Gemeinsamer Bundesausschuss

# Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

# und

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

## Vorgang: 2019-B-135 Lorlatinib

Stand: August 2018

| I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA | |
|---|---|
| **Lorlatinib<br>[zur Behandlung des ALK-positiven NSCLCs nach vorheriger TKI-Therapie]** | |
| **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“*<br>• Arzneimittel zur Behandlung des NSCLCs mit aktivierenden EGFR-Mutationen oder BRAF-V600-Mutationen wurden nicht berücksichtigt<br>• Arzneimittel zur Behandlung des NSCLCs mit ausschließlich plattenepithelialer Histologie wurden ebenfalls nicht berücksichtigt |
| Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein. | *Nicht angezeigt* |
| Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen | **Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:**<br>• Alectinib (ALK-positives NSCLC, Erstlinie): Beschluss vom 21.06.2018<br>• Alectinib (ALK-positives NSCLC, nach Crizotinib): Beschluss vom 19.10.2017<br>• Ceritinib (ALK-positives NSCLC, Erstlinie): Beschluss vom 01.02.2018<br>• Ceritinib (ALK-positives NSCLC, nach Crizotinib): Beschluss vom 16.03.2017<br>• Crizotinib (ALK-positives NSCLC, Erstlinie): Beschluss vom 16.06.2016<br>• Crizotinib (ROS1-positives NSCLC): Beschluss vom 16.03.2017<br>**Richtlinien:**<br>Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie - Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (Off-Label-Use):<br>• Carboplatin-haltige Arzneimittel bei fortgeschrittenem nicht-kleinzelligem Bronchialkarzinom (NSCLC) – 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**<br>**ATC-Code**<br>**Handelsname** | **Anwendungsgebiet**<br>(Text aus Beratungsanforderung/Fachinformation) |
| Zu prüfendes Arzneimittel: | |
| Lorlatinib | Geplantes Anwendungsgebiet:<br>Lorviqua als Monotherapie wird angewendet bei erwachsenen Patienten zur Behandlung des ALK-positiven, fortgeschrittenen nicht-kleinzelligen Lungenkarzinoms (NSCLC), welche im Vorfeld mit einem oder mehreren ALK Tyrosinkinase-Inhibitoren (TKIs) behandelt wurden, mit Ausnahme von Patienten, welche Crizotinib als einzigen TKI erhielten. |
| **Chemotherapien:** | |
| Carboplatin<br>L01XA02<br>generisch | Off-Label-Indikation für Carboplatin: Kombinationstherapie des fortgeschrittenen NSCLC (palliativ) |
| Cisplatin<br>L01XA01<br>generisch | Cisplatin wird angewendet zur Behandlung des fortgeschrittenen oder metastasierten nichtkleinzelligen Bronchialkarzinoms.<br>Cisplatin kann als Mono- oder Kombinationstherapie angewendet werden.<br>(Cisplatin Teva® 1 mg / ml Konzentrat) |
| Docetaxel<br>L01CD02<br>generisch | Nicht-kleinzelliges Bronchialkarzinom:<br>Docetaxel ist in Kombination mit Cisplatin zur Behandlung von Patienten mit nicht resezierbarem, lokal fortgeschrittenem oder metastasiertem, nicht-kleinzelligem Bronchialkarzinom ohne vorausgegangene Chemotherapie angezeigt.<br>(Docetaxel-ratiopharm® 20 mg/ml Konzentrat) |
| Gemcitabin<br>L01BC05<br>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.<br>(Gemcitabin Kabi 38 mg/ml Konzentrat) |
| Ifosfamid<br>L01AA06<br>Holoxan® | Nicht-kleinzellige Bronchialkarzinome:<br>Zur Einzel- oder Kombinationschemotherapie von Patienten mit inoperablen oder metastasierten Tumoren. |

| | |
|---|---|
| Mitomycin<br>L01DC03<br>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 […].<br>(Mitomycin Teva® 1 mg/ml) |
| Paclitaxel<br>L01CD01<br>generisch | Fortgeschrittenes nicht-kleinzelliges Bronchialkarzinom (NSCLC):<br>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.<br>(Paclitaxel-GRY® 6 mg/ml Konzentrat) |
| Nab-Paclitaxel<br>L01CD01<br>Abraxane® | Abraxane ist in Kombination mit Carboplatin indiziert für die Erstlinienbehandlung des nicht-kleinzelligen Bronchialkarzinoms bei erwachsenen Patienten, bei denen keine potentiell kurative Operation und/oder Strahlentherapie möglich ist. |
| Pemetrexed<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. Alimta in Monotherapie ist angezeigt für die Erhaltungstherapie bei lokal fortgeschrittenem oder metastasiertem nicht-kleinzelligen Lungenkarzinom außer bei überwiegender plattenepithelialer Histologie bei Patienten, deren Erkrankung nach einer platinbasierten Chemotherapie nicht unmittelbar fortgeschritten ist. |
| Vindesin<br>L01CA03<br>Eldesine® | Kombinationschemotherapie:<br>Lokal fortgeschrittenes oder metastasiertes nicht-kleinzelliges Bronchialkarzinom (Stadium IIIB, IV). |
| Vinorelbin<br>L01CA04<br>generisch | Behandlung des nicht kleinzelligen Bronchialkarzinoms (Stadium 3 oder 4).<br>(Vinorelbin onkovis 10 mg/ml Konzentrat) |
| **Proteinkinase-Inhibitoren:** | |
| Alectinib<br>L01XE36<br>Alecensa® | Alecensa wird als Monotherapie angewendet zur Erstlinienbehandlung des Anaplastische-Lymphomkinase (ALK)-positiven, fortgeschrittenen nicht-kleinzelligen Lungenkarzinoms (non-small cell lung cancer, NSCLC) bei erwachsenen Patienten.<br>Alecensa wird als Monotherapie angewendet zur Behandlung des Anaplastische-Lymphomkinase (ALK)-positiven, fortgeschrittenen nicht-kleinzelligen Bronchialkarzinoms (non-small cell lung cancer, NSCLC) bei erwachsenen Patienten, die zuvor mit Crizotinib behandelt wurden. |
| Ceritinib<br>L01XE28<br>Zykadia® | Zykadia wird als Monotherapie angewendet bei erwachsenen Patienten zur Erstlinienbehandlung des fortgeschrittenen, Anaplastische-Lymphomkinase(ALK)-positiven, nichtkleinzelligen Bronchialkarzinoms (NSCLC).<br>Zykadia wird angewendet bei erwachsenen Patienten zur Behandlung des fortgeschrittenen, Anaplastische-Lymphomkinase(ALK)-positiven, nicht-kleinzelligen Bronchialkarzinoms (NSCLC), die mit Crizotinib vorbehandelt wurden. |

| | |
|---|---|
| Crizotinib<br>L01XE16<br>Xalkori® | XALKORI als Monotherapie wird angewendet bei:<br>• Erwachsenen zur Erstlinienbehandlung des Anaplastische-Lymphom-Kinase (ALK)-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, NSCLC)<br>• Erwachsenen zur Behandlung des vorbehandelten Anaplastische-Lymphom-Kinase (ALK)-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (non small cell lung cancer, NSCLC)<br>• Erwachsenen zur Behandlung des ROS1-positiven, fortgeschrittenen nicht kleinzelligen Lungenkarzinoms (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: 2018-B-135 (Lorlatinib)

| | |
|---|---|
| Auftrag von: | Abt. AM |
| Bearbeitet von: | Abt. FB Med |
| Datum: | 12. Juli 2018 |

# Inhaltsverzeichnis

## Abkürzungsverzeichnis

| | |
|---|---|
| ALK | Anaplastic Lymphoma Kinase |
| ASCO | American Society of Clinical Oncology |
| AWMF | Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften |
| BSC | Best supportive care |
| CIS | Cisplatin |
| DAHTA | DAHTA Datenbank |
| DOC | Docetaxel |
| ECOG-PS | Eastern Cooperative Oncology Group Performance Status |
| EORTC | European Organisation for QLQ Research and Treatment of Cancer Quality of Life Questionnaire |
| EGFR | Epidermal Growth Factor Receptor |
| G-BA | Gemeinsamer Bundesausschuss |
| GIN | Guidelines International Network |
| GoR | Grade of Recommendations |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| HR | Hazard Ratio |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen |
| k.A. | Keine Angaben |
| KI | Konfidenzintervall |
| LoE | Level of Evidence |
| M+ | mutation positive (EGFR) |
| NGC | National Guideline Clearinghouse |
| NICE | National Institute for Health and Care Excellence |
| OR | Odds Ratio |
| OS | Overall Survival |
| PAX | Paclitaxel |
| PEM | Pemetrexed |
| PFS | Progression Free Survival |

| | |
|---|---|
| QoL | Quality of Life |
| RCT | Randomized Controlled Trial |
| RR | Relatives Risiko |
| SIGN | Scottish Intercollegiate Guidelines Network |
| TKI | Tyrosinkinsaseinhibitor |
| TRIP | Turn Research into Practice Database |
| TTP | Time to Progression |
| WHO | World Health Organization |
| WT | Wild Type |

# 1 Indikation

zur Behandlung des ALK-positiven NSCLCs (non-small cell lung cancer) nach Versagen von Alectinib oder Ceritinib

# 2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *metastasiertes nicht-kleinzelliges Lungenkarzinom (NSCLC)* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 13.03.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1324 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 23 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

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# 3 Ergebnisse

## 3.1 IQWiG Berichte/G-BA Beschlüsse

**G-BA, 2017 [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 – Alectinib

Siehe auch IQWiG, 2017 [14,15].

**Anwendungsgebiet**

Alecensa wird als Monotherapie angewendet zur Behandlung des Anaplastische-Lymphomkinase (ALK)-positiven, fortgeschrittenen nicht-kleinzelligen Bronchialkarzinoms (non-small cell lung cancer, NSCLC) bei erwachsenen Patienten, die zuvor mit Crizotinib behandelt wurden.

a) Patienten, für die eine Behandlung mit Docetaxel oder Pemetrexed oder Ceritinib infrage kommt:

**Zweckmäßige Vergleichstherapie**

Docetaxel *oder* Pemetrexed *oder* Ceritinib

**Fazit / Ausmaß des Zusatznutzens / Ergebnis**

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Docetaxel oder Pemetrexed:

Anhaltspunkt für einen geringen Zusatznutzen.

b) Patienten, für die eine Behandlung mit Docetaxel oder Pemetrexed oder Ceritinib nicht infrage kommt:

**Zweckmäßige Vergleichstherapie**

Best-Supportive-Care

**Fazit / Ausmaß des Zusatznutzens / Ergebnis**

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care:

Ein Zusatznutzen ist nicht belegt.

**G-BA, 2017 [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 (Ablauf der Befristung)

Siehe auch IQWiG, 2016 [16].

**Anwendungsgebiet**

Zykadia wird angewendet bei erwachsenen Patienten zur Behandlung des fortgeschrittenen, Anaplastische-Lymphomkinase (ALK)-positiven, nicht-kleinzelligen Bronchialkarzinoms (NSCLC), die mit Crizotinib vorbehandelt wurden.

a.) Für Patienten, für die eine Behandlung mit Docetaxel oder Pemetrexed infrage kommt.

b.) Für Patienten, für die eine Behandlung mit Docetaxel oder Pemetrexed nicht infrage kommt

**Zweckmäßige Vergleichstherapie**

a) Docetaxel oder Pemetrexed

b) Best-Supportive-Care

**Fazit / Ausmaß des Zusatznutzens / Ergebnis**

a) gegenüber Docetaxel oder Pemetrexed:

Anhaltspunkt für einen beträchtlichen Zusatznutzen.

b) Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care:

Ein Zusatznutzen ist nicht belegt.

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**G-BA, 2016 [9].**

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Crizotinib (neues Anwendungsgebiet) vom 16.06.2016

Siehe auch IQWiG, Jahr [17].

**Anwendungsgebiet**

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

**Vergleichstherapie**

a) Patienten, bei denen eine Chemotherapie angezeigt ist

Docetaxel oder Pemetrexed zur Behandlung von Patienten, bei denen eine Chemotherapie angezeigt ist (dies können insbesondere Patienten mit ECOG-Performance-Status 0, 1 und gegebenenfalls 2 sein).

b) Patienten, bei denen eine Chemotherapie nicht angezeigt ist

Best-Supportive-Care zur Behandlung von Patienten, bei denen eine Chemotherapie nicht angezeigt ist (dies können insbesondere Patienten mit ECOG-Performance-Status 4, 3 und gegebenenfalls 2 sein).

**Fazit / Ausmaß des Zusatznutzens / Ergebnis**

a) Anhaltspunkt für einen beträchtlichen Zusatznutzen.

b) Ein Zusatznutzen ist nicht belegt.

## 3.2 Cochrane Reviews

Es konnten keine relevanten Cochrane Reviews identifiziert werden.

## 3.3 Systematische Reviews

**He X et al., 2015 [13].**

Efficacy and safety of docetaxel for advanced non-small-cell lung cancer: a meta-analysis of Phase III randomized controlled trials

**Fragestellung**

We intended to conduct a systematic review and meta-analysis for all the eligible Phase III randomized controlled trials and to compare the risk–benefit information between docetaxel and other representative NSCLC drugs such as pemetrexed or vinca alkaloid in order to get a more credible result and evaluate the benefit of docetaxel for NSCLC treatment.

**Methodik**

Population: advanced NSCLC

Intervention: docetaxel

Komparator: pemetrexed or vinca alkaloid

Endpunkt: overall response rate (ORR), median survival time, progression-free survival (PFS), disease control rate, and toxicities

Recherche/Suchzeitraum: Cochrane Library, PubMed, Embase, and the ISI Web of Knowledge to January 24, 2015

Qualitätsbewertung der Studien: Jadad Score

**Ergebnisse**

Anzahl eingeschlossener Studien: 7 RCTs (n=2080 patients)

Charakteristika der Population:

**Table 1** Characteristics of the seven eligible Phase III randomized trials in this meta-analysis

| Study | Study region | Intervention | Number | Median age (years) | Male (%) | Stage | Outcome | Jadad score |
|---|---|---|---|---|---|---|---|---|
| Rodrigues-Pereira et al[20] | Argentina | Doc (75 mg/m$^2$) + Carb | 105 | 58.9 | 47.6 | Stage IIIB/IV | SWT, OS, | 3 |
| | | Pem (500 mg/m$^2$) + Carb | 106 | 60.1 | 60.4 | | PFS | |
| Karampeazis et al[23] | Greece | Doc (38 mg/m$^2$) | 66 | 75.5 | 92.4 | Stage IIIB/IV | OS, ORR, | 4 |
| | | Vin (25 mg/m$^2$) | 64 | 77 | 93.8 | | TTP, Toxl | |
| Vergnenegre et al[21] | France | Doc (75 mg/m$^2$) | 75 | 64 | 85.3 | Stage IIIB/IV | OS, PFS, | 3 |
| | | Pem (500 mg/m$^2$) | 75 | 62 | 82.7 | | ORR, Toxl | |
| Krzakowski et al[25] | France | Doc (75 mg/m$^2$) | 275 | 60 | 75.3 | Stage III/IV | PFS, ORR, | 4 |
| | | Vfl (320 mg/m$^2$) | 262 | 61.9 | 75 | | OS | |
| Kudoh et al[24] | Japan | Doc (60 mg/m$^2$) | 88 | 76 | 77.5 | Stage IIIB/IV | OS, PFS, | 3 |
| | | Vin (25 mg/m$^2$) | 91 | 76 | 74.7 | | ORR, Toxl | |
| Hanna et al[22] | United States | Doc (75 mg/m$^2$) | 288 | 57 | 75.3 | Stage III/IV | OS, PFS, | 3 |
| | | Pem (500 mg/m$^2$) | 283 | 59 | 68.6 | | ORR, Toxl | |
| Kubota et al[26] | Japan | Doc (60 mg/m$^2$) + Cis | 151 | 63 | 64.2 | Stage IV | OS, ORR, | 3 |
| | | Vds (3 mg/m$^2$) + Cis | 151 | 64 | 68.2 | | Toxl | |

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

**Studienergebnisse:**

Overall survival

No significant difference was found in the pooled HR for OS between docetaxel and pemetrexed as both first-line and second-line treatment (HR 1.10, 95% CI: 0.76–1.59, P=0.62; HR 1.05, 95% CI: 0.88–1.24, P=0.60, respectively).

OS for docetaxel versus vinca alkaloid as first-line treatment was not statistically different (HR 0.78, 95% CI: 0.56–1.08, P=0.14). There was also no difference in OS between docetaxel and vinca alkaloid as second-line treatment (HR 0.97, 95% CI: 0.80–1.18, P=0.78) (1 RCTs).

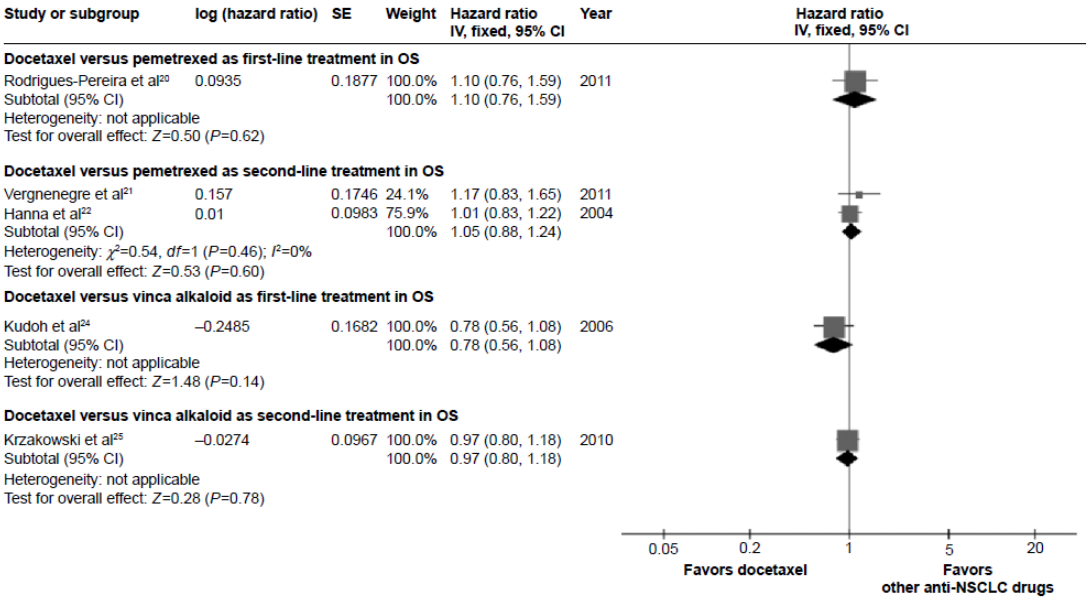


**Figure 2** Comparison of OS between docetaxel and other anti-NSCLC drug interventions.
**Abbreviations:** CI, confidence interval; IV, inverse variance; NSCLC, non-small-cell lung cancer; OS, overall survival; SE, standard error.

Progression-free survival

Similar to the result of OS, there was no significant difference in PFS between docetaxel and pemetrexed as both first-line and second-line treatment (HR 1.10, 95% CI: 0.81–1.49, P=0.54; HR 1.03, 95% CI: 0.86–1.23, P=0.74, respectively).

In terms of docetaxel with vinca alkaloid as first-line treatment, there was a significant statistical difference in PFS (HR 0.63, 95% CI: 0.45–0.82, P=0.001). However, docetaxel was associated with no significant improvement in PFS compared with vinca alkaloid as second-line treatment (HR 1.00, 95% CI: 0.83–1.19, P=0.96) (Figure 3).

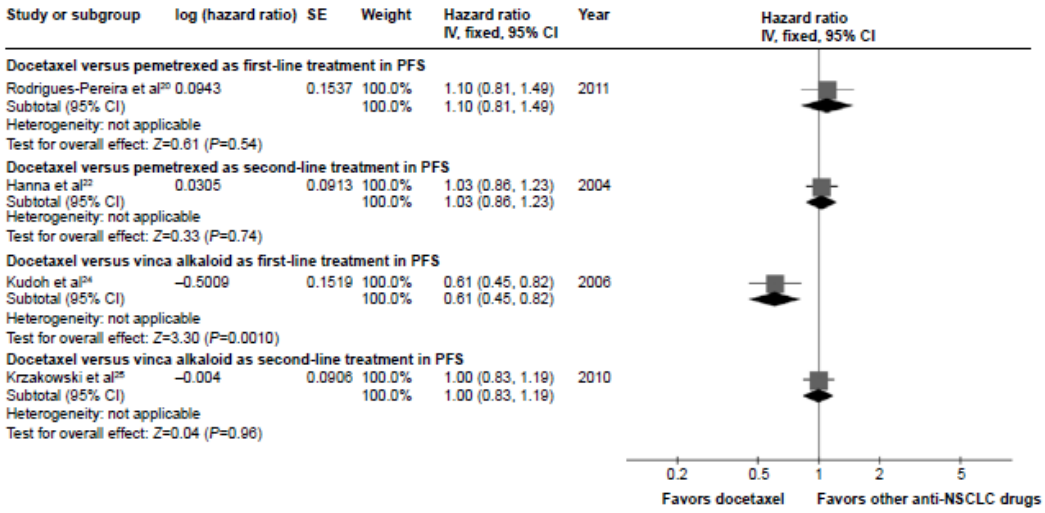


**Figure** 3 Comparison of PFS between docetaxel and other anti-NSCLC drug interventions.
**Abbreviations:** CI, confidence interval; IV, inverse variance; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; SE, standard error.

Grade 3/4 hematological and non-hematological toxicity

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

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

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

**Table 5** Comparison of grade 3/4 toxicity between docetaxel and vinca alkaloid as second-line treatment

| Grade 3/4 toxicity symptom | Docetaxel | Vinca alkaloid | OR (95% CI) | *P*-value |
|---|---|---|---|---|
| Hematologic events | | | | |
| Neutropenia | 82/277 | 90/274 | 0.86 (0.60, 1.23) | 0.41 |
| Anemia | 8/277 | 20/274 | 0.38 (0.16, 0.87) | 0.02 |
| Thrombocytopenia | 1/277 | 6/274 | 0.16 (0.02, 1.35) | 0.09 |
| Leukopenia | 59/277 | 64/274 | 0.89 (0.59, 1.33) | 0.56 |
| Febrile neutropenia | 13/277 | 9/274 | 1.45 (0.61, 3.45) | 0.40 |
| Non-hematologic events | | | | |
| Diarrhea | 5/277 | 2/274 | 2.50 (0.48, 13.00) | 0.28 |
| Nausea | 3/277 | 4/274 | 0.74 (0.16, 3.33) | 0.69 |
| Vomiting | 3/277 | 5/274 | 0.59 (0.14, 2.49) | 0.47 |

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


Referenzen zur Zweitlinie

21. Vergnenegre A, Corre R, Berard H, et al; 0506 GFPC Team. Cost-effectiveness of second-line chemotherapy for non-small cell lung cancer: an economic, randomized, prospective, multicenter phase III trial comparing docetaxel and pe**metrexed: the GFPC 05-06 study.** J Thorac Oncol. 2011;6:161–168.
22. 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: 1589–1597.
25. Krzakowski M, Ramlau R, Jassem J, et al. Phase III trial comparing vinflunine with docetaxel in second-line advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy. J Clin Oncol. 2010;28:2167–2173.

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20. Rodrigues-Pereira J, Kim JH, Magallanes M, et al. A randomized phase 3 trial comparing pemetrexed/carboplatin and docetaxel/carboplatin as first-line treatment for advanced, nonsquamous non-small cell lung cancer. J Thorac Oncol. 2011;6:1907–1914.
24. Kudoh S, Takeda K, Nakagawa K, et al. Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). J Clin Oncol. 2006;24:3657–3663.
26. Kubota K, Watanabe K, Kunitoh H, et al; Japanese Taxotere Lung Cancer Study Group. Phase III randomized trial of docetaxel plus cisplatin versus vindesine plus cisplatin in patients with stage IV non-small-cell lung cancer: the Japanese Taxotere Lung Cancer Study Group. J Clin Oncol. 2004;22:254–261.
23. Karampeazis A, Vamvakas L, Agelidou A, et al. Docetaxel vs. vinorelbine in elderly patients with advanced non – small-cell lung cancer: a hellenic oncology research group randomized phase III study. Clin Lung Cancer. 2011;12:155–160.


**Anmerkung/Fazit der Autoren**

According to the results of our study, docetaxel is a more effective and safer agent as first-line therapy in NSCLC compared with vinca alkaloid. As for second-line treatment, docetaxel causes no effective difference except for lower toxicity occurrence when compared with vinca alkaloid. There was no difference in efficacy between docetaxel and pemetrexed. However, docetaxel leads to a higher rate of neutropenia and lower rate of anemia symptom compared with pemetrexed in clinical application.

*Kommentare zum Review*

- Vortherapien nicht beschrieben

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**Zhong A et al., 2015 [23].**

The efficacy and safety of pemetrexed-based doublet therapy compared to pemetrexed alone for the second-line treatment of advanced non-small-cell lung cancer: an updated meta-analysis

**Fragestellung**

Pemetrexed is currently recommended as the second-line treatment for patients with advanced non-small-cell lung cancer (NSCLC). However, it is unclear whether pemetrexed-based doublet therapy improves treatment efficacy and safety. Thus, this meta-analysis was performed to resolve this controversial question.

**Methodik**

Population:

patients diagnosed pathologically with NSCLC and treated previously

Intervention:

single-agent pemetrexed

Komparator:

pemetrexed-based doublet

Endpunkt:

progression-free survival (PFS), overall survival (OS), objective response rate (ORR)

Recherche/Suchzeitraum:

PubMed, Embase, and the Cochrane Central Register of Controlled Trials bis 03/ 2015

Qualitätsbewertung der Studien:

Cochrane risk of bias tool

**Ergebnisse**

Anzahl eingeschlossener Studien:

Ten trials that pooled 1,281 patients in the pemetrexed-based doublet arm and 1,238 patients in the pemetrexed-alone arm were included in this meta-analysis

Charakteristika der Population:

- Of the ten studies, eight were randomized Phase II trials,10–13,15,16,18,19 and the other two were randomized Phase III trials.14,17
- Among these studies, two compared pemetrexed plus carboplatin with pemetrexed alone,10,15 two compared pemetrexed plus erlotinib with pemetrexed alone,16,18 one compared pemetrexed plus enzastaurin with pemetrexed alone,11 one compared pemetrexed plus bortezomib with pemetrexed alone,12 one compared pemetrexed plus matuzumab with pemetrexed alone,13 one compared pemetrexed plus vandetanib with pemetrexed alone,14 one compared pemetrexed plus nintedanib with pemetrexed alone,17 and one compared pemetrexed plus eribulin mesylate with pemetrexed alone.19
- Using the Jadad scale, three trials scored 5, two scored 4, four scored 3, and one scored 2.

**Studienergebnisse:**

Pemetrexed alone, an improved PFS was observed in Phase III trials (HR, 0.83; 95% CI, 0.73–0.95; P=0.005) in those that received a combination with erlotinib (HR, 0.61; 95% CI, 0.46–0.81; P=0.001), treated with targeted drug (HR, 0.85; 95% CI, 0.77–0.94; P=0.001), and

with a non-squamous histology (HR, 0.80; 95% CI, 0.71– P=0.001). Regarding OS, a prolonged survival time was observed in nonsquamous NSCLC patients who received the combination of pemetrexed and erlotinib (HR, 0.71; 95% CI, 0.54–0.94; P=0.02). No statistically significant differences were observed in other subgroup analyses.

**Table 2** Pooled and subgroup analysis of OS and PFS

| Subgroup | Number of trials | OS, HR (95% CI) | PFS, HR (95% CI) |
|---|---|---|---|
| All | 10 | 0.92 (0.83–1.02) | **0.86 (0.75–0.99)** |
| Phase | | | |
| II | 8 | 0.89 (0.74–1.07) | 0.89 (0.72–1.09) |
| III | 2 | 0.97 (0.83–1.14) | **0.83 (0.73–0.95)** |
| Combined agent | | | |
| Erlotinib[a] | 2 | **0.71 (0.54–0.94)** | **0.61 (0.46–0.81)** |
| Target drug | 8 | 0.93 (0.82–1.05) | **0.85 (0.77–0.94)** |
| Carboplatin | 2 | 0.92 (0.74–1.13) | 0.84 (0.54–1.31) |
| Histology | | | |
| Squamous | 3 | 0.62 (0.31–1.21) | 0.94 (0.64–1.40) |
| Nonsquamous | 6 | 0.98 (0.94–1.02) | **0.80 (0.71–0.91)** |

**Notes:** [a]Patients all had a nonsquamous histology. The figures in bold indicate the pooled HR was significantly different between pemetrexed-based doublet therapy and pemetrexed alone.
**Abbreviations:** OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

## Safety

There were significantly higher incidences of grade 3–4 neutropenia and thrombocytopenia in the pemetrexed-based doublet arm compared with the single-agent pemetrexed arm. However, there were no significant differences in the incidence of grade 3–4 anemia, fatigue, or leukopenia between groups (Table 3). Except for the grade 3–4 anemia and leukopenia, no significant interstudy heterogeneity was observed.

**Table 3** Outcome of grade 3 or 4 toxicities in a meta-analysis comparing pemetrexed-based doublet therapy with pemetrexed alone

| Toxicity | Trials | Pemetrexed-based doublet therapy | Pemetrexed alone therapy | Heterogeneity | | OR (95% CI) | *P*-value |
|---|---|---|---|---|---|---|---|
| | | | | *P* | $I^2$ | | |
| Grade 3–4 anemia | 7 | 43/719 | 52/737 | 0.076 | 47.5 | 0.85 (0.56–1.28) | 0.43 |
| Grade 3–4 neutropenia | 8 | 122/528 | 61/547 | 0.56 | 0 | 2.01 (1.45–2.78) | 0.00 |
| Grade 3–4 thrombocytopenia | 6 | 57/479 | 16/476 | 0.44 | 0 | 3.77 (2.16–6.59) | 0.00 |
| Grade 3–4 fatigue | 7 | 55/706 | 54/677 | 0.59 | 0 | 1.04 (0.70–1.55) | 0.59 |
| Grade 3–4 leukopenia | 7 | 65/536 | 41/515 | 0.125 | 38.3 | 1.66 (0.90–3.05) | 0.10 |


10. Smit EF, Burgers SA, Biesma B, et al. Randomized phase II and pharmacogenetic study of pemetrexed compared with pemetrexed plus carboplatin in pretreated patients with advanced non-small-cell lung cancer. J Clin Oncol. 2009;27:2038–2045.
11. Chiappori A, Bepler G, Barlesi F, et al. Phase II, double-blinded, randomized study of enzastaurin plus pemetrexed as second-line therapy in patients with advanced non-small cell lung cancer. J Thorac Oncol. 2010;5:369–375.
12. Scagliotti GV, Germonpré P, Bosquée L, et al. A randomized phase II
study of bortezomib and pemetrexed, in combination or alone, in patients with previously treated advanced non-small-cell lung cancer. Lung Cancer. 2010;68:420–426.
13. Schiller JH, von Pawel J, Schütt P, et al. Pemetrexed with or without matuzumab as second-line treatment for patients with stage IIIB/IV non-small cell lung cancer. J Thorac Oncol. 2010;5:1977–1985.
14. De Boer RH, Arrieta Ó, Yang CH, et al. Vandetanib plus pemetrexed for the second-line treatment of advanced nonsmall-cell lung cancer: a randomized, double-blind phase III trial. J Clin Oncol. 2011;29:1067–1074.
15. Ardizzoni A, Tiseo M, Boni L, et al. Pemetrexed versus pemetrexed and carboplatin as second-line chemotherapy in advanced non–small-cell lung cancer: results of the GOIRC 02-2006 randomized phase II
study and pooled analysis with the NVALT7 trial. J Clin Oncol. 2012;30:4501–4507.
16. Lee DH, Lee JS, Kim SW, 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;49:3111–3312.
17. Hanna NH, Kaiser R, Sullivan RN, et al. Lume-lung 2: a multicenter, randomized, double-blind, phase III study of nintedanib plus pemetrexed versus placebo plus pemetrexed in patients with advanced nonsquamous non-small cell lung cancer (NSCLC) after failure of first-line chemotherapy [Abstract 8034]. J Clin Oncol. 2013;31.

18. Dittrich C, Szekely ZP, Vinolas N, et al. A randomised phase II study of pemetrexed versus pemetrexed + erlotinib as second-line treatment for locally advanced or metastatic non-squamous non-small cell lung cancer. Eur J Cancer. 2014;50:1571–1580.
19. Waller CF, Vynnychenko I, Bondarenko I, et al. An open-label, multicenter, randomized phase Ib/II study of eribulin mesylate administered in combination with pemetrexed versus pemetrexed alone as second-line therapy in patients with advanced nonsquamous non-small-cell lung cancer. Clin Lung Cancer. 2015;16(2):92–99. doi: 10.1016/j.cllc.2014.10.001.

**Anmerkung/Fazit der Autoren**

In conclusion, the treatment of advanced NSCLC patients using pemetrexed-based doublet therapy improved PFS and ORR, but not OS, and it also increased toxicity. Thus, the use of pemetrexed-based combination chemotherapy as second-line treatment for NSCLC patients should be considered carefully. Additional RCTs with larger samples are warranted to confirm these findings. The effectiveness of other chemotherapy drugs in combination with pemextred needs to be evaluated for the treatment of NSCLC.

*Kommentare zum Review*

- Vortherapien unklar
- Zum Teil nicht zugelassene AM als Komparator

## 3.4 Leitlinien

**Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft (DKG) et al. 2018 [18].**

AWMF, DKG

S3-Leitlinie Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms Version 1.0

**Leitlinienorganisation/Fragestellung**

Die Leitlinie adressiert die Versorgung aller Patienten mit einem Lungenkarzinom sowie darüber hinaus die Versorgung bzgl. Früherkennung von Bürgern mit einem erhöhten Risiko für ein Lungenkarzinom.

**Methodik**

Grundlage der Leitlinie

- Diese S3-Leitlinie ist maximal bis 2022 oder bis zur nächsten Aktualisierung gültig.
- Neuerungen in der aktuellen LL: u.a. Therapien des Stadium IV (ohne Indikation zur definitiven Lokaltherapie, palliativmedizinische Behandlung beim Lungenkarzinom
- formalen Konsensusverfahrens.: durch die AWMF moderierte, nominale Gruppenprozesse bzw. strukturierte Konsensuskonferenzen.
- Interdisziplinäre LL-Entwicklungsgruppe
- Interessenskonflikte dargelegt und Umgang beschrieben

Recherche/Suchzeitraum:

- Molekular stratifizierte Therapie (05.06.2014); Molekular stratifizierte Therapie (05.06.2014); Anti VEGF (22.07.2014)

LoE

- Cochrane Risk of Bias Tool

GoR

**Tabelle 6: Schema der Empfehlungsgraduierung für Empfehlungen 2018**

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

**Tabelle 7: Konsensusstärke**

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

**Empfehlungen**

### 8.6.6. Systemtherapie bei Patienten mit ALK-Translokation oder weiteren bekannten Treibermutationen (ECOG 0-4)

8.6.6.2. Zweitlinientherapie nach Versagen einer platinbasierten Standardchemotherapie

| 8.101. | Evidenzbasierte Empfehlung | 2018 |
|---|---|---|
| Empfehlungsgrad<br>A | ALK positiven NSCLC-Patienten mit Progress nach platinbasierter Standardchemotherapie, die in der Erstlinie keinen ALK-Inhibitor erhalten haben, soll Crizotinib angeboten werden. | |
| Level of Evidence<br>1b | Literatur: [875] | |
| | Konsensstärke: 100 % | |

8.6.6.3. Therapie nach Crizotinib-Versagen

| 8.102. | Evidenzbasierte Empfehlung | 2018 |
|---|---|---|
| Empfehlungsgrad<br>A | ALK-Inhibitoren der zweiten Generation sollen ALK positiven NSCLC Patienten bei Crizotinib/ALK-TKI Versagen angeboten werden. | |
| Level of Evidence<br>1b | Literatur: [876] | |
| | Konsensstärke: 85 % | |

In der ASCEND-5 Phase-III-Studie wurden 231 ALK-positive Patienten, die eine Progression nach Vorbehandlung mit Chemotherapie und Crizotinib erlitten hatten, randomisiert einer Behandlung mit Ceritinib (n=115) oder Chemotherapie (n=116, davon n=113 tatsächlich behandelt) mit Pemetrexed oder Docetaxel zugeführt.

Der primäre Zielparameter PFS betrug 5,4 Monate unter Ceritinib gegenüber 1,6 Monaten unter Chemotherapie (HR 0,49, p<0,001). Das OS zeigte zum Zeitpunkt der Analyse keinen signifikanten Unterschied zwischen beiden Gruppen (18,1 gegenüber 20,1 Monate). Es muss allerdings berücksichtigt werden, dass 75 der 113 Patienten in der Chemotherapiegruppe nach Progress in den Ceritinib Arm wechselten.

Die häufigsten Nebenwirkungen waren Übelkeit (58 %), Diarrhö (68 %), Erbrechen (44 %), Fatigue (22 %) und erhöhte Transaminasen (22-23 %) sowie Gewichtsabnahme (27 %) allerdings im Wesentlichen nicht schwerer Graduierung. Schwere Nebenwirkungen (Grad 3,4) beinhalteten Transaminasenerhöhung (1-3 %) und Dyspnoe (2 %) [877].

Weitere ALK-Inhibitoren der nächsten Generation, deren Nutzen derzeit geprüft wird, sind: Alectinib [878], Brigatinib [879].

875. Shaw, A.T., et al., Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med, 2013. 368(25): p. 2385-94.
876. Shaw, A.T., et al., Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med, 2014. 370(13): p. 1189-97.
877. Shaw, A.T., et al., Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol, 2017. 18(7): p. 874-886.
878. Shaw, A.T., et al., Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. Lancet Oncol, 2016. 17(2): p. 234-42.

879. Gettinger, S.N., et al., Activity and safety of brigatinib in ALK-rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial. Lancet Oncol, 2016. 17(12): p. 1683-1696.

8.6.6.4. Therapie nach Versagen der zugelassenen ALK-Inhibitoren Crizotinib und Ceritinib

| 8.103. | Evidenzbasierte Empfehlung | 2018 |
|---|---|---|
| EK | ALK positive NSCLC-Patienten mit Versagen von zugelassenen ALK-Inhibitoren sollten nach Möglichkeit in klinische Studien oder Compassionate-Use-Programme mit weiteren ALK-Inhibitoren eingeschlossen werden. Falls dies nicht möglich ist, werden sie mit Chemotherapie entsprechend Wildtyp-Patienten behandelt.<br>Pemetrexed hat die höchste intrinsische Effektivität bei ALK + Tumoren. | |
| | Konsensstärke: 100 % | |

Ist eine Studienteilnahme nicht möglich, werden diese Patienten in Abhängigkeit von ihrem Allgemeinzustand entweder mit einer platinbasierten Chemotherapie oder einer Monochemotherapie behandelt. Die platinbasierte Chemotherapie sollte als Kombinationspartner Pemetrexed enthalten, die erste Wahl einer Monochemotherapie sollte ebenfalls Pemetrexed sein, da in der Zweitlinienstudie zum Einsatz von Crizotinib vs. Zweitlinienchemotherapie [875] die Ansprechrate und das PFS in den ALK+ Patienten mit Pemetrexed höher lagen als mit Docetaxel.

Die Ansprechrate von Crizotinib war in der intent-to treat Analyse höher als mit Chemotherapie: 66% (95% CI, 58-73) mit Crizoti-nib verglichen mit 29% (95% CI, 21-39) mit Pemetrexed und 7% (95% CI, 2-16) mit Docetaxel. Auch Das PFS war mit einer HR von 0,59 gegenüber Pemetrexed (95% CI, 0,43 bis 0,80; P<0,001) und mit einer HR von 0,3 gegenüber Docetaxel (95% CI, 0,21 bis 0,43, P<0,001) verbessert.

875. Shaw, A.T., et al., Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med, 2013. 368(25): p. 2385-94.

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**National Comprehensive Cancer Network, 2018 [19].**

NCCN

Non-Small Cell Lung Cancer, Vers. 03.2018

**Leitlinienorganisation/Fragestellung**

Diagnose, Pathologie, Staging, Therapie des NSCLC

**Methodik**

Grundlage der Leitlinie

- Update von 01.2018
- Allgemeiner NCCN-Methodenreport beschreibt systematische Evidenzaufbereitung mit Konsensusprozessen
- Suche in Pubmed seit 2017

LoE, GoR:  Diskussion der Literatur und Empfehlungen im Expertenpanel

**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.**

Sonstige methodische Hinweise

- Repräsentativität der Gremien unklar
- ob formalisierte Konsensusverfahren angewendet werden ist unklar
- industriefinanziert
- Bewertung der Studien unklar

**Empfehlung**

Subsequent Therapy

- Response assessment with CT of known sites of disease with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.

Sensitizing *EGFR* Mutation
- First-line therapy
  - Afatinib[1]
  - Erlotinib[2]
  - Gefitinib[3,4]
  - Osimertinib[5]
- Subsequent therapy
  - Osimertinib[6]

*ALK* Rearrangement
- First-line therapy
  - Alectinib[7,8]
  - Ceritinib[9]
  - Crizotinib[10,11]
- Subsequent therapy
  - Alectinib[12,13]
  - Brigatinib[14]
  - Ceritinib[15]

*ROS1* Rearrangement
- First-line therapy
  - Ceritinib[16]
  - Crizotinib[17]

*BRAF* V600E Mutation
- First-line therapy
  - Dabrafenib/trametinib[18]
- Subsequent therapy
  - Dabrafenib/trametinib[19,20]

PD-L1 Expression
- First-line therapy
  - Pembrolizumab[21,22]
- Subsequent therapy
  - Atezolizumab[23]
  - Nivolumab[24,25]
  - Pembrolizumab[26]

For patients with *ALK* rearrangements who progress during or after first-line targeted therapy, recommended subsequent therapy also depends on whether the progression is asymptomatic or symptomatic and includes: 1) considering local therapy; 2) continuing alectinib, crizotinib, or ceritinib; 3) taking ceritinib (if not previously given); 4) taking alectinib (if not previously given); 5) taking brigatinib; or 6) taking a first-line systemic therapy regimen for nonsquamous NSCLC. After further progression on subsequent targeted therapy, first-line combination chemotherapy options for NSCLC are recommended for patients with PS of 0 to 1 such as carboplatin/paclitaxel.[136,890] Other chemotherapy options are also recommended for patients with PS 2, such as docetaxel (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC). Note that immune checkpoint inhibitors are not recommended as subsequent therapy for patients with *ALK* rearrangements. Patients with ALK-positive NSCLC and very high PD-L1 expression do not respond to pembrolizumab.[272] In addition, those with *MET* exon 14 mutations and high PD-L1 expression also do not respond to immunotherapy.[891]

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**Government Cancer Council Australia, 2017 [2].**

Cancer Australia

Clinical practice guidelines for the treatment of lung cancer

**Leitlinienorganisation/Fragestellung**

What is the optimal second-line therapy in patients with stage IV inoperable NSCLC?

**Methodik**

Grundlage der Leitlinie

Systematischer Review und Konsensusprozess über Empfehlungen.

Alle Aussagen sind mit Literaturstellen (Meta-Analysen oder RCTs) belegt.

Recherche/Suchzeitraum:

- u.a. Pubmed bis 2018, Embase bis 2017

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" |

## Empfehlungen

What is the optimal second-line therapy in patients with stage IV inoperable NSCLC?

Empfehlung 1 (Empfehlungsgrad B)

In unselected patients previously treated for advanced NSCLC not suitable for immunotherapy, chemotherapy with docetaxel or pemetrexed may be used as second-line therapy. Pemetrexed is preferred in non-squamous cell carcinoma histology, and docetaxel is preferred in squamous cell carcinoma.

In previously treated patients with advanced NSCLC, single agent docetaxel 75 mg/m2 improves survival compared with best supportive care or vinorelbine and ifosfamide. (LoE: II)

In previously treated patients with advanced NSCLC not suitable for immunotherapy, single agent pemetrexed has similar efficacy but fewer side effects than three-weekly docetaxel. (LoE: II

In previously treated patients with advanced NSCLC, compared with docetaxel, pemetrexed appears to have greater efficacy in non-squamous cell carcinoma histology, and inferior efficacy in squamous cell carcinoma. (LoE: I)

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 May;18(10):2095-103 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/10811675.
Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, 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 Jun;18(12):2354-62 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/10856094.
Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, 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 May 1;22(9):1589-97 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/15117980.
Standfield L, Weston AR, Barraclough H, Van Kooten M, Pavlakis N. Histology as a treatment effect modifier in advanced non-small cell lung cancer: a systematic review of the evidence. Respirology 2011 Nov;16(8):1210-20 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/21801275.

Empfehlung 2 (Empfehlungsgrad A)

Doublet therapy is not recommended as second-line treatment of advanced NSCLC.

Doublet therapy as second-line treatment of advanced NSCLC increases response rate and progression free survival, but is more toxic and does not improve overall survival compared with single agent chemotherapy. (LoE: I)

Di 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 Apr 10;27(11):1836-43 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/19273711.
Qi WX, Tang LN, He AN, 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 Jan 19 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/22258853.

What is the optimal third-line therapy in unselected patients with stage IV inoperable NSCLC?

Empfehlung 3 (Empfehlungsgrad B)

In fit, previously treated patients with advanced NSCLC who have received two lines of therapy, single agent docetaxel administered 3 weekly can be considered.

Kawaguchi T, Ando M, Asami K, Okano Y, Fukuda M, Nakagawa H, et al. Randomized phase III trial of erlotinib versus docetaxel as second- or third-line therapy in patients with advanced non-small-cell lung cancer: Docetaxel and Erlotinib Lung Cancer Trial (DELTA). J Clin Oncol 2014 Jun 20;32(18):1902-8 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/24841974.

What is the optimal third-line therapy in unselected patients with stage IV inoperable NSCLC?

Empfehlung 1 (Empfehlungsgrad B)

In fit, previously treated patients with advanced NSCLC who have received two lines of therapy, single agent docetaxel administered 3 weekly can be considered.

Kawaguchi T, Ando M, Asami K, Okano Y, Fukuda M, Nakagawa H, et al. Randomized phase III trial of erlotinib versus docetaxel as second- or third-line therapy in patients with advanced non-small-cell lung cancer: Docetaxel and Erlotinib Lung Cancer Trial (DELTA). J Clin Oncol 2014 Jun 20;32(18):1902-8 Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/24841974.

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**Nasser Hanna et al., 2017 [12].**

ASCO

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

**Leitlinienorganisation/Fragestellung**

**Methodik**

Grundlage der Leitlinie

- Update der LL von 2015
- An Update Committee of the American Society of Clinical Oncology NSCLC Expert Panel based recommendation on a systematic review of randomized controlled trials from February 2014 to February 2016.
- The guideline recommendations were crafted, in part, using the GuideLines Into DEcision
- Support (GLIDES) methodology and accompanying BRIDGE-Wiz softwareTM. The process incorporates distilling the actions involved, identifying who will carry them out, to whom, under what circumstances, and clarifying if and how end users can carry out the actions consistently. This process helps the Expert Panel focus the discussion, avoid using unnecessary and/or ambiguous language, and clearly state its intentions.
- The methodological review is completed by a member of the CPGC'S Methodology Subcommittee and/or by ASCO guidelines staff using AGREE II instrument.

**LoE**

| 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 direction of this net |
| **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 the net effect. |
| **Low** | Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change the magnitude and/or |
| **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 the topic until better |

**GoR**

| 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 "weak"). The results of the formal consensus process are |
| **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 choose to provide a rating for the strength |
| **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 would achieve the level of agreement needed |

| 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 considerations (discussed in the guideline's |
| **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 compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation. |

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| **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. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation. |

Weitere Informationen zur Leitlinienmethodik: http://www.instituteforquality.org/guideline-development-process

**Empfehlungen**

Without a tumor EGFR-sensitizing mutation or ALK or ROS1 gene rearrangement and with PS of 0 or 1 (and appropriate PS of 2):

- In patients with high PD-L1 expression (TPS $ 1%) and no contraindications who received first-line chemotherapy and have not received prior immune therapy, single-agent nivolumab, pembrolizumab, or atezolizumab is recommended *(Evidence quality: high; Strength of recommendation: strong).*
- In patients with negative or unknown tumor PD-L1 expression (TPS , 1%) and no contraindications who received first-line chemotherapy, nivolumab, or atezolizumab, a variety of combination cytotoxic chemotherapies are recommended *(Evidence quality: high; Strength of recommendation: strong).*
- Other checkpoint inhibitors, combination checkpoint inhibitors, and immune checkpoint therapy with chemotherapy are not recommended.
- In patients who received an immune checkpoint inhibitor as first-line therapy, a variety of combination cytotoxic chemotherapies are recommended *(Platinum based [Evidence quality: high; Strength of recommendation: strong*]; Non–platinum based *[Informal consensus; Evidence quality: low; Strength of recommendation: strong])*.
- In patients with contraindications to immune checkpoint inhibitor therapy after first-line chemotherapy, docetaxel is recommended *(Evidence quality: intermediate; Strength of recommendation: moderate).*
- In patients with non–squamous cell carcinoma who have not previously received pemetrexed, pemetrexed is recommended *(Evidence quality: intermediate; Strength of recommendation: moderate).*

ALK gene rearrangement (no change from 2015). The Panel notes that in May 2017, while this guideline was in development, the FDA approved an ALK inhibitor (that was not a prespecified agent included in the ASCO systematic literature search) based on a 137-patient, phase I/II, single-arm study with five cohorts in the second-line or greater setting that was presented at the 2016 ASCO Annual Meeting. It was published in The Lancet Oncology in December 2016 (PubMed had not indexed the publication as of May 9, 2017, and therefore, it was outside the parameters of the systematic review for the guidelines).33

Third-Line Treatment for Patients

- In patients without a tumor EGFR-sensitizing mutation or ALK or ROS1 gene rearrangement and with non–squamous cell carcinoma and PS of 0 or 1 (and appropriate PS of 2), who received chemotherapy with or without bevacizumab an immune checkpoint

therapy, single-agent pemetrexed or docetaxel are options *(Type: informal consensus; Evidence quality: low; Strength of recommendation: strong).*

The Panel notes that the 2015 recommendation was as follows: When disease progresses on or after second-line chemotherapy, treatment with erlotinib may be recommended as third-line therapy for patients with a PS of 0 to 3 who have not received prior erlotinib or gefitinib (note: since the 2015 publication, as of October 2016, patients are only eligible for erlotinib in the second- line if they have EGFR [exon 19 or 21] mutations).35 The Panel has decided to sunset this recommendation as a result of the Panel's assessment that with the advent of immunotherapy, the magnitude of benefits of options that were recommended in the third-line in previous versions of the guideline does not seem as convincing.

Fourth-Line Treatment for Patients

Patients and clinicians should consider and discuss experimental treatment, clinical trials, and continued best supportive (palliative) care.

Data are not sufficient to make a recommendation for or against using cytotoxic drugs as fourthline therapy; patients should consider experimental treatment, clinical trials, and continued best supportive (palliative) care.

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| **Ellis PM, Vella ET, Ung YT and the Lung Cancer Disease Site Group, 2016 [8].**<br><br>**ASCO**<br><br>Systemic Treatment for Patients with Advanced Non-Small Cell Lung Cancer | Fragestellung/Zielsetzung<br>• Clinical Question B4: What is the most effective second-line therapy for patients with stage IIIB/IV NSCLC with ALK rearrangement with progression after first-line crizotinib?<br>• Clinical Question B5: What is the optimal second-line treatment for elderly patients with stage IIIB/IV NSCLC?<br>• Clinical Question C: Is there a role for third-line therapy or beyond in the treatment of stage IIIB/IV NSCLC? |
| | Methodik<br>Grundlage der Leitlinie: update von 2009 und 2010, in 2016 Adaptation der aktuellen Leitlinie der American Society of Clinical Oncology (ASCO) mit ergänzenden systematischen Übersichten zu den klinischen Fragestellungen (siehe oben), methodisches Vorgehen orientiert an AGREE II, internes formales Abstimmungsverfahren, externes Review, COI z.T. vorhanden<br>LoE und GoR: Studienqualität geprüft und detailliert dargestellt, Empfehlungsstärken über die Formulierung abgebildet<br>Sonstige methodische Hinweise<br>– Further information: PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*<br>– The following recommendations were endorsed with no modifications: A1.a, A1.b, A2.a.2, A2.b, A3, A3.a, A4, A5, A6, A7, and do not appear in Table 3-2 (siehe Anhang).<br>– Systematisches Review: MEDLINE (1946 to February 16, 2016), EMBASE (1996 to February 16, 2016), and PubMed (February 16, 2016) databases were searched for RCTs.<br>– Inclusion Criteria<br>o Phase II or III RCTs comparing treatment with immune checkpoint inhibitors with chemotherapy; and |

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| | o Stage IIIB or IV NSCLC; and<br>o Fully published papers or published abstracts of trials that reported at least one of the following outcomes by treatment group: OS, PFS, response rate, or adverse events.<br>– Exclusion Criteria<br>o Pilot trials, dose-escalation trials, or case series (including expanded access programs) studies.<br>o Letters and editorials that reported clinical trial outcomes.<br>o Conference abstracts published before 2013.<br>– Empfehlungen sind mit Literaturstellen verknüpft |
| | Freitext/Empfehlungen/Hinweise<br>• <u>Clinical Question B4: What is the most effective second-line therapy for patients with stage IIIB/IV NSCLC with ALK rearrangement with progression after first-line crizotinib?</u><br>Patients whose tumours have ALK rearrangements and who received crizotinib in the first-line setting may be offered the option of chemotherapy (after first-line recommendations for patients with NSCC [see Recommendation A2]) or ceritinib in the second-line setting.<br>• <u>Clinical Question B5: What is the optimal second-line treatment for elderly patients with stage IIIB/IV NSCLC?</u><br>The evidence does not support the selection of a specific second-line chemotherapy drug or combination based on age alone. As stated in Recommendation A8, age alone is not a contraindication to chemotherapy for NSCLC.<br>• <u>Clinical Question C: Is there a role for third-line therapy or beyond in the treatment of stage IIIB/IV NSCLC?</u><br>When disease progresses during or after second-line chemotherapy, treatment with erlotinib may be recommended as third-line therapy for patients with a PS of 0 to 3 who have not received prior erlotinib or gefitinib.<br>Docetaxel, erlotinib, gefitinib, or pemetrexed may be used in patients with stage IIIB/IV NSCLC with negative or unknown EGFR/ALK status and NSCC after progression on nivolumab or pembrolizumab, although data are limited.<br>Docetaxel, erlotinib, or gefitinib may be used in patients with stage IIIB/IV NSCLC with negative or unknown EGFR/ALK status and SCC after progression on nivolumab or pembrolizumab, although data are limited. |
| **Scottish Intercollegiate Guidelines Network (SIGN), 2014 [20].** Management | **1. Fragestellung**<br>In patients with NSCLC (locally advanced or metastatic disease), what is the most effective <u>first/second line</u> systemic anticancer therapy (chemotherapy, targeted therapy, EGFR Inhibitors)?<br>Outcomes: Overall survival, progression-free survival, toxicity, quality of life |
| | ***2.*** **Methodik**<br>**Grundlage der Leitlinie:**<br>systematische Recherche und Bewertung der Literatur, Entwicklung durch |

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| of lung cancer | multidisziplinäre Gruppe von praktizierenden klinischen ExpertInnen, Expertenreview, öffentliche Konsultation<br>**Suchzeitraum:**<br>2005 - 2012<br>**LoE/GoR:** |

| KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS | |
|---|---|
| LEVELS OF EVIDENCE | |
| $1^{++}$ | High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias |
| $1^{+}$ | Well conducted meta-analyses, systematic reviews, *or* RCTs with a low risk of bias |
| $1^{-}$ | Meta-analyses, systematic reviews, or RCTs with a high risk of bias |
| $2^{++}$ | High quality systematic reviews of case control or cohort studies<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 |

### 3. Empfehlungen

**Zweitlinientherapie**

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. **(LoE 1+)**

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.

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. **(LoE 1+)**

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-

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| | 103.<br>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 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000;18(12):2354-62.<br><br>Weekly docetaxel is not recommended over three-weekly due to increased toxicity. **(LoE 1+)**<br><br>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.<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. **(LoE 1++)**<br>Di 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.<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><u>Recommendations</u><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>• 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)** |
| **Alberta Provincial Thoracic Tumour Team, 2013 [1].** Non-small cell lung cancer - stage IV. Alberta Health Services | **Fragestellung**<br>When is palliation recommended, and what are the recommended <u>palliative treatment options</u> for patients with inoperable stage III non-small cell lung cancer? What is the optimal <u>second-line</u> therapy for patients with stage IV NSCLC?<br>**Methodik**<br>***Grundlage der Leitlinie:***<br>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>**Suchzeitraum**:<br>bis 2013<br>***LoE/GoR:***<br>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 |

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| | the recommendations<br><br>*Sonstige methodische Hinweise*<br>• *direkte Verknüpfung von Literatur mit Empfehlung nicht durchgängig gegeben*<br>• *kein formaler Konsensusprozess 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>**Non-Small Cell Lung Cancer, Stage IV Guideline**<br><u>Recommendations</u><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>**65.** Kowalski DM, Krzakowski M, Ramlau R, Jaskiewicz P, Janowicz-Zebrowska A. Erlotinib in salvage treatment of patients with advanced non-small cell lung cancer: results of an expanded access programme in Poland. Wspolczesna Onkol. 2012;16(2):170-175.<br>→squamous-cell (n = 23), adenocarcinoma (n = 20), or broncho-alveolar carcinoma (n = 2), keine Infos zu EGFR<br><br>**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.<br>→= Zulassungsstudie<br><br>**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.<br>→ (gehört zu Sherperd)<br><br>**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.<br>→ EGFR-Expressionsstatus erfasst, keine signifikanten Unterschiede beim OS beobachtet (Gesamtpopulation als auch Subgruppe zum EGFR-Expressionstatus)<br><br>**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.<br>→elderly patients with NSCLC not selected for EGFR expression<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 Review (pCODR) and has also been approved for provincial coverage in Alberta.<br>10. Testing for ALK mutations should take place for all eligible patients with |

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| | advanced NSCLC and adenocarcinoma (including adenosquamous) histology who are being considered for second line therapy with crizotinib.<br><br>Quellen:<br>**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.<br>**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.<br>**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.<br>**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.<br>**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.<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>**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>**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>… |
| **Wauters I et al., 2013 [22 ]. Belgian Health Care Knowledge Centre** Non-small cell and small cell lung cancer: diagnosis, treatment and follow-up | **Fragestellung**<br>4. What are the best treatment options for patients with metastatic and recurrent NSCLC? |
| | **Methodik**<br>***Grundlage der Leitlinie:***<br>• developed using a standard methodology based on a systematic review of the evidence (further details: https://kce.fgov.be/content/kce-processes)<br>• developed by adapting (inter)national CPGs to the Belgian context (formal methodology of the ADAPTE group: www.adapte.org)<br>• in general, and whenever necessary, included guidelines updated with more recent evidence<br>• AGREE II instrument used to evaluate the methodological quality of the identified CPGs (www.agreetrust.org)<br>• quality of systematic reviews assessed by using the Dutch Cochrane checklist (www.cochrane.nl)<br>• critical appraisal of randomized controlled trials: Cochrane Collaboration's Risk of Bias Tool used<br>• 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.<br>***Suchzeitraum:***<br>• searches for guidelines: 20 February 2012 (23 guidelines retained for full-text evaluation),<br>• update searches: between April, 2012 and January, 2013<br>***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<br>2. Inconsistency<br>3. Indirectness<br>4. Imprecision<br>5. Publication bias | 1. Large effect<br>2. Dose-response<br>3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed | High (⊕⊕⊕⊕)<br>Moderate (⊕⊕⊕⊖)<br>Low (⊕⊕⊖⊖)<br>Very low (⊕⊖⊖⊖) |
| Observational studies | Low | | | |

**Empfehlungen**

*5.3.3. Second and third line chemotherapy - Other Considerations:*

A preliminary meta-analysis shows a pooled effect on progression free survival favoring chemotherapy and no effect on overall survival. This subgroup analysis should be treated with extreme caution, as in most studies only in a minority of patients EGFR status could be determined. However, the claims of the investigators that the effect is similar in EGFR mutated and non mutated patients is not supported by the facts, because the test for interaction used could not possibly have the power to detect this difference.

Figure 3 – Pooled (subgroup) effect on progression free survival in EGFR wildtype patients

| Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|
| DELTA | 0.3646 | 0.1468 | 25.6% | 1.44 [1.08, 1.92] |
| INTEREST | 0.2151 | 0.1413 | 27.7% | 1.24 [0.94, 1.64] |
| TAILOR | 0.3577 | 0.1369 | 29.5% | 1.43 [1.09, 1.87] |
| TITAN | 0.2231 | 0.1791 | 17.2% | 1.25 [0.88, 1.78] |
| Total (95% CI) | | | 100.0% | 1.35 [1.16, 1.56] |

Heterogeneity: Chi² = 0.91, df = 3 (P = 0.82); I² = 0%
Test for overall effect: Z = 3.99 (P < 0.0001)

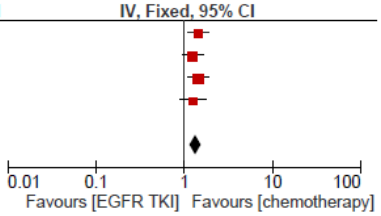
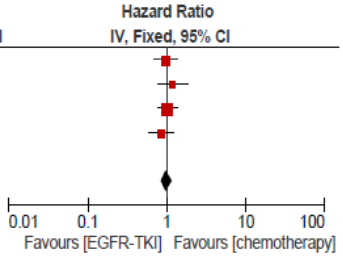



Figure 4 – Pooled (subgroup) effect on overall survival EGFR wildtype patients

| Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|
| DELTA | -0.0202 | 0.179 | 24.2% | 0.98 [0.69, 1.39] |
| HORG | 0.174 | 0.2221 | 15.7% | 1.19 [0.77, 1.84] |
| INTEREST | 0.0198 | 0.1435 | 37.7% | 1.02 [0.77, 1.35] |
| TITAN | -0.1625 | 0.1863 | 22.4% | 0.85 [0.59, 1.22] |
| Total (95% CI) | | | 100.0% | 0.99 [0.84, 1.18] |

Heterogeneity: Chi² = 1.40, df = 3 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.94)




*Conclusion*

Second line chemotherapy has a statistically significant effect on overall survival in

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| | patients with advanced NSCLC and an adequate PS when the disease has progressed during or after first-line, platinum-based therapy.<br>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.<br>Combination second line therapies have a marginal effect on progression free survival compared to monotherapy but no proven effect on overall survival.<br><br>*Recommendation*<br>• 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)<br>• Crizotinib is recommended as second-line therapy in ALK mutation-positive patients. (SoE: strong / LoE: low)<br>• 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)<br>*Good clinical practice*<br>It is recommended to offer radiotherapy for palliation of local symptoms to patients with NSCLC.<br><br>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.<br>7. Landelijke werkgroep longtumoren IKNL. Niet-kleincellig longcarcinoom - Landelijke richtlijn, Versie 2.0. In. 2.0 ed; 2011.<br>74. Group NM-aC, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet. 2010;375(9722):1267-77.<br>121. Botrel TE, et al. Efficacy of bevacizumab (Bev) plus chemotherapy (CT) compared to CT alone in previously untreated locally advanced or metastatic non-small cell lung cancer (NSCLC): systematic review and metaanalysis. Lung Cancer. 2011;74(1):89-97.<br>122. Lima AB, Macedo LT, Sasse AD. Addition of bevacizumab to chemotherapy in advanced non-small cell lung cancer: a systematic review and meta-analysis. PLoS ONE. 2011;6(8):e22681.<br>123. Reck M, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol. 2010;21(9):1804-9.<br>124. Niho S, et al. Randomized phase II study of first-line carboplatin-paclitaxel with or without bevacizumab in Japanese patients with advanced nonsquamous non-small-cell lung cancer. Lung Cancer. 2012;76(3):362-7.<br>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.<br>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. |

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| **Socinski MA et al., 2013 [21].**<br><br>Treatment of Stage IV Non-small Cell Lung Cancer | **1. Fragestellung**<br>Therapie des NSCLC Stage IV |
| | **2. Methodik**<br>**Grundlage der Leitlinie:**<br>A writing committee was assembled and approved according to ACCP policies as described in the methodology article of the lung cancer guidelines – systematische Suche und Bewertung der Literatur – Formulierung und Konsentierung der Empfehlung nach standardisierten Verfahren - Update der Versionen aus 2003 und 2007<br>**Literatursuche:**<br>focused primarily on randomized trials, selected metaanalyses, practice guidelines, and reviews. In addition, phase 2 controlled studies that provided relevant information (eg, for toxicity or particular patient subgroups) were included.<br>**Suchzeitraum:**<br>bis 12/2011<br>**LoE und GoR**<br>Lewis SZ, Diekemper R, Addrizzo-Harris DJ. Methodology for development of guidelines for lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* . 2013 ; 143 ( 5 )( suppl ): 41S - 50S .<br>***Sonstige methodische Hinweise***<br>• *direkte Verknüpfung von Literatur mit Empfehlung nicht durchgängig gegeben* |
| | **3. Empfehlungen**<br>**General Approach** (Recommendations adapted from First and Second Editions)<br>2.1.1. In patients with a good performance status (PS) (ie, Eastern Cooperative Oncology Group [ ECOG] level 0 or 1) and stage IV non-small cell lung cancer (NSCLC), a platinum-based chemotherapy regimen is recommended based on the survival advantage and improvement in quality of life (QOL) over best supportive care (BSC). **.(Grade 1A)**<br>Remark: Patients may be treated with several chemotherapy regimens (carboplatin and cisplatin are acceptable, and can be combined with paclitaxel, docetaxel, gemcitabine, pemetrexed or vinorelbine)<br>2.2.2. In patients with stage IV NSCLC and a good PS, two-drug combination chemotherapy is recommended. The addition of a third cytotoxic chemotherapeutic agent is not recommended because it provides no survival benefit and may be harmful. **(Grade 1A)** |

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| | .<br>**Second and Third Line Treatment**<br>4.1.1. In patients with stage IV NSCLC who have good PS (ECOG 0-2), second-line treatment with erlotinib or docetaxel (or equivalent single-agent such as pemetrexed) is recommended **(Grade 1A)**.<br>4.1.2. In patients with stage IV NSCLC who have good PS (ECOG 0-2), third-line treatment with erlotinib improves survival compared with BSC and is recommended **(Grade 1B)** .<br>Remark: No recommendation can be given about the optimal chemotherapeutic strategy in patients with stage IV NSCLC who have received three prior regimens for advanced disease.<br>**Special Patient Populations and Considerations**<br>5.1.1. In elderly patients (age > 69–79 years) with stage IV NSCLC who have good PS and limited co-morbidities, treatment with the two drug combination of monthly carboplatin and weekly paclitaxel is recommended **(Grade 1A)** .<br>*Remark:* In patients with stage IV NSCLC who are 80 years or over, the benefi t of chemotherapy is unclear and should be decided based on individual circumstances.<br>6.2.1.For patients with stage IV NSCLC with a PS of 2 in whom the PS is caused by the cancer itself, double agent chemotherapy is suggested over single agent chemotherapy **(Grade 2B)** .<br>6.2.2. In patients with stage IV NSCLC who are an ECOG PS of 2 or greater, it is suggested not to add bevacizumab to chemotherapy outside of a clinical trial **(Grade 2B)** .<br>7.1.1. In patients with stage IV NSCLC early initiation of palliative care is suggested to improve both QOL and duration of survival **(Grade 2B)** . |

## 3.5 Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

**CADTH, 2017 [4].**

pCODR: Final Recommendation: Alectinib

siehe auch: **CADTH, 2017 [3].** Alectinib (Alecensaro) NSCLC; Final Clinical Guidance Report

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| pERC RECOMMENDATION | pERC does not recommend reimbursement of alectinib (Alecensaro) as monotherapy for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib and have central nervous system (CNS) metastases.<br><br>The Committee made this recommendation as it was not confident of the net clinical benefit of alectinib because of limitations in the evidence from available clinical trials. While pERC was confident that alectinib produces a CNS tumour response, the Committee was unable to determine how alectinib compares with other treatments with respect to outcomes important to decision-making, including overall survival (OS), progression-free survival (PFS), and quality of life.<br><br>pERC noted that alectinib aligned with patient values as there is a need for more effective treatment options, other than chemotherapy and whole-brain radiation therapy (WBRT), that have tolerable side effects for patients with ALK-positive NSCLC who have progressed on or are intolerant to crizotinib and have CNS metastases.<br><br>pERC concluded that, at the submitted price, alectinib was not cost-effective compared with chemotherapy (pemetrexed with or without cisplatin); however, there was considerable uncertainty in the cost-effectiveness estimates because of a lack of direct comparative effectiveness data in the submitted economic evaluation. |

**CADTH, 2017 [6].**

Ceritinib (Zykadia) for Non-Small Cell Lung Cancer; Final recommendation

Siehe auch: **CADTH, 2017 [5].** Ceritinib (Zykadia) for Non-Small Cell Lung Cancer; Final Clinical Guidance Report

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| **pERC RECOMMENDATION** | pERC recommends reimbursement of ceritinib (Zykadia) monotherapy for patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cance (NSCLC) who have disease progression on or intolerance to crizotinib conditional on the cost-effectiveness being improved to an acceptable level.<br><br>pERC made this recommendation because the Committee was confident of the net clinical benefit of ceritinib, based on statistically significant and clinically meaningful improvements in progression-free survival (PFS) compared to chemotherapy. The Committee acknowledged that quality of life with ceritinib was similar to chemotherapy; however, ceritinib is associated with manageable but not insignificant toxicity compared with chemotherapy. pERC agreed that ceritinib aligned with patient values, as there is a clear unmet need for more effective treatment options. However, the increased toxicity profile compared with chemotherapy tempered pERC's conclusions with respect to alignment with patient values.<br><br>The Committee also concluded that, at the submitted price, ceritinib was not cost-effective compared with chemotherapy and would require a substantial price reduction. |

**CADTH, 2014 [7]. Crizotinib (Xalkori) Resub Advanced NSCLC; Final Clinical Guidance Report**

## 1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall benefit to crizotinib in treatment of patients with ALK-positive advanced or metastatic NSCLC as second-line systemic therapy. Crizotinib has demonstrated a clear clinically and statistically significant benefit in terms of progression-free survival compared to standard second-line chemotherapy in one Phase III randomised study.

# 4 Detaillierte Darstellung der Recherchestrategie

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

| # | Suchfrage |
|---|---|
| 1 | [mh “Carcinoma, Non-Small-Cell Lung”] |
| 2 | (((non next small) or nonsmall) next cell next lung):ti,ab,kw |
| 3 | (tumor* or tumour* or carcinoma* or adenocarcinoma* or neoplasm* or sarcoma* or cancer*):ti,ab,kw |
| 4 | advanced:ti,ab,kw or metastat*:ti,ab,kw or metastas*:ti,ab,kw or recurren*:ti,ab,kw or relaps*:ti,ab,kw |
| 5 | #2 and #3 and #4 |
| 6 | nsclc*:ti,ab,kw |
| 7 | #1 or #5 or #6 |
| 8 | #7 from 2013 to 2018 |

### SR, HTAs in Medline (PubMed) am 13.03.2018

| # | Suchfrage |
|---|---|
| 1 | Carcinoma, Non-Small-Cell Lung[mh] |
| 2 | ((((non[tiab]) AND small[tiab]) OR nonsmall[tiab]) AND cell[tiab]) AND lung[tiab] |
| 3 | (((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[Tiab]) OR adenocarcinoma*[tiab]) OR neoplasm*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab] |
| 4 | (#2 AND #3) OR #1 |
| 5 | (#4) AND ((((advanced[Tiab]) OR metastat*[Tiab]) OR metastas*[Tiab]) OR recurren*[Tiab] or relaps*[tiab]) |
| 6 | (#5) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Tiab] OR studies[Tiab] OR database*[Tiab] OR literature[Tiab] OR publication*[Tiab] OR Medline[Tiab] OR Embase[Tiab] OR Cochrane[Tiab] OR Pubmed[Tiab])) AND systematic*[Tiab] AND (search*[Tiab] OR research*[Tiab]))) OR ((((((((((HTA[Tiab]) OR technology assessment*[Tiab]) OR technology report*[Tiab]) OR (systematic*[Tiab] AND review*[Tiab])) OR (systematic*[Tiab] AND overview*[Tiab])) OR meta-analy*[Tiab]) OR (meta[Tiab] AND analyz*[Tiab])) OR (meta[Tiab] AND analys*[Tiab])) OR (meta[Tiab] AND analyt*[Tiab]))) OR (((review*[Tiab]) OR overview*[Tiab]) AND ((evidence[Tiab]) AND based[Tiab])))))) |
| 7 | ((#6) AND ("2013/03/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) |

### Leitlinien in Medline (PubMed) am 13.03.2018

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

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|---|---|
| 7 | (#4 AND #5) OR #6 |
| 8 | #1 OR #2 OR #3 OR #7 |
| 9 | (#8) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title]) |
| 10 | ((#9) AND ("2013/03/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT ((Humans[mh] AND animals[MeSH:noexp]) NOT ("The Cochrane database of systematic reviews"[Journal]))) |

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