Gemeinsamer Bundesausschuss

# Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

# und

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

## Vorgang: 2014-B-061 Ceritinib

Stand: September 2014

# I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

**Ceritinib**
**zur Behandlung des Crizotinib-vorbehandelten Anaplastische-Lymphom-Kinase (ALK)-positiven, fortgeschrittenen nicht-kleinzelligen Bronchialkarzinoms.**

| **Kriterien gemäß 5. Kapitel § 6 VerfO** | |
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| 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“*<br>Nicht berücksichtigt wurden Arzneimittel mit expliziter Zulassung für die Erstlinien-Chemotherapie. |
| 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 | • Änderung der AM-RL in Anlage 9: Off-Label-Use vom 21. November 2006: Off-Label-Indikationserweiterung für Carboplatin zur Kombinationstherapie des NSCLC.<br>• Beschluss vom 2. Mai 2013 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen – Crizotinib<br>• Beschluss vom 8. Mai 2014 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen – Afatinib |
| 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**<br>**ATC-Code**<br>**Handelsname** | **Anwendungsgebiet**<br>(Text aus Fachinformation) |
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| Zu bewertendes Arzneimittel: | |
| Ceritinib<br>n.b.<br>Zykadia® | Zykadia wird angewendet bei erwachsenen Patienten zur Behandlung des fortgeschrittenen, Anaplastische-Lymphomkinase(ALK)-positiven, nicht-kleinzelligen Bronchialkarzinoms (NSCLC), die mit Crizotinib vorbehandelt wurden. |
| **Chemotherapeutika:** | |
| Ifosfamid<br>L01AA06<br>(Holoxan®) | Mono- oder Kombinationschemotherapie des inoperablen oder metastasierten nicht-kleinzelligen Bronchialkarzinoms. |
| Pemetrexed<br>L01BA04<br>(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 (siehe Abschnitt 5.1).<br>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<br>ist (siehe Abschnitt 5.1).<br>ALIMTA in Monotherapie ist angezeigt zur Behandlung in Zweitlinientherapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie (siehe Abschnitt 5.1). |
| Gemcitabin<br>L01BC05<br>(Bendacitabin®) | Gemcitabin ist in Kombination mit Cisplatin als Erstlinientherapie von Patienten mit lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Bronchialkarzinom (NSCLC) angezeigt. Eine Gemcitabin-Monotherapie kann bei älteren Patienten oder solchen mit einem Performance Status 2 in Betracht gezogen werden. |
| Vindesin<br>L01CA03<br>(Eldesine®) | Kombinationschemotherapie: Lokal fortgeschrittenes oder metastasiertes nicht-kleinzelliges Bronchialkarzinom (Stadium IIIB, IV). |
| Vinorelbin<br>L01CA04<br>(Navelbine®) | i.v.: Zur Anwendung als Monotherapie oder in Kombination mit Cisplatin zur Behandlung des fortgeschrittenen nicht kleinzelligen Bronchialkarzinoms (Stadium III oder IV) bei Patienten in gutem Allgemeinzustand.<br>oral: Behandlung des nicht kleinzelligen Bronchialkarzinoms (Stadium 3 oder 4). |
| Etoposid<br>L01CB01 | Kombinationstherapie folgender Malignome:<br>– Kleinzelliges Bronchialkarzinom, |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
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| (Riboposid®) | – Palliative Therapie des fortgeschrittenen NSCLC bei Patienten mit gutem Allgemeinzustand (Karnofsky-Index >80%). |
| Paclitaxel<br>L01CD01<br>(Paclit®) | Paclitaxel in Kombination mit Cisplatin ist für die Behandlung des nicht-kleinzelligen Bronchialkarzinoms (NSCLC) bei Patienten indiziert, für die potenziell kurative chirurgische Maßnahmen und/oder Strahlentherapie nicht angezeigt sind. |
| Docetaxel<br>L01CD02<br>(Taxotere®) | Zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem NSCLC nach Versagen einer vorausgegangenen Chemotherapie. In Kombination mit Cisplatin zur Behandlung von Patienten mit nicht resezierbarem, lokal fortgeschrittenem oder metastasiertem, nicht kleinzelligem Bronchialkarzinom ohne vorausgegangene Chemotherapie. |
| Mitomycin<br>L01DC03<br>(Mitomycin medac®) | 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:<br>– nicht-kleinzelliges Bronchialkarzinom.<br>[…] |
| Cisplatin<br>L01XA01<br>(Cisplatin medac®) | – fortgeschrittene nicht-kleinzellige Bronchialkarzinome<br>[…] |
| Carboplatin<br>L01XA02<br>(n.a.) | Off-Label-Indikation: Zur palliativen Therapie des fortgeschrittenen nicht-kleinzelligen Bronchialkarzinoms (NSCLC) bei Patienten mit einem erhöhten Risiko für Cisplatin-induzierte Nebenwirkungen (z.B. vorbestehende Neuropathie oder relevante Hörschädigung, besondere Neigung zu Übelkeit, Niereninsuffizienz, Herzinsuffizienz) im Rahmen einer Kombinationstherapie. Für die Kombinationstherapie des NSCLC zugelassene Wirkstoffe: Cisplatin, Docetaxel, Erlotinib, Etoposid, Gemcitabin, Ifosfamid, Mitomycin, Paclitaxel, Pemetrexed, Vindesin, Vinorelbin. (G-BA-Beschluss vom 21.11.2006, AM-RL Anlage VI) |
| **Proteinkinase-Inhibitoren:** | |
| Gefitinib<br>L01XE02<br>(Iressa®) | Iressa® ist angezeigt zur Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Lungenkarzinom (NSCLC) mit aktivierenden Mutationen der EGFR-TK. |
| Erlotinib<br>L01XE03<br>(Tarceva®) | 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 |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
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| | relevante Wirkungen durch die Behandlung gezeigt werden. |
| Afatinib<br>L01XE13<br>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 (siehe Abschnitt 5.1). |
| Crizotinib<br>L01XE16<br>(Xalkori®) | Xalkori® wird angewendet bei Erwachsenen zur Behandlung des vorbehandelten Anaplastische-Lymphom-Kinase (ALK)-positiven, fortgeschrittenen nicht kleinzelligen Bronchialkarzinoms (non small cell lung cancer, NSCLC). |

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

# Abteilung Fachberatung Medizin

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

## Vorgang: 2014-B-061 (Ceritinib)

Datum: 14.08.2014

# Recherche und Synopse der Evidenz zur Bestimmung der zVT:



## Indikation für die Recherche:

Zykadia® wird angewendet bei Erwachsenen zur Behandlung des Crizotinib-vorbehandelten Anaplastische-Lymphom-Kinase (ALK)-positiven, fortgeschrittenen nicht-kleinzelligen Bronchialkarzinoms (non small cell lung cancer, NSCLC).

## Berücksichtigte Wirkstoffe/Therapien:

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

Die Recherche ergab **618** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt wurden **18** Quellen in die synoptische Evidenzübersicht aufgenommen.

Abkürzungen

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| AEs | Adverse events |
| ALK | Anaplastic Lymphoma Kinase |
| AM | Arzneimittel |
| AWMF | Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften |
| ÄZQ | Ärztliches Zentrum für Qualität in der Medizin |
| BSC | Best-Supportive-Care |
| DAHTA | Deutsche Agentur für Health Technology Assessment |
| DGHO-Onkopedia | Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie |
| ECOG | Eastern cooperative oncology group |
| EGFR | Epidermal Growth Factor Receptor |
| ESMO | European Society for Medical Oncology |
| FEM | Fixed effects model |
| G-BA | Gemeinsamer Bundesausschuss |
| GIN | Guidelines International Network |
| GoR | Grade of Recommendation |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| HR | Hazard ratio |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen |
| KRAS | Kirsten rat sarcoma viral oncogene homolog |
| LoE | Level of Evidence |
| NGC | National Guideline Clearinghouse |
| NICE | National Institute for Health and Care Excellence |
| NIHR HSC | National Institute for Health Research Horizon Scanning Centre |
| NSCLC | non-small cell lung cancer (nichtkleinzelliges Bronchialkarzinom) |
| OR | Odds ratio |
| ORR | Overall response rate |
| OS | Overall survival |
| PEM | Pemetrexed |
| PFS | Progression free survival |
| PS | Performance status |
| QOL | Quality of life |
| RCT | Randomized controlled trial |
| REM | Random effects model |
| RR | Risk ratio |
| SACT | systemic anticancer therapy |
| TAX | Docetaxel |
| TKI | tyrosine-kinase inhibitor |
| TRIP | Turn Research into Practice Database |
| vs. | versus |

**IQWiG Berichte/G-BA Beschlüsse**

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| **G-BA, 2014 [1]**<br><br>Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Afatinib | **Anwendungsgebiet:** EGFR-TKI-naive erwachsenen Patienten mit lokal fortgeschrittenem und/oder metastasiertem nicht-kleinzelligen Lungenkarzinom (NSCLC) mit aktivierenden EGFR-Mutationen<br><br>2.1 Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie - Begründung auf Basis der Kriterien nach 5. Kapitel § 6 Absatz 3 VerfO:<br><br>zu 4. Für das vorliegende Anwendungsgebiet wird davon ausgegangen, dass sich die Patienten mit NSCLC im Krankheitsstadium III B bis IV befinden (Stadieneinteilung nach IASLC, UICC), ohne Indikation zur kurativen Resektion, Strahlenbehandlung bzw. Radiochemotherapie. Die Behandlung erfolgt symptomorientiert palliativ sowie in Abhängigkeit von Krankheitsverlauf, Allgemeinzustand, Erfolg und Verträglichkeit der Erstlinientherapie, Begleiterkrankungen, Tumorhistologie, EGFR-Status und Therapiewunsch des Patienten. **Tumore mit aktivierenden Mutationen des EGFR** weisen in der Regel eine **nicht-plattenepitheliale** Histologie auf und sind in der Regel **ALK-negativ**. … |
| **G-BA, 2013 [2]**<br><br>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. | **Anwendungsgebiet:** Zur Behandlung des vorbehandelten Anaplastische-Lymphom-Kinase (ALK)-positiven, fortgeschrittenen nicht kleinzelligen Bronchialkarzinoms (non small cell lung cancer, NSCLC).<br><br>a) Patienten, bei denen eine Chemotherapie angezeigt ist.<br>Zweckmäßige Vergleichstherapie: 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).<br>• Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der Chemotherapie mit Docetaxel oder PEM: Anhaltspunkt für einen *beträchtlichen* Zusatznutzen.<br><br>b) Patienten, bei denen eine Chemotherapie nicht angezeigt ist.<br>Zweckmäßige Vergleichstherapie: 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).<br>• Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber BSC: Ein Zusatznutzen ist *nicht belegt.* |
| **Institut für Qualität und Wirtschaftlichkeit im Gesundheitsw** | …<br><br>Zusammenfassend ist ein Zusatznutzen für erwachsene Patienten mit vorbehandeltem fortgeschrittenen ALK-positiven NSCLC nicht belegt. Die Gesamtaussage des Zusatznutzens basiert auf der Aggregation des auf |

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| **esen, 2013 [3]**<br><br>[A12-15] Crizotinib - Nutzenbewertung | Endpunktebene abgeleiteten Ausmaßes des Zusatznutzens in den Teilpopulationen, die sich aus der zweckmäßigen Vergleichstherapie ergaben.<br><br>Das Vorgehen zur Ableitung einer Gesamtaussage zum Zusatznutzen stellt einen Vorschlag des IQWiG dar. Über den Zusatznutzen beschließt der G-BA. |
| **Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen, 2013 [4]**<br><br>[A13-13] Addendum zum Auftrag A12-15 (Crizotinib) | Wie bereits in der Dossierbewertung beschrieben, eignet sich die Studie PROFILE 1007 zur Untersuchung des Zusatznutzens von Crizotinib im Vergleich zur Chemotherapie (Docetaxel / PEM) in der Chemotherapie-Population. Das ist eine Population von Patienten mit vorbehandeltem anaplastische Lymphomkinase(ALK)-positiven, fortgeschrittenen nicht kleinzelligen Bronchialkarzinom (NSCLC), bei denen eine Chemotherapie angezeigt ist (dies können insbesondere Patienten mit Eastern Cooperative Oncology Group [ECOG] PS 0, 1 und gegebenenfalls 2 sein). Die Studie kann keine Aussage machen zum Vergleich von Crizotinib und BSC für Patienten in der BSC–Population, bei denen eine Chemotherapie nicht angezeigt ist (dies können insbesondere Patienten mit ECOG PS 4, 3 und gegebenenfalls 2 sein). Für diese Population hat der pU mit der Stellungnahme keine neuen Daten vorgelegt. Das vorliegende Addendum kann deshalb ausschließlich Aussagen zur Chemotherapie-Population machen. |

## Cochrane Reviews

Zur Fragestellung wurden keine Cochrane Reviews identifiziert.

## Systematische Reviews

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| **Zhao N, et al. 2014 [5]** | 1. Fragestellung<br><br>We sought to evaluate the effectiveness of EGFR-TKI as second-line treatment in EGFR wild-type NSCLC. |
| **Efficacy of epidermal growth factor receptor inhibitors versus chemotherapy as second-line** | 2. Methodik<br><br>**Population:** previously treated advanced NSCLC with wild-type EGFR<br><br>**Intervention:** EGFR TKIs<br><br>**Komparator:** chemotherapy<br><br>**Endpunkte:** progression-free survival (PFS), overall survival (OS), objective response rate (ORR) |

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| **treatment in advanced non-small-cell lung cancer with wild-type EGFR: a meta-analysis of randomized controlled clinical trials** | Suchzeitraum: July 31, 2013<br>**Anzahl eingeschlossene Studien/Patienten (Gesamt):** 6/990 (5 phase III)<br>**Qualitätsbewertung der Studien:** Jadad scale<br>**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<br>**„Publication bias“:** tested by funnel plot |
| | 3. Ergebnisdarstellung<br>• all studies reached Jadad score of 3<br>PFS (EGFR-TKIs vs. chemotherapy)<br>• 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<br>• gefitinib and erlotinib significantly inferior to chemotherapy<br>• erlotinib vs. chemotherapy: HR 1,37; 95 % KI 1,16 – 1,63, p = 0,0003<br>• gefitinib vs. chemotherapy: HR 1,35; 95 % KI 1,10 – 1,67, p = 0,004<br>• head-to-head trials: results favored chemotherapy more obviously (HR 1,53; 95 % KI 1,29 – 1,81; p < 0.00001<br>• 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)<br>OS and ORR<br>• equal results |
| | 4. Anmerkungen/Fazit der Autoren<br>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.<br>*Hinweise durch FB Med:*<br>• *study quality not further discussed*<br>• *no evidence of publication bias*<br>• *authors declared no potential conflicts of interest*<br>• *work supported by Key Technologies R&D Programof Guangzhou (2011Y2-00014), Key Laboratory Program ofGuangdong (2012A061400006) (Y.L. Wu)* |
| **Yang X, Yang K, Kuang K. 2014 [6]** | 1. Fragestellung<br>• Efficacy of (EFGR-TKIs: gefitinib or erlotinib) monotherapy in previously treated non-small-cell lung cancer (NSCLC) |

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| **The efficacy and safety of EGFR inhibitor monotherapy in non-small cell lung cancer: a systematic review** | 2. Methodik<br><br>**Population:** advanced NSCLC<br><br>**Intervention:** gefitinib or erlotinib<br><br>**Komparator:** placebo or BSC<br><br>**Endpunkte:** PFS and OS<br><br>**Suchzeitraum:** December 2013<br><br>**Anzahl eingeschlossene Studien/Patienten (Gesamt):** 14/8 970 (3 front-line, 2 second-line, 9 maintenance)<br><br>**Qualitätsbewertung der Studien:** scrutinized – no further information<br><br>**Heterogenitätsuntersuchungen:** $\chi 2$ test, I2 statistic used, values of 50 % regarded as representing low heterogeneity, FEM with Mantel-Haenszel method used, once the results were homogeneous; otherwise, random-effect model with DerSimonian and Laird method adopted, sensitivity analysis was also conducted to examine the impact of the overall results from this study<br><br>**„Publication bias“:** plotting the HRs against their standard errors, Begg-adjusted rank correlation test and Egger regression asymmetry test performed |
| | 3. Ergebnisdarstellung<br><br><u>OS</u><br><br>• HR (EGFR-TKIs mono vs. placebo) 0,88, 95 % KI 0,82 – 0,96, I2 = 50.5% - significantly increased<br>• patients with EGFR mutation positive had more pronounced benefit<br>• second-line therapy group: HR 0,80; 95 % KI 0,63 – 1,01; I2 = 74,6%, p = 0,047<br>• EGFR-mutation patients: HR 0,987; 95 % KI 0,881 – 1,105; I2 = 12,8%, p = 0,330<br><br><u>PFS</u><br><br>• HR (EGFR-TKIs) 0,71, 95 % KI 0,63 – 0,81, I2 = 81,2%<br>• patients with EGFR mutation positive had more pronounced benefit<br><br><u>adverse reactions (EGFR TKIs vs. placebo)</u><br><br>• diarrhea (OR) 3,635; 95 % KI 2,377 to 5,557<br>• rashes (OR) 5,664; 95 % KI 8,869 to 27,665<br>• anorexia (OR) 1,555; 95 % KI 1,060 to 2,283<br>• anemia (OR) 1,481; 95 % KI 1,114 to 1,969 |
| | 4. Anmerkungen/Fazit der Autoren<br><br>The results show that monotherapy therapy with EFGR-TKIs produce a significant OS and PFS benefit for patients with NSCLC compared with placebo or BSC, especially for the patients who had adenocarcinomas, non- |

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| | smokers and patients with EGFR gene mutations. |
| **Li N, et al. 2014 [7]**<br><br>**Meta-Analysis of EGFR Tyrosine Kinase Inhibitors Compared with Chemotherapy as Second-Line Treatment in Pretreated Advanced Non-Small Cell Lung Cancer** | 1. Fragestellung<br><br>We performed this meta-analysis to compare the efficacy and safety of EGFR-TKIs vs. chemotherapy as second-line treatment for pretreated advanced NSCLC. … Preplanned subgroup analyses to explore potential effect on PFS, OS based on EGFR mutation status were scheduled. |
| | 2. Methodik<br><br>**Population:** advanced NSCLC (previously treated with platinum compounds)<br><br>**Intervention:** EGFR TKI<br><br>**Komparator:** standard second-line chemotherapy (docetaxel or PEM)<br><br>**Endpunkte:** progression-free survival (PFS), overall survival (OS), objective response rate (ORR), grade 3–4 toxicities<br><br>**Suchzeitraum:** July 2013<br><br>**Anzahl eingeschlossene Studien/Patienten (Gesamt):** 10/3 825<br><br>**Qualitätsbewertung der Studien:** not mentioned<br><br>**Heterogenitätsuntersuchungen:** Q statistic and $I^2$ statistic used, if considered statistically significant, REM used, otherwise FEM<br><br>**„Publication bias“:** Egger’s test and Begg’s funnel plots used |
| | 3. Ergebnisdarstellung<br><br><u>PFS</u><br><br>• HR 1,03; 95 % KI 0,87 – 1,21; p = 0,73; $I^2$ = 78,7%, p (heterogeneity) = 0,001 - equivalent efficacy<br>• subgroup analysis<br>  o HR (second-line chemotherapy for EGFR mutation negative patients) 1,35; 95 % KI 1,09 – 1,66; p = 0,01; $I^2$ = 55,7%, p (heterogeneity) = 0,046 - significantly improved<br>  o HR (EGFR-TKIs for EGFR mutation positive patients) 0,28; 95 % KI 0,15 – 0,53; p = 0,001; $I^2$ = 4,1%, p (heterogeneity) = 0,35 - significantly improved<br><br><u>OS, ORR</u><br><br>• results of main and subgroup analyses equal<br><br><u>grade 3–4 toxicities</u><br><br>• EGFR-TKIs: more grade 3–4 rash, less fatigue/asthenia disorder, leukopenia, thrombocytopenia |
| | 4. Anmerkungen/Fazit der Autoren<br><br>Our analysis suggests that chemotherapy in the second-line setting can prolong PFS in EGFR M- patients, whereas it has no impact on OS. EGFR-TKIs seem superior over chemotherapy as second-line therapy for EGFR M+ |

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| | patients. Our findings support obtaining information on EGFR mutational status before initiation of second-line treatment.<br><br>*Hinweise durch FB Med:*<br>• *The authors have no support or funding to report.*<br>• *The authors have declared that no competing interests exist.*<br>• *no evidence of publication bias exists* |
| **Lee JK, et al. 2014 [8]**<br><br>**Epidermal growth factor receptor tyrosine kinase inhibitors vs conventional chemotherapy in non-small cell lung cancer harboring wild-type epidermal growth factor receptor: a meta-analysis** | 1. Fragestellung<br>To determine the association between first-generation EGFR TKI vs chemotherapy and survival in advanced NSCLC patients with WT EGFR. |
| | 2. Methodik<br>**Population:** advanced NSCLC with wild type (WT) EGFR<br>**Intervention:** EGFR TKI<br>**Komparator:** conventional chemotherapy<br>**Endpunkte:** primary - progression-free survival (PFS), secondary - objective response rate, overall survival<br>**Suchzeitraum:** through December 2013<br>**Anzahl eingeschlossene Studien/Patienten (Gesamt):** 11/1 605 (7 studies on second line treatment or later)<br>**Qualitätsbewertung der Studien:** not mentioned<br>**Heterogenitätsuntersuchungen:** $\chi$ 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)<br>**„Publication bias“:** funnel plot method togetherwith the Egger test for asymmetry to assess the possibility of publication bias |
| | 3. Ergebnisdarstellung<br>• 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)<br>• No statistically significant subgroup difference was identified in terms of line of treatment (first-line vs. second- or later-line), experimental drug, dominant ethnicity, or EGFR mutation analysis method<br>• association of chemotherapy with improvement in PFS also significant in second- or later-line trials (HR, 1.34; 95%CI, 1.09-1.65)<br>• 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) |

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| | • no statistically significant difference observed with respect to overall survival (HR for TKI, 1.08; 95%CI, 0.96-1.22) |
| | 4. Anmerkungen/Fazit der Autoren<br><br>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.<br><br>*Hinweise durch FB Med:*<br>• *Arbeit aus staatlichen Mitteln gefördert*<br>• *Interessenkonflikterklärungen offengelegt* |
| **Qi W-X, et al. 2013 [9]**<br><br>**Overall Survival Benefits for Combining Targeted Therapy as Second-Line Treatment for Advanced Non-Small-Cell-Lung Cancer: A Meta-Analysis of Published Data** | 1. Fragestellung<br><br>We thus performed a meta-analysis of RCTs to compare the efficacy and safety of combining targeted therapy vs. erlotinib alone as second-line treatment for advanced NSCLC. |
| | 2. Methodik<br><br>**Population:** Patients with pathologically confirmed of advanced NSCLC and previously treated<br><br>**Intervention:** combined targeted therapy<br><br>**Komperator:** erlotinib alone or erlotinib plus placebo<br><br>**Endpunkte:** overall survival (OS), progression-free survival (PFS), overall response rate (ORR), grade 3 or 4 adverse event (AEs)<br><br>**Suchzeitraum:** 1980 bis 2012<br><br>**Anzahl eingeschlossene Studien/Patienten (gesamt):** 8/2 417<br><br>**Qualitätsbewertung der Studien:** jadad score<br><br>**Heterogenitätsuntersuchungen:** x2-based Q statistic used, considered statistically significant when p (heterogeneity) < 0,05 or I2>50%, if existed, data analyzed by REM (the DerSimonian and Laird method)<br><br>**„Publication bias“-Berechnung:** Begg and Egger tests |

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| | 3. Ergebnisdarstellung (gesamt)<br>• significantly improved OS (HR 0.90, 95%CI: 0.82–0.99, p = 0.024), PFS (HR 0.83, 95%CI: 0.72–0.97, p = 0.018), and ORR (OR 1.35, 95%CI 1.01–1.80, p = 0.04) under combined targeted therapy<br>• More incidence of grade 3 or 4 rash, fatigue and hypertension were observed in combining targeted therapy.<br>Ergebnissdarstellung (Subgruppen):<br>• Sub-group analysis based on phases of trials, EGFR-status and KRAS-status also showed that there was a tendency to improve PFS and OS in combining targeted therapy, except that PFS for patients with EGFR-mutation or wild type KRAS favored erlotinib monotherapy.<br>• because of a small number of patients with EGFR-status reported in these trials, it should be careful when interpreting these results<br>• only 283 patients with EGFR mutation were included in meta-analysis<br>• more trials still needed to identify molecular biomarkers that are predictive of efficacy |
| | 4. Anmerkungen/Fazit der Autoren<br>With the available evidence, combining targeted therapy seems superior over erlotinib monotherapy as second-line treatment for advanced NSCLC. More studies are still needed to identify patients who will most likely benefit from the appropriate combining targeted therapy.<br>*Hinweise FB Med:*<br>• *no evidence of publication bias*<br>• *Funding: The study was supported by grants from the National Natural Science Foundation of China (81001191) and Science and Technology Commission of Shanghai (10PJ1408300). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*<br>• *Competing Interests: The authors have declared that no competing interests exist.* |

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| **Scottish Intercollegiate Guidelines Network (SIGN). 2014 [10]**<br><br>Management of lung cancer | **Fragestellung**<br><br>14. In patients with NSCLC (locally advanced or metastatic disease), what is the most effective second line systemic anticancer therapy (chemotherapy, targeted therapy, EGFR Inhibitors)?<br><br>Outcomes: Overall survival, progression-free survival, toxicity, quality of life |
| | **Methodik**<br><br>Grundlage der Leitlinie: systematische Recherche und Bewertung der Literatur, Entwicklung durch multidisziplinäre Gruppe von praktizierenden klinischen ExpertInnen, Expertenreview, öffentliche Konsultation<br><br>Suchzeitraum: 2005 - 2012<br><br>LoE/GoR: siehe Anhang dieser Synopse<br><br>Sonstige methodische Hinweise<br><br>• *keine Empfehlung zur gesuchten Indikation*<br>• *Hintergrundtext (siehe unten) ohne Quellenangaben* |
| | **Freitext/Empfehlungen**<br><br>8.1 Molecular testing of predictive biomarkers in patients with NSCLC<br><br>… Other molecular abnormalities which may be tested for include anaplastic lymphoma kinase (ALK) gene rearrangement …. Drugs targeting these mutations are at various stages of development.<br><br>8.4 second line therapy<br><br>In patients who are PS ≤ 2 at the time of progression of their advanced NSCLC, second line treatment with single agent docetaxel, erlotinib or PEM improve survival rates compared to BSC.<br><br>**236.** Tassinari D, Scarpi E, Sartori S, Tamburini E, Santelmo C, Tombesi P, et al. Second-line treatments in non-small cell lung cancer. A systematic review of literature and metaanalysis of randomized clinical trials. Chest 2009;135(6):1596-609. **(LoE 1+)**<br><br>Second line docetaxel improved time to progression, survival and quality of life. Patient's opioid requirements and weight loss were reduced with docetaxel compared to BSC only. This was clearest in the patients who received 100 mg/m2 rather than 75 mg/m2 every three weeks, however the higher dose was associated with more overall toxicity, and is not recommended as standard.<br><br>**237.** Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, 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):2095-103. **(LoE 1+)**<br><br>**238.** Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, et al. Randomised phase III trial of docetaxel versus vinorelbine or ifosfamide inpatients with advanced non-small cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX |

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| | 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000;18(12):2354-62. **(LoE 1+)**<br><br>Weekly docetaxel is not recommended over three-weekly due to increased toxicity.<br><br>**239.** Tassinari D, Carloni F, Santelmo C, Tamburini E, Agli LL, Tombesi P, et al. Second line treatments in advanced platinum-resistant non small cell lung cancer: A critical review of literature. Rev Recent Clin Trials 2009;4(1):27-33. **(LoE 1+)**<br><br>Randomised evidence does not support the use of combination SACT as second line treatment for patients with advanced NSCLC based on an increase in toxicity without any gain in survival.<br><br>**240.** D i Maio M, Chiodini P, Georgoulias V, Hatzidaki D, Takeda K, Wachters FM, et al. Meta-analysis of single-agent chemotherapy compared with combination chemotherapy as second-line treatment of advanced non-small-cell lung cancer. J Clin Oncol 2009;27(11):1836-43. **(LoE 1++)**<br><br>Second line erlotinib improves overall survival compared to BSC in patients with NSCLC. Median survival was improved with moderate toxicity. The response rate was 8.9% in the erlotinib group and less than 1% in the placebo group (p<0.001); the median duration of the response was 7.9 months and 3.7 months, respectively. Progression-free survival was 2.2 months and 1.8 months, respectively (HR 0.61, adjusted for stratification categories; p<0.001). Overall survival was 6.7 months and 4.7 months, respectively (HR 0.70; p<0.001) in favour of erlotinib.<br><br>**236.** (see above)<br><br>**241.** Noble J, Ellis PM, Mackay JA, Evans WK. Second-line or subsequent systemic therapy for recurrent or progressive non-small cell lung cancer: A systematic review and practice guideline. J Thorac Oncol 2006;1(9):1042-58. **(LoE 1++)**<br><br>Compared with single agent docetaxel, treatment with PEM resulted in clinically equivalent efficacy outcomes, but with significantly fewer side effects in the second-line treatment of patients with advanced predominantly non-squamous cell NSCLC.<br><br>**241.** (see above)<br><br>Recommendations<br><br>Second line systemic anticancer therapy with single agent docetaxel or erlotinib should be considered for patients with performance status 0-2 recurrent NSCLC who have been previously treated with first line SACT for advanced disease. **(A)**<br><br>Second line systemic anticancer therapy with pemetrexed should be considered for patients with advanced non-squamous cell NSCLC who have been previously treated with first line SACT for advanced disease. **(A)** |
| **Gridelli C, et al. 2014 [11]**<br><br>Treatment of advanced non-small-cell lung | **Fragestellung**<br><br>Which Is the Best Treatment for Patients With ALK Gene Rearrangements?<br><br>What Is the Role for Chemotherapy in Patients With ALK Rearrangements?<br><br>Is There a Role for Continuing Crizotinib Beyond Progression?<br><br>**Methodik** |

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| cancer with epidermal growth factor receptor (EGFR) mutation or ALK gene rearrangement: results of an international expert panel meeting of the Italian Association of Thoracic Oncology | Grundlage der Leitlinie: consensus meeting in Sperlonga, Italy, May 2013, systematic literature search<br><br>panel composition: 9 medical oncologists (4 from Italy, 2 from the United States, and 1 each from Hong Kong, Taiwan, and Spain), experts involved in the principal clinical trials—completed and ongoing—in this field<br><br>Suchzeitraum: until 2013<br><br>LoE/GoR: not stated[1]<br><br>Sonstige methodische Hinweise<br><br>• *Interessenkonflikterklärungen am Ende des Textes veröffentlicht*<br>• *Konsensusprozess nicht als formales Verfahren beschrieben*<br>• *Auswahl der Literatur nicht beschrieben*<br><br>[1] When discussing the recent data that would potentially result in changes in clinical practice, the panelists considered that several limitations may significantly affect their strength: (1) some data are still unpublished in peer-reviewed journals and the discussion was based on meeting presentations; (2) some data are based on case series and not on RCTs; and (3) there are no direct comparative data among the EGFR TKIs and the discussion on this topic was based on indirect comparison among the trials. |
| | **Freitext/Empfehlungen**<br><br>Which Is the Best Treatment for Patients With ALK Gene Rearrangements?<br><br>• use of crizotinib justified in any line of treatment<br>• discussion based on phase I/II trial18 and on the phase III trial comparing crizotinib vs. chemotherapy as second-line treatment<br><br>**Shaw AT**, Kim DW, Nakagawa K, et al. Crizotinib vs. chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013; 368:2385-94<br><br>• results of 2 RCTs comparing crizotinib vs. platinum-based chemotherapy as first-line treatment still awaited<br><br>PROFILE 1014 [A Clinical Trial Testing the Efficacy of Crizotinib vs. Standard Chemotherapy PEM Plus Cisplatin or Carboplatin in Patients With ALK Positive Nonsquamous Cancer of the Lung], ClinicalTrials.gov Identifier NCT01154140<br><br>similar study conducted in East Asian patients, ClinicalTrials.gov Identifier NCT01639001<br><br>What Is the Role for Chemotherapy in Patients With ALK Rearrangements?<br><br>• chemotherapy is justified in any line of treatment, but preferably following failure of crizotinib treatment<br>• no robust data to recommend a specific chemotherapy regimen in ALK+ cases<br>• preliminary data suggest that ALK+ tumors are particularly sensitive to PEM<br><br>**Camidge DR**, Kono SA, Lu X, et al. Anaplastic lymphoma kinase gene rearrangements in non-small cell lung cancer are associated with prolonged progression-free survival on PEM. J Thorac Oncol 2011; 6:774-80<br><br>**Lee JO**, Kim TM, Lee SH, et al. Anaplastic lymphoma kinase translocation: a predictive |

biomarker of PEM in patients with non-small cell lung cancer. J Thorac Oncol 2011; 6:1474-80

- in the RCT of Shaw et al. (see above) 99 patients (57%) in the control arm received PEM and 72 (41%) received docetaxel, ORR was 65.7% in the crizotinib arm, 29.3% with PEM and 6.9% with docetaxel, median PFS was 7.7 months with crizotinib, 4.2 months with PEM, and 2.6 months with docetaxel
- trial was not designed to explore differences between the 2 cytotoxic agents, but these data suggest higher activity and efficacy of PEM compared with docetaxel
- an indirect comparison of the efficacy of PEM in series of ALK+ and ALK- patients did not produce clear evidence that PEM is particularly active in ALK+ cases, with the exception of first-line treatment with cisplatin/PEM, which produced a longer PFS compared with the ALK- cohort that received the same treatment

**Shaw AT**, Varghese AM, Solomon BJ, et al. PEM-based chemotherapy in patients with advanced, ALK-positive non-small cell lung cancer. Ann Oncol 2013; 24:59-66

- interpretation of the specific interaction between PEM efficacy and ALK status complicated by the finding that among patients with a never/light smoking history treated with first-line platinum/PEM, there was no difference in PFS between ALK+ and ALK- patients
- evidence cannot be considered definitive, PEM has been chosen as reference chemotherapy for ALK+ patients in an ongoing randomized phase II trial conducted by the Southwest Oncology Group (SWOG 1300)
- patients with systemic progression while receiving crizotinib after clinical benefit (objective response or at least 3 months of stable disease) are randomized to receive PEM alone or PEM in combination with crizotinib

Is There a Role for Continuing Crizotinib Beyond Progression?

- no solid evidence supporting the efficacy of continuing crizotinib beyond disease progression
- in some cases (patients presenting with minimal progression and asymptomatic disease or those with oligoprogression that can be managed by local treatment, continuation of crizotinib beyond progression could be justified

**Weickhardt AJ**, Scheier B, Burke JM, et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogeneaddicted non-small-cell lung cancer. J Thorac Oncol 2012; 7:1807-14

- discussion based on data of the phase I trial and of the phase III second-line trial describing a proportion of patients who continued crizotinib beyond progression

**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 2012; 13:1011-9

- of the 69 patients with disease progression, 39 (56.5%) continued to

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| | receive crizotinib for more than 2 weeks because, in the opinion of the investigators, they were deriving clinical benefit<br>• In some cases, use of crizotinib beyond progression was particularly long: 12 patients received crizotinib for at least a further 6 months.<br>• in the RCT of Shaw et al. (see above) 58 patients continued crizotinib beyond progression, with a median duration of further treatment of 16 weeks (range, 3-73 weeks)<br>• These data only support the feasibility of prolonged administration, however, and are not sufficient to prove the effectiveness of this strategy. |
| **Alberta Provincial Thoracic Tumour Team. 2013 [12]**<br><br>**Non-small cell lung cancer stage IV** | **Fragestellung**<br><br>What is the optimal second-line therapy for patients with stage IV NSCLC? |
| | **Methodik**<br><br><u>Grundlage der Leitlinie:</u> 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<br><br><u>Suchzeitraum:</u> bis 2013<br><br><u>LoE/GoR:</u> 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<br><br>*Sonstige methodische Hinweise*<br><br>• *Kein formaler Konsensusprozess beschrieben*<br>• *Auswahl und Bewertung der Literatur nicht beschrieben*<br>• *no direct industry involvement in the development or dissemination of this guideline*<br>• *authors have not been remunerated for their contributions*<br>• *Some members of the Alberta Provincial Thoracic Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.* |
| | **Freitext/Empfehlungen**<br><br><u>Recommendations</u><br><br>…<br><br>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.<br><br>9. Crizotinib has been approved for second-line treatment of patients who are positive for ALK-rearrangements from the pan-Canadian Oncology Drug |

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| | Review (pCODR) and has also been approved for provincial coverage in Alberta.<br><br>…<br><br>Discussion and literature<br><br>**Second-line chemotherapy**<br><br>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.<br><br>**85.** Stinchcombe TE, Socinski MA. Considerations for second-line therapy of non-small cell lung cancer. *Oncologist.* 2008;13 Suppl 1:28-36.<br>**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.<br>**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.<br>**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.<br>**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.<br>**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.<br>**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.<br>**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.<br>**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.<br>**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.<br>**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.<br>**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.<br>**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.<br>**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.<br>**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 2011;6(12):2120-2129.
**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.
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**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

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| | cancer. *Cancer.* Jul 15 2012;118(14):3579-3586.<br><br>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.<br><br>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.<br><br>**117.** Shaw AT, Kim DW, Nakagawa K, et al. Phase III study of crizotinib versus pemetrexed or docetaxel chemotherapy in patients with advanced ALK-positive non-small cell lung cancer (NSCLC) (PROFILE 1007). Paper presented at: Congress of the European Society for Medical Oncology 20122012.<br><br>**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.<br><br>As a result of these, and other promising results, the US FDA have approved crizotinib for patients with ALK-positive advanced or metastatic NSCLC.<br><br>**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.<br><br>The results of these early trials are promising, and, along with other clinical trials currently underway, may strengthen support for the role of prospective genotyping in the selection of therapy for patients with advanced NSCLC. Indeed, guidelines from the National Comprehensive Cancer Network and the European Society for Medical Oncology now recommend ALK gene rearrangement testing to better treat those patients with advanced NSCLC who are ALK-positive. |
| **Brodowicz T, et al. 2012 [13]** | **Fragestellung**<br><br>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 |

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| **Third CECOG consensus on the systemic treatment of non-small-cell lung cancer** | therapeutic options. |
| | **Methodik**<br><br>Grundlage der Leitlinie: evidence-based consensus from experts from Europe and the United States based on systematic literature search<br><br>Suchzeitraum: until December 2009<br><br>LoE/GoR: Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology<br><br>*Sonstige methodische Hinweise*<br><br>• *Kein formaler Konsensusprozess beschrieben*<br>• *Auswahl und Bewertung der Literatur nicht beschrieben*<br>• *14 author disclosures given, remaining authors have declared no conflicts of interest* |
| | **Freitext/Empfehlungen**<br><br>second-line systemic therapy<br><br>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 nonsquamous NSCLC [II,B]) or the EGFR TKI erlotinib [I,B].<br><br>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.<br><br>**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.<br><br>**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.<br><br>**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.<br><br>**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.<br><br>**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.<br><br>**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.<br><br>**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.<br><br>**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; 366(9496): 1527–1537.<br><br>**46.** Zhu CQ, da Cunha Santos G, Ding K et al. Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21. |

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| | J Clin Oncol 2008; 26(26): 4268–4275.<br>**47.** Hirsch FR, Varella-Garcia M, Bunn PA Jr., et al. Epidermal growth factor receptor in non-small-cell lung carcinomas: correlation between gene copy number and protein expression and impact on prognosis. J Clin Oncol 2003; 21(20): 3798–3807.<br>targeted treatment options<br>…<br>3 Patients with EML4-ALK fusion tumors benefit from specific targeted therapy against EML4-ALK fusion. The role of routinely carried out EML4-ALK fusion testing for clinical practice is awaiting the results from ongoing clinical trials.<br>EML4-ALK fusion: The fusion gene EML4-Anaplastic Lymphoma Kinase (ALK) was first reported in NSCLC only a few years ago.<br>**53.** Soda M, Choi YL, Enomoto M et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007; 448(7153): 561–566.<br>A clinical dose-escalation phase I study with an oral MET and ALK inhibitor PF-02341066 showed for NSCLC patients with tumors harboring an activating ALK gene fusion an objective RR of 64% and a disease control rate of 90%.<br>**54.** Bang Y, KE , Shaw AT, Kwak EL. Clinical activity of the oral ALK inhibitor PF-02341066 in ALK-positive patients with non-small cell lung cancer (NSCLC). J Clin Oncol (Meeting Abstracts) 2010; 28: 3.<br>Although the ALK fusion either with EML4 or with other fusion partners is relatively infrequent in NSCLC (4%–5%), there still is a substantial number of patients who might have a significant clinical benefit from this well-tolerated therapy.<br>**55.** Choi YL, Soda M, Yamashita Y et al. EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors. N Engl J Med 2010; 363(18): 1734–1739. |

**Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren**

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| **NICE technology appraisal guidance, 2013 [14]**<br><br>Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene | 1 Guidance<br><br>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.<br>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. |

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| **Semlitsch T, Jeitler K, 2013 [15]**<br><br>Crizotinib (Xalkori®) for the treatment of anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) | 5 Current treatment<br><br>As second line therapy the following treatments are recommended:<br>• single agent chemotherapy (docetaxel or PEM)<br>• targeted agent therapy (e.g. erlotinib)<br>• a platinum based combination therapy for patients with EGFR mutation and progressive disease after tyrosine kinase inhibitor treatment (e.g. erlotinib)<br><br>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. |
| **National Horizon Scanning Centre, 2010 [16]**<br><br>Crizotinib for locally advanced or metastatic ALK positive non-small cell lung cancer (NSCLC) - second or third line | **Target group:** NSCLC: locally advanced or metastatic; positive for anaplastic lymphoma kinase (ALK) fusion gene – second or third line.<br><br>**Innovation and/or advantages:** If licensed, crizotinib would be the first agent to selectively target EML4-ALK (ALK fusion gene) translocation in patients with NSCLC. This may potentially provide a new treatment option for a subset of patients with NSCLC who do not respond to conventional therapies.<br><br>**Existing comparators and treatments:** Treatment options for locally advanced or metastatic NSCLC include radiation therapy, chemotherapy with radiation therapy and chemotherapy alone. Chemotherapy may be recommended for patients provided they have a good PS.<br>Second line chemotherapy regimens for advanced and/or metastatic NSCLC include:<br>• Docetaxel (Taxotere) - a mitosis inhibitor.<br>• Erlotinib (Tarceva) - an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (not recommended by NICE in patients for whom docetaxel is unsuitable).<br>• PEM (Alimta) - a thymidylate synthase and dihydrofolate reductase inhibitor (not recommended by NICE).<br>• Gefitinib (Iressa) - EGFR tyrosine kinase inhibitor (NICE unable to recommend as no evidence submission received from the manufacturer or sponsor).<br><br>There is currently no recommended pharmacological treatment available for patients with NSCLC who have progressed after previous cytotoxic chemotherapy (first/second line) and who are resistant to EGFR-tyrosine kinase inhibitor (erlotinib or gefitinib). EML4-ALK is strongly associated with resistance to EGFR tyrosine kinase inhibitors. |
| **NiHR Horizon Scanning Centre, 2013 [17]**<br><br>LDK378 for | **Target Group:** Non-small cell lung cancer (NSCLC): locally advanced or metastatic; anaplastic lymphoma kinase (ALK)-activated (ALK-positive) – second and subsequent lines.<br><br>**Innovation and/or advantages:** If licensed, LDK378 (Anmerkung FB Med: Ceritinib) would offer an additional treatment option for a subset of patients with locally advanced or metastatic ALK-activated NSCLC who have not responded to previous therapies, including chemotherapy. |

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| ALK-activated advanced non-small cell lung cancer - second and subsequent lines | **Existing comparators and treatments:** Treatment options for locally advanced or metastatic NSCLC include radiation therapy, chemotherapy with radiation therapy and chemotherapy alone. Chemotherapy may be recommended for patients provided they have a good PS. A NICE clinical guideline and technology appraisals recommends a combination of premetrexed, docetaxel, gemcitabine, paclitaxel or vinorelbine plus carboplatin or cisplatin as first line chemotherapy options for patients with stage III or IV NSCLC and a good PS. Bevacizumab, in addition to platinum-based chemotherapy is also licensed for the first line treatment of unresectable advanced, metastatic or recurrent NSCLC (not recommended by NICE). In the presence of activating EGFR mutation, NICE recommends the use of either gefitinib or erlotinib in place of first line chemotherapy. Second line treatment options for advanced and/or metastatic NSCLC include:<br>• Docetaxel (monotherapy) − a mitosis inhibitor.<br>• Erlotinib (monotherapy) − an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor.<br>• PEM − a thymidylate synthase and dihydrofolate reductase inhibitor (not recommended by NICE).<br>• Gefitinib − EGFR tyrosine kinase inhibitor (NICE unable to recommend because no evidence submission was received from the manufacturer or sponsor).<br>• Crizotinib − a tyrosine kinase inhibitor − licensed for previously treated ALK-positive advanced non-small cell lung cancer (NICE technology appraisal in development).<br><br>The EML4-ALK mutation is strongly associated with resistance to EGFR tyrosine kinase inhibitors. Crizotinib is currently the only licensed treatment available for patients with NSCLC who have progressed after previous cytotoxic chemotherapy (first/second line) and who have a tumour bearing an ALK translocation. The only other treatment option for the majority of patients will be BSC, which aims to relieve symptoms, improve disease control, quality of life and increase survival. |
| **Scottish Medicines Consortium, 2013 [18]**<br><br>Crizotinib (Xalkori) - treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung | crizotinib (Xalkori®) is accepted for use within NHS Scotland.<br><br>Indication under review: treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).<br><br>In a phase III clinical study in patients with previously treated anaplastic lymphoma kinase (ALK)-positive advanced NSCLC, crizotinib significantly increased progression-free survival compared with standard chemotherapy.<br><br>This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of crizotinib. This SMC advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower. |

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| cancer (NSCLC) | |

**Primärstudien**

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

**Detaillierte Darstellung der Recherchestrategie:**

Cochrane Library (Cochrane Database of Systematic Reviews) am 21.07.2014

| Suchschritt | 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 (Word variations have been searched) |
| #3 | tumor* or tumour* or carcinoma* or adenocarcinoma* or neoplasm* or sarcoma* or cancer*:ti,ab,kw (Word variations have been searched) |
| #4 | #2 and #3 |
| #5 | nsclc*:ti,ab,kw (Word variations have been searched) |
| #6 | #1 or #4 or #5 |
| #7 | #1 or #4 or #5 Publication Year from 2009 to 2014 |

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

| Suchschritt | 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 (Word variations have been searched) |
| #3 | tumor* or tumour* or carcinoma* or adenocarcinoma* or neoplasm* or sarcoma* or cancer*:ti,ab,kw (Word variations have been searched) |
| #4 | #2 and #3 |
| #5 | nsclc*:ti,ab,kw (Word variations have been searched) |
| #6 | advanced or metastas* or metastat* or recurren* or ((3rd or third or 2nd or second) and line) or (stage next III*) or (stage next IV):ti,ab,kw (Word variations have been searched) |
| #7 | (#4 or #5) and #6 |
| #8 | #1 or #7 |
| #9 | #1 or #7 Publication Year from 2009 to 2014 |

MEDLINE (PubMed) am 21.07.2014

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

| Suchschritt | Suchfrage |
|---|---|
| #5 | nsclc*[Title/Abstract] |
| #6 | (#4) OR #5 |
| #7 | ((((((advanced[Title/Abstract]) OR metastas*[Title/Abstract]) OR metastat*[Title/Abstract]) OR recurren*[Title/Abstract])) OR ((((((3rd[Title/Abstract]) OR third[Title/Abstract]) OR 2nd[Title/Abstract]) OR second[Title/Abstract])) AND line[Title/Abstract])) OR ((stage III*[Title/Abstract]) OR stage IV[Title/Abstract]) |
| #8 | (#6) AND #7 |
| #9 | (#1) OR #8 |
| #10 | (#9) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) |
| #11 | (#9) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract])))) |
| #12 | (#10) OR #11 |
| #13 | (#12) AND ("2009/07/01"[PDAT] : "2014/07/21”[PDAT]) |

MEDLINE (PubMed) nach Leitlinien am 21.07.2014

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

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

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## Anhang

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

**Abbildung 1: aus SIGN 2014**