe Français de Pneumo-Cancérologie; INFORM = Iressa in NSCLC FOR Maintenance; INTEREST = IRESSA Non-small-cell lung cancer Trial Evaluating REsponse and Survival against Taxotere; ISTANA = Iressa as Second-line Therapy in Advanced NSCLC; KCSG = Korean Cancer Study Group; non-sq ¼ Non-Squamous; PROSE = Predicting Response to Second-Line Therapy Using Erlotinib; PS = performance status; SATURN = Sequential Tarceva in Unresectable NSCLC; SIGN =Second-line Indication of Gefitinib in NSCLC; SWOG = South West Oncology Group; TAILOR =Tarceva Italian Lung Optimization Trial; TITAN = Tarceva In Treatment of Advanced NSCLC; TKI = tyrosine kinase inhibitor; WT = wild type.

aProgression-free survival analyses for patient number in parentheses, but patient characteristics reported for all patients.

bOnly randomized patients with wild type EGFR.

cThree-arm trial including 464 randomized patients but only 2 arms included here.

dIncludes bevacizumab in both arms.

eTotal for progression-free survival, total for overall survival is 345.

Berücksichtigte RCTs (Reihenfolge siehe Tabelle oben):

26. Cufer T, et al. Phase II, open-label, randomized study (SIGN) of single-agent gefitinib (IRESSA) or docetaxel as second-line therapy in patients with advanced (stage IIIb or IV) nonesmall-cell lung cancer. Anticancer Drugs 2006; 17:401-9.

27. Maruyama R, et al. Phase III study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with nonesmall-cell lung cancer. J Clin Oncol 2008; 26:4244-52.

28. Herbst RS, et al. Phase II study of efficacy and safety of bevacizumab in combination with

chemotherapy or erlotinib compared with chemotherapy alone for treatment of recurrent or refractory nonesmall-cell lung cancer. J Clin Oncol 2007; 25:4743-50.

29. Douillard JY, et al. Molecular predictors of outcome with gefitinib and docetaxel in previously treated nonesmall-cell lung cancer: data from the randomized phase III INTEREST trial. J Clin Oncol 2010; 2009:744-52.

30. Lee DH, et al. Randomized phase III trial of gefitinib versus docetaxel in nonesmall-cell lung cancer patients who have previously received platinum-based chemotherapy. Clin Cancer Res 2010; 16:1307-14.

36. Li H, Wang X, Hua F. Second-line treatment with gefitinib or docetaxel for advanced nonesmall-cell lung cancer [in Chinese]. Chin J Clin Oncol 2010; 37: 16-8.

31. Ciuleanu T, et al. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, nonesmall-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. Lancet Oncol 2012; 13:300-8.

32. Karampeazis A, et al. Pemetrexed versus erlotinib in pretreated patients with advanced nonesmall-cell lung cancer: a Hellenic Oncology Research Group (HORG) randomized phase 3 study. Cancer 2013; 119: 2754-64.

33. Ahn MJ, et al. Randomized phase III trial of gefitinib or pemetrexed as second line treatment in patients with nonesmall-cell lung cancer previously treated with platinum-based chemotherapy (KCSG-LU08-01). J Thorac Oncol 2011; 6(Suppl 2):s317 (abstract no O10.04).

9. Zhou Q, et al. Final results of CTONG 0806: a phase II trial comparing pemetrexed with gefitinib as second-line treatment of advanced nonsquamous NSCLC patients with wild-type EGFR. J Thorac Oncol 2013; 8(Suppl 2):S194 (abstract O15.07).

8. Garassino MC, et al. Erlotinib versus docetaxel as secondline treatment of patients with advanced nonesmall-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. Lancet Oncol 2013; 14: 981-8.

34. Gregorc V, et al. Predictive value of a proteomic signature in patients with nonesmall-cell lung cancer treated with second-line erlotinib or chemotherpay (PROSE): a biomarker-statified, randomised phase 3 trial. Lancet Oncol 2014; 15:713-21.

35. Kawaguchi T, et al. Randomised phase III trial of erlotinib versus docetaxel as second or third-line therapy in patients with advanced none small-cell lung cancer: docetaxel and erlotinib lung cancer trial (DELTA). J Clin Oncol 2014; 32:1902-8.

37. Li N, et al. A randomized phase 2 trial of erlotinib versus pemetrexed as second-line therapy in the treatment of patients with advanced EGFR wild-type and EGFR FISH-positive lung adenocarcinoma. Cancer 2014; 120:1379-86.

PFS

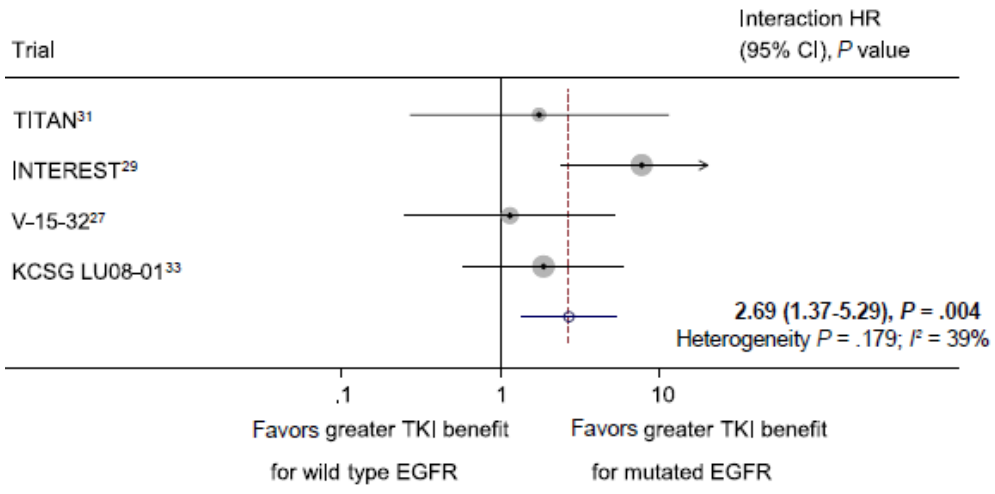

Abbildung 1: Tyrosine Kinase Inhibitor (TKI) Versus Chemotherapy in the Second-Line Setting: Interaction Between Treatment Effect and Epidermal Growth Factor Receptor (EGFR) Mutation Status for Progression-Free Survival. The Circles Represent (Fixed Effect) Meta-Analysis of the Hazard Ratios (HRs) Representing the Interaction Between the Effect of Treatment (TKI) in Wild Type EGFR Compared With Mutated EGFR; the Horizontal Lines Show the 95% CI.

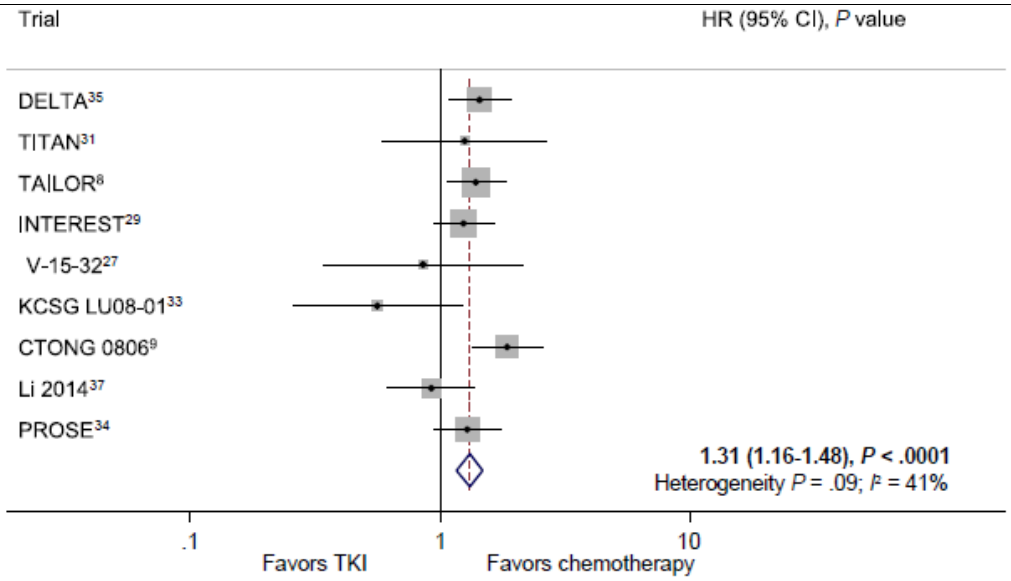

Abbildung 2: TKI Versus Chemotherapy in the Second-Line Setting: Effect of Treatment in 1 302 Patients With Wild Type EGFR on Progression-Free Survival. Each Square Denotes the HR for That Trial With the Horizontal Lines Showing the 95% CI. The Size of the Square Is Directly Proportional to the Amount of Information Contributed by That Trial. The Diamond Gives the Pooled HR From the Fixed Effect Model; the Center of the Diamond Denotes the HR and the Extremities, the 95% CI.

OS

Based on the available data, there was no evidence of an interaction between the effect of TKIs on OS and EGFR mutational status (interaction HR, 1.15; 95% CI, 0.60-2.18; P = .68. This relationship appeared consistent across trials (heterogeneity P = .37; I2, 4%).

3. Anmerkungen/Fazit der Autoren

There was a suggestion that benefits of TKIs on PFS decreased with increasing proportions of patients with wild type EGFR (p = 0,11). Chemotherapy should be standard second-line treatment for patients with advanced NSCLC and wild type EGFR. TKIs might be unsuitable for unselected patients. TKIs appear to benefit all patients compared with no active treatment as maintenance treatment, however, direct comparisons with chemotherapy are needed.

Hinweise FB Med:

- *work supported by the UK Medical Research Council, sponsors had no role in study design, data collection, data analysis, data interpretation, or writing; corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication*
- *The authors have stated that they have no conflicts of interest.*

Xu JL et al., 2015 [20].

Chemothera

1. Fragestellung

Whether a combination of chemotherapy and erlotinib is beneficial for advanced non-small cell lung cancer (NSCLC) remains controversial. This study aimed to summarize the currently available evidence and compare the efficacy and safety of chemotherapy plus erlotinib versus chemotherapy alone for treating

py plus Erlotinib versus Chemotherapy Alone for Treating Advanced Non-Small Cell Lung Cancer: A Meta-Analysis

advanced NSCLC.

2. Methodik

Population: patients with NSCLC, keine Erhaltungstherapie

Intervention: erlotinib plus standard chemotherapy

Komparator: standard chemotherapy alone

Endpunkte: OS, PFS

Suchzeitraum: bis 10 / 2014

Anzahl eingeschlossene Studien/Patienten (Gesamt): *9 / 3 599 (RCT)*

Qualitätsbewertung der Studien: Cochrane Handbook for Systematic Reviews of Interventions, which appraised sequence generation, allocation concealment, performance bias, detection bias, attrition bias, reporting bias, and other biases.

Heterogenitätsuntersuchungen: I^2 statistic

„Publication bias“: subjective funnel plots and objective Begg's and Egger's tests

3. Ergebnisdarstellung

- nine trials finally included for this meta-analysis
- five provided information on EGFR-mutation status (table 1)

Table 1. Summary of Characteristics of the Included Studies. Abbreviations: E: erlotinib, Carb: carboplatin, Cisp: cisplatin, Pac: paclitaxel, Gem: Gemci- tabine, Pem: Pemetrexed, NA: Not available

Study	No. of patients	Dominant ethnicity	Female	Age (range)	Drug delivery	Treatment comparison	Non-smoker	EGFR-mutant	EGFR-wild-type
Herbst, 2005	1079	Caucasian/934	424	24–84	Continuous	E+Carb+Pac vs. Carb+Pac +Placebo	116	29	198
Thomas, 2013	146	NA	73	69–90	Continuous	E+Gem vs. E vs. Gem	240	24	19
Lee, 2013	240	Asian/240	157	NA	Intercalated	E+Pem vs. E vs. Pem	219	97	136
Wu, 2013	451	Asian/451	179	31–96	Intercalated	E+Gem+Cisp or Carb vs. Gem+Cisp or Carb +Placebo	219	97	136
Auliac, 2014	151	NA	115	NA	Intercalated	E+docetaxel vs. E vs. docetaxel	11	NA	98

10. Auliac JB, et al. Randomized open-label noncomparative multicenter phase II trial of sequential erlotinib and docetaxel versus docetaxel alone in patients with non-small-cell lung cancer after failure of first-line chemotherapy: GFPC 10.02 study. Lung Cancer. 2014; 85: 415–419.

11. Wu YL, et al. Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomised, double-blind trial. Lancet Oncol. 2013; 14: 777–786. doi: 10.1016/S1470-2045(13)70254-7

12. Stinchcombe TE, et al. A retrospective analysis of VeriStrat status on outcome of a randomized phase II trial of first-line therapy with gemcitabine, erlotinib, or the combination in

elderly patients (age 70 years or older) with stage IIIB/IV non-small-cell lung cancer. J Thorac Oncol. 2013; 8: 443–451.

13. Lee DH, et al. Three-arm randomised controlled phase 2 study comparing pemetrexed and erlotinib to either pemetrexed or erlotinib alone as second-line treatment for never-smokers with non-squamous non-small cell lung cancer. Eur J Cancer. 2013; 49: 3111–3121.

16. Herbst RS, et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol. 2005; 23: 5892–5899.

Risk of bias and publication bias assessment

- two did not provide details about random sequence generation [12, 16]
- one showed concealment procedures [11]
- three were open-label [10, 12, 13]
- three had independent persons who performed the outcome assessment [10, 11, 16]
- one did not show details about the blinding of outcome assessment [12]
- three conducted efficacy analysis on an intention-to-treat basis [11, 13, 16]
- one missed two cases in both arms [10]
- four did not selectively report data [10–13], while the protocol of one was not available [16], judge whether this trial selectively reported data not assessable
- No significant publication bias was detected for any of the measured outcomes by funnel plots.

PFS (Subgruppenanalyse)

- No significant difference was shown in PFS between the chemotherapy plus erlotinib group and the chemotherapy group in patients with EGFR wild-type tumors (HR = 0.87 [95% CI 0.70, 1.08], P = 0.21) (Abbildung 3).

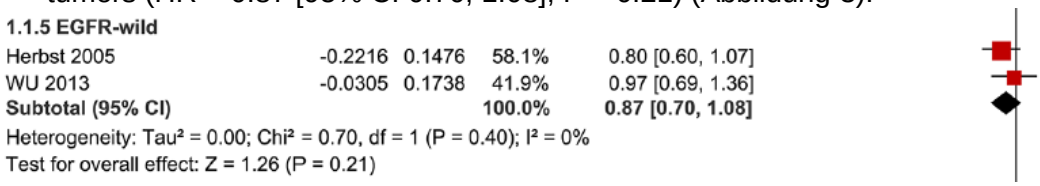

Abbildung 3: Forest Plot of Subgroup Analysis for PFS.

OS (Subgruppenanalyse)

- No significant difference in OS was noted in patients with EGFR wild-type tumors (HR = 0.78 [95% CI 0.59, 1.01], P = 0.06) (Abbildung 4).

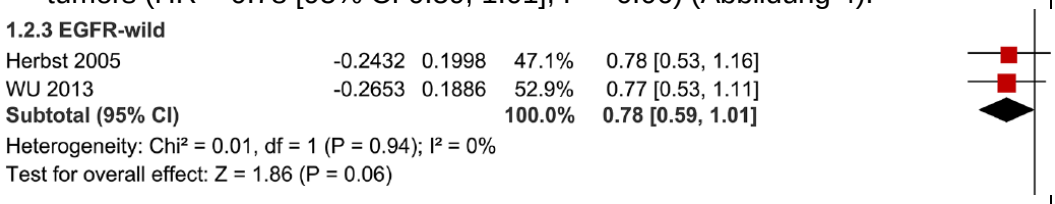

Abbildung 4: Forest Plot of Subgroup Analysis for OS.

Adverse Events

- data for grade 3 or 4 adverse events available in five studies [9–11, 15, 16]
- more incidences of grade 3 or 4 anemia (OR = 1.48 [95% CI 1.12, 1.97], P = 0.006), rash (OR = 12.34 [95% CI 5.65, 26.95], P<0.00001), and diarrhea (OR = 4.25 [95% CI 2.16, 8.38], P<0.0001) in the erlotinib and

	chemotherapy combination treatment • no difference in incidences of grade 3 or 4 neutropenia (OR = 1.02 [95% CI 0.83, 1.24]], P = 0.86), leucopoenia (OR = 1.31 [95% CI 0.80, 2.14], P = 0.29), or thrombocytopenia (OR = 1.26 [95% CI 0.91, 1.74], P = 0.17)
	4. Fazit der Autoren Combination of chemotherapy and erlotinib is a viable treatment option for patients with NSCLC, especially for patients who never smoked and patients with EGFR mutation-positive disease. In addition, intercalated administration is an effective combinatorial strategy. *Hinweise FB Med:* • *study supported by Key projects of Biomedicine Department, Science and Technology Commission of Shanghai Municipality (Project No11411951200), funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript* • *The authors have declared that no competing interests exist.* • *Ergebnisse lassen keine Aussagen für Erst- vs. Zweitlinie zu (nicht untersucht)* • *Achtung: Anwendungsgebiet der First-Line-Erhaltungstherapie mit Erlotinib jetzt beschränkt auf Patienten mit Tumoren, die eine aktivierende EGFR-Mutation aufweisen (siehe Rote-Hand-Brief zu Erlotinib vom 14.01.2016)*
Zhao N, et al., 2014 [21]. **Efficacy of epidermal growth factor receptor inhibitors versus chemotherapy as second-line treatment in advanced non-small-cell lung cancer with wild-type EGFR: a meta-**	1. Fragestellung We sought to evaluate the effectiveness of EGFR-TKI as second-line treatment in EGFR wild-type NSCLC.
	2. Methodik **Population:** previously treated advanced NSCLC with wild-type EGFR **Intervention:** EGFR TKIs **Komparator:** chemotherapy **Endpunkte:** progression-free survival (PFS), overall survival (OS), objective response rate (ORR) **Suchzeitraum**: July 31, 2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 6/990 (5 phase III) **Qualitätsbewertung der Studien:** Jadad scale **Heterogenitätsuntersuchungen:** x2-based Q test; p > 0,05 indicates low heterogeneity; p ≤ 0,05 reflects high heterogeneity, if significant random-effects model used, if not significant FEM used **„Publication bias“:** tested by funnel plot
	3. Ergebnisdarstellung • all studies reached Jadad score of 3

analysis of randomized controlled clinical trials	PFS (EGFR-TKIs vs. chemotherapy) • HR 1,37; 95 % KI 1,20 – 1,56; p < 0,00001 – in the second-/third-line treatment of EGFR wild-type NSCLC, PFS significantly inferior in EGFR-TKI group compared with chemotherapy group • gefitinib and erlotinib significantly inferior to chemotherapy • erlotinib vs. chemotherapy: HR 1,37; 95 % KI 1,16 – 1,63, p = 0,0003 • gefitinib vs. chemotherapy: HR 1,35; 95 % KI 1,10 – 1,67, p = 0,004 • head-to-head trials: results favored chemotherapy more obviously (HR 1,53; 95 % KI 1,29 – 1,81; p < 0.00001 • subgroup trials, which had only subgroup analyses for EGFR wild-type patients: PFS not significantly different (HR 1,16; 95 % KI 0,94 – 1,43; p = 0,17) OS and ORR • equal results
	4. Fazit der Autoren: Chemotherapy improves PFS significantly but not OS, compared with EGFR-TKIs as a second-line treatment in advanced NSCLC with wild-type EGFR. Whether EGFR-TKIs should be used in EGFR wild-type patients should be considered carefully. *Hinweise FB Med:* • *study quality not further discussed* • *no evidence of publication bias* • *authors declared no potential conflicts of interest* • *work supported by Key Technologies R&D Programof Guangzhou (2011Y2-00014), Key Laboratory Program ofGuangdong (2012A061400006) (Y.L. Wu)* • *Achtung: Anwendungsgebiet der First-Line-Erhaltungstherapie mit Erlotinib jetzt beschränkt auf Patienten mit Tumoren, die eine aktivierende EGFR-Mutation aufweisen (siehe Rote-Hand-Brief zu Erlotinib vom 14.01.2016)*
Lee JK, et al., 2014 [12]. **Epidermal growth factor receptor tyrosine kinase inhibitors vs conventional**	1. Fragestellung To determine the association between first-generation EGFR TKI vs chemotherapy and survival in advanced NSCLC patients with WT EGFR.
	2. Methodik **Population:** advanced NSCLC with wild type (WT) EGFR **Intervention:** EGFR TKI **Komparator:** Conventional chemotherapy **Endpunkte:** primary - progression-free survival (PFS), secondary - objective response rate, overall survival **Suchzeitraum:** through December 2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 11/1 605 (7 studies

chemotherapy in non-small cell lung cancer harboring wild-type epidermal growth factor receptor: a meta-analysis.	on second line treatment or later) **Qualitätsbewertung der Studien:** risk of bias by Cochrane Collaboration's tool **Heterogenitätsuntersuchungen:** χ 2 statistic used, I2 statistic also calculated, predefined subgroup analyses performed: line of treatment (first vs second or later), experimental drug (erlotinib vs gefitinib), ethnicity (Asiandominant vs white-dominant trials), and EGFR mutation analysis method (direct sequencing only vs more sensitive platforms; eg, fragment length analysis, amplificationrefractory mutation system, and mass spectrometric genotyping) **„Publication bias":** funnel plot method togetherwith the Egger test for asymmetry to assess the possibility of publication bias
	3. Ergebnisdarstellung • among patients with WT EGFR tumors, chemotherapy associated with improvement of PFS, compared with TKI (HR for TKI, 1.41; 95%CI, 1.10-1.81) • no statistically significant subgroup difference identified in terms of line of treatment (first-line vs. second- or later-line), experimental drug (erlotinib vs. gefitinib), dominant ethnicity, or EGFR mutation analysis method • association of chemotherapy with improvement in PFS also significant in second- or later-line trials (HR, 1.34; 95%CI, 1.09-1.65) • objective response rate higher with chemotherapy (92/549, 16.8%, vs 39/540, 7.2%, for TKI; relative risk for TKI, 1.11; 95%CI, 1.02-1.21) • no statistically significant difference observed with respect to overall survival (HR for TKI, 1.08; 95%CI, 0.96-1.22)
	4. Fazit der Autoren: Among patients with advanced NSCLC harboring WT EGFR, conventional chemotherapy, compared with first-generation EGFR TKI, was associated with improvement in PFS but not overall survival. *Hinweise FB Med:* • *study quality not further discussed* • *Arbeit aus staatlichen Mitteln gefördert* • *Interessenkonflikterklärungen offengelegt* • *Achtung: Anwendungsgebiet der First-Line-Erhaltungstherapie mit Erlotinib jetzt beschränkt auf Patienten mit Tumoren, die eine aktivierende EGFR-Mutation aufweisen (siehe Rote-Hand-Brief zu Erlotinib vom 14.01.2016)*
Di et al., 2014 [5]. **Effectiveness and Safety of**	1. Fragestellung Meta-analysis to compare the efficacy and safety of pemetrexed and docetaxel for non-small cell lung cancer (NSCLC)
	2. Methodik **Population:** Patients with NSCLC **Intervention/ Komparator:** Pemetrexed vs. Docetaxel oder pemetrexed-based

Pemetrexed Versus Docetaxel as a Treatment for Advanced Non-small Cell Lung Cancer: a Systematic Review and Meta-analysis.	doublet vs. docetaxel-based with the same doublet **Endpunkt:** overall response rate (ORR), median survival time, progression free survival (PFS), disease control rate (DCR), 1-3yr survival rate, toxicities **Suchzeitraum:** systematical search of the Cochrane Library, PubMed, Embase, China Biology Medicine Database for randomized controlled trials (RCTs). We limited the languages to English and Chinese. Two reviewers independently screened articles and assessed the methodological quality of included trials, and then extracted data. **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 6 RCTs/n = 1 414 **Qualitätsbewertung der Studien:** methods of the Cochrane Collaboration for assessing risk of bias Heterogenitätsanalysen:
	• Ergebnisdarstellung **Table 2. Quality of Included Trials** All the six trials included in our study didn't report allocation concealment, and four of them didn't report blinding and two of them were open label trials, which might have resulted in an overestimation of the effect. <u>efficacy</u> • no statistically significant differences in overall response rate, survival time, progression-free survival, disease control rate, and 1-2yr survival rate (p>0.050) • patients in the pemetrexed arms had significantly higher 3-yr survival rate (p=0.002) <u>grade 3 or 4 toxicity</u> • pemetrexed: lower rate of febrile neutropenia, neutropenia, leukocyts toxicity (p<0.001) • no significant difference in anemia between the two arms (p=0.08) • pemetrexed: higher rate of thrombocytopenia toxicity (p=0.03) • pemetrexed: lower rate of diarrhea and alopecia
	5. Fazit der Autoren: Pemetrexed was almost as effective as docetaxel in patients with advanced NSCLC. At the same time, pemetrexed might increase the 3-yr survival rate. As for safety, pemetrexed led to lower rate of grade 3-4 febrile neutropenia, neutropenia, leukocytes, diarrhea and alopecia toxicity. However, it was

Included Trials	Random allocation	Allocation concealment	Blinding	Intent-to-treat analysis	Lost to follow-up
Chen et al., 2008	Yes	Not report	Not report	Not report	Yes
Hanna et al., 2004	Yes	Not report	Not report	Yes	Yes
Jose et al., 2011	Yes	Not report	Open-label	Yes	Yes
Li et al., 2012	Yes	Not report	Not report	Not report	Yes
Socinski et al., 2010	Yes	Not report	Not report	Yes	Yes
Sun et al., 2013	Yes	Not report	Open-label	Yes	Yes

	associated with a higher rate of grade 3-4 thrombocytopenia. … all the samples of the included trials were too small, we are not sure about the effect which hasn't been overestimated or underestimated. Finally, the quality levels of most trials included were graded as "B", which may be at a high risk of bias. … Hence the results of our review must be interpreted with caution. *Hinweise FB Med:* • *Theoretical support was given by Evidence Based Medical Center of Lanzhou University (The Fund Project Number: 2013-EBM-KT-02)* • *Keine Angaben zu Finanzierung und Interessenkonflikten* • *Ergebnisse lassen keine Aussagen zur Subgruppen mit ALK+, EGFR-Wildtypen oder Adenokarzinom zu (gesonderte Analysen fehlen)*

Leitlinien

Masters GA, 2015 [13].

American Society of Clinical Oncology (ASCO)

Systemic Therapy for Stage IV Non–Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

1. Fragestellung

CLINICAL QUESTION B4: What is the most effective second-line therapy for patients with stage IV NSCLC with ALK rearrangement with progression after first-line crizotinib?

2. Methodik

Grundlage der Leitlinie: An Update Committee of the American Society of Clinical Oncology NSCLC Expert Panel based recommendation on a systematic review of randomized controlled trials.

- Update: letzte Version von 2009
- Suchzeitraum: from January 2007 to February 2014
- *Empfehlungen basieren auf externer Evidenz, informalem oder formalem Konsens (siehe unten), Entscheidungsprozess nicht abschließend transparent*
- *Weitere Kriterien für die Qualität einer LL:*
  - *systematische Recherche in PubMed, Auswahlkriterien beschrieben*
  - *Treffer systematisch qualitätsbewertet und Ergebnisse in Evidenztabellen dargestellt*
  - *Empfehlungen sind indirekt mit Literaturstellen verknüpft (Zitate im Hintergrundtext)*
  - *Expertenreview vor Veröffentlichung*
  - *Aktualisierungsbedarf regelmäßig kontrolliert*

LoE: Guide for Rating Strength of Evidence

Rating	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (e.g., balance of benefits versus harms) and further research is very unlikely to change either the magnitude or
Intermediate	Intermediate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect, however it might alter the magnitude of
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change the
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. Reliance on consensus opinion of experts may be reasonable to provide guidance on

GoR: Guide for Strength of Recommendations

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on: a) strong evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with no or minor exceptions; c) minor or no concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling

Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: a) good evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with minor and/or few exceptions; c) minor and/or few concerns about study quality; and/or d) the extent of panelists' agreement. Other
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: a) limited evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, but with important exceptions; c) concerns about study quality; and/or d) the extent of panelists' agreement.

Guide for Types of Recommendations

Type of Recommendation	Definition
Evidence-based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
Formal Consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or
Informal Consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may
No Recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process

3. Empfehlungen

Recommendation B4

Patients whose tumors have ALK rearrangements and who received crizotinib in the first-line setting may be offered the option of chemotherapy (after first-line recommendations for patients with NSCC [see Recommendation A2]) or ceritinib in the second-line setting.

- **chemotherapy**: type: evidence based, benefits outweigh harms; evidence quality: high; strength of recommendation: **strong**;
- **ceritinib**: type: evidence based, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: **moderate**

42. Shaw AT, et al: Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med 370:1189-1197, 2014 – Phase I, n = 130, 68 % mit Crizotinib vorbehandelt

43. Kim DW, Mehra R, Tan DSW: Ceritinib in advanced anaplastic lymphoma kinase (ALK)-rearranged (ALK_) non-small cell lung cancer (NSCLC): Results of the ASCEND-1 trial. J Clin Oncol 32:506s, 2014 (suppl 5s; abstr 8003) – updated results of Shaw, 2014; n = 255

56. Shaw AT, et al: Crizotinib versus chemotherapy in advanced ALKpositive lung cancer. N Engl J Med 368:2385-2394, 2013 - offene Phase III, n = 347, one prior platinum-based regimen

102b. US Food and Drug Administration: Ceritinib. http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm395386.htm - Zulassung auf Basis einarmiger Phase I Studie (siehe oben Shaw, 2014 und Kim, 2014)

	Recommendation A2 For patients who have the characteristics described in Clinical Question A2 (siehe unten) and who have non-squamous histology, the following options are acceptable: • Cisplatin-based combinations (type: evidence based, benefits outweigh harms; evidence quality: high; strength of recommendation: **strong**) • Carboplatin-based combinations (type: evidence based, benefits outweigh harms; evidence quality: high; strength of recommendation: **strong**) • Nonplatinum doublets (type: evidence based, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: **weak**) CLINICAL QUESTION A2: What is the most effective first-line therapy for patients with stage IV NSCLC with non-SCC (NSCC), negative or unknown EGFR-sensitizing mutation and ALK gene rearrangement status, and PS 0 to 1 or possibly PS 2? ***Third-Line Treatment for Patients:*** • Who have not received erlotinib or gefitinib and have PS 0 to 3: erlotinib may be recommended. • Data are insufficient to recommend routine third-line cytotoxic drugs.
NCCN, 2015 [14]. Non-Small Cell Lung Cancer (Vers. 7.2015)	**Fragestellung** Diagnose, Pathologie, Staging, Therapie des NSCLC
	Methodik Update der LL von 2014. Literatursuche: in PubMed zwischen 06/2013 und 06/2014 Diskussion der Literatur und Empfehlungen im Expertenpanel. GoR, LoE: Alle Empfehlungen entsprechen der Kategorie 2A, sofern nicht explizit anders spezifiziert. **NCCN Categories of Evidence and Consensus** **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. **Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. **All recommendations are category 2A unless otherwise noted.**

Empfehlungen (siehe Anhang)

Literatur zu Crizotinib: Shaw AT, et al. Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis. Lancet Oncol. 2011 Oct;12(11):1004-12

Literatur zu Ceritinib: Shaw AT, et al: Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med 370:1189-1197, 2014 (siehe oben Masters, et al. 2015)

Australian Government, Cancer Council Australia. 2015 [2].

Clinical practice guidelines for the treatment of lung cancer

Fragestellung

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

Methodik

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

Suchzeitraum: bis 2012

LoE (nur die hier benötigten):

I: A systematic review of level II studies

II: A randomised controlled trial

GoR:

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

Sonstige methodische Hinweise

- *Empfehlung spezifiziert Therapielinie nicht*

Freitext/Empfehlungen/Hinweise

Evidence summary	LoE
Progression free survival is significantly longer among patients treated with initial chemotherapy, than those treated with gefitinib in patients known not to have EGFR mutations.	II
Literatur	
Mok TS, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009 Sep 3;361(10):947-57	
Recommendation	Grade
Where EGFR mutation status is negative or unknown, patients should be treated with standard chemotherapy.	B
Practice piont(s)	
The evidence in support of large treatment benefits with first-line EGFR TKIs in response rate and progression free survival argues for consideration of obtaining adequate tumour tissue where possible, to enable molecular testing	

	for the presence of activating EGFR gene mutations. This will enable clinicians to offer patients initial EGFR TKIs versus empirical therapy, bearing in mind that overall survival for EGFT GMT + patients does not appear to be compromised, as long they go on to receive EGFR TKIs after chemotherapy.
Scottish Intercollegiate Guidelines Network (SIGN). 2014 [16]. Management of lung cancer	**Fragestellung** 13/14. In patients with NSCLC (locally advanced or metastatic disease), what is the most effective first/second line systemic anticancer therapy (chemotherapy, targeted therapy, EGFR Inhibitors)? Outcomes: Overall survival, progression-free survival, toxicity, quality of life
	Methodik Grundlage der Leitlinie: systematische Recherche und Bewertung der Literatur, Entwicklung durch multidisziplinäre Gruppe von praktizierenden klinischen ExpertInnen, Expertenreview, öffentliche Konsultation Suchzeitraum: 2005 - 2012 LoE/GoR: siehe Anhang dieser Synopse Sonstige methodische Hinweise • *keine Empfehlung zur Zweitlinientherapie speziell bei negativem oder unbekanntem EGFR-Mutationsstatus*
	Freitext/Empfehlungen 8.2 First line therapy for patients with stage IIIB and IV NSCLC Results from a meta-analysis and systematic review demonstrate the benefit of SACT for patients with advanced non-small cell lung cancer (absolute improvement in survival of 9% at 12 months versus control). **220.** Burdett S, et al. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: A systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. J Clin Oncol 2008;26(28):4617-25. **(LoE 1++)** 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. No particular combination of these agents in regimens with platinum has been shown to be more effective. **221.** Anderson H, et al. Gemcitabine plus best supportive care (BSC) vs BSC in inoperable non-small cell lung cancer - a randomised trial with quality of life as the primary outcome. UK NSCLC Gemcitabine Group. Non-Small Cell Lung Cancer. Br J Cancer 2000;83(4):447-53. **(LoE 1+)** **222.** Ranson M, et al. Randomized trial of paclitaxel plus supportive care versus supportive care for patients with advanced non-small-cell lung cancer. J Natl Cancer Inst 2000;92(13):1074-80. **(LoE 1+)** **223.** Roszkowski K, et al. A multicenter, randomized, phase III study of docetaxel plus best supportive care versus best supportive care in chemotherapynaive patients with metastatic or non-resectable localized non-small cell lung cancer (NSCLC). Lung Cancer 2000;27(3):145-57 **(LoE 1+)** **224.** Gridelli C. The ELVIS trial: a phase III study of single-agent vinorelbine as first-line treatment in elderly patients with advanced non-small cell lung cancer. Elderly Lung Cancer

Vinorelbine Italian Study. Oncologist 2001;6(Suppl 1):4-7 **(LoE 1+)**

225. Schiller JH, et al. Comparison of four chemotherapy regimens for advanced nonsmall- cell lung cancer. N Engl J Med 2002;346(2):92-8. **(LoE 1+)**

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

226. Goffin J, et al. First-line systemic chemotherapy in the treatment of advanced non-small cell lung cancer: A systematic review. J Thorac Oncol 2010;5(2):260-74 **(LoE 1++)**

227. Lima JP, et al. Optimal duration of first-line chemotherapy for advanced non-small cell lung cancer: a systematic review with meta-analysis. Eur J Cancer 2009;45(4):601-7. **(LoE 1+)**

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.

228. Scagliotti GV, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapynaive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26(21):3541-51. **(LoE 1+)**

229. Scagliotti GV, et al. Survival without toxicity for cisplatin plus pemetrexed versus cisplatin plus gemcitabine in chemonaïve patients with advanced non-small cell lung cancer: a risk-benefit analysis of a large phase III study. Eur J Cancer 2009;45(13):2298-303. **(LoE 1+)**

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

228. siehe oben

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.

230. Bria E, et al. Outcome of advanced NSCLC patients harboring sensitizing EGFR mutations randomized to EGFR tyrosine kinase inhibitors or chemotherapy as first-line treatment: a meta-analysis. Ann Oncol 2011;22(10):2277-85. **(LoE 1+)**

231. Rosell R, 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. **(LoE 1++)**

Randomised evidence does not support the use of sACT in combination with a TKI in any patient group.

231. siehe oben

232. Feld R, et al. Use of the epidermal growth factor receptor inhibitors gefitinib and erlotinib in the treatment of non-small cell lung cancer: A systematic review. J Thorac Oncol 2006;1(4):367-

	76. **(LoE 1++)** Recommendations Patients who have advanced disease, are performance status 0-1, have predominantly non squamous NSCLC and are EGFR mutation negative should be offered combination systemic anticancer therapy with cisplatin and pemetrexed. **(A)**
Wauters I, et al., 2013 [19]. **Belgian Health Care Knowledge Centre** Small cell and non-small cell lung cancer: diagnosis, treatment and follow-up	**Fragestellung** 3. What are the best treatment options for patients with locally advanced NSCLC (stage cIIIA-cIIIB)? 4. What are the best treatment options for patients with metastatic and recurrent NSCLC?
	Methodik ***Grundlage der Leitlinie:*** • developed using a standard methodology based on a systematic review of the evidence (further details: https://kce.fgov.be/content/kce-processes) • developed by adapting (inter)national CPGs to the Belgian context (formal methodology of the ADAPTE group: www.adapte.org) • in general, and whenever necessary, included guidelines updated with more recent evidence • AGREE II instrument used to evaluate the methodological quality of the identified CPGs (www.agreetrust.org) • quality of systematic reviews assessed by using the Dutch Cochrane checklist (www.cochrane.nl) • critical appraisal of randomized controlled trials: Cochrane Collaboration's Risk of Bias Tool used • When new RCTs were found in addition to an existing meta-analysis, or in case subgroup analysis was needed for certain topics, meta-analysis was performed using Review Manager Version 5. ***Suchzeitraum:*** • searches for guidelines: 20 February 2012 (23 guidelines retained for full-text evaluation), • update searches: between April, 2012 and January, 2013 ***LoE, GoR:*** GRADE

Table 1 – Levels of evidence according to the GRADE system

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

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

Sonstige methodische Hinweise

- *Crizotinib nur in der Zweitlinie empfohlen*
- *keine Empfehlung zur Therapie speziell nach Versagen von Crizotinib*

Freitext/Empfehlungen/Hinweise

4.3.4. Molecular techniques to guide targeted treatment

EGFR, KRAS, and ALK (anaplastic lymphoma kinase) mutations are almost always mutually exclusive (i.e. mutations of only 1 of the 3 genes occur within any individual tumour).

Pathology and molecular testing

Recommendation: If no activating EGFR mutation is present, an ALK rearrangement test should be done to identify patients potentially eligible for crizotinib treatment.

Literatur:

46. Lindeman NI, Cagle PT, Beasley MB, Chitale DA, Dacic S,Giaccone G, et al. Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors: Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. Arch Pathol Lab Med. 2013.

5.3. TREATMENT OF METASTATIC (STAGE CIV) AND RECURRENT NSCLC

5.3.3. Second and third line chemotherapy

Conclusions:

There is preliminary evidence from 1 phase III trial that crizotinib as second line treatment improves progression free survival but not overall survival in

	ALK-mutation positive NSCLC. Second line chemotherapy has a statistically significant effect on overall survival in patients with advanced NSCLC and an adequate PS when the disease has progressed during or after first-line, platinum-based therapy. Docetaxel or pemetrexed (only in non-squamous NSCLC) are acceptable as second-line therapy for patients with advanced NSCLC with adequate PS when the disease has progressed during or after first-line, platinumbased therapy as there is no evidence that one is superior to another. Erlotinib and gefitinib only have a proven effect in EGFR mutation positive NSCLC. Combination second line therapies have a marginal effect on progression free survival compared to monotherapy but no proven effect on overall survival. **Recommendations:** • It is recommended to offer second-line chemotherapy for patients with advanced NSCLC with adequate performance status when the disease has progressed during or after first-line therapy. (SoE: strong / LoE: moderate) • Crizotinib is recommended as second-line therapy in ALK mutation-positive patients. (strength of recommendation: strong, LoE low) • The use of pemetrexed (only in non-squamous NSCLC) or docetaxel is acceptable as second-line therapy for patients with advanced NSCLC with adequate performance status when the disease has progressed during or after first-line, platinum-based therapy. (SoE: weak / LoE: very low) 4. Azzoli CG, Temin S, Giaccone G. 2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer. J Oncol Pract. 2012;8(1):63-6. 7. Landelijke werkgroep longtumoren IKNL. Niet-kleincellig longcarcinoom - Landelijke richtlijn, Versie 2.0. In. 2.0 ed; 2011. 125. Qi WX, Shen Z, Yao Y. Meta-analysis of docetaxel-based doublet versus docetaxel alone as second-line treatment for advanced non-small-cell lung cancer. Cancer Chemotherapy and Pharmacology. 2012;69(1):99-106. 126. Qi W-X, Tang L-N, He A-N, Shen Z, Yao Y. Effectiveness and safety of pemetrexed-based doublet versus pemetrexed alone as second-line treatment for advanced non-small-cell lung cancer: a systematic review and meta-analysis. J Cancer Res Clin Oncol. 2012;138(5):745-51. 127. Jiang J, Huang L, Liang X, Zhou X, Huang R, Chu Z, et al. Gefitinib versus docetaxel in previously treated advanced non small-cell lung cancer: a meta-analysis of randomized controlled trials. Acta Oncol. 2011;50(4):582-8. 128. Ciuleanu T, Stelmakh L, Cicenas S, Miliauskas S, Grigorescu AC, Hillenbach C, et al. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. Lancet Oncol. 2012;13(3):300-8. 129. Kawaguchi, et al. 2014 (DELTA) 130. Garassino MC, et al. 2013 (TAILOR) 131. Karampeazis A, Voutsina A, Souglakos J, Kentepozidis N, Giassas S, Christofillakis C, et al. Pemetrexed versus erlotinib in pretreated patients with advanced non-small cell lung cancer: A Hellenic Oncology Research Group (HORG) randomized phase 3 study. Cancer. 2013. 132. Semlitsch. Crizotinib (Xalkori®) for the treatment of anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC). 2013. Horizon Scanning in Oncology.
Alberta Provincial	**1. Fragestellung** What is the optimal second-line therapy for patients with stage IV NSCLC?

Thoracic Tumour Team. 2013 [1]. Non-small cell lung cancer stage IV	• **Methodik** Grundlage der Leitlinie: systematic literature search, evidence tables, AGREE used for retrieved guidelines, working group reviewed currency and acceptability of all relevant literature, then circulated a draft of the updated guideline to entire provincial tumour team for final feedback and approval Suchzeitraum: bis 2013 LoE/GoR: no use of formal rating schemes for describing the strength of the recommendations, rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations *Sonstige methodische Hinweise* • *Crizotinib nur in der Zweitlinie empfohlen* • *keine Empfehlung zur Therapie speziell nach Versagen von Crizotinib* • *Empfehlung 8. schließt „non-squamous" nicht ein* • *Kein formaler Konsensusprozess beschrieben* • *Auswahl und Bewertung der Literatur nicht beschrieben* • *no direct industry involvement in the development or dissemination of this guideline* • *authors have not been remunerated for their contributions* *Some members of the Alberta Provincial Thoracic Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.*
	2. Freitext/Empfehlungen Recommendations … 8. Second-line or subsequent chemotherapy options for advanced NSCLC include single-agent docetaxel or erlotinib for patients with squamous cell carcinoma histology, or single agent treatment with a drug that has not been previously used. 9. Crizotinib has been approved for second-line treatment of patients who are positive for ALK-rearrangements from the pan-Canadian Oncology Drug Review (pCODR) and has also been approved for provincial coverage in Alberta. … Discussion and literature **Second-line chemotherapy** The Alberta Provincial Thoracic Tumour Team recommends therapy with single-agent docetaxel or erlotinib for patients with squamous cell carcinoma histology, or single-agent PEM for patients with adenocarcinoma tumour

	histology in the second-line treatment of advanced NSCLC (recommendation #8). All three agents have been reported to produce similar rates of response and overall survival, therefore the choice of which agent to use will depend on the patient's tumour histology, comorbidities, toxicity from previous treatments, risk for neutropenia, smoking history, and patient convenience and preference. **85.** Stinchcombe TE, Socinski MA. Considerations for second-line therapy of non-small cell lung cancer. *Oncologist.* 2008;13 Suppl 1:28-36. **86.** Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol.* May 2000;18(10):2095-2103. **87.** Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol.* Jun 2000;18(12):2354-2362. **88.** Dancey J, Shepherd FA, Gralla RJ, Kim YS. Quality of life assessment of second-line docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy: results of a prospective, randomized phase III trial. *Lung Cancer.* Feb 2004;43(2):183-194. **89.** Gridelli C, Gallo C, Di Maio M, et al. A randomised clinical trial of two docetaxel regimens (weekly vs 3 week) in the second-line treatment of non-small-cell lung cancer. The DISTAL 01 study. *Br J Cancer.* Dec 13 2004;91(12):1996-2004. **90.** Camps C, Massuti B, Jimenez A, et al. Randomized phase III study of 3-weekly versus weekly docetaxel in pretreated advanced non-small-cell lung cancer: a Spanish Lung Cancer Group trial. *Ann Oncol.* Mar 2006;17(3):467-472. **91.** Chen YM, Shih JF, Perng RP, Tsai CM, Whang-Peng J. A randomized trial of different docetaxel schedules in non-small cell lung cancer patients who failed previous platinum-based chemotherapy. *Chest.* Apr 2006;129(4):1031-1038. **92.** Schuette W, Nagel S, Blankenburg T, et al. Phase III study of second-line chemotherapy for advanced non-small-cell lung cancer with weekly compared with 3-weekly docetaxel. *J Clin Oncol.* Nov 20 2005;23(33):8389-8395. **93.** Gervais R, Ducolone A, Breton JL, et al. Phase II randomised trial comparing docetaxel given every 3 weeks with weekly schedule as second-line therapy in patients with advanced non-small-cell lung cancer (NSCLC). *Ann Oncol.* Jan 2005;16(1):90-96. **94.** Lai CL, Tsai CM, Chiu CH, et al. Phase II randomized trial of tri-weekly versus days 1 and 8 weekly docetaxel as a second-line treatment of advanced non-small cell lung cancer. *Jpn J Clin Oncol.* Dec 2005;35(12):700-706. **95.** Di Maio M, Perrone F, Chiodini P, et al. Individual patient data meta-analysis of docetaxel administered once every 3 weeks compared with once every week second-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol.* Apr 10 2007;25(11):1377-1382. **96.** Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol.* May 1 2004;22(9):1589-1597. **97.** Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies. *Oncologist.* Mar 2009;14(3):253-263. **98.** Weiss GJ, Langer C, Rosell R, et al. Elderly patients benefit from second-line cytotoxic chemotherapy: a subset analysis of a randomized phase III trial of pemetrexed compared with docetaxel in patients with previously treated advanced non-small-cell lung cancer. *J Clin Oncol.* Sep 20 2006;24(27):4405-4411. **99.** Vansteenkiste J, Solomon B, Boyer M, et al. Everolimus in combination with pemetrexed in patients with advanced non-small cell lung cancer previously treated with chemotherapy: a phase I study using a novel, adaptive Bayesian dose-escalation model. *J Thorac Oncol.* Dec

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100. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med.* Jul 14 2005;353(2):123-132.

101. Florescu M, Hasan B, Seymour L, Ding K, Shepherd FA. A clinical prognostic index for patients treated with erlotinib in National Cancer Institute of Canada Clinical Trials Group study BR.21. *J Thorac Oncol.* Jun 2008;3(6):590-598.

102. Ciuleanu T, Stelmakh L, Cicenas S, Esteban E. Erlotinib versus docetaxel or pemetrexed as second-line therapy in patients with advanced non-small-cell lung cancer (NSCLC) and poor prognosis: efficacy and safety results from the phase III TITAN study. . In: Oncol JT, ed. Vol 52010.

103. LeCaer H, Greillier L, Corre R, et al. A multicenter phase II randomized trial of gemcitabine followed by erlotinib at progression, versus the reverse sequence, in vulnerable elderly patients with advanced non small-cell lung cancer selected with a comprehensive geriatric assessment (the GFPC 0505 study). *Lung Cancer.* Jul 2012;77(1):97-103.

104. Parikh PM, Vaid A, Advani SH, et al. Randomized, double-blind, placebo-controlled phase II study of single-agent oral talactoferrin in patients with locally advanced or metastatic non-small-cell lung cancer that progressed after chemotherapy. *J Clin Oncol.* Nov 1 2011;29(31):4129-4136.

105. Azzoli CG, Patel JD, Krug LM, et al. Pralatrexate with vitamin supplementation in patients with previously treated, advanced non-small cell lung cancer: safety and efficacy in a phase 1 trial. *J Thorac Oncol.* Nov 2011;6(11):1915-1922.

Treatments for ALK-Positive Rearrangements

EML4-ALK fusion gene is present in approximately two to seven percent of such tumours, and is mutually exclusive with K-Ras and EGFR mutations.

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

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

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

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

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

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

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

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

	TKIs was shorter in ALK-positive patients compared to other groups. **116.** Lee JK, Park HS, Kim DW, et al. Comparative analyses of overall survival in patients with anaplastic lymphoma kinase-positive and matched wild-type advanced nonsmall cell lung cancer. *Cancer.* Jul 15 2012;118(14):3579-3586. In the pre ALK-inhibitor era, therefore, ALK-positive patients experienced shorter survival on par with wild type patients. In addition, ALK-positive patients were more resistant to EGFR TKI treatment than wild type patients. Recently, a phase II clinical trial by Kim et al (see above) and a phase III clinical trial by Shaw et al. investigated the efficacy and safety of crizotinib; building off the results from an earlier phase I, single-arm clinical trial by Camidge et al. In the study by Kim et al, published as an abstract at the ASCO 2012 conference, patients with ALK-positive NSCLC were given 250mg BID crizotinib in three-week cycles. An ORR of 53% and 12-week DCR of 85% was observed with a median PFS of 8.5 months. Significant improvements in post-treatment pain, cough, and global QoL were reported. In the phase III clinical trial conducted by Shaw et al, also published as an abstract, this time at the ESMO 2012 conference, crizotinib was compared to standard CT for advanced NSCLC. Like before, 250mg BID crizotinib was administered to 173 patients with another 174 patients receiving either 500mg/m2 PEM (57%) or 75mg/m2 docetaxel (41%). Crizotinib prolonged PFS to median of 7.7 months from 3 months for those treated with standard CT (HR 0.49, CI 0.37-0.64, p<0.0001). The ORR was significantly higher in those treated with crizotinib (65% vs. 20%; p<0.0001). The OS data were still not mature. As there was significant crossover from the standard CT group to the crizotinib group it is possible that OS results may not significantly differ. That said, however, the authors believe crizotinib should be the new standard of care for individuals with ALK-positive advanced NSCLC. **117.** Shaw AT, Kim DW, Nakagawa K, et al. Phase III study of crizotinib versus pemetrexed or docetaxel chemotherapy in patients with advanced ALK-positive non-small cell lung cancer (NSCLC) (PROFILE 1007). Paper presented at: Congress of the European Society for Medical Oncology 2012. **118.** Camidge DR, Bang YJ, Kwak EL, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol. Oct 2012;13(10):1011-1019. As a result of these, and other promising results, the US FDA have approved crizotinib for patients with ALK-positive advanced or metastatic NSCLC. **119.** Kimura H, Nakajima T, Takeuchi K, et al. ALK fusion gene positive lung cancer and 3 cases treated with an inhibitor for ALK kinase activity. *Lung Cancer.* 2012;75(1):66-72. The results of these early trials are promising, and, along with other clinical trials currently underway, may strengthen support for the role of prospective genotyping in the selection of therapy for patients with advanced NSCLC. Indeed, guidelines from the National Comprehensive Cancer Network and the European Society for Medical Oncology now recommend ALK gene rearrangement testing to better treat those patients with advanced NSCLC who are ALK-positive.
Brodowicz T,	**1. Fragestellung**

et al. 2012 [3]. **Central European Cooperative Oncology Group (CECOG)** Third CECOG consensus on the systemic treatment of non-small-cell lung cancer	It is the aim of the present consensus to summarize minimal quality-oriented requirements for individual patients with NSCLC in its various stages based upon levels of evidence in the light of a rapidly expanding array of individual therapeutic options.
	2. Methodik Grundlage der Leitlinie: evidence-based consensus from experts from Europe and the United States based on systematic literature search Suchzeitraum: until December 2009 LoE/GoR: Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology *Sonstige methodische Hinweise* • *Kein formaler Konsensusprozess beschrieben* • *Auswahl und Bewertung der Literatur nicht beschrieben* • *14 author disclosures given, remaining authors have declared no conflicts of interest*
	3. Freitext/Empfehlungen second-line systemic therapy 1 The data from RCTs on second-line therapy are sufficient to recommend either a cytotoxic agent (docetaxel for squamous NSCLC [II,B] or PEM for non squamous NSCLC [II,B]) or the EGFR TKI erlotinib [I,B]. 2 An EGFR TKI should be strongly considered in patients with EGFR-activating mutations in their tumors who have not received it as first-line treatment [II,B]. Sequencing of chemotherapy after EGFR TKIs has not been defined and remains an important open issue. **38.** Barlesi F, Jacot W, Astoul P, Pujol JL. Second-line treatment for advanced nonsmall cell lung cancer: a systematic review. Lung Cancer 2006;51(2): 159–172. **39.** Weiss GJ, Rosell R, Fossella F et al. The impact of induction chemotherapy on the outcome of second-line therapy with pemetrexed or docetaxel in patients with advanced non-small-cell lung cancer. Ann Oncol 2007; 18(3): 453–460. **40.** Shepherd FA, Dancey J, Ramlau R et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000; 18(10): 2095–2103. **41.** Fossella FV, DeVore R, Kerr RN et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000; 18(12): 2354–2362. **42.** Hanna N, Shepherd FA, Fossella FV et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004; 22(9): 1589–1597. **43.** Kim ES, Hirsh V, Mok T et al. Gefitinib versus docetaxel in previously treated nonsmall-cell lung cancer (INTEREST): a randomised phase III trial. Lancet 2008;372(9652): 1809–1818. **44.** Shepherd FA, Rodrigues Pereira J, Ciuleanu T et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005; 353(2): 123–132. **45.** Thatcher N, Chang A, Parikh P et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet 2005;

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de Marinis F et al., 2011 [4]. **Italian Associatlon of Thoracic Oncology (AIOT)** Treatment of advanced non-small-cell-lung cancer: Italian Association of Thoracic Oncology	**1. Fragestellung** Chemotherapy or EGFR lnhibitors for second-line treatment?
	2. Methodik Systematische Literatursuche und formaler Konsensusprozess, up-to-date, cllnlcal practice guidellnes, subsequently updated for this manuscrlpt on December 2010 ***Suchzeitraum:*** 2004 bis 2009 ***LoE, GoR*** *(siehe Anhang)* *Sonstige methodische Hinweise* – *Methodische Schritte entsprechen Agency for Healthcare Policy Research (AHCPR) System US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research.*
	3. Empfehlungen *3.8. Question 8. Chemotherapy or EGFR lnhibitors for second-line treatment?*

(AIOT) clinical practice guidelines.	… Overall, there are no definitive data to recommend an EGFR tyrosine kinase Inhibitor or chemotherapy as second-line treatment in **NSCLC patients with EGFR mutation negative or unknown status**. Erlotinib is currently the only drug approved for use in clinical practice as third-line treatment. There are no available trials designed to define the efficacy of third-line chemotherapy in advanced NSCLC. *3.8.1. Recommendations* • In patients wlth advanced NSCLC and EGFR mutation negative or unknown status, with progressive disease after first-line treatment chemotherapy (docetaxel or pemetrexed in non-squamous histology) or erlotinib should be offered. There are no conclusive data to help the choice between chemotherapy and erlotinib. (**LoE IB, GoR A)** 60. Shepherd FA, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small—cell lung cancer previously treated with platinum based chemotherapy.J Clin Oncol 2000;18:2085-103. 61. Fossella FV, et al. Randomized phase III trial of docetaxel versus vinorelbine or lfosfamide ln patients with non-small cell lung cancer previously treated with platinum-containing chemotherapy regimens. J Clin Oncol 2000;18:2354-62. 68. Hanna N, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy,J Clln Oncol 2004;22:1589-97. 78. Shepherd FA, Rodrtgues Perelra J, Cluleanu T, Tan EH, Hlrsh V, Thongprasert s, et al. Erlotlnlb in previously treated non·small-celllungcancer. N Engl J Med 2005;353:123-32. 79. Tsao MS, et al. Erlotinlb in Jung cancer: molecular and cllnlcal predictors of outcome. N Eng! J Med 2005;353:133-44. 80. Zhu CQ. et al, RoleofKRAS and EGFR as blomarkers of response to erlotinlb in National Cancer Institute of Canada Clinlcal Trials Group Study BR.21.j Clin Oncol2008;26:4268-75. 81. Thatcher N, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non~small-ceiJ Jung cancer: results from a randomised, placebo-controlled, multicentre study (lressa Survival Evaluation in Lung can~cer).Lancet 2005;366:1527-37. 82. Shepherd FA, et al. Comparison ofgef1tinlb and docetaxel in patlents wlth preueated advanced non-small cell lung cancer (NSCLC): meta-analysls from four dinlcal trials. J Clln Oncol 2009;27(155):4095 (abstr 8011). 83. Klm FS, et al. Gefltinib versus docetaxel in previously treated non~sma\lcelllung cancer (JNTERFST): a randomlsed phase 111 trial.lancet 2008;372:1809-18. 84. Lee D, et al. A random\zed open-labe! study of gefitlnlb versus docetaxelln patlents wlth advanced/metastatlc non~small cell Jungcancer (NSCLC) who have previou sly received pl atlnum-ba sed ehernotherapy. J Clin Oncol2008;26:430s (a bstr 8025). 85. Cufer T, et al. Phase II, open-labe!, randomlzed study (SIGN) of slngle-agent gefitinib (IRESSA} or docetaxel as second-Jine therapy in patients with advanced (Stage lllbor IV)non-small-cell Jung cancer. Anticancer Drugs 2006; 17:401-9. 86. Maruyama R, et al. Phase III study, V-15-32, of gefi.tlnib versus docetaxel ln previously treated Japanese patients with non-small-cell Jung cancer. J Clln Oncol 2008;26:4244-52. 87. Vamvakas L, Agelaki S, Kentepozidis NK, Karampeazls A, Pallls AG, Christophyllakls c, et al. Pemetrexed (MTA) compared with erlotinlb (ERL) in pretreated patients with advanced non~small cell Jung cancer (NSClC): Results of a randomized phase III Hellenie Oncology Research Group trial. J Clln Oncol 2010;28(15S):543s (abstr7519). 88. Ciuleanu T, Stelma kh L, Cice nass, Esteban E. Erlotinlb versus docetaxel or pemetrexed as second~line therapy in patients with advanced non-small-celllung cancer(NSCLC)and poorprognosis: efficacy and safety results from the phase III TITAN study.ln: Presented at Chicago Thoraeie Multidisclplinary Symposium. 2010 fabstr LBOA5).

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Semlitsch T et al. 2013 [17]. Crizotinib (Xalkori®) for the treatment of anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) **Institute for Health Technology Assessment Ludwig Boltzmann Gesellschaft**	**Current treatment** As second line therapy the following treatments are recommended: • single agent chemotherapy (docetaxel or PEM) • targeted agent therapy (e.g. erlotinib) • a platinum based combination therapy for patients with EGFR mutation and progressive disease after tyrosine kinase inhibitor treat-ment (e.g. erlotinib) For ALK-positive NSCLC patients the targeted agent crizotinib is the currently recommended treatment option as first or second line therapy. Chemotherapy is an appropriate option for these patients with disease progression on crizotinib. As patients with the ALK fusion oncogene do not appear to respond to EGFR tyrosine kinase inhibitors, erlotinib therapy is not recommended.
NICE technology appraisal guidance, 2013 [15]. Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene	**1 Guidance** 1.1 Crizotinib is not recommended within its marketing authorisation, that is, for treating adults with previously treated anaplastic-lymphoma-kinase-positiveadvanced non-small-cell lung cancer. 1.2 People currently receiving crizotinib that is not recommended according to 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

Primärstudien

Da ausreichend Information aus aggregierter Evidenz vorliegt, wurde keine Suche nach Primärstudien durchgeführt.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 12.10.2015**

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

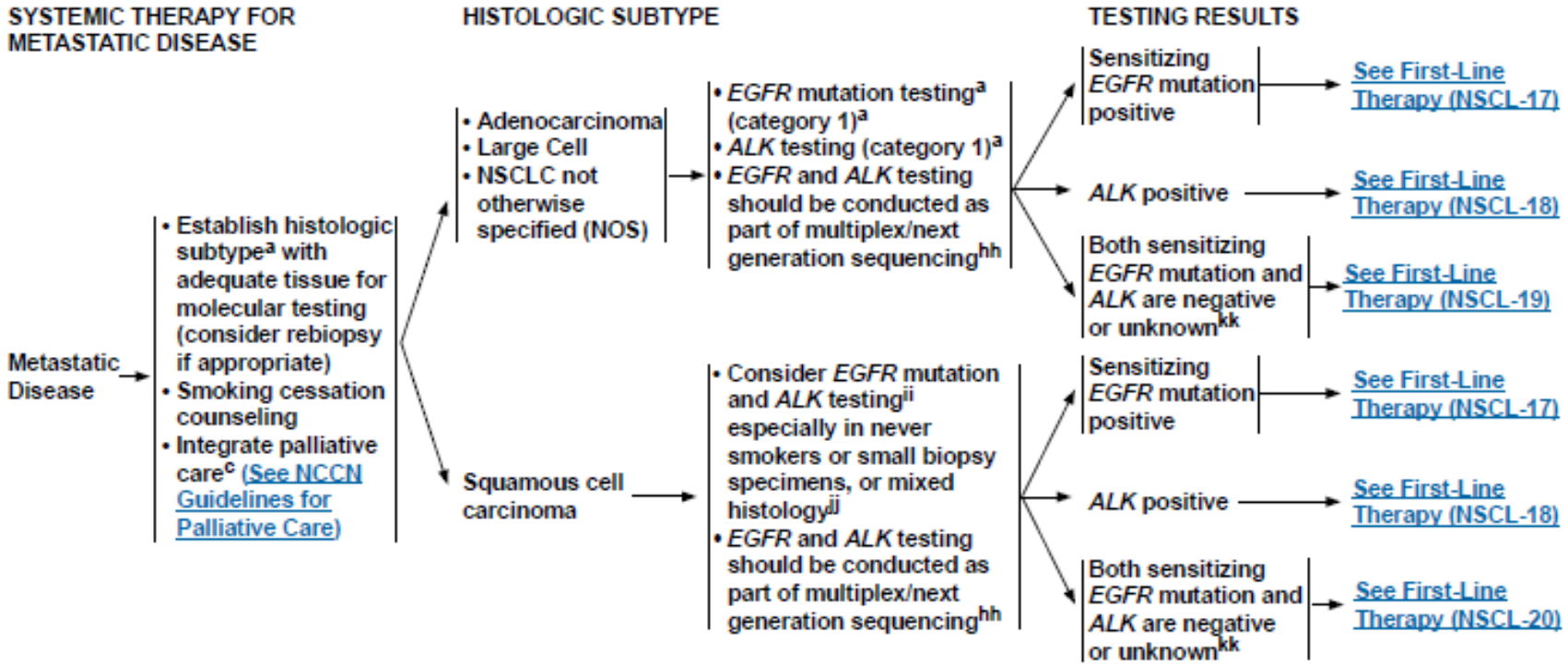
SR, HTAs in Medline (PubMed) am 13.10.2015

#	Suchfrage
1	Carcinoma, Non-Small-Cell Lung[MeSH]
2	(((non[Title/Abstract]) AND small[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	#1 OR #4
6	(((advanced[Title/Abstract]) OR metastat*[Title/Abstract]) OR metastas*[Title/Abstract]) OR recurren*[Title/Abstract]
7	#5 AND #6
8	(((((drug[Title/Abstract]) OR (drug therap*)[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR treat[Title/Abstract]) OR treatment*[Title/Abstract]
9	#7 AND #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 ("2010/10/01"[PDAT] : "2015/10/13"[PDAT])

Leitlinien in Medline (PubMed) am 13.10.2015

#	Suchfrage	Treffer
1	Carcinoma, Non-Small-Cell Lung[MeSH]	35111
2	(((non[Title/Abstract]) AND small[Title/Abstract]) AND cell[Title/Abstract]) AND lung[Title/Abstract]	40784
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]	2404402
4	#2 AND #3	40469
5	#1 OR #4	48942
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title] OR Consensus Development Conference[ptyp])	237
7	(#6) AND ("2010/10/01"[PDAT] : "2015/10/13"[PDAT])	85

Anhang:



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

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

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

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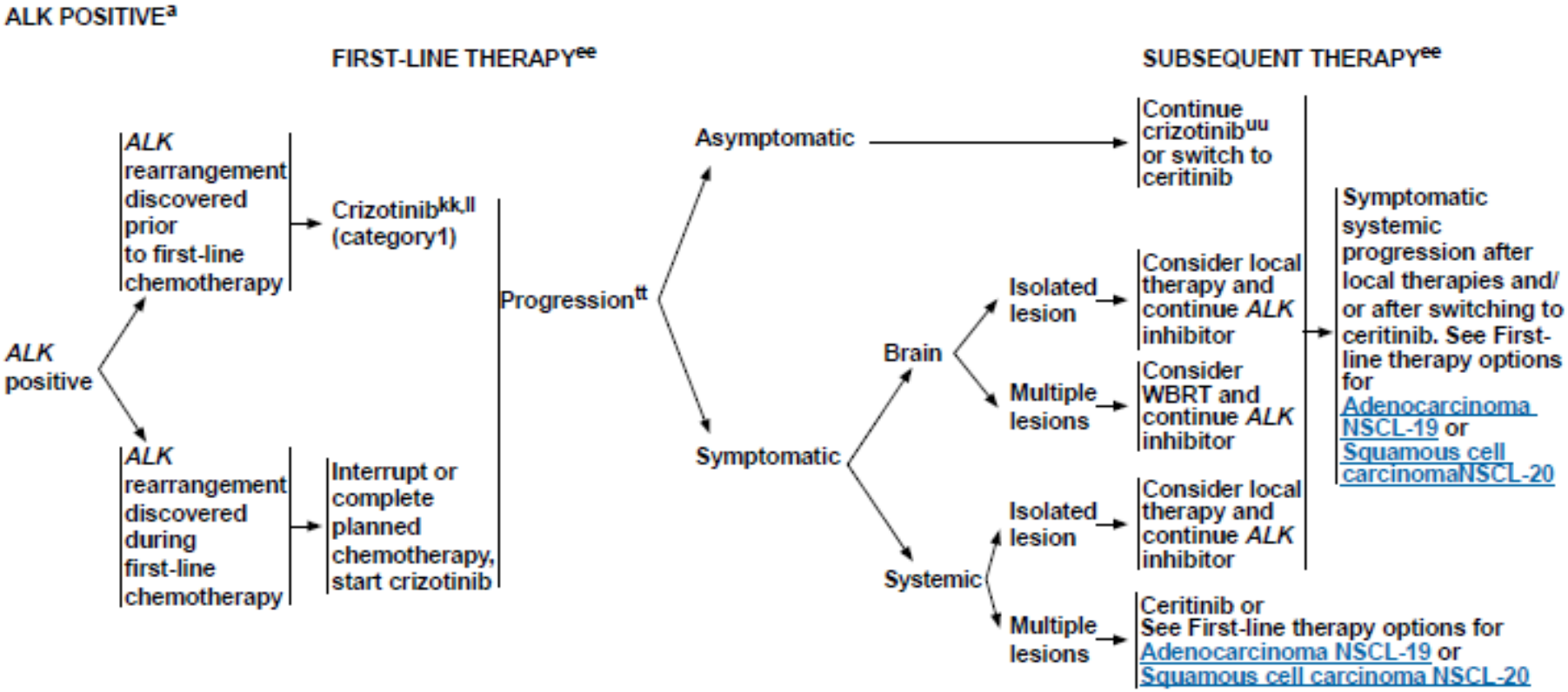
Abbildung 5: aus NCCN, 2015



[a] See Principles of Pathologic Review (NSCL-A).
[ee] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[kk] Consider ROS1 testing; if positive, may treat with crizotinib. Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in *ROS1*-rearranged non-small cell lung cancer. N Engl J Med 2014;371:1963-1971.
[ll] For performance status 0-4.
[tt] Patients who are intolerant to crizotinib may be switched to ceritinib.
[uu] For rapid radiologic progression or threatened organ function, alternate therapy should be instituted.

Abbildung 6: aus NCCN, 2015 (NSCL-18)

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (1 OF 3)

ADVANCED DISEASE:

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

First-line Therapy

- Bevacizumab + chemotherapy or chemotherapy alone is indicated in PS 0-1 patients with advanced or recurrent NSCLC. Bevacizumab should be given until disease progression.
- Erlotinib is recommended as a first-line therapy in patients with sensitizing *EGFR* mutations and should not be given as first-line therapy to patients negative for these *EGFR* mutations or with unknown *EGFR* status.
- Afatinib is indicated for patients with sensitizing *EGFR* mutations.
- Crizotinib is indicated for patients with *ALK* rearrangements.
- There is superior efficacy and reduced toxicity for cisplatin/pemetrexed in patients with nonsquamous histology, in comparison to cisplatin/gemcitabine.
- There is superior efficacy for cisplatin/gemcitabine in patients with squamous histology, in comparison to cisplatin/pemetrexed.
- Two drug regimens are preferred; a third cytotoxic drug increases response rate but not survival. Single-agent therapy may be appropriate in select patients.
- Cisplatin or carboplatin have been proven effective in combination with any of the following agents: paclitaxel, docetaxel, gemcitabine, etoposide, vinblastine, vinorelbine, pemetrexed, or albumin-bound paclitaxel.
- New agent/non-platinum combinations are reasonable alternatives if available data show activity and tolerable toxicity (eg, gemcitabine/docetaxel, gemcitabine/vinorelbine).
- Response assessment after 1-2 cycles, then every 2-4 cycles.

Abbildung 7: aus NCCN, 2015 (NSCL-F)

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (2 OF 3)

Maintenance Therapy

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

- Continuation Maintenance: Bevacizumab given in combination with chemotherapy should be continued until evidence of disease progression or unacceptable toxicity, as per the design of the clinical trials supporting their use.
  - Continuation of bevacizumab after 4–6 cycles of platinum-doublet chemotherapy and bevacizumab (category 1).
  - Continuation of pemetrexed after 4–6 cycles of cisplatin and pemetrexed chemotherapy, for patients with histologies other than squamous cell carcinoma (category 1).
  - Continuation of bevacizumab + pemetrexed after 4 to 6 cycles of bevacizumab, pemetrexed, cisplatin/carboplatin, for patients with histologies other than squamous cell carcinoma.
  - Continuation of gemcitabine after 4–6 cycles of platinum-doublet chemotherapy (category 2B).
- Switch Maintenance: Two studies have shown a benefit in progression-free and overall survival with the initiation of pemetrexed or erlotinib after first-line chemotherapy, in patients without disease progression after 4–6 cycles of therapy.
  - Initiation of pemetrexed after 4–6 cycles of first-line platinum-doublet chemotherapy, for patients with histologies other than squamous cell carcinoma (category 2B).
  - Initiation of erlotinib after 4–6 cycles of first-line platinum-doublet chemotherapy (category 2B).
  - Initiation of docetaxel after 4–6 cycles of first-line platinum-doublet chemotherapy in patients with squamous cell carcinoma (category 2B).
- Close surveillance of patients without therapy is a reasonable alternative to maintenance.

Subsequent Therapy

- In patients who have experienced disease progression either during or after first-line therapy, the following are established second-line agents.
  - Nivolumab improves survival when compared with docetaxel.
  - Docetaxel is superior to vinorelbine or ifosfamide.
  - Pemetrexed is considered equivalent to docetaxel with less toxicity in patients with adenocarcinoma and large cell carcinoma.
  - Ramucirumab + docetaxel improves survival when compared to docetaxel alone.
  - Erlotinib is superior to best supportive care.
  - Afatinib is indicated for patients with sensitizing *EGFR* mutations.
  - Ceritinib is indicated for patients with *ALK* rearrangements who have disease progression on or are intolerant to crizotinib.

Continuation After Disease Progression

- With the exception of targeted agents (erlotinib, gefitinib, afatinib, crizotinib, ceritinib) in patients with *EGFR*-sensitizing mutations or *ALK* rearrangements who have experienced objective regressions with targeted therapy, no agent should be continued after disease progression has been documented except in selected situations. (refer to discussion section)

Abbildung 8: aus NCCN, 2015 (NSCL-F)

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (3 OF 3)

Agents listed below are used in the treatment of patients with NSCLC. Most are used in combination, while others are used as monotherapy (eg, maintenance or second-line/subsequent therapy).

- Cisplatin[1-9]
- Carboplatin[4,6-11]
- Paclitaxel[1,4,6,8-11]
- Docetaxel[5,7,8,12,13]
- Vinorelbine[7,9,10]
- Gemcitabine[3,5,6,8,9,13]
- Etoposide[4]
- Irinotecan[9]
- Vinblastine
- Mitomycin
- Ifosfamide[12]
- Pemetrexed[14,15]
- Erlotinib[16]
- Bevacizumab[17]
- Albumin-bound paclitaxel[18-20] †
- Crizotinib[21]
- Afatinib[22]
- Ceritinib[23]
- Ramucirumab[24]
- Nivolumab[25,26]

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

Abbildung 9: aus NCCN, 2015 (NSCL-F)

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

Abbildung 10: aus de Marinis F et al., 2011

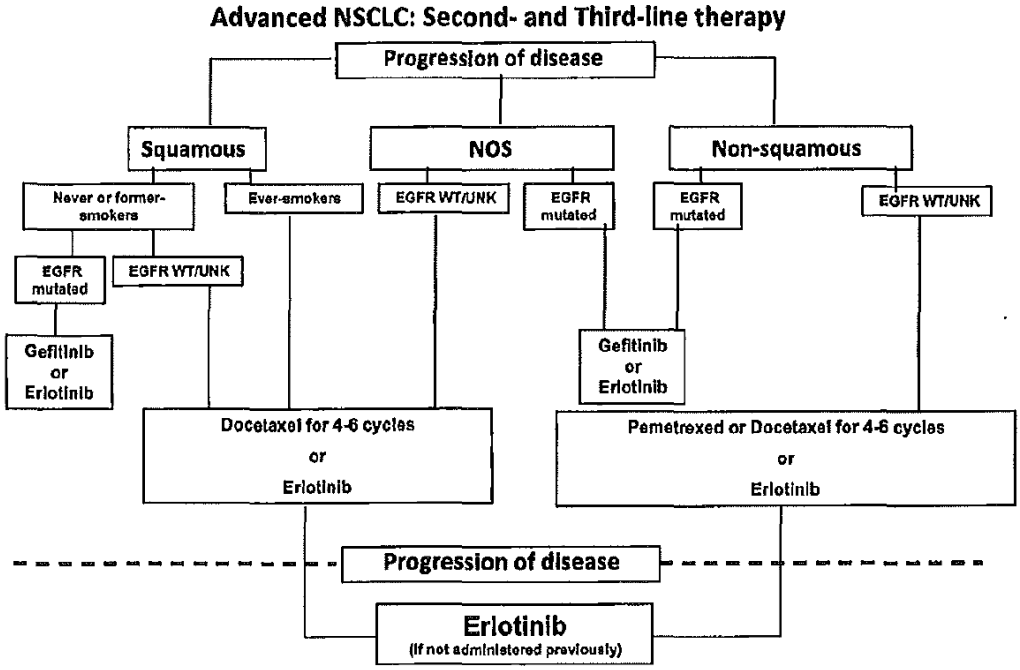

Fig. 3. Suggested algorithm for second- and third-line treatment of advanced non-small-cell lung cancer (NOS: not otherwise specified; EGFR: epidermal growth factor receptor; WT: wild type; and UNK: unknown).

Abbildung 11: aus de Marinis F et al., 2011.

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