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Leitlinienprogramm Onkologie

Leitlinienreport zur S3-Leitlinie Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms

Version 1.0 – Februar 2018

AWMF-Registernummer: 020/007OL

Leitlinienreport

DKG Krebsgesellschaft · Deutsche Krebshilfe Helfen. Forschen. Informieren. · AWMF

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1. Informationen zum Leitlinienreport

1.1. Autoren des Leitlinienreports

Prof. Dr. Dieter Ukena, Bremen, Heidrun Rexer, Thomas Langer

1.2. Herausgeber

Leitlinienprogramm Onkologie der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (AWMF), Deutschen Krebsgesellschaft e.V. (DKG) und Deutschen Krebshilfe (DKH).

1.3. Federführende Fachgesellschaften der Leitlinie

Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e.V.

Deutsche Krebsgesellschaft e. V.

DKG KREBSGESELLSCHAFT

1.4. Finanzierung der Leitlinie

Diese Leitlinie wurde von der Deutschen Krebshilfe im Rahmen des Leitlinienprogramms Onkologie gefördert.

1.5. Kontakt

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Kuno-Fischer-Straße 8
14057 Berlin

leitlinienprogramm@krebsgesellschaft.de
www.leitlinienprogramm-onkologie.de

1.6. Zitierweise des Leitlinienreports

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms, Leitlinienreport 1.0, 2018, AWMF Registernummer 020/007 OL, http://leitlinienprogramm-onkologie.de/Lungenkarzinom.98.0.html, (abgerufen am TT.MM.JJJJ)

1.7. Weitere Dokumente zur Leitlinie

Bei diesem Dokument handelt es sich um den Leitlinienreport zur Aktualisierung der S3-Leitlinie Lungenkarzinom 2013-2018, die im Rahmen des Leitlinienprogramms Onkologie erfolgte. Das Vorgehen bei der Ersterstellung der Leitlinie (2006-2010) ist in einem gesonderten Leitlinienreport (siehe unten) beschrieben.

Neben der Langversion wird es folgende ergänzende Dokumente zu dieser Leitlinie geben:

- Kurzversion der Leitlinie
- Laienversion (Patientenleitlinie)
- Leitlinienreport zum Erstellungsprozess der Leitlinie 2006-2010
- Dokument mit Evidenztabellen der Version 2010

Diese Leitlinie und alle Zusatzdokumente sind über die folgenden Seiten zugänglich.

- Leitlinienprogramm Onkologie (http://leitlinienprogramm-onkologie.de/Lungenkarzinom.98.0.html
- AWMF (www.awmf.org/leitlinien/)
- Guidelines International Network (www.g-i-n.net)

1.8. Abkürzungsverzeichnis

Abkürzung	Erläuterung
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V.
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
DKG	Deutsche Krebsgesellschaft e. V.
DKH	Deutsche Krebshilfe e. V.
GEKID	Gesellschaft der epidemiologischen Krebsregister in Deutschland e. V.
G-I-N	Guidelines International Network
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
NGC	National Guideline Clearinghouse
OL	Leitlinienprogramm Onkologie

2. Geltungsbereich und Zweck der Leitlinie

2.1. Adressaten

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.

Die Empfehlungen der Leitlinie richten sich an alle Ärzte und Angehörige von Berufsgruppen, die mit der Versorgung von Patienten mit Lungenkarzinomen befasst sind (Internisten, Pneumologen, Radiologen, Nuklearmediziner, Pathologen, Thoraxchirurgen, Radioonkologen, Hämatoonkologen, Psychoonkologen, Pflegekräfte) und an alle an Lungenkrebs erkrankte Patienten und deren Angehörige.

Weiterhin kann die Leitlinien von der (Fach)Öffentlichkeit und den folgenden Institutionen zur Information über die gute medizinische Praxis genutzt werden:

- medizinisch-wissenschaftliche Fachgesellschaften und Berufsverbände
- Interessenvertretungen der Patienten (Patienten- und Selbsthilfeorganisationen)
- Qualitätssicherungseinrichtungen und Projekte sowie gesundheitspolitische Einrichtungen und Entscheidungsträger auf Bundes- und Länderebene: Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Zentralinstitut für die kassenärztliche Versorgung in Deutschland (ZI), Gemeinsamer Bundesausschuss (GBA), Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG), das Robert-Koch-Institut (RKI) Institut für Qualitätssicherung und Transparenz im Gesundheitswesen (IQTiG), Arbeitsgemeinschaft Deutsche Tumorzentren (ADT), Gesellschaft der Epidemiologischen Krebsregister in Deutschland (GEKID) etc.
- Kostenträger

Der Anwendungsbereich der Leitlinie umfasst den ambulanten und stationären Versorgungssektor.

2.2. Zielsetzung

Ziele der vorliegenden S3-Leitlinie sind:

- Unterstützung von Ärzten, betroffenen Patienten und Bürgern mit einem erhöhten Risiko für ein Lungenkarzinom bei medizinischen Entscheidungen durch evidenzbasierte und formal konsentierte Empfehlungen
- Schaffung einer Grundlage für inhaltlich gezielte ärztliche Aus-, Fort- und Weiterbildungsmaßnahmen
- flächendeckende Umsetzung einer multidisziplinären, qualitätsgesicherten und sektorübergreifenden Versorgung des Lungenkarzinoms
- Optimierung der Diagnosekette und der stadiengerechten Therapie sowohl bei der Ersterkrankung als auch beim Rezidiv bzw. bei einer Metastasierung

Durch die Umsetzung dieser Ziele soll mittel- und langfristig die Mortalität der Patienten mit Lungenkarzinomen gesenkt und die Lebensqualität erhöht werden.

2.3. Gültigkeitsdauer und Aktualisierungsverfahren

Diese S3-Leitlinie ist maximal bis 2022 oder bis zur nächsten Aktualisierung gültig. Vorgesehen sind regelmäßige Überprüfungen der Aktualität und Anpassungen bei dringendem Änderungsbedarf. Kommentare und Hinweise für den Aktualisierungsprozess sind ausdrücklich erwünscht und können an folgende Adresse gesendet werden: lungenkarzinom@leitlinienprogramm-onkologie.de

3. Zusammensetzung der Leitliniengruppe

3.1. Koordination und Redaktion

Prof. Dr. Dieter Ukena

Ko-Koordinator: Prof. Dr. Nicola Schönfeld

3.2. Steuergruppe für Aktualisierung 2017

Die Steuergruppe setzte sich wie folgt zusammen:

- Frau B. Bayal (Vertreterin Selbsthilfegruppe)
- W. Eberhardt (Essen) [Vertreter Onkologie]
- M. Flentje (Würzburg) [Vertreter Strahlentherapie]
- M. Follmann (Berlin) [Vertreter OL Office]
- F. Griesinger (Oldenburg) [Vertreter Onkologie]
- H. Hoffmann (Heidelberg) [Vertreter Thoraxchirurgie + ZK Lungenkrebszentren]
- Frau M. Nothacker (Berlin) [Vertreter AWMF]
- B. Passlick (Freiburg) [Vertreter Thoraxchirurgie]
- N. Schönfeld (Berlin) [Vertreter Pneumologie]
- W. Schütte (Halle) [Vertreter Pneumologie]
- M. Stuschke (Essen) [Vertreter Strahlentherapie]
- D. Ukena (Bremen) [Vertreter Pneumologie]
- Frau S. Wesselmann (Berlin) [Vertreter DKG-Zertifizierung]

3.2.1. Beteiligte Fachgesellschaften und Autoren

In Tabelle 1sind die an der Ersterstellung (Version 2010) und ersten Aktualisierung im Rahmen des Leitlinienprogramms Onkologie (Version 1.0) beteiligten Fachgesellschaften und anderen Organisationen sowie die jeweils benannten Fachexperten/Fachexpertinnen aufgelistet[1]. In Tabelle 2 sind die Mitglieder der Arbeitsgruppen für die Aktualisierung der Leitlinie (Version 1.0) aufgeführt.

[1] bei Wechseln bzgl. der mandatierenden Organisation zwischen Ersterstellung und Aktualisierung wurde das Mandat bei der Aktualisierung 2013-2017 angegeben.

Tabelle 1: Beteiligte Fachgesellschaften und Organisationen

Beteiligte Fachgesellschaften und Organisationen	Mandatsträger
Arbeitsgemeinschaft Chirurgische Onkologie - Viszeralchirurgie in der Deutschen Krebsgesellschaft e. V. (CAO-V)	Beate Rau**
Arbeitsgemeinschaft Internistische Onkologie in der Deutschen Krebsgesellschaft e. V. (AIO)	Karl Deppermann*** ; Wilfried Eberhardt***; Rudolf M. Huber***; Tobias Overbeck**; Martin Reck***; Martin Sebastian**; Jutta Hübner*; Berthold Fischer*; Thomas Gauler*; Norbert Niederle*; Ernst Späth-Schwalbe*; Martin Wolf*
Arbeitsgruppe biologische Krebstherapie	Markus Horneber*
Berufsverband Deutscher Pathologen	Alfred Böcking*; Philipp Schnabel**, Klaus Junker**
Berufsverband der niedergelassenen Hämatologen und Onkologen (BNHO)	Hans Werner Tessen*
Bundesverband der Pneumologen (BdP)	Andreas Hellmann*
Deutsche Gesellschaft für Arbeitsmedizin und Umweltmedizin (DGAUM)	Thomas Kraus*; Dennis Nowak*** [2] Uta Ochmann*;
Deutsche Gesellschaft für Epidemiologie (DGEpi)	Irene Brüske*; Heinz-Erich Wichmann*
Deutsche Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie (GMDS)	Heike Bickeböller*; Heinz-Erich Wichmann*
Deutsche Gesellschaft für Nuklearmedizin (DGN)	Richard P. Baum*; Dirk Hellwig*
Deutsche Gesellschaft für Palliativmedizin (DGP)	Martin Weber*; Wiebke Nehls**; Susanne Riha***
Arbeitsgemeinschaft Prävention und integrative Medizin in der Onkologie in der Deutschen Krebsgesellschaft e. V.(PRiO)	Josef Beuth*, Ralph Mücke***
Arbeitsgemeinschaft Onkologische Thoraxchirurgie in der Deutschen Krebsgesellschaft e. V. (AOT)	Frank Noack***
Arbeitsgemeinschaft Onkologische Thoraxchirurgie in der Deutschen Krebsgesellschaft e. V. (AOT) und Deutsche Gesellschaft für Thoraxchirurgie (DGT)	Hans Hoffmann***
Arbeitsgemeinschaft Psychoonkologie (PSO)	Andreas Werner*; Martin Wickert*; Susanne Singer**
Arbeitskreis Supportive Maßnahmen in der Onkologie (ASORS)	Maria Steingräber*; Andreas S. Lübbe* Hartmut Link**

[2] Bei der Aktualsierung als Fachexperte ad personam beteiligt für die Aktualsierung der arbeitsmedizinischen Abschnitte

Beteiligte Fachgesellschaften und Organisationen	Mandatsträger
Deutsche Gesellschaft für Hämatologie und Onkologie (DGHO)	Frank Griesinger***; Jürgen Wolf** Uwe Martens*; Alexander Schmittel*
Deutsche Gesellschaft für Pathologie e. V. (DGPath)	Rainer M. Bohle*; Iver Petersen*; Klaus Junker**
Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e.V. (DGP)	Stefan Andreas*; Nikolas Dickgreber*; Thomas Fink*; Detlef Kirsten*; Susanne Lang*; Martin Steins*; Helmut Teschler*; Heinrich Worth*; Lutz Freitag*; Hubert Hautmann*; Thorsten Blum***; Joachim Ficker***; Andreas Gröschel**; Sylvia Gütz***; David Heigener**; Felix Herth***; Nicolas Schönfeld***; Wolfgang Schütte***; Dieter Ukena***; Christian Witt***
Deutsche Gesellschaft für Radioonkologie (DEGRO)	Martin Stuschke***; Michael Flentje*; Christian Rübe*
Deutsche Gesellschaft für Thoraxchirurgie (DGT)	Servet Bölükbas**; Thomas Graeter** Christian Kugler**; Joachim Pfannschmidt**; Robert Scheubel**; Hendrik Dienemann*; Stephan Eggeling*; Godehard Friedel*; Bernward Passlick*; Georgios Stamatis*; Erich Stoelben*; Lothar Swoboda*
Deutsche Röntgengesellschaft (DRG)	Jens Vogel-Claussen*** ; Dag Wormanns***; Claus Peter Heußel*; Stefan Diederich*; Hans-Ulrich Kauczor*
Hauptverband der gewerblichen Berufsgenossenschaften (HVBG), Deutsche gesetzliche Unfallversicherung (DGUV)	Frank Hoffmeyer*
Institut für Sozialmedizin, Epidemiologie und Gesundheitsökonomie, Charité Berlin	Jacqueline Müller-Nordhorn*; Thomas Reinhold*
Österreichische Gesellschaft für Pneumologie (ÖGP)	Otto Burghuber***; Maximilian Hochmair**; Andrea Mohn-Staudner***; Klaus Kirchbacher*
Österreichische Gesellschaft für Radioonkologie (ÖGRO)	Thomas Auberger*; Boris Pokrajac*
Zentralverband der Physiotherapeuten/Krankengymnasten (ZVK)	Michaela Franke*
Pneumologisch-onkologische onkologische Arbeitsge-meinschaft in der Deutschen Krebsgesellschaft e. V. (POA)	Wolfgang Brückl***; Fernando Gamarra***; Christian Grohé***; Christoph Schäper***; Monika Serke***; Günter Tessmer***; Michael Thomas***
Konferenz Onkologischer Kranken- und Kinderkrankenpflege (KOK)	Paradies, Kerstin**; Elke Irlinger Wimmer*

Beteiligte Fachgesellschaften und Organisationen	Mandatsträger
Krebsgesellschaft Nordrhein-Westfalen	Klaus-Michael Müller*
Selbsthilfe Lungenkrebs	Barbara Baysal***; Werner Kleinert**
Kompetenz-Centrums Onkologie des MDK	Klaus-Peter Thiele**
Universität Köln (als Fachexperte ad personam beteiligt)	Reinhard Büttner** (ohne Stimmrecht)
Arbeitsgemeinschaft Deutscher Tumorzentren (ADT)	Hagen Barlag** (für Aktualisierung der Qualitätsindikatoren)

Zeitraum der Beteiligung

* = 2006-2010;
** = 2013-2018;
*** = 2006-2018;

Tabelle 2: Arbeitsgruppen des Aktualisierungsprozesses 2013-2018 und deren Mitglieder

Arbeitsgruppe	Mitglieder der Arbeitsgruppe (AG-Leiter fett markiert)
Früherkennung	**H. Hoffmann**, W. Brückl, J. Ficker, F. Gamarra, F. Herth, C. Witt, D. Wormanns, J. Vogel-Claussen
Pathologie	**K. Junker**, S. Bölükbas, K. Deppermann, C. Grohé, S. Gütz, R.M. Huber, C. Kugler
Therapie NSCLC IV	**M. Serke**, T. Graeter, A. Gröschel, J. Pfannschmidt, M. Reck, M. Serke, W. Eberhardt, F. Griesinger, J. Wolf
Patienteninformation/ Palliativ	**W. Nehls,** D. Heigener, H. Link, W. Nehls, T. Overbeck, S. Riha, R. Scheubel, M. Sebastian, G. Tessmer, M. Thomas, J. Wolf, W. Kleinert
Qualitätsindikatoren	T. Blum, F. Noack, B. Rau, C. Schäper, S. Singer, K. Junker, M. Thomas, H. Hoffmann, H. Barlag, F. Griesinger, J. Ficker, H. Barlag, S. Wesselmann (Federführung und Organisation), M. Follmann (Moderation)

3.3. Patientenbeteiligung

Die Leitlinie wurde unter direkter Beteiligung von zwei Patientenvertretern erstellt.

Frau Baysal und Herr Kleinert waren von Beginn an in die Erstellung der Leitlinie eingebunden und nahmen mit eigenem Stimmrecht an den Konsensuskonferenzen teil.

3.3.1. Beteiligte externe Experten

- Dr. Katrin Schaller, Dr. Ute Mons (Deutsches Krebsforschungszentrum) für die Aktualisierung des Kapitels zu Risikofaktoren

3.3.2. Methodische Begleitung

Durch das Leitlinienprogramm Onkologie:

- Dipl.-Soz.Wiss. Thomas Langer (OL-Office)
- Dr. med. Markus Follmann MPH MSc (OL-Office)
- Dr. med. Monika Nothacker MPH (AWMF-IMWi)

Durch externe Auftragnehmer:

- Dr. rer. medic. Tim Mathes (Literaturrecherche und Qualitätsbewertung für die Aktualisierung 2018)
- Dr. med. Simone Wesselmann, MBA (Aktualisierung der Qualitätsindikatoren)

4. Fragestellungen und Gliederung

Die Gliederung der Leitlinie kann der Langversion 1.0 (2018) entnommen werden. Von der Steuergruppe (siehe Kapitel 3.2) wurden für die Aktualisierung der Leitlinie die folgenden Themen priorisiert:

- Früherkennung
- Pathologie
- Therapie des NSCLC im Stadium IV
- Palliativmedizinische Behandlung (Palliative Care)
- Qualitätsindikatoren

Die folgenden Aspekte waren maßgeblich für die Priorisierung dieser Themen:

Früherkennung

In Anbetracht der hohen Mortalität von Lungenkrebs ist die Früherkennung ein enorm wichtiges Thema. Bislang gab es keine Untersuchungsmethode, welche zur Früherkennung flächendeckend und verlässlich eingesetzt werden. In 2011 wurden die Ergebnisse des National Lung Screening Trial (NLST) des National Cancer Institute der USA publiziert. Unter Einsatz der CT-Thorax Untersuchung in low dose Technik wurde im NLST eine Reduktion der Mortalität an Lungenkarzinom bei Risikoprobanden nachgewiesen [National Lung Screening Trial Research Team: Radiology 2011, 258: 243; N Engl J Med 2011: 10.1056/NEJM0a1102873].

Pathologie

Eine wichtige histologische Gruppe der nicht-kleinzelligen Lungenkarzinome (NSCLC), die Adenokarzinome, wurden vollständig neu klassifiziert. [IASLC/ATS/ERS International Multidisciplinary Classification of Lung Adenocarcinoma, J Thorac Oncol 2011, 6: 244]. Dieser neuen Klassifikation kommt prognostische Bedeutung zu.

Des Weiteren hatten molekularbiologischen Untersuchungen hinsichtlich Mutation von Wachstumsrezeptoren signifikant an Bedeutung gewonnen, da sie entscheidend für die Therapiefestlegung im metastasierten Stadium sind. Das Anforderungsprofil an die pathologische Untersuchung von Gewebsproben wurde erheblich ausgeweitet. Unter dem Stichwort „personalisierte Therapie“ musste diskutiert werden, inwieweit eine ausführliche molekularbiologische Analyse der Tumorproben Voraussetzung für die Festlegung einer dezidierten medikamentösen Therapie ist

Therapie des NSCLC im Stadium IV

Unter dem Stichwort „Personalisierte Therapie“ oder „Stratifizierende Therapie“ hatten sich die Prinzipien insbesondere der Chemotherapie im metastasierten Stadium tiefgreifend geändert. Dieses galt in 2013 insbesondere für die Erstlinien-Chemotherapie bei Nachweis einer EGFR-Mutation sowie für die Zweitlinien-Chemotherapie bei Nachweis einer EML4-ALK-Translokation [pars pro toto: Maemondo et al., N Engl J Med 2010, 362: 2380-8; Rosell et al., Lancet Oncol 2012, 13: 239-46; Kwak et al., N Engl J Med Aktualisierungsantrag 6

2010, 363: 1693-703].

Ein weiterer Aspekt der Chemotherapie im metastasierten Stadium des NSCLC mit neuen wissenschaftlichen Erkenntnisse war die sog. Erhaltungschemotherapie: nach Abschluss der Erstlinienchemotherapie kann durch die sich sofort anschließende Therapie mit dem Tyrosinkinase-Inhibitor Erlotinib oder dem Zytostatikum Pemetrexed eine Verlängerung des Progression-freien Überlebens (PSF) –allerdings nicht der Gesamtüberlebenszeit- erreicht werden [Cappuzzu et al., Lancet Oncol 2010, 11: 521-29; Paz-Ares et al., Lancet Oncol 2012, 13: 247-55].

Im Zuge der Aktualisierungsprozesses wurde weitere neue Arzneimittel für die Therapie des Lungenkarzinoms zugelassen. Dies machte weitere Diskussionen der Therapieempfehlungen notwendig.

Palliativmedizinische Behandlung

Durch die Zertifizierung von Lungenkrebszentren mit der damit verbundenen Forderung, für eine ganzheitliche Patientenversorgung Verantwortung zu tragen, wurde die Bedeutung der palliativmedizinischen Versorgung stark akzentuiert. Dabei wurde auch deutlich, dass trotz teilweise großer Anstrengungen in einzelnen Zentren weitere Ressourcen (sowohl räumlich als auch personell) zur Verfügung gestellt werden mussten, um eine adäquate Versorgung der häufig schwerkranken Lungenkrebspatienten zu ermöglichen.

Auch wissenschaftlich gab es wichtige Ergebnisse bzgl. des Nutzens von Palliative Care hinsichtlich Lebensqualität und Lebensdauer von Patienten mit Lungenkrebs. So wurde in einer randomisierten Vergleichsstudie von Patienten mit metastasiertem Lungenkarzinom gezeigt, dass der frühzeitige Einsatz palliativmedizinischer Maßnahmen nicht nur die Lebensqualität signifikant besserte, sondern auch zu einer signifikanten Verlängerung der medianen Überlebenszeit (11,6 Monate vs. 8,9 Monate, p=0,002) führte [Temel et al., N Engl J Med 2010, 363: 733-42]. Wissenschaftlich basierte Empfehlungen zur palliativmedizinischen Versorgung wurden daher als notwendig erachtet. Darüber hinaus sollten die Erkenntnisse und Empfehlungen der S3-Leitlinie Palliativmedizin (Fertigstellung in 2015) implementiert werden bzw. die Vertreter der S3-Leitliniengruppe Palliativmedizin sollten in die Arbeit der Leitliniengruppe Lungenkarzinom eingebunden werden, um spezifisch pneumologische Aspekte in der palliativmedizinischen Versorgung von Patienten mit Lungenkarzinom zu berücksichtigen.

Qualitätsindikatoren

In der S3-Leitlinie „Lungenkarzinom“ (Version 2010) waren neun Qualitätsindikatoren definiert worden. Keiner dieser Qualitätsindikatoren wurden allerdings prospektiv evaluiert. Wie in der Leitlinie ausgeführt wird, sollten die in der LL aufgeführten Qualitätsindikatoren nur für interne Qualitätssicherungsmaßnahmen verwendet werden, jedoch keinesfalls für eine externe Qualitätssicherung herangezogen werden.

Die bisherigen Diskussionen in der Zertifizierungskommission „Lungenkrebszentren“ der DKG verdeutlichten, dass ein erheblicher Bedarf hinsichtlich der eindeutigen Definition der Qualitätsindikatoren und hinsichtlich der systematischen Erfassung besteht.

Im Zuge des Aktualisierungsprozesses ergaben sich weitere Aktualisierungserfordernisse:

- Kapitel zur Stadieneinteilung (Staging) aufgrund der in 2017 publizierten 8. Auflage der TNM-Klassifikation

- Das Kapitel zur Patientenaufklärung wurde aktualisiert, um nach Erscheinen der S3-Leitlinie zur Palliativmedizin das dort konsentierte Vorgehen in die Leitlinie spezifisch für diese Entität abzubilden.

Nach dem Kick-Off-Treffen der Leitliniengruppe am 01. 07. 2014 wurden zu den priorisierten Themen die in PICO-Fragen definiert:

Tabelle 3: PICO-Fragen für die Aktualisierung der S3-Leitlinie Lungenkarzinom (2013-2018)

	Population	Intervention	Kontrolle	Outcome	Studien-typ
Themengebiet:Früherkennung					
Low Dose- CT	Population mit bekanntem Risiko, primär (Ex-)Raucher, aber auch andere	Low Dose- CT	1.Rö-Thorax 2. PET CT/MR 3.Bronchoskopie / Bronchiallavage 4.Exhalatanalyse/Sputum 5. Molekulare Marker im Blut (Proteomics, - profile, RNA, genetische Clusteranalysen) 6. Keine Früherkennung	Karzinom-spezifische Mortalität Gesamt-mortalität Falsch positive Befunde Unerwünschte Wirkungen aus Folgeeingriffen Weniger Wichtig gewertet: Lebensqualität (mit validierten Instrumenten) Verringerung der Morbidität	RCT
Low Dose- CT	Population mit unbekanntem Risiko	Low Dose- CT	1.Rö-Thorax 2. PET CT/MR 3.Bronchoskopie / Bronchiallavage 4.Exhalatanalyse/Sputum 5. Molekulare Marker im Blut (Proteomics, - profile, RNA, genetische Clusteranalysen) 6. Keine Früherkennung	Karzinom-spezifische Mortalität Gesamtmortalität Falsch positive Befunde Unerwünschte Wirkungen aus Folgeeingriffen Weniger Wichtig gewertet: Lebensqualität	RCT

	Population	Intervention	Kontrolle	Outcome	Studien-typ
				Verringerung der Morbidität	
Themengebiet: Pathologie					
Immunhisto-chemische Marker	V.a. Lungenkarzinom (alle)	IHC Marker (TTF1, P63, p40, ck7, ck5/6, napsin a, CD56, synaptophysin, chromogranin, KI67, mesenchymale Marker: vimentin, ….., Pan Zytokeratine, Ausschlussmarker: LCA	Keine IHC	Diagnostische Güte von histologischen Typen und patientenrelvante Endpunkte (für RCT)	SR, Querschnittsstudien, (prospektive) Kohortenstudien (delayed cross-sectional studies) und RCT.
Molekular-pathol. Testung	NSCLC St 3b 4	Molecular Testung/Marker (EGFR, ALK, ROS, K-RAS, N-RAS)	Keine Testung/Marker	OS, PFS, ORR, QoL PRO (Prognostische Validität)	SR, RCT und (nicht interventionelle) prospektive Kohortenstudien (inception cohort studies).
Aufarbeitung Lymphknoten	Operierte NSCLC St 1-3	Komplette Aufarbeitung (Serienschnitt) des LK	Einzelner Schnitt	Diagnostische Güte Tumorstadium N-Stadium) Typen und patientenrelvante Endpunkte (für RCT)	SR, Querschnittsstudien, prospektive Kohortenstudien (delayed cross-sectional studies)
Prognostische Faktoren	Prognost. ungünstige, (G3L1V1[alternativ]) operierte NSCLC	Adjuvante Chemotherapie	Keine Chemotherapie	OS, PFS, Lokalreziiv	SR, RCT und prospektive Kohortenstudien.

	Population	Intervention	Kontrolle	Outcome	Studien-typ
Resektionsränder	Operierte Patienten SCLC/ NSCLC St 1-3	R-Angabe, Completeness of resection Close margin, positive margin, icroscopic involved, capsular invasion, R1, R2, Ro	‚incomplete' Wide margin…..	OS, lokal Rezidiv. (Prognostische Validität)	SR, RCT und (nicht interventionelle) prospektive Kohortenstudien (inception cohort studies).
Themengebiet: Therapie NSCLC Stadium IV					
Molekular stratifizierte . Therapie	NSCLC Stadium IV mit molek. Alteration (EGF/EGFR)	First line TKI + second line TKI (Erlotinib, Gefitinib, Afatinib)	Chemotherapie (Zytostatika)	OS, PFS ORR QoL PRO und Tox	SR, RCT, prospektive Kohortenstudien und alle vergleichende Studien falls Registerauswertungen. Ausgeschlossen: explorative Subgruppenanalysen* Publikationsdatum: ab 2006; Second line TKI nicht beschränkt
	NSCLC Stadium IV mit molek. Alteration (ALK)	First line TKI (Ceritinib, Crizotinib, Vandetinib)			
	NSCLC Stadium IV mit molek. Alteration (ROS1)	First line TKI (keine Einschränkung)			

	Population	Intervention	Kontrolle	Outcome	Studien-typ
Erhaltungs-therapie	St4	Continuous maintenance Switch maintenance	Observation	OS, PFS ORR QoL PRO und Tox	SR, RCT, prospektive Kohortenstudien und alle vergleichende Studien falls Registerauswertungen. ≥ 80 Patienten Ausgeschlossen: Phase 1. Studien Ausgeschlossen: explorative Subgruppenanalysen*
Nachsorge	St 4 nach Abschluss Firstline THe	6 Wo Interval	>6Wochen Symptom orientierte Kontrolle	OS, Inzidenz von 2. Therapie	SR, RCT, prospektive Kohortenstudien und alle vergleichende Studien falls Registerauswertungen. Ausgeschlossen: explorative Subgruppenanalysen*
Anti VEGF	NSCLC St4	1st line +	1st line -	OS, PFS ORR QoL PRO und Tox, DCR	SR, RCT, prospektive Kohortenstudien und alle vergleichende Studien falls Registerauswertungen. ≥ 80 Patienten

	Population	Intervention	Kontrolle	Outcome	Studien-typ
					Ausgeschlossen: Phase 1. Studien Ausgeschlossen: explorative Subgruppenanalysen*
Anti VEGF	NSCLC St4	2nd line +	2nd line -	OS, PFS ORR QoL PRO und Tox, DCR	SR, RCT, prospektive Kohortenstudien und alle vergleichende Studien falls Registerauswertungen. ≥ 80 Patienten Ausgeschlossen: Phase 1. Studien Ausgeschlossen: explorative Subgruppenanalysen*
OMD (Oligometastatic disease)	NSCLC St4	Lokal Th (Radio oder Resektion) + CT	Alleinige CT	OS, PFS ORR QoL PRO und Tox	SR, RCT, prospektive Kohortenstudien und alle vergleichende Studien falls Registerauswertungen. ≥ 40 Patienten Ausgeschlossen: explorative Subgruppenanalysen*

	Population	Intervention	Kontrolle	Outcome	Studien-typ
Th beim PS2 Pat.	>=PS2	Kombi Chemotherapie	Monochemotherapie	OS, PFS ORR QoL PRO und Tox	SR, RCT, prospektive Kohortenstudien und alle vergleichende Studien falls Registerauswertungen. ≥ 80 Patienten Ausgeschlossen: Phase 1. Studien Ausgeschlossen: explorative Subgruppenanalysen*
Themengebiet: Palliativmedizin					
	Patienten mit metastasiertem Krebs oder Lungenkrebs (Stadium IV)	Strukturierte* palliativmedizinische Intervention	Keine strukturierte/ spezifische palliativmedi-zinische Intervention	Entscheidend: 1.Lebensqualität = Quality of Life (mehrere validierte Instrumente = FACT-L, TOI, LCSS, EORTCQ30 LC Symptom subscale) 2.Verbesserung Angst/Depression 3.Verschlechterung Angst/Suizidrate Als wichtig, aber nicht entscheidend bewertet: 1.Gesamtmortalität 2.Aggressivität der	RCT, Systematische Übersichtsarbeit.

	Population	Intervention	Kontrolle	Outcome	Studien-typ
				Therapie am ebens-ende 3.Anzahl Patienten-verfügungen (resuscitation preferences?) Als weniger wichtig bewertet: 1.Verringerung der Anzahl erforderlicher Kriseninterventionen (Unplanned contacts/emergency contact) 2.Cost effectiveness	
	Patienten mit Lungenkarzinom, aus anderen Gründen als PICO 1 nicht kurativ behandelbar	Strukturierte palliativ-medizinische Intervention	Keine strukturierte/ spezifische palliativmedi-zinische Intervention	Entscheidend: 1.Lebensqualität = Quality of Life (mehrere validierte Instrumente = FACT-L, TOI, LCSS, EORTCQ30 LC Symptom subscale) 2.Verbesserung Angst/Depression 3.Verschlechterung Angst/Suizidrate Als wichtig, aber nicht entscheidend bewertet: 1.Anzahl Patienten-verfügungen (resuscitation preferences?)	RCT, Systematische Übersichtsarbeit

	Population	Intervention	Kontrolle	Outcome	Studien-typ
				Als weniger wichtig bewertet: 1.Cost effectiveness 2. Gesamtmortalität 3.Aggressivität der Therapie am Lebensende	

* Definition der Intervention: regelmäßiger Kontakt mit interdisziplinärem Team, d.h. palliativmedizinisch geschulten Ärzten/Schwestern, mit strukturiertem Screening auf palliativmedizinische Bedürfnisse und symptomorientierte Behandlung sowie emotionaler, sozialer und spiritueller Bedürfnisse, partizipative Entscheidungsfindung

RCT: randomized controlled trial; SR: systematic review; OS: Overall Survival; PFS: Progression Free Survival; ORR: Overall Response Rate, QoL: Quality of Life; PRO: Patient reported outcomes; Tox: Toxicity; SRE: skeletal-related events; IHC: Immunhistochemisch; EGF(R): Epidermal Growth Factor (Receptor); ALK: Anaplastische-Lymphom-Kinase; ROS1: Proto-oncogene tyrosine-protein kinase gene; TKI: tyrosine-kinase inhibitor; FACT-L: Functional Assessment of Cancer Therapy – Lung; TOI: Therapy-Trial Outcome Index; LCSS: Lung Cancer Symptom Scale; EORTCQ30 LC Symptom subscale: European Organisation for Research and Treatment of Cancer Quality Lung Cancer Symptom subscale; CT: Computertomografie; PET: Positronen-Emissions-Tomographie; MR: Magnetresonanz; RNA: Ribonukleinsäure; DCR: disease control rat

5. Methodisches Vorgehen

5.1. Leitlinienadaptation

Für den Aktualisierungsprozess 2013-2018 erfolgte keine systematische Aufarbeitung und Berücksichtigung existierender evidenzbasierter Leitlinien.

5.2. Systematische Recherchen

Zu den in Kapitel 4 aufgeführten PICO-Fragen erfolgte eine systematische Literaturrecherche und Bewertung der Literatur durch das Institut für Forschung in der Operativen Medizin (IFOM) der Privatuniversität Witten/Herdecke.

Die Methodik und die Ergebnisse der systematischen Recherchen werden im Folgenden dargestellt. Zur Identifikation weiterer relevanter Literatur wurden klinische Experten befragt sowie die Referenzen der eingeschlossenen Studien und systematischen Reviews zu verwandten Fragestellungen geprüft.

Zusätzliche Literatur - vor allem zu neuen Arzneimittel – wurde darüber hinaus auch im weiteren Verlauf des Aktualisierungsprozesses durch die beteiligten Fachexperten ergänzt.

Alle folgenden Angaben sind dem Evidenzbericht des IFOM (Version vom 29.04.2015) entnommen.

5.2.1. Suchstrategie und Studienselektion

Es wurde eine systematische Recherche in MEDLINE (via PubMed) durchgeführt. Tabelle 4 enthält die Suchstrategien für die jeweilige Fragestellung. Zur Identifikation weiterer relevanter Literatur wurden klinische Experten befragt sowie die Referenzen der eingeschlossenen Studien und systematischen Reviews zu verwandten Fragestellungen geprüft.

Tabelle 4: Recherchestrategien der Aktualisierungsrecherchen

Thema (Recherchedatum)	Suchstrategie
Früherkennung	
Low-dose CT (07.05.2014)	(Lung Neoplasms[mesh] OR ((Lung[tiab] OR pulmonary[tiab] OR bronchial[tiab] OR bronchogenic[tiab] OR respiratory[tiab]) AND (cancer[tiab] OR carcinoma[tiab] OR carcinomas[tiab] OR Neoplasms[tiab] OR Neoplasms[mesh] OR Neoplasm[tiab] OR tumour[tiab] OR tumours[tiab] OR tumor[tiab] OR tumors[tiab] OR sarcoma[tiab] OR sarcomas[tiab]))) AND („Early Detection of Cancer“[mesh] OR „Detection“[tiab] OR Mass Screening[mesh] OR screening[tiab]) AND (("Tomography, X-Ray Computed"[mesh] OR ct[tiab] OR computed tomograph* [tiab])) AND ("2006/06/01"[Date - Entrez] : "3000"[Date - Entrez]) AND ((Randomized Controlled Trial [PTyp] OR Controlled Clinical Trial [PTyp] OR randomized [TiAb] OR randomised [TiAb] OR placebo [TiAb] OR clinical trials as topic [MeSH] OR randomly [TiAb] OR

Thema (Recherchedatum)	Suchstrategie
	trial [TiAb])) NOT (animals [MeSH Terms] NOT humans [MeSH Terms])
Pathologie	
Immunhistochemische Marker (12.05.2014)	(Lung Neoplasms[mesh] OR ((Lung[tiab] OR pulmonary[tiab] OR bronchial[tiab] OR bronchogenic[tiab] OR respiratory[tiab]) AND (cancer[tiab] OR carcinoma[tiab] OR carcinomas[tiab] OR Neoplasms[tiab] OR Neoplasms[mesh] OR Neoplasm[tiab] OR tumour[tiab] OR tumours[tiab] OR tumor[tiab] OR tumors[tiab] OR sarcoma[tiab] OR sarcomas[tiab]))) AND („Immunohistochemistry“[mesh] OR "thyroid transcription factor 1"[tiab] OR TTF 1[tiab] OR "thyroid transcription factor I"[tiab] OR TTF I[tiab] OR TTF1 protein, human [Supplementary Concept] OR "P63"[tiab] OR "TP63"[tiab] OR TP63 protein, human [Supplementary Concept] OR "P40"[tiab] OR "TP40"[tiab] OR Interleukin-12 Subunit p40[mesh] OR anti-pancytokeratin immunoglobulin[Supplementary Concept] OR pancytokeratin[tiab] OR pankeratin[tiab] OR Cytokeratin 7[tiab] OR keratin 7[tiab] OR ck 7[tiab] OR k7[tiab] OR Keratin-7[mesh] OR Napsin A[tiab] OR nap a[tiab] OR NAPSA protein, human [Supplementary Concept] OR CD56[tiab] OR Antigens, CD56[mesh] OR NCAM[tiab] OR FOXK1 protein, human[Supplementary Concept] OR FOXK1[tiab] OR katanin-like 1 protein, human[Supplementary Concept] OR katanin-like[tiab] OR kl1[tiab] OR ae1[tiab] OR ae3[tiab] OR Anion Exchange Protein 1, Erythrocyte[mesh] OR SLC4A3 protein, human[Supplementary Concept] OR Anion Exchange Protein[tiab] OR Neural Cell Adhesion Molecules[mesh] OR synaptophysin[tiab] OR Synaptophysin[mesh] OR sy38[tiab] OR p38[tiab] OR pt38[tiab] OR chromogranin [tiab] OR Chromogranins[mesh] OR CHG[tiab] OR CHGA[tiab] OR CHGB[tiab] OR ki67[tiab] OR Ki-67 Antigen[mesh] OR MKI67[tiab] OR MKI67IP protein, human [Supplementary Concept] OR vimentin[tiab] OR Vimentin[mesh] OR R28[tiab] OR pan[tiab] OR PAN-1 protein, C elegans[Supplementary Concept] OR Cytokeratin[tiab] OR Ck[tiab] OR leukocyte common antigen[tiab] OR LCA[tiab]) AND ((ROC Curve[Mesh] OR c statistic[tiab] OR area under the curve[tiab] OR auc[tiab] OR sensitivity and specificity [Mesh] OR sensitivity[TIAB] OR specificity[TIAB] OR pre test probability[TIAB] OR pretest probability[TIAB] OR post test probability[TIAB] OR predictive value[TIAB] OR likelihood ratio[TIAB] OR diagnostic accuracy[TIAB] OR roc[tiab] OR receiver operating characteristics[tiab] OR False positive[tiab] OR False negative[tiab] OR “Molecular Diagnostic Techniques”[mesh] OR ((Randomized Controlled Trial[PTyp] OR Controlled Clinical Trial[PTyp] OR randomized[TiAb] OR randomised[TiAb] OR placebo[TiAb] OR clinical trials as topic[MeSH] OR randomly[TiAb] OR trial[TiAb]) NOT (animals[MeSH Terms] NOT humans[MeSH Terms])))) AND ("2006/06/01"[Date - Entrez] : "3000"[Date - Entrez])

Thema (Recherchedatum)	Suchstrategie
Molekularpathologische Testung (05.06.2014)	(carcinoma, non small cell lung [mesh] OR ((Lung[tiab] OR pulmonary[tiab] OR bronchial[tiab] OR bronchogenic[tiab] OR respiratory[tiab]) AND (cancer[tiab] OR carcinoma[tiab] OR carcinomas[tiab] OR Neoplasms[tiab] OR Neoplasms[mesh] OR Neoplasm[tiab] OR tumour[tiab] OR tumours[tiab] OR tumor[tiab] OR tumors[tiab] OR sarcoma[tiab] OR sarcomas[tiab]) AND (non Oat [tiab] OR non small[tiab])) AND (stag*[tiab] AND (III[tiab] OR three[tiab] OR 3[tiab] OR IV[tiab] OR four[tiab] OR 4[tiab]))) AND („pathology, Molecular“[mesh] OR Molecular Diagnostic Techniques[mesh] OR Receptor, Epidermal Growth Factor[mesh] OR epidermal growth factor receptor[tiab] OR EGFR[tiab] OR anaplastic lymphoma kinase [Supplementary Concept] OR anaplastic lymphoma kinase [tiab] OR ALK [tiab] OR CD246[tiab] OR ROS1 protein, human [Supplementary Concept] OR Reactive oxygen species[tiab] OR ROS [tiab] OR ROS1 [tiab] OR KRAS protein, human [Supplementary Concept] OR KRAS[tiab] OR K RAS[tiab] OR Kirsten rat sarcoma viral oncogene homolog[tiab] OR NRAS protein, human[Supplementary Concept] OR NRAS[tiab] OR “N RAS”[tiab]) AND ((prognosis[mesh] OR Predict*[tiab] OR Predictive value of tests[mh] OR ROC Curve[Mesh] OR c statistic[tiab] OR area under the curve[tiab] OR auc[tiab] OR predictive value[TIAB] OR ((Randomized Controlled Trial[PTyp] OR Controlled Clinical Trial[PTyp] OR randomized[TiAb] OR randomised[TiAb] OR placebo[TiAb] OR clinical trials as topic[MeSH] OR randomly[TiAb] OR trial[TiAb]) NOT (animals[MeSH Terms] NOT humans[MeSH Terms])))) AND ("2006/06/01"[Date - Entrez] : "3000"[Date - Entrez])
Aufarbeitung Lymphknoten (03.07.2014)	(carcinoma, non small cell lung [mesh] OR ((Lung[tiab] OR pulmonary[tiab] OR bronchial[tiab] OR bronchogenic[tiab] OR respiratory[tiab]) AND (cancer[tiab] OR carcinoma[tiab] OR carcinomas[tiab] OR Neoplasms[tiab] OR Neoplasms[mesh] OR Neoplasm[tiab] OR tumour[tiab] OR tumours[tiab] OR tumor[tiab] OR tumors[tiab] OR sarcoma[tiab] OR sarcomas[tiab]) AND (non Oat [tiab] OR non small[tiab])) AND (stag*[tiab] AND (I[tiab] OR one[tiab] OR 1[tiab] OR II[tiab] OR two[tiab] OR 2[tiab] OR III[tiab] OR three[tiab] OR 3[tiab]))) AND (serial section*[tiab] OR serial cut*[tiab]) AND ("2006/06/01"[Date - Entrez] : "3000"[Date - Entrez]) AND ((prognosis[mesh] OR Predict*[tiab] OR Predictive value of tests[mh] OR Scor*[tiab] OR Observ*[tiab] OR Observer variation[mh] OR stratification[tiab] OR ROC Curve[Mesh] OR discrimination[tiab] OR discriminate[tiab] OR c statistic[tiab] OR area under the curve[tiab] OR auc[tiab] OR calibration[tiab] OR indices[tiab] OR algorithm[tiab] OR multivariable[tiab] OR sensitivity and specificity [Mesh] OR sensitivity [TIAB] OR specificity [TIAB] OR pre test probability* [TIAB] OR pretest probability* [TIAB] OR post test probability* [TIAB] OR predictive value* [TIAB] OR likelihood ratio* [TIAB] OR diagnostic accura* [TIAB] OR roc[tiab] OR receiver operating characteristics[tiab] OR False positive[tiab] OR False negative[tiab] OR detect*[tiab]) OR (Randomized Controlled Trial[PTyp] OR Controlled Clinical Trial[PTyp] OR randomized[TiAb] OR randomised[TiAb] OR placebo[TiAb] OR clinical trials as topic[MeSH] OR randomly[TiAb] OR trial[TiAb]) NOT

Thema (Recherchedatum)	Suchstrategie
	(animals[MeSH Terms] NOT humans[MeSH Terms])) AND ("2006/06/01"[Date - Entrez] : "3000"[Date - Entrez])
Prognostische Faktoren (23.06.2014)	(carcinoma, non small cell lung [mesh] OR (Lung[tiab] OR pulmonary[tiab] OR bronchial[tiab] OR bronchogenic[tiab] OR respiratory[tiab]) AND ((cancer[tiab] OR carcinoma[tiab] OR carcinomas[tiab] OR Neoplasms[tiab] OR Neoplasms[mesh] OR Neoplasm[tiab] OR tumour[tiab] OR tumours[tiab] OR tumor[tiab] OR tumors[tiab] OR sarcoma[tiab] OR sarcomas[tiab]) AND (non Oat [tiab] OR non small[tiab]))) AND (resect*[tiab] OR surgery[tiab] OR remov*[tiab] OR ablation[tiab] OR excision[tiab]) AND (Chemotherapy, Adjuvant[mesh] OR (adjuvant[tiab] AND (chemotherapy[tiab] OR Antineoplastic Agents[mesh] OR Cytostatic Agents[mesh]))) AND ("2006/06/01"[Date - Entrez] : "3000"[Date - Entrez]) NOT (animals [MeSH Terms] NOT humans [MeSH Terms])
Resektionsränder (03.07.2014)	(Small Cell Lung Carcinoma[mesh] OR ((Lung[tiab] OR pulmonary[tiab] OR bronchial[tiab] OR bronchogenic[tiab] OR respiratory[tiab]) AND (cancer[tiab] OR carcinoma[tiab] OR carcinomas[tiab] OR Neoplasms[tiab] OR Neoplasms[mesh] OR Neoplasm[tiab] OR tumour[tiab] OR tumours[tiab] OR tumor[tiab] OR tumors[tiab] OR sarcoma[tiab] OR sarcomas[tiab])) AND Oat [tiab]OR small[tiab]) OR (carcinoma, non small cell lung [mesh] OR ((Lung[tiab] OR pulmonary[tiab] OR bronchial[tiab] OR respiratory[tiab]) AND (cancer[tiab] OR carcinoma[tiab] OR carcinomas[tiab] OR Neoplasms[tiab] OR Neoplasms[mesh] OR Neoplasm[tiab] OR tumour[tiab] OR tumours[tiab] OR tumor[tiab] OR tumors[tiab] OR sarcoma[tiab] OR sarcomas[tiab]) AND (non Oat [tiab] OR non small[tiab])) AND (stag*[tiab] AND (IV[tiab] OR four[tiab] OR 4[tiab] OR III[tiab] OR three[tiab] OR 3[tiab]))) AND (surgical margin [tiab] OR resection margin[tiab]) AND ("2006/06/01"[Date - Entrez] : "3000"[Date - Entrez]) AND (prognosis[mesh] OR (prognosis[mesh] OR Predict*[tiab] OR Predictive value of tests[mh] OR Scor*[tiab] OR Observ*[tiab] OR Observer variation[mh] OR stratification[tiab] OR ROC Curve[Mesh] OR discrimination[tiab] OR discriminate[tiab] OR c statistic[tiab] OR area under the curve[tiab] OR auc[tiab] OR calibration[tiab] OR indices[tiab] OR algorithm[tiab] OR multivariable[tiab] OR ((Randomized Controlled Trial[PTyp] OR Controlled Clinical Trial[PTyp] OR randomized[TiAb] OR randomised[TiAb] OR placebo[TiAb] OR clinical trials as topic[MeSH] OR randomly[TiAb] OR trial[TiAb]) NOT (animals[MeSH Terms] NOT humans[MeSH Terms]))))
Therapie NSCLC IV	
Molekular stratifizierte Therapie (05.06.2014)	(Lung Neoplasms[mesh] OR ((Lung[tiab] OR pulmonary[tiab] OR bronchial[tiab] OR bronchogenic[tiab] OR respiratory[tiab]) AND (cancer[tiab] OR carcinoma[tiab] OR carcinomas[tiab] OR Neoplasms[tiab] OR Neoplasms[mesh] OR Neoplasm[tiab] OR tumour[tiab] OR tumours[tiab] OR tumor[tiab] OR tumors[tiab] OR sarcoma[tiab] OR sarcomas[tiab]))) AND (stag*[tiab] AND (IV[tiab] OR four[tiab] OR 4[tiab])) AND (EGFR tyrosine kinase inhibitor 324674 [Supplementary Concept] OR TKI[tiab] OR tyrosine kinase inhibitor[tiab] OR

Thema (Recherchedatum)	Suchstrategie
	erlotinib[Supplementary Concept] OR gefitinib[Supplementary Concept] OR BIBW 2992[Supplementary Concept] OR Ceritinib[Supplementary Concept] OR Crizotinib[Supplementary Concept] OR erlotinib[tiab] OR gefitinib[tiab] OR afatinib[tiab] OR Ceritinib[tiab] OR Crizotinib[tiab] OR vandetinib[tiab])
Erhaltungstherapie (17.06.2014)	(Lung Neoplasms[mesh] OR ((Lung[tiab] OR pulmonary[tiab] OR bronchial[tiab] OR bronchogenic[tiab] OR respiratory[tiab]) AND (cancer[tiab] OR carcinoma[tiab] OR carcinomas[tiab] OR Neoplasms[tiab] OR Neoplasms[mesh] OR Neoplasm[tiab] OR tumour[tiab] OR tumours[tiab] OR tumor[tiab] OR tumors[tiab] OR sarcoma[tiab] OR sarcomas[tiab]))) AND (stag*[tiab] AND (IV[tiab] OR four[tiab] OR 4[tiab])) AND (Maintenance Chemotherapy[mesh] OR (maintenance AND (chemotherapy[tiab] OR therapy[tiab] OR therapy[mesh] OR drug therapy[mesh] OR Cytostatic Agents[mesh]))))
Nachsorge (01.07.2014)	(Lung Neoplasms[mesh] OR ((Lung[tiab] OR pulmonary[tiab] OR bronchial[tiab] OR bronchogenic[tiab] OR respiratory[tiab]) AND (cancer[tiab] OR carcinoma[tiab] OR carcinomas[tiab] OR Neoplasms[tiab] OR Neoplasms[mesh] OR Neoplasm[tiab] OR tumour[tiab] OR tumours[tiab] OR tumor[tiab] OR tumors[tiab] OR sarcoma[tiab] OR sarcomas[tiab]))) AND (stag*[tiab] AND (IV[tiab] OR four[tiab] OR 4[tiab])) AND (Aftercare[mesh] OR aftercare[tiab] OR after care [tiab] OR aftertreatment[tiab] OR follow-up[ti] OR follow-up intervals [tiab])
Anti VEGF (22.07.2014)	(carcinoma, non small cell lung [mesh] OR ((Lung[tiab] OR pulmonary[tiab] OR bronchial[tiab] OR bronchogenic[tiab] OR respiratory[tiab]) AND (cancer[tiab] OR carcinoma[tiab] OR carcinomas[tiab] OR Neoplasms[tiab] OR Neoplasms[mesh] OR Neoplasm[tiab] OR tumour[tiab] OR tumours[tiab] OR tumor[tiab] OR tumors[tiab] OR sarcoma[tiab] OR sarcomas[tiab]) AND (non Oat [tiab] OR non small[tiab])) AND (stag*[tiab] AND (IV[tiab] OR four[tiab] OR 4[tiab]))) AND (((Vascular Endothelial Growth Factor A[mesh] OR Vascular Endothelial Growth Factor [tiab] OR VEGF[tiab]) AND (therapy[mesh] OR drug therapy[mesh] OR chemotherapy[mesh] OR Antineoplastic Agents[mesh])) OR (bevacizumab[Supplementary Concept] OR bevacizumab [tiab]OR avastin[tiab] OR vandetanib[tiab] OR vandetanib[Supplementary Concept] OR caprelsa[tiab] OR sorafenib[tiab] OR sorafenib[Supplementary Concept]OR nexavar [tiab] OR caprelsa[tiab] OR sunitinib [tiab] OR sunitinib [Supplementary Concept]OR sutent [tiab] OR ramucirumab [tiab] OR ramucirumab[Supplementary Concept]))
Oligometastatic disease (29.10.2014)	(carcinoma, non small cell lung [mesh] OR ((Lung[tiab] OR pulmonary[tiab] OR bronchial[tiab] OR bronchogenic[tiab] OR respiratory[tiab]) AND (cancer[tiab] OR carcinoma[tiab] OR carcinomas[tiab] OR Neoplasms[tiab] OR Neoplasms[mesh] OR Neoplasm[tiab] OR tumour[tiab] OR tumours[tiab] OR tumor[tiab] OR tumors[tiab] OR sarcoma[tiab] OR sarcomas[tiab]) AND (non Oat [tiab] OR non small[tiab]))) AND (oligometastatic[tiab] OR OMD[tiab] OR solitary metastas*[tiab] OR isolated metastas*[tiab])

Thema (Recherchedatum)	Suchstrategie
Therapie bei PSII Patienten (23.07.2014)	(Lung Neoplasms[mesh] OR ((Lung[tiab] OR pulmonary[tiab] OR bronchial[tiab] OR bronchogenic[tiab] OR respiratory[tiab]) AND (cancer[tiab] OR carcinoma[tiab] OR carcinomas[tiab] OR Neoplasms[tiab] OR Neoplasms[mesh] OR Neoplasm[tiab] OR tumour[tiab] OR tumours[tiab] OR tumor[tiab] OR tumors[tiab] OR sarcoma[tiab] OR sarcomas[tiab])) AND (PS2[tiab] OR PSII[tiab] OR PS3[tiab] OR PSIII [tiab] OR PS4[tiab] OR PSIV [tiab] OR performance status II[tiab] OR performance status III[tiab] OR performance status IV[tiab] OR performance status 2[tiab] OR performance status 3[tiab] OR performance status 4[tiab]) AND (chemotherapy[tiab] OR therapy[tiab] OR therapy[mesh] OR drug therapy[mesh] OR Cytostatic Agents[mesh] OR Carbo-MVE protocol [Supplementary Concept] OR Antineoplastic Combined Chemotherapy Protocols[mesh]))
Palliative Maßnahmen	
Strukturierte palliative Maßnahmen (29.09.2014)	(Lung Neoplasms[mesh] OR ((Lung[tiab] OR pulmonary[tiab] OR bronchial[tiab] OR bronchogenic[tiab] OR respiratory[tiab]) AND (cancer[tiab] OR carcinoma[tiab] OR carcinomas[tiab] OR Neoplasms[tiab] OR Neoplasms[mesh] OR Neoplasm[tiab] OR tumour[tiab] OR tumours[tiab] OR tumor[tiab] OR tumors[tiab] OR sarcoma[tiab] OR sarcomas[tiab]))) AND (“Palliative Care”[mesh] OR Hospice and Palliative Care Nursing[mesh] OR Terminal Care[mesh] OR Hospice Care[mesh] OR (palliative[tiab] OR "end of life" [tiab] OR terminal[tiab] AND (Progressive Patient Care[mesh] OR care[tiab] OR therapy[tiab] OR therapy[mesh] OR "Nursing Care"[mesh] OR "Patient Care Planning"[mesh] OR medicine[tiab] OR team[tiab] OR “patient care team”[mesh]))) AND (((Randomized Controlled Trial [PTyp] OR Controlled Clinical Trial [PTyp] OR randomized [TiAb] OR randomised [TiAb] OR placebo [TiAb] OR clinical trials as topic [MeSH] OR randomly [TiAb] OR trial [TiAb]) NOT (animals [MeSH Terms] NOT humans [MeSH Terms])) OR ("Meta-Analysis" [Publication Type] OR "Meta-Analysis as Topic" [Mesh] OR meta analy* [TIAB] OR metaanaly* [TIAB] OR systematic review* [TIAB] OR systematic literature review* [TIAB] OR "Review Literature as Topic" [Mesh] OR ((selection criteria [TIAB] OR inclusion criteria [TIAB] OR data extraction [TIAB]) AND review [Publication Type])) NOT ("Comment" [Publication Type] OR "Letter" [Publication Type] OR "Editorial" [Publication Type]) AND (english [la] OR german [la]))

Die in den Datenbanken und über die Handrecherche identifizierte Literatur wurde von zwei Gutachtern unabhängig selektiert. Zunächst wurden die Abstracts sämtlicher in den Datenbanken erzielten Treffer auf Erfüllung der a-priori definierten Einschlusskriterien hin geprüft und anschließend, bei potentieller Relevanz die Volltexte geprüft. Unstimmigkeiten wurden bis zum Konsens diskutiert. Für die Bereiche Therapie und Pathologie wurde bezüglich des Studientyps hierarchisch vorgegangen. D.h. es wurde für die jeweilige PICO-Fragestellung zunächst auf das höchste Evidenzlevel zurückgegriffen. Systematische Reviews wurden ggf. um aktuelle Studien ergänzt, die noch nicht in dem systematischen Review eingeschlossen waren.

5.2.2. Ergebnisse der primären Literaturrecherche

Durch die Recherche in den Datenbanken und durch Prüfung der Referenzen wurden insgesamt 5443 Treffer identifiziert. Bei 345 Publikationen wurden die Volltexte auf Erfüllung der Einschlusskriterien geprüft. 96 Publikationen erfüllten alle Einschlusskriterien. Der Selektionsprozess ist in Abbildung 1 dargestellt. Die Ergebnisse der Studienselektion für die einzelnen Themen sind in Box 1 dargestellt.

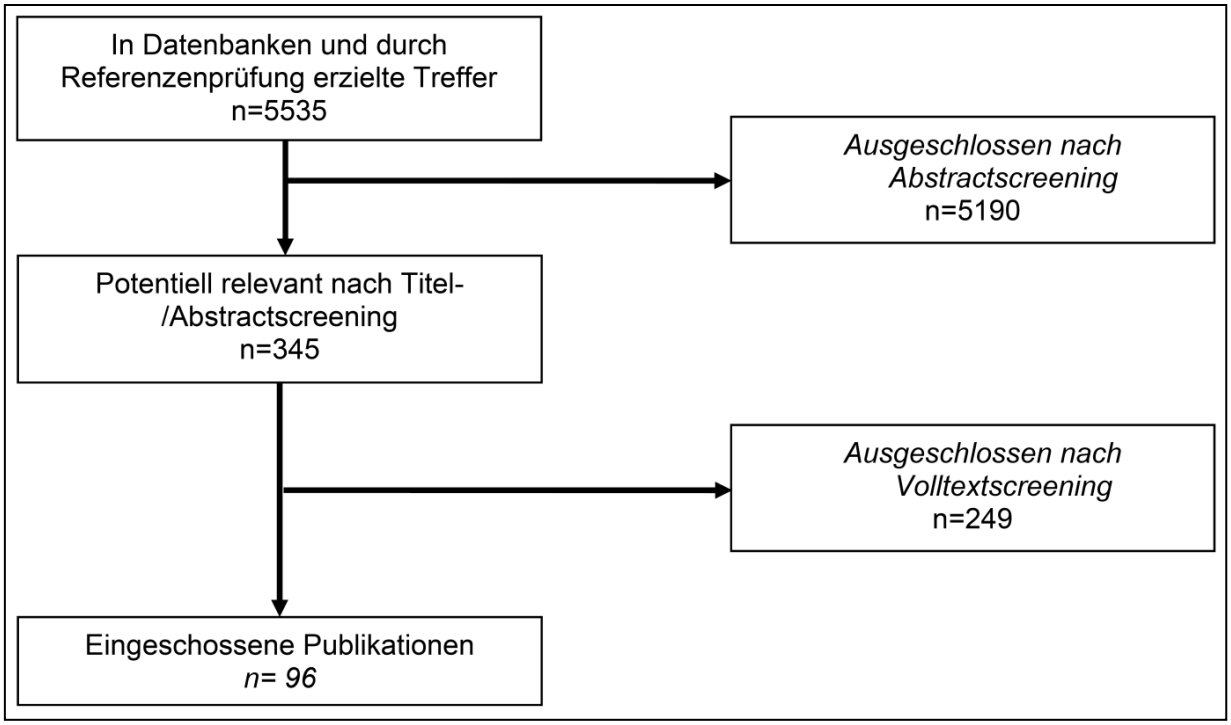


Abbildung 1: Flow-Chart zur Primärrecherche

Identifiziert durch Recherche
Screening: n=438

Pathologie
Immunhistochemische Marker: n=1312
Molekular-pathologische Testung: n=431
Aufarbeitung LK: n=5
Prognostische Faktoren: n=602
Resektionsränder: n=169

Therapie
Molekular stratifiziert Therapie: n=478
Erhaltungstherapie: n=200
Nachsorge: n=135
Anti VEGF: n=165
OMD: n=107
Denosumab: n=37
PSII: n=302

Palliativ: n=1154

Geprüfte Volltextpublikationen

Screening: n=26

Pathologie
Immunhistochemische Marker: n=99
Molekular-pathologische Testung: n=52
Aufarbeitung LK: n=0
Prognostische Faktoren: n=15
Resektionsränder: n=9

Therapie
Molekular stratifiziert Therapie: n=36
Erhaltungstherapie: n=12
Nachsorge: n=1
Anti VEGF: n=33
OMD: n=7
Denosumab: n=1
PSII: n=25

Palliativ: n=29

Eingeschlossene Studien

Screening: n=9

Pathologie (37 [79])
Molekular-pathologische Testung: n=22
(immunhistochemische Marker: n=42)
Aufarbeitung LK: n=0
Prognostische Faktoren: n=8
Resektionsränder: n=7

Therapie (n=45)
Molekular stratifiziert Therapie: n=11
Erhaltungstherapie: n=6
Nachsorge: n=0
Anti VEGF: n=17
OMD: n=2
Denosumab: n=0
PSII: n=8

Palliativ: n=5

Abbildung 2: Ergebnisse der Literaturrecherche nach Themengebieten

5.2.3. Studienbewertung

5.2.3.1. Einteilung des Studientyps und Vergabe des Level of Evidence

Die Klassifikation des Studientyps erfolgt entsprechend des Algorithmus von Hartling et al [1]. Das „Level of Evidence“ (LoE) wurde entsprechend der Vorgaben des Oxford

Centre for Evidence-Based Medicine zugeteilt [2] (siehe Kapitel 12.6). Die Basis des Level of Evidence bildet dabei der Studientyp. Darüber hinaus wurde das Risk of Bias und die Präzision der Effektschätzer berücksichtigt.

Bei prognostischen Studien bei denen als Studientyp Fallserien oder prognostische Kohortenstudien mit schlechter Qualität (d.h. unter anderem keine Durchführung einer Adjustierung für Confounder) zugrunde lagen, wurde das Level of Evidence 4 vergeben.

5.2.3.2. Studienbewertung (systematische Verzerrung)

Für die Studienbewertung von Primärstudien zu Interventionen wurde das Cochrane Risk of Bias Tool verwendet [3] (siehe Kapitel 12.7). Jede Frage wurde mit „hohem Risiko für Verzerrung“, „niedrigem Risiko für Verzerrung“, oder „unklarem Risiko für Verzerrung“ bewertet. Da auf Grund der Breite der Fragestellung eine a-priori Definition des Items „other source of bias“ nicht möglich erschien, wurde falls dieses Item nicht mit „low risk of bias“ bewertet wurde, der Grund hierfür angegeben. Studien die die Effektivität einer diagnostischen Maßnahme bzgl. klinischer und/ oder patientenrelevanter Endpunkte erfassen, wurden ebenfalls mit dem Cochrane Risk of Bias Tool bewertet.

Studien zur diagnostischen Güte (Endpunkt falsch positive) wurden mit dem Quality Assessment for Diagnostic Accuracy (QUADAS-II) Instrument bewertet [4] (siehe Kapitel 12.8). Jede Frage wurde mit „hohes Risiko für Verzerrung“, „niedriges Risiko für Verzerrung“, oder „unklares Risiko für Verzerrung“ bewertet. Falls in Studien zu Diagnosemaßnahmen sowohl die diagnostischen Güte als auch klinische und/oder patientenrelevanter Endpunkte erfasst wurden, wurden beide Instrumente angewendet (Cochrane Risk of Bias Tool und QUADAS-II).

Das Risiko für systematische Verzerrung von Studien zur prognostischen Güte wurde mit dem Quality in Prognosis Studies (QUIPS) Instrument bewertet [5] (Kapitel 12.9). Jedes Item wurde mit „hohem Risiko für Verzerrung“, „niedrigem Risiko für Verzerrung“, „moderatem Risiko für Verzerrung“, „unklarem Risiko für Verzerrung“ oder „nicht anwendbar“ bewertet.

Systematische Reviews wurden mit „A measurement tool for the assessment of multiple systematic reviews” (AMSTAR) bewertet [6] (siehe Kapitel 12.10). Die einzelnen Fragen wurden mit „ja“, „nein“, „nicht zu beantworten“ und „nicht anwendbar“ beantwortet.

Die Bewertung der Gefahr für systematische Verzerrung bzw. methodologische Qualität wurde unabhängig von zwei Gutachtern vorgenommen. Jegliche Diskrepanz wurde bis zum Konsens diskutiert.

5.2.4. Datenextraktion in Evidenztabellen

Die Daten der eingeschlossenen identifizierten Studien wurden in Evidenztabellen extrahiert. Diese sind in Kapitel 12.2 aufgeführt.

Die gesamte Datenextraktion wurde von einem Gutachter vorgenommen und zur Verifizierung von einem zweiten Gutachter kontrolliert. Jegliche Differenz wurde bis zum Konsens diskutiert. Mehrere Publikationen die auf derselben Studie bzw. demselben Studienkollektiv basierten wurden zusammengeführt (z.B. Subgruppenanalysen, weitere Endpunkte). Veröffentlichungen von mehreren Studien in einer Publikation wurden separat extrahiert.

Aufgrund der sehr hohen Trefferzahlen musste angesichts der begrenzten Ressourcen auf eine Datenextraktion der Publikation zum Thema immunhistochemische Marker verzichtet werden.

5.2.4.1. Primärstudien

Es wurden die folgenden Daten in standardisierten vorab getesteten Tabellen extrahiert:

- Ein-/Ausschlusskriterien: Alle demografische und klinische Ein-/Ausschlusskriterien wurden extrahiert. Formale Einschlusskriterien wurden nicht berücksichtigt (z.B. Einverständniserklärung).
- Region: Land in dem die Studie durchgeführt wurde.
- Prognosestudien: Setting in dem die Studie durchgeführt wurde (z.B. Krankenhaus).
- Interventions-/Kontrollgruppe (Interventionsstudien): Für die Interventions-/Kontrollgruppe wurden für pharmakologische Therapien jeweils die Dosierung, die Häufigkeit der Einnahme/Anwendung, die Applikationsform, die Dauer der Anwendung und ggf. weiter relevante Informationen (z.B. Halbwertszeit, ROC) aufgeführt. Für Operationsverfahren (z.B. Resektion) und apparative Maßnahmen (z.B. Low-Dose-CT) wurden Angaben zur Durchführung und technische Angaben extrahiert.
- Studien zur diagnostischen Güte (Index-/Referenztest): Beschreibung des Index- und Referenztests einschließlich Angaben zur Durchführung und Interpretation. Angaben zum Zeitintervall zwischen Index- und Referenztest.
- Prognosestudien: Angaben zur Definition/Messung des Faktors.
- Patientenfluss: Angegeben wurden die Anzahl an randomisierten/ eingeschlossenen und analysierten Patienten sowie Patienten, die die Studie vollständig abgebrochen haben (Drop-Outs + Lost-to-Follow-Ups). Falls diese nicht pro Gruppe angeben waren, sondern lediglich gruppenbezogene Angaben zum Patientenfluss bezüglich der Analyse gemacht wurden, wurde die Differenz zwischen randomisierten/ eingeschlossenen und ausgewerteten Patienten angegeben. Die Angaben beziehen sich soweit nicht anders angegeben auf den primären Endpunkt.
- Interventionsstudien: Ergebnisse zu den Endpunkten der Studien (vgl. PICOS-Tabellen). Die Ergebnisse wurden, soweit nicht anders angegeben, für die Intention-to-Treat-Population angegeben.
- Studien zur diagnostischen Güte: Es wurden die falsch positiven Befunde (1 minus Sensitivität und 1 minus positiv prädiktiver Wert) einschließlich zugehöriger Angaben zur statistischen Sicherheit (Konfidenzintervall oder p-Wert), extrahiert.
- Prognosestudien: Für kategoriale Variablen wurden die relativen Effektmaße (Odds Ratio, relatives Risiko, Hazard Ratio) und für metrische Variablen die Effektdifferenzen angegeben. Zu allen Maßen wurde die statistische Signifikanz mit berichtet (Konfidenzintervall oder p-Wert).

Für Ereignisse wurde für jeden der Endpunkte die Rate (%) oder für seltene Ereignisse die Anzahl je Gruppe extrahiert und falls angegeben, die relativen Effektmaße (Odds Ratio, Relatives Risiko, Hazard Ratio). Die relativen Effektmaße wurden vereinheitlicht, so dass die Kontrollgruppe immer die Referenzkategorie darstellt (Nenner des Vergleichs). D.h. relative Effektmaße >1 für positive Endpunkte (z.B. Überleben) bedeuten, dass die Interventionsgruppe überlegen ist (höheres Überleben in der Interventionsgruppe) und für negative Endpunkte (z.B. Mortalität), dass die Kontrollgruppe unterlegen ist (höhere Mortalität in der Interventionsgruppe). Vice versa gilt der Zusammenhang für Effektmaße <1. Die Ergebnisse wurden zu diesem Zweck ggf. umgepoolt. Die statistische Signifikanz wurde mit Konfidenzintervallen oder alternativ mit p-Werten angegeben. Für kontinuierliche Variablen wurde der Mittelwert bzw. die Mittelwertdifferenz mit Konfidenzintervallen angegeben bzw. der p-Wert, falls das Konfidenzintervall nicht in den Publikationen berichtet ist. Falls kein zweiseitiger Test angewendet wurde d.h. non-inferiority, superiority, ist dies in Klammern hinter dem p-Wert vermerkt einschließlich non-inferiority/superiority Margin. Für adjustierte Analysen wurden die Adjustierungsfaktoren berichtet. Bei mehreren Erhebungszeitpunkten wurde, mit Ausnahme der primären Endpunkte auf den letzten Follow-up zurückgegriffen, vorausgesetzt es handelt sich um eine kumulative Betrachtung aller Ereignisse. Falls Behandlungsphase und Follow-up nur separat betrachtet worden sind, wurden die Ergebnisse jeweils für die einzelne Periode angegeben. Für jeden Endpunkt wurde der Erhebungszeitpunkt (nach Randomisierung) bzw. die Dauer des Follow-ups angegeben. Angaben zu unerwünschten Ereignissen (z.B. Toxizität) wurden deskriptiv dargestellt. Die Darstellung erfolgt soweit nicht anders angegeben entsprechend der As-Treated-Population.

Ergebnisse zu Subgruppenanalysen wurden nur extrahiert, wenn diese die oben genannten Kriterien für Subgruppen erfüllten und sich auf grundlegende Abweichungen in der Therapie bezogen.

Für patientenberichtete Endpunkte wurden Angaben zur Messung des Endpunktes gemacht (z.B. Lebensqualität).

5.2.4.2. Systematische Reviews

Die Datenextraktionen für die systematischen Reviews umfassen Angaben zu den Ein- und Ausschlusskriterien für die Studienauswahl, den Recherchezeitraum sowie Angaben zur Intervention und Kontrolle bzw. dem Index und Referenztest oder dem prognostischen Faktor (siehe oben). Für die gepoolten Ergebnisse (Metaanalysen) wurden das relative Effektmaß oder die (standardisierte) mittlere Differenz extrahiert. Des Weiteren wurde für jeden Vergleich die Heterogenität (I^2, Q) und die Anzahl an einbezogenen Studien (N) und Patienten angegeben (n). Falls keine Metaanalyse durchgeführt wurden ist, wurden die Ergebnisse für die einzelnen Studien extrahiert. Zudem wurden die Ergebnisse mittels modified Vote-Counting zusammengefasst. Modified-Vote-Counting umfasst die Angabe der Effektrichtung, die Angabe der Anzahl an Vergleichen die diese Effektrichtung zeigen, die Angabe der Anzahl an statistisch signifikanten Vergleichen, die diese Effektrichtung zeigen und die Anzahl an Vergleichen/ einbezogenen Studien insgesamt für den jeweiligen Endpunkt.

6. Formulierung der Empfehlungen und formale Konsensusfindung

In der Leitlinie wird zu allen Empfehlungen zusätzlich die Stärke der Empfehlung (Empfehlungsgrad) ausgewiesen.

Hinsichtlich der Stärke der aktualisierten Empfehlung (gekennzeichnet mit „2018“) werden in der Leitlinie drei Empfehlungsgrade unterschieden (A/B/0), die sich auch in der Formulierung der Empfehlungen widerspiegeln. Für die Empfehlungen, die nicht im Rahmen der Aktualsierung bearbeitet wurden (gekennzeichnet mit „2010“) gelten weiterhin die Empfehlungsgraduierung der Version aus 2010. Diese sieht vier Empfehlungsgrade (A/B/C/D) vor, die in Kapitel 2.3.2 der Langversion erläutert wird.

Für die Ableitung der Empfehlungsstärken galt das in Kapitel 6.1 dargestellte Vorgehen entsprechend dem AWMF-Regelwerk [7].

Die Empfehlungen inklusive der Empfehlungsstärken wurden von der Leitliniengruppe unter Nutzung formaler Konsensverfahren formuliert. Dies waren maßgeblich Konsensuskonferenzen, die durch AWMF-zertifizierte Leitlinienberater moderiert wurden sowie Online-Konsentierungen mittels DELPHI-Abstimmungen (siehe Tabelle 5). Bei den Online-Abstimmungen wurden die vorgeschlagenen Empfehlungen jeweils in der ersten Abstimmungsrunde angenommen. Lediglich bzgl. der immunhistochemischen Untersuchung auf PD-L1-Expression erfolgte eine Neuabstimmung aufgrund eines Verbesserungsvorschlags (‚parallel zur molekularpathologischen Testung‘ und starker Empfehlungsgrad).

Empfehlungen und Statement mussten ein Konsens von mehr als 75 % erreichen, um angenommen zu werden.

Der Konsensusprozess während der Konferenz fand wie folgt statt:

- Vorstellung der vorgeschlagenen Empfehlung inkl. des Hintergrundes ihrer Entwicklung im Rahmen der AGs, der Evidenzgrundlage und der Begründung des Empfehlungsgrades durch die jeweiligen AG-Leiter/Fachexperten;
- Rückfragen und Diskussion durch das Plenum mit ggf. Einbringen von neuen Vorschlägen bzw. Änderungen;
- Abstimmung im anonymen Verfahren mittels TED-Systems;
- Bei fehlendem Konsens: Fortführung der Diskussion und erneute Abstimmung.

Die Protokolle der Konsensuskonferenzen sowie die Ergebnisse der Online-Abstimmungen können auf Anfrage beim OL-Office eingesehen werden.

Zur Vorbereitung der Konsensuskonferenzen wurden Online-Vorabstimmungen (über www.surveymonkey.de) durchgeführt. Die Abstimmungen bei den Konsensuskonferenzen erfolgten unter Verwendung eines elektronischen Abstimmungssystems (TED-System), um ein anonymisiertes Abstimmungensverhalten zu gewährleisten.

Die Abfolge der Konsensverfahren ist in Tabelle 5 dargestellt.

Tabelle 5: Ablauf der Konsensfindungsprozesse

Prozess	Datum/ Zeitraum	Themen
Kick-off	01.07.2013	Vorstellung der Themen für die Aktualisierung Vorstellung der anstehenden Prozesse (Vorgehen bei der Erstellung einer S3-Leitlinie, Interessenkonfliktmanagment, externe Literaturrecherche, Ableitung von Qualitätsindikatoren, Erstellen einer Patientenleitlinie) Einteilung in Steuergruppe und Arbeitsgruppen (AGs). Weitere Organisation der Formulierung PICO-Fragen für die externe Recherche
Treffen der Steuergruppe und AG-Sprecher	18.11.2013	Konkretisierung der Schlüsselfragen nach dem PICO-Schema für die externe Literaturrecherche.
Telefonkonferenz der Steuergruppe	22. 01. 2014	Priorisieruing der Schlüsselfragen zur Einholung einer Kostenkalkulation für die externe Literaturrecherche
Treffen der Steuergruppe und AG-Sprecher	13.07.2015	Sichtung der Ergebnisse der Literaturrecherche. Formulierung von Überarbeitungs/Ergänzungsvorschläge für die Recherche Definition von Arbeitspaketen für die AGs.
1. Konsensuskonferenz	11. 01. 2016	Früherkennung Patientenaufklärung Pathologie
2. Konsensuskonferenz	13.04.2016	Reste von Früherkennung/ Pathologie/Patientenaufklärung Palliativmedizin NSCLC IV – Erhaltungstherapie und Therapie bei Performance Status 2
3. Konsensuskonferenz	01.06.2016	Reste von Pathologie/Patientenaufklärung/Palliativmedizin NSCLC IV Therapie
Online-Nachabstimmungen	09.2016 – 07.2017	Necitumumab Erlotinib und Bevacizumab bei EGFR mutierten Patienten Immunhistochemische Untersuchung auf PD-L1-Expression Pembrolizumab Aktualisierungen im Kapitel Diagnosesicherung und Staging-Untersuchungen (T-Status)

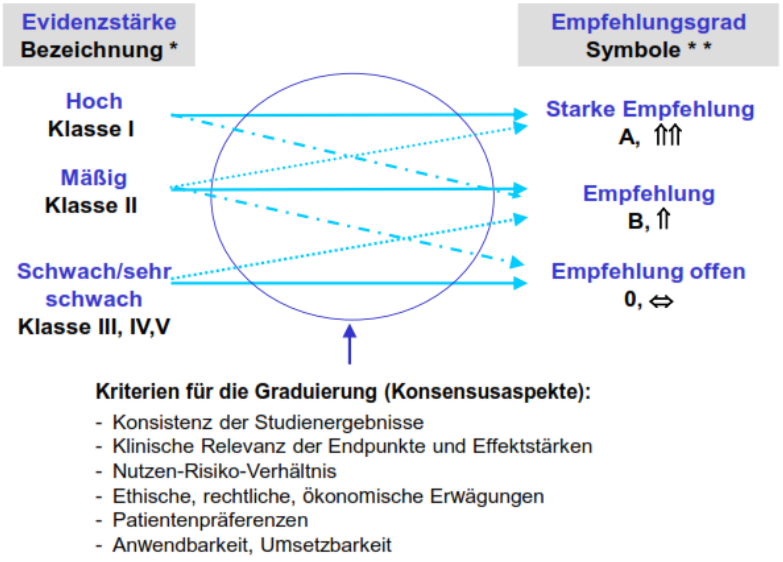
Prozess	Datum/ Zeitraum	Themen
		Endobronchiale Elektroverfahren
Öffentliche Konsultationsphase	Anfang Juni 2017 – Mitte August 2017	Alle Themen
Review durch die beteiligten Fachgesellschaften	Februar 2018	Alle Themen

6.1. Festlegung des Empfehlungsgrades

Grundsätzlich erfolgte eine Anlehnung der evidenzbasierten Empfehlungen hinsichtlich ihres Empfehlungsgrades an die Stärke der verfügbaren Evidenz (siehe Abbildung 1), d.h. ein hoher Evidenzgrad (z.B. Metaanalysen/systematische Übersichten von RCTs oder mehrere methodisch hochwertige RCTs), d.h. eine hohen Sicherheit bzgl. der Ergebnisse soll in der Regel auch zu einer starken Empfehlung (Empfehlungsgrad A, „soll“) führen.

Zusätzlich wurden weitere Kriterien bei der Wahl des Empfehlungsgrads berücksichtigt. Die folgenden Kriterien konnten zu einem Abweichen der Empfehlungsstärke nach oben oder unten führen:

- Konsistenz der Studienergebnisse, Bsp.: Die Effektschätzer der Studienergebnisse gehen in unterschiedliche Richtungen und zeigen keine einheitliche Tendenz.
- Klinische Relevanz der Endpunkte und Effektstärken, Bsp.: Es liegen zwar Studien mit Ergebnissen in eine Richtung vor, jedoch wird die Bedeutung der gewählten Endpunkte und/oder Effektstärken als nicht relevant eingeschätzt.
- Nutzen-Risiko-Verhältnis, Bsp.: Dem nachgewiesenen Nutzen einer Intervention steht in relevanter Schadensaspekt gegenüber, der gegen eine uneingeschränkte Empfehlung spricht.
- Ethische Verpflichtungen, Bsp.: Downgrading: Aus ethischen Gründen kann eine Intervention mit nachgewiesenem Nutzen nicht uneingeschränkt angeboten werden. Upgrading: Starke Empfehlung auf Basis von z.B. Fall-Kontroll-Studien, da aus ethischen Gründen ein RCT nicht durchführbar ist.
- Patientenpräferenzen, Bsp.: Eine Intervention mit nachgewiesenem Nutzen wird nicht stark empfohlen, da sie von den Patienten als belastend oder nicht praktikabel abgelehnt wird.
- Anwendbarkeit, Umsetzbarkeit in der Versorgung, Bsp.: Eine Intervention mit nachgewiesenen positiven Effekten kann nicht empfohlen werden, weil sie im regionalen Versorgungssystem aus strukturellen Gründen nicht angeboten werden kann



*: blau = Evidenzstärke nach GRADE bzgl. des gesamten ‚body of evidence', schwarz = Evidenzklassifikation bzgl. Einzelstudien, z.B. nach Oxford;
**: Empfehlungsgraduierung im Programm für Nationale Versorgungsleitlinien. Die Empfehlungen werden nach Möglichkeit analog formuliert: Starke Empfehlung: „soll"; (abgeschwächte) Empfehlung: „sollte"; Negativ-Empfehlungen werden entweder rein sprachlich ausgedrückt („nicht" / „kann verzichtet werden") bei gleichen Symbolen oder sprachlich mit zusätzlich nach unten gerichteten Pfeilen; Offene Empfehlungen drücken eine Handlungsoption in Unsicherheit aus („kann erwogen werden" / „kann verzichtet werden").
Quelle: modifiziert AWMF-Regelwerk [7]

7. Ableitung der Qualitätsindikatoren

Im Rahmen des Leitlinienprogramms Onkologie werden Qualitätsindikatoren in einem standardisierten Prozess aus den Empfehlungen der Leitlinien abgeleitet. Die detaillierte Beschreibung der Methodik findet sich auf der Homepage des Leitlinienprogramms Onkologie [8].

Die Generierung der Qualitätsindikatoren wurde in folgenden Schritten durchgeführt:

7.1. Bestandsaufnahme

Es erfolgte eine systematische Recherche nach existierenden Qualitätsindikatoren zum Lungenkarzinom (siehe Kapitel 12.4)

7.2. Vorbereitung Anwesenheitstreffen (Erstellung einer Primärliste potentieller QI)

Soweit möglich, wurden im Vorfeld des Anwesenheitstreffens aus den starken Empfehlungen der Leitlinien-Aktualisierung (n= 47) potentielle Indikatoren mit Definition von Zähler und Nenner abgeleitet. Damit wurden die Empfehlungen der LL-Kapitel 4.1 Früherkennung-Bildgebende Verfahren, 4.2 Früherkennung–Sputumzytologie, 5.6 Diagnostik-Pathologie, 6. Patientenaufklärung und 7.5 Stadium IV berücksichtigt. Außerdem wurden die bereits bestehenden QI der LL von 2008 aufgeführt. Diese Liste und das Dokument mit den internationalen QI wurden den Mitgliedern der AG im Vorfeld des Anwesenheitstreffens zugesandt.

7.3. Anwesenheitstreffen (Diskussion und primäre Sichtung)

Das Treffen der AG QI, die aus Mitgliedern der Leitliniengruppe, je einem Vertreter der klinischen Krebsregister, des Zertifizierungssystems und des OL bestand, fand am 21.09.2016 statt. In dem Treffen wurde den Teilnehmern der Prozessablauf der QI-Erstellung sowie das Bewertungsinstrument des OL erläutert. Außerdem wurde die unter Punkt 2 generierte Zusammenstellung aus den Empfehlungen der Leitlinie, der QI von 2008 und der nationalen/internationalen QI diskutiert und entschieden, ob aus der jeweiligen Empfehlung ein potentieller QI generiert werden könne. Folgende Ausschlusskriterien kamen bei diesem ersten Screening zur Anwendung:

Tabelle 6: Gründe für einen Ausschluss der Empfehlung aus der Liste der potentiellen QI

Nr.	1	2	3	4
Begründung	Empfehlung ist nicht operationalisierbar (Messbarkeit nicht gegeben)	Fehlender Hinweis auf Verbesserungspotential	Fehlende Verständlichkeit u/o großer Erhebungsaufwand in Verhältnis zu Nutzen	Sonstiges (mit Freitexteingabe in Liste der Empfehlungen)

Die Diskussion und primäre Sichtung der QIs ergab ein Set von 12 potentiellen QIs (9 potent. QI´s aus den neuen Empfehlungen, 3 aus dem Set der QI´s von 2008). Bei der primären Sichtung der starken Empfehlungen wurden weitere Maßnahmen für die Implementierung der Empfehlungen identifiziert, die zusätzlich zu den potentiellen QI

umgesetzt werden sollen und die an die verantwortlichen Mitglieder der LL-Gruppe rückgemeldet wurden (siehe Langversion der Leitlinie).

In der Sitzung zeigte sich zudem, dass die Expertise einiger Fachdisziplinen nicht ausreichend vertreten war, um die Empfehlungen und ihre Eignung für potentielle QI umfassend einschätzen zu können. Aus diesem Grund wurden nach dem Treffen die Sprecher der Arbeitsgruppen und weitere Mitglieder der LL-Gruppe erneut per mail angeschrieben und um Mithilfe gebeten. Auf die erneute Nachfrage, meldeten sich 6 weitere Mitglieder, denen in online-Telefonaten der Prozess und das Bewertungsinstrument erläutert wurden.

7.4. Bewertung:

Das vorselektierte Set der 12 potentiellen QI wurde mit dem Bewertungsinstrument des Leitlinienprogramms Onkologie mittels eines standardisierten Bogens durch das interdisziplinäre Gremium der Leitliniengruppe bewertet. Jeweils mit dem unten abgebildeten Bogen erhielten die Bewertenden seitens der Krebsregister und des Zertifizierungssystems der DKG pro Indikatorvorschlag die Informationen zur Datenverfügbarkeit. Angenommen wurden die QI, bei denen mind. 75% der Teilnehmer die Kriterien 1,2,3 und 5 mit „Ja“ und das Kriterium 4 mit „Nein“ bewertet haben. Die Auswertung dieser Abstimmungen erfolgte durch einen Methodiker, der nicht am QI-Entwicklungsprozess teilgenommen hatte.

QI-Nr.	Möglicher Qualitätsindikator		Empfehlung oder Statement	Angaben der S3-Leitlinie im Hinblick auf Qualitätsziel	
1.	Z				
	N				
				Nein	**Ja**
1.	**Kriterium:** Der Qualitätsindikator erfasst für den Patienten relevante Verbesserungspotentiale.				
2.	**Kriterium:** Der Indikator ist klar und eindeutig definiert.				
3.	**Kriterium:** Der Qualitätsindikator bezieht sich auf einen Versorgungsaspekt, der von den Leistungserbringern beeinflusst werden kann.				
4.	**Kriterium:** Gibt es Risiken zur Fehlsteuerung durch den Indikator, die nicht korrigierbar sind?				
5.	**Kriterium:** Die Daten werden beim Leistungsbringer routinemäßig dokumentiert oder eine zusätzliche Erhebung erfordert einen vertretbaren Aufwand				

Zusätzlich bestand die Möglichkeit, zu den im Folgenden genannten Kriterien Kommentare abzugeben:

	Kommentar
Risikoadjustierung Können spezifische Merkmale von Patienten z.B. Alter, Komorbidität oder Schweregrad der Erkrankung die Ausprägung des QI beeinflussen?	
Implementierungsbarrieren Gibt es Implementierungsbarrieren, die es zu beachten gilt?	

7.5. Telefonkonferenz:

Nach der schriftlichen Bewertung erfolgte am 19.12.2016 eine moderierte Telefonkonferenz, in der die Ergebnisse der Bewertung diskutiert wurden. Auf Basis der Bewertungen und der Diskussion wurden 5 neue QI und die 3 QI der LL 2008 in das Set der finalen QI aufgenommen.

Die Primärliste der potentiellen Qualitätsindikatoren inklusive der Ausschlussgründe, die o.g. Zusammenstellung der internationalen QI und die Ergebnisse der schriftlichen Bewertung sind auf Anfrage im Leitliniensekretariat oder Office des Leitlinienprogramms Onkologie erhältlich.

8. Reviewverfahren und Verabschiedung

Eine vorläufige Version der aktualisierten Leitlinie (Konsultationsfassung) konnte im Rahmen einer öffentlichen Konsultation durch die (Fach)Öffentlichkeit über einen Zeitraum von mindenstens 6 Wochen begutachtet werden. Anschließend wurden die Präsidien bzw. Vorstände alle beteiligten Fachgesellschaften\Organisationen um Prüfung und formale Zustimmung zur aktualisierten Leitlinie gebeten. Hierbei bestand ebenfalls die Möglichkeit, auf Fehler hinzuweisen und Änderungen vorzuschlagen.

Die eingegangenen Kommentare zur Konsultationsfassung wurden strukturiert erfasst anonymisiert zusammengestellt. Anschließend wurden Vorschläge zum Umgang mit den Kommentaren im Rahmen der Steuergruppe erarbeitet. Im Rahmen einer Telefonkonfernenz wurden die vorgeschlagenen Änderungen bzw. begründeten Beibehaltungen durch die gesamte Leitliniengruppe konsentiert.

In Tabelle 7 sind die eingegangenen Kommentare und der von der Leitliniengruppe beschlossene Umgang mit den Kommentaren dargelegt.

Tabelle 7: Eingegagene Kommentare zur Konsultationsfassung und deren Bewertung

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
6.6. 10 / 124	Statement 6.57: Anhand des zur Verfügung stehenden Tumorgewebes/der Tumorzellen von allen nicht kurativ behandelbaren nichtplattenepithelialen NSCLC sollen molekularpathologische Untersuchungen hin sichtlich aller therapeutisch relevanten molekularer Veränderungen (nach gegenwärtigem Stand vor Erstlinientherapie als Mindestanforderung EGFR-Mutatio-nen in den Exonen 18-21, ALK-Fusionen und ROS1-Fusionen) eingeleitet werden. Dies gilt ebenfalls für Plattenepi-thelkarzinome von Nie-Rauchern/Leichtrauchern.	Statement 6.57: Anhand des zur Verfügung stehenden Tumorgewebes/der Tumorzellen von allen nicht kurativ behandelbaren nichtplattenepithelialen NSCLC sollen molekular-pathologische Untersuchungen hinsichtlich aller therapeutisch relevanten molekularer Veränderungen (nach gegenwärtigem Stand vor Erstli-nientherapie als Mindestanforderung EGFR-Mutationen in den Exonen 18-21, ALK-Fusionen, ROS1 -Fusionen und BRAF V600 Mutationen) eingeleitet werden. Dies gilt ebenfalls für Plattenepi-thelkarzinome von Nie-Rauchern/Leichtrauchern	Siehe allgemeine Begründung zur Berücksichtigung von BRAF V600 Mutationen	Änderung angenommen
8.6.1 / 197	Empfehlungen zur molekularen Testung Anhand des zur Verfügung stehenden Tumorgewebes/der Tumorzellen von allen nicht kurativ behandelbaren nichtplattenepi-thelialen NSCLC sollen molekularpathologische Untersuchungen hinsichtlich aller therapeutisch relevanten molekularen Veränderungen (nach gegenwärtigem Stand vor Erstlinien-therapie als Mindestanforderung EGFR-Mu-tationen in den Exonen 18-21, ALK-Fusionen und ROS1-Fusionen) eingeleitet werden. Dies gilt ebenfalls für Platten-epithelkarzinome von Nie-Rauchern/Leicht-rauchern.	Empfehlungen zur molekularen Testung Anhand des zur Verfügung stehenden Tumorgewebes/der Tumorzellen von allen nicht kurativ behandelbaren nichtplattenepithelialen NSCLC sollen molekular-pathologische Untersuchungen hinsichtlich aller therapeutisch relevanten molekularen Veränderungen (nach gegenwärtigem Stand vor Erstli-nientherapie als Mindestanforderung EGFR-Mutationen in den Exonen 18-21, ALK-Fusionen und ROS1-Fusionen, BRAF V600 Mutationen) eingeleitet werden. Dies gilt ebenfalls für Plattenepi-thelkarzinome von Nie-Rauchern/Leichtrauchern	Siehe allgemeine Begründung zur Berücksichtigung von BRAF V600 Mutationen	Änderung angenommen
8.6.2.1/200	Statement 8.56: Bei Therapie-naiven Patienten im Stadium IV, welche keine the-rapierbaren Mutationen (z.B. EGFR, EML-4-ALK, ROS1) aufweisen, und welche in Gewebeproben eine PD-L1-Expression von >50 % der Tumorzel-len aufweisen, sollte	Statement 8.56: Bei Therapie-naiven Patienten im Stadium IV, welche keine the-rapierbaren Mutationen (z.B. EGFR, EML4-ALK, ROS1, BRAF V600) aufweisen, und welche in Gewebeproben eine PD-L1-Expression von >50 % der Tumorzellen aufweisen, sollte Pem-brolizumab (200	Siehe allgemeine Begründung zur Berücksichtigung von BRAF V600 Mutationen	Änderung angenommen

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
	Pembrolizumab (200 mg i.v. alle 3 Wochen) als Erstlinientherapie angeboten werden.	mg i.v. alle 3 Wochen) als Erst-linientherapie angebo-ten werden.		
8.6.8/242	Statement 8.97 Bei Patienten mit Wild-typkonfiguration für EGFR, ALK, ROS1 und Versagen auf platinba-sierte Che-motherapie sollte eine umfassende Genotypisie-rung auf bekannte Treibermuta-tionen stattfin-den, um bei dem Nachweis einer solchen eine zielgerichtete Therapie im Rahmen einer Studie oder im Off-Label-Use zu ermöglichen. Diese Analyse sollte insbesondere BRAF-V600E-Mutati-onen, HER2-Mu-tationen, MET-Amplifi-kationen, MET-Exon-14-Mutationen und RET-Fusionen beinhal-ten. Diese Analyse sollte in Zusammenar-beit mit einem sowohl in der molekularen Mul-tiplex-Diagnostik als auch in der Beurteilung der klini-schen Rele-vanz von erhobenen molekularen Be-funden erfahrenen Zentrum vorgenommen wer-den, um eine hohe Qualität der molekularen Diag-nostik und der klini-schen Empfehlung als auch – vor dem Hinter-grund der dynamischen Entwicklung – eine um-fassende Analyse auf alle potentiell thera-pierbaren Treibermuta-tionen und eine ent-sprechende Dokumen-tation zu ge-währ-leisten.	Statement 8.97 Bei Patienten mit Wild-typkonfiguration für EGFR, ALK, ROS1, BRAF V600 und Versagen auf platinba-sierte Chemotherapie sollte eine umfassende Geno-typisierung auf bekannte Treibermutationen stattfin-den, um bei dem Nachweis einer solchen eine zielge-richtete Therapie im Rahmen einer Studie oder im Off-Label-Use zu ermöglichen. Diese Analyse sollte insbesondere ~~BRAF-V600E-Mutationen,~~ HER2-Muta-tionen, MET-Amplifika-tionen, MET-Exon-14-skip-ping-Mutationen und RET-Fu-sionen beinhalten. Diese Analyse sollte in Zusam-menarbeit mit einem so-wohl in der molekularen Multiplex-Diagnostik als auch in der Beurteilung der klinischen Relevanz von erhobenen moleku-laren Befunden erfahre-nen Zent-rum vorgenom-men werden, um eine hohe Qualität der mole-kularen Diagnostik und der klinischen Emp-fehlung als auch – vor dem Hintergrund der dynami-schen Entwick-lung – eine umfassende Analyse auf alle poten-tiell therapierbaren Trei-bermutationen und eine entsprechende Doku-mentation zu gewähr-leisten.	Siehe allgemeine Begründung zur Be-rücksichtigung von BRAF V600 Mutati-onen	Änderung ange-nommen
8.6.6.1.	Crizotinib soll in der Erstlinienbehandlung ALK positiver NSCLC Patienten angeboten werden. […]	Ein für die Erstlinientherapie zugelassener ALK-Inhi-bitor (Crizotinib oder Ceritinib (oder Alectinib nach Zulassung) soll in der Erstlinienbe-handlung ALK po-sitiver NSCLC Patienten angeboten werden. Hintergrund	(A) Soria JC et al., First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. The Lancet, Bei Progress unter Therapie mit Crizotinib und fehlender Möglichkeit des Einschlusses in eine	Während der Konsultation wurde bereits eine geänderte Empfehlung konsentiert: NSCLC-Patienten mit einer ALK-

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
		Mit Crizotinib wird in der Erstlinie […] Atemnot, Schmerzen (QLQ-LC13)) gesehen [861]. Mit Ceritinib wird in der Erstlinienbehandlung ALK positiver NSCLC Patienten im Vergleich zu einer platinbasierter Stan-dardtherapie ein signifikant besseres PFS, eine höhere ORR, eine bessere Symptomreduktion und eine höhere Lebensqualität erreicht [A]. Ein Vorteil für das Gesamtüberleben konnte aufgrund des erlaubten Crossovers in der randomisierten Studie nicht gezeigt werden. In der ASCEND-4 Studie [A], einer Phase III Studie (n=376) bei Patienten mit fortgeschrittenem nicht vorbehandeltem Nicht-kleinzel-ligem Lungenkarzinom, wurde eine Behandlung mit Ceritinib-Monothera-pie (1x750 mg täglich) mit Platinbasierter Chemotherapie (Cisplatin 75mg/m2 oder Carbo-platin AUC 5,6) in Kombination mit Pemetrexed 500mg/m2 alle 3 Wochen, bis zu 6 Zyklen) verglichen. Crossover nach Chemotherapie-versagen zu einer Ceri-tinib-Behandlung war erlaubt. Das mediane PFS (primärer Endpunkt) war für Ceritinib mit 16.6 Mon. vs. 8.1 Mon. signifikant überlegen (HR 0.55). Die ORR war mit 72,5% vs. 26,7% ebenfalls deutlich überlegen. Eine Verlängerung des Ge-samtüberlebens konnte aufgrund der Cross-over-Option nicht beobachtet werden (72% der Patienten im Che-motherapiearm wurden bei Progress mit Ceritinib oder einem anderen ALK-Inhibitor behandelt). Ceritinib –spezifische Nebenwirkungen beinhalteten gastrointestinale Nebenwirkungen und asymptomatische Leberwerterhöh-ungen. Bis auf die Laborveränderungen waren schwere (CTC grade 3,4) symptomatische Nebenwirkungen alle im niedrigen einstelligen Prozentbereich	Studie mit einem Nächstgenerations-ROS1-Inhibitor sollte, abhängig vom Allgemeinzustand des Patienten, entweder mit einer platinbasierten Kombinations-chemotherapie oder einer Monotherapie angeboten werden (siehe Kapitel Chemotherapie). 2017; 4:917-929. http://dx.doi.org/10.1016/S0140-6736(17)30123-X (B) Cho et al., ASCENDE 8: A Randomized Phase 1 Study of Ceritinib 450 mg or 600 mg Taken With a Low-Fat Meal Versus 750 mg in Fasted State in Patients With Anaplastic Lymphoma Kinase (ALK)-Rearranged Metastatic Non–Small Cell Lung Cancer, J Thoracic Oncology, 2017, ePub ahead of print. http://dx.doi.org/10.1016/j.jtho.2017.07.005 Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, Ou SHI, Perol M, Dziadziuszko R, Rosell R, Zeaiter A, Mitry E, Golding S, Balas B, Noe J, Morcos PN, Mok T. Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer. NEJM 2017 DOI: 10.1056/NEJMoa1704795 Gadgeel S, Peters S, Mok T, Shaw AT, Kim DW, Ou SHI, Perol M, Dziadziuszko R, Ahn JS, Rosell R, Zeaiter A,Mitry E, Nueesch E, Balas B, Camidge DR. Alectinib vs crizotinib in	Translokation soll in der Erstlinientherapie ein ALK-Inhibitor angeboten werden.

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
		(Häufigkeit Grad 3,4 NW: Erhöhte Transaminasen 17-31%, Diarr-hoe 5%, Erbrechen 5%) Lebensqualitätsunter-suchungen ergaben einen hochsignifikanten Vorteil für Ceritinib. Le-bensqualitätsanalysen wurden mit den LCSS, QLQ-C30-, QLQ-LC13 und EQ-5D Scores gemessen. Die Verbesserung der LQ, ausgehend vom Therapiebe-ginn, war unter Ceritinib signifikant besser. Auch die Verbesserung physikalischer, sozialer und emotionaler Funktions-bereiche war, ausgehend vom Therapiebe-ginn, unter Ceritinib signifikant besser. Ein signifikanter Vorteil wurde auch für die Symptom-kontrolle (Dyspnoe, Husten, Atemnot, Schmerzen (QLQ-LC13)) gesehen. Nur in den Bereichen die mit gastrointestinalen Beschwerden verknüpft waren, zeigte sich eine Verschlechterung für Ceritinib [A]. Gastrointestinale Nebenwirkungen einer Ceritinib Therapie lassen sich durch Einnahme einer verringerten Dosis von 450 mg zusammen mit einer leichten Mahlzeit reduzieren [B]. Die Bioverfügbarkeit von Ceritinib steigt durch die gleichzeitige Nahrungsaufnahme an. Die Dosierung „450 mg mit einer leichten Mahlzeit“ ist bioäquivalent zu einer Dosis von „750 mg auf nüchternen Magen“ [B]. Ein head-to head Vergleich zwischen Crizotinib und Ceritinib liegt nicht vor. Alectinib wurde in einer Dosierung von 2x600 mg p.o. gegen Crizotinib 2x250 mg p.o. in der ALEX Studie hinsichtlich des Untersucher-bestimmten PFS als primären Endpunkt geprüft. Weitere Endpunkte waren durch ein unabhängiges Komitee bestimmtes PFS, Zeit bis zur ZNS-Progression, Ansprechrate und Überleben.Mit einer medianen Follow-up Zeit von 17,6 Monaten (Crizotinib) und 18,6 Monaten	treatment-naïve *ALK*+ NSCLC: CNS efficacy results from the ALEX study. ESMO 2017	

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
		(Alectinib) war das Prüfer-bestimmte PFS unter Alectinib signifikant günstiger als mit Crizotinib (12 Monate Ereignisfreies Überleben 48,7 vs. 68,4%, HR 0,47 [95% CI, 0,34 bis 0,65]; P<0,001); das mediane Progressionsfreie Überleben war mit Alectinib nicht erreicht (95% CI, 17,7 Monate bis nicht bestimmbar), das mediane Progressions-freie Überleben mit Crizotinib betrug 11,1 Monate (95% CI, 9,1 bis 13,1 Monate). Das durch ein unabhängiges Komitee bestimmte PFS betrug 25,7 Monate [95% CI, 19,9 bis nicht bestimmbar) vs. 10,4 Monate [95% CI, 7,7 bis 14,6 Monate] mit einer HR für Progression oder Tod von 0,50 [95% CI, 0,36 bis 0,70]; P<0,001.) Das Risiko für eine ZNS Progression betrug 12% im Alectinib Arm vs. 45% im Crizotinib Arm mit einer HR von 0,16; 95% CI, 0,10 bis 0,28; P<0,001).Die Ansprechrate betrug für Alectiinib 82,9%; 95% CI, 76,0 bis 88,5) und für Crizotinib 75,5%; 95% CI, 67,8 bis 82,1 %)(P = 0,09Pt mit ausmessbaren ZNS Metastasen hattetn eine Ansprechrate im ZNS von 17/21 (81%, 95% CI, 58 to 95%) im Alectinib Arm) und von 11/ 22 (50%) im Crizotinib Arm (95% CI, 28 to 72%). Eine intrakranielle komplette Remission erreichten 8/21 Patienten unter Alectinib (38%) und 1/22 Patienten (5%) mit Crizotinib. Die mediane Dauer des Ansprechens im ZNS betrug 17,3 Monate (95% CI, 14,8 bis nicht bestimmbar) und 5,5 Monate (95% CI,2,1 bis 17,3) für Alectinib bzw. Crizotinib. In einer Auswertung, die beim ESMO 2017 vorgestellt wurde, war das Risiko für Patienten mit ZNS Metastasen nach einem Jahr im ZNS einen Progress zu erleiden 58,3% für Crizotinib und 16% für Alectinib (HR 0,18, 95% CI 0,09-0,36, p<0,0001), Für Paitenten,		

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
		die keine ZNS Metastasierung hatten bei Einschluss in die Studie war das Risiko, im ZNS einen Progress zu erleiden 31,5% für Crizotinib und 4,6% für Alectinib (HR 0,14, 95% CI 0,06-0,22, p<0,0001). Beim Datenschluss waren 35 Patienten (23%) im Alectinib Arm und 40 Patienten (26%) im Crizotinib Amr verstorben. Die 12 Monate Überlebensraten betrugen 84,3% (95% CI, 78,4 bis 90,2) für Alectinib und 82,5% (95% CI, 76,1 bis 88,9) für Crizotinib. Die HR für das OS betrug 0,76 (95% CI, 0,48 bis 1,20) und war nicht signifikant unterschiedlich, die medianen Überlebensraten waren in beiden Armen nicht erreicht). Grad 3 bis 5 unerwünschte Ereignisse waren mit Alectinib seltener alsmit Crizotinib (41% vs. 50%). Unerwünschte Ereignisse traten unter Alectinib häufiger auf als unter Crizotinib für folgende Parameter: Anämie 20% vs. 5%, Myalgie (16% vs. 2%), erhöhtes Bilirubin 15% vs. 1%, Gewichtszunahme: 10% vs. 0%), Muskel und Knochenschmerzen: 7% vs. 2%, erhöhte Lichtempfindlichkeit: 5% vs. 0%. Unerwünschte Ereignisse traten unter Crizotinib häufiger auf betreffs folgender Parameter: Übelkeit: 48% vs. 14%, Durchfall: 45% vs. 12%, Erbrechen 38% vs.7%. Unerwünschte Ereignisse, die zu einer Dosisreduktion, Unterbrechung oder Abbruch der Therapie führten waren für Alectinib bei 16%, 19%, und 11% und für Crizotinib bei 21%, 25%, und 13%.		

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
8.6.4 / 222 Empf. 8.77.	„Bei Patienten mit Nicht-Plattenepi-thelkarzinom und PDL1-Negativität sollten in die Entscheidung der Positionierung der Therapie in die Zweit- oder Drittlinie klinische Faktoren wie Rezidivzeit-punkt, Rau-cherstatus, Mutationssta-tus, Komorbiditäten, und die Verträglichkeit der Erstlinien-therapie einbezogen werden.“	„Bei Patienten mit Nicht-Plattenepi-thelkarzinom und PD-L1-Negativität sollten in die Entscheidung der Positionierung der Therapie **in** die Zweit- oder Dritt-linie klinische Faktoren wie Rezidiv-zeitpunkt und Tumordynamik, Rau-cherstatus, Muta-tionsstatus, Komorbiditäten, und die Verträglichkeit der Erstlinienthera-pie einbezogen werden.“	Neben Zeitpunkt des Rezidivs sollte auch die Tumordynamik als klinischer Faktor Berücksichtigung finden (Relevanz für Positionierung der Therapie-optionen) Reck M et al: Lancet Oncol 2014; 15: 143–55	Änderung angenommen
S. 207 Platt-enepithel-karzinom	Bei Patienten mit Plattenepithelkarzinom und einer EGFR-Expression größer 1% in der immunhistochemischen Untersuchung (IHC) kann als Erstlinientherapie Cisplatin/Gemcita-bin in Kombination mit Necitumumab angeboten werden. Nach der Erstlinientherapie kann bei fehlendem Krankheitsprogress und bei guter Verträglichkeit der Therapie eine Erhaltungstherapie mit Necitumumab angeboten werden.	Nab-Paclitaxel plus Carboplatin bei Patienten mit Plattenepithel-Histologie als valide Therapieoption mit aufnehmen	Evidenz für überlegene Wirksamkeit und Verträglichkeit von Nab-Paclitaxel plus Carboplatin versus konventionellem Paclitaxel (in Kombination mit Carbo-platin) bei Patienten mit Plattenepithel-Histologie. In der randomisierten Zulas-sungsstudie von NabPaclita-xel in Kombination mit Carbo-platin für die Erstlinientherapie des fortgeschrittenen NSCLC konnte eine signifikante Ver-besserung der Ansprechrate sowohl für das Gesamtkol-lektiv (primärer Endpunkt; 33% vs. 25%, response rate ratio [RRR]: 1.313; 95% CI, 1.082-1.593; p = 0.005) als auch für die Subgruppe der Patienten mit Plattenepithel-Histologie (43% des Studien-kollektivs) gegenüber kon-ventionellem Paclitaxel plus Carboplatin gezeigt werden (41% vs. 24 %; RRR: 1.680; 95% CI 1.271–2.221; p < 0.001).[1-2] Socinski MA, Bondarenko I, Karaseva NA et al. Weekly Nab-Paclitaxel in combination with carboplatin versus	Zu Nab-Paclitaxel wurde ein Abschnitt im Hintergrundtext ergänzt

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
			solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. J Clin Oncol 2012; 30: 2055 – 2062 Socinski MA, Okamoto I, Hon JK, Hirsh V, Dakhil SR, Page RD, Orsini J, Yamamoto N, Zhang H, Renschler MF. Safety and efficacy analysis by histology of weekly Nab-Paclitaxel in combination with carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer. Ann Oncol. 2013 Sep;24(9):2390-6. doi: 10.1093/annonc/mdt235. Epub 2013 Jul 10.	
S. 211 ECOG 2 Pa-tien-ten	Bei Patienten mit ECOG 2 ohne wesentliche Komorbiditäten sollen platinbasierte Kombinationen, z.B. Carbo/-Pacli oder Carbo/Pem angeboten werden. (…) Hintergrund Üblicherweise werden ECOG-2-Patienten von Therapiestudien ausgeschlossen, sodass die Datenlage knapp ist. (…) Für einige große Phase-III-Studien existieren Subgruppenanalysen von eingeschlossenen ECOG-2-Patienten, es gibt einige Phase II- und III–Studien und eine Metaanalyse.	Hinweis zu Phase II Daten (ABOUND PS2, Gajra et al., ASCO 2017) mit aufnehmen	Phase II Evidenz Nab-Paclitaxel plus Carboplatin bei ECOG 2 Patienten: Gajra et al.: In die ABOUND .PS2 Studie wurden ausschließlich Chemotherapie-naïve Patienten mit fortgeschrittenem oder metastasiertem NSCLC eingeschlossen, die einen ECOG PS von 2 aufwiesen (n=40). Ziel der Studie war es, Verträglichkeit und Wirksamkeit eines für dieses Patientenkollektiv modifizierten Regimen bestehend aus 4 Zyklen Nab-Paclitaxel (Tag 1 und 8, alle 3 Wochen) und Carboplatin (AUC 5, Tag 1 alle 3 Wochen) gefolgt von einer Nab-Paclitaxel Monotherapie (Tag 1 und 8, alle 3 Wochen) zu untersuchen. Fazit: Das	Zu Nab-Paclitaxel wurde ein Abschnitt im Hintergrundtext ergänzt.

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
			modifizierte Nab-Paclitaxel/Carbo-platin Regime war für ECOG PS2 Patienten gut tolerierbar. Grad 3/4 TEAEs waren vorwiegend hämatologischer Natur. Es wurde eine Gesamt-ansprechrate von 30% und eine Krankheitskontrollrate von 75 % erreicht[1]. Das Überleben war mit historischen Chemotherapie-Daten in diesem Kollektiv vergleichbar[2-5], wobei sich die Lebensqualität für die Mehrheit der Patienten stabilisierte oder verbesserte.[1] Gajra A, et al. Poster at ASCO 2017 [abstract 9058]. Safety and Efficacy of Nab-Paclitaxel–Based Therapy in Patients With Non-Small Cell Lung Cancer and Performance Status 2: Results From ABOUND.PS2 Zukin M, et al. *J Clin Oncol*. 2013;31:2849-2853. Randomized phase III trial of single-agent pemetrexed versus carboplatin and pemetrexed in patients with advanced non-small-cell lung cancer and Eastern Cooperative Oncology Group performance status of 2. Morabito A, et al. *Lung Cancer*. 2013;81:77-83. Randomized phase III trial of gemcitabine and cisplatin vs. gemcitabine alone inpatients with advanced non-small cell lung cancer and a performance status of 2:The CAPPA-2 study	

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
			Reynolds C, et al. *J Clin Oncol*. 2009;27:5808-5815. Randomized Phase III Trial of Gemcitabine-Based Chemotherapy With In Situ RRM1 and ERCC1 Protein Levels for Response Prediction in Non–Small-Cell Lung Cancer Langer CG, et al. *J Thorac Oncol*. 2008;3:623-630. Phase III Trial Comparing Paclitaxel Poliglumex (CT-2103, PPX) in Combination with Carboplatin Versus Standard Paclitaxel and Carboplatin in the Treatment of PS 2 Patients with Chemotherapy-Naï ve Advanced Non-small Cell Lung Cancer	
220	Der erste Immuncheckpoint-Inhibitor, der für die Therapie des Lungenkarzinoms zugelassen ist, ist der voll humanisierte anti-PD1 Antikörper Nivolumab. Dieser PD-1 Antikörper inhibiert die PD1-PDL1- Interaktion und aktiviert das Immunsystem gegen den Tumor.	**Eine Änderung entsprechend des derzeitigen Zulassungsstatus der Anti PD-1 Antikörper ist wünschenswert:** Für die Therapie des Lungenkarzinoms sind der voll humanisierte anti-PD1 Antikörper Nivolumab sowie der humanisierte PD-1 Antikörper Pembrolizumab zugelassen. Beide Anti PD-1 Antikörper inhibieren die PD1-PDL1-Interaktion und aktivieren das Immunsystem gegen den Tumor.	Pembrolizumab ist seit August 2016 für die Zweitlinientherapie des NSCLC zugelassen, unabhängig von der zugrundeliegenden Histologie.	Der Satz wurde geändert (war der erste …. Der zugelassen wurde…)
225	Der zweite in der Zweitlinientherapie des NSCLC geprüfte Immun-Checkpoint-Inhibitor ist der nicht voll humanisierte anti-PD1 Antikörper Pembrolizu-mab. In einer Phase-I/II-Studie wurde eine Ansprech-rate von 45,2 % bei einer >50 % i-gen Expression von PDL1 gezeigt [839]. Diese Daten wurden in einer Phase-III-Studie gegen den Kontrollarm Docetaxel überprüft [835]. In diese	Eine Streichung der entsprechend markierten Textteile sowie eine Korrektur bezüglich Lebensqualitätsdaten sowie Zulassungsstatus von Pembrolizumab sind wünschenswert: Der zweite in der Zweitlinientherapie des NSCLC geprüfte Immun-Checkpoint-Inhibitor ist der nicht voll humanisierte anti-PD1 Antikörper Pembro-lizumab.	Entsprechend der Publikation von Herbst et al. gibt es keinen wissenschaftlichen Beleg dafür, dass das Abwarten der zentralen PD-L1 Testung für den Einschluss von ca. 60% der gescreenten Patienten verantwortlich ist. Vielmehr hat sich in drei KEYNOTE Studien zu Pembrolizumab (KN001,	Der Hintergrundtext wurde überarbeitet (teilweise schon während der Konsultation)

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
	Studie wurden nur PDL1 positive Patienten eingeschlossen, das Ergebnis der zentralen Testung musste abgewartet werden, was zu einer Rekrutierung von nur etwa 60 % der gescreenten Population führte, so dass eine hohe Selektion in der Studie stattfand. 1034 Patienten wurden eingeschlossen, 345 erhielten Pembrolizumab 2 mg/kg, 346 Pembrolizumab 10 mg/kg, und 343 Docetaxel 75 mg/m2. Das mediane OS betrug 10,4 Monate mit Pembrolizumab 2 mg/kg, 12,7 Monate mit Pembroli-zumab 10 mg/kg, und 8,5 Monate mit Docetaxel. Die Unterschiede zwischen Pem-brolizumab und Docetaxel waren jeweils signifikant (HR 0,71, 2 mg /kg KG, p=0· 0008, HR 0· 61,p<0· 0001). Das mediane PFS betrug 3,9 Monate mit Pembrolizumab 2 mg/kg, 4,0 Monate mit Pembrolizumab 10 mg/kg, und 4,0 Monate mit Docetaxel, diese Unterschiede erreichten nicht das in der Studie präspezifizierte Signi-fikanzniveau von p<0,001. Bei Patienten mit einer PDL1 Expression von mehr als 50 % war das mediane OS signifikant durch Pembrolizu-mab verlängert, 14,9 (2 mg) (HR 0,54, p= 0,0002) bzw. 17,3 (HR 0,5, p<0,0001) vs. 8,2 Monate (Docetaxel). Grad 3–5 behandlungs-assoziierte Nebenwirkungen waren seltener mit Pembrolizumab als mit Docetaxel (13 % bei 2 mg/kg, 16 % bei 10 mg/kg, und 35 % bei Doceteaxel. Lebens-qualitätsdaten liegen noch nicht vor. Diese Daten führten zur Zulassung der Substanz durch die FDA bei PDL1 + Patienten, die Zulassung durch die EMA ist beantragt.	In einer Phase-I/II-Studie wurde eine Ansprech-rate von 45,2 % bei einer >50 % igen Expression von PDL1 gezeigt [839]. Diese Daten wurden in einer Phase-III-Studie gegen den Kontrollarm Docetaxel überprüft [835]. In diese Studie wurden nur PDL1 positive Patienten eingeschlossen, das Ergebnis der zentralen Testung musste abgewartet werden, was zu einer Rekrutierung von nur etwa 60 % der gescreenten Population führte, so dass eine hohe Selektion in der Studie stattfand. 1034 Patienten wurden eingeschlossen, 345 erhielten Pembrolizumab 2 mg/kg, 346 Pembrolizumab 10 mg/kg, und 343 Docetaxel 75 mg/m2. Das mediane OS betrug 10,4 Monate mit Pembrolizumab 2 mg/kg, 12,7 Monate mit Pembrolizumab 10 mg/kg, und 8,5 Monate mit Docetaxel. Die Unterschiede zwischen Pem-brolizumab und Docetaxel waren jeweils signifikant (HR 0,71, 2 mg /kg KG, p=0· 0008, HR 0· 61,p<0· 0001). Das mediane PFS betrug 3,9 Monate mit Pembrolizumab 2 mg/kg, 4,0 Monate mit Pembrolizumab 10 mg/kg, und 4,0 Monate mit Docetaxel, diese Unterschiede erreichten nicht das in der Studie präspezifizierte Signi-fikanzniveau von p<0,001. Bei Patienten mit einer PDL1 Expression von mehr als 50 % war das mediane OS signifikant durch Pembrolizu-mab verlängert, 14,9 (2 mg) (HR 0,54, p= 0,0002) bzw. 17,3 (HR 0,5, p<0,0001) vs. 8,2 Monate (Docetaxel). Grad 3–5 behandlungs-assoziierte Nebenwirkungen waren seltener mit Pembrolizumab als mit Docetaxel (13 % bei 2 mg/kg, 16 % bei 10 mg/kg, und 35 % bei Doceteaxel. Lebensqualitätsdaten liegen noch nicht vor. Diese Daten führten zur Zulassung der Substanz durch die FDA bei PDL1 + Patienten, die Zulassung durch die EMA ist beantragt. Auch die Lebens-qualitätsanalysen waren signifikant günstiger für Pembrolizumab als für Doce-taxel. Pembrolizumab ist seit	KN010, KN024) gezeigt, dass die PD-L1 Prävalenz beim NSCLC ca. 60% beträgt. Dies wurde von Aggarwal et al. auf dem ESMO 2016 publiziert. (Herbst et al.; Lancet 2016; 387: 1540–50) (Aggarwal et al., ESMO 2016, Abstract 1060P) Entsprechend der Publikation von Herbst et al. findet sich kein wissenschaftlicher Beleg dafür, dass die Dauer für die Bestimmung des PD-L1 Status zu einer wie auch immer gearteten Selektion der Patienten beigetragen hat. Die hier verwendete Formulierung ist ungenau und spiegelt eine nicht belegbare Interpretation der Daten wieder. (Herbst et al.; Lancet 2016; 387: 1540–50) Für Pembrolizumab liegen seit dem WCLC Kongress 2016 Daten zur Lebensqualität zu Gunsten Pembrolizumab im Vergleich zu Docetaxel vor. (Brahmer et al., WCLC 2016, Abstract 7153) Pembrolizumab ist seit August 2016 für die Zweitlinientherapie des NSCLC zugelassen, unabhängig von der zugrundeliegenden Histologie.	

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
		August 2016 für die Zweit-linientherapie des fortgeschrittenen NSCLC zugelassen, unabhängig von der zu-grundeliegenden Histologie. Der dritte Immuncheckpoint-Inhibitor, für den Phase III Daten vorliegen, ist der anti-PDL-1 Antikörper Atezolizumab. Dieser wurde in der OAK Studie in der Zweitlinientherapie bei Patienten mit metastasiertem NSCLC aller Histologien und unabhängig von der PDL-1 Expression gegen den Zweitlinienstandard Docetaxel überprüft. Im Gegensatz zu den Studien mit Nivolumab und Pembrolizumab wurde sowohl die Expression von PDL-1 auf Tumorzellen, aber auch auf Immunzellen untersucht und die Patienten in drei Strata eingeteilt, solche mit hoher Expression (TC3/IC3), mittlere Expression (TC1-2/IC1-2) und fehlende Expression (TC0/IC0). Von 2050 gescreenten Patienten wurden 1225 Patienten in die Studie eingeschlossen und zwischen Docetaxel 75 mg/m2 alle 3 Wochen i.v. oder Atezolizumab 1200 mg flat dose i.v. alle 3 Wochen randomisiert. Das statistische Design wurde im Laufe der Studie geändert, die Anzahl der rekrutierten Patienten von 850 auf 1225 erhöht. Der primäre Endpunkt das Überleben in der ITT Population (850 Patienten) und in der TC1/2/3 oder IC 1/2/3 Population. Das mediane Überleben wurde in der ITT Population mit 13,8 (95% CI 11,8-15,7) für Atezolizumab gegenüber 9,6 Monate (CI 8,6-11,2) für Docetaxel mit einer HR von 0,73 (95% CI 0,62-0,87), p= 0,0003 und mit einem medianen OS von 15,7 (95% CI 12,6-18,0) für Atezolizumab gegenüber 10,3 (8,8 – 12,0) für Docetaxel HR9,74 (95% CI 0,53 – 0,93) p=0,0102 in der TC1/2/3 oder IC 1/2/3 verbessert. Damit waren die koprimären	(Fachinformation Pembrolizumab/KEYTRUDA Stand Juli 2017)	

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
		Endpunkte erreicht. In der Chemotherapiegruppe erhielten 17% der Patienten nachfolgende eine Immuntherapie, in der Regel Nivolumab, in der Atezolizumab Gruppe nur 4%. In der Atezolizumabgruppe erhielten 41% nachfolgend eine Chemotherapie, im Chemotherapiearm waren es 31%. Das PFS war mit einer HR von 0,95 (95% CI 0,82 – 1,10) mit 2.8 (95% CI 2,6 – 3,0) mit Atezolizumab und 4,0 Monate mit Docetaxel (95% CI 3,3-4,2). Das mediane Überleben war in allen bezogen auf die PD-L1 Expression definierten Subgruppen verbessert, inklusive der Patienten ohne PD-L1 Expression (HR 0,75). Die deutlichste Verbesserung des medianen Überlebens bezog sich auf die 16% der Patienten mit einer TC3 oder IC3 mit einer HR von 0,41. Die einzige Gruppe, die nicht profitierte mit einer HR von 1,24 waren Patienten mit einer EGFR Mutation. Grad 3 und 4 Nebenwirkungen traten bei 37% der Patienten im Atezolizumab Arm und in 54% der Patienten im Docetaxel Arm auf. Analysen zur Lebensqualität sind bisher nicht publiziert. Die Zulassung durch die EMA erfolgte im September 2017.		
Allgemeine Begründung zur Berücksichtigung von BRAF V600 Mutationen Die Kombination aus Dabra-fenib und Trametinib ist seit März 2017 für die Therapie des fortgeschrittenen nicht-kleinzelligen Lungenkarzi-noms mit einer BRAF V600 Mutation bei Patienten der Erst- und Zweitlinie zuge-lassen. Der Zulassungstext lautet: Dabrafenib in Kombination mit Trametinib ist angezeigt zur Behandlung von er-wachsenen Patienten mit fortgeschrittenem nicht-kleinzelligen Lungenkarzi-nom mit einer BRAF-V600-Mutation (Fachinformation Tafinlar, Stand 05/2017). Trametinib in Kombination mit Dabrafenib ist angezeigt zur Behandlung von erwachsenen Patienten mit fortgeschrittenem nicht-kleinzelligen Lungenkarzi-nom mit einer BRAFV600-Mutation (Fachinformation Mekinist, Stand 03/2017).				Siehe oben

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
	Die Kombination aus Dabra-fenib und Trametinib ist somit die derzeit einzige zugelassene zielgerichtete Therapie für Patienten mit fortgeschrittenem NSCLC und BRAF V600-Mutation. Die Zulassung der Substanz beruht auf den Daten der BRF113928 Studie (https://clinicaltrials.gov/ct2/show/NCT01336634?term=NCT01336634&rank=1 aufgerufen am 12.07.2017; NCT01336634). Es handelt sich hierbei um eine nicht-randomisierte, offene Phase II Studie mit 3 Kohorten. Relevant für die Zulassung war hierbei Kohorte B (n=57) und C (n=36), in der NSCLC-Patienten mit BRAF V600E-Mutation im Stadium IV in der Erst-, bzw. in der Zweit- bis Viertlinie mit der Kombination aus Dabrafenib und Trametinib behandelt wurden. Primärer Endpunkt war jeweils die Overall Response Rate (ORR, Investigator assessed). Die Ergebnisse der Kohorte B (Zweit- bis Viertlinie) wurden 2016 in Lancet Oncology publiziert (Planchard D, et al. Dabrafenib plus Trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial Lancet Oncol. 2016 Jul; 17(7): 984 – 93.). Zusätzlich wurden zum ASCO 2017 aktuelle Daten veröffentlicht, die auch in den jeweiligen aktuellen Fachinformationen abgebildet sind (Planchard D et al. Updated Survival of Patients With Previously Treated BRAF V600E–Mutant Advanced Non-Small Cell Lung Cancer Who Received Dabrafenib or Dabrafenib Plus Trametinib in the Phase 2 BRF113928 Study Presented at ASCO Annual Meeting, Chicago, IL, June 2–6, 2017. Poster Abs #9075; Fachinformation Tafinlar, Stand 05/2017; Fachinformation Mekinist, Stand 03/2017): ORR: 66,7 % DoR (Median): 9,8 Monate PFS (Median): 10,2 Monate OS (Median): 18,2 Monate Die Ergebnisse der Kohorte C (Erstlinie) sind mit Ausnahme der ORR und des vorläufigen OS (siehe Fachinformation Tafinlar, Stand 05/2017; Fachinformation Mekinist, Stand 03/2017) bisher noch nicht publiziert: ORR: 61,1 % OS (Median): 24,6 Monate (Die Ereignisrate für die Berechnung des OS war 28 %, der festgelegte Medianwert ist folglich noch nicht ausgereift) Aus Sicht von Novartis ist durch diese Wirksamkeitsdaten eine Aufnahme von BRAF V600 in die aktuelle Leitlinie in Analogie zu den etablierten Treibern EGFR, ALK und ROS-1 (insbesondere bzgl. der Testung vor der Erstlinientherapie) gerechtfertigt. Dies auch in Anbetracht potentieller Behandlungsalternativen: Chemotherapie: Auch wenn keine direkten Vergleichsdaten zur Wirksamkeit von Dabrafenib und Trametinib vs. Chemotherapie in der Erstlinie vorhanden sind, so zeigt ein indirekter Vergleich (Registerdaten von BRAF V600 positiven NSCLC Patienten, die den Ein- und Ausschlusskriterien der BRF113928 entsprechen und mit Chemotherapie behandelt wurden, Novartis Data on File; Bestandteil des Value Dossiers für die Nutzenbewertung nach § 35a SGB V) einen Vorteil der zielgerichteten Behandlung: Para-meter Dabrafenib / Trametinib			

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
Kohorte C (n=36) Platinbasierte Chemotherapie + Drittgenerations- zytostatikum (n=26) ORR 61,1 % 38,5 % OS 24,6 (noch nicht ausgereift, siehe oben) 10,5 Checkpoint-Inhibitoren: Die Zulassung von Checkpoint-Inhibitoren in der Erstlinie ist aktuell auf Patienten mit einem PD-L1 Status von ≥50% eingeschränkt. Für Patienten mit einem PD-L1 Status von <50% wird (für den Fall, dass der BRAF Status nicht von vorneherein bekannt ist) die Chemotherapie in der Leitlinie empfohlen, die im indirekten Vergleich eine geringere Wirksamkeit gegenüber Dabrafenib und Trametinib zeigt (siehe oben). Die Erstlinienzulassung von Pembrolizumab bezieht sich, wie oben erwähnt, auf Patienten mit einem PD-L1 Status von ≥ 50%. Zudem sind Patienten in der Erstlinie ausgeschlossen, die ALK oder EGFR positive Tumormutationen aufweisen, da diese in einem geringerem Ausmaß von der Checkpoint Inhibition durch Pembrolizumab profitieren und deshalb in der Erstlinie mit Vertretern der zielgerichteten Therapie behandelt werden sollten (Fachinformation Keytruda Stand 05/2017). Zur Wirksamkeit der Therapie von NSCLC Patienten mit einer BRAF V600 Mutation mit Pembrolizumab gibt es unseres Wissens keine Daten. Somit ist aus Sicht von Novartis die Testung auf eine BRAF V600 Mutation vor Einleitung der Erstlinientherapie (auch in Gegenwart der Zulassung von Pembrolizumab) essentiell, um eine optimale Therapieentscheidung für den Patienten treffen zu können.				
2.1 / 26-27	**Kapitel 8.6: Stadium IV (ohne Indikation zur definitiven Lokaltherapie)** Auch für die Tyrosinkinase-Inhibition der Oncogene EML4-ALK und ROS1gab es therapieentscheidende Neuentwicklungen, welche den Stellenwert der bisher etablierten zytostatischen Chemotherapie stark relativierten (siehe 8.6.7.)	**Kapitel 8.6: Stadium IV (ohne Indikation zur definitiven Lokaltherapie)** Auch für die Kinase-Inhibition der Oncogene EML4-ALK, ROS1 und BRAF V600 gab es therapieentscheidende Neuentwicklungen, welche den Stellenwert der bisher etablierten zytostatischen Chemotherapie stark relativierten (siehe 8.6.7.)	**Tyrosinkinase-Inhibition** wurde in Kinase Inhibition geändert, da BRAF=Serin/Threonin-Kinase Zusätzlich: siehe allgemeine Begründung zur Berücksichtigung von BRAF V600 Mutationen	Text geändert
6.6.10 / 125	Nach Sicherung der Tumordiagnose und Abschluss der histologischen Typisierung können anhand des zur Verfügung stehenden Tumorgewebes/der Tumorzellen molekularpathologische Untersuchungen eingeleitet wer-den. Therapeutisch relevant sind derzeit EGFR-Mutationen sowie ALK- und ROS1-Translokationen bei pulmonalen Adenokarzino-men und nicht-klein-zelligen	Nach Sicherung der Tumordiagnose und Abschluss der histologischen Typisierung können anhand des zur Verfügung stehenden Tumorgewebes/der Tumorzellen molekularpathologische Untersuchungen eingeleitet werden. Therapeutisch relevant sind derzeit EGFR-Mutationen sowie ALK- und ROS1-Translokatio-nen und BRAF V600 Mutationen bei pulmonalen Adenokarzinomen und nicht-kleinzelligen	Siehe allgemeine Begründung zur Berücksichtigung von BRAF V600 Mutationen	Text geändert

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
	Karzinomen mit einer Adenokarzinom-Komponente sowie Plattenepithelkarzino-men von Nie- oder Leichtrauchern im Sta-dium IV (siehe Kapitel 8.6).	Karzinomen mit einer Adenokarzinom-Kompo-nente sowie Plattenepi-thelkarzinomen von Nie- oder Leichtrauchern im Stadium IV (siehe Kapitel 8.6).		
6.6.10/127	**Abbildung 6** Stufe 3 Molekularpathologische Untersuchungen: z.B. EGFR, ALK, ROS-1	**Abbildung 6** Stufe 3 Molekularpathologische Untersuchungen: z.B. EGFR, ALK, ROS-1, BRAF V600	Siehe allgemeine Begründung zur Berücksichtigung von BRAF V600 Mutationen	Die Abbildung wurde geändert
Zwischen 8.6.7.2 und 8.6.8/242	n/a	**Einfügen eines neuen Kapitels zwischen 8.6.7.2 und 8.6.8:** 8.6.8 Systemtherapie bei Patienten mit BRAF V600 Mutation (BRAF V600 + NSCLC) BRAF-V600-Mutationen finden sich bei ca. 1-3% der Patienten mit Ade-nokarzinom der Lunge. Eine Testung vor Beginn der Erstlinienthera-pie ist obligat (zu Methodik und Qualitätsan-forderungen der Diagnostik siehe Kapitel 6.6.10 Untersuchungen auf molekulare Ziel-strukturen). 8.6.8.1 Erstlinientherapie Vorschlag zur Konsens-findung: Bei Patienten mit BRAF V600 Mutation (BRAF V600 + NSCLC) soll in der Erst-linientherapie die Kombination aus Dabrafenib und Trametinib angeboten *werden.* Hintergrund *Siehe* allgemeine *Begründung: BRAF V600*	Siehe allgemeine Begründung zur Berücksichtigung von BRAF V600 Mutationen	Kapitel war während der Konsultation ergänzt worden
8.6.8 / 242	**Therapie bei** sonstigen **Treibermutationen beim NSCLC** Neben den aktivierenden EGFR-Mutationen und ALK- sowie ROS1-Fusionen gibt es weitere	**Therapie bei sonstigen Treibermutationen beim NSCLC** Neben den aktivierenden EGFR-Mutationen, ALK- sowie ROS1-Fusionen und BRAF V600 Mutationen gibt	Siehe allgemeine Begründung zur Berücksichtigung von BRAF V600 Mutationen	Text wurde geändert

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
	zielgerichtet behandelbare Treibermuta-tionen beim NSCLC. Die Evidenz ist hier jedoch noch nicht ausreichend, um Empfehlungen für eine Erstli-nienbehandlung auszusprechen.	es weitere zielgerichtet behandelbare Treibermutati-onen beim NSCLC. Die Evidenz ist hier jedoch noch nicht ausreichend, um Empfehlungen für eine Erstli-nienbehandlung auszusprechen.		
8.6.8 / 242-243	BRAF-V600E-Mutatio-nen finden sich bei ca. 1-3 % der Patienten mit Adenokarzinom der Lunge. In einer re-trospektiven europäi-schen Kohorten-studie von Patienten mit fort-geschrittenem BRAF-V600E positivem NSCLC (n=35) zeigte sich bei Behandlung mit verschiedenen BRAF-Inhibito-ren (Ve-murafenib 29, Dabra-fenib 9, Sorafenib 1), die in der Erstlinie (14 %) oder im Rezidiv (86 %) eingesetzt wur-den, eine Ansprechra-te (ORR) von 53 % (95% CI: 35.1-70.2) und eine Krank-heits-kontrollrate (DCR) von 85 % (95% CI: 68.9-95.0). Das PFS war 9.3 Monate, das mediane Ge-samtüber-leben 25.3 Monate (Gautschi et al., JTO 2015) [869]. In einer prospektiven Phase II Bas-ket-Studie wurden 20 Patienten mit fort-geschrit-tenem BRAF-V600E positivem NSCLC mit dem BRAF Inhibitor Vemu-rafenib behandelt. Die An-sprechrate war 42% (95% CI: 20-67), das mediane PFS 7.3 Monate [870]. In der Interimanalyse einer Phase II Studie mit dem BRAF Inhibitor Dabrafe-nib (in Europa zugelassen für die Be-handlung des V600E positiven fortgeschrit-tenen malignen Mela-noms) war die An-sprechrate bei 17 Pa-tienten mit BRAF V600E positivem rezi-diviertem NSCLC 54 % [871]. Somit deuten diese Daten da-rauf hin, dass Patienten mit einer V600E-BRAF-Mutation insbe-sondere mit der Kom-bination ei-nes BRAF- und eines MEK-Inhibi-tors, beispiels-weise mit der beim Melanom zugelassenen Kombi-nation von Dabrafenib und Trametinib, ein deutlich höheres The-rapieansprechen und	~~BRAF-V600E-Mutatio-nen finden sich bei ca. 1-3 % der Patienten mit Adenokarzinom der Lunge. In einer retro-spektiven europäischen~~ Kohortenstudie ~~von Pa-tienten mit fortgeschrit-tenem BRAF-V600E positivem NSCLC (n=35) zeigte sich bei Behandlung mit ver-schiedenen BRAF-Inhi-bitoren (Vemurafenib 29, Da-brafenib 9, Sora-fenib 1), die in der Erst-linie (14 %) oder im Re-zidiv (86 %) eingesetzt wurden, eine An-sprech-rate (ORR) von 53 % (95% CI: 35.1-70.2) und eine Krankheitskontroll-rate (DCR) von 85 % (95% CI: 68.9-95.0). Das PFS war 9.3 Monate, das mediane Gesamtüberleben 25.3 Monate (Gautschi et al., JTO 2015) [869]. In einer prospektiven Phase II Basket-Studie wurden 20 Patienten mit fortgeschrittenem BRAF-V600E positivem NSCLC mit dem BRAF Inhi-bitor Vemurafenib behandelt. Die An-sprechrate war 42% (95% CI: 20-67), das mediane PFS 7.3 Mo-nate [870]. In der Inte-rimanalyse einer Phase II Studie mit dem BRAF Inhibitor Dabrafenib (in Europa zugelas-sen für die Behandlung des V600E positiven fort-geschrittenen malignen Melanoms) war die An-sprech-rate bei 17 Pa-tienten mit BRAF V600E positivem re-zidi-viertem NSCLC 54 % [871]. Somit deuten diese Daten darauf hin, dass Patienten mit einer V600E-BRAF-Mutation insbesondere mit der Kombination ei-nes BRAF- und eines MEK-Inhibitors, beispielswei-se mit der beim Mela-nom zugelassenen Kombination von Dabra-fenib und Trametinib, ein deutlich höhe-res Therapieansprechen und eine höhere Krank-heitskontrolle haben verglichen mit einer Rezidivche-motherapie.~~	Durch Aufnahme der BRAF V600 Muta-tion in die oben genannten Kapitel entfällt die Erwähnung in diesem Kapi-tel	Text wurde ge-ändert

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
	eine höhere Krank-heitskontrolle haben verglichen mit einer Rezidivchemotherapie.			
8.6.12 / 257	**Abbildung 12**	Hinzufügen von BRAF auf der Ebene von EGFR, ALK und ROS-1	Siehe allgemeine Begründung zur Berücksichtigung von BRAF V600 Mutationen	Algorithmus wurde geändert
16	**Tabelle 35 Qualitätsindikator**	Einfügen zwischen QI4 und QI5 **Erstlinientherapie** **mit BRAF V600-spezifischer TKI-Therapie bei Patienten mit BRAF V600 positivem NSCLC im Stadium IV** *Inhalte der Tabelle analog zu EGFR, ALK, ROS-1*	Siehe allgemeine Begründung zur Berücksichtigung von BRAF V600 Mutationen	Es wurde kein QI definiert, da der Prozess zu diesem Zeiotpunkt abgeschlossen war
16	**QI 3: Erstlinientherapie mit ALK-spezifischer TKI-Therapie bei Patienten mit ALK positivem NSCLC im Stadium IV**	**7.38 Erstlinientherapie bei Chemo-therapie-naiven Patienten** Crizotinib oder Ceritinib soll in der Erstlinienbehandlung ALK positiver NSCLC Patienten angeboten werden	Siehe 8.6.6.1	Empfehlung wurde geändert, siehe oben.
8.6.6.3.	Ceritinib zeigte in einer Phase I und einer Phase II Studie in der Behandlung ALK positiver NSCLC Patienten nach Crizotinib Versagen eine hohe klinische Effektivität bei akzeptabler und handhabbarer Toxizität. ALK positive NSCLC-Patienten, die unter Crizotinib-Therapie ein Rezidiv erleiden, profitieren von einer Behandlung mit dem Nächstgenerationsinhibitor Ceritinib. In der ASCEND-1 Phase I Studie war unter 80 ALK+ NSCLC Patienten, die mit Crizotinib vorbehandelt waren, die Effektivität bei einer Dosierung von mindestens 400 mg / Tg. wie folgt: ORR 56% (95% CI, 45 – 67), PFS 6.9	Ceritinib zeigte in einer Phase III Studie in der Behandlung ALK positiver NSCLC Patienten nach Crizotinib Versagen eine hohe klinische Effektivität bei akzeptabler und handhabbarer Toxizität. ALK positive NSCLC-Patienten, die unter Crizotinib-Therapie ein Rezidiv erleiden, profitieren von einer Behandlung mit dem Nächstgenerationsinhi-bitor Ceritinib. 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	(C) Shaw AT 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, The Lancet Oncology 2017, 18:874-886. https://doi.org/10.1016/S1470-2045(17)30339-X	Der Hintergrundtexte wurde überarbeitet.

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
	Monate (95% CI, 5.3 – 8.8). Die häufigsten Nebenwirkungen waren Übelkeit (82%), Diarrhö (75%), Erbrechen (65%), Fatigue (47%) und erhöhte Transaminasen (35%) allerdings im Wesentlichen nicht schwerer Graduierung. Schwere Nebenwirkungen (Grad 3,4) beinhalteten Transaminasenerhöh-ung (21%) und Diarrhö (7%) [863, 864]. Die Effektivität von Ceritinib bei Crizotinib-vorbehandelten ALK+ NSCLC Patienten wurde in der ASCEND-2 Phase II Studie bestätigt (ORR 38.6% (95% CI, 30.5, 47.2) PFS 5.7 Mon. (95% CI: 5.4,7.6) (Mok et al., J Clin Oncol 33, 2015 (suppl; abstr 8059). Somit liegen für diese klinische Situation keine randomisierten Daten gegen Chemotherapie vor. Allerdings ist die Effektstärke der Ce-ritinib-Therapie (ORR 56%, DCR > 80%) deutlich höher im Vergleich zur Wirksamkeit von Standard-chemotherapie sowohl in der Erstlinie also auch im Rezidiv, so dass die Empfehlung hier eindeutig zugunsten des Nächstgene-rations-ALK-Inhibitors ausfällt. Weitere ALK-Inhibitoren der nächsten Generation, deren Nutzen derzeit geprüft wird, sind: · Alectinib [865], · Brigatinib [866].	(n=115) oder Chemotherapie (n=116, davon n=113 tatsächlich behandelt) mit Pemetre-xed oder Docetaxel zugeführt. Der primäre Zielpara-meter 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 Transami-nasenerhöhung (1-3%) und Dyspnoe (2%) [C]. ~~Die Effektivität von Ceritinib bei Crizotinib-vorbehandelten ALK+ NSCLC Patienten wurde in der ASCEND-2 Phase II Studie bestätigt (ORR 38.6% (95% CI, 30.5, 47.2) PFS 5.7 Mon. (95% CI: 5.4,7.6) (Mok et al., J Clin Oncol 33, 2015 (suppl; abstr 8059). Somit liegen für diese klinische Situation keine randomi-sierten Daten gegen Chemotherapie vor. Allerdings ist die Effektstärke der Ceritinib-Therapie (ORR 56%, DCR > 80%) deutlich höher im Vergleich zur Wirksamkeit von Stan-dardchemotherapie sowohl in der Erstlinie also auch im Rezidiv, dass Die Empfehlung fällt eindeutig zugunsten des Nächstgenerations-ALK-Inhibitors aus.~~ Weitere ALK-Inhibitoren der nächsten Generation, deren Nutzen derzeit geprüft wird, sind:		

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
		· Alectinib [865], · Brigatinib [866].		
8.6 / S 203	„Als Kombinationspartner stehen die Zytostatika der zwe-iten Generation wie Etoposid, Vindesin, Mitomycin und Ifosfamid oder der sog. dritten Gene-ration, wie Gemcitabin, Paclitaxel, Docetaxel, Vinorelbin und Pemet-rexed zur Verfügung“	„Als Kombinationspartner stehen die Zytostatika der zweiten Generation wie Etoposid, Vindesin, Mitomycin und Ifosfamid oder der sog. Dritten Generation, wie Gemcitabin, Paclitaxel, nab-Paclitaxel, Docetaxel, Vinorelbin und Pemetrexed zur Verfügung“	Nab-Paclitaxel ist konventionellem Paclitaxel hinsichtlich der Wirksamkeit vergleichbar, in der Subgruppe der >70-Jährigen und beim Plattenepithel-Ca möglicherweise sogar überlegen (Socinski MA et al.; J Clin Oncol. 2012; 30(17):2055-62).	Der Hintergrundtexte wurde überarbeitet
8.6.4 / 224	„Nintedanib, ein Angiokinase Tyrosinkinaseinhibitor, wurde in der LUME-Lung-1-Studie in Kombination mit Docetaxel randomisiert und placebo-kontrolliert mit Docetaxel geprüft.“	„Nintedanib, ein oraler, dreifach zielgerichteter Angiokinase Tyro-sinkinaseinhibitor wurde in der LUME-Lung-1-Studie in Kombination mit Docetaxel bei 1314 Patienten mit einem vorbehandelten NSCLC mit der Kombination Placebo/Docetaxel verglichen. Die Nintedanib-Dosis betrug 200 mg zweimal täglich an den Tagen 2 bis 21 eines 3-wöchentlichen Be-handlungszyklus mit Docetaxel.	Angaben zu Zielstrukturen, zum Studiendesign, zu Patientenzahlen und geprüfter Dosierung sollten in dem Detailgrad wie für andere Therapieoptionen in diesem Kapitel dargestellt werden Reck M et al: Lancet Oncol 2014; 15: 143–55 Fachinformation Vargatef, aktueller Stand der Information	Der Hintergrundtexte wurde überarbeitet.
8.6.4 / 224	„Auch in dieser Studie war das PFS zugunsten der Kombina-tion mit Nintedanib signifikant verbessert (medianes PFS +0,7 Monate, HR 0,79) [838].“	„In dieser Studie war das PFS in der ITT zugunsten der Kombination mit Nintedanib signifikant verbessert (medianes PFS +0,7 Monate, HR 0,79). Bei der zu-lassungsrelevan-ten Population der Patienten mit einem Adenokarzinom wurde unter Nintedanib+Docetaxel eine signifikante PFS-Verlän-gerung erreicht (Medianes PFS 4,2 vs. 2,8 Monate, HR 0,84) [838].“	Bei den Angaben zum PFS fehlt der Bezug zur ITT und die Angabe des PFS-Vorteils in der zulassungsrelevanten Population der Patienten mit Adenokarzinom (Follow-Up-Analyse PFS, Datenschnitt finale OS-Analyse) Reck M et al: Lancet Oncol 2014; 15: 143–55 Fachinformation Vargatef, aktueller Stand der Information	Keine Änderung des Hintergrundtextes, da die relevanteren Vorteile bzgl. des OS dargelegt werden.

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
8.6.4 / 224	„Zusätzlich zeigte sich in einer Analyse der Überlebenszeit von Patienten mit einem Adenokarzinom, die innerhalb von 9 Monaten nach Beginn der Erstlinientherapie randomisiert wurden, eine zusätzliche Verlängerung der Überlebenszeit für die Kombination Docetaxel/Nintedanib im Vergleich zu Docetaxel (Mediane Überlebenszeit: 10,9 versus 7,9 Monate, HR 0,75) [838]."	„Zusätzlich zeigte sich in einer präspezifizierten Analyse des sekundären Endpunktes der Überlebenszeit von Patienten mit einem Adenokarzinom, die innerhalb von 9 Monaten nach Beginn der Erstlinientherapie progredient waren und randomisiert wurden, eine zusätzliche Verlängerung der Überlebenszeit für die Kombination Docetaxel/Nintedanib im Vergleich zu Docetaxel (Mediane Überlebens-zeit: 10,9 versus 7,9 Monate, HR 0,75) [838]."	Es fehlt der Hinweis auf die präspezifizierte Analyse und auf den Progress vor Randomisierung (Patienten mit Progress und Studieneintritt < 9 Monate) Reck M et al: Lancet Oncol 2014; 15: 143–55 Fachinformation Vargatef, aktueller Stand der Information	Text wurde korrigiert
Afati-nib 8.6.3 / 221	Das Gesamtüberleben betrug 8,7 vs. 7,9 Monate (HR 0,81, p= 0.0077).	Das Gesamtüberleben betrug 7,9 vs. 6,8 Monate (HR 0,81, p= 0.0077).	Soria et al: Lancet Oncol 2015; 16: 897–907	Text wurde korrigiert
Afati-nib 8.6.5 / 231	Zur LUX-Lung 3 Studie fehlt die Ansprechrate	Die Ansprechrate betrug 69% vs. 44%. (Analog zum Text zur LUX-Lung 6 Studie)	Sequist et al: J Clin Oncol. 2013 Sep 20;31(27):3327-34	Die Anpsrechrate (gemessen durch unabhängigen Review wurde korrigiert (56 vs. 23). Die vorgeschlagenen Daten zu den Ansprechraten gemessen durch ‚Investigator'wurde nicht ergänzt. Da ohne Zusatzinformation.
Afati-nib 8.6.5 / 233	In einer zweiten, bisher nur als Abstract publizierten Metaanalyse, in der individuelle Patientendaten eingegangen sind, konnten Erlotinib und Gefitinib kei-nen Überlebensvorteil bei Exon	In einer zweiten ~~bisher nur als Abstract~~ publizierten Meta-analyse, in die individuelle Pa-tientendaten eingegangen sind, konnten Erlotinib und Gefitinib keinen Überle-bensvorteil bei Exon 19 dele-tierten	Lee CK et al: JNCI J Natl Cancer Inst (2017) 109(6): djw279	Zitat wurde ergänzt.

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
	19 deletierten Patienten zeigen (Lee CK J Clin Oncol 2015;33(suppl; abstr 8072).	Patienten zeigen (Lee CK JNCI J Natl Cancer Inst (2017) 109(6): djw279).		
Afatinib 8.6.5 / 233	LUX-Lung 7 Studie: In einer Phase IIB wurden erste Daten zum Head-to Head Vergleich von Gefitinib gegen Afatinib bei 319 Patienten mit einer Del 19 oder einer Exon 21 L8585R geprüft. 319 Patienten wurden randomisiert, Afatinib erhielten 160, Gefitinib 159. Der primäre Endpunkt PFS war statistisch signifikant zugunsten von Afatinib verbessert (HR = 0,73; p = 0.0165), die Ansprechrate betrug 70 % vs. 56 %, p = 0.0083) bei allen Mutationen, 73 % vs. 66 % bei Exon 19 Deletionen und 66 % vs. 42 % bei Exon 21 L858R Mutationen. Überlebensdaten liegen noch nicht vor, die Rate an Therapieab-brüchen aufgrund von Toxizität lag in beiden Armen bei 6,3%.	In einer Phase IIB wurden erste Daten zum Head-to Head Vergleich von Gefitinib gegen Afatinib bei 319 Patienten mit einer Del 19 oder einer Exon 21 L8585R geprüft. 319 Patienten wurden randomisiert, Afatinib erhielten 160, Gefitinib 159. Der primäre Endpunkt PFS war statistisch signifikant zugunsten von Afatinib verbessert (HR = 0,73; p = 0.0165), die Ansprechrate betrug 70% vs. 56%, p = 0.0083) bei allen Mutationen, 73% vs. 66% bei Exon 19 Deletionen und 66% vs. 42% bei Exon 21 L858R Mutationen. Für das mediane Gesamtüberleben zeigte sich ein statistisch nicht signifikanter Trend zur Verbesserung unter Afatinib (HR 0,86; p= 0,2580). Die Rate an Therapieabbrüchen aufgrund von Toxizität lag in beiden Armen bei 6,3%.	Paz-Ares et al: Annals of Oncology 0: 1–9, 2017	Angaben zum Gesamtüberleben (keine signifikanten Unterschiede wurden ergänzt)
S. 203 Dritt-gene-ra-tions-zyto-stati-ka	Als Kombinationspartner stehen die Zytostatika der zweiten Generation wie Etoposid, Vindesin, Mitomycin und Ifosfamid oder der sog. dritten Generation, wie Gemcitabin, Paclitaxel, Docetaxel, Vinorelbin und Pemetrexed zur Verfügung	Nab-Paclitaxel als zugelassenes Drittgenerationszytostatikum mit aufnehmen;	In der Phase III Zulassungsstudie zur Erstlinientherapie beim fortgeschrittenen oder metastasierten NSCLC zeigte sich Nab-Paclitaxel (in Kombination mit Carbopla-tin) dem konventionellem Paclitaxel (in Kombination mit Carboplatin) bzgl. des primären Endpunkts überlegen. Die Phase III Zulassungsstudie schloss 1052 NSCLC-Patienten mit Stadium IIIB–IV ein, die noch keine Chemotherapie erhalten hatten bzw. bei denen eine vorangegangene adjuvante Chemotherapie mindestens 12 Monate zurücklag. Die Pa-tienten erhielten als randomi-siert entweder 100 mg/m² Nab-Paclitaxel an den	Nab-Paclitaxel wurde ergänzt.

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
			Tagen 1, 8, 15 kombiniert mit Carboplatin AUC = 6 an Tag 1 eines jeden 21-Tage-Zyklus oder konventionelles Paclitaxel 200 mg/m² an Tag 1 kombiniert mit Carboplatin AUC = 6 an Tag 1 eines jeden 21-Tage-Zyklus. Primärer Endpunkt der Studie war die Gesamtan-sprechrate, die durch verblin-dete, zentralisierte, unab-hängige radiologische Ana-lysen nach den RECIST-Kriterien ermittelt wurde. Die Kombination Nab-Paclitaxel plus Carboplatin erhöhte sig-nifikant die Gesamtansprech-rate im Vergleich zu konv. Paclitaxel plus Carboplatin (33 vs. 25%; p = 0,005). Patienten mit Plattenepithel-karzinom profitierten besonders von Nab-Paclitaxel plus Carboplatin. (41% mit Nab-Paclitaxel im Vergleich zu 24% mit konv. Paclitaxel (RRR [Response Rate Ratio] 1,68; p < 0,001)). Dies ent-spricht einer Verbesserung der Ansprechrate um 68% und ist besonders vor dem Hintergrund bemerkenswert, dass für diesen histologischen Subtyp nach wie vor wirk-samere Therapiestrategien dringend benötigt werden [9]. Bei Patienten mit Nicht-Plat-tenepithel-NSCLC war die Gesamtansprechrate ver-gleichbar mit konv. Paclitaxel (ORR 26 vs. 25%; p = 0,808). In den sekundären End-punkten der Phase-III-Studie ergaben sich weitere numeri-sche, jedoch nicht signifikante Vorteile für Nab-Paclitaxel. Das mediane progressions-freie	

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
			Überleben (PFS) lag bei Nab-Paclitaxel bei 6,3 Mona-ten, bei konv. Paclitaxel bei 5,8 Monaten (p = 0,214). Das me-diane Gesamtüberleben (OS) war bei Patienten im Nab-Paclitaxel-Arm um etwa 1 Monat verlängert (12,1 vs.11,2 Monate; p = 0,271). Trotz der höheren kumulati-ven Dosis an Paclitaxel, die Patienten im Nab-Paclitaxel-Arm er-hielten, wurde diese Verabreichungs-form besser toleriert. So entwickelten sig-nifikant weniger Patienten, die Nab-Paclitaxel erhielten, eine sensori-sche Neuropathie (alle Grade, 46 vs. 62%; p = 0,001). Schwere sensorische Neuropathien Grad ≥ 3 traten unter Nab-Paclitaxel bei nur 3%, unter konv. Paclitaxel dagegen bei etwa 11% der Patienten auf (p < 0,001) und bildeten sich mit Nab-Paclita-xel deutlich schneller zurück als unter konv. Paclit-axel (Verbesserung von Grad ≥ 3 auf Grad 1: Nab-Paclitaxel median 38 Tage, konv. Paclitaxel median 104 Tage). Außerdem wurden unter Nab-Paclitaxel-Therapie weniger Grad ≥ 3 Neutropenien, Arthralgien und Myal-gien beobachtet. Im konv. Paclita-xel-Arm traten dagegen weni-ger Grad ≥ 3 Thrombozyto-penien und Anämien auf [1]. Auch die Untersuchung der pati-entenbasierten Einschät-zungen zur Lebensqualität spiegelte die bessere Ver-träglichkeit von Nab-Paclitaxel im Vergleich zu konv. Paclita-xel wieder [2]. Signifikant we-niger Patienten, die	

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
			mit Nab-Paclitaxel behandelt wurden, berichteten über Neuropathie- und Taxan-assoziierte Symp-tome wie neuropathische Schmerzen in Händen und Füßen oder Hörverlust [2]. Socinski MA, Bondarenko I, Karaseva NA et al. Weekly Nab-Paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. J Clin Oncol 2012; 30: 2055 – 2062 Hirsh V, Okamoto I, Hon JK et al. Patient-reported neuropathy and taxane-associated symptoms in a phase 3 trial of Nab-Paclitaxel plus carboplatin versus solventbased paclitaxel plus carboplatin for advanced nonsmall-cell lung cancer. J Thorac Oncol 2014; 9: 83 –90	
S. 205 Stel-len-wert der Monoche-mo-the-ra-pie Bei älte-ren Pa-tien-ten (> 70 Jahre)	Stellenwert der Monochemotherapie Bei älteren Patienten (> 70 Jahre) (…): Höheres Alter (> 70 Jahre) allein sollte kein Aus-schluss-grund von einer platinbasierten Kombi-nationstherapie sein. Die retrospektiven Kohor-tenanalyse einer Phase-III-Studie, in der Cisplatin mit verschiedenen Kombinationspartnern ge-prüft wurde, zeigt, dass bei Patienten > 70 Jahre ohne rele-vane Komorbidität die Cisplatinba-sierte Kombinationsche-motherapie gleiche	Nab-Paclitaxel plus Carboplatin bei älteren Patienten als valide Therapieoption mit aufnehmen	Evidenz für die gute Wirksamkeit und Verträglichkeit von Nab-Paclitaxel plus Carboplatin bei älteren Patienten: In der randomisierten Zulas-sungsstu-die, bei der Nab-Paclitaxel plus Car-boplatin gegen konventionelles Pacli-taxel plus Carboplatin bei 1052 Pati-enten mit fortge-schrittenem NSCLC getestet wurde, konnte neben der sig-nifikanten Verbesserung der An-sprechrate für das Ge-samtkollektiv	Hinweis zur Sub-gruppenanalyse wurde ergänzt.

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
	Effektivität / Nebenwirkungen hatte wie bei Patienten < 70 Jahre		auch ein signifi-kanter Vorteil bzgl. des Ge-samtüberlebens für die älteren Patienten (19.9 für Nab-Paclitaxel versus 10.4 Monate für konv. Paclitaxel; p = 0,009) gezeigt werden. In der Studie wurden Patienten zwischen 24 und 84 Jahre eingeschlossen, 15% des Studienkollektivs waren ≥ 70 Jahre alt.[1-2] Die gute Wirksamkeit und Verträglichkeit von Nab-Paclitaxel plus Carboplatin bei älteren Patienten wurde durch eine prospektive Phase IV Studie mit 284 Patienten ≥ 70 Jahre noch mal bestätigt.[3] Socinski MA, Bondarenko I, Karaseva NA et al. Weekly Nab-Paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. J Clin Oncol 2012; 30: 2055 – 2062 Socinski MA, Langer CJ, Okamoto I, Hon JK, Hirsh V, Dakhil SR, Page RD, Orsini J, Zhang H, Renschler MF. Safety and efficacy of weekly nab®-paclitaxel in combination with carboplatin as first-line therapy in elderly patients with advanced non-small-cell lung cancer. Ann Oncol 2013; 24 (2): 314-321.	

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
			Langer CJ, et al. Poster at ASCO 2017 [abstract 9059]. ABOUND.70+: Safety and Efficacy of Nab-Paclitaxel/Carboplatin in Elderly Patients With Advanced Non-Small Cell Lung Cancer	
S. 284 9.6.7. PCI	Bei Patienten mit Teil- oder Vollremission nach erfolgter Chemotherapie verlängert die zusätzliche Schädelbestrahlung die Überlebenszeit und erhöht die 1-Jahres-Überlebensrate auch in der Patientengruppe mit primärer Fernmetastasierung. Belegt wurde dies durch die EORTC Studie von Slot-man et al. [1115], [1116], die insgesamt 283 auswertbare Patienten aufgenommen hatte. Diese hatten unter einer initialen Chemotherapie über 4-6 Zyklen mit einer partiellen oder kompletten Remission angesprochen. Anschließend erfolgte eine Randomisation auf eine prophylaktische Schädel-bestrahlung oder keine. Die Rate der symptomatischen Hirnmetastasierung betrug nach einem Jahr in der bestrahlten Gruppe knapp 15 % im Vergleich zu 40 % bei nicht durchgeführter RT, die 1-Jahres-Überlebensraten betrugen 27 % vs. 13 % für bestrahlte versus nicht bestrahlte Patienten (Evidenzgrad 1b). Der deutliche Überlebensvorteil könnte auch dadurch erklärt werden, dass die prophylakti-sche Schädelbestrahlung die Rate der Hirnmetastasierung erheblich reduziert und Patienten mit extracerebraler Progression von einer effektiven Zweitlinientherapie stärker profitieren könnten.	Bei Patienten mit einem hohen Risiko für eine neu-rokognitive Verschlechterung, sollte die Indikation zur PCI kritisch hinterfragt werden. Bei Patienten mit Extensive Disease, die auf eine Induktionschemotherapie angesprochen hatten, liegen divergierende Studienergebnisse zur PCI vor. Die rein über die klinische Symptomatik gesteuerte Studie der EORTC zeigte eine Verlängerung der medianen Überlebenszeit von 5,4 auf 6,7 Monate. In der MRT-gesteuerten, japanischen Phase III Studie zeigte sich ein medianes OS von 11,6 Monaten (95% CI 9,5–13,3) in der PCI Gruppe und ein medianes OS von 13,7 Monaten (10–16,4) in der Observationsgruppe. Eine PCI kann im Stadium ED durch regelmäßigen MRT Schädel Kontrollen (alle 3 Monate) ersetzt werden.	Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2017;18:663–671.	Diesen Kapitel war nicht Gegentand der Aktualisierung. Wir nehmen den Hinweis für die folgenden Aktualisierungen aber gerne auf.
S. 283 **Bestrah-lung bei**	Slavage Radiotherapie bei rezidivierenden Hirnmetastasen ist bisher nicht enthalten.	Bei rezidivierenden Hirnmetastasen nach vorangegangener PCI oder GH-Bestrahlung kann eine erneute Re-GH Bestrahlung bei ausgewählten Patienten mit adäquatem Karnofsky Index evaluiert werden. Bei	Bernhardt D, Bozorgmehr F et al.: Outcome in patients with small cell lung cancer re-irradiated for brain metastases after prior prophylactic cranial	Diesen Kapitel war nicht Gegentand der Aktualisierung. Wir

Kapi-tel / Seite	Entwurfstext der Leitlinie	Vorgeschlagene Änderung	Begründung (mit Literaturangaben)	Konsentierte Entscheidung /Begründung
cerebraler Metasta-sierung:		Patienten mit wenigen Hirnmetastasen, die eine ablative Lokaltherapie erlauben, kann in der Rezidivsituation auch eine stereotaktische Radiotherapie (SRS, Cyber-knife, Gammaknife) evaluiert wer-den, um neurokog-nitive Defizite zu vermeiden.	irradiation. Lung Cancer 09/2016; 101., DOI:10.1016/j.lung-can.2016.09.010 □ Olson AC, Wegner RE, Rwigema JCM, et al. Clinical outcomes of reirradiation of brain metastases from small cell lung cancer with Cyberknife stereotactic radiosurgery. J. Cancer Res. Ther. 2012;8:411–6. □ Harris S, Chan MD, Lovato JF, et al. Gamma knife stereotactic radiosurgery as salvage therapy after failure of whole-brain radiotherapy in patients with small-cell lung cancer. Int. J. Radiat. Oncol. Biol. Phys. 2012;83:e53–9. □ Nakazaki K, Higuchi Y, Nagano O, et al. Efficacy and limitations of salvage gamma knife radiosurgery for brain metastases of small-cell lung cancer after whole-brain radiotherapy. Acta Neurochir. (Wien). 2013;155:107–13; discussion 113–4.	nehmen den Hinweis für die folgenden Aktualisierungen aber gerne auf.

9. Unabhängigkeit und Umgang mit Interessenkonflikten

Die Deutsche Krebshilfe stellte über das Leitlinienprogramm Onkologie (OL) die finanziellen Mittel zur Verfügung. Diese Mittel wurden eingesetzt für Personalkosten, Büromaterial, Literaturbeschaffung und die Konsensuskonferenzen (Raummieten, Technik, Verpflegung, Moderatorenhonorare, Reisekosten der Teilnehmer). Die Erarbeitung der Leitlinie erfolgte in redaktioneller Unabhängigkeit von der finanzierenden Organisation. Alle Mitglieder legten während des Leitlinienprozesses eine schriftliche Erklärung zu eventuell bestehenden Interessenkonflikten vor. Die offengelegten Interessenkonflikte sind in Kapitel 12.1) aufgeführt.

Der Umgang mit Interessenkonflikten wurde in der konstituierenden Sitzung der Steuergruppe am 04.12.2012 und beim Kick-off-Meeting am 01. 07. 2013 sowie beim Treffen der Leitliniengruppe am 11.01.2016 thematisiert. Die Bewertung der offengelegten Interessenkonflikte und die Festlegung von protektiven Maßnahmen erfolgte zunächst durch die Steuergruppe und anschließend durch die gesamte Leitliniengruppe beim Kick-off-Meeting am 01. 07. 2013 und bei der Konsensuskonferenz am 11.01.2016. Folgende Beschlüsse zum Umgang mit den offengelegten Interessenkonflikten wurden getroffen:

- Personen, die für Firmen der Gesundheitswirtschaft beratend tätig waren (advisory board) sollten keine AG-Leitung übernehmen.
- Der LL-Koordinator Hr. Ukena nahm an keiner Abstimmung teil.

Darüber hinaus gehende Regeln zu Stimmenthaltungen wurde nicht festgelegt. Es wurde angeregt, dass sich Personen, die für sich bei Einzelfragen einen Interessenkonflikt sehen, diesen anzeigen und sich nicht an der Abstimmung beteiligen. Dies erfolgte bei der Empfehlung zu Pembrolizumab durch zwei Personen.

An dieser Stelle möchten wir allen Mitarbeitern für ihre ausschließlich ehrenamtliche Mitarbeit an dem Projekt danken.

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12. Anlagen

12.1. Ergebnisse der Interessenkonflikterklärungen

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit [1]	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften [2]	Finanzielle Zuwendungen (Drittmittel) [3]	Eigentümerinteresse (z. B. Patent, Urheberrecht, Verkaufslizenz) [4]	Besitz von Geschäfts-anteilen, Aktien, Fonds [5]	Persönliche Beziehungen [6]	Mitgliedschaft Fachgesellschaften/Berufsverbände, andere Leitlinien-gruppen [7]	wissenschaftliche oder persönliche Interessen [8]	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
Barbara Baysal	Nein	Ja	Nein	Nein	Nein	Nein	Nein	Nein	EU-Rentnerin seit 2001
Dr. Torsten Gerriet Blum	Nein	Nein	Nein	Nein	Nein	Nein	Ja DGP	Nein	HELIOS Klinikum Emil von Behring GmbH
PD Dr. Servet Bölükbas	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Dr. Horst Schmidt Klinik
Prof. Dr. Wolfgang Brückl	Ja Roche, Lilly, Boehringer, Pfizer, Astra Zeneca	Ja Roche, Lilly, Boehringer, Pfizer, Astra Zeneca	Nein	Nein	Nein	Nein	Ja DKG, AIO, PCA ABC Studiengruppe	Nein	Klinikum Nürnberg, Unternehmer der Stadt Nürnberg
Dr. Karl Matthias Deppermann	Ja Roche, Lilly, Boehringer Ingelheim, Astra Zeneca	Ja Roche, Lilly, Boehringer Ingelheim, Astra Zeneca	Nein	Nein	Nein	Nein	Ja Stellvertretener Sprecher der POA, Mitglied der Leitgruppe der AG Thorakale Onkologie in der AIO	Nein	HELIOS Klinikum Erfurt
Dr. Wilfried Eberhardt	Ja Astra Zeneca, Roche Pharma, Eli	Ja Astra Zeneca, Roche Pharma, Eli Lilly, GSK, Boehringer Ingelheim,	Ja Eli Lilly, IASLC	Nein	Nein	Nein	Ja AIO, DGHO, DKG, BDI, ESMO,	Nein	Universitätsklinikum Essen, Universität Duisburg-Essen

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit [1]	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften [2]	Finanzielle Zuwendungen (Drittmittel) [3]	Eigentümerinteresse (z. B. Patent, Urheberrecht, Verkaufslizenz) [4]	Besitz von Geschäfts-anteilen, Aktien, Fonds [5]	Persönliche Beziehungen [6]	Mitgliedschaft Fachgesellschaften/Berufsverbände, andere Leitlinien-gruppen [7]	wissenschaftliche oder persönliche Interessen [8]	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
	Lilly, GSK, Boehringer Ingelheim, Teva Pharma, Bistrol Myers Squibb, Novartis Pharma, Pfizer Pharma, Bayer, MerckSerono, Merck (USA)	Novartis Pharma, Pfizer Pharma, MerckSerono, Merck (USA), Pierre Fabre, Hexal Pharma, SanofiAventis					ASCO, IASLC, Marburger Bund		
Prof. Dr. Joachim H. Ficker	Ja Lilly, Pfizer, Roche	Ja Lilly, Pfizer, Roche	Ja Regelmäßig multiple Therapiestudien Phase I-IV für eine Vielzahl von Pharmaunter-nehmen bzw. deren Auftragnehmer (CRO) in meiner Klinik (Mittelflüsse zugunsten Klinikum Nürnberg)	Nein	Ja Besitz von International-en Aktienfonds mit einem geringen wechselnden Anteil auch von Pharma-Aktien	Nein	Ja DGP	Nein	Klinikum Nürnberg
Dr. Markus Follmann	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	DKG
Dr. Fernando Gamarra	Nein	Nein	Nein	Nein	Nein	Nein	Ja DGP, DKG, European Respiratory	Nein	Klinikum der Ludwig-Maximilians Universität München

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit [1]	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften [2]	Finanzielle Zuwendungen (Drittmittel) [3]	Eigentümerinteresse (z. B. Patent, Urheberrecht, Verkaufslizenz) [4]	Besitz von Geschäfts-anteilen, Aktien, Fonds [5]	Persönliche Beziehungen [6]	Mitgliedschaft Fachgesellschaften/Berufsverbände, andere Leitlinien-gruppen [7]	wissenschaftliche oder persönliche Interessen [8]	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
							Society (chair der „Lung Cancer Group"), American Thoracic Society		
PD Dr. Thomas Graeter	Ja KLS MARTIN, Lasertechnik	Ja Vortrag Metastasenchirurgie, Sponsor Bayer 2010	Nein	Nein	Nein	Nein	Ja DGT, AOT	Nein	Klinik Löwenstein
Prof. Dr. F. Griesinger	Ja Roche, Boehringer Ingelheim, Pfizer, Merck, Sanofi, Lilly	Ja Roche, Boehringer Ingelheim, Pfizer, Merck, Sanofi, Lilly	Nein	Nein	Nein	Nein	Ja DGHO Onkopedia	Nein	Stiftung Pius-Hospital Oldenburg
Prof. Dr. Christian Grohé	Ja Lilly, Roche, Boehringer, Otsuka	Ja Lilly, Roche, Boehringer, Astra, Otsuka	Ja Otsuka (Hyponatriämie-Studie), Lilly (Tumordokumentation)	Nein	Nein	Nein	Ja DGP, DKG	Nein	Paul-Gerhardt-Diakonie – EV. Lungenklinik Berlin
Dr. Andreas Gröschel	Ja Lilly, Roche, Boehringer, Amgen, Merck Sorono	Ja Lilly, Roche, Boehringer, Merck Sorono	Nein	Nein	Nein	Nein	Ja DGP, DKG, AIO, POA, ERS	Nein	Ambulantes Aachener Lungenzentrum, Universitätsklinikum des Saarlandes
Dr. Sylvia Gütz	Ja Boehringer Ingelheim	Ja	Nein	Nein	Nein	Nein	Ja DGP, DKG	Nein	Ev. Diakonissenkranken-haus Leipzig, Klinikum St, Georg

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit [1]	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften [2]	Finanzielle Zuwendungen (Drittmittel) [3]	Eigentümerinteresse (z. B. Patent, Urheberrecht, Verkaufslizenz) [4]	Besitz von Geschäfts-anteilen, Aktien, Fonds [5]	Persönliche Beziehungen [6]	Mitgliedschaft Fachgesellschaften/Berufsverbände, andere Leitlinien-gruppen [7]	wissenschaftliche oder persönliche Interessen [8]	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
		Boehringer Ingelheim, Pierre Fabre, Roche, Lilly							
Dr. David Heigener	Ja Pfizer, Lilly, Roche, Boehringer	Ja BMS, Amgen, Pfizer, Boehringer, Lilly, Roche, Novartis	Nein	Nein	Nein	Nein	Ja DGP, Deutsche Gesellschaft für Palliativmedizin	Nein	LungenClinic Grosshansdorf GmbH
Felix Herth	Ja Uptake Medical, Aeris, Olympus Medical, PneumRx, Boston Scientific, Roche Diagnoctics, Intermune, Novartis, Lilly, Pulmonx	Ja Uptake Medical, Aeris, PneumRx, Boston Scientific, Roche Diagnoctics, Intermune, Novartis, Lilly, Pulmonx, Astra Zeneca, Allmiral, Takeda, Pierre Fabre, Boehringer Ingelheim	Ja BMBF, DFG	Nein	Nein	Nein	Nein	Nein	Universitätsklinik Heidelberg
Dr. Maximilian Hochmair	Nein	Nein	Nein	Nein	Nein	Nein	Ja ÖGP, Europäische Gesellschaft für Pneumologie	Nein	Otto Wagner Spital Wien
Dr. Hans Hoffmann	Ja LL Immunotherapy board GSK	Ja Bezahlte Vorträge bei verschiedenen Industriegesponserten Symposien	Nein	Nein	Nein	Nein	Ja DGT, DGP, DKG	Ja Zertifizierungskommission Lungenkrebszentren DKG	Thoraxklinik Heidelberg

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit [1]	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften [2]	Finanzielle Zuwendungen (Drittmittel) [3]	Eigentümerinteresse (z. B. Patent, Urheberrecht, Verkaufslizenz) [4]	Besitz von Geschäfts-anteilen, Aktien, Fonds [5]	Persönliche Beziehungen[6]	Mitgliedschaft Fachgesellschaften/Berufsverbände, andere Leitlinien-gruppen [7]	wissenschaftliche oder persönliche Interessen [8]	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
Prof. Dr. Rudolf M. Huber	Ja Roche, Lilly, Boehringer, Pfizer	Ja Roche, Lilly, Boehringer, Pfizer, Pierre Fabre	Nein	Nein	Nein	Nein	Ja DGP, DKG, DGHO, ERS, ACCP, ASCO. IASLC	Nein	Universität München
Prof. Dr. Klaus Junker	Ja Novartis Pharma GmbH	Ja Astra Zeneca GmbH	Nein	Nein	Nein	Nein	Ja DKG, Deutsche Gesellschaft für Pathologie, Bundesverband Deutsche Pathologie, DGP, Deutsche Gesellschaft für Thoarxchirurigie	Nein	Klinikum Bremen Mitte gGmbH
wProf. Dr. Ina B. Kopp	Nein	Nein	Nein	Nein	Nein	Nein	Ja Ständige Kommission Leitlinien der AWMF (Stellv. Vorsitzende), Deutsches Netzwerk Evidenzbasierte medizin (Sprecherin des FB Leitlinien), Deutsche Gesellschaft für Chirurgie	Ja Planungsgruppe NVL-Programm Lenkungsausschuss OL und KoQK wissenschaftl. Beirat AQUA AG Dokumentation des NKP Gutachterin für DAkkS	AWMF

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit [1]	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften [2]	Finanzielle Zuwendungen (Drittmittel) [3]	Eigentümerinteresse (z. B. Patent, Urheberrecht, Verkaufslizenz) [4]	Besitz von Geschäfts-anteilen, Aktien, Fonds [5]	Persönliche Beziehungen[6]	Mitgliedschaft Fachgesellschaften/Berufsverbände, andere Leitlinien-gruppen [7]	wissenschaftliche oder persönliche Interessen [8]	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
Dr. Christian Kugler	Nein	Ja Astra Zeneca, Lilly, Novartis, Roche	Nein	Nein	Nein	Nein	Ja Präsident Dt. Gesellschaft für Thoraxchirurgie, Vorstandsmitglied Dt. Gesellschaft für Chirurgie, Mitglied der AG AOT innerhalb der DKG	Nein	LungenClinic Großhansdorf
Prof. Dr. Dr. Hartmut Link	Ja Amgen, Teva, Vofor-Pharma	Ja Amgen, Chugai, Hanssen, Novartis-Hexal, Teva, Vifor-Pharma	Ja Janssen, Roche, Teva	Nein	Nein	Nein	Ja DGHO, DKG, AIO, ASORS, EORTC: Anaemia Working Party, DGIM	Nein	Westpfalz-Klinikum GmbH Kaiserslautern
Wiebke Nehls	Nein	Ja Palliative Care Ausbildung für Ärzte – Wannsee Akademie	Nein	Nein	Nein	Nein	Ja Deutsche Gesellschaft für Palliativmedizin, DGP, Mandatsträgerin S3-Leitlienien Palliativmedizin	Nein	HELIOS Klinium Emil von Behring, Berlin
Dr. Frank Noack	Nein	Nein	Nein	Nein	Nein	Nein	Ja DGT, DGCH	Nein	Klinik für Thoraxchirurgie Mönchengladbach
Dr. Monika Nothacker, MPH	Nein	Nein	Nein	Nein	Nein	Nein	Ja DKG, DNebM	Nein	AWMF, ÄZQ (bis 6/12)

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit [1]	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften [2]	Finanzielle Zuwendungen (Drittmittel) [3]	Eigentümerinteresse (z. B. Patent, Urheberrecht, Verkaufslizenz) [4]	Besitz von Geschäfts-anteilen, Aktien, Fonds [5]	Persönliche Beziehungen [6]	Mitgliedschaft Fachgesellschaften/Berufsverbände, andere Leitlinien-gruppen [7]	wissenschaftliche oder persönliche Interessen [8]	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
Dr. Overbeck	Ja Roche, Astra Zeneca, Boehringer Ingelheim, Lilly	Ja Roche, Lilly, Boehringer Ingelheim	Nein	Nein	Nein	Nein	Ja AIO, DKG	Nein	Universitätsmedizin Göttingen
Prof. Dr. Joachim Pfannschmidt	Nein	Nein	Nein	Nein	Nein	Nein	Ja DGT	Nein	HELIOS Klinikum Emil von Behring
Prof. Dr. Beate Rau	Nein	Nein	Ja CareFusion	Nein	Nein	Nein	Ja Mandatsträger der CAO-V, ESSO, ASCO, DGCH, DGAV, BDC, ISC, IAH, ASORS, DKG, CAO-S, Onkozert, Sprecher der AG Gendermedizin der DGAV	Nein	Charité Universitätsmedizin Berlin
PD Dr. Martin Reck	Ja Hoffmann-La Roche, Lilly, Pfizer, Astra-Zeneca, Boehringer Ingelheim, BMS	Ja Hoffmann-La Roche, Lilly, Pfizer, Astra-Zeneca, Boehringer Ingelheim, BMS	Nein	Nein	Nein	Nein	Ja ESMO, Guideline Group	Nein	LungenClinic Großhansdorf
Dr. S. Riha	Ja Boehringer Ingelheim	Ja Novartis Pharma GmbH	Nein	Nein	Nein	Nein	Ja DGP, DKG, DGP, DGNTF	Nein	Fachkrankenhaus Coswig GmbH

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit [1]	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften [2]	Finanzielle Zuwendungen (Drittmittel) [3]	Eigentümerinteresse (z. B. Patent, Urheberrecht, Verkaufslizenz) [4]	Besitz von Geschäfts-anteilen, Aktien, Fonds [5]	Persönliche Beziehungen [6]	Mitgliedschaft Fachgesellschaften/Berufsverbände, andere Leitlinien-gruppen [7]	wissenschaftliche oder persönliche Interessen [8]	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
	Pharma GmbH, Lilly Deutschland GmbH								
PD Dr. Christoph Schäper	Ja Lilly, Boehringer Ingelheim, Roche	Ja Lilly, Boehringer Ingelheim, Roche, GFK, Helios, Aktion Bronchialkarzinom (ABC), Pfizer, Astra Zeneca, Glaxo, Bayer Tessinium Geriatriezentrum, GSK, Novartis, POA	Ja Bayer, United Therapeutics, Actelion, GMIHO, GSK, Milenyi, ABC, Klinikum Mannheim, Krankenhaus Großhansdorf, Ergonex, Gilead, Böhringer, Novartis, Furiex, Mondogen	Nein	Nein	Nein	Ja Ärztekammer Mecklenburg-Vorpommern, DGP, DGI, Landesverband der Pneumologen M.-V., Landesverband der Internisten M.-V., DKG als Mitglied der POA aktuell im Vorstand vertreten, Lungennetz-Mecklenburg Vorpommern e.V. im Vorstand als Schatzmeister (verein aktuell in Liquidation befindlich)	Nein	Universitätsmedizin Greifswald
PD Dr. Robert Scheubel	Nein	Ja Boehringer Ingelheim	Nein	Nein	Nein	Nein	Nein	Nein	Waldburg-Zeil Kliniken Wangen
Dr. Nicolas Schönfeld	Nein	Nein	Ja Boehringer, Gilead, Intermune	Nein	Nein	Nein	Ja DGP, DKG	Nein	HELIOS Klinikum Emil von Behring GmbH

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit [1]	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften [2]	Finanzielle Zuwendungen (Drittmittel) [3]	Eigentümerinteresse (z. B. Patent, Urheberrecht, Verkaufslizenz) [4]	Besitz von Geschäfts-anteilen, Aktien, Fonds [5]	Persönliche Beziehungen [6]	Mitgliedschaft Fachgesellschaften/Berufsverbände, andere Leitlinien-gruppen [7]	wissenschaftliche oder persönliche Interessen [8]	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
PD Dr. W. Schütte	Ja Lilly, AstraZeneca, Roche, Boehringer Ingelheim	Ja AstraZeneca, Boehringer Ingelheim, Amgen, Lilly, Roche	Ja Roche, Amgen	Nein	Nein	Nein	Ja Berufsverband der Pneumologen	Nein	Krankenhaus Martha-Maria Halle-Dölau gGmbH
Dr. Martin Sebastian	Ja Pfizer, Lilly, TEVA, Boehringer Ingelheim, Fresenius Biotech, Novartis (jeweils finanziell kompensiert), CureVac (unbezahlt)	Ja Novartis, Roche, Lilly, Pfizer, Abbott, Amgen, Boehringer Ingelheim, Fresenius Biotech Bezahlte Autorenschaft: Chugai	Ja Boehringer Ingelheim	Nein	Nein	Nein	Ja DKG, DGP, AIO, DGIM, IASLC	Nein	Universitätsklinikum Frankfurt seit 01.09.2011, zuvor Universitätsklinikum Mainz
Dr. Monika Serke	Ja Fa. Lilly, Fa. Roche, Fa. Boehringer Ingelheim, Fa. Pfizer	Ja Roche, Pfizer	Nein	Nein	Nein	Nein	Ja DGP, AIO, POA	Nein	Lungenklinik Hemer
Prof. Dr. Susanne Singer	Nein	Nein	Nein	Nein	Nein	Nein	Ja AG PSO der DKG, EORTC Quality of Life Group	Nein	Universität Mainz, vorher Universität Leipzig und Bergische Universität Wuppertal
Prof. Dr. M. Stuschke	Ja AOK	Ja Roche	Ja	Nein	Nein	Nein	Ja	Nein	Universität Duisburg-Essen

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit [1]	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften [2]	Finanzielle Zuwendungen (Drittmittel) [3]	Eigentümerinteresse (z. B. Patent, Urheberrecht, Verkaufslizenz) [4]	Besitz von Geschäfts-anteilen, Aktien, Fonds [5]	Persönliche Beziehungen [6]	Mitgliedschaft Fachgesellschaften/Berufsverbände, andere Leitlinien-gruppen [7]	wissenschaftliche oder persönliche Interessen [8]	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
			Amgen, multizentrische Studien in 2014				DEGRO, Berufsverband deutscher Strahlentherapeuten		
Günter Tessmer	Ja Lilly Eli	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Evangelische Lungenklinik Berlin
Michael Thomas	Ja Pfizer, Roche, Lilly, AstraZeneca, Novartis, GSK	Ja Lilly, Pfizer, Roche	Ja Lilly, Roche	Nein	Nein	Nein	Nein	Nein	Thoraxklinik Heidelberg
Prof. Dr. Dieter Ukena	Nein	Ja AZ, Boehringer Ingelheim, Lilly	Nein	Nein	Nein	Nein	Ja DGP	Nein	Klinikum Bremen-Ost
Jens Vogel-Claussen	Nein	Ja Siemens	Nein	Nein	Nein	Nein	Nein	Nein	MHH
Dr. Simone Wesselmann	Nein	Nein	Nein	Nein	Nein	Nein	Ja DKG	Nein	DKG
Prof. Dr. Christian Witt	Ja Bayersdorf AG, TESA	Ja Roche, Lilly, Pfizer Gilead, Novartis	Nein	Nein	Nein	Nein	Ja DGP, DKG, POA	Nein	Charité-CCM
Prof. Dr. Jürgen Wolf	Nein	Ja AstraZeneca, BMS, Boehringer Ingelheim, Clovis MSD, Novartis, Pfizer, Roche	Ja Bayer, Boehringer Ingelheim, Novartis, Pfizer, Roche	Nein	Nein	Nein	Nein	Nein	Universitätsklinikum Köln

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit [1]	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften [2]	Finanzielle Zuwendungen (Drittmittel) [3]	Eigentümerinteresse (z. B. Patent, Urheberrecht, Verkaufslizenz) [4]	Besitz von Geschäfts-anteilen, Aktien, Fonds [5]	Persönliche Beziehungen [6]	Mitgliedschaft Fachgesellschaften/Berufsverbände, andere Leitlinien-gruppen [7]	wissenschaftliche oder persönliche Interessen [8]	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
Dag Wormanns	Ja Median Technologies	Ja Novartis, AstraZeneca	Nein	Ja Patent: Philps	Nein	Nein	Ja Deutsche Röntgengesellschaft	Nein	Ev. Lungenklinik Berlin

1 = Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheitswirtschaft (z.B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftragsinstituts oder einer Versicherung

2 = Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung

3 = Finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben oder direkte Finanzierung von Mitarbeitern der Einrichtung von Seiten eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung

4 = Eigentümerinteresse an Arzneimitteln/Medizinprodukten (z. B. Patent, Urheberrecht, Verkaufslizenz)

5 = Besitz von Geschäftsanteilen, Aktien, Fonds mit Beteiligung von Unternehmen der Gesundheitswirtschaft

6 = Persönliche Beziehungen zu einem Vertretungsberechtigten eines Unternehmens Gesundheitswirtschaft

7 = Mitglied von in Zusammenhang mit der Leitlinienentwicklung relevanten Fachgesellschaften/Berufsverbänden, Mandatsträger im Rahmen der Leitlinienentwicklung

8 = Politische, akademische (z.B. Zugehörigkeit zu bestimmten „Schulen“), wissenschaftliche oder persönliche Interessen, die mögliche Konflikte begründen könnten

12.2. Evidenztabellen

12.2.1. Thema: Früherkennung

Study/Reference	Region, setting inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
National Lung Screening Trial Research, T., et al., Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med, 2011. 365(5): p. 395-409. National Lung Screening Trial Research, T., et al., Baseline characteristics of participants in the randomized national lung screening trial. J Natl Cancer Inst, 2010. 102(23): p. 1771-9. Pinsky, P.F., et al., The National Lung Screening Trial: results stratified by demographics, smoking history, and lung cancer histology. Cancer, 2013. 119(22): p. 3976-83. Aberle, D.R., et al., Results of the two incidence screenings in the National Lung Screening Trial. N	**Region/Setting** USA, 33 Screening centres **Inclusion criteria** 55–74 years Current or former smokers with a cigarette smoking history of at least 30 pack-years Ability to lie on the back with arms raised over the head **Exclusion criteria** Metallic implants or devices in the chest or back, such as pacemakers or Harrington fixation rods	**Index test(s)** ***Intervention(s)*** Low dose CT (1.5 mSv, <25s, multidetector ≥4 detectors) 3 rounds at 1-year intervals A positive lowdose CT screening test was defined as the finding of one or more indeterminate (noncalcified) nodules measuring at least 4 mm in the longest diameter or, less commonly, mediastinal masses, pleural disease, or atelectasis of more than one segment ***Control*** Chest radiography (0.02 mSv, <40s) 3 rounds at 1-year intervals	**Mortality due to lung neoplasm (within 7 years after first enrolment, median 6.5 years)** **356 (247/ 100,000)/ 443 (309/ 100,000); RRR = 20%; 6.8 - 26.7** **Mortality due to lung neoplasm (median 5.5 years)** 354/442; 30.9 per 10,000 person years/ 24.9 per 10,000 person years 6.3 fewer death per 10,000 person-years; 2.4- 10.1 Test of interaction for mortality due to lung neoplasm	**Study type** RCT (one arm of RCT for diagnostic accuracy [false positive results]) **Level of evidence** 1b (2b for measures of diagnostic accuracy) **Risk of bias** Generation of allocation sequence: + Allocation concealment: ? Blinding of participants and personal: -

Study/Reference	Region, setting inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
Engl J Med, 2013. 369(10): p. 920-31. Kovalchik, S.A., et al., Targeting of low-dose CT screening according to the risk of lung-cancer death. N Engl J Med, 2013. 369(3): p. 245-54. Patz, E.F., Jr., et al., Overdiagnosis in low-dose computed tomography screening for lung cancer. JAMA Intern Med, 2014. 174(2): p. 269-74.	Treatment for, or evidence of, any cancer other than nonmelanoma skin cancer or carcinoma in situ (with the exception of transitional cell carcinoma in situ or bladder carcinoma in situ) in the 5 years prior to eligibility assessment History of lung cancer History of removal of any portion of the lung, excluding needle biopsy Requirement for home oxygen supplementation Unexplained weight loss of more than 15 pounds in the 12 months prior to eligibility assessment Recent hemoptysis Pneumonia or acute respiratory infection treated	Positive test was defined as the finding of a noncalcified nodule of any size or another abnormality potentially related to lung cancer **Reference standard (only positive screening results)** Medical records documenting diagnostic evaluation procedures. Beyond office visits and physicalexaminations, imaging examinations, including diagnostic chest CT and F-fluorodeoxyglucose– positron-emission tomography (FDG-PET), were the most commonly performed procedures **Time interval between index and reference test** Not specified (within one year) **Included/randomised patients** *T1 (one year after randomization)* 26,722/ 26,732	Former (RR=0.91) vs. current smokers (RR=0.81); >0.4 Test of interaction for mortality due to lung neoplasm Age; >0.4 Test of interaction for mortality due to lung neoplasm Women (RR=0.73) vs. men (RR=0.92); 0.08 Overall mortality (within 7 years after first enrolment, median 6.5 years) 1877/ 2000; RRR = 6.7%; 1.2 - 13.6 Test of interaction for overall mortality Former	Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: + ***QUADAS-II*** Selection of patients: + Conduct/interpretation of index test: + Conduct/interpretation of reference test: ?

Study/Reference	Region, setting inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	with antibiotics in the 12 weeks prior to eligibility assessment **Prior testing** Patients with chest CT examination in the 18 months prior to eligibility assessment were excluded **Patient characteristics** ***Age at randomization*** <55 (%): <0.1/ <0.1 55–59 (%): 42.8/ 42.7 60–64 (%): 30.6/ 30.7 65–69 (%): 17.8/ 17.8 70–74 (%): 8.8/ 8.8 ≥75 (%): <0.1/ <0.1 ***Female*** (%): 41.0/ 41.0 ***Race or ethnic group***	*T2 (two years after randomization)* 26,732/ 26,110 **Analysed patients** *T1* 24,715/ 24,089 *T2* 24,102/ 23,346 **Attrition** *T1* 2007/ 2643 *T2* 2620/ 3386 **Excluded from analysis (reason)** ITT according to authors NR (false positive results)	(RR=0.914) vs. current smokers (RR=0.944); NS Test of interaction for overall mortality Age; NS Test of interaction for overall mortality Women (RR=0.921) vs. men (RR=0.936); NS False positive results T1 97.6%/ 95.6%; NR; NR T2 94.8%/ 93.4%; NR; NR <u>Adverse events from follow up procedure (within 6 years after first enrolment)</u>	Patient flow: ?

Study/Reference	Region, setting inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	White (%): 90.9/ 90.8 Black (%): 4.5/ 4.4 Asian (%): 2.1/ 2.0 American Indian/ Alaska Native(%): 0.3/ 0.4 Native Hawaiian/ Pacific Islander(%): 0.3/ 0.4 More than one race or ethnic group (%): 1.2/ 1.3 Data missing(%): 0.6/ 0.8 ***Hispanic ethnic group*** Hispanic or Latino (%): 1.8/ 1.7 Neither Hispanic nor Latino (%): 97.6/ 97.4 Data missing (%): 0.6/ 0.9 ***Smoking status*** Current (%): 48.1/ 48.3 Former (%): 51.9/ 51.7		*Lung cancer confirmed* *Thoracotomy, Thoracoscopy, or Mediastinoscopy* At least one complication (%): 32.4/ 31.2; NR Major complication (%): 13.9/ 11.6; NR Death (%): 1/ 2.1; NR *Bronchoscopy* At least one complication (%): 9.2/ 8.7; NR Major complication (%): 2.6/ 2.2; NR Death (%): 5.3/ 10.9; NR *Needle Biopsy* At least one complication (%): 21.2/ 3.4; NR Major complication (%): 0/ 0; NR Death (%): 3.0/ 3.4 *No Invasive Procedure*	

Study/Reference	Region, setting inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
			At least one complication (%): 16.1/ 7.1; NR Major complication (%): 6.5/ 6.7; NR Death (%): 0/ 6.7 *Lung cancer not confirmed* *Thoracotomy, Thoracoscopy, or Mediastinoscopy* At least one complication (%): 15.9/ 15.6; NR Major complication (%): 5.5/ 2.2; NR Death (%): 1.2/ 0; NR *Bronchoscopy* At least one complication (%): 4.8/ 0; NR Major complication (%): 0.9/ 0; NR Death (%): 1.8/ 0; NR *Needle Biopsy*	

Study/Reference	Region, setting inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
			At least one complication (%): 10.6/ 4.2; NR Major complication (%): 0/ 0; NR Death (%): 0/ 0; NR *No Invasive Procedure* At least one complication (%): 0.1/ 0.2; NR Major complication (%): <0.1/ 0.1; NR Death (%): <0.1/ 0.1	
Croswell, J.M., et al., Cumulative incidence of false-positive test results in lung cancer screening: a randomized trial. Ann Intern Med, 2010. 152(8): p. 505-12, W176-80.	**Region/setting** USA, 6 screening centres **Inclusion criteria** 55 to 74 years Cigarette smoking history of 30 pack-years or more, and were current smokers or had quit in the past 10 years	**Index test(s)** ***Intervention(s)*** Low-dose CT (120 to 140 V peak, 60 ma, scan time of 1 s, 5-mm collimation, pitch of 2 or equivalent, and contiguous reconstructions.) 2 rounds at 1-year intervals ***Control***	**False positive results (12 month)** **33%/ 15%; NR; sign.**	**Study type** RCT (one arm of RCT for diagnostic accuracy[false positive results]) **Level of evidence** 1b (2b for measures of diagnostic accuracy) **Risk of bias**

Study/Reference	Region, setting inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	Exclusion criteria Previous lung cancer Removal of part or all of a lung Current treatment of any cancer except nonmelanoma skin cancer **Prior testing** Patient with chest CT within 24 months of enrolment were excluded **Patient characteristics** ***Age*** 65–74 y (%):32/ 32 55–64 y (%):68/ 68 Female (%):42/ 40 Current smoker (%):58/ 57	Chest radiography (high-kilovolt equipment at a tube-to-receiver distance of 6 to 10 feet) 2 rounds at 1-year intervals **Reference standard** No specific diagnostic algorithm for follow-up of positive results Center personnel abstracted medical records ***Results of record screening*** Imaging examinations: 308 / 110 Minimally invasive procedure: 25 / 6 Moderately invasive procedure: 20 / 7 Major surgical procedure: 8 / 4 Any invasive procedure: 33 / 9 **Time interval between index and reference test**		Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: + Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Study/Reference	Region, setting inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	Smoking history 60 pack-years (%):42/ 43 30–59 pack-years (%):58/ 57	not specified (within one year) **Included/randomised patients** 1660/ 1658 **Analysed patients** 1610/ 1580 **Attrition** 29/ 14 **Excluded from analysis (reason)** 50 (missed or declined all screenings) 78 (missed or declined all screenings)		***QUADAS-II*** Selection of patients: + Conduct/interpretation of index test: + Conduct/interpretation of reference test:: ? Patient flow: +
Infante, M., et al., A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial. Am J Respir Crit Care Med, 2009. 180(5): p. 445-53.	**Region/Setting** Italy, 2 centres **Inclusion criteria** 60-74 years Active or quit < 10 years prior to accrual	**Intervention(s)** Chest X-ray Sputum cytology testing Spiral CT images of the whole lungs were obtained during maximal inspiration at the end of a single breathhold using a single-slice	**Mortality due to lung neoplasm (5 years, median 33.7 months);1.6%/ 1.7%; NR; 0.84** Overall mortality (5 years, median 33.7); 2.0%/ 2.1%; NR; 0.93	**Study type** RCT **Level of evidence** 1b **Risk of bias**

Study/Reference	Region, setting inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
Infante, M., et al., Surgical procedures in the DANTE trial, a randomized study of lung cancer early detection with spiral computed tomography: comparative analysis in the screening and control arm. J Thorac Oncol, 2011. 6(2): p. 327-35. Infante, M., et al., Lung cancer screening with spiral CT: baseline results of the randomized DANTE trial. Lung Cancer, 2008. 59(3): p. 355-63.	At least 20 pack-years Male **Exclusion criteria** Severe comorbidity, life expectancy < 5 years Severe heart failure Chronic respiratory insufficiency O2 saturation levels < 94% at rest Renal dialysis Uncontrolled hypertension Severe vascular disease in active smoker Uncompensated diabetes Other severe metabolic disturbances Dementia	scanner with low-dose setting (140 kvp, 40 mA), and reconstructed in overlapping contiguous 5mm increments, 1.25 pitch, with a high-resolution bone algorithm (width 1700, level −600). Hard copies of lung Spiral CT results were considered positive if they showed abnormalities suggestive of malignancy, such as noncalcified pulmonary nodules ≥10mm in diameter or smaller but showing spiculated margins, or non-nodular lesions such as a hilar mass, focal ground-glass opacities, major atelectasis, endobronchial lesions, mediastinal adenopathy, pleural effusion or pleural masses In total, five yearly LDCT screening rounds **Control** Chest X-ray Sputum cytology testing Medical interview and physical examination (five yearly)	Procedures performed in patients without malignancy (5 years, median 33.7 months); 22%/ 16%; NR; NR Invasive procedures (5 years, median 33.7 months); 7.5%/ 3.0%; NR; <0.0001 Procedure related complications (5 years, median 33.7 months); 28.6%/ 19%; NR; NR	Generation of allocation sequence: + Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: + +

Study/Reference	Region, setting inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	Drug or alcohol addiction Schizophrenia or other severe psychiatric conditions Conditions carrying severe disability Previous malignancy (except non-melanoma skin cancer) any organ site, if treated <10 years prior to accrual Early squamous cancer of the larynx/oral cavity, <5 years **Patient characteristics** Smokers (%): 55/56.9 Pack-years (mean, 95% CI): 47.3, 45.7–49.0/ 47.2, 45.5–49.0 Age in years (mean, 95% CI): 64.3, 64.0–64.7/ 64.6, 64.3–64.9	**Included/randomised patients** 1276/ 1196 **Analysed patients** 1276/ 1196 **Attrition** 3.4%/ 5.3% **Excluded from analysis (reason)** NA		

Study/Reference	Region, setting inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	Co-morbid conditions Respiratory (%): 35.0/ 30.99 Hypertension(%): 35.7/ 37.4 Cardiac (%): 12.5/ 13.8 Peripheral vascular (%):10.2/ 9.0 Diabetes (%): 8.2/ 8.3 Other (%): 35.4/ 35.6			
Pastorino, U., et al., Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. Eur J Cancer Prev, 2012. 21(3): p. 308-15.	**Region/Setting** Italy, hospitals **Inclusion criteria** 49 years and above Current or former smokers (having quit smoking within 10 years of recruitment) with at least 20 pack-years of smoking **Exclusion criteria**	**Intervention(s)** Primary prevention (smoking cessation) with pulmonary function rest evaluation + blood sample collection Group 1. Biennial LDCT (120 kV, 30mAs, 0.75mm collimation, gantry rotation time 0.5s, pitch 1.5, 16 slice) Group 2. Annual LDCT (120 kV, 30mAs, 0.75mm collimation,	**Mortality due to lung neoplasm (5 years, median 4.4 years); 6/ 12/ 7; HR=1.52 (CT arms vs. control); 0.21 (p-value overall), 0.63-3.65 (95% CI for HR of CT arms vs. control)** Overall mortality (5 years, median 4.4 years); 20/ 31/ 20; HR=1.39 (CT arms vs. control); 0.13 (p-value	**Study type** RCT **Level of evidence** 1b **Risk of bias** Generation of allocation sequence: +

Study/Reference	Region, setting inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	History of cancer within the previous 5 years **Patient characteristics** ***Age*** <55 (%): 32.0/ 33.1/ 38.1 55-59 (%): 30.6/ 28.4/ 27.7 60-64 (%): 22.0/ 23.0/ 20.6 65-69 (%):12.1/ 11.3/ 10.1 ≥70 (%): 3.4/ 4.2/ 3.3 Median: 58/ 57/ 57 ***Female (%):*** 31.5/ 31.6/ 36.7 ***Smoking Status*** Former (%): 31.7/ 31.1/ 10.3 ***Duration of smoking***	gantry rotation time 0.5s, pitch 1.5, 16 slice) Participants with nodules greater than 250.mm³ were referred for additional workup, including fluorine 18-fluorodeoxyglucose PETor lung biopsy. **Control** Primary prevention (smoking cessation) with pulmonary function rest evaluation + blood sample collection **Included/randomised patients** 1186/ 1190/ 1723 **Analysed patients** 4097 **Attrition** 2 **Excluded from analysis (reason)** NA	overall), 0.83-2.34 (95% CI for HR of CT arms vs. control)	Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, setting inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	<30 (%): 8.3/ 8.6/ 8.1 30-39 (%): 49.2/ 50.8/ 49.7 40-49 (%): 37.3/ 34.6/ 35.9 ≥ 50 (%): 5.2/ 6.1/ 6.3 ***Cigarettes per day*** <20 (%): 23.8/ 22.0/ 33.0 20-29 (%): 51.8/ 52.0/ 42.4 30-39 (%): 11.9/ 11.9/ 14.0 ≥ 40 (%): 12.6/ 14.0/ 10.6 ***Pack years of cigarettes*** Median: 39/ 39/ 38 ***FEV1 (predicted)*** <90 (%): 27.7/ 28.2/ 19.2			
Pedersen, J.H., et al., The Danish randomized lung cancer CT screening trial--overall design and results of the prevalence	**Region/Setting** Denmark, one center **Inclusion criteria**	**Intervention(s)** CT scans of the study were performed on a MDCT scanner (16	**Mortality due to lung neoplasm (5.5 years, median 4.81 years); 0.73%/ 0.54%; 0.428**	**Study type** RCT **Level of evidence**

Study/Reference	Region, setting inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
round. J Thorac Oncol, 2009. 4(5): p. 608-14. Petersen, R.H., et al., Lung cancer screening and video-assisted thoracic surgery. J Thorac Oncol, 2012. 7(6): p. 1026-31. Saghir, Z., et al., CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. Thorax, 2012. 67(4): p. 296-301.	50-70 years Current or former smokers with at least 20 pack years of smoking history Former smokers quit after the age of 50 years and be abstinent for <10 years Ability to climb two flights of stairs (36 steps) without pausing Lung function measured by spirometry and forced expiratory volume in the first second had to be at least 30% of predicted. **Exclusion criteria** Weight over 130 kg History of cancer diagnosis and treatment Lung tuberculosis Illness that would shorten life expectancy to <10 years	rows Philips Mx 8000). Scans were performed supine after full inspiration with caudocranial scan direction including the entire ribcage and upper abdomen with a low dose technique, 120kV and 40 mAs Nodules were classified into four categories according to size and other characteristics: Nodules up to 15 mm in maximal diameter with benign characteristics (for calcified nodules up to 20 mm) (category 1) and nodules below 5 mm (category 2) were tabulated and no further action taken. Nodules with a diameter between 5 and 15 mm not classified as benign were considered indeterminate and were rescanned after 3 months (category 3). Nodules exceeding 15 mm (category 4) and all growing nodules (category 5) were referred for diagnostic investigation, in addition to nodules with suspicious morphology	Overall mortality (5.5 years, median 4.81 years); 2.97%/ 2.05%; 0.059	1b **Risk of bias** Generation of allocation sequence: + Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: +

Study/Reference	Region, setting inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	Chest CT received during the last year for any reason **Patient characteristics (n)** ***Age*** 49: 8/ 6 50–54: 586/ 586 55–59: 676/ 699 60–64: 604/ 571 65–69: 169/ 184 70–74: 9/ 6 Female (%): 22.1/ 22.7 ***FEV1 (Mean, SD)*** Male: 3.3 L, 0.7/ 3.3 L, 0.7 Female: 2.4 L, 0.5/ 2.4 L, 0.5 ***Smoking status***	Nodules category 3, 4, or 5 regarded as screening test positive Five rounds annual **Control** Lung function tests (five annual) **Included/randomised patients** 2052/ 2052 **Analysed patients** NR **Attrition** 15/ 14 **Excluded from analysis (reason)** NA		Other source of bias: +

Study/Reference	Region, setting inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	Current smoker: 1545/ 1579 Former smoker: 507/ 473 ***Smoking duration*** (years) *Current smokers* <26: 22/ 24 26–30: 81/ 85 31–35: 303/ 307 36–40: 504/ 511 41–45: 395/ 400 >45: 240/ 252 *Former smokers* <26: 19/ 12 26–30: 53/ 56 31–35: 143/ 130 36–40: 164/ 167 41–45: 96/ 76 >45: 31/ 32 Missing: 1/ 0			

Study/Reference	Region, setting inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	Cigarettes/day *Current smokers* <10: 158/ 170 10–20: 713/ 701 21–30: 419/ 412 >40: 111/ 103 None: 28/ 45 Missing: 117/ 148 *Former smokers* <10: 22/ 22 10–20: 257/ 239 21–30: 137/ 136 >40: 69/ 46 None: 1/ 4 Missing: 21/ 23 ***Duration of smoking (former smokers)*** <5: 386/ 353 6–10: 110/ 111			

Study/Reference	Region, setting inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	>10: 8/ 9 Missing: 3/ 0			

12.2.2. Thema: Pathologie – Molekular

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
Camps, C., et al., The identification of KRAS mutations at codon 12 in plasma DNA is not a prognostic factor in advanced non-small cell lung cancer patients. Lung Cancer, 2011. 72(3): p. 365-9.	*Included* NR *Attrition* NR *Analyzed* 308 *Excluded from analysis* NR	*Inclusion* Clinical stage IIIB or IV Not undergone previous chemotherapy treatment *Exclusion* Two primary tumors at the time of diagnosis *Patient characteristics* Age (median, range): 60, 31–80 Male (%): 83.8 Female (%): 16.2 Histology	*Setting* NR *Country* Spain	KRAS (allelic discrimination method using fluorogenic RT-PCR, with a GeneAmp 7000 SDS)	Median (month) PFS; mutated vs. wild type; 5.43 vs. 5.77; 0.277 Median (month) OS; mutated vs. wild type; 9.07 vs. 10.03; 0.514	Univariate	*Study type* Cohort study *Level of evidence* 4 *Risk of bias* Participation: ? Attrition: ? PF measurement: + Outcome measurement: + Confounding: - Statistical analysis: -

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		SCC(%): 30.5 ADC(%): 50.6 Others(%): 18.8 Stage IIIB(%): 15.9 IV(%): 84.1 ECOG-PS 0(%): 25.6 1(%): 72.4 Other (%): 1.9 *Treatment* Cisplatin (75 mg/m²) and docetaxel (75 mg/m²) on day 1 every 3 weeks					

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
Bonanno L. et al., Prognostic and Predictive Implications of *EGFR* Mutations, *EGFR* Copy Number and *KRAS* Mutations in Advanced Stage Lung Adeno-carcinoma. Anticancer Research, 2010. 30: p. 5121-28.* *Study is included in the systematic review and meta-analysis of Meng et al.	*Included* 67 *Attrition* NR *Analyzed* 60 (EGFR) 62 (KRAS) *Excluded from analysis* 7 (EGFR-FISH) 5 (KRAS)	*Inclusion* Advanced stage lung adenocarcinoma Therapeutic or diagnostic surgery At least one of the following clinical features: - non-smoker (<100 cigarettes in a lifetime) - former light smoker (<10 packs per year and stopped smoking ≤15 years before sample collection) - female gender *Exclusion* NR	*Setting* Hospital *Country* Italy	EGFR (PCR, pre-sequencing kit, sequenced with both forward and reverse primers, automated sequencing) EGFR (FISH, classified Colorado scoring criteria) KRAS (PCR, pre-sequencing kit, sequenced with both forward and reverse	Median (weeks) OS; EGFR mutated vs. EGFR wild type 99 vs. 92; 0.87 Median OS; EGFR mutated vs. EGFR wild type: NR; NS Median (weeks) OS; FISH positive vs. FISH negative: 177 vs. 57; 0.048 Median OS; FISH positive vs. FISH negative: NR; NS Median(weeks) OS; KRAS positive vs. KRAS negative ; 44 vs. 125; 0.03	Univariate Univariate Univariate Univariate Univariate	*Study type* Cohort study *Level of evidence* 4 *Risk of bias* Participation: - Attrition: ? PF measurement: + Outcome measurement: + Confounding: - Statistical analysis: -

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Patient characteristics Age (median, range): 64, 35-81 Female (%): 48 Male (%): 52 Smoking status Never smoker (%): 57 Former light smoker (%): 22 Current smoker (%): 21 Histology ADC (%): 78 BAC features (%): 22 Stage IIIB(%): 19 IV(%): 81		primers, automated sequencing)	Median OS; KRAS positive vs. KRAS negative: HR=3.52; 1.39-8.9 Median (weeks) PFS; KRAS positive vs. KRAS negative : 11 vs. 28; 0.001	Multivariate (factors NR) Univariate	

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		CNS metastasis No (%): 91 Yes (%): 9 EGFR mutation status (M+: n=16/ WT: n=44) Age (median), M+/WT: 64/ 63 Female (%), M+/WT: 33.3/ 66.4 Male (%), M+/WT: 20/ 80 Smoking status Never smoker (%), M+/WT: 37.1/ 62.9 Former light smoker (%),M+/WT: 23/ 77 Current smoker (%), M+/WT: 0/ 100 Histology					

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		ADC (%), M+/WT: 25.5/ 74.5 BAC features > 80% (%), M+/WT: 33.3/ 66.4 Stage IIIB(%), M+/WT: 0/ 100 IV(%), M+/WT: 34/ 66 CNS metastasis No (%), M+/WT: 24.1/ 75.9 Yes (%), M+/WT: 50/ 50 *EGFR FISH status (positive: n=34/ negative: n=26)* Age (median), +/-: 68 /59 Female (%), +/-: 61.6/ 38.5				

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Set-ting, coun-try	Factor (definition and/or measure-ment if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment fac-tors	Study type, risk of bias
		Male (%), +/-: 53/ 47 Smoking status Never smoker (%), +/-: 58.8/ 41.2 Former light smoker (%), +/-: 50/ 50 Current smoker (%), +/-: 58.3/ 41.7 Histology ADC (%), +/-: 54.9/ 45.1 BAC features > 80% (%), +/-: 55.6/ 44.4 Stage IIIB(%), +/-: 61.5/ 38.5 IV(%), +/-: 55.3/ 44.7 CNS metastasis No (%), +/-: 58.2/ 41.8					

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Yes (%), M+/WT: 60/ 40 *KRAS mutation status (M+: n=12/ WT: n=50)* Age (median), M+/WT: 61/ 64 Female (%), M+/WT: 9.7/ 90.3 Male (%), M+/WT: 29/ 71 Smoking status Never smoker (%), M+/WT: 12.5/ 88.8 Former light smoker (%),M+/WT: 54.5/ 45.5 Current smoker (%), M+/WT: 15.4/ 84.6 Histology					

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		ADC (%), M+/WT: 18.9/ 81.1 BAC features > 80% (%), M+/WT: 22.2/ 77.8 Stage IIIB(%), M+/WT: 15.4/ 84.6 IV(%), M+/WT: 20.4/ 79.6 CNS metastasis No (%), M+/WT: 17.9/ 82.1 Yes (%), M+/WT: 33.3/ 66.7 *Treatment* Chemo 1st line: 45 Chemo 2nd line: 16 Chemo 3nd line: 8 TKIs 1st line: 6					

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Set-ting, coun-try	Factor (definition and/or measure-ment if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment fac-tors	Study type, risk of bias
		TKIs 2nd line: 11 TKIs 3nd line: 3					

Chen X., et al., Effect of gefitinib challenge to initial treatment with non-small cell lung cancer Biomedicine & Pharmacotherapy, 2011. 65: p. 542-6.	*Included* 61 *Attrition* NR *Analyzed* 61 *Excluded from analysis* NR	*Inclusion* Stage IIIB and IV chemotherapy-native Received gefitinib as first-line treatment At least one measurable focus according to RECIST standard Gefitinib 250 mg orally once a day and 28-day cycle *Exclusion* NR *Patient characteristics* Gender Male: 24 Female: 37 Age Age < 70 years: 45 Age ≥ 70 years: 16 Smoking status Smokers: 19 Nonsmokers: 42 Histology Adeno: 38 BAC: 6	*Setting* NR *Country* China	EGFR (NR)	ORR (follow-up NR) mutation vs. unknown or wild type; 50% vs. 14.2%; 0.003 Median (month) OS; mutation vs. unknown or wild type; 17 vs. 11; 0.000 Median (month) PFS; mutation vs. unknown or wild type; 9 vs. 2.5; 0.000	Univariate	*Study type* Cohort study *Level of evidence* 4 *Risk of bias* Participation: + Attrition: ? PF measurement: ? Outcome measurement: ? Confounding: - Statistical analysis: -

		Squamous: 12 Adenosquamous . 5 Clinical stage IIIb: 17 IV: 44 Brain metastasis: 4 PS value ≤2: 46 3-4: 15 EFGR status Mutation: 26 Unknown or wild type: 35					

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
Fiala O., et al., Gene mutation in squamous cell NSCLC: Insignificance of EGFR, KRAS and PIK3CA mutations in prediction of EFGR-TKI treatment efficacy Anticancer research, 2013. 33: p. 1705-12.	*Included* 223 *Attrition* NR *Analyzed* 179 EGFR 174 KRAS *Excluded from analysis* 44 (EGFR) 49 (KRAS)	*Inclusion* Stage IIIB and IV *Exclusion* NR *<u>Patient characteristics</u>* *EGFR mutation status (M+[mutated]: n=16/ WT[wild type]: n=163)* Age (median): 69/ 62 Female (%): 31.3/ 16.6 Male (%): 68.8/ 83.4 Smoking status Current or former smoker (%): 68.8/ 96.8 Never smoker (%): 31.3/ 3.2 EGFR-TKI Gefitinib (n=91, %): 68.8/ 49.1	*Setting* Hospital *Country* Czech Republic	EFGR (PCR processed with a special DNA extraction step or DNA was extracted with standard spin column procedure) KRAS (PCR processed with a special DNA extraction step or DNA was extracted with standard spin column procedure)	Median (month) PFS; EGFR mutated vs. EGFR wild type; 2.9 vs. 1.9; 0.425 Median (month) OS; EGFR mutated vs. EGFR wild type; 6.8 vs. 7.8; 0.673 Median (month) PFS; KRAS mutated vs. KRAS wild type; 1.3 vs. 2.0; 0.120 Median (month) OS; KRAS mutated vs. KRAS wild type; 5.7 vs. 8.2; 0.039	Univariate	*Study type* Cohort study *Level of evidence* 4 *Risk of bias* Participation: - Attrition: ? PF measurement: + Outcome measurement: ? Confounding: - Statistical analysis: -

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Erlotinib (n=88, %): 31.3/ 50.9 Stage IIIB (%): 50/ 36.2 IV (%): 50/ 63.8 Treatment line 1 (%): 12.5/ 13.5 2 (%): 81.3/ 46 3 (%): 6.3/ 39.3 4 (%): 0/ 1.2 ECOG PS 1 (%): 75/ 65 2 (%): 25/ 31.9 others (%): 0/ 3.1 *KRAS mutation status (M+: n=14/ WT: n=160)* Age (median): 56/ 63 Female (%): 35.7/ 16.3 Male (%): 64.3/ 83.8 Smoking status					

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Current or former smoker (%): 85.7/ 94.4 Never smoker (%): 14.3/ 5.1 EGFR-TKI Gefitinib (%): 50/ 49.4 Erlotinib (%): 50/ 50.6 Stage IIIB (%): 28.6/ 38.8 IV (%): 71.4/ 61.3 Treatment line 1 (%): 0/ 2.5 2 (%): 64.3/ 66.3 3 (%): 35.7/ 30.6 4 (%): 0/ 0.6 ECOG PS 0 (%): 7.1/ 13.8 1 (%): 71.4/ 46.3 2 (%): 21.4/ 38.8 3 (%): 0/ 1.3 ADC:43					

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		SLC: 16					
Hirsch et al., Increased EGFR gene copy number detected by fluorescent in situ hybridization predicts outcome in non-small-cell lung cancer patients treated with cetuximab and chemotherapy. Journal of clinical	*Included* 76 *Attrition* NR *Analyzed*	*Inclusion* Not previously treated with chemotherapy or radiotherapy Stage IIB (Pleural infusion) or stage IV disease without brain metastases Performance status of o or 1	*Setting* NR *Country* USA	EGFR (FISH: positive if tumors with ≥4 copies of the EGFR gene in ≥40% of cells or tumors with EFGR gene amplification)	Median (month) OS; positive vs. negative; 15 vs. 7 (HR=0.58); 0.046 Median (month) PFS; positive vs. negative; 6 vs. 3 (HR=0.45); 0.0011	Univariate	*Study type* RCT *Level of evidence* 4 *Risk of bias* Participation: -

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
oncology, 2008. 26 (20): p. 3351-57.	NR *Excluded from analysis* -	Adequate organ function Sequential treatment arm: Paclitaxel 225 mg/m² and carboplatin every 3 weeks plus concurrent cetuximab 400 mg%m²by 2 h infusion on day 1 in week 1 and then 250 mg/m² by 1 h infusion weekly for 4 cycles followed by maintenance cetuximab Concurrent treatment arm: sequential paclitaxel plus carboplatin for 4 cycles followed by cetuximab *Exclusion* NR *Patient characteristics* Female (%): 44 Male (%): 56 Age (median): 64			Median (%) ORR; positive vs. negative; 45 vs. 26; NR FISH positive vs. FISH negative; NR; 0.049 OS (follow-up NR)	Multivariate (factors included treatment arm and EGFR FISH status)	Attrition: ? PF measurement: + Outcome measurement: ? Confounding: - Statistical analysis: -

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Race White (%): 84 Black (%): 9 Asian (%): 6 Unknown (%): 1 Smoking status Current smoker (%): 39 Former light smoker (%): 48 Never smoker (%): 12 Histology ADC (%): 57 Squamos cell carcinoma (%): 18 Other (%): 25 Stage IIIB (%): 9 IV (%): 91					
Kappers et al., Soluble epidermal growth factor receptor (sEGFR) and carcinoembryonic	*Included* 145	*Inclusion* Advanced non-small cell lung cancer	*Setting* Hospital	Soluble EGFR determined by a sandwich quantitative enzyme-	Median (month) OS; sEGFR ≥55 µg/l/ sEGFR <55 µg/l; 0.033	Univariate	*Study type* Cohort study *Level of evidence*

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
antigen (CEA) concentration in patients with non-small cell lung cancer: correlation with survival after erlotinib and gefitinib treatment. E-cancer 2010, 4:178: p: 1-11	*Attrition* NR *Analyzed* 102 *Excluded from analysis* 43	Not responding to conventional chemotherapy or unable to receive chemotherapy due to poor medical condition Treated with gefitinib or erlotinib ≥14 days Treated with gefitinib: daily dose of 250 mg or treated with erlotinib: daily dose of 150 mg Pre-treatment serum available for SEGFR analysis *Exclusion* NR *Patient characteristics* Age (mean, SD): 59, 12.2 Gender: Male: 54 Female: 48	*Country* Netherlands	linked immunosorbent assay	OS (median follow-up 161 days); per sEGFR µg/l/ increment (not specified); HR = 1.044; 1.014-1.075	Multivariate (age, gender, smoking status, tumour stage, histology and treatment drug, CEA levels)	4 *Risk of bias* Participation: ? Attrition: ? PF measurement: + Outcome measurement: + Confounding: - Statistical analysis: -

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Smoking status: Non: 21 Former/Current: 78 Tumour stage: III: 20 IV: 81 Histology: Adenocarcinoma: 66 Non-small cell, undifferentiated: 20 Squamous cell carcinoma: 13 Drug: Gefitinib: 67 Erlotinib: 35 sEGFR (µg/l, mean): <55: 43 ≥55: 59					

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
Kelly et al., Evaluation of KRAS mutations, antgiogenic biomarkers and DCE-MRI in patients with advanced non-small cell lung cancer receiving sorafenib; Clin. Cancer Research 2011, 17 (5): p.1190-1199	*Included* 37 *Attrition* NR *Analyzed* 34 (KRAS) NR (EGFR) *Excluded from analysis* 3 (KRAS) NR (EGFR)	*Inclusion* Age ≥18 years ECOG performance status 0-1 Life expectancy >3 months Histologic or cytologic confirmation of recurrent or progressive advanced NSCLC Only on lone of prior chemotherapy *Exclusion* Patients with symptomatic brain metastases (unless they had treatment and stable disease for at least 3 month without steroids) Excluded in second protocol: patients with squamous cell carcinoma *Patient characteristics*	*Setting* NR *Country* USA	KRAS (Pyrosequencing technology on a PyroMark Q24 instrument and the PyroMark Q24 KRAS v2.0 kit) EGFR (pyrosequencing using a Genetic Analyzer 3130cl)	Median (month) OS; KRAS wildtype vs. KRAS mutant; 13.2 vs.7.2; p=0.59 Median (month) PFS; KRAS wildtype vs. KRAS mutant; 3.6 vs.2.6; p=0.51 Median ORR; KRAS wildtype vs. KRAS mutant; NR; no correlation (according authors) Median OS; EGFR wildtype vs. EGFR mutant; NR; no correlation (according authors) Median PFS; EGFR wildtype vs. EGFR mutant; NR; no correlation (according authors)	Univariate	*Study type* Cohort study *Level of evidence* 4 *Risk of bias* Participation: - Attrition: ? PF measurement: + Outcome measurement: + Confounding: - Statistical analysis: -

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Female (%): 49 Male (%): 51 Age (median): 61 Histology ADC (%): 60 Adenocarcinoma wit BAC features: 24 Squamous cell carcinoma (%): 8 Poorly differentiated carcinoma (%): 5 Others: 3 Race White (%): 68 African American (%): 13 Asian (%): 11 Hispanic/Latino (%): 8 ECOG PS 0 (%): 14 PS 1 (%): 86 No. of prior chemotherapy and targeted regimens			Median ORR; EGFR wildtype vs. EGFR mutant; NR; no correlation (according authors)		

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		1 (%): 46 2 (%): 11 3 (%): 22 4 (%): 8 5 (%): 8 6 (%): 5 Previous therapy Platinum (%): 89 Taxane (%): 78 Erlotinib/ Gefitinib (%): 43 Bevacizumab (%): 40 Pemetrexed (%): 35					
Kim et al., EGFR mutation: Significance as a stratification factor in the era of molecular-targeted therapy; Oncology letters 2011: 2; p: 383-387	*Included* 116 *Attrition* NR *Analyzed* 83	*Inclusion* Stage IIIB/IV Received chemotherapy alone EGFR mutational status was known *Exclusion* NR *Patient characteristics*	*Setting* NR *Country* Japan	EGFR (peptide nucleic acid/ locked nucleic acid PCR clamp method, designed to detect 11 different EGFR mutations)	Median (month) OS; KRAS mutation vs. wild type; 26.8 vs. 10.6 (HR=2.053); 1.033-4.080	Multivariate (gender, performance status, histology, smoking status)	*Study type* Cohort study *Level of evidence* 2b *Risk of bias* Participation: + Attrition: ?

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
	Excluded from analysis 33	Age (median, range): 65, 36-82 Gender Male: 44 Female: 39 Performance status 0-1: 70 2-4: 13 Histology Adenocarcinoma: 66 Squamous cell carcinoma: 3 Large-cell caricinoma: 14 Tumour stage IIIB:16 IV: 67 Smoking status Current smoker: 20 Former smoker: 25 Never smoker: 38 EGFR Mutation: 28 Wild-type: 55					PF measurement: + Outcome measurement: + Confounding: + Statistical analysis: ?

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		First-line chemotherapy Platinum based: 68 Single-agent: 15 No. of regimens (median, range): 3, 1-9 EGFR-TKI treatment yes: 52 no: 31					
Lin et al.; Chemotherapy response in East Asian Non-small cell lung cancer patients harboring wild-type or activating mutation of epidermal growth factor receptors; Journal of Thoracic Oncology 2010: 5 (9) p:1424-29	*Included* 122 *Attrition* NR *Analyzed* 105	*Inclusion* Patients who have archived tissue blocks for analysis of tumor EGFR gene *Exclusion* NR *Patient characteristics (Wild-type EGFR/ Mutated EGFR)*	*Setting* Medical centres *Country* China	EGFR (DNA was extracted from paraffin blocks. Fragments of DNA between exons 18 and 21 were amplified by the nested-reverse transcription polymerase chain reaction)	Median (months) OS; EGFR wild type vs. mutated mutation; 18.6 vs. 20.6; p=0.2159 Median (months) PFS; EGFR wild type vs. mutated mutation; 6.6 vs. 6.1; p=0.2501 Median (%) ORR; EGFR wild type vs. mutated; 30.6 vs. 44.6; p=0.162	Multivariate analysis (gender, smoking status, histology) Univariate	*Study type* Cohort study *Level of evidence* 2b *Risk of bias* Participation: + Attrition: ?

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
	Excluded from analysis 17	Total (%): 52.5/ 47.5 Age <65 (%): 10/ 90 >65 (%): 73.2/ 26.8 Gender Men(%): 58.7/ 41.3 Women (%): 42.6/ 57.4 Smoking status Current (%): 71.1/ 28.9 Former (%): 39.1/ 60.9 Never (%): 45.9/ 54.1 Histology Adenocarcinoma (%): 48.5/ 51.5 Nonadenocarcinoma (%): 68/ 32 Staging Locally advanced IIIA/IIIB (%): 88.2/ 11.8 Metastatic IIIB/IV (%): 46.7/ 53.3 Prior surgery Yes (%): 61.5/ 38.5 No (%): 50/ 50 Gefitinib or Erlotinib use Yes (%): 31.5/ 68.5 No (%): 69.1/ 30.9					PF measurement: + Outcome measurement: + Confounding: + Statistical analysis: + +

Lynch et al., A randomized phase 2 study of erlotinib alone and in combination with bortezomib in previously treated advances non-small cell lung cancer; Journal od thoracic oncology 2009: 4(8), p.:1002-9	*Included* 51 *Attrition* NR *Analyzed* 32 *Excluded from analysis* 19	*Inclusion* Aged ≥18 years with histologically or cytologically confirmed, relapsed or refractory locally stage IIIb or stage IV Measurable disease by RECIST, life expectancy >3months, ECOG PS ≤1 Patients must receive one prior line of conventional cytotoxic chemotherapy for stage IIIb or IV NSCLC Documented progressive disease during or since last prior therapy Received erlotinib alone or erlotinib plus bortezomib *Exclusion* Received previous treatment with bortezomib, an anti-EGFR antibody or anti EGFR-TKI or undergone chemotherapy, radiation therapy, mono clonal antibody therapy or major surgery within 4 weeks before enrolment	*Setting* NR *Country* US and Canada	KRAS (using PCR/ligase detection reaction) EGFR (using PCR/ ligase reaction and capillary electrophoresis, plus fluorescent PCR using primers flanking the hotspot for insertions/ deletions in exon 19)	Median (month) PFS; KRAS mutant vs. KRAS wildtype; NR; ns Median (month) ORR; KRAS mutant vs. KRAS wildtype; 18% vs. 20%; 1.00 Median (month) PFS; EGFR mutant vs. wildtype; 4.3 vs. 1.5; ns Median (month) ORR; EGFR mutant vs. wildtype; 50% vs. 9%; 0.046	Univarate	*Study type* RCT *Level of evidence* 2b *Risk of bias* Participation: + Attrition: + PF measurement: + Outcome measurement: + Confounding: - Statistical analysis: -

		Preexisting interstinal lung disease, grade ≥2 peripheral neuropathy, grade > diarrhea or vomiting or inadequate organ function *Patient characteristics (Erlotinib alone/ Erlotinib plus bortezomib)* Age (median,range): 64, 45-82/62, 36-81 *Sex* Female (%): 48/ 56 Male (%): 52/44 Race White (%): 80/ 84 Black (%): 12/ 4 Asian/ Pacific Islander (%): 8/ 4 Other: -/8 ECOG performance status 0 (%): 28/ 29 1 (%): 72/ 67 3 (%): -/ 4 Histology ADC (%): 56/ 56					

		Squamos cell carcinoma (%): 28/ 28 Pure bronchioalveolar carcinoma (%): 0/ 4 Large cell carcinoma (%): 4/ 4 Other (%): 12/ 12 Stage IIIB (%): 12/ 16 IV (%): 88/ 84 History of smoking (ever smoked, %): Yes: 80/ 84 No: 20/ 16 No. of prior lines of therapy (%): 0: 12/ 4 1: 84/ 76 2 or more: 4/ 20 Prior platinum-based therapy (%): 76/ 88 Prior single-agent therapy (%): 8/ 8					
Mack et al., EGFR mutations detected in plasma are associated with patient outcome in erloinib plus docetacel-	*Included* NR	*Inclusion* Patients with cytologically and histologically defined NSCLC	*Setting* NR	EGFR (DNA was extracted using QIAamp DNA Blood mini kit. Exons 19, 20 and 21 by allele-specific PCR assay	Median (months) PFS; EFGR wildtype vs. mutation; 18.3 vs. 4; 0.012	Univariate	*Study type* Cohort study *Level of evidence*

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
treated non-small cell lung carcinoma; Journal of thoracic oncology (2009); 4 (12); p: 1466-72,	*Attrition* NR *Analyzed* 49 *Excluded from analysis* NR	Docetaxel 70 mg day 1 and erlotinib 600–800 mg days 2, 9, and 16 on a 21-d cycle (14.6% of patients) or Docetaxel 70–75 mg day 1 and erolotinib 150–300 mg days 2–16 on a 21-d cycle (25.0% of patients) or docetaxel 70 mg day 1 and erlotinib 200 mg days 2–16 on a 21-d cycle (60.4 % of patients) *Exclusion* NR *Patient characteristics* *Characteristics* Age (median, range): 59, 34-79 Sex Female (%): 56.3 Male (%): 43.7 Smoking status	*Country* USA	using Scorpion-amplification refractory mutation system, patient was considered positive if a mutation was detected either in plasma or in tumor)	Median (months) OS; EFGR wildtype vs. mutation; 39.6 vs. 17.8; ns Response rate; EFGR wildtype vs. mutation; NR; association (according authors)		4 *Risk of bias* Participation: ? Attrition: ? PF measurement: + Outcome measurement: ? Confounding: - Statistical analysis: -

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Never-smoker (%): 33.3 Former/current smoker (%): 66.7 ECOG performance status 0 (%): 50 ≥1 (%): 50 Race African descent (%): 4.2 White (%): 91.6 East/ South East Asian (%): 4.2 Histological type Adenocarinoma (%): 66.6 Squamous cell carcinoma (%): 14.6 Other (%): 18.8					
Pallis et al., A phase II trial of erlotinib as front-line treatment in clinically selected patients with non-small-cell lung cancer; Clinical lung cancer: 13 (2),p:129-35	*Included* 49 *Attrition* NR *Analyzed* 36	*Inclusion* Chemotherapy-naïve non-smokers (<100 cigarettes in life) or histological or cytological confirmed inoperable lically advanced (stage IIIB) or metastativ (stage IV) NCSLC and histologic feature of adenocarcinoma	*Setting* NR *Country* Greece	DNA sequencing of exons 18-21 of EFGR and exon 2 of KRAS (determined by direct forward and reverse sequencing of the PCR).	ORR (18.9 months); EGFR mutated vs. wild type; 66.7% vs. 14.9%; 0.006 Median (months) PFS; EGFR mutated vs. wild type;12.4 vs.5.8; 0.078 Median (months) OS; EGFR mutated vs. wild	Univariate	*Study type* Cohort study *Level of evidence* 4 *Risk of bias* Participation: ?

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
	Excluded from analysis 13	≥18 years At least 1 unidimensionally measureable lesion ECOG performance status 0-2 Life expectancy >3 months Adequate organ function Central nervous system metastases provided that they had been irradiated and were clinically and radiologically stable Absence of active infection No history of cardiac disease Erlotinib 150 mg per day orally *Exclusion* NR			type; not reached vs.12.97; 0.045 ORR (18.9 months); KRAS mutated vs. wild type; 0 vs. 32.2%; 0.303 Median(months) PFS; KRAS mutated vs. wild type; 3.8 vs.7.5; 0.279 Median [months] OS; KRAS mutated vs. wild type; 6.2 vs.16.2; 0.523		Attrition: ? PF measurement: + Outcome measurement: ? Confounding: - Statistical analysis: -

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Patient characteristics Age (median, Range): 68, 36-81 Sex Male (%): 34.7 Female (%): 65.3 Performance status 0 (%): 22.4 1 (%): 71.4 2 (%): 6.1 Stage IIIB (%): 14.3 IV (%): 85.7 Histologic type AdenoCA (%): 93.9 Bronchoalveolar (%): 6.1 Grade I (%): 12.2 II (%): 26.5 III (%): 14.3 Unknown (%): 46.9					
Ren et al., Tumor gene mutations and messenger RNA expression: correlation with clinical response to icotinib hydrochloride in non-small cell lung cancer;	*Included* 28 *Attrition* NR	*Inclusion* Histologically or cytologically confirmed to be with stage III or IV NSCLC Measurable tumors with Response Evaluation criteria in solid tumors	*Setting* NR *Country* China	EGFR and KRAS (evaluated by Mutant-enriched liquidchip technology)	ORR (at least 2 years); EGFR mutated vs. wildtype; 43% vs. 0; 0.041 Median (days) PFS; EGFR mutated vs.	Univariate	*Study type* Cohort study *Level of evidence* 4

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
Chinese Medical Journal 2011; 124 (1); p: 19-25	*Analyzed* 14 *Excluded from analysis* NR	European Co-operative oncology group ≤1 Previous cytotoxic chemotherapy treatment No chemotherapy for at least three weeks before and had recovered from any previous chemotherapy toxicity Received Icotinib *Exclusion* NR *Patient characteristics* Sex Female: 8 Male: 6 Age (median, range): 53.5, 40-67 Histologic type Adenocarcinoma: 11 Bronchioles alveolar carcinoma: 1			wildtype; 141 vs. 61; 0.850 Median (days) OS; EGFR mutated vs. wildtype; not reached vs.140; p=NR ORR (at least 2 years); KRAS mutated vs. wildtype; 0 vs.25%; 1.00 Median (days) PFS; KRAS mutated vs. wildtype; 86 vs.128.5; 0.3716 Median (days) OS: KRAS mutated vs. wildtype: NR vs.not reached; NR		*Risk of bias* Participation: ? Attrition: ? PF measurement: + Outcome measurement: ? Confounding: - Statistical analysis: -

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Squamous cell carcinoma: 2 Stage III: 3 IV: 11					
Schmid-Bindert et al., Phase II study of pemetrexed and cisplatin plus cetuximab followed by pemetrexed and cetuximab maintenance therapy in patients with advanced nonsquamous non-small cell lung cancer; Lung Cancer (2013): 81; p: 428-34	*Included* 113 *Attrition* NR *Analyzed* 47 *Excluded from analysis* 66	*Inclusion* ≥18 years Histological confirmed measurable stage III or IV nonsquamous NSCLC Eastern Cooperative Oncology Group 0-1 Tissue availability for detection of EGFR expression Estimated life expectancy of ≥ 12 weeks Treated with 4-6 cycles pemerexed 500 mg/m² IV plus cisplatin 75 mg /m² IV on day 1 of each 21-day cycle; cetuximab 400 mg/m² IV Cycle 1/ day 1 with subsequent doses of 250 mg/m² IV weekly	*Setting* NR *Country* Germany	KRAS (detected using the QIAGEN KRAS PCR Kit)	Median ORR; KRAS mutated vs. wild type; NR; no significant association (according authors) Median PFS; KRAS mutated vs. wild type; NR; no significant association (according authors)	Univariate	*Study type* Cohort study *Level of evidence* 4 *Risk of bias* Participation: - Attrition: ? PF measurement: + Outcome measurement: ? Confounding: - Statistical analysis: -

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Exclusion Prior systemic chemotherapy, immunotherapy, targeted therapy or biological therapy for NSCLC Patients with symptomatic central nervous system metastasis < 1 year prior to enrollment Serious conditions within 6 months of study treatment Common Terminology Criteria for Adverse Events≥grade 1 peripheral neuropathy or major surgery within 4 weeks of study entry Unwilling or unable to take folic acid, vitamin B12 or corticosteroids Uncontrollable clinically significant third-space fluid					

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Patient characteristics All treated Age (median, range): 59.7, 38.1-78.7 Sex Male (%): 63.7 Caucasian (%): 100 ECOG PS 0 (%): 49.6 1 (%): 50.4 Disease stage IIIB (%): 8 IV (%): 92					
Schneider et al., Epidermal growth factor receptor-related tumor markers and clinical outcomes with erlotinib in non-small cell lung cancer; Journal of thoracic oncology (2008); 3 (12). P: 1446-1453* *Study is included in the systematic review and	*Included* 393 *Attrition* - *Analyzed* 293 (EGFR ICH)	*Inclusion* ≥18 years Histologically or cytologically confirmed, unresectable stage IIB/IV NSCLC Eastern cooperative oncology group performance status 0-3 1 or 2 prior courses of standard chemotherapy or radiotherapy or were	*Setting* NR *Country* Germany	EGFR protein expression (EGFR PharmDx immunohistochemistry kit)	PFS (maximum 800 days); EGFR IHC <10% vs. ≥10%; HR = 0.79; 0.59-1.06 OS (maximum 800 days); EGFR IHC <10% vs. ≥10%; HR=0.84 ; 0.61-1.14 PFS (maximum 800 days); EGFR IHC none	Univariate	*Study type* Cohort study *Level of evidence* 4 *Risk of bias* Participation: +

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
meta-analysis of Meng et al.	208 (EGFR FISH) 195 (KRAS/EGFR mutations) *Excluded from analysis* 100 (EGFR ICH) 185 (EGFR FISH) 185 (KRAS/EGFR mutations) 195	suitable for such treatment At least 3 or 4 weeks since last treatment (surgery within 4 weeks allowed, if fully recovered) Full recovery from toxicities due to prior therapy Adequate haematological renal and hepatic function Life expectancy ≥12 weeks Negative pregnancy test for women of child-bearing potential Erlotinib 150 mg p.o. per day *Exclusion* Evidence of unstable systemic disease Prior treatment with anti-EFGR agents Previous malignancies (last 5 years, other than		EGFR FISH (samples with high gene copy number were classed as FISH-positive)	vs. any; HR=0.73; 0.51-1.04 OS (maximum 800 days); EGFR IHC none vs. any; HR = 0.73; 0.51-1.06 Response (maximum 800 days); EGFR IHC ≥10% vs. <10%; OR=2.08; 0.46-9.34 Response (maximum 800 days); EGFR (IHC any) vs. none; OR=2.41; 0.31-18.83 Median (months) OS; FISH positive vs. FISH negative; 8.6 vs. 6.1; NR PFS (maximum 800 days); FISH negative vs. positive; HR = 0.58; 0.42-0.82		Attrition: ? PF measurement: + Outcome measurement: ? Confounding: - Statistical analysis: -

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		successful treatment for cervical carcinoma/ skin cancer) Untreated brain metastasis or spinal cord compression Significant ophthalmologic abnormalities *Patient characteristics* Age (median, range): 65, 31-90 Gender Female (%): 41 Male (%): 59 Ethnic origin Caucasian (%): 99 Oriental (%): 1 Histology Adenocarcinoma (%): 51 Squamous cell carcinoma (%): 32 Other (%): 18 Smoking status Never-smoker (%): 24		EGFR exon 18-21 (nested primers PCR with Hot Star Taq)	OS (maximum 800 days); FISH negative vs. positive; HR = 0.63; 0.43-0.91 Response (maximum 800 days); FISH positive vs. negative; OR=3.32, 1.09-10.14 PFS (maximum 800 days); EGFR wildtype vs. mutation; HR= 0.31; 0.13-0.78 OS (maximum 800 days); EGFR wildtype vs. mutation; HR = 0.33; 0.12-0.91 Response (maximum 800 days); EGFR mutation vs. wildtype; OR=33.0, 2.96-370.4 PFS (maximum 800 days); KRAS wildtype vs. mutation; HR=1.56; 0.92-		

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Former or current smoker (%): 75 ECOG PS 0 (%): 22 1 (%): 51 2 (%): 21 3 (%): 5 Stage IIIB (%): 21 IV (%): 79 Line of therapy 1st (%): 19 2nd (%): 40 3rd (%): 37 Tumor characteristics (positive) EGFR IHC (≥10%, %): 81 EGFR IHC (%): 88 EGFR FISH (%): 24 EGFR mutations (%): 7 KRAS mutations (%): 15		KRAS 2 and 3 (nested primers PCR with Hot Star Taq)	2.65 OS; KRAS wildtype vs. mutation; HR=1.64; 0.97-2.80 Response (maximum 800 days); KRAS mutation vs. wildtype; 9.0% vs. 0; 0.590		

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
Wu et al., Frequent EGFR mutations in nonsmall cell lung cancer presenting with miliary intrapulmonary carcinomatosis; European respiratory journal (2013); 41 (2). P:417-24.	*Included* 85 *Attrition* NR *Analyzed* 60 *Excluded from analysis* NR	*Inclusion* Patients with miliary intrapulmonary carcinomatosis at initial diagnosis *Exclusion* NR *Patient characteristics (EGFR mutation/ wild-type)* Age (median, range): 61.2, 41.3-87.7/ 61.7, 39.1-79.6 Sex Female: 21/ 14 Male: 21/4 Smoking Nonsmokers: 31/ 16 Former/ current smokers: 11/ 2 ECOG PS 0-1: 33/ 15 2-4: 9/ 3 Tumour type Nonadenocarcinoma: 1/ 1	*Setting* University hospital *Country* Taiwan	EGFR (using a QiAmp DNA Mini kit , Exons 18-21 was amplified by independent rounds of PCR which were purified and sequenced by using Big Dye Terminator Sequencing Kit)	Median (months) PFS; EGFR mutated vs. wild type: 9.2 vs. 2.7; <0.001 Median (months) OS; EGFR mutated vs. wild type; 17.8 vs. 10.6; 0.008 OS; EGFR mutated vs. wild type; HR=0.19; 0.08-0.44	Univariate Univariate Multivariate (adjusted for sex, age, smoking status, tumour type, extra pulmonary metastasis, EGFR mutation status, EGFR-TKI use and treatment order)	*Study type* Cohort study *Level of evidence* 2b *Risk of bias* Participation: ? Attrition: ? PF measurement: + Outcome measurement: ? Confounding: + Statistical analysis: +

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Adenocarcinoma: 41/ 17 Distant metastasis Bone: 28/ 9 Brain: 17/ 5 Liver: 12/ 5 Adrenal gland: 6/ 2 Others: 5 / 2					

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
Yoshida et al. Clinical outcome of advanced non-small cell lung cancer patients screened for epidermal growth factor receptor gene mutations; L Cancer Res Clin Oncol (2010), 136. P: 527-535.	*Included* 100 *Attrition* NR *Analyzed* NR *Excluded from analysis* NR	*Inclusion* Inoperable stage IIIB/IV NSCLC Adults (≥20 years) with cytological or histological confirmation of locally advanced or metastatic NSCLC Underwent prospective screening for EGFR mutations ≥1 measureable or assessable lesion according to Response Evaluation Criteria in Solid Tumors Geftinib treatment or cytotoxic chemotherapy *Exclusion* Pulmonary fibrosis, interstitial pneumonia or prior treatment with EGFR TKI or antibody	*Setting* Cancer center *Country* Japan	EGFR (exon 19 deletion mutation determined by common fragment analyses using PCR with FAM-labled primer set, PCR products were subjected to electrophoresis on an ABI PRISM 310 instrument)	ORR first-line gefitinib (median 22.2 months); EGFR mutated vs. wild-type: 87% vs. 0; NR ORR after second-line gefitinib (median 22.2 months); EGFR mutated vs. wild-type: 80 vs. 0; NR ORR to first-line cytotoxic chemotherapy (median 22.2 months); EGFR mutated vs. wild-type; 32% vs. 28%; 0.7198 ORR to second-line cytotoxic chemotherapy (%); EGFR mutated vs. wild-type; 20 vs. 6.9; 0.1690 Median (months) PFS in patients treated with cytotoxic chemotherapy as first-line therapy; EGFR mutated vs. wild type; HR	Univariate Multivariate (adjusted for stage, age, gender,	*Study type* Cohort study *Level of evidence* 2b *Risk of bias* Participation: + Attrition: ? PF measurement: + Outcome measurement: ? Confounding: + Statistical analysis: +

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Patient characteristics (Mutation/ Wild-type) Sex Female: 33/ 14 Male: 15/ 38 p<0.0001 Age ≤60: 18/ 23 >60: 30/29 p=0.4942 Histology Adenocarcinoma: 47/ 48 Non-adenocarcinoma: 1/ 4 p=0.1985 Smoking status Never smoker: 32/ 11 Smoker: 16/ 41 p<0.0001 Stage of initial diagnosis IIIB: 7/ 17 IV: 41/ 35 p=0.0341 ECOG PS at initial diagnosis 0/1: 42/ 40 2: 2/ 7			= 1.095; 0.668-1.794 Median (months) PFS in patients treated with cytotoxic chemotherapy as second-line therapy; EGFR mutated vs. wild type; HR = 0.954; 0.528-1.722 OS after first-line treatment; EGFR mutation yes vs. no; HR=1.928; 1.048-3.545	smoking history and PS)	

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		3: 3/ 3 4: 1/ 2 p(0/1 vs.≥2) =0.169 Timing of mutation screening Pre-treatment: 31/ 30 After first-line treatment: 11/16 After second-line treatment: 6/ 5 After third-line treatment: 0/ 1 p=0.4803 Mutation genotype Exon 19 deletion: 23/ - L858R: 25/ -					

Zhang et al.; Role of EGFR SNPs in survival of advanced lung adenocarcinoma patients treated with Gefitinib; Gene (2013), 517; p: 60-64.	*Included* 128 *Attrition* NR *Analyzed* 57 *Excluded from analysis* NR	*Inclusion* At least one measurable lesion with a minimum size in at least one diameter of ≥10 mm for liver, lung, brain or lymph node metastases WHO performance status of 0-1 Life expectancy of ≥3 months Received Gefitinib orally *Exclusion* Previous other EGFR-TKI treatment, pneumonectomy or severe cardio-pulmonary diseases *Patient characteristics* Sex Female (%): 51.6 Male (%): 48.4 Smoking status Smoker (%): 32 Non-smoker (%): 68 Tumor stage at diagnosis IIIB (%): 25 IV (%): 75 EGFR mutation status	*Setting* Hospital/ later outpatient setting *Country* China	EGFR (Genotypes determined by Mass Array system)	PFS (median 16.6 months); EGFR mutated vs. wild type; HR=1.16; 0.90-1.50 OS (median 16.6 months); EGFR mutated vs. wild type; HR=1.14; 0.85-1.53	Multivariate (adjusted for sex, age, smoking status, stages)	*Study type* Cohort study *Level of evidence* 2b *Risk of bias* Participation: - Attrition: ? PF measurement: + Outcome measurement: ? Confounding: + Statistical analysis: -

		Positive (%): 21.9 Negative (%): 22.6 Unidentified (%): 55.5 Age (median, range): 55.2, 32-80					

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
Zhu et al.; Efficacy and clinical/ molecular predictors of erlotinib monotherapy for Chinese advanced non-small cell lung cancer; Chin Med Journal (2010); 22, p: 3200-3205.	*Included* 79 *Attrition* NR *Analyzed* 17 biomarker analysis) *Excluded from analysis* 62	*Inclusion* Histologically or cytological diagnosis of NSCLC Stage IIIB or IV Existence of measurable focus No prior use of anti-EGFR agents Erlotinib p.o. 150 mg per day *Exclusion* NR *Patient characteristics* Age (median, range)): 60.9, 35-83 Sex Male (%): 63.3 Female (%): 36.7 ECOG Performance status 0 (%): 38 1 (%): 31.5 2 (%): 13.9	*Setting* NR *Country* China	EGFR exon 19/21/ KRAS gene mutations (mutant-enriched PCR assay and multiplex branched DANN essay, high expression defined as EGFR mRNA > 75% percentile)	ORR (minimum 3 months); EGFR mRNA expression high vs. mid-low; 16.7 vs. 36.4; 0.600 ORR(minimum 3 months); EGFR mutation vs. wild-type; 50 vs. 11.1; 0.131 ORR(minimum 3 months); KRAS mutation yes vs. no; 0 vs. 35.7; 0.515 Median (weeks) PFS; EGFR mutation vs. wild-type; 66 vs. 12; 0.018 Median (weeks) PFS: EGFR mRNA expression high vs. mid-low; 36 vs. 220.123 Median (weeks) PFS; KRAS mutation yes vs. no; NR0.97	Univariate	*Study type* Cohort study *Level of evidence* 4 *Risk of bias* Participation: + Attrition: ? PF measurement: + Outcome measurement: ? Confounding: - Statistical analysis: -

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		3(%): 16.5 Stage IIIB (%): 38 IV (%): 62 Differentiation High (%): 24.1 Mid-low (%): 62 Unknown (%): 13.9 Histologic type AdenoCA (%): 88.6 Squamous cell carcinoma (%): 10.1 Adenosquamous carcinoma (%): 1.3 Smoking status Former or current smoker (%): 49.4 Non-smoker (%): 50.6 Time since initial diagnosis ≥1 year (%): 44.3 <1year (%): 55.7 Prior chemotherapy Yes (%): 69.6 No (%): 30.4 Rash No (%): 39.1 Yes (%): 60.9					

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Further chemotherapy Yes (%): 39.2 No (%): 60.8 EGFR mRNA expression High (%): 35.3 Mid-low (%): 64.7 EGFR gene mutation Exon 19 mutation (%): 29.4 Exon 21 mutation (%): 17.6 No (%): 52.9 KRAS gene mutation Yes (%): 17.6 No (%): 82.4					
Zhou et al., Epidermal growth factor receptor genotype in plasma DNA and outcome of chemotherapy in the Chinese patients with advanced non-small cell lung cancer; Chin Med Journal (2011); 124 (21) P: 3510-514	*Included* 1NR *Attrition* NR *Analyzed* 145	*Inclusion* Being diagnostically confirmed with the disease by pathologists Receiving confirmed first-line chemotherapy for at least two cycles Having response data for chemotherapy and targeted therapy	*Setting* NR *Country* China	EGFR (Denaturating high performance liquid chromatography method)	ORR (follow-up NR); mutation vs. wild-type; 37% vs. 31.9%; 0.525 Median (months) PFS; EGFR mutation vs. wild-type; 4 vs. 3; ns OS (follow-up NR); EGFR wildtype vs. mutation; HR=0.187; 0.141-0.412	Univariate Multivariate (factors NR)	*Study type* Cohort study *Level of evidence* 2b *Risk of bias* Participation: ? Attrition: ?

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
	Excluded from analysis NR	Availability of peripheral blood from before chemotherapy *Exclusion* NR *Patient characteristics (EGFR mutation/ wild-type)* Age (mean, range): 60.5, 27-76/ 62, 42-78 Gender Male (%): 53.7/ 54.9 Female (%): 46.3/ 45.1 Histology Adenocarcinoma (%): 87/ 64.8 Non-adenocarcinoma (%): 13/ 35.2 Disease stage III (%): 33.3/ 25.3 IV (%): 66.7/ 74.7 ECOG 0-1 (%): 88.9/ 87.9 2 (%): 11.1/ 12.1					PF measurement: + Outcome measurement: ? Confounding: ? Statistical analysis: ?

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Chemotherapy regimens Platinum-based (%): 92.6/ 90.1 Nonplatiunum-based (%): 7.4/ 9.9 Cemotherapy cycles (mean, SD): 17, 3.2/ 26, 2.9					

+ low risk of bias; - high risk of bias, O moderate risk of bias; ? unclear risk of bias, CG: control group; CI: confidence interval; IG: intervention groups; NR: not reported; PF: prognostic factor; ns: not statistical significant

Review/reference	Inclusion/exclusion criteria search period	Prognostic factor	Effect (RR /OR/HR/ MD/SDM [CI]; I2/ Q; N; n)	Level of Evidence and methodological quality
Meng et al., Prognostic value of KRAS mutations in patients with non-small cell lung cancer: A systematic review and meta-analysis; Lung Cancer 2013; 81: p: 1-10	Inclusion criteria KRAS mutation was measured mainly in the primary lung cancer tissue, not in plasma Comparisons of overall survival according to KRAS mutation status, the	KRAS (subgroup stage IIIb-IV)	OS KRAS negative vs. KRAS positive; HR=1.30 [95%CI: 0.99-1.71]; I^2=55.3%, 3; 8; 975	Study type Systematic review with meta-analyses Level of evidence 2a Risk of bias

Review/reference	Inclusion/exclusion criteria search period	Prognostic factor	Effect (RR /OR/HR/ MD/SDM [CI]; I2/ Q; N; n)	Level of Evidence and methodological quality
	number of patients with KRAS should be more than five Hzard ration (HRs) for overall survival according to KRAS mutation status either had to be reported or could be calculated from the data presented When the same author or group reported results obtained from the same patient population in more than one article, the most recent report it the most informative one was included Published as a full text in English Exclusion criteria NR			A-priori design: ? Two reviewers: + Literature search: + Status of publication: - List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: + Conflict of interest: -

Review/reference	Inclusion/exclusion criteria search period	Prognostic factor	Effect (RR /OR/HR/ MD/SDM [CI]; I2/ Q; N; n)	Level of Evidence and methodological quality
	Search period Till November 31, 2012			

+ yes; - no, ? can't answer; O not applicable, CG: control group; CI: confidence interval; IG: intervention groups; NR: not reported

12.2.3. Thema: Pathologie – prognostische Faktoren

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
Amini et al. The role of consolidation therapy for stage III non-small cell lung cancer with persistent N2 disease after induction chemotherapy. Ann Thracic surg (2012), 94. P.: 914-21.	**Region** USA **Inclusion criteria** Stage III NSCLC Treated with induction chemotherapy followed by surgery **Exclusion criteria** Tumors not of non-small cell origin Not having N2 disease at the time of surgery	**Intervention(s)** ***Adjuvant chemotherapy*** Erlotinib n=2 Cisplatin + gemcitabine n=1 Carboplatin + taxol n=1 Pemetrexed n=1 Erlotinib + pemetrexed n=1 **Included patients**	OS (median 28.1 month) NR/NR; HR= 4.29; 1.634-11.24 Local recurrence free survival (median 28.1 month) NR/NR; HR = 1.157; 0.298-4.484	NR	**Study type** Cohort study **Level of evidence** 2b- **Risk of bias** Generation of allocation sequence: - Allocation

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Death within 1 month of surgery Who did not receive postoperative radio therapy (PORT) **Patient characteristics** Age: (median, range): 61, 40-74 **Sex** Female (%): 55.7 ***Smoking status*** Never (%): 24.6 Former (%): 32.8 Current (%); 42.6 ***Karnofsky performance* status** 90-100 (%): 44.3 80 (%): 47.5 <80 (%): 8.2 ***Clinical T status*** T1 (%): 18 T2 (%): 54.1	61 **Analysed patients** 42/14 **Attrition** NR **Excluded from analysis (reason)** NR			concealment: - Blinding of participants and personal: - Blinding of outcome assessment: + Incomplete outcome data: ? Selective reporting: + Other source of bias: - (results are reported inconsistently)

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	T3 (%) 16.4 T4 (%): 11.5 ***Clinical N status*** N0 (%): 1.6 ***Clinical M status*** M0 (%): 100 ***Level of N2 involvement at surgery*** Single station (%): 73.8 Multiple station (%) 26.2 ***Tumor histology*** Moderate (%): 27.9 Poor (%): 62.3 unclear (%): 9.8 ***RECIST response*** CR/RR (%): 47.5 SD/PD (%): 47.5 ***Type of surgery*** Lobectomy/ bilobectomy (%): 80.3 Wedge/ segmentectomy (%): 6.6 Pneumonectomy (%): 13.1				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Pathologic T status T1 (%): 29.5 T2 (%): 55.7 T3 (%): 8.2 T4 (%): 6.6 ***Postoperative chemotherapy*** Concurrent (%) 14.8 Adjuvant (%): 6.6 Both (%): 3.3 None (%): 75.4				
Butts et al., Randomized Phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II non-small-cell lung cancer: Updated survival analyses of JBR-10. Journal of clinical oncology (2010), 28 (1); p.: 29-34.	**Region** USA **Inclusion criteria** ≥18 years Completely resected T2N0, T1N1 or T2N1 non-small-cell lung cancer Acceptable baseline characteristics ECOG performance status of 0 or 1	**Intervention(s)** Adjuvant chemotherapy: 50 mg cisplatin per m² body-surface area on day 1 and 8 every 4 weeks for four cycles and 25 mg of vinorelbine per m² **Control** Observation	**OS (median 9.3 years) 47.1%/ 40.4%; HR= 1.28; 1.01-1.64** Disease specific survival (median 9.3 years);63.6/56.2;HR= 1.37; 1.04-1.81	**Drug-related adverse events among patients who received at least one dose of vinorelbine plus cisplatin** Fatigue (%): 81 Anorexia (%): 55 Alopecia (%): 32 Local toxicity (%): 35 Diarrhea (%): 23 Nausea (%): 80 Vomiting (%): 48 Constipation (%): 47 Infection (%): 22	**Study type** RCT **Level of evidence** 2b **Risk of bias** Generation of allocation sequence: ? Allocation concealment: ?

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
Winton T. et al., Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer, NEJM (2005), 352 (25), p: 2586-2597.	Mandatory: Preoperative computed computer tomographic scan and intraoperative mediastinal lymph-node resection or biopsy of nodes that were 1.5 cm or larger **Exclusion criteria** Incomplete preoperative or intraoperative staging Incomplete resection, wedge or segmental resection Iinvolvement of tracheobronchial angle nodes (station 10) or more central mediastinal nodes Mixed histologic features	**Included/randomised patients** 240/ 242 **Analysed patients** 240/ 242 **Attrition** 18/15 **Excluded from analysis (reason)** NR (received at least one dose)		Febrile neutropenia (%): 7 Hearing loss (%): 21 Sensory neuropathy (%): 48 Motor neuropathy (%): 15 Dyspnea (%): 18 Thrombocytopenia (%): 32 Anemia (%): 93 Neuropenia (%): 88 ALT elevation (%): 18 Creatinine elevation (%): 16 Bilirubin elevation (%): 4	Blinding of participants and personal: - Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: ?

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	A T3 tumor, or diffuse lobar or multifocal bronchioalveolar carcinoma, melanoma, or other cancer treated within the previous five years Clinically significant cardiac dysfunction, active infection, or neurologic or psychiatric disorders **Patient characteristics** Age (median): 60.5/ 61 Female (%):34/ 36 ***ECOG PS*** 0 : 120/ 116 1 : 122/123 ***Smoking status*** ever smoked (%):96/ 91 No longer smoking (%): 84/ 85				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Postsurgical stage T2N0 (%): 46/ 45 T1N1 (%): 16/ 13 T2N1 (%): 38/ 42 ***Histology*** Adenocarcinoma (%): 53/ 53 Squamous (%): 37/38 Other (%): 10/ 9 ***Comorbidity*** None (%):66.5 / 77 Present (%): 33.5/ 32 ***RAS mutation*** Absent (%):68/ 71 Present (%): 24/ 24 Unknown (%):8/ 5 ***Tumor diameter (stage IB)*** <4 cm : 45/ 54 ≥4 cm : 66/ 54				
Douillard J-Y. et al.; Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA	**Region** Europe **Inclusion criteria** Stage I (T2N0 only),	**Intervention(s)** Vinorelbine 30 mg/m² on days 1, 8, 15 and 22 (cycles repeated every 4 weeks) for maximum of 16 doses	**Progression free survival (median 76/ 77 months)** **14%/8%; HR= 1.316; 1.099-1.563**	**WHO grade >0** Neutropenia (%): 92/ 4 Anaemia (%): 78/ 6 Thrombocytopenia (%): 14/ 1	**Study type** RCT **Level of evidence** 2b

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
non-small-cell lung cancer (Adjuvant Navelbine International trial Association [ANITA]: a randomized controlled trial Lancet Oncol 2006; 7: p. 719-27.	stage II and stage IIIA NSCLC Complete resection of the primary tumor (all margins free of disease: R0) Age 18-75 years WHO performance status ≤2 Adequate biological functions **Exclusion criteria** History of concurrent malignant disease (apart from adequately treated non-melanoma skin cancer or in-situ cervical cancer) Previous primary tumors **Patient characteristics**	and cisplatin 100 mg/ m² on days1, 29, 57 and 85 **Control** Observation **Included/randomised patients** 407/ 433 **Analysed patients** 407/ 433 **Attrition** NR **Excluded from analysis (reason)** **NA**	Median progression free survival (months) 36.3/20.7;NR;NR OS (median 76/77 months) Difference between groups 8.4%; HR= 1.25; 1.042-1.515 Median survival (months) 65.7/43.7; NR; ns The test of interaction for survival Nodal status positive vs. negative; 0.004	Febrile neutropenia (%): 9/ 0 Infection (%): 32/ 10 Nausea or vomiting (%): 80/ 7 Diarrhoea (%): 16/ 2 Constipation (%): 45/ 5 Anorexia (%): 71/ 17 Asthenia (%): 82/ 32 Peripheral neuropathy (%): 28/ 1 Alopecia (%): 57/ 0	**Risk of bias** Generation of allocation sequence: ? Allocation concealment: - Blinding of participants and personal: - Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Age (median, range): 59, 32-75/ 59, 18-75 < 55 years (%): 33/35 ≥ 55 years (%): 67/ 65 **Sex** Female (%): 14/ 13 ***Time from surgery to randomization (days,*** median, range): 34 , 6-5/ 33, 7-53 ***Type of surgery*** Pneumonectomy (%): 38/ 36 Lobectomy (%): 57/ 58 Other (%): 4/ 5 ***Postoperative stage*** I (%): 36/ 36 II (%): 22/ 26 IIIA (%): 41/ 37 ***Lymph nodal status*** N0 (%): 44/ 43 N1 (%): 26/ 31 N2 (%): 29/ 24 ***Histology*** Squamous-cell carcinoma (%): 59/ 58 Non squamous cell		Local relapse (median 76/ 77 months) 12% vs. 18%; NR; 0.025		

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	carcinoma (%): 40/ 41 ***WHO-performance status*** 0 (%):48/ 52 1 (%): 47/ 44 2 (%): 3/ 3				
Felip et al., Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early stage non-small-cell lung cancer; Journal of clinical oncology; 2010; 28 (19): p. 3138-3145.	**Region** Europe **Inclusion criteria** Clinical stage IA Tumor size > 2 cm, IB, II or T3N1 NSCLC considered Resectable Age ≥ 18 years Eastern Cooperative Oncology Group PS: 0-2 Absence of previous chemotherapy or radiotherapy	**Intervention(s)** Surgery and adjuvant chemotherapy with paclitaxel (200 mg per square meter of bodysurface area, IV over 3 hours) followed by carboplatin; 6.0 mg/mL/min IV over 30 to 60 min) Treatment was repeated every 3 weeks for three cycles **Control** Surgery alone + observation	**Disease free survival (5 years)** **36.6%/34.1%; HR=1.042; 0.82-1.33** OS (5 years) 45,5/44%; HR = 0.99; 0.606-1.613	Neutropenia (%): 27.3/ NR Thrombocytopenia (%): 15.8/ NR Anemia (%): 42.4/ NR Nausea & vomiting (%): 31.7 / NR Febrile neutropenia (%): 0.7/ NR Diarrhea (%): 11.5/ NR Hyperglycemia (%): 15.8/ NR Arthralgias (%): 23.7 / NR Myalgias (%): 28.8 / NR Fatigue (%): 33.8 / NR Sensory neuropathy (%): 32.4/ NR Allergic reaction (%): 2.2/ NR	**Study type** RCT **Level of evidence** 2b **Risk of bias** Generation of allocation sequence: ? Allocation concealment: + Blinding of participants and personal: -

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Adequate hematologic, hepatic and renal function Deemed fit for chemotherapy and proposed surgical resection **Exclusion criteria** Previous cancer other than nonmelanoma skin cancer or carcinoma in situ to the cervix Clinically significant cardiac dysfunction, active infection or neurologic or psychiatric disorders ***Patient characteristics*** Age (median, range): 64, 33-81/ 64 36-89, **Sex**	**Included/randomised patients** 211/ 212 **Analysed patients** 210/ 210 **Attrition** NR **Excluded from analysis (reason)** 0/0			Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Female (%): 13.8/ 12.4 ***ECOG performance status*** 0 (%):45.2/ 48.6 1 (%):52.9/ 50 ***Histological features*** Squamous-cell carcinoma (%):49/ 50 Adenocarcinoma (%):32.9/ 33.8 Large-cell carcinoma (%):11.4/ 10 Others (%):6.7/ 6.2 ***Clinical stage*** T1N0 (%):14.3/ 9.5 T2N0 (%):63.3/ 63.8 T2N1 (%): 11.9/ 11.9 T3N0 (%):8.6/ 12.4				
Gottfried M. et al., Cisplatin-based three drugs combination (NIP) as induction and adjuvant treatment in locally advanced non-small cell lung cancer, Journal of thoracic	**Region** Europe **Inclusion criteria** Present histologic and/or cytologic evidence of NSCLC	**Intervention(s)** Adjuvant cisplatin-based three drugs combination (NIP) chemotherapy (two cycles): vinorelbine 25 mg/ m² IV in days 1 and 5, isofamide/	**Median survival (months)** **31.8/ 32.3; NR; NR** Median disease-free survival (months) 16.8/ 16.8; NR; NR	**Adjuvant/ Control** Nausea/vomiting (%): 12.5/ 0 Alopecia (%): 19/ 0 Infection (%): 6/ 3 Asthenia (%): 6/ 3 Pain (%): 0/ 6	**Study type** RCT **Level of evidence** 2b **Risk of bias**

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
oncology (2008), 3 (2), p: 152- 57.	Locally advanced disease (T3/T4 or IIIA tumors) without any previous treatment Aged ≥18 Eastern Cooperative Oncology Group performance status ≤2 Life expectancy ≥3 months At least one assessable lesion, with blood and biochemical parameters within normal ranges **Exclusion criteria** Superior vena cava syndrome Central nervous system metastasis Second malignancy (except adequately	mesna 3 g/m² on day 1, cisplatin 80 mg/ m² IV on day 1 repeated every 21 days. Three courses of NIP were given unless rapid disease progression occurred. **Control** Observation **Included/randomised patients** 37/ 42 **Analysed patients** 37/ 42 **Attrition** NR **Excluded from analysis (reason)** NR		Anorexia (%): 0/ 3	Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: + Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	treated basal cell carcinoma of the skin and carcinoma in situ of the uterine cervix) Active infectious disease Pregnancy Neurologic disorders which could interfere with the evaluation of neurologic toxicity and mentally incapacitated patients Family, social or environmental conditions impairing adequate follow-up and protocol compliance Breast-feeding **Patient characteristics**				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Age (median, range): 59, 35-75 ***Sex*** Female (%): 15 ***Histology*** Squamous cell (%): 52 Adenocarcinoma (%): 31 Large cell carcinoma (%): 6 NSCLC (NOS) (%): 11 ***Stage at diagnosis*** IIB (%): 28 IIIA (%): 65 IIIB (%): 7 ***Performance status*** 0-1 (%): 99 2 (%): 1 **T diameter** (cm, median, range): 5.5, 1.2–10.6 N0 (%): 34 N1 (%): 1 N2 (%): 65				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
Nakagawa K. et al., Randomised study of adjuvant chemotherapy for completely resected p-stage i-IIA non-small cell lung cancer; British Journal of Cancer (2006): 95; p: 817-821.	**Region** Japan **Inclusion criteria** Untreated primary lung cancer Histologically confirmed diagnosis of squamous cell carcinoma, adenocarcinoma, or large cell carcinoma Pathologically documented stage I, II; IIIA disease, diploidy or aneuploidy in analysis if nuclear DNA of primary tumor Age ≤ 75 years in patients with stage I disease or ≤ 70 years in patients with stage II and IIIA disease ECOG PS 0,1, or 2	**Intervention(s):** Group B (Stage I): single daily oral administration of UFT (oral anti-cancer drug, combination of Uracil and Tegaful) Group D (Stages II and IIIA): two 28-day courses of chemotherapy with cisplatin (80 mg m^{-2}) on day 1 and vindesine (3 mg m^{-2}) on day 1 and 8, starting 3-6 weeks after surgery, followed by single daily oral administration of UFT at 400 mg day^{-1} for at least 1 year **Control** Group A (Stage I): observation	**OS (8 year)** **Group A vs. Group B: 57.6% / 74.2; NR; 0.045** **Group C vs. Group D: 36.8%/ 38; NR; 0.52.** Disease-free survival (8 year) Group A vs. B: NR; NR; ns Group C vs. D; NR; NR; ns	**Group A / D** Leucopenia : 10/ 26 Thrombocytopenia : 2/ 5 Anaemia : 1/ 14 AST: 6/ NR ALT: 7/ NR Anorexia : 19/ 27 Nausea/ Vomiting: 9/ 18 Diarrhoea: 4/ 5 Stomatitis: 4/ 4 Alopecia: 1/ 15	**Study type** RCT **Level of evidence** 2b **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: + Incomplete outcome data: ?

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Adequate organ function **Exclusion criteria** Serious concurrent conditions **Patient characteristics** ***<u>Group B/ A</u>*** ***Sex*** Male : 49/ 49 Female : 36/ 38 Age (average): 60.2/ 60.9 ***PS*** 0: 66/ 66 1: 19/19 2: 0/ 2 ***pT*** 1: 45/41 2 : 40/ 46 ***Stage*** I: 85/ 87	Group C (Stages II and IIIA): observation **Included/ randomised patients** A / B: 87/ 85 C /D: 48/ 47 **Analysed patients** A/B: 87/ 85 C/D: 48/ 47 **Attrition** NR **Excluded from analysis (reason)** NR			Selective reporting: + Other source of bias: - (no adjustment for multiple comparisons)

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Histology Adenocarcinoma: 68/ 67 Squamous cell carcinoma: 15/ 17 Large cell carcinoma: 2/ 3 ***DNA pattern*** Diploidy: 17/ 18 Aneuploidy: 68/ 69 ***<u>Group D/ C</u>*** ***Sex*** Male: 35/ 35 Female: 12/ 13 Age (average): 60.5/ 59.3 **PS** 0: 35/ 36 1: 10/12 2: 2/ 0 **pT** 1: 13/ 12 2: 24/ 24				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	3: 10/ 12 ***Stage*** II: 17/ 16 IIIA: 30/ 32 ***Histology*** Adenocarcinoma: 27/ 29 Squamous cell carcinoma: 17/ 17 Large cell carcinoma: 3/ 2 ***DNA pattern*** Diploidy: 8/ 10 Aneuploidy: 39/ 38				
Ou W. et al.; Adjuvant carboplatin-based chemotherapy in resected stage IIIA-N2 non-small cell lung cancer; Journal of thoracic oncology (2010), 5 (7); p: 1033-41.	**Region** China **Inclusion criteria** Age 18 to 75 Eastern Cooperative Performance status ≤1 No significant weight loss	**Intervention(s)** Surgery plus adjuvant vinorelbine (25 mg/m² administered as a 10-minute infusion on days 1 and 8)/ carboplatin OR paclitaxel (175 mg/m² given as a 3-hour infusion in day 1) /carboplatin (AUC=5) doublets	**Median OS (months)** **33/ 24; NR; ns** **OS (median 35/ 28 months) NR/NR; HR=1.505; 1.040-2.178** Median disease free survival (months)	**Vinorelbine/Paclitaxel/CG** Severe adverse events (%): 5.3/ 2.4/ NR Leukopenia (%): 21.1/ 17.1/ NR Neutropenia (%): 47.5/ 36.6/ NR Anemia (%): 2.6/ 2.4/ NR Nausea (%): 2.6/ 2.4/ NR Vomiting (%): 2.6/ 2.4/ NR	**Study type** RCT **Level of evidence** 2c **Risk of bias** Generation of allocation sequence:

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Adequate bone marrow reserves CT scans for chest, abdomen, and magnetic resonance imaging or CT scans of brain to exclude any systematic involvement **Exclusion criteria** Prior malignancy Coexisting serious nonstabilized Active uncontrolled infection Received previous chemotherapy, immunotherapy or thoracic irradiation Underwent sleeve or wedge resection of the tumor	**Control** surgery plus observation **Included/randomised patients** 79 (n=38:vinorelbine plus carboplatin/ n=41: paclitaxel plus carboplatin) / 71 **Analysed patients** 79/ 71 **Attrition** NR **Excluded from analysis (reason)** NR	32/ 20; NR; NR Disease free survival (median 35/ 28 months) NR/ NR; HR=1.560; 1.064-2.287 Local regional recurrence median 35/ 28 months) 27.8%/21.1%; NR; 0.340		- Allocation concealment: - Blinding of participants and personal: - Blinding of outcome assessment: + Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Patient characteristics Age (median, range): 54, 31-73/ 59, 24-75 p=0.629 ***Sex*** Male (%) 70.8/ 76.1 Female (%): 29.2/ 23.9 p=0.475 ***Histologic features*** Squamous (%): 22.8/ 33.8 Nonsquamous (%): 79.2/ 69.2 p=0.133 ***T stage*** T1 (%): 10.1/ 12.7 T2 (%): 69.6/ 52.1 T3 (%): 20.3/ 35.2 p=0.076 ***N stage (Metastatic no. of LN)*** 1-3 (%): 60.8/ 66.2 4-10 (%): 38.0/ 32.4 >10 (%): 1.2/ 1.4 p=0.775				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Metastatic level of LN F1 (%): 63.3/ 77.5 F2 (%): 32.9/ 19.7 F3 (%): 3.8/ 2.8 p=0.164 ***Extent of reception*** Lobectomy (%): 86.1/ 76.1 Pneumonectomy (%): 13.9/ 23.9 p=0.116				

+ low risk of bias; - high risk of bias, ? unclear risk of bias, CG: control group; CI: confidence interval; IG: intervention groups; NR: not reported; not statistical significant

Review/reference	Inclusion, exclusion criteria search period (patients marked bold)	Intervention (IG), control (CG)	Outcomes (HR [CI or p]; n)	Level of evidence and methodological quality
Douillard J-Y. et al.; Adjuvant cisplatin and vinorelbine for completely resected non-small cell lung cancer; Journal of thoracic oncology (2010), 5 (2), p: 220-28.	***Inclusion criteria*** Randomized trials performed after the NSCLC meta-analysis published in 1995 Included only patients with completely resected NSCL	***Intervention(s)*** Cisplatin-vinorelbine adjuvant chemotherapy ***Control***	**OS (median 5.2 years)** **Chemotherapy vs. observation; HR= 1.25 [1.099-1.429]; n = 2823**	***Level of evidence*** 2a ***Methodological quality***

Review/reference	Inclusion, exclusion criteria search period (patients marked bold)	Intervention (IG), control (CG)	Outcomes (HR [CI or p]; n)	Level of evidence and methodological quality
	Compared cisplatin-based chemotherapy versus no chemotherapy Squamous cell: 48.5% ***Exclusion criteria*** Trials using concomitant radiochemotherapy or preoperative chemotherapy Incompletely resected patients Included in the 1995 meta-analysis ***Search period*** 1995-2003	Observation	Disease-free survival (median 5.2 years); Chemotherapy vs. observation; HR= 1.333 [1.176-1.493]; n=2965	NA (individual patient data meta-analysis)

CG: control group; CI: confidence interval; IG: intervention groups; NR: not reported; ns: not statistical significant

12.2.4. Thema Pathologie – Resektionsränder

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
Chen F., Clinicopathological characteristics of surgically resected pulmonary pleomorphic carcinoma; Europ. Journal of Cardio-Thoracic Surgery. 2012; 41: 1037-1042.	*Included* 28 *Attrition* 2 *Analyzed* 26 *Excluded from analysis* 2 (tumour was not completely resected surgically due to its invasion of the	*Inclusion* Pulmonary resection for pleomorphic carcinoma *Exclusion* - *Patient characteristics* Age (median range): 69,49-83 Gender Male: 24 Female: 2 Presenting symptoms Yes: 15 No: 11 CEA levels High (≥ 5ng/ml): 6 Low (< 5ng/ml): 20 Smoking habits	*Setting* Hospital *Country* Japan	Microscopically complete/ incomplete resection (determining the extent of resection by intraoperative frozen tissue examinations)	OS (2 year); complete resection yes vs. no; 86.5% vs. NR; 0.037 OS (5 year); complete resection yes vs. no; 51.9% vs. NR; 0.037 OS (NR); invasion to the visceral pleural surface yes vs. no; yes > no; 0.048	Univariate	*Study type* Cohort study *Level of evidence* 4 *Risk of bias* Participation: + Attrition: ? PF measurement: + Outcome measurement: + Confounding: -

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
	thoracic aorta [n=1] and small-cell carcinoma was also detected in the resected lung [n=1])	Yes: 22 No: 4 Tumour location Upper lobe: 22 Lower lobe: 4 Tumour size (mm) range (median): 14-100 (45) P-T stage 1: 2 2: 15 3: 7 4: 2 PI factor 0: 5 1: 7 2: 4 3: 10 P-N stage 0: 19 1: 5 2: 2 P-staging I: 12 II: 9 III: 5 Microscopically					Statistical analysis: -

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		complete resection Yes: 23 No: 3 Adjuvant chemotherapy Yes: 9 No: 17					
Chua T.C., Surgical management of melanoma lung metastasis: an analysis of survival outcomes in 292 consecutive patients: Annals of surgical oncology 2012; 19: 1774-1781.	*Included* 292 *Attrition* NR *Analyzed* 292 *Excluded from analysis* -	*Inclusion criteria* Patients undergoing surgical management of melanoma lung metastasis Intrathoracic lesions that appeared technically resectable on diagnostic imaging General and functional risks were considered to be tolerable Any extrathoracic disease was planned for	*Setting* Hospital *Country* Australia	Marginal involvement (R0= microscopically clear R1= microscopically involved R2= Macroscopically involved)	OS (median 20 months); marginal involvement no vs. yes; HR=1.4; 1.1-1.7 PFS (median 20 months); marginal involvement no vs. yes; HR=1.5; 1.2-1.9	Multivariate (no. of pulmonary metastasis; size of largest lung metastasis; Cancer stage of primary tumor; positive lymph node) Multivariate (no. of pulmonary metastasis; size of largest lung metastasis; Cancer stage of primary tumor; Time from diagnosis of	*Study type* Cohort study *Level of evidence* 2b *Risk of bias* Participation: + Attrition: ? PF measurement: +

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		resection either synchronously or as a staged procedure Pathologic features consistent with melanoma in preoperative biopsy Primary lesion controlled *Exclusion criteria* NR *Patient characteristics* Sex Male (%): 71 Female (%): 29 Age (mean, SD): 58, 14 Median (range): 59 (19-84) Primary melanoma site				primary tumor; Disease-free interval; histologic subtype of primary melanoma; positive lymph node)	Outcome measurement: ? Confounding: + Statistical analysis: +

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Extremity (%): 35 Trunk (%): 26 Head and neck (%): 26 Unknown (%): 11 Histologic subtype of primary melanoma Nodular (%): 31 Superficial spreading (%): 25 Occult (%): 16 Desmoplastic (%): 9 Not classified (%): 16 American joint committee on cancer stage of primary tumor I (%): 23 II (%): 47 III (%): 17 IV (%): 13 No. of pulmonary metastasis (mean, SD): 2, 3 Median (range): 1					

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		(1-40) 1 (%): 59 2-3 (%): 32 >3 (%): 9 Size of largest metastasis (cm, mean, SD): 3, 2 Median (range): 2 (1.15) ≤2cm (%): 52 >2cm (%): 48 Extent of lung involvement Unilateral (%): 94 Bilateral (%): 6 Time from diagnosis of primary tumor (month) Median (range): 44 (0-479) Disease-free interval (month) Median (range): 22 (0-479) Prior treatment of nonpulmonary recurrences					

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		No (%): 62 Yes (%): 38					

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
Collaud S., Long-term outcome after en bloc resection of non-small-cell lung cancer invading the pulmonary sulcus and spine: Journal of thoracic oncology: 2013: 8 (12): 1538-1544.	*Included* 48 *Attrition* NR *Analyzed* 48 *Excluded from analysis* NR	*Inclusion criteria* Underwent en bloc surgical resection of NSCLC invading the pulmonary sulcus and spine without evidence of distant metastasis *Exclusion criteria* Tumor infiltration into the spinal canal or into the brachial plexus at C7 nerve root and above were generally considered to be inoperable *Patient characteristics* Age (median, range): 62, 32 – 78 Sex Female: 17	*Setting* Hospital *Country* Canada	Complete resection (R0: resection with microscopic tumor-free margins)	OS (median 26 months); residual margin R1/R2 vs. R0; HR= 0.577; 0.125 – 2.672	Multivariate (response to induction; ICU length of stay)	*Study type* Cohort study *Level of evidence* 2b *Risk of bias* Participation: + Attrition: ? PF measurement: + Outcome measurement: + Confounding: + Statistical analysis:

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Male: 31 Tumor histology Squamous cell carcinoma (%): 40 Adenocarcinoma (%): 33 Large-cell carcinoma (%): 6 Other (%): 21 Clinical stage IIB (%): 6 IIIA (%): 92 IIIB (%): 2 Inductions treatment chemoradiation (%): 94 chemotherapy (%): 2 radiation (%): 2 Two stage procedure (%): 48 Resection Complete: 42 Incomplete: 6					+

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
Koike T; Risk factor analysis of locoregional recurrence after sublobar resection in patients with clinical stage IA non-small cell lung cancer: Journal of thoracic and cardiovascular surgery (2013): 372-378.	*Included* 328 *Attrition* NR *Analyzed* 328 *Excluded from analysis* NR	*Inclusion criteria* Clinical stage IA NSCLC Undergone segmentectomy or wedge resection Exclusion criteria Nonperipherally located carcinoma Multiple lung carcinomas, Pleural dissemination, positive pleural effusion or lavage cytology Planned an adjuvant therapy after surgical resection Adenocarcinoma in situ. *Patient characteristics*	*Setting* Hospital *Country* Japan	Microscopic surgical margin	Locoregional recurrence (median: 58 months); negative vs. positive surgical margin; HR=3.888; 1.634-9.255 Disease-specific survival (median: 62 months); negative vs. positive surgical margin; HR=3.211; 1.427-7.255 Locoregional recurrence (median: 58 months); visceral pleura invasion absent vs. present; 2.272; 1.282-4.027 Disease-specific survival (median: 62 months); visceral pleura invasion absent vs. present; 2.553; 1.503-4.338	Multivariate (sex, tumor location, reason for sublobar resection, pulmonary resection extent, lyphadenectomy extent, tumor histology, microscopic surgical margin, lymph node metastasis, lymphatic permeation and vascular invasion, age BI, preoperative serum CEA, tumor size on preoperative radiologic imaging, Cons/Tumor ratio on CT, tumor size in the resected lung specimens).	*Study type* Cohort study *Level of evidence* 2b *Risk of bias* Participation: + Attrition: ? PF measurement: + Outcome measurement: ? Confounding: +

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Age ≤ 71 y (%): 54 > 71 y (%): 46 Sex Male (%): 60 Female (%): 40 Smoking status 0 (%): 42 <0-600 (%): 10 >600 (%): 48 CEA Within normal range (%): 84 Elevated (%): 16 Tumor location Right upper or middle lobe (%): 35 Right lower lobe (%): 21 Left upper lobe (%): 27 Left lower lobe (%): 17 Tumor size ≤2.0 cm (%): 76 2,1-2.0 cm (%): 24 Cons/ Tumor ratio					Statistical analysis: +

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		≤75% (%): 27 > 75% (%): 63 Reason for sublobar resection Compromised (%): 49 Intentional (%): 51 Pulmonary resection extent Sampling only (%): 74 Systematic mediastinal node dissection (%): 26 Tumor histology Adenocarcinoma (%): 82 Squamous cell carcinoma (%): 14 Tumor size, pathologic ≤2.0 cm (%): 75 2.1-3.0 cm (%): 20 Microscopic surgical margin Positive (%): 3 Negative (%): 97					

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Lymph node metastasis Absent (%): 97 Present (%): 3 Visceral pleural invasion Absent (%): 79 Present: 21					
Moretti L., Prognostic factors for resected non-small cell lung cancer with oN2 Status: Implications for use of postoperative radiotherapy; Oncologist (2009): 14 (11): 1106-1115.	*Included* 83 *Attrition* NR *Analyzed* 83 *Excluded from analysis*	*Inclusion criteria* Resection consisting of a lobectomy or pneumonectomy Pathological confirmation of pN2 NSCLC Complete information on tumor size, tumor location, extent of disease/ lymph node involvement, surgical margin status,	*Setting* Hospital *Country* USA	Extracapsular extension Surgical margin	Local recurrence-free survival (median 64 months); positive extracapsular extension (ECE) vs. negative ECE; HR=0.311; 0.118-0.799 OS (2 years); negative vs. positive margin; 37% (26-47) vs. 18% (8-27); 0.016	Extracapsular extension (local recurrence-free surviva): multivariate (radiotherapy, chemotherapy, age at diagnosis and gender) Other comparisons: univariate	*Study type* Cohort study *Level of evidence* 2b *Risk of bias* Participation: -

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
	NA	ECE status, cause of death *Exclusion criteria* Received neoadjuvant chemotherapy/ radiation therapy Patient characteristics Gender Female (%) 42.2 Male (%): 57.8 Age at diagnosis ≤60 yrs (%): 39.8 >60 yrs (%): 60.2 Histology SCC (%): 36.1 Other (%): 63.9 Tumor size ≤40 mm (%): 54.2 >40 mm (%): 45.8 n of nodal stations involved ≤1 (%): 39.8			Local recurrence-free survival (2 years); negative vs. positive margin; 59%(45-73) vs. NA; 0.753		Attrition: ? PF measurement: ? Outcome measurement: ? Confounding: + Statistical analysis: +

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		>1 (%): 60.2 Surgical margins Negative (%): 85.5 Positive (%): 14.5 ECE Negative (%): 83.1 Positive (%): 16.9					
Sawabata N. et al.; Clinical implications of the margin cytology findings and margin/ tumor size ratio in patients who underwent pulmonary excision for peripheral non-small cell lung cancer: Surgery Today (2012): 42: 238-244.	*Included* 37 *Attrition* NR *Analyzed* 37 *Excluded from analysis* NR	*Inclusion criteria* NSCLC *Exclusion criteria* NR *Patients characteristics* Age (median, range): 71, 50- 82 Sex Male (%): 54 Tumor size (mm, median, range): 15, 5-35 Histology Adenocarcinoma (%): 86	*Setting* Hospital *Country* Japan	Margin cytology (cells were extracted from the margin by running a glass slide across the surgical margin to extract cells, samples were stained and examined (run-across method)) Margin tumor size ratio	OS (5 years); margin cytology negative vs. positive: HR= 3.8; 1.2-12.0 OS (5 years); margin tumor size ratio >1 vs. <1: HR= 0.3; 0.06-1.1	Multivariate (age, gender, tumor size, lymph nodes, stapling pattern, tumor location and margin cytology) Univariate	*Study type* Cohort study *Level of evidence* 2b *Risk of bias* Participation: + Attrition: ? PF measurement: +

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Squamous cell carcinoma (%): 11 Margin distance (mm, median, range): 10, 0-25 Tumor location Easy (%): 68 Difficult (%): 32 Lobe Right upper (%): 27 Right lower (%): 19 Left upper (%): 30 Left lower (%): 22					Outcome measurement: + Confounding: - Statistical analysis: + +
Tomaszek S. et al.; Bronchial resection margin length and clinical outcome in non-small cell lung cancer; European Journal of cardio-thoracic surgery (2011) 40: 1151-1156.	*Included* 496 *Attrition* NR *Analyzed* 496	*Inclusion criteria* ≥18 years Complete resection for NSCLC without distant metastasis *Exclusion criteria* Previous surgical resection of pulmonary malignancies	*Setting* Hospital *Country* USA	Margin close/ wide	Local recurrence rate (mean 35.2); margin length > 20mm vs. ≤ 20mm; HR=1.17; 0.77-1.78 Local recurrence rate (mean 35.2); 1 mm increase in bronchial margin resection length; HR=1.002 ; 0.99-1.02 OS (mean 35.2); margin length ≤ 20mm vs. > 20mm; HR=1.16; 0.91-1.48	Multivariate (age, gender, lymph node status)	*Study type* Cohort study *Level of evidence* 2b *Risk of bias* Participation: + +

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
	Excluded from analysis NR	Died within 30 days of surgery Multiple tumor site of the same histology or of different histology with unknown histologic origin of the recurrence *Patients` characteristics* Gender Male (%): 68.5 Female (%): 31.5 Age at resection (mean, SD): 65.9, 10.6 Smoking status at resection Never smokers (%): 12.1 Former smoker (%): 66.9 Active smoker (%): 21			OS (mean 35.2); 1 mm decrease in bronchial margin resection length; HR=1.01; 0.997-1.01		Attrition: ? PF measurement: ? Outcome measurement: + Confounding: + Statistical analysis: +

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Chemo- or radiation therapy None (%): 78.1 Neoadjuvant chemoradiation therapy (%): 5.6 Adjuvant therapy Chemotherapy (%): 6.9 Radiation therapy (%): 6.4 Combined (%): 3 Greatest tumor diameter (mm, mean, SD): 43.2, 24.2 Bronchial margin length (mm; mean, SD): 23.3 ±15.9 Recurrence (n=190) Local only (%): 18.4 Distant only (%): 53.2 Both local and distant (%): 28.4					

Study/reference	Patient flow	Inclusion, exclusion criteria and baseline characteristics of study population	Setting, country	Factor (definition and/or measurement if relevant)	Effect (outcome; compared categories or effect direction; effect measure and size; 95% CI or p-value)	Adjustment factors	Study type, risk of bias
		Pneumonectomy (%): 21.2 Lobectomy (%): 69.0 Bilobectomy (%): 5.6 Sleeve lobectomy (%): 3.2 Sleeve pneumonectomy (%): 1.0 Squamous cell carcinoma (%): 53.6 Adenocarcinoma (%): 32.3 Others: (%): 14.1					

+ low risk of bias; - high risk of bias, O moderate risk of bias; ? unclear risk of bias, CG: control group; CI: confidence interval; IG: intervention groups; NR: not reported; PF: prognostic factor, ns: not statistical significant

12.2.5. Thema: Erhaltungstherapie

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
Ahn, J.S., et al., A randomized, phase II study of vandetanib maintenance for advanced or metastatic non-small-cell lung cancer following first-line platinum-doublet chemotherapy. Lung Cancer, 2013. 82(3): p. 455-60.	**Region** Korea **Inclusion criteria** Patients with a complete response (CR),partial response (PR), or SD after completion of 4 cycles of standardchemotherapy Histologically or cytologically confirmed locally advanced or metastatic NSCLC Completition of 4 cycles of first-line chemotherapy Age ≥18 years WHO performance status 0-1	**Intervention(s)** Vandetanib plus best supportive care 37.5 mg sequential sunitinib daily **Control** Placebo(orally) plus best supportive care **Included/randomised patients** 76/42 **Analysed patients** 76/42 **Attrition** NR **Excluded from analysis (reason)**	Median overall survival (months) 15.6/20.8 ; NA; upper bound of CIs not reached Overall survival (median follow-up: 12.1 months [Vandetanib], 17.0 month [placebo]) NR; HR=0.76; 0.342 **Median progression-free survival (months)** 2.7/1.7 ; NA; ns (CIs not overlap) **Progression-free survival survival (median follow-up: 12.1 months [Vandetanib], 17.0 month**	**All grades** Rash (%): 77.3/26.2 Diarrhea (%): 60/9.5 Cough(%): 50.7/54.8 Productive cough (%): 38.7/35.7 Anorexia (%): 38.7/16.7 Pruritus (%): 30.7/16.7 Dyspnea (%):25.3/11.9 Insomnia (%): 18.7/4.8	**Study type** RCT **Level of evidence** 1b **Risk of bias** Generation of allocation sequence: + Allocation concealment: ? Blinding of participants and personal: + Blinding of outcome assessment: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	Maximum interval between the last day of the final 4th chemotherapy cycle and randomization was 21 days **Exclusion criteria** Prior treatment with EGFR-targeted or angiogenesis-targeted treatment Any unresolved toxicity greater than NCI CTCAE grade 2 from previous anticancer therapy **Patient characteristics** Age (median): 61/60.5 Men (%): 62.7/66.7 Women (%): 37.3/33.3 ***WHO PS***	1/0 (not received treatment)	**[placebo], RECIST criteria)** 28/ 7; HR=1.50; 0.99-2.27 ORR survival (median follow-up: 12.1 months [Vandetanib], 17.0 month [placebo], RECIST criteria) 18.7%/2.4%; OR=9.41; 1.12–74.35	Hypertension (%): 17.3/0 Nausea (%): 17.3/14.3 Chest pain (%): 16/11.9 Dry skin (%): 13.3/0	Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	0 (%): 26.7/23.8 1 (%): 73.3/76.2 ***Histology*** Adenocarcinoma (%): 74.7/73.8 Squamous cell carcinoma (%): 14.7/21.4 Other (%): 10.7/4.8 ***Smoking habits*** Non-smoker (%): 37.3/33.3 Ex-smoker (%): 25.3/31 Smoker (%): 37.3/35.7 ***Disease stage*** IIIB (%): 20/28.6 IV (%): 80/71.4				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	Response to previous therapy Partial response (%): 58.7/71.4 Stable disease (%): 41.3/28.6				
Aisner, J., et al., Vandetanib plus chemotherapy for induction followed by vandetanib or placebo as maintenance for patients with advanced non-small-cell lung cancer: a randomized phase 2 PrECOG study (PrE0501). J Thorac Oncol, 2013. 8(8): p. 1075-83.	**Region** United States **Inclusion criteria** Primary or recurrent, advanced (stage IIIB or IV) NSCLC measurable by RECIST Any histologic subtype were eligible, including squamous cell carcinoma ECOG PS of 0 or 1 Age ≥18 years	**Intervention(s)** Induction docetaxel (75 mg/m2) + carboplatin (area under the curve of 6) on day 1 of a 21-day cycle, and daily vandetanib (100 mg/day orally) for four cycles, followed by daily vandetanib (300 mg/day orally) until progression **Control**	Median overall survival (months) 9.8/9.4; NA; ns (CIs overlap) Overall survival (median follow-up: 13.5 months) 37.5%/33%; NR; 0.68 **Median progression-free survival (months)**	***Grade* 1** Allergy/immunology: 4/3 Auditory/ear: 2/1 Blood/bone marrow: 4/1 Cardiac arrhythmia:4/3 Cardiac general: 3/7 Constitutional symptoms: 9/18	**Study type** RCT **Level of evidence** 1b **Risk of bias** Generation of allocation sequence: + Allocation concealment: -

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	Adequate organ function, normal calcium and magnesium **Exclusion criteria** Previous cytotoxic chemotherapy or targeted therapy for advanced or metastatic disease Cardiac dysfunction Greater than 1 grade neuropathy Known sensitivity to carboplatin **Patient characteristics** Age (median): 63.5/63 <50 (%): 12.5/7.3 50-59 (%): 20/31.7	Induction docetaxel (75 mg/m2) + carboplatin (area under the curve of 6) on day 1 of a 21-day cycle, and daily vandetanib (100 mg/day orally) for four cycles, followed by daily placebo until progression **Included/randomised patients** 80/82 **Analysed patients** 80/82 (efficacy) 77/81 (safety) **Attrition** NR	4.5/4.2; NA; ns (CIs overlap) **Progression-free survival (**median follow-up: 13.5 months**, RECIST criteria)** 89%/95%; NR; 0.07 Overall response (median follow-up: 13.5 months, RECIST criteria) 15/15; NR; NR	Dermatology/skin: 12/11 Endocrine: 2/3 Gastrointestinal: 17/17 Bleeding: 15/7 Infection: 0/2 Lymphatics: 5/9 Metabolic/laboratory:18/9 Musculoskeletal/soft tissue:1/4 Neurology: 14/13 Ocular/visual: 3/7 Pain: 15/10	Blinding of participants and personal: + Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	60-69 (%): 42.5/28.1 ≥70 (%): 25/32.9 Male (%): 52.5/51.2 Female (%): 47.5/48.8 ***Ethnicity*** White, non-Hispanic (%): 82.5/87.8 White, Hispanic (%): 0/2.4 Black, non-Hispanic (%): 11.3/9.8 Black, Hispanic (%): 1.3/0 Asian (%): 1.3/0 Native Hawaiian/Pacific Islander (%): 1.3/0 Other (%): 2.5/0 ***Stage***	**Excluded from analysis (reason)** 3/1 (safety, not received induction)		Pulmonary/upper respiratory: 19/12 Renal/genitourinary: 4/2 Sexual/reproductive function: 0/1 Syndromes: 1/0 Vascular: 1/4 Worst degree: 1/2 **Grade 2** Allergy/immunology: 5/3 Auditory/ear: 1/1 Blood/bone marrow: 4/3	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	IIIB with malignant effusion (%): 6.3/11 IV (%): 85/80.5 Recurrent (%): 8.8/8.5 ***ECOG PS*** O (%): 33.8/41.5 1 (%): 66.3/58.5 ***Histology*** Adenocarcinoma (%): 57.5/58.5 Squamos cell carcinoma (%): 23.8/19.5 Large cell carcinoma (%): 5.0/0 Bronchialveolar (%): 0/3.7 Adenosquamos (%): 2.5/2.4			Cardiac arrhythmia: 3/6 Cardiac general: 3/8 Constitutional symptoms: 27/17 Dermatology/skin: 23/28 Endocrine: 0/1 Gastrointestinal: 29/20 Bleeding: 4/3 Infection: 10/16 Lymphatics: 6/4 Metabolic/laboratory: 5/7	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	NSCLC, NOS (%): 11.3/14.6 Other (%): 0/1.2 ***Smoking history*** Ever smoker (%): 92.5/93.8 Current smoker (%): 20.3/27.6			Musculoskeletal/soft tissue: 3/7 Neurology:11/6 Ocular/visual:1/3 Pain: 16/19 Pulmonary/upper respiratory:6/8 Renal/genitourinary: 0/2 Sexual/reproductive function: 1/0 Syndromes: 0/2 Vascular: 2/7 Worst degree: 8/8	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
				Grade 3 Allergy/immunology: 1/2 Blood/bone marrow: 9/16 Cardiac arrhythmia: 5/7 Cardiac general: 4/3 Constitutional symptoms: 8/14 Coagulation: 0/2 Dermatology/skin: 13/5 Endocrine:1/0 Gastrointestinal: 15/25 Bleeding: 1/1	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
				Hepatobiliary/pancreas: 1/1 Infection: 4/10 Lymphatics: 0/1 Metabolic/laboratory: 12/15 Musculoskeletal/soft tissue: 3/4 Neurology: 9/10 Pain: 10/15 Pulmonary/upper respiratory: 8/12 Renal/genitourinary: 1/3 Secondary malignancy: 17/0	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
				Syndromes: 1/0 Vascular: 5/3 Worst degree: 23/25 **Grade 4** Allergy/immunology: 2/0 Blood/bone marrow: 31/28 Cardiac arrhythmia: 1/0 Cardiac general: 1/1 Constitutional symptoms: 1/1 Dermatology/skin: 1/2 Gastrointestinal: 2/1	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
				Infection: 4/4 Metabolic/laboratory: 0/3 Musculoskeletal/soft tissue: 1/0 Pain: 2/0 Pulmonary/upper respiratory: 0/1 Vascular: 3/5 Worst degree: 34/35 **Grade 5** Blood/bone marrow: 0/1 Cardiac general: 2/0	

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				Constitutional symptoms: Death: 5/6 Bleeding: 0/2 Hepatobiliary/pancreas: Infection: 0/3 Metabolic/laboratory: 1/1 Neurology: 1/0 Pulmonary/upper respiratory: 1/1 Renal/genitourinary: 1/0 Worst degree: 10/	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
Alfonso, S., et al., A randomized,multicenter,placebo-controlled clinical trial of racotumomab-alum vaccine as switch maintenance therapy in advanced non-small-cell-lung cancer patients. Clin Cancer Res, 2014.	**Region** Cuba **Inclusion criteria** Age ≥18 years Histo- or cytologically stage IIIB-IV NSCLC Achievement CR, PR or SD after the standard first-line therapy Measurable disease ECOG PS ≤2 Adequate renal, hepatic and haematological functions First-line chemotherapy with regimens included vinblastine or etoposide	**Intervention(s)** 15 doses of 1 mg of racotumomab-alum Induction phase consisted on 5 doses, administered every 2 weeks After induction, vaccination every 4 weeks, for one year (10 doses) After completed treatment (15 doses of vaccine or placebo), the blinding was opened, and only patients in the racotumomab arm continued vaccination every 4 weeks, even beyond progression. **Control**	**Median overall survival (months)** 8.23/6.80; NA; ns (CIs overlap) **Overall survival (2 years)** 18.4%/6.7%; HR=1.59; 1.15-2.17 Median progression-free survival (months) 5.33/3.90; NA; ns (CIs overlap) Progression-free survival (max 84 months, RECIST criteria) NR; HR=1,37; 1.01-1.89	Burning in injectionsite (%): 41.9/31.3 Pain in injectionsite (%): 33.7/24.7 Bonepain (%): 18.6/19.1 Cough (%): 8.1/12.4 Dyspnea (%): 5.8/5.6 Asthenia (%): 16.3/11.2 Anorexia (%): 7/7.9 Expectoration (%): 1.2/3.4 Induration (%): 11.6/10.1	**Study type** RCT **Level of evidence** 1b **Risk of bias** Generation of allocation sequence: + Allocation concealment: ? Blinding of participants and personal: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	combined with cisplatin or carboplatin. **Exclusion criteria** Immunotherapy or other investigational drugs Hypersensitivity to any component of the formulation Pregnancy or lactating Uncontrolled chronic diseases History of severe allergic reactions Brain metastates or other primary neoplastic lesion Active infections, symptomatic congestive heart failure, unstable angina,	Placebo **Included/randomised patients** 87/89 **Analysed patients** 87/89 (efficacy) 86/89 (safety) **Attrition** NR **Excluded from analysis (reason)** 1/0 (safety: received treatment)		Headache (%): 9.3/10.1 Pruritus (%): 10.5/5.6 Fever (%): 9.3/13.5 Increased volume in injection site (%): 10.5/3.4 Local erythema (%): 12.8/12.4 Myalgia (%): 5.8/7.9 Arthralgia (%): 5.8/5.6	Blinding of outcome assessment: + Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	cardiac arrhythmia or psychiatric disorders Receiving systemic corticosteroids at the time of inclusion Positive serology Hepatitis B, C or HIV **Patient characteristics** Age ≤ 60 years (%): 43.7/46.1 Age ≥ 60 years (%): 56.3/53.9 Female (%): 32.3/33.7 Male (%): 67.8/66.3 ***ECOG PS*** 0 (%): 46/44.9 1 (%): 51.7/50.6				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	2 (%): 2.3/4.5 ***Race*** White (%): 80.5/79.8 Afro-Caribbean (%): 12.6/14.6 Other (%): 6.9/5.6 ***Smoking history*** Current smoker (%): 18.45/21.3 Former smoker (%): 77/73 Non smoker (%): 4.6/5.6 ***Tumor histology*** Squamos cell carcinoma (%): 37.9/37.1 Adenocarcinoma (%): 28.7/34.8 Large cell carcinoma (%): 20.7/15.7				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	NSCLC NOS (%): 12.6/12.4 ***Disease stage*** IIIB (%): 55.2/57.3 IV (%): 44.8/42.7 ***First-line treatment*** CT (%): 100/100 RT (%): 57.5/57.3 ***First line chemotherapy*** Platinum compounds (%): 100/100 Cisplatin/Vinblastine (%): 33.3/20.9 Cisplatine/Etoposide (%): 7.1/5.8 Carboplatin/Vinblastine (%): 46.4/58.1 Carboplatin/Etoposide (%): 13.1/15.1				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	Response to first-line treatment CR (%): 2.3/5.6 PR (%): 43.7/57.3 SD (%): 54/37.1				
Belani, C.P., et al., Quality of life in patients with advanced non-small-cell lung cancer given maintenance treatment with pemetrexed versus placebo (H3E-MC-JMEN): results from a randomised, double-blind, phase 3 study. Lancet Oncol, 2012. 13(3): p. 292-9. Ciuleanu, T., et al., Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung	**Region** USA **Inclusion criteria** Age ≥18 years Histological or cytological diagnosis of stage IIIB (with pleural effusion or positive supraclavicular lymph nodes) or stage IV NSCLC before first-line induction therapy Estimated life expectancy of at least 12 weeks	**Intervention(s)** Four cycles of platinum-based induction therapy Pemetrexed (500 mg/m², Eli Lilly, Indianapolis, IN, USA) intravenously on day 1 plus best supportive care in 21-day cycles. **Control** Placebo (0·9% sodium chloride) intravenously on day 1 plus best	Median overall survival (months) 13.4/10.6; NA; ns (CIs overlap) Overall survival (median follow-up: 11.2 months) NR; HR=1.27; 1.05-1.54 **Median progression-free survival (months)** 4.0/ 2.0; NA; ns (CIs overlap)	**Drug related** Anaemia (%): 15/5 Leucopenia (%): 6/1 Neutropenia (%): 6/0 Thrombocytopenia (%): 4/1 ALT (%): 10/4 AST (%): 8/4 Fatigue (%) 24/10	**Study type** RCT **Level of evidence** 1b **Risk of bias** Generation of allocation sequence: + Allocation concealment: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
cancer: a randomised, double-blind, phase 3 study. Lancet, 2009. 374(9699): p. 1432-40.	ECOG PS of 0 or 1 Adequate organ function **Exclusion criteria** Previous malignancy other than NSCLC Uncontrolled cardiac disorder Progressive brain metastases Uncontrolled third-space fluid collection Inability to take corticosteroids, folic acid, or vitamin B12 Pregnancy or breastfeeding **Patient characteristics**	supportive care in 21-day cycles. Four cycles of platinum-based induction therapy **Included/randomised patients** 441/222 **Analysed patients** 441/222 **Attrition** >50% (Quality of life) **Excluded from analysis (reason)** -	**Progression-free survival (median follow-up: 11.2 months, RECIST criteria)** NR; HR=1.67; 1.37- 2.04 ORR (2 years, RECIST criteria) 3.4%/ 0.5%; NR; 0.042 Disease control rate (median follow-up: 11.2 months, RECIST criteria) 49.1%/ 28.9%; NR; <0.0001 Median time to worsening of Symptoms (month, LCSS)	Constipation (%): 5/3 Nausea (%): 19/5 Vomiting (%): 9/1 Diarrhoea (%): 5/3 Anorexia (%): 19/5 Fever (%): 3/<1 Rash or desquamation (%): 10/3 Any mucositis or stomatitis (%): 7/2 Pruritus (%): 3/<1	Blinding of participants and personal: + Blinding of outcome assessment: + Incomplete outcome data: ? Selective reporting: + Other source of bias:

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	Age (mean): 60.6/60.4 Male (%): 73/73 Female (%): 27/27 ***Ethnic origin*** White (%): 63/67 East/west Asian (%): 32/30 Other (%): 4/3 ***Disease stage*** IIIB (%): 18/21 IV (%): 82/79 ***Smoking status*** Smoker (%): 73/71 Never-smoker (%): 26/28 Unknown (%): <1/<1 ***ECOG PS*** 0 (%): 40/38		5.75/3.71; NA; ns (CIs overlap) Time to worsening of Symptoms (follow-up NR, LCSS) 5·75/3.71; HR=0·86; 0.66–1.12	Sensory neuropathy (%): 9/4 Alopecia (%): 4/<1 Any infection (%): 5/2 Creatinine clearance (%): 4/<1	

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	1 (%): 60/62 ***Histology*** Non squamous (%): 74/70 Adenocarcinoma (%): 50/48 Large cell (%): 2/5 Other or indeterminate (%): 21/18 Squamos (%): 26/30 ***Best response to induction treatment*** CP+PR (%): 47/52 Stable disease (%): 52/48 ***Induction regimen*** Docetaxel-carboplatin (%): 5/3 Docetaxel-cisplatin (%): 2/2				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	Paclitaxel-carboplatin (%): 30/27 Paclitaxel-cisplatin (%): 6/9 Carboplatin plus taxane (%): 35/30 Carboplatin plus gemcitabine (%): 24/22 Cisplatin plus taxane (%): 8/11 Cisplatin plus gemcitabine (%): 33/38 ***LCSS item (mean)*** Loss of appetite: 23/23.5; 14/19 Fatigue: 33.5/33.9; 30/28 Cough: 19.9/19.6; 9/9 Dyspnoea: 21.4/20.1; 10/8				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	Haemoptysis: 2.8/3.5; 0/0 Pain: 14.8/22.8; 4/5 Symptom distress: 20.9/23.2; 11/14 Interference with activity level: 32.9/33.3; 25.5/27 Overall quality of life: 33.5/33.3; 30/31				
Cappuzzo, F., et al., Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol, 2010. 11(6): p. 521-9.	**Region** 26 countries **Inclusion criteria** Age ≥18 years Histologically documented, measurable (RECIST) unresectable or metastatic NSCLC	**Intervention(s)** Oral erlotinib 150 mg/day **Control** Placebo **Included/randomised patients**	Median overall survival (months) 12.0/11.0; NA; NR Overall survival (median follow-up: 11.4 months [erlotinib], 11.5 [placebo]) NR; HR=1.23; 1.05-1.43	**Treatment-related** ***All grades*** One or more (%): 65/20 Rash (%): 60/8 Pruritus (%): 6/2 Diarrhoea (%): 18/3	**Study type** RCT **Level of evidence** 1b **Risk of bias** Generation of allocation sequence:

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	Completion of four cycles of standard platinum-doublet chemotherapy without disease progression ECOG PS 0 or 1 Adequate renal, heapatic, and haematological function Negative pregnancy test for females of childbearing age **Exclusion criteria** Previous exposure to anti-EGFR agents Uncontrolled, symptomatic brain metastases Any other malignancies within the previous 5 years	438/451 **Analysed patients** 437/447 **Attrition** NR **Excluded from analysis (reason)** 1/4 (efficacy [PFS], progressed before randomisation) 0/0 (safety)	**Median progression-free survival (months)** 12.3/ 11.1; NA; NR **Progression-free survival (median follow-up: 11.4 months [erlotinib], 11.5 [placebo], RECIST criteria)** NR; HR=1.40; 1.22-1.61 **Progression-free survival (6 months, RECIST criteria)** 25%/15%; NR; statistical significant (CIs not overlapping) ORR (median	General disorders and administration site conditions (%): 9/3 Anorexia (%): 5/2 Infections and infestations (%): 5/<1	+ Allocation concealment: + Blinding of participants and personal: + Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	Patient characteristics Age (median): 60/60 Male (%): 73/75 Female (%): 27/25 ***Stage*** IIIB (%): 26/24 IV (%): 74/76 ***Ethnic origin*** Caucasian (%): 84/83 Asian (%): 14/15 Other (%): 1/1 ***ECOG PS*** 0 (%): 31/32 1 (%): 69/68 ***Smoking status*** Current smoker (%): 55/56		follow-up: 11.4 months [erlotinib], 11.5 [placebo], RECIST criteria) 11.9%/5.4%; NR; 0.0006 Diseases control rate (12 weeks, RECIST criteria) 40.8%/27.4; NR; 0. 0001 Time to deterioration in quality life (median follow-up: 11.4 months [erlotinib], 11.5 [placebo], FACT-L) NR; HR=0.96; 0.79–1.16;		

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	Former smoker (%): 28/27 Never smoker (%): 18/17 ***Histology*** Adenocarcinoma/bronchoalveolar carcinoma (%): 47/44 Squamos-cell carcinoma (%): 38/43 Other (%): 15/13 ***Response to previous chemotherapy*** Complete response (%): <1/<1 Partial response (%): 42/47 Stable disease (%): 58/52 Other/unknown (%): <1/1 ***EGFR IHC status***				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	Positive (%): 70/69 Negative (%): 14/13 Indeterminate (%): 4/5 Missing (%): 12/12 ***EGFR mutation status*** Activating mutation (%): 5/6 Other mutation (%): 2/<1 Wild-type (%): 45/42 Missing (%): 40/43				
Gaafar, R. M., et al. (2011). "A double-blind, randomised, placebo-controlled phase III intergroup study of gefitinib in patients with advanced NSCLC, non-progressing after first line platinum-based chemotherapy (EORTC 08021/ILCP	**Region** United States and Europe **Inclusion criteria** Histologically or cytologically confirmed stage IIIB or IV NSCLC	**Intervention(s)** Gefitinib (250 mg daily) **Control** Placebo	**Median overall survival (months)** 10.9/9.4; NA; NR **Overall survival (median follow up: 41months)** NR; HR=1.23; 0.89-1.69	**Treatment related non-haematological** ***Grade 3*** Cardiovascular/general (%): 0/2.3	**Study type** RCT **Level of evidence** 1b

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01/03)." Eur J Cancer 47(15): 2331-2340	Not amenable to local therapy Non-progressing after prior platinum based chemotherapy (2-6 cycles) Without unacceptable toxicity Age ≥18years WHO PS 2 or less Adequate renal, hepatic and haematological functions **Exclusion criteria** Previous EGFR therapy, symptomatic brain metastasis, other malignancies, pregnancy or breast-feeding and interstitial pulmonary disease	**Included/randomised patients** 86/87 **Analysed patients** 87/86 **Attrition** 9/15 **Excluded from analysis (reason)** 86/85 (safety, started treatment)	Median progression-free survival (months) 4.1/2.9; NA; NR Progression-free survival (median follow up: 41months, RECIST criteria) NR; HR=1.64; 1.20-2.22 ORR (time point NR, RECIST criteria) 12%/1%; NR; 0.004 Diseases Control rate (time point NR, RECIST criteria) 79%/66%; NR; 0.07	Fatique (%): 4.7/1.2 Rash/desquamation (%): 1.2/0 Dermatology/skin (%): 1.2/0 Anorexia (%): 0/1.2 Diarrhoea (%): 1.2/0 Vomiting (%): 1.2/0 Gastrointestinal (%): 0/1.2 Hepatic-other (%): 8.2/0	**Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: + Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	Patient characteristics Age (median): 61/62 Male (%): 78/76 Female (%): 22/24 ***Clinical stage*** IIIB (%): 19/15 IV (%): 81/85 ***PS*** 0 (%): 36/35 1 (%): 57/61 2 (%): 7/5 ***Prior platinum chemotherapy*** Cisplatin-based (%): 45/56 Carboplatin-based (%): 55/44			Infection without neutropenia (%): 1.2/1.2 Dizziness/lightthead-edness (%): 0/1.2 Neurology (%): 0/3.5 Pain (%): 4.7/7 Cough (%): 1.2/3.5 Dyspnoea (%): 4.7/5.8 Pulmonary (%): 0/1.2 Renal/genitourinary (%): 2.4/0 Other toxicity (%): 4.7/3.5	Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	Cis/Carbo-platin based (%): 1/0 ***Response to chemotherapy*** Complete/partial response (%): 40/40 Stable disease (%): 61/60 ***Histological type*** Squamos (%): 17/22 Adenomacarcinoma (%): 57/46 Undifferentiated (%): 15/17 Large cell carcinoma (%): 11/15 ***Smoking status*** Non-smoker (%): 21/23			***Grade 4*** Cardiovascular/general (%): 0/1.2 Rash/desquamation (%): 1.2/0 Hepatic-other (%): 1.2/1.2 Dyspnoea (%): 0/1.2 Renal/genitourinary (%): 1.2/0 Other toxicity (%): 3.5/1.2 **Treatment related haematological/biochemical** ***Grade 3***	

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	Current smoker (%): 29/26 Former smoker (%): 49/48 Missing (%): 1/2			Absolute neutrophil count (%):1.2/0 Platelets (%): 1.2/0 Haemoglobin (%): 0/2.3 Bilirubin (%): 1.2/1.2 Hypernatraemia (%): 1.2/0 Hyponatraemia (%): 8.2/8.1 Hyperkalaemia (%): 1.2/0 Hypokalaemia (%): 1.2/1.2 Alkaline phosphatase (%): 1.2/0	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
				SGPT, ALAT (%): 8.2/0 SGOT, ASAT (%): 8.2/1.2 ***Grade 4*** Hypernatraemia (%): 0/1.2 Hypocalcaemia (%): 1/1.2 SGPT, ALAT (%): 2.4/1.2	
Johnson, E.A., et al., Phase III randomized, double-blind study of maintenance CAI or placebo in patients with advanced non-small cell lung cancer (NSCLC) after completion of initial therapy (NCCTG 97-24-51). Lung Cancer, 2008. 60(2): p. 200-7.	**Region** USA **Inclusion criteria** Age ≥18 years Histologically or cytologically confirmed stage III or IV NSCLC	**Intervention(s)** Oral carboxyaminoimidazole (CAI) at a dose of 250 mg daily **Control** Placebo **Included/randomised**	**Median overall survival (months)** 11.4/10.5; NA; NR **Overall survival (median follow-up: 29.6 [CAI], 28.3 [placebo])** NR; NA; 0.54	***Grade 1/2*** Fatigue (%): 46.7/26.1 Anorexia (%): 31.1/13 Nausea (%): 60/30.4	**Study type** RCT **Level of evidence** 1b **Risk of bias** Generation of allocation sequence:

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	Completion of only one chemotherapy regimen (with or without thoracic radiation) within the previous 6 weeks Complete response, partial response or stable disease Initial chemotherapy minimum of 3 and a maximum of 6 months ECOG PS 0,1 or 2 Adequate bone marrow, hepatic and renal function Expected survival of at least 3 months **Exclusion criteria** Woman who were pregnant, nursing or not	94/92 **Analysed patients** 94/92 (efficacy) 65%/79% (quality of life) **Attrition** 7/14 (survival analyses) **Excluded from analysis (reason)** NR (safety, received treatment, in at least 25% of patients in either arm) 25%/21% (quality of life, not completed questionnaire)	Median progression-free survival (months) 2.8/ 2.4; NA; NR Progression-free survival (median follow-up: 29.6 [CAI], 28.3 [placebo], WHO criteria) NR; NR; 0.50 Patients with 10 points decline in quality life (8 weeks, FACT-L) 63%/49%; NR; 0.18	Vomiting (%): 28.9/14.1 Ataxia (%): 22.2/13 Neuro-sensory (%): 51.1/44.6 Anemia (%): 48.9/55.4 ***Grade 3*** Fatigue (%): 7.8/3.3 Nausea (%): 2.2/0 Vomiting (%): 3.3/0 Ataxia (%): 11.1/3.3 Neuro-sensory (%): 8.9/0	+ Allocation concealment: ? Blinding of participants and personal: + Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	utilizing adequate contraception Untreated brain metastases Planned additional chemotherapy, radiotherapy or immunotherapy or participation in another phase III trial **Patient characteristics** Age (mean): 67.5/64 Female (%): 45/40 Male (%): 55/60 ***PS*** 0 (%): 41/39 1 (%): 52/50 2 (%): 7/11 ***Race***				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	White (%): 97/97 Black or African American (%): 1/0 American Indian or Alaska Native (%): 1/1 Not reported (%): 2/1 ***Prior response*** Complete (%): 5/4 Partial (%): 40/49 Regression (%): 10/9 Stable (%): 45/38 Platinum based initial therapy (%): 76/79 ***Smoking status*** Never (%): 12/11 Former (%): 57/62 Current (%): 21/16				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	Not reported (%): 10/11 ***Stage*** IIIA/IIIB (%): 23/21 IV (%): 77/79 ***Histology*** Bronchoalveolar/large cell (%): 6/14 NOS NSCLC/not available (%): 17/12 Adenocarcinoma (%): 54/60 Squamos (%): 22/14				
Paz-Ares, L., et al., Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin	**Region** Primarily European **Inclusion criteria** Advanced nonsquamos NSCLC stage IIIB to IV	**Intervention(s)** Four cycles of pemetrexed (500 mg/m2 intravenously and cisplatin (75 mg/m2 IV) on day 1 of 21-day cycles	Median overall survival (months) 16.9/14.0; NA; ns (CIs overlap) Overall survival (2 years)	***All grades*** Patients with ≥1 laboratory adverse event (%): 24/7 Anemia (%):14/4	**Study type** RCT **Level of evidence** 1b

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol, 2012. 13(3): p. 247-55. Paz-Ares LG, de Marinis F, Dediu M, et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. J Clin Oncol 2013; 31:2895. Pujol JL, Paz-Ares L, de Marinis F, Dediu M, et al Long-term and low-grade safety results of a phase III study (PARAMOUNT): maintenance	At least one measurable lesion per RECIST No prior systemic chemotherapy for lung cancer ECOG PS of 0 to 1 **Exclusion criteria** Concurrent administration of other antitumour therapy and tumour histology CNS metastases were eligible if the metastases were stable and successfully treated with local therapy (that is, stable treated meta stases), and the patient was off corticosteroids for at least 4 weeks	Maintenance pemetrexed (500 mg/m2 on day 1 of 21-day cycles) plus BSC **Control** Four cycles of pemetrexed (500 mg/m2 intravenously and cisplatin (75 mg/m2 IV) on day 1 of 21-day cycles Maintenance Placebo plus BSC **Included/randomised patients** 359/180 **Analysed patients**	32%/21%; HR=1.28; 1.04-1.56 Median progression-free survival (months) 4.4/2.8; NA; statistical significant (CIs not overlapping) Progression-free survival (median follow up: 24.3 months, RECIST criteria) NR; HR=1.67; 1.38-2.00 ORR (median follow up: 5.0 months, RECIST criteria) 3%/0.6%; NR; 0.18	Neutropenia (%): 8/<1 Leukopenia (%): 4/0 Thrombocytopenia (%): 3/<1 Alanine aminotransferase (%): 3/<1 Fatigue (%): 16/11 Nausea (%): 11/2 Vomiting (%): 6/2 Mucositis/stomatitis (%): 5/2 Oedema (%): 5/3	**Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: + Blinding of outcome assessment: + Incomplete outcome data: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
pemetrexed plus best supportive care versus placebo plus best supportive care immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. Clin Lung Cancer. 2014 Nov;15(6):418-25.	**Patient characteristics** Age (median): 61/62 <65 (%): 66/62 ≥65 (%): 34/38 Male (%): 56/62 Female (%): 44/38 ***Race/ethnicity*** Asian (%): 4/4 African (%): 1/0.6 White (%): 94/95 ***Smoking status*** Smoker (%): 76/80 Nonsmoker (%): 23/19 Unknown (%): 0.6/1 ***ECOG PS*** 0 (%): 31/33	359/180 >80% (quality of life) **Attrition** 4/0 **Excluded from analysis (reason)** ≤20% (quality of life, not completed questionnaire)	Diseases Control rate (median follow up: 5.0 months, RECIST criteria) 71%/60%; NR; 0.009 Quality of life (after treatment, EQ-5D index score) 0.77/0.79; NR; ns Quality of life (after treatment, EQ-5D VAS) 71.08/ 71.02; NR; ns	Anorexia (%): 4/1 Pain (%): 4/2 Infection (%): 3/2 Diarrhoea (%): 3/2 Neuropathy (%): 3/6 Watery eye (%): 3/<1 Constipation (%): 2/3	Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	1 (%): 68/66 2-3 (%): 0.3/1 ***Disease stage before maintenance therapy*** IIIB (%): 9/10 IV (%): 91/90 ***Best tumor response to induction therapy*** Complete/partial response (%): 44/42 Stable disease (%): 53/53 Progressive disease (%): 0.3/1 Unknown (%): ¾ ***Time from start of induction therapy to randomisation (months)*** Median: 2.96/2.96				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	Histology Bronchalveolar (%): 2/1 Adenocarcinoma (%): 85/88 Large-cell carcinoma (%): 7/7 Other or indeterminate (%): 7/4				
Cai, K.C., et al., Gefitinib maintenance therapy in Chinese advanced-stage lung adenocarcinoma patients with EGFR mutations treated with prior chemotherapy. Neoplasma, 2015. 62(2): p. 302-7.	**Region** China **Inclusion criteria** Advanced-stage non-small cell lung cancer (NSCLC) with or without EGFR mutations to platinum-based chemotherapy Stage IIIB or IV NSCLC No prior chemotherapy or radiotherapy	**Intervention(s)** Cisplatin (80-120 mg/m2 body surface area) and Paclitaxel injection (Ta..xol, 135-250 mgtmz body surface area), once every three weeks (group-Gefitinib maintenance Gefitinib maintenance therapy of 250 mg/day by oral administration	Overall survival (1 year) 100%/57.1%; NR; 0.06 Progression-free survival (1 year) 28.6%/6.7%; NR; 0.407	NR	**Study type** RCT **Level of evidence** 2b **Risk of bias** Generation of allocation sequence: -

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	PS <2 Wild-type EGFR **Exclusion criteria** NR **Patient characteristics** EGFR mutation status positive n=15 Age (mean): 61 Male (%): 34.8 Female (%): 87.5 ***Smoking*** Yes (%): 33.3 No (%): 69.2	(group 3) until disease progression or the development of intolerable side effect **Control** Cisplatin (80-120 mg/m2 body surface area) and Paclitaxel injection (Ta..xol, 135-250 mgtmz body surface area), once every three weeks (group Gefitinib maintenance Placebo **Included/randomised patients** NR **Analysed patients** 7/7 **Attrition**			Allocation concealment: - Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
		NR **Excluded from analysis (reason)** NR			
Giaccone, G., et al., A phase III study of belagenpumatucel-L, an allogeneic tumour cell vaccine, as maintenance therapy for non-small cell lung cancer. Eur J Cancer, 2015. 51(16): p. 2321-9.	**Region** 8 countries (North America, Europe, India) **Inclusion criteria** Histologically confirmed diagnosis of stage IIIA (T3N2), IIIB or IV NSCLC Stable disease or response following up to 6 cycles of a platinum-based frontline chemotherapy regimen, with or without radiation therapy Patients 18–75 years of age	**Intervention(s)** Maintance Belagenpumatucel-L (2.5 X 10^7 cells per dose) 20 cycles of treatment 18 cycles of monthly intradermal injections followed by two quarterly cycles of intradermal injections **Control** Placebo **Included/randomised patients** 270/262	**Median overall survival** (months) 20.3/ 17.8; NA; ns (CIs overlap) **Overall survival** (max 48 months) NR; HR=1.06 ; 0.83-1.37 Median progression-free survival (months) 4.3/4.0; NA; ns (CIs overlap) Progression-free survival (max 48 months, RECIST criteria)	**Grade 1 and 2 (reported more than 20 times)** Arthralgia: 29/31 Back pain: 28/22 Cough: 71/65 Decreased appetite: 32/16 Erythema: 35/7 Extremity pain: 21/15 Fatigue: 66/54	**Study type** RCT **Level of evidence** 1b **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal:

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	ECOG performance status of 0, 1 or 2 Estimated life expectancy of at least 12 weeks No other antitumour therapies within four weeks of randomisation. **Exclusion criteria** Concurrent systemic steroids, bone metastases that required immediate therapy, uncontrolled pleural effusions, serious non-malignant disease and previous malignancies unless in remission for P2 years **Patient characteristics** Age (mean): 61.5/60.5	**Analysed patients** 270/262 **Attrition** NR **Excluded from analysis (reason)** NR	NR; HR=1.01; 0.83-1.22 ORR (max 48 months, RECIST criteria) 2.5%/0.4%; NR; 0.123	Headache: 48/28 Induration: 22/4 Injection site reaction: 260/62 Musculoskeletal pain: 34/21 Nasopharyngitis: 26/11 Nausea: 40/36 Non-cardiac chest pain: 23/9 Pyrexia: 25/17 Rash: 23/10 Respiratory tract infection: 33/28	+ Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	Men (%): 58/58 Women (%): 42/42 ***Race*** White (%): 88/90 Black (%): 2/2 Asian (%): 8/8 Not specified (%): 2/1 ***Ethnicity*** Hispanic (%): 2/1 Non-hispanic (%): 98/99 ***Stage*** Stage IIIA (%): 8/8 Stage IIIB/IV (%): 92/92 ***Histology*** Adenocarcinoma (%): 60/54 Squamos (%): 24/31				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	Large Cell (%): 6/5 Adenosquamos carcinoma (%): 2/2 Undifferentiated (%): 4/2 Other/not specified (%): 4/3 ***Brain metastases*** Positive (%): 7/7 Negative (%): 93/93 ***Pre-randomisation therapies*** Prior chemoRT (%): 29/27 Non prior chemoRT (%): 71/73 Prior bevacizumab (%): 11/10 Non prior bevacizumab (%): 89/90				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	Enrolment by region North America (%): 42/41 Rest of the World (%): 58/59 ***PS (ECOG)*** 0 (%): 44/50 1 (%): 51/45 2 (%): 3/2				
Zhang, L., et al., Gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804): a multicentre, double-blind randomised phase 3 trial. Lancet Oncol, 2012. 13(5): p. 466-75.	**Region** China **Inclusion criteria** Chinese patients Locally advanced/metastatic NSCLC Disease control after first-line platinum-based doublet chemotherapy	**Intervention(s)** Gefitinib (250 mg/day orally) administered 3–6 weeks postchemotherapy **Control** Placebo (orally) administered 3–6 weeks postchemotherapy.	Median overall survival (months) 18.97%/16.00 %; NA; NR Overall survival (median follow-up 17.83 month) 112/118; HR=1.14; 0.88-1.47	NR	**Study type** RCT **Level of evidence** 1b **Risk of bias** Generation of allocation sequence:

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
Zhao H1, Fan Y, Ma S, Song X J Thorac Oncol. 2014 Dec 24. Final overall survival results from a phase III, randomised, placebo-controlled, parallel-group study of gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804)., on behalf of the INFORM investigators.	**Exclusion criteria** **Patient characteristics** Age(median): 55/55 Men (%): 56/62 Women (%): 44/38 **Histology** Adenmocarcinoma(%): 71/70 Squamous (%): 18/20 Others (%): 11/10 **Disease stage** IIIB (%): 39/30 IV (%): 61/70 **WHO PS** 0 (%): 47/49 1 (%): 51/49 2 (%): 2/3	**Included/randomised patients** 296 **Analysed patients** 148/148 147/148 **Attrition** 1/1 (progression free survival) 21/12 (overall survival) 123/116 (FACT-L) **Excluded from analysis (reason)** 1/0 (safety, not received treatment) 25/32 (FACT-L, no assessable results)	**Median progression-free survival (months)** 4.8/2.6; NA ; statistical significant (CIs not overlapping) **Progression-free survival (median follow-up 15.9 month, RECIST criteria)** NR; HR = 2.38; 1.81-3.03 ORR (median follow-up 15.9 month, RECIST criteria) 24/1%; OR=54.10; 7.17–408 Diseases control rate (median follow-up 15.9 month, RECIST criteria)		+ Allocation concealment: + Blinding of participants and personal: + Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Study type, level of evidence and risk of bias
	Smoking history Nonsmoker (%): 53/55 Ex-smoker (%): 39/37 Current smoker (%): 8/8 **Type of first chemotherapy** Taxane (%): 41/45 Nontaxane (%): 59/55 **Response to first chemotherapy** PR or CR (%): 39/34 SD (%): 61/66		72%/51%; 2.69; 1.62–4.46 Sustained clinically relevant improvement in cancer symptoms (time point NR, FACT-L) 28%/10%; OR = 3·41; 1.65–7.06		

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p [adjustment factors]; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
Belani, C.P., et al., Multicenter, randomized trial for stage IIIB or IV non-small-cell lung cancer using weekly paclitaxel and carboplatin followed by maintenance weekly paclitaxel or observation. J Clin Oncol, 2003. 21(15): p. 2933-9.	Region NR Inclusion criteria 18 years of age or older Histologically or cytologically conformed, inoperable, stage IIIB or IV NSCLC One bidimensionally measurableIndicator lesion that had not been previously irradiated Performance status had to be 0 to 2 Life expectancy of ≥ 12 weeks and adequateHematologic, renal and hepatic function Fully recovered patient from all adverse effects if prior radiation therapy or major surgery (had to be completed at least 3 weeks before enrollment)	Intervention(s) Paclitaxel cycle consisted of 70 mg/m² weekly for 3 of 4 weeks continued until disease progression, development of intercurrent illness, intolerable toxicity, patient refusal of further treatment, or investigator decision to terminate treatment Paclitaxel was reduced by one dose level for grade 2 neuropathy Control Observation	Median time to progression (weeks) 38/29; NA; 0.124 Median survival time (weeks) 75/60; NA; 0.243 Overall survival (2 years) 32%/26%; NR; NR	At least one AE 86%/NR At least one Grade 3 or 4 AE 45%/NR	Study type RCT Level of evidence 2b Risk of bias Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p [adjustment factors]; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Stable disease or better on initial therapy Exclusion criteria Prior chemotherapy Measurable neuropathy, active serious infection, or other serious underlying medical conditions Patient characteristics Age (median): 66/65 Male (%): 63/62 *Stage* IIIB (%): 28/22 IV (%): 72/78 *Performance status (ECOG)* 0-1 (%): 91/ 92 2 (%): 9/8	Included/randomised patients NR Analysed patients 65/65 Attrition NR Excluded from analysis (reason) NA (not received treatment, patients were removed from the study for grade 3 or greater neuropathy)			Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p [adjustment factors]; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
Brodowicz, T. Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: a phase III trial. Lung Cancer. 2006 52(2):155-63.	Region NR Inclusion criteria NSCLC stage IIIB disease with pleural effusion and/or positive supraclavicular nodes, or stage IV disease, Not amenable to curative treatment Other forms of therapy than chemotherapy had to be completed at least 3 weeks before study enrollment. Karnofsky performance status (KPS) ≥70 Measurable disease Age≥19 years Estimated life expectancy of at least 12 weeks	Intervention(s) Best supportive care Gemcitabine 1250 mg/m2 on days 1 and 8 of a 21-day cycle until documented progressive disease (PD), or request for discontinuation by the patient or physician Patients requiring palliative radiotherapy were considered to have PD Control Best supportive care	Response rate (median 20.5/17) 50.7%/ 45.6%; NR; 0.554 Median overall survival (months) 10.2/8.1; NR; 0.172 Median time to progression or death (month) 3.6/2.0; NA; < 0.001 Progression or death (median 20.5/17) NR; HR=1.429; 1.11-2.00	Neutropenia (% of cycles): 14.9/NR Thrombocytopenia (% of cycles): 1.7/NR Anemia (% of cycles): 2.6/NR Leukopenia (% of cycles): 2.3/NR Nausea/vomiting (% of cycles): 0.8/NR Alopecia (% of cycles): 4.3/NR Hemorrhage (% of cycles): 0//NR Pulmonary (% of cycles): 0.5/NR Hepatic ALT/AST (% of cycles): 0.2//NR	Study type RCT Level of evidence 2b Risk of bias Generation of allocation sequence: ? Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p [adjustment factors]; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Adequate bone marrow reserve Childbearing potential Patients who demonstrated complete response, partial response, or stable disease within 1 month after the fourth cycles gemcitabine Exclusion criteria Prior chemotherapy Prior radiotherapy (up to 60 Gy) was permitted if the irradiated area was not the only source of measurable disease Active infection Presence of symptomatic central nervous system metastases Inadequate liver function Inadequate renal function Serious	Included/randomised patients 215 (ratio 2:1) Analysed patients 99 in total (progression) NR for other outcomes Attrition NR Excluded from analysis (reason) 116 in total (NR, outcome progression) NR for other outcomes		Bilirubin (% of cycles): 0//NR	Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p [adjustment factors]; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	concomitant systemic disorder incompatible with the study Second primary malignancy Patient characteristics Age (median): 58/68 Male (%): 70.3/79.4 Stage IIIB (%): 27.5/26.5 IV (%): 72.5/73.5 KPS > 80 (%): 47.8/48.5 ≤ 80 (%): 52.2/51.5 Histology Squamous cell carcinoma (%): 42.0/38.2 Adenocarcinoma (%): 44.9/39.7 Large cell (%): 4.3/2.9				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p [adjustment factors]; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Other (%): 8.7/9.1 Prior therapy Radiation (%): 13.0/7.4 Surgery (%): 19.6/20.6 Metastatic sites of disease Lung (%): 42.0/42.6 Lymph node (%): 65.2/61.8 Liver (%): 13.8/19.1 Bone (%): 15.2/11.8 Adrenal (%): 8.7/10.3 Visceral tumor sites positive (%): 91.3/88.2 < 3 organs involved (%): 79.7/72.1 ≥ 3 organs involved (%): 20.3/27.9				
Mubarak, N. A randomized, phase 2 study	Region Egypt, Lebanon, and Saudi Arabia	Intervention(s) Pemetrexed (500 mg/m2 every 21	Response rate (time period) 0/0; NA, NA	Dyspnea (%): 7.1/14.8 Anemia (%): 10.7/3.7	Study type RCT

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p [adjustment factors]; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
comparing pemetrexed plus best supportive care versus best supportive care as maintenance therapy after first-line treatment with pemetrexed and cisplatin for advanced, non-squamous, non-small cell lung cancer. BMC Cancer. 2012 24;12:423.	Inclusion criteria ≥18 years Estimated life expectancy of ≥12 weeks Performance statusof 0 or 1 Histologic or cytologic diagnosis of stage IIIB (with pleural effusion and/or positive supraclavicular nodes) or stage IV NSCLC with nonsquamous histology that was not amenable to curative therapy No prior systemic anticancer therapy for lung cancer Creatinine clearance (CrCl) ≥45 mL/min Serum creatinine <1.5 x ULN Adequate bone marrow reserve and liver function	days) and best supportive care Maintenance therapy commenced on day 1 of the fifth cycle and continued until disease progression, unacceptable toxicity, or another permitted reason for discontinuation Median number of cycles of pemetrexed given was 4.0 Control Best supportive care Included/randomised patients 28/27 Analysed patients	Median overall survival (months) 12.2/11.8; NR; ns Overall survival (1 year) 54.4%/49.5%; HR=1.053; 0.508-2.174 Median progression-free survival (months) 3.2/3.2; NA; ns Progression-free survival NR; HR=1.539; 0.833 – 2.857 (adjusted for best tumour response, sex,	Chest/thorax pain (%): 10.7/11.1 Neutropenia (%): 7.1/0.0 Abnormal alanine aminotransferase (%): 7.1/3.7 Fatigue (%): 3.6/7.4 Nausea (%): 7.1/0.0 Vomiting (%): 7.1/0.0	Level of evidence 2b- (single results with wide confidence interval) Risk of bias Generation of allocation sequence: + Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: + Selective reporting: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p [adjustment factors]; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Atleast one unidimensionally measurable lesion Prior surgery and radiotherapy were allowed if patients had recovered at least 4 weeks before the initiation of induction therapy No disease progression Exclusion criteria Any serious concomitant systemic disorder Brain metastasis Clinically significant third-space fluid collections Significant weight loss (>10%) during the 6 weeks before study entry Pregnancy or breast-feeding Inability to interrupt aspirin or other nonsteroidal anti-	28/27 Attrition 5/2 Excluded from analysis (reason) -	baseline disease stage performance status)		Other source of bias: - (groups not balanced)

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p [adjustment factors]; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	inflammatory agents for a 5-day period (or 8-day period for long-acting agents such as piroxicam) Inability or unwillingness to take folic acid, dexamethasone (or equivalent) or vitamin B12 supplementation Patient characteristics Age (median): 61/59 Male (%): 71.4/63.0 Smoking status Current (%): 28.6/22.2 Former (%): 28.6/40.7 Never (%): 42.9/37.0 Stage IIIB (%): 32.1/37.0 IV (%): 67.9/63.0 Performance status				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p [adjustment factors]; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	0 (%): 28.6/22.2 1 (%): 71.4/77.8 Histology Adenocarcinoma (%): 67.9/77.8 Large cell (%): 28.6/18.5 Mixed cell (%): 3.6/3.7 Prior response Complete (%): 0.0/3.7 Partial (%): 35.7/40.7 Stable (%): 60.7/48.1 Unknown (%): 3.6/7.4 Race Caucasian (%): 92.9/96.3 African (%): 7.1/3.7 Prior therapy Radiotherapy (%): 7.1/3.7 Curative surgery (%): 0.0/7.4				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p [adjustment factors]; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
Pérol, M. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol. 2012 1;30(28):3516-24. Bylicki, O., et al., Efficacy of pemetrexed as second-line therapy in advanced	Region France Inclusion criteria Age 18 to 70 years Histologically or cytologically documented stage IV NSCLC or stage IIIB NSCLC with documented pleural involvement Measurable disease Performance status (PS) of 0 or 1 Exclusion criteria Prior therapy with an EGFR inhibitor Concurrent radiotherapy except for bone metastasis Pre-existing interstitial lung disease	Intervention(s) 1) Continuation maintenance with gemcitabine (1,250mg/m2 day 1, day 8 of a 3-week cycle); median number of treatment cycles was four (range 1 to 19); median duration of treatment was 10.9 weeks 2) Switch maintenance with erlotinib (150 mg/d); median duration of treatment was 12.1 weeks Maintenance treatment was continued until disease progression, unacceptable toxicity, or death	Median overall survival (months) 1) 12.1/10.8; NA; NR 2) 11.4/10.8; NA; NR Overall survival (median 25.6) 1) NR/NR; HR =1.124; 0.860 -1.440 2) NR/NR; HR=1.140; 0.885-1.471 Median progression-free survival (months) 1) 3.8/1.9; NA; NR 2) 2.9/1.9; NA; NR Progression-free survival (median follow-up 25.6)	≥ 1 serious AE unrelated to disease progression (%): 22.7/23.2/18.7 ≥ 1 grade 3/4 AE related to treatment (%): 27.9/15.5/2.6 Anemia (%): 38.3/15.5/7.7 Neutropenia (%): 42.2/3.2/4.5 Thrombocytopenia (%): 39.0/1.3/1.3 Rash (%): 3.9/63.2/0.0 Diarrhea (%): 5.2/20.0/0.6 Anorexia (%): 7.1/5.2/2.6 Asthenia (%): 27.3/17.4/7.1	Study type RCT Level of evidence 1b Risk of bias Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p [adjustment factors]; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
NSCLC after either treatment-free interval or maintenance therapy with gemcitabine or erlotinib in IFCT-GFPC 05-02 phase III study. J Thorac Oncol, 2013. 8(7): p. 906-14.	Any other malignancies within the previous 5 years (except for treated carcinoma in situ of the cervix or basal cell skin cancer) Symptomatic brain metastasis Patient characteristics Age (median): 58/56/60 Male (%): 73.4/72.9/72.9 Smoking status Current and former (%): 89.0/89.0/92.3 Never (%): 11.0/11.0/7.7 Stage IIIB (%): 9.3/7.4/9.2 IV (%): 90.7/92.6/90.8 Unknown (%): 1.9/4.5/1.3 Performance status	Subgroup analysis subsequent pemetrexed At the occurrence of disease progression, all patients were being proposed second-line chemotherapy with pemetrexed Pemetrexed was administered by a 10 minutes intravenous perfusion the first day of each 21-day cycle Subsequent treatments after second-line pemetrexed were selected at the discretion of each investigator Control	1) NR/NR; HR=1.786; 1.388-2.272 2) NR/NR; HR=1.440; 1.136-1.851 Subgroup analysis subsequent pemetrexed Median progression-free survival (months) 4.2/3.9; NA; NR 4.2/3.9; NA; NR Progression-free survival (time period NR) 1) NR/NR; HR =1.235; 0.943-1.613 2) NR/NR; HR =1.205; 0.917-1.563	Deterioration of general condition (%): 6.5/6.5/5.8 Infection (%): 6.5/5.2/1.3 Renal failure (%): 4.5/5.2/1.3 Pneumonia (%): 4.5/5.8/2.6 Treatment-related deaths (absolute number): 2/0/0 Subgroup analysis subsequent pemetrexed Anemia (%): 7.0/4.3/5.4 Neutropenia (%): 19.3/9.5/13.1 Thrombocytopenia (%): 8.8/3.4/6.2	Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p [adjustment factors]; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	0 (%): 40.1/37.9/44.2 1 (%): 53.9/55.6/52.6 2 (%): 4.6/5.2/2.6 3 (%): 1.3/1.3/0.6 Unknown (%): 1.3/1.3/0.6 Brain metastases (%): 3.2/1.3/0.6 Histology Adenocarcinoma (%): 65.6/62.6/66.5 Squamous cell carcinoma (%): 22.1/17.4/19.4 Unknown (%): 12.3/20.0/14.2 Response to induction chemotherapy Objective response (%): 52.6/52.9/52.9 Stable disease (%): 47.4/47.1/47.1	Observation Included/randomised patients 154/155/155 Analysed patients 149/153/152 Attrition 144/145/148 Excluded from analysis (reason) 5/2/3 (no adequate data on progression) Analysed patients (subgroup analysis subsequent pemetrexed) 114/116/130	Median overall survival (months from beginning of second-line pemetrexed) 1) 8.3/7.5; NA; NR 2) 9.1/7.5; NA; NR Overall survival (time period NR) 1) NR/NR; HR =1.235; 0.935-1.630 2) NR/NR; HR=1.25; 0.952-1.630 Objective response rate (time period NR) 1) 6.0%/14.6%; NR; ns 2) 12.3%/14.6%; NR; ns	Fatigue (%): 2.6/9.5/10.8 Infection (%): 2.6/3.4/2.3 Pain (%): 4.4/3.4/3.1	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p [adjustment factors]; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Patient characteristics (subgroup analysis subsequent pemetrexed) Age (median): 58/59/56 Male (%): 70.2/73.3/72.3 Smoking status Never-smoker (%): 12.3/12.9/6.2 Current/former smoker (%): 87.7/87.1/93.8 Stage IIIB (%): 9.0/8.2/9.4 IV (%): 91.0/91.8/90.6 Performance status 0 (%): 41.6/36.0/44.2 1 (%): 54.9/59.6/54.3 2 (%): 3.5/3.5/0.8 Histologic types				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p [adjustment factors]; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Squamous cell carcinoma (%): 20.2/15.5/21.5 Adenocarcinoma (%): 67.5/65.5/63.1 Other: NSCLC, NOS (%): 12.2/19.0/15.3. Response after CT induction Stable disease (%): 44.7/43.1/43.1 Complete/partial response (%): 55.3/56.9/56.9				
Westeel, V. Randomized study of maintenance vinorelbine in responders with advanced non-small-cell lung cancer. J Natl Cancer Inst, 2005. 97(7): p. 499-506.	Region France Inclusion criteria Histologically confirmed stage IIIB and IV NSCLC Performance status ≤2 ≤ 75 years	Intervention(s) Vinorelbine Intravenously at a dose of 25 mg · m−2 · wk−1 for 6 months, beginning 16 weeks after the first MIC cycle in patients treated with induction chemotherapy and 17 weeks after	Median overall survival (months) 12.3/12.3; NA; NR Overall survival (2 years) 20%/20%; NR; NR	Anemia (%): 9.2/NR Leukopenia (%): 46.9/NR Thrombocytopenia (%): 3.4/NR Infetion (%): 12.6/NR Hemorrhage (%): 1.1/NR Ileus (%): 3.4/NR Pulmonary (%): 6.9/NR	Study type RCT Level of evidence 2b Risk of bias Generation of allocation sequence: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p [adjustment factors]; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Patients with stage IIIB disease were required to have no contraindications to thoracic radiotherapy Leukocyte count above 3000/ µL Neutrophil count above 1500/ µL Platelet count above 150 000/ µL Serum creatinine level below 130 µmol/L Exclusion criteria Prior chemotherapy or thoracic radiotherapy, but patients who experienced recurrences after surgery were eligible Brain metastases Previous cancer except for basal cell carcinoma of the skin	the first MIC cycle in patients treated with induction chemoradiation Maintenance vinorelbine was stopped after any grade 4 toxicity other than neutropenia was observed Mean duration was 13.8, the median total delivered dose was 450 mg, and the median dose intensity was 23 mg · m−2 · wk−1 Control Observation Vinorelbine treatment was not allowed in patients	Overall survival (median 10.4/11.9) NR/NR; HR =0.926; 0.680-1.266 Median progression-free survival (months) 5/3; NR; NR Progression-free survival (median follow-up 10.4/11.9) HR=1.299; 0.935-1.786 Progression-free survival (2 years) 13%;15%; NR; NR	Peripheral neuropathy (%): 6.9/NR Cardiac (%): 1.1/NR Others (%): 9.2/NR	Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: + Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p [adjustment factors]; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Interstitial pneumonitis Severe cardiac disease Cirrhosis Responders to induction chemotherapy Patient characteristics Age (median): 62/63 Male (%): 95.6/90.0 Stage IIIB (%): 47.3/56.7 IV (%): 52.7/43.3 Performance status 0 (%): 33.0/33.3 1 (%): 51.6/57.8 2 (%): 15.4/8.9 Histology Squamous (%): 60.4/58.9	assigned to the observation group at any time Investigators were advised to treat patients with progressive disease in both arms with etoposide (80 mg · m−2 · day−1) and cisplatin (30 mg · m−2 · day−1) on days 1 through 3 every 4 weeks Included/randomised patients 91/90 Analysed patients 91/90 87/0 (for safety) Attrition			

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p [adjustment factors]; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Adenocarcinoma (%): 30.8/28.9 Large cell (%): 8.8/12.2 Response to induction treatment at random assignment Complete (%): 13.2/6.7 Partial (%): 86.8/93.3	NR Excluded from analysis (reason) 4/90 (not received any treatment, no available data)			

+ low risk of bias; - high risk of bias, ? unclear risk of bias, CG: control group; CI: confidence interval; IG: intervention groups; NR: not reported; ns: not statistical significant

12.2.6. Molekular stratifizierte Therapie NSCLC IV

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
Kim, Y.S., et al., Randomized Phase II Study of Pemetrexed Versus Gefitinib in Previously Treated Patients with Advanced Non-small Cell Lung Cancer	**Region** Korea, USA **Inclusion criteria** Histologically- or cytologically-proven advanced (stage IIIB or IV) or recurrent NSCLC Disease progression after first-line or second-line chemotherapy ≥18 years ECOG performance status (PS) < 2 At least one measurable lesion Adequate bone marrow Normal and functions Life expectancy of at least 3 months Brain metastasis were eligible if treated with radiation therapy and clinically stable	**Intervention(s)** Gefitinib 250 mg was administered orally once daily (1 cycle for 21 days) Cycles were repeated until disease progression, unacceptable toxicity Pemetrexed 500 **Control** Pemetrexed 500 mg/m² was administered intravenously over 10 minutes on day 1 of every 21-day cycle	Median overall survival (months) 8.5/8,5; NA; NR Overall survival (median follow-up: 60.6 months) 90%/89%; NR; NR **Median progression-free survival (months)** 2.0/2.0 ; NA; ns **Progression-free survival (6 months, RECIST criteria)** 15%/22%; NR; 0.35 ORR (median follow-up: 60.6 months, RECIST criteria)	**Hematologic toxicity** Anemia (%): 21/51 Leukocytopenia (%): -/4 Neutropenia (%): -/6 Thrombocytopenia (%): -/6 **Non- hematologic toxicity** Skin rash (%): 46/11 Fatigue (%) 21/45 Anorexia (%): 42/40 Nausea (%): 25/21 Vomiting (%): 15/9 Stomatitis (%): 19/9 Constipation (%): 2/21 Diarrhea (%): 17/9 Infection (%): 8/15 Edema (%): 4/4 Interstitial lung disease (%): -/4	**Study type** RCT **Level of evidence** 2b **Risk of bias** Generation of allocation sequence: + Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment:

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Exclusion criteria Chronic diarrhea of any grade, inflammatory bowel disease, uncontrolled comorbid illness, or other malignancies Squamous cell histology or activating *EGFR* mutations **Patient characteristics** Age (mean): 67/64 Men (%): 73/70 ***PS (ECOG)*** 0 (%): 10/11 1 (%): 54/57 2 (%): 35/32 ***Histology*** Adenocarcinoma (%): 65/62 Squamous cell carcinoma (%): 19/21	Cycles were repeated until disease progression, unacceptable toxicity **Included/randomised patients** 48/47 **Analysed patients** 48/47 NR (efficacy) **Attrition** NR **Excluded from analysis (reason)** -	8%/13%; NR; 0.52 Diseases control rate (median follow-up: 60.6 months, RECIST criteria) 8%/13%; NR; 0.36		- Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	LCNEC (%): 2/2 NSCLC not otherwise specified (%): 15/15 ***Stage at treatment*** IIIB (%): 4/6 IV (%): 96/94 ***Metastatic sites*** Lung to lung (%): 44/38 Pleura (%): 54/34 Brain (%): 8/15 >2 sites (%): 48/38 ***Treatment sequence*** 2nd- line (%): 63/68 3rd - line (%): 38/32 ***Smoking habits*** Current and former smokers (%): 69/70 Never smokers (%): 31/30 ***Previous chemotherapy***				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Platinum-based combinations (%): 83/87 Non-platinum combinations (%): 8/6 Monotherapy without platinum (%): 8/6 ***Previous best response to first-line treatment*** Complete response (%): 2/0 Partial response (%): 52/68 Stable disease (%): 29/26 Progressive disease (%): 17/6 ***EGFR mutation*** Mutant (%): 2/2 Wild- Type (%): 48/28 Unknown (%): 50/70				
Paz-Ares, L., et al., Necitumumab plus pemetrexed and cisplatin as first-line therapy	**Region** 20 countries **Inclusion criteria** Age of 18 or older	**Intervention(s)** Patients received cisplatin 75 mg/m² and pemetrexed 500	**Median overall survival (months)** 11.3/11.5; NA; ns (CIs overlapping)	Neutropenia (%): 32/32 Anaemia (%): 26/31 Fatigue (%): 56/51	**Study type** RCT **Level of evidence**

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
in patients with stage IV non-squamous non-small-cell lung cancer (INSPIRE): an open-label, randomised, controlled phase 3 study. Lancet Oncol, 2015. 16(3): p. 328-37.	Histologically or cytologically confirmed stage IV non-squamous NSCLC who not Chemotherapy for the treatment of advanced disease Measurable disease ECOG performance status of 0–2 Adequate organ function **Exclusion criteria** Symptomatic brain metastases Clinically significant third-space fluid retention requiring repeated drainage4 Peripheral neuropathy of grade 2 or worse Major surgery or investigational therapy in the 4 weeks before randomization Superior vena cava syndrome contraindicating hydration Clinically relevant coronary artery disease	mg/m² on day 1 of a 3-week cycle for a maximum of six cycles with necitumumab 800 mg on days 1 and 8 After six cycles of study therapy, patients without progressive disease in the necitumumab group continued with necitumumab **Control** Patients received cisplatin 75 mg/m² and pemetrexed 500 mg/m² on day 1 of a 3-week cycle for a maximum of six cycles	**Overall survival (median follow-up: 24.5 months [necitumumab], 25.6 months [9])** 75%/77%; HR= 1.01; 0.84–1.21 Median progression-free survival (months) 5.6/5.6; NA; ns Death or diseases progression (median follow-up: 24.5 months [necitumumab], 25.6 months [9], RECIST criteria) 73%/75%; HR=0.96; 0.80–1.16 ORR (median follow-up: 24.5 months [necitumumab], 25.6 months [9], RECIST criteria)	Hypomagnesaemia (%): 27/13 Skin reaction (%): 78/19 Rash (%): 76/16 Hypersensitivity or infusion-related reaction (%): 2/1 Eye disorders (%): 16/12 Interstitial lung disease (%): 1/1 Arterial thromboembolic events (%): 4/6 Venous thromboembolic events (%): 13/8 Unexplained death (%): 4/2	1b **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: ? Selective reporting:

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Uncontrolled congestive heart failure Myocardial infarction within 6 months before randomization Ongoing or active infection History of clinically significant neurological or psychiatric disorders, including dementia, seizures, bipolar disorder Serious uncontrolled medical disorders or psychological disorder Allergy or history of hypersensitivity reaction to any of the treatment components Concurrent active malignancy other than adequately treated basal-cell carcinoma of the skin or preinvasive carcinoma of the cervix History of drug abuse **Patient characteristics** Age (mean): 61/60	Observed until radiographically documented progressive disease **Included/randomised patients** 315/318 **Analysed patients** 315/318 (efficacy) 304/312 **Attrition** NR **Excluded from analysis (reason)** 11/6 (safety, not received study drug)	31%/32%; OR=0.96; 0.68–1.34 Quality of live (time point NR, LCSS) NR; NR; similar (according study authors) Quality of live (time point NR, EQ-5D) NR; NR; similar (according study authors)		+ Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Men (%): 68/66 ***Age group (years)*** <65 (%): 63/68 >65 (%): 37/32 <70 (%): 83/84 >70 (%): 17/16 ***PS (ECOG)*** 0 (%): 37/42 1 (%): 58/52 2 (%): 5/6 Missing (%): <1/0 ***Smoking habits*** Current smoker (%): 76/75 Ex- light smoker (%): 8/8 Never smokers (%): 16/17 ***Disease histology*** Adenocarcinoma (%): 89/90 Large- cell carcinoma (%): 8/8				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Other (%): 2/2 Missing (%): <1/0 ***Ethnic origin*** White (%): 93/94 Asian (%): <1/0 Other (%): 7/6 ***Previous anticancer therapy*** Surgery (%): 26/29 Radiotherapy (%): 10/13 Systemic (adjuvant or neoadjuvant) (%): 3/3				
Solomon BJ, Mok T, Kim DW et al., N Engl J Med. 2014 Dec 4;371(23):2167-77. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. PROFILE 1014	**Region** Different countries **Inclusion criteria** Age of 18 years Histologically or cytologically confirmed locally advanced, recurrent, or metastatic nonsquamous NSCLC that was positive for an *ALK* rearrangement	**Intervention(s)** Oral crizotinib, at a dose of 250 mg twice daily Administered every 3 weeks for a maximum of six cycles	Overall survival (1 year) 84%/79%; HR=1.22; 0.79-1.85 **Median progression-free survival (months)** 10.9/7.0; NA; statistical significant (CIs not overlapping)	Vision disorder (%): 71/9 Diarrhea (%): 61/13 Edema (%): 49/12 Vomiting (%): 46/36 Constipation (%): 43/30 Elevated aminotransferases (%): 36/13	**Study type** RCT **Level of evidence** 1b **Risk of bias** Generation of allocation sequence: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
Investigators (Phase III Studie: Crizo vs. Chemo)	Received no previous systemic treatment for advanced disease Measurable disease ECOG performance status of 0, 1, or 2 Adequate hepatic, renal, and bone marrow function Brain metastases eligible if neurologically stable for at least 2 weeks before enrollment and the patient had no ongoing requirement for glucocorticoids **Exclusion criteria** NR **Patient characteristics** Age (mean): 52/54 Men (%): 40/37 ***PS (ECOG)*** 0 or 1 (%): 94/95	Treatment was continued until RECIST-defined disease progression, development of unacceptable toxic effects **Control** Intravenous chemotherapy (pemetrexed, at a dose of 500 mg per square meter of body-surface area, plus either cisplatin, at a dose of 75 mg per square meter, or carboplatin, target area under the curve of 5 to 6 mg per milliliter per minute	**Progression-free survival median follow-up: 17.4 [crizotinib] months, 16.7 [9] months, RECIST criteria)** NR; HR=2.22; 1.67-2.86 ORR (median follow-up: 17.4 months [crizotinib], 16.7 months [9], RECIST criteria) 74%/45%; NR; <0.001 Change from baseline in quality of life (time point NR, EQ-5D) NR; Crizotenib>control; 0.002 Change from baseline in quality of life (time point NR, QLQ-C30)	Upper respiratory infection (%): 32/12 Abdominal pain (%): 26/12 Dysgeusia (%): 26/5 Headache (%): 22/15 Pyrexia (%): 19/11 Dizziness (%): 18/10 Pain in extremity (%): 16/7 Fatigue (%): 29/38 Neutropenia (%): 21/30 Stomatitis (%): 12/20 Asthenia (%): 13/24 Anemia (%): 9/32 Leukopenia (%): 7/15 Thrombocytopenia (%): 1/18 Nausea (%): 56/59 Decreased appetite (%): 30/34 Cough (%): 23/20	Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	2 (%): 6/5 ***Histology*** Adenocarcinoma (%): 94/94 Nonadenocarcinoma (%): 6/6 ***Smoking habits*** Current smoker (%): 6/3 Former smoker (%): 33/32 Never smokers (%): 62/65 ***Ethnic origin*** White (%): 53/50 Asian (%): 45/47 Other (%): 2/4 ***Extent of disease*** Locally advanced (%): 2/2 Metastatic (%): 98/98 ***Time since first diagnosis- mo*** Median: 1.2/1.2 Range: 0- 114.0/ 0-93.6	Administered every 3 weeks for a maximum of six cycles Treatment was continued until RECIST-defined disease progression, development of unacceptable toxic effects **Included/randomised patients** 172/171 **Analysed patients** 172/171 (efficacy) NR (quality of life)	NR; Crizotenib>control; <0.001 Reduction in symptoms (time point NR, QLQ-C30) NR; Crizotenib>control, <0.05 (pain, dyspnea, fatigue, insomnia, nauses and vomiting); Crizotenib>control, p>0.05 (constipation); Control> Crizotenib, p<0.05 (diarrhea) Reduction in symptoms (time point NR, QLQ-LC13) NR; Crizotenib>control, p<0.05 (dyspnea, cough, chest pain, arm or shoulder pain,	Neuropathy (%): 20/22 Dyspnea (%): 18/15	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Brain metastases present – no.(%): 26/27	171/169 (safety) **Attrition** 8/8 **Excluded from analysis (reason)** 0/2 (events before cross-over) NR (quality of life and symptoms, at least one post baseline)	alopecia, and pain in other parts of the body); Crizotenib>control, p>0.05 (hemoptysis, sore mouth); Control> Crizotenib, p<0.05 (peripheral neuropathy); Control> Crizotenib, p>0.05 (dysphagia)		
Wu, Y.L., et al., First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III,	**Region** China, Malaysia, Philipines **Inclusion criteria** ≥18 years Histologically or cytologically confirmed stage IIIB/IV EGFR mutation-positive NSCLC ECOG PS of 0–2	**Intervention(s)** Erlotinib (oral; 150 mg once daily until progression/ unacceptable toxicity **Control**	Median overall survival (months) 26.3/25.5; NA; NR Overall survival (median follow-up: 28.9 months [Erlotinib], 27.1 months [Gemcitabine]) 52%/51%; HR=1.10; 0.76-1.59	Nausea (%): 4.5/57.7 Vomiting (%): 6.4/53.8 Diarrhea (%): 45.5/8.7 Constipation (%): 1.8/18.3 Mouth ulcers (%): 5.5/2.9 Rash (%): 70.9/10.6 Pruritus (%): 10/6.7 Alopecia (%): 5.5/9.6	**Study type** RCT **Level of evidence** 2b **Risk of bias** Generation of allocation sequence: ?

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
randomized, open-label, ENSURE study. Ann Oncol, 2015. 26(9): p. 1883-9.	**Exclusion criteria** Prior chemotherapy or agents targeting HER receptors Inability to take oral medication ≥grade 2 peripheral neuropathy Brain metastases History of any malignancies within 5 years Surgery within 4 weeks of the study **Patient characteristics** Age (mean): 57.5/56 Men (%): 38.2/39.3 ***PS (ECOG)*** 0 (%): 14.7/14.4 1 (%): 78.9/79.8 2 (%): 6.4/5.8 ***Histology***	Gemcitabine 1250 mg/m² i.v. days 1 and 8 plus cisplatin 75 mg/m² i.v. day 1, every 3 weeks for up to four cycles **Included/randomised patients** 110/107 **Analysed patients** 110/107 (efficacy) **Attrition** 0/2 **Excluded from analysis (reason)**	**Median progression-free survival (months)** 11.0/5.6; NA; NR **Progression-free survival (median follow-up: 28.9 months [Erlotinib], 27.1 months [Gemcitabine], RECIST criteria)** NR; HR=2.38; 1.51-3.70 ORR (median follow-up: 28.9 months [Erlotinib], 27.1 months [Gemcitabine], RECIST criteria) 62.7%/ 33.6%; NR; NR Diseases control rate (median follow-up: 28.9 months [Erlotinib], 27.1	Dry skin (%): 9.1/1.9 Dermatits acneiform (%): 8.2/0 Leukopenia (%): 6.4/49 Neutropenia (%): 4.5/51 Anemia (%): 7.3/46.2 Thrombocytopenia (%): 1.8/19.2 White blood cell count decreased (%): 2.7/15.4 Platelets decreased (%): 0.9/14.4 Alanine aminotransferase increased (%): 11.8/1.9 Neutrophils decreased (%): 1.8/9.6 Bilirubin increased (%): 10/0 Fatigue (%): 5.5/19.2 Pyrexia (%): 7.3/12.5	Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Adenocarcinoma (%): 94.5/94.4 Squamous cell carcinoma (%): 1.8/1.9 Other (%): 3.6/3.6 ***Smoking habits*** Current smoker (%): 24.5/29 Former smoker (%): 3.6/1.9 Never smokers (%): 71.8/69.2 ***Stage of disease*** IIIB (%): 9.1/6.5 IV (%): 90.9/93.5 ***Tissue- assessed EGFR mutation*** type Exon 19 deletion (%): 52.3/57 Exon 21 L858R mutation (%): 47.7/43 ***Country*** China (%): 79.1/82.2	0/3 (safety not received treatment)	months [Gemcitabine], RECIST criteria) 89.1%/76.6%; NR; NR	Chest discomfort (%): 5.5/2.9 Cough (%): 17.3/8.7 Dyspnea (%): 5.5/2.9 Decreased appetite (%): 12.7/28.8 Hypokalemia (%): 5.5/6.7 Paronychia (%): 15.5/0 Dizziness (%): 6.4/13.5 Headache (%): 4.5/6.7 Backpain (%): 7.3/5.8 Insomnia (%): 4.5/7.7 Neutropenia (%): 0.9/25 Leukopenia (%): 0.9/14.4 Anemia (%): 0.9/12.5 Thrombocytopenia (%): 0/6.7 Decreased white blood cell count (%): 0/6.7 Decreased neutrophil count (%): 0/5.8	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Non China (%): 20.9/17.8			Rash (%): 6.4/1	
Zhou C, Wu YL, Chen G, et al. : Final overall survival results from a randomised, phase III study of erlotinib versus chemotherapy as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer (OPTIMAL, CTONG-0802). Ann Oncol. 2015 Jul 3. Zhou, C. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR	**Region** China **Inclusion criteria** More than 18 years of age Advanced or recurrent stage IIIB or IV NSCLC with a confirmed activating mutation of EGFR ie, an exon 19 deletion or an exon 21 L858R point mutation Measurable disease according to RECIST ECOG performance status of 0–2, and adequate haematological, biochemical, and organ function **Exclusion criteria** Uncontrolled brain metastases	**Intervention(s)** Oral erlotinib 150 mg once daily until disease progression or unacceptable toxic effects **Control** Platinum-based doublet chemotherapy (intravenous gemcitabine 1000 mg/m² on days 1 and 8 and intravenous carboplatin [area under the curve=5] on day 1 of a 3-week	Median overall survival (months) 22.8/27.2; NA; NR Overall survival (median follow-up 15.6 month) 80%/83%; NR; NR Overall survival (median follow-up 25.9 month) 37%/37%; NR; NR **Progression free survival (median follow-up 15.6 month)** **NR/NR; HR= 6.25; 3.847-10.00**	Neutropenia (%): 6/69 Thrombocytopenia (%): 4/64 Anaemia (%): 5/72 Infection (%): 17/10 Skin rash (%): 73/19 Diarrhoea (%): 25/6 Stomatitis (%): 13/1 Paronychia (%): 4/0 Vomiting or nausea (%): 1/46 Constipation (%): 9/15 Increased ALT (%): 37/33 Fatigue (%): 5/24	**Study type** RCT **Level of evidence** 1b **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: -

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol, 2011. 12(8): p. 735-42. Chen, G. Quality of life (QoL) analyses from OPTIMAL (CTONG-0802), a phase III, randomised, open-label study of first-line erlotinib versus chemotherapy in patients with advanced EGFR mutation-positive non-small-cell lung cancer (NSCLC). Ann	Previous systemic anticancer therapy for advanced disease **Patient characteristics** Age (median): 57/59 Male (%): 41/40 ***PS (ECOG)*** 0-1 (%): 91/96 2 (%): 9/4 ***Smoking status*** Present or former smoker (%): 28/31 Non-smoker (%): 72/69 ***Histology*** Adenocarcinoma (%): 88/86 Non-adenocarcinoma (%): 12/14 ***EGFR mutation*** Exon 19 deletion (%): 52/54 L858R mutation (%): 48/46	cycle (up to four cycles) **Included/randomised patients** 83/82 **Analysed patients** 82/72 71/54 (quality of life) **Attrition** 61/82 **Excluded from analysis (reason)** 1/10 (not received treatment) 12/28 (quality of life: not received	**Median progression free survival (months)** **13.1/4.6; NA; statistical significant** Response rate (median follow-up 15.6 month) 83/36; NR; 0.0001 *Mean change in functioning (baseline to cycle 2, FACT-L)* Physical well-being NR/NR; NR; 0.003 Social/family well-being NR/NR; NR; 0.303 Emotional well-being NR/NR; NR; 0.036 Functional well-being NR/NR; NR; 0.093		Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
Oncol, 2013. 24(6): p. 1615-22.	***Disease stage*** IIIB (%): 13/7 IV (%): 87/93	treatment, not completed questionnaire)	Lung cancer subscale NR/NR; NR; 0.004		

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
Garassino, M.C., et al., Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. Lancet Oncol, 2013. 14(10): p. 981-8.	Region Italia Inclusion criteria Wild-type *EGFR* Recurrence or progression after failing platinum-based chemotherapy. ECOG performance status of 2 or less Adequate vital functions Exclusion criteria Previous treatment with taxanes or anti-EGFR drugs Patient characteristics Age (mean): 66/67 Men (%): 71/66	Intervention(s) Erlotinib 150 mg was given orally every day. Received a median of two cycles, with a median dose of 137 mg/day. Control Docetaxel was given intravenously, at either 75 mg/m² every 21 days, or 35 mg/m² on days 1, 8, and 15, every 28 days. Median of thee cycles, with a median dose per cycle of 91 mg/m2 for the weekly schedule and 75 mg/m2 for the 3-weekly schedule	Median overall survival (months) 5.4/8.2; NR; ns (CIs overlap) Overall survival (1 year) 31.8%/39.6%; HR= 0.73; 0.53–1.00 Median progession-free survival (months) 2.4/2.9; NR; ns Progression-free survival (6 months) 16.5%/27.3%; HR= 0.71; 0.53 –0.95 ORR	Febrile neutropenia (%): 0 / 5 Neutropenia (%): 3/30 Diarrhoea (%): 30/21 Alopecia (%): 2/33 Asthenia (%): 37/49 Neurological (%): 5/16 Nausea or vomiting (%): 10/23 Dermatological (%): 58/4	Study type RCT Level of evidence 1b Risk of bias Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: + Selective reporting: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	PS (ECOG) 0 (%): 48/48 1 (%): 44/45 2 (%): 8/6 *Histology* Squamous (%): 28/21 Adenocarcinoma (%): 63/75 Large-cell carcinoma (%): 1 /1 Bronchoalveolar (%): 3/0 Others (%): 5/3 *Smoking habits* Current and former smokers (%): 83/73 Never smokers (%): 17/27 *Ethnic origin* White (%): 99/99 Asian (%): 1 /1	Included/randomised patients 112/110 Analysed patients 109/110 (efficacy) 97/100 (ORR) 107/104 (safety) Attrition NR Excluded from analysis (reason) 3/0 (efficacy, ineligible for genotyping) 5/6 (safety, not received allocated intervention)	3.0/15.5; NR; 0.003		Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Previous chemotherapy First line (%): 92/93 Adjuvant (%): 8/6 Unknown (%): 0/1 Previous best response to first-line treatment Complete response (%): 1/0 Partial response (%): 44/35 Stable disease (%): 24/35 Progressive disease (%): 31/29	12/13 (ORR, not received allocated intervention, no evaluable response)			
Han, JY. First-SIGNAL: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. J Clin Oncol, 2012. 30(10): p. 1122-8.	Region Korea Inclusion criteria Chemotherapy-naive never-smokers older than age 18 years	Intervention(s) Gefitinib 250 mg/d orally until disease progression Median duration of treatment for gefitinib was 163 days	Median overall survival (months) 27.2/25.6; NR; NR Overall survival (50 months)	NR	Study type RCT Level of evidence 2b Risk of bias

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
(subgroup EGFR mutation)	Stage IV adenocarcinoma of the lung with measurable or nonmeasurable disease Performance status of 0 to 2 Adequate bone marrow, liver, and renal function EFGR mutation Exclusion criteria Known severe hypersensitivity to gefitinib or any constituents of this product Any evidence of clinically active interstitial lung disease Severe or uncontrolled systemic disease	Control Intravenous infusion of gemcitabine 1,250 mg/m² on days 1 and 8 plus cisplatin 75 mg/m² on day 1 cycles were repeated every 3 weeks for up to a maximum of nine cycles as tolerated Median number of GP cycles was six Included/randomised patients NR/NR Analysed patients 26/16 Attrition NR/NR	NR; NR; HR= 1.043; 0.498 – 2.182 Median progression free survival (months) 8.0/6.3; NR; NR Progression-free survival (30 months) NR/NR; HR= 1.838; 0.909 – 3.717 ORR (time period NR) 94.6%/37.5%; NR; 0.002 Median change in quality of Life (baseline to week 21,QLQ-C30) NR;NR; 0.513		Generation of allocation sequence: + Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: + Incomplete outcome data: ? Selective reporting: + Other source of bias: - (subgroup analysis)

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Concomitant use of phenytoin, carbamazepine, rifampin, barbiturate, or St John's wort Nonstable brain metastasis Patient characteristics NR	Excluded from analysis (reason) NR/NR	*Median change in quality of Life (baseline to week 21, LC13)* Dyspnea: NR; NR; 0.95 Coughing: NR; NR; 0.199 Hemoptysis: NR; NR; 0.006 (in favour of Gefitinib) Sore mouth: NR; NR;0.007 (in favour of Gefitinib) Dysphagia: NR; NR; 0.004 (in favour of Gefitinib) Peripheral neuropathy: NR; NR; 0.789 Alopecia: NR; NR; 0.004 (in favour of Gemcitabine) Pain in chest: NR; NR; 0.214		

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
			Pain in arm or shoulder: NR; NR; 0.149 Pain in other parts: NR; NR; 0.652 Pain medication: NR; NR; 0.632		
Karampeazis, A. Pemetrexed versus erlotinib in pretreated patients with advanced non-small cell lung cancer: a Hellenic Oncology Research Group (HORG) randomized phase 3 study. Cancer, 2013. 119(15): p. 2754-64. (subgroup EGFR mutation)	Region NR Inclusion criteria Pemetrexed-naive and TKI-naive patients with documented stage IV NSCLC who experience disease progression after 1 or 2 chemotherapy lines Patients aged <65 years must have received a platinum-based regimen, which was not mandatory for older patients	Intervention(s) Erlotinib (150 mg/day orally; median duration 3.2 months) Control Pemetrexed (500 mg/m^2 over a 1-hour as an intravenous infusion on day 1, every 3 weeks; median, 3 cycles)	Overall survival (median 27.3/29.0) NR/NR; HR= 0.52; 0.10 – 2.69 ORR (median 27.3/29.0) No differences	NR	Study type RCT Level of evidence 2b- Risk of bias Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: -

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Performance status (PS) from 0 to 2 Adequate bone marrow tests Life expectancy ≥ 3 months Clinically stable with irradiated brain metastases EFGR mutation Exclusion criteria Squamous cell histology (Amendment after July 2008) Second primary tumor Active infection Severe heart disease Uncontrolled diabetes mellitus Patient characteristics	Included/randomised patients NR Analysed patients 5/6 Attrition NR Excluded from analysis (reason) NR			Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: - (subgroup analysis)

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	NR				
Kawaguchi, T. 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. (subgroup analysis)	Region Japan Inclusion criteria Age 20 years or older NSCLC with stage IV disease Previous treatment with one or two chemotherapy regimens, including at least one platinum agent Evaluable or measurable disease by computed tomography (CT) or magnetic resonance imaging Performance status of 0 to 2 EGFR mutation	Intervention(s) Erlotinib (150 mg per day) was administered orally Control Docetaxel was administered every 3 weeks as a 1-hour intravenous infusion of 60mg/m² Included/randomised patients NR Analysed patients 5/6 Attrition NR	Median overall survival (months) Not reached/27.8 months; NA; NR Overall survival (40 months) HR=NR/NR; HR= 2.632; 0.909 –10.00 Test of interaction for survival EGFR positive vs. EGFR negative; 0.20 Median progression free survival (months) 9.3/7.0; NA; NR	NR	Study type RCT Level of evidence 2b Risk of bias Generation of allocation sequence: + Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data: ?

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Exclusion criteria Previous exposure to EGFR-TKI or docetaxel, symptomatic brain metastasis Second active cancer Interstitial pneumonia or pulmonary fibrosis detected by chest CT Patient characteristics NR	Excluded from analysis (reason) NR	Progression free survival (32 months) HR=NR/NR; HR= 1.21; 0.654 – 2.236 Test of interaction for progression free survival EGFR positive vs. EGFR negative; 0.03		Selective reporting: + Other source of bias: - (subgroup analysis)
Mitsudomi, T. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3	Region Japan Inclusion criteria Confirmed stage IV NSCLC Harbouring activating EGFR mutations (either exon 19 deletion or L858R in exon 21)	Intervention(s) Gefi tinib (250 mg/day, administered orally) Continued until progression of the disease, development of unacceptable toxic effects, a request by the patient	Overall survival (median 81 days) NR/NR; 0.611; 0.279-1.335 Median progression free survival (months) 9.2/6.3; NR; sign.	Rash (%): 85/8 Alanine aminotransferase (%): 70/19 Aspartate aminotransferase (%): 70/40 Dry skin (%): 54/3 Diarrhoea (%): 54/40 Fatigue (%): 39/83	Study type RCT Level of evidence 2b Risk of bias

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
trial. Lancet Oncol, 2010. 11(2): p. 121-8.	Aged 75 years or young erWHO performance status 0–1 Measurable or non-measurable disease according to the Response Evaluation Criteria in Solid Tumours (RECIST) Adequate organ function Patients with postoperative recurrence, treated with adjuvant therapy other than cisplatin plus docetaxel, were included when the interval between the end of adjuvant chemotherapy and registration exceeded 6 months for platinum-doublet therapy and more than 1 month for oral tegafur plus uracil therapy	to discontinue treatment, serious ,noncompliance with the protocol, or completion of thee to six chemotherapy cycles Control Docetaxel (60 mg/m², administered intravenously over a 1 h period) followed by cisplatin (80 mg/m², administered intravenously over a 90-min period) Continued until progression of the disease, development of unacceptable toxic eff ects, a request by the patient to discontinue	Progression free survival (median 81 days) NR/NR; HR= 2.045; 1.41-2.976 Objective response rate (median 81 days) 62.1%/32.2%; NR; <0.0001	Paronychia (%): 32/1 Stomatitis (%): 22/15 Nausea (%): 17/94 Constipation (%): 16/44 Alopecia (%): 9/76 Sensory disturbance (%): 8/26 Leucocytopenia (%): 15/49 Thrombocytopenia (%): 14/0 Neutropenia (%): 8/84 Anemia (%): 38/17	Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Exclusion criteria Previous drug therapy that had targeted EGFR History of interstitial lung disease Severe drug allergy Active infection or other serious disease condition Symptomatic brain metastases Poorly controlled pleural effusion, pericardial effusion or ascites necessitating drainage, active double cancer, or severe hypersensitivity to drugs containing polysolvate 80 Patients in pregnancy or lactation, or whose participation in the trial was judged to be inappropriate by the attending doctor	treatment, serious ,non-compliance with the protocol, or completion of three to six chemotherapy cycles Included/randomised patients 88/89 Analysed patients 87/88 (for safety) 86/86 (for efficacy) Attrition NR Excluded from analysis (reason) 1/1 (safety, not received therapy) 2/3 (efficacy, not received therapy, exon			

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Patient characteristics Age (median): 64.0/64.0 Male (%): 27/26 *PS (ECOG)* 0 (%): 56/52 1 (%): 30/34 *Histological type* Adenocarcinoma (%): 83/84 Adenosquamous carcinoma (%): 0/1 Squamous-cell carcinoma (%): 1/0 Non-small-cell-lung cancer; not otherwise specified (%): 2/1 *Smoking history* Never (%): 61/57	18 mutation, allergic reaction, insufficient consent)			

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Former/current (%): 25/29 *Stage* Postoperative recurrence (%): 35/36 With postoperative adjuvant chemotherapy (%): 19/23 Without postoperative adjuvant chemotherapy (%): 16/13 IIIB (%): 10/9 IV (%): 41/41 *EGFR mutation* Exon 19 detection (%): 50/37 L858R (%): 36/49				
Mok, T. S. "Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma." N Engl J Med,	Region Hong Kong, China, Indonesia, Japan, Malaysia, the	Intervention(s) Gefitinib (250 mg per day, administered orally)	Overall survival (time period NR) NR/NR; HR= 1.28; 0.833-2.00	NR	Study type RCT Level of evidence

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
2009. 361(10): 947-957. (subgroup analysis)	Philippines, Singapore, Taiwan, and Thailand Inclusion criteria 18 years of age or older Confirmed stage IIIB or IV non–small-cell lung cancer with histologic features of adenocarcinoma (including bronchoalveolar carcinoma) Nonsmokers (defined as patients who had smoked <100 cigarettes in their lifetime) or former light smokers (those who had stopped smoking at least 15 years previously and had a total of ≤10 pack-years of smoking) Performance status 0 to 2 Measurable disease according to RECIST	Median treatment duration 6.4 months Control Paclitaxel (200 mg per square meter of body-surface area, administered intravenously over a 3-hour period on the first day of the cycle) followed immediately by carboplatin (at a dose calculated to produce an area under the concentration–time curve of 5.0 or 6.0 mg per milliliter per minute, administered intravenously over a period of 15 to 60 minutes) in cycles of once	Progression free survival (medain follow-up 5.6) NR/NR; HR= 2.08; 1.56-2.78 – Test of interaction for progression free survival EGFR positive vs. EGFR negative ; <0.001) Objective response rate (time period NR) 71.2%/47.3%; NR; 0.001 Clinical relevant sustained improvement in		2b Risk of bias Generation of allocation sequence: + Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	At least 1 measurable lesion not previously irradiated, adjuvant chemotherapy permitted if not platinum-based and completed > 6 months previously, adequate hepatic function EGFR mutation positive Exclusion criteria Previous chemotherapy or biologic or immunologic therapy Patient characteristics Age < 65 years (%): 72.0/69.8 Male (%): 18.2/20.2 *PS (ECOG)* 0 or 1 (%): 90.2/94.6	every 3 weeks for up to 6 cycles. Median treatment duration 3.4 months Included/randomised patients 132/129 (baseline characteristics) Analysed patients NR (survival outcomes) 131/128 (FACT-L) Attrition NR Excluded from analysis (reason) NR 1/1 (FACT-L)	functioning (time period NR, FACT-L) 70.2%/44.5%; HR = 3.01; 1.79-5.07		

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Smoking history Never smoker (%): 93.9/94.6				
Rosell, R. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol, 2012. 13(3): p. 239-46.	Region France, Italy, and Spain Inclusion criteria Stage IIIB (with pleural effusion) or stage IV NSCLC Measurable or evaluable disease Activating EGFR mutations (exon 19 deletion or L858R mutation in exon 21) Age older than 18 years Exclusion criteria	Intervention(s) Oral erlotinib (150 mg per day) Median duration of treatment was 8.2 months (range 0.3–32.9, IQR 3.1–12.0) Control 3 week cycles of standard intravenous chemotherapy (75 mg/m² cisplatin plus 75 mg/m² docetaxel on day 1 or 75 mg/m² cisplatin on day 1 plus 1250	Median overall survival (months) 19.3/19.5; NA; ns Overall survival (median follow-up 18.9 /14.4 months) 56/64; HR= 0.96; 0.60-1-54 Median progression free survival (months) 9.7/5.2; NA; sign. Progression free survival (median follow-up 18.9 /14.4 months)	Fatigue (%): 57/72 Rash (%): 80/5 Diarrhoea (%): 57/18 Appetite loss (%): 31/34 Anaemia (%): 12/49 Neutropenia (%): 0/40 Alopecia (%): 14/18 Neuropathy (%): 9/14 Arthralgia (%): 11/6 Thrombocytopenia (%): 1/15 Aminotransferase rise (%): 6/6 Febrile neutropenia (%): 0/4	Study type RCT Level of evidence 1b Risk of bias Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: -

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	History of chemotherapy for metastatic disease (neoadjuvant or adjuvant chemotherapy was allowed if it ended ≥6 months before entry to study) Patient characteristics Age (median): 65/65 Male (%): 33/22 *PS (ECOG)* 0 (%): 31/34 1 (%): 55/52 2 (%): 14/14 *Smoking status* Never smoked (%): 66/72 Previous smoker (%): 26/14 Current smoker (%): 8/14 *Histological diagnosis*	mg/m² gemcitabine on days 1 and 8) Median duration of chemotherapy treatment was 2.8 months (range 0.7−5.1, IQR 1.0−2·6) Included/randomised patients 86/87 Analysed patients 86/87 (efficacy) 84/82 (safety) Attrition NR/NR Excluded from analysis (reason) 0/0 (intention to treat)	NR/NR; HR= 2.70; 1.85-4 Progression free survival (2 years) 11%/0%; NA; NR Response rate (median follow-up 18.9 /14.4 months, per protocol) 56%/15%; NR; NR	Pneumonitis (%): 1/1	Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Adenocarcinoma (%): 95/90 Bronchoalveolar adenocarcinoma (%): 0/2 Large-cell carcinoma (%): 3/1 Squamous-cell carcinoma (%): 1/0 Other (%): 0/7 *EGFR mutation* Exon 19 deletion (%): 66/67 L858R mutation in exon 21 (%): 34/33 *Clinical stage* N3 (not candidate for thoracic radiotherapy) (%): 1/0 IIIA (%): 1/0 IIIB (malignant pleural effusion) (%): 7/6				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	IV (%): 91/94 *Bone metastasis* Yes (%): 33/33 No (%): 67/67 *Brain metastasis* Yes (%): 10/13 No (%): 90/87				
Sequist, LV. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol, 2013. 31(27): p. 3327-34.	Region 25 countries in Asia, Europe, North America, South America, and Australia Inclusion criteria Tumor had to harbor an activating mutation in EGFR when tested Treatment-naive advanced lung adenocarcinoma	Intervention(s) Oral afatinib (40 mg once per day) for a median of 11.0 months (16 cycles) Treatment continued until investigator-assessed progression Control Intravenous cisplatin (75 mg/m²) and pemetrexed (500	Overall survival (median follow-up 16.4 months) NR/NR; HR= 1.12; 0.73 – 1.73 Median overall survival not reached Median progression free survival (months) 11.1/6.9; NA; NR	Diarrhea (%): 95.2/15.3 Rash/acne (%): 89.1/6.3 Stomatitis/mucositis (%): 72.1/15.3 Paronychia (%): 56.8/0.0 Dry skin (%): 29.3/1.8 Decreased appetite (%): 20.5/53.2 Pruritus (%): 18.8/0.9 Nausea (%): 17.9/65.8 Fatigue (%): 17.5/46.8	Study type RCT Level of evidence 1b Risk of bias Generation of allocation sequence: + Allocation concealment: ?

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Performance status 0 or 1 Adequate end-organ function Measurable disease according to RECIST Exclusion criteria - Patient characteristics Age (median): 61.5/61.0 Male (%): 36.1/33.0 *PS (ECOG)* 0 (%): 40.0/35.7 1 (%): 60.0/63.5 2 (%): 0.0/0.9 *Smoking history* Never (%): 67.4/70.4	mg/m²) once every 21 days up to a maximum of six cycles Median number of chemotherapy cycles was six Treatment continued until investigator-assessed progression Included/randomised patients 230/115 Analysed patients 230/115 (efficacy) 229/111 (safety) Attrition NR Excluded from analysis (reason)	Progression free survival (median follow-up 16.4 months) 20%/3%; HR= 1.72; 1.28 – 2.33 HR= Objective response rate (median follow-up 16.4 months) 56%/23%; NR; 0.001 Clinically meaningful worsening of cough (patient reported, time period NR) NR/NR; HR= 0.60; 0.41 – 0.87	Vomiting (%): 17.9/42.3 Epistaxis (%): 13.1/0.9 Cheilitis (%): 12.2/0.9 Anemia (%): 3.1/27.9 Constipation (%): 2.6/18.9 Leukopenia (%): 1.7/18.9 Neutropenia (%): 0.9/31.5	Blinding of participants and personal: - Blinding of outcome assessment: + Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Former (%): 30.4/27.8 Current (%): 2.2/1.7 *Adenocarcinoma stage* IIIB with pleural effusion (%): 8.7/14.8 IV (%): 91.3/85.2 *EGFR mutation* Exon 19 deletion (%): 49.1/49.6 L858R (%): 39.6/40.9 Other (%): 11.3/9.6 *Race* White (%): 26.5/26.1 East Asian (%): 71.7/72.2 Other (%): 1.7/1.7	1/4 (safety; not received treatment)	Clinically meaningful worsening of dyspnea (patient reported, time period NR) NR/NR; HR= 0.68; 0.50 – 0.93 Deterioration of pain (patient reported, time period NR) NR/NR; HR= 0.83; 0.62 – 1.10		
Wu, Y. Afatinib versus cisplatin plus gemcitabine for first-line treatment of	Region China, Thailand, and South Korea	Intervention(s) Oral continuous afatinib (40 mg per day)	Median overall survival (months) 22.1/22.2; NA, ns	Diarrhoea (%): 88.3/10.6 Rash or acne (%): 80.8/8.8	Study type RCT Level of evidence

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol, 2014. 15(2): p. 213-22.	Inclusion criteria Untreated stage IIIB (with pleural eff usion) or IV lung adenocarcinoma Performance status of 0 or 1 Measurable disease according to RECIST Adequate organ function EGFR mutation-positive tumor tissue at the screening stage Exclusion criteria - Patient characteristics Age (median): 58/58	Median duration of treatment with afatinib was 398 days (IQR 173–537). Control Intravenous gemcitabine (1000 mg/m², on day 1 and day 8) plus cisplatin (75 mg/m², on day 1), in a 3-week schedule for a maximum of 6 cycles Median number of treatment cycles was four Included/randomised patients 242/122 Analysed patients	Overall survival (median follow-up 16.6 months) NR/NR; HR= 0.95; 0.68 – 1.33 Median progression free survival (months) 11.0/5.6; NA; sign. Progression free survival (median follow-up 16.6 months) NR/NR; HR= 3.57; 2.564 – 5.00 Objective response rate (time period NR) 66.9%/23.0%; OR = 7.28; 4.36 – 12.18	Stomatitis or mucositis (%): 51.9/5.3 Paronychia (%): 32.6/0.0 Epistaxis (%): 12.6/0.9 Pruritus (%): 10.9/0.0 Decreased appetite (%): 10.0/40.7 Fatigue (%): 10.0/36.3 Vomiting (%): 9.6/80.5 Nausea (%): 7.5/75.2 Constipation (%): 1.7/12.4 Bone marrow failure (%): 0.0/4.4 Alanine aminotransferase concentration increase (%): 20.1/15.9	2b Risk of bias Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Male (%): 36.0/32.0 *PS (ECOG)* 0 (%): 19.8/33.6 1 (%): 80.2/66.4 *Smoking history* Never smoked (%): 74.8/81.1 Other current or ex-smoker (%): 21.9/15.6 < 15 pack-years and stopped > 1 year ago (%): 3.3/3.3 *Adenocarcinoma stage* IIIB with pleural effusion (%): 6.6/4.9 IV (%): 93.4/95.1 *EGFR mutation* Exon 19 deletion (%): 51.2/50.8	242/122 (efficacy) 239/113 (safety) Approx. 85% (patient reported outcomes) Attrition NR Excluded from analysis (reason) 0/0 (efficacy) 3/9 (safety, not received treatment)	*Patient reported outcomes (time period NR)* Improvement in overall health status (QLQ-C30) 62.7%/32.7%; NR; 0.0001 Deterioration in overall health status (QLQ-C30) NR/NR; HR 0.56; 0.41 – 0.77 Improvement in cough NR/NR; in favour of intervention; <0.0001 Deterioration in cough NR/NR; HR = 0.45; 0.30–0.68 Improvement in dyspnoea	Aspartate aminotransferase concentration increase (%): 15.1/10.6 Anaemia (%): 5.4/27.4 Hypokalaemia (%): 5.4/13.3 Leucopenia (%): 3.3/51.3 Neutropenia (%): 2.1/54.0 Hyponatraemia (%): 1.7/8.8 Haemoglobin concentration decreased (%): 1.7/17.7 Neutrophil count decreased (%): 0.8/25.7 White blood cell count decreased (%): 0.8/23.9 Thrombocytopenia (%): 0.8/18.6	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	L858R (%): 38.0/37.7 Uncommon (%): 10.7/11.5 *Race* South-east Asian (%): 5.8/8.2 South Korean (%): 4.5/1.6 Chinese (%): 89.7/90.2		NR/NR; in favour of intervention; <0.0001 Improvement in dyspnoea (rested) NR/NR; in favour of intervention; 0.594 Improvement in dyspnoea (walked) NR/NR; in favour of intervention; <0.0001 Improvement in dyspnoea (climbed stairs) NR/NR; in favour of intervention;<0.0001 Deterioration in dyspnoea NR/NR; HR = 0.54; 0.40–0.73 Improvement in shortness of breath	Platelet count decreased (%): 0.8/10.6	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
			NR/NR; in favour of intervention; 0.006 Improvement in pain NR/NR; in favour of intervention; 0.003 Improvement in have pain NR/NR; in favour of intervention; 0.015 Improvement in pain affecting daily activities NR/NR; in favour of intervention; 0.079 Improvement in pain in chest NR/NR; in favour of intervention; 0.021 Improvement in pain in arm or shoulder		

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
			NR/NR; in favour of intervention; 0.14 Improvement in pain in other parts NR/NR; in favour of intervention; 0.092 Deterioration in pain NR/NR; HR = 0.70; 0.51–0.96		
Zhou, C. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol, 2011. 12(8): p. 735-42.	Region China Inclusion criteria More than 18 years of age Advanced or recurrent stage IIIB or IV NSCLC with a confirmed activating mutation of EGFR ie, an exon 19 deletion or an exon 21 L858R point mutation	Intervention(s) Oral erlotinib 150 mg once daily until disease progression or unacceptable toxic effects Median duration of treatment was 55.5 weeks (range 3.1 – 93.0) Control	Overall survival (median follow-up 15.6 month) 80%/83%; NR; NR Progression free survival (median follow-up 15.6 month) NR/NR; HR= 6.25; 3.847-10.00	Neutropenia (%): 6/69 Thrombocytopenia (%): 4/64 Anaemia (%): 5/72 Infection (%): 17/10 Skin rash (%): 73/19 Diarrhoea (%): 25/6 Stomatitis (%): 13/1 Paronychia (%): 4/0	Study type RCT Level of evidence 2b Risk of bias Generation of allocation sequence: + Allocation concealment: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
Chen, G. Quality of life (QoL) analyses from OPTIMAL (CTONG-0802), a phase III, randomised, open-label study of first-line erlotinib versus chemotherapy in patients with advanced EGFR mutation-positive non-small-cell lung cancer (NSCLC). Ann Oncol, 2013. 24(6): p. 1615-22.	Measurable disease according to RECIST ECOG performance status of 0–2, and adequate haematological, biochemical, and organ function Exclusion criteria Uncontrolled brain metastases Previous systemic anticancer therapy for advanced disease Patient characteristics Age (median): 57/59 Male (%): 41/40 *PS (ECOG)* 0-1 (%): 91/96 2 (%): 9/4	Platinum-based doublet chemotherapy (intravenous gemcitabine 1000 mg/m² on days 1 and 8 and intravenous carboplatin [area under the curve=5] on day 1 of a 3-week cycle (up to four cycles) Median duration of treatment 10.4 weeks (range 1.0 – 18.9) Included/randomised patients 83/82 Analysed patients 82/72	Median progression free survival (months) 13.1/4.6; NA; sign. Response rate (median follow-up 15.6 month) 83/36; NR; 0.0001 *Mean change in functioning (baseline to cycle 2, FACT-L)* Physical well-being NR/NR; NR; 0.003 Social/family well-being NR/NR; NR; 0.303 Emotional well-being NR/NR; NR; 0.036 Functional well-being NR/NR; NR; 0.093	Vomiting or nausea (%): 1/46 Constipation (%): 9/15 Increased ALT (%): 37/33 Fatigue (%): 5/24	Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Smoking status Present or former smoker (%): 28/31 Non-smoker (%): 72/69 *Histology* Adenocarcinoma (%): 88/86 Non-adenocarcinoma (%): 12/14 *EGFR mutation* Exon 19 deletion (%): 52/54 L858R mutation (%): 48/46 *Disease stage* IIIB (%): 13/7 IV (%): 87/93	71/54 (quality of life) Attrition 61/82 Excluded from analysis (reason) 1/10 (not received treatment) 12/28 (quality of life: not received treatment, no complete questionnaire)	Lung cancer subscale NR/NR; NR; 0.004		

+ low risk of bias; - high risk of bias, ? unclear risk of bias, CG: control group; CI: confidence interval; IG: intervention groups; NR: not reported; not statistical significant

12.2.7. Thema: Anti-VEGF-Therapie

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
Doebele, R.C., et al., Phase 2, randomized, open-label study of ramucirumab in combination with first-line pemetrexed and platinum chemotherapy in patients with nonsquamous, advanced/metastatic non-small cell lung cancer. Cancer, 2015. 121(6): p. 883-92.	**Region** Sydney, Australia **Inclusion criteria** Patients ≥18 years Histologically or cytocologically confirmed stage IV nonsquamous NSCLC Measurable disease at the time of study entry defined by RECIST ECOG performance status score of 0 to 2 Adequate organ function **Exclusion criteria** Previous chemotherapy for stage IV NSCLC	**Intervention(s)** Induction combination treatment for a minimum of four 21-day cycles (up to 6 cycles). Patients without evidence of disease progression then entered a maintenance phase and received pemetrexed plus ramucirumab. Ramucirumab was administered iv at a dose of 10 mg/ kg over 60 minutes on day 1 of each cycle. Pemetrexed was administered at a dose of 500 mg/m2 intravenously over 10 to 15 minutes on day 1 of each cycle. Platinum therapy was the investigator's choice. Carboplatin was administered at a dose	Median overall survival (months) 13.9/10.4; NA; 0.8916 Overall survival (2 years) 76.8%/69.0; HR=0.97; 90%CI: 0.70-1.35 **Median progression-free survival** (months) 7.2/5.6; NA; 0.1318 **Progression-free survival** (20 months, RECIST criteria)	**Drug-related** ***Any*** Patients with ≥1TEAE (%): 100/98.6 Fatigue (%): 65.7/62.3 Nausea (%): 52.2/56.5 Anemia (%): 46.3/55.1 Neutropenia (%): 35.8/23.2 Vomiting (%): 35.8/36.2 Thrombocytopenia (%): 34.3/24.6 Constipation (%): 29.9/30.4 Decreased appetite (%): 29.9/26.1 Edema peripheral (%): 29.9/20.3 Diarrhea (%): 28.4/30.4	**Study type** RCT **Level of evidence** 1b **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: -

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Recent (within 28days) or planned surgery Untreated central nervous system metastases Increased risk of pulmonary bleeding as determined by radiologically documented evidence or major blood vessel invasion or encasement by cancer Serious nonhealing wound, ulcer or bone fracture within 28 days before randomization Increased risk of bleeding complications as indicated by uncontrolled thrombotic or hemorrhagic disorders Poorly controlled hypertension Clinically relevant coronary artery disease	with an area under the curve of 6 over 30 minutes on day 1 of each cycle approximately 30 minutes after the end of the pemetrexed infusion. Cisplatin was administered at a dose of 75 mg/m2 over 120 minutes on day 1 of each cycle. **Control** Induction combination treatment for a minimum of four 21-day cycles (up to 6 cycles). Patients without evidence of disease progression then entered a maintenance phase and received pemetrexed was administered iv at a dose of 10 mg/ kg over 60 minutes on day 1 of each cycle.	NR; HR=1.33; 90%CI: 0.97-1.81 ORR (20 month, RECIST criteria) 49.3%/38.0%; NR; 0.1797 Disease control rate (follow-up NR) 85.5/70.4; NR; 0.0316	Headache (%): 28.4/11.6 Epistaxis (%): 25.4/7.2 Back pain (%): 23.9/13 Dyspnea (%): 22.4/21.4 Insomia (%): 22.4/14.5 **Events of special interest** ***Any grade*** Hypertension (%): 19.4/5.8 Blood pressure increase (%):4.5/0 Infusion-related reactions (%): 1.5/0 Bleeding/haemorrhage events (%): 38.8/18.8 Arterial thrombotic events (%): 10.4/4.3 Acute myocardial infarction (%): 1.5/0	Blinding of outcome assessment: - Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Myocardial infarction within 6 months before randomization Uncontrolled congestive heart failure Chronic daily treatment with aspirin (<325 mg/day Other known inhibitors of platelet function History of gross hemoptysis within 2 months of trial entry Any grade 3 or 4 gastrointestinal bleeding within 3 months before study entry **Patient characteristics** Treated: safety population (%):97.1/97.2 Age 18 to <65y (%): 53.6/52.1	Pemetrexed was administered at a dose of 500 mg/m2 intravenously over 10 to 15 minutes on day 1 of each cycle. Platinum therapy was the investigator's choice. Carboplatin was administered at a dose with an area under the curve of 6 over 30 minutes on day 1 of each cycle approximately 30 minutes after the end of the pemetrexed infusion. Cisplatin was administered at a dose of 75 mg/m2 over 120 minutes on day 1 of each cycle. **Included/randomised patients** 69/71 **Analysed patients** 69/71 (efficacy)		Angina pectoris (%): 3/1.4 Cardiorespiratory arrest (%): 0/1.4 Intestinal ischemia (%): 1.5/0 Ischemic cerebal infarction (%): 1.5/0 Myocardial infarction (%):3.0/1.4 Peripheral vascular disorder (%): 1.5/0 Congested heart failure (%): 1.5/0 Gastrointestinal perforation (%): 1.5/0 Healing complication (%): 3/0 Proteinuria (%): 6/4.3 Venous thrombotic events (%): 11.9/7.2	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Age ≥65y (%): 46.4/47.9 Male (%): 52.2/63.4 Female (%): 47.8/36.6 ***ECOG performance status*** 0-1 (%): 92.8/91.5 2 (%): 4.3/5.6 Missing (%): 2.9/2.8 ***Histology*** Adenocarcinoma (%): 87/87.3 Large cell carcinoma (%): 1.4/4.2 Squamos cell carcinoma (%): 0/0 Adenosquamous (%): 0/2.8 NSCLC, NOS (%): 8.7/4.2 Other (%): 2.9/1.4 ***Smoking habits*** <100 cigarettes in lifetime	67/69 (safety) **Attrition** 3/3 **Excluded from analysis (reason)** 2/2 (safety, patients with at least 1 adverse event)			

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	No (%): 84.1/77.5 Yes (%): 15.9/22.5 ***Ethnic origin*** White (%): 87/91.5 Asian (%): 1.4/5.6 Black (%): 11.4/2.8 ***Carboplatin therapy: patients treated (%): 70.1/69.6*** ***Cisplatin therapy: patients treated (%): 29.9/30.4***				
Garon EB, Ciuleanu TE, Arrieta O Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression	**Region** 26 countries on 6 continents **Inclusion criteria** Aged ≥18 years Squamous or non-squamous stage IV NSCLC who had progressed during or after a first-line platinum-based	**Intervention(s)** Intravenous docetaxel 75 mg/m² plus intravenous ramucirumab 10 mg/kg on day 1 of a 21 day cycle. **Control**	**Median overall survival** (months) 10.5/ 9.1; NA; ns (CIs overlap) **Overall survival (median follow-up: 9.5 month [ramucirumab], 8.8 month [placebo])**	**Any (%):** 98/ 95 Fatigue (%): 55/49 Decreased appetite (%): 29/25 Diarrhoea (%): 32/27 Nausea (%): 27/27 Alopecia (%): 26/25 Stomatitis (%): 23/13	**Study type** RCT **Level of evidence** 1b **Risk of bias**

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet. 2014 Aug 23;384(9944):665-73..	chemotherapy regimen with or without bevacizumab or maintenance therapy Recurrent disease who had received adjuvant or neoadjuvant therapy or chemoradiotherapy for locally advanced disease if their disease had progressed up to 6 months after completion of adjuvant or neoadjuvant platinum-based therapy, or if their disease had progressed more than 6 months after therapy and during or after one subsequent platinumbased chemotherapy regimen Measurable or non-measurable disease with ECOG 0-1 **Exclusion criteria** Previous therapy for advanced or metastatic disease	Intravenous docetaxel 75 mg/m² plus placebo on day 1 of a 21 day cycle. **Included/randomised patients** 628/625 **Analysed patients** 628/625 (efficacy) 47%/49% (quality of life) 627/618 (safety) **Attrition** 9/10 **Excluded from analysis (reason)** 1/7 (safety, not received one dose) 53%/51% (quality of life, not responded questionnaire)	NR; HR=1.16; 1.02-1.33 Median progression-free survival (months) 4.5/3.0 ; NA; NA; ns (CIs overlap) Progression-free survival (median follow-up: 9.5 month [ramucirumab], 8.8 month [placebo], RECIST criteria) NR; HR=1.32; 1.16-1.47 ORR (median follow-up: 9.5 month [ramucirumab], 8.8 month [placebo], RECIST criteria)	Neuropathy (%): 23/20 Dyspnoea (%): 22/24 Cough (%): 21/20 Pyrexia (%): 17/13 Peripheral oedema (%): 16/8 Constipation (%): 16/17 Mucosal inflammation (%): 16/7 Vomiting (%): 14/14 Lacrimation increased (%): 13/4 Myalgia (%): 12/10 Arthralgia (%): 11/8 Back pain (%): 11/8 Abdominal pain (%): 11/10 Dysgeusia (%): 11/7 Insomnia (%): 11/8	Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: + Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	was EGFR tyrosine kinase inhibitor monotherapy Major blood vessel involvement, intratumour cavitation, poorly controlled hypertension, gastrointestinal perforation or fistulae, arterial thromboembolic event within 6 months, gross haemoptysis within 2 months, or grade 3–4 gastrointestinal bleeding within 3 months **Patient characteristics** Age (median): 62/61 Men (%): 67/66 ***Histology*** Non- Squamous (%): 74/72 Squamous (%): 25/27 Unknown (%): 1/1 ***Smoking Habits***		23%/14%; OR=1.89; 1.41–2.54 Diseases control rate (median follow-up: 9.5 month [ramucirumab], 8.8 month [placebo], RECIST criteria) 64%/53%; OR=1.60; 1.28–2.01 Patients with >15mm increase in quality life (30 days, LCSS) NR ; HR=1.00; 0.84–1.19	Headache (%): 11/11 **Haematological adverse events** Neutropenia (%): 55/45 Leucopenia (%): 21/19 Anaemia (%): 21/28 Febrile neutropenia (%): 16/10 Thrombocytopenia (%): 13/5 **Adverse events of special interest** Bleeding or haemorrhage (%): 29/15 Epistaxis (%): 19/6 Gastrointestinal haemorrhage (%): 3/2 Pulmonary haemorrhage (%): 8/7 Haemoptysis (%): 6/5 Hypertension (%): 11/5	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Ever (%): 74/72 Never (%): 25/27 Unknown (%): <1/<1 ***Ethnic Origin*** White(%): 84/80 Asian(%): 12/14 Black(%): 3/3 Other(%): 2/3 ***ECOG performance status*** 0 (%): 33/32 1 (%): 67/68 ***Region of origin*** East Asia (South Korea or Taiwan) (%): 7/7 Other (%): 93/93 ***Disease*** Measurable (%):96/96 Non – measurable (%): 4/4			Infusion-related reaction (%): 4/4 Proteinuria (%): 3/1 Venous thromboembolic (%): 3/6 Renal failure (%): 2/2 Arterial thromboembolic (%): 2/2 Congestive heart failure (%): 1/1 Gastrointestinal perforation (%): 1/<1	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	EGFR status Wild type (%): 33/32 Mutant (%): 2/3 Unknown or missing (%): 65/66 ***Best response to platinum-based chemotherapy*** CR,PR,or SD(%): 67/67 PD(%): 28/29 Missing(%): 5/4 ***Previous maintenance treatment*** No (%): 79/77 Yes (%): 21/23 ***Previous taxane*** No (%): 76/76 Yes (%): 24/24 ***Previous bevacizumab treatment***				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	No (%): 86/85 Yes (%): 14/15 ***Time since previous therapy*** < 9 months (%): 64/60 > 9 months (%): 36/40 Missing (%): <1/0				
Novello, S., et al., Motesanib plus carboplatin/paclitaxel in patients with advanced squamous non-small-cell lung cancer: results from the randomized controlled MONET1 study. J Thorac Oncol, 2014. 9(8): p. 1154-61.	**Region** 32 countries **Inclusion criteria** Patients ≥18 years Histologically confirmed unresectable stage IIIB with pericardial/pleural effusion or stage IV/recurrent NSCLC Measurable or non-measurable disease	**Intervention(s)** Motesanib 125 mg once daily Chemotherapy (carboplatin, [area under the curve 6 mg/mL·min]/paclitaxel, 200 mg/m²) beginning on day 1 of each 3-week cycle up to a maximum of six cycles. Treatment was planned to continue until patients	**Median overall survival** (months) 11.1/ 10.7; NA; ns (CIs overlap) **Overall survival** (2 years) 21%/12%; HR=1.12; 0.89-1.41 Median progression-free survival (months)	**Serious occurring within 6 months of treatment initation** Patients with any (%): 46/28 ***Any serious adverse events*** Diarrhea (%): 7/<1 Dehydration (%): 5/2 Dyspnea (%): 4/3 Neutropia (%): 4/3	**Study type** RCT **Level of evidence** 1b **Risk of bias** Generation of allocation sequence: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Exclusion criteria Life expectancy less than 3 months ECOG PS greater than or equal to 2 Untreated or symptomatic central nervous system metastases Prior chemotherapy, including adjuvant chemotherapy within 52 weeks of randomization Prior targeted therapy central or peripheral radiation within 28 or 14 days Arterial or venous thrombosis within 12 months Pulmonary haemorrhage or gross hemoptysis within 6 months of randomization	experienced disease progression, had unacceptable toxicity, or withdrew consent, for a maximum of 36 months. Motesanib was discontinued permanently if more than two dose reductions were required, grade 3/4 toxicity recurred after a dose delay and/or reduction, or grade 3/4 toxicity persisted for more than 3 weeks **Control** Placebo Chemotherapy (carboplatin, [area under the curve 6 mg/mL·min]/paclitaxel, 200 mg/m^2) beginning on day 1 of each 3-week cycle	4.9/5.1; NA; ns (CIs overlap) Progression-free survival (2 years, RECIST criteria) 68/57; HR=1.18; 0.90-1.54 ORR (2 years, RECIST criteria) 38% / 35%; 2.6%; -7.4 - 12.6	Anemia (%): 4/3 Pneumonia (%): 3/5 Vomiting (%): 3/2 Febrile neutropenia (%): 3/<1 Hemoptysis (%): 3/<1 Thrombocytopenia (%): 3/<1 Pulmonary haemorrhage (%): 3/0 Asthenia (%): 2/<1 Fatique (%): 2/<1 Nausea (%): 2/<1 Pleural effusion (%): 2/0 Hypotension (%): 2/1 Abdominal pain (%): 2/<1 Decreased appetite (%): 2/0 Sepsis (%): 2/0	Allocation concealment: + Blinding of participants and personal: + Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Bleeding disthesis or bleeding within 14 days Uncontrolled hypertension Inadequate renal cardiac, hepatic, or hematologic function **Patient characteristics** Age (mean): 62/59.5 Men (%): 80/84 ***ECOG performance status*** 0 (%): 35/37 1 (%): 65/62 Missing: 0/<1 ***Histology*** Adenocarcinoma (%): 0/1 Squamos cell carcinoma (%): 96/97 Undifferentiated (%): <1/0	up to a maximum of six cycles. Treatment was planned to continue until patients experienced disease progression, had unacceptable toxicity, or withdrew consent, for a maximum of 36 months. Placebo was discontinued permanently if more than two dose reductions were required, grade 3/4 toxicity recurred after a dose delay and/or reduction, or grade 3/4 toxicity persisted for more than 3 weeks **Included/randomised patients** 182/178 **Analysed patients**		Pyrexia (%): <1/2 **Troughout the study** ***Patients with any (%): 95/91*** Worst grade 3 (%): 33/27 Worst grade 2 (%): 10/9 Worst grade 1 (%): 20/12 ***Adverse events with ≥5% difference in incidence between arms*** Diarrhea (%): 38/16 Alopecia (%): 34/40 Nausea (%): 28/21 Hypertension (%): 26/9 Vomiting (%): 22/17 Decreased appetite (%): 22/14 Anemia (%): 18/25 Weight decreased (%): 17/8	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Other (%): 4/2 ***Smoking habits*** Past or present smoker (%): 84/89 ***Ethnic origin*** White (%): 73/74 Asian (%): 21/16 Hispanic (%): 5/6 Black (%): <1/3 Other (%): <1/<1 ***Disease stage at study entry*** Stage IIIB with pericardial/pleural effusion (%): 15/14 Stage IV/recurrent (%): 85/86 ***Weight loss*** <5% in previous 6months (%): 76/76	182/178 (efficacy) 181/173 (safety) **Attrition** Lost to follow-up: 1/0 **Excluded from analysis (reason)** 1/5 (safety, not received treatment)		Thrombocytopenia (%): 15/8 Headache (%): 13/6 Abdominal pain (%): 11/5 Arthralgia (%): 10/17 Dehydration (%): 9/3 Depression (%): 7/2 Chest pain 6/14 ***Patients with serious (%): 47/29*** ***Serious grade ≥3 adverse events in ≥2% of patients in either treatment arm (%): 45/27*** Diarrhea (%): 5/0 Neutropenia (%): 4/3 Dyspnea (%): 4/4 Dehydration (%): 4/1 Pneumonia (%): 3/4	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Brain metastases Yes (%): 5/5 No (%): 95/95 No information (%): <1/1 ***Previous chemotherapy*** Adjuvant (%): 1/2 ***Previous best response to first-line treatment*** Complete response (%): 1/0 Partial response (%): 44/35 Stable disease (%): 24/35 Progressive disease (%): 31/29			Pulmonary haemorrhage (%): 3/0 Non-small-cell lung cancer (%): 3/2 Anemia (%): 2/2 Vomiting (%): 2/1 Febrile neutropenia (%): 2/<1 Pleural effusion (%): 2/0 Abdominal pain (%): 2/<1 Nausea (%): 2/<1 Fatique (%): 2/0 Decreased appetite (%): 2/0 Sepsis (%): 2/0 Thrombocytopenia (%): 2/<1	
Ramalingam, S.S., et al., Randomized	**Region**	**Intervention(s)**	Median overall survival (months)	**Linifanib 12.5/linifanib 7.5/placebo**	**Study type**

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
phase II study of carboplatin and paclitaxel with either linifanib or placebo for advanced nonsquamous non-small-cell lung cancer. J Clin Oncol, 2015. 33(5): p. 433-41.	USA and non US countries **Inclusion criteria** Patients ≥18 years Cytologically or histologically confirmed recurrent stage IIIB (pleural or pericardial effusion) or IV (metastatic) predominantly nonsquamous NSCLC not amenable to surgical resection or radiation with curative intent Presence of measurable disease ECOG performance status ≤1 Adequate bone marrow, renal and liver function **Exclusion criteria**	Linifanib 12.5 mg (intervention group 1), or linifanib 7.5 mg (intervention group 2) Carboplatin (AUC 6 mg/mL/min) and paclitaxel (200mg/m²) were administered intravenously on day 1 of an every-21-day cycle, and linifanib (7.5 or 12.5 mg) or placebo was self-administered orally once daily on a continuous schedule. Carboplatin and paclitaxel were given to a maximum of six cycles or until criteria for discontinuation were met **Control** Placebo Carboplatin (AUC 6 mg/mL/min) and paclitaxel (200mg/m²) were	13.0/11.4/11.3; NA; ns (CIs overlap) Overall survival (798 days) 54%/44%/45% (12 month); HR= 1.13, p=0. 650 (linifanib 12.5 mg vs. placebo); HR=0.93, p=0. 779 (linifanib 7.5 mg vs. placebo) **Median progression-free survival (months)** 7.3/8.3/5.4; NA; ns (CIs overlap) **Progression-free survival (504 days, RECIST)**	***Any (%): 100/97.6/97.9*** Diarrhea (%): 44.7/31/21.3 Thrombocytopenia (%): 40.4/31/14.9 Anemia (%): 17/40.5/19.1 Hypertension (%): 27.7/14.3/4.3 Dysphonia (%): 14.9/28.6/2.1 Weight decrease (%):21.3/7.1/2.1 PPE (%): 17/7.1/0 Hypothyroidism (%): 10.6/7.1/0 Pneumothorax (%): 8.5/9.5/0 Oral candidiasis (%): 6.4/9.5/0 ***Any grade ¾ (%):72.3/85.7/57.4***	RCT **Level of evidence** 1b **Risk of bias** Generation of allocation sequence: + Allocation concealment: ? Blinding of participants and personal: + Blinding of outcome assessment: ?

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Radiation therapy or major surgery ≤21 days before study entry Untreated brain or meningeal metastases Full therapeutic dose of anticoagulation therapy Central thoracic tumor lesion as defined by location within the hilar structures History of significant cancer-related bleeding Proteinuria (grade >1) Uncontrolled hypertension Left ventricular ejection fraction less than 50% History of myocardial infarction, stroke, or transient ischemic attack ≤6 months before study entry Antiretroviral therapy for HIV disease	administered intravenously on day 1 of an every-21-day cycle, and linifanib (7.5 or 12.5 mg) or placebo was self-administered orally once daily on a continuous schedule. Carboplatin and paclitaxel were given to a maximum of six cycles or until criteria for discontinuation were met **Included/randomised patients** 47/44/47 **Analysed patients** 47/44/47 (efficacy) 47/42/47 (safety) **Attrition** 0/0/1 **Excluded from analysis (reason)**	NR; HR=1.56, p=0.118 (linifanib 12.5 mg vs. placebo); HR=1.97, p=0.022 (linifanib 7.5 mg vs. placebo) ORR (504 days, RECIST) 31.9%/43.2%/25.5%; NR; p=0.50 (linifanib 12.5 mg vs. placebo); p=0.066 (linifanib 7.5 mg vs. placebo)	Diarrhea (%): 8.5/2.4/2.1 Thrombocytopenia (%): 29.8/16.7/2.1 Anemia (%): 4.3/11.9/8.5 Hypertension (%): 10.6/4.8/2.1 Dysphonia (%): 2.1/0/0 Weight decrease (%): 2.1/2.4/0 PPE (%): 8.5/0/0 Hypothyroidism (%): 0/0/0 Pneumothorax (%): 2.1/0/0 Oral candidiasis (%): 0/0/0 ***Any serious (%): 53.2/59.5/34***	Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Another active malignancy within the past 5 years Severe GI disease that could interfere with drug absorption Pregnancy or breastfeeding **Patient characteristics** **(linifanib 12.5/linifanib 7.5/placebo)** Age (mean): 60/61.5/61 <65 (%): 72.3/70.5/63.8 ≥65 (%): 27.7/29.5/36.2 Men (%): 57.4/56.8/57.4 ***ECOG performance status*** 0 (%): 34/29.5/31.9 1 (%): 66/70.5/68.1 ***Histology*** Adenocarcinoma (%): 85.1/95.2/89.4	0/2/0 (safety, at least one dose linifanib)			

Study/Reference	Region, inclusion criteria, exclusion criteria and base-line characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect meas-ure or mean differ-ence; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Large cell (%): 6.4/5.3/0 Other (%): 8.5/0/10.6 ***Smoking habits*** Smoker (%): 80.9/88.6/83.0 ***Country*** US (%): 23.4/29.5/27.7 Outside US (%): 76.6/70.5/72.3 ***Ethnic origin*** White (%): 87.2/93.2/89.4 Asian (%): 4.3/6.8/4.3 Black (%): 4.3/0/4.3 Other (%): 4.3/0/2.1 ***Disease*** Locally advanced (%): 4.3/4.8/8.5 Metastatic (%): 95.7/95.2/91.5				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
Reck M, Kaiser R, Mellemgaard A, Douillard JY, Orlov S, Krzakowski M, von Pawel J, Gottfried M, Bondarenko I, Liao M, Gann CN, Barrueco J, Gaschler-Markefski B, Novello S; Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial.LUME-Lung 1 Study Group. Lancet Oncol. 2014 Feb;15(2):143-55.	**Region** 27 countries, (23 European countries, China, South Korea, India and South Africa) **Inclusion criteria** ≥18 years Patients with histologically or cytologically confi rmed stage IIIB/IV recurrent NSCLC (all histologies) who received one previous chemotherapy regimen Patients with relapse or failure of one previous first-line chemotherapy regimen In the case of recurrent disease one additional previous regimen was allowed for adjuvant, neoadjuvant, or	**Intervention(s)** Docetaxel 75 mg/m² by intravenous infusion on day 1 plus nintedanib 200 mg twice daily orally on days 2–21, every 3 weeks Until unacceptable adverse events or disease progression **Control** Patients were assigned to docetaxel 75 mg/m² by intravenous infusion on day 1 plus placebo on days 2–21, every 3 weeks Until unacceptable adverse events or disease progression Treatment was continued until unacceptable adverse events or disease progression	Median overall survival (months) 10.1/9.1; NA; ns (CIs not overlapping) Overall survival (median follow-up: 31.7 months) NR; HR=1.06; 0.95-1.20 **Median progression-free survival (months)** 3.5/2.7; NA; statistical significant (CIs not overlapping) **Progression-free survival (median follow-up: 31.7**	**Any serious AE (%):** 34.4/31.5 **Any AE (%):** 93.6/93 Diarrhoea (%): 42.3/21.8 Decreased neutrophils (%): 37.1/35.9 Fatigue (%): 30.4/26.9 Increased ALT (%): 28.5/8.4 Decreased white blood cell count (%): 24.5/24.4 Nausea (%): 24.2/18 Increased AST (%): 22.5/6.6 Decreased appetite (%): 22.2/15.6 Dyspnoea (%): 19/16.8 Vomiting (%): 16.9/9.3 Alopecia (%): 16.4/18.2 Cough (%): 15.2/16.8	**Study type** RCT **Level of evidence** 1b **Risk of bias** Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: + Blinding of outcome assessment:

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	neoadjuvant plus adjuvant therapy Eligibility criteria included ECOG performance status of 0 or 1 At least one target lesion measurable **Exclusion criteria** Active brain metastases Patients with previous docetaxel or VEGFR inhibitors with the exception of bevacizumab Radiographic evidence of cavitary or necrotic tumours, centrally located tumours with radiographic evidence of local invasion of major blood vessels, or a recent history (<3 months) of clinically significant haemoptysis or a major thrombotic or	**Included/randomised patients** 655/659 **Analysed patients** 655/659 (efficacy) 652/655 (safety) **Attrition** 5/5 **Excluded from analysis (reason)** 3/4 (safety, not received treatment)	**month, RECIST criteria)** NR; HR=1.18; 1.04-1.33 ORR (median follow-up: 31.7 month, RECIST criteria) 4.4%/3.3%; OR=1.34; 0·76–2·39 Diseases control rate (median follow-up: 31.7 month, RECIST criteria) 54%/ 41·3%; OR=1.68; 1·35–2·09	Neutropenia (%): 13.8/14.4 Pyrexia (%): 12.7/15 Decreased haemoglobin (%): 11.2/12.2 Constipation (%): 5.4/11.6 Asthenia (%): 8.9/9.8 Chest pain (%): 8.6/9.5 Febrile neutropenia (%): 7.4/4.9 Anaernia (%): 5.4/7.5 Pneumonia (%): 5.1/5.5 Hypokalaernia (%): 4.1/3.1 Increased GGT (%): 4/0.9 Leucopenia (%): 4/5.2 Hyperglycaernia (%): 3.7/4.6 Hypnoatraernia (%): 3.4/2 Pleural effusion (%): 2.3/2.9	+ Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and base-line characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect meas-ure or mean differ-ence; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	clinically relevant major bleeding event in the past 6 months **Patient characteristics** Age (mean): 60/60 Men (%): 72.7/72.7 ***PS (ECOG)*** 0 (%): 28.5/28.7 1 (%): 71.3/71.3 ***Histology*** Squarnous- cell carcinoma (%): 42.1/42.3 Adenocarcinoma (%): 49.2/51 Large – cell carcinoma (%): 3.8/2.4 Combination (%): 0.6/0.8 Other (%): 4.3/3.5 ***Clinical stage at diagnosis***			Increased hepatic enzyme (%): 1.5/0	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Stage < IIIB (%): 16/15.9 Stage IIIB (%): 22.6/22.2 Stage IV (%): 60.9/61.9 Missing (%): 0.5/0 ***Metastases at screening (%):*** 89.8/91.8 ***Brain metastases at baseline (%):*** 5.8/5.8 ***Baseline sum of longest diameters (mm):*** 49-123.4/ 48.5-121 ***Months since first diagnosis (median):*** 8.8/8.6 ***Previous surgery (%):*** 21.8/21.5 ***Previous radiotherapy (%):*** 29.2/28.5 ***Smoking habits*** Current and former smokers (%): 74.8/75.6				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Never smokers (%): 25.2/24.4 ***Ethnic origin*** White (%): 81.4/80.4 Asian (%): 17.7/18.7 Black or African American (%): 0.6/0.8 American Indian or Alaskan native (%): 0.3/0.2 ***Previous first line therapy (%): 98.6/98.8*** Platinum- based therapy (%): 97.2/97.7 Non- platinum based therapy (%): 2.8/2.3 ***First – line bevacizumab (%):*** 4.1/3.5 **Previous best response to first-line treatment** Complete response (%): 2/2.9				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Partial response (%): 33.1/27.2 Stable disease (%): 38.5/38.2 Progressive disease (%): 19.7/21.4 Not known or unavailable (%): 6.7/10.3				
Seto, T., et al., Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. Lancet Oncol, 2014. 15(11): p. 1236-44.	**Region** Japan **Inclusion criteria** Histologically or cytologically confirmed srage IIIB/IV or postoperative recurrent non-squamous NSCLC with activating EGFR mutation Patients ≥20 years ECOG performance status 0 or 1 Adequate haematological, hepatic or renal function	**Intervention(s)** Erlotinib plus bevacizumab group received bevacizumab 15 mg/kg by intravenous infusion on day 1 of a 21-day cycle and erlotinib orally once daily at 150 mg/day, starting from day 1 of cycle 1. Patients remained on treatment until disease progression or unacceptable toxicity **Control**	Overall survival (median follow-up was 20.4 months) 17%/23%; NR; NR **Median progression-free survival** (months) 16/9.7; NA; significant (CIs not overlapping) **Progression-free survival** (median	**Erlotinib plus bevacizumab / Erlotinib alone** ***All*** Rash (%): 99/99 Diarrhoea (%): 81/78 Paronychia (%): 76/65 Dry skin (%): 75/58 Stomatitis (%): 63/60 Haemorrhagic event (%): 72/29 Liver function disorder or abnormal hepatic function (%): 44/51	**Study type** RCT **Level of evidence** 1b **Risk of bias** Generation of allocation sequence: + Allocation concealment:

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	One or more measurable lesion based on RECIST 1.1 **Exclusion criteria** Confirmation of Thr790Met mutation Presence of brain metastases History or presence of haemoptysis or bloody sputum Any coagulation disorder, tumor invading or abutting major blood vessels Coexistence or history of interstitial lung disease Previous receipt of EGFR inhibitors or VEGF receptor inhibitors **Patient characteristics**	Erlotinib alone group received erlotinib orally once a day at 150 mg/day. Patients remained on treatment until disease progression or unacceptable toxicity **Included/randomised patients** 77/77 **Analysed patients** 75/77 **Attrition** NR **Excluded from analysis (reason)** 2/0 (received treatment)	follow-up was 20.4 months, RECIST) NR; HR=1.85; 1.27-2.78 ORR (median follow-up was 20.4 months, RECIST) 69%/64%; NR; 0.495 DCR (median follow-up was 20.4 months) 99%/88/; NR; 0.0177 Quality of life (FACT-L, till treatment discontinuation [115 days]) Intervention<control; NR; ns	Hypertension (%): 76/13 Pruritus (%): 45/42 Weight decreased (%): 44/25 Decreased appetite (%): 35/34 Proteinuria (%): 52/4 Dysgeusia (%): 27/22 Nasopharyngitis (%): 27/19 Constipation (%): 23/19 Alopecia (%): 17/18 Nausea (%): 16/19 Vomiting (%): 19/9 Malaise (%): 13/13 Insomnia (%): 11/10 Pyrexia (%): 9/12 Upper respiratory tract infection (%): 12/9	+ Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Erlotinib plus group/Erlotinib alone Age (mean): 67/67 <75 (%): 84/81 ≥75 (%): 16/19 Men (%): 40/34 Female (%): 60/66 ***ECOG performance status*** 0 (%): 57/53 1 (%): 43/47 ***Histology*** Adenocarcinoma (%): 85.1/95.2/89.4 Large cell (%): 6.4/5.3/0 Other (%): 8.5/0/10.6 ***Smoking habits*** Never smoker (%): 56/58 Former light smoker (%): 12/8			Conjunctivitis (%): 11/9 Peripheral oedema (%):11/8 Fatique (%): 13/4 Nail disorder (%): 12/5 Dry eye (%): 11/4 Dyphonia (%): 11/1	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Other (%): 32/34 ***Clinical stage at screeening*** IIIB (%): 1/0 IV (%): 80/81 Postoperative recurrence (%): 19/19 ***EGFR mutation type*** Exon 19 detection (%): 53/52 Exon 21 Leu858Erf mutation (%): 47/48				
Zinner, R.G., et al., PRONOUNCE: randomized, open-label, phase III study of first-line pemetrexed + carboplatin followed by maintenance pemetrexed versus paclitaxel +	**Region** USA **Inclusion criteria** Chemotherapy naïve adults Patients ≥18 years	**Intervention(s)** Paclitaxel+carboplatin+bevacizumab followed by bevacizumab After four cycles of induction therapy every 21 days, maintenance continued until disease progression or intolerance. Planned	Median overall survival (months) 11.7/10.5; NA; ns (CIs overlap) Overall survival (2 year)	***Grad 3*** Anemia (%): 5.4/18.1 Neutropenia (%): 22.3/21.1 Thrombocytoenia (%): 4.2/15.2 Febrile neutropenia (%): 1.2/0	**Study type** RCT **Level of evidence** 1b **Risk of bias**

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
carboplatin + bevacizumab followed by maintenance bevacizumab in patients ith advanced nonsquamous non-small-cell lung cancer. J Thorac Oncol, 2015. 10(1): p. 134-42.	Cytologically or histologically confirmed stage IV nonsquamous NSCLC ECOG PS 0 or 1 Measurable disease by RECIST Adequate organ function **Exclusion criteria** Contraindications for pemetrexed or bevacizumab or for general radiotherapy within 2 weeks, stereotactic brain radiotherapy within 7 days, major surgery within 28 days, minor surgery within 3 months before day 1 Use of an investigational agent within 30 days of randomization	chemotherapy doses were pemetrexed 500 mg/m²; carboplatin, area under the curve = 6, (as of December 31, 2010, maximum possible dose of 900 mg), paclitaxel 200 mg/m²; bevacizumab 15 mg/kg. **Control** Pemetrexed+carboplatin followed by pemetrexed After four cycles of induction therapy every 21 days, maintenance continued until disease progression or intolerance. Planned chemotherapy doses were pemetrexed 500 mg/m²; carboplatin, area under the curve = 6, (as of December 31, 2010, maximum possible dose of 900 mg), paclitaxel 200 mg/m²; bevacizumab 15 mg/kg.	17.6%/18.0%; HR=1.07; 0.83 - 1.36 Median progression-free survival (follow-up: 1-41 months) 5.49/4.44; NA; NR Progression-free survival (follow-up: 1-41 months) NR; HR= 1.06; 0.84 - 1.35 ORR (follow-up: 1-41 months) 27.4%/23.6%; NR; 0.414 DCR (follow-up: 1-41 months)	Hypertension (%): 2.4/0 Thrombosis/embolism (%): 1.8/1 Any hemorrhagic events (%): 0/1.2 Sensory neuropathy (%): 2.4/0 ***Grad 4*** Anemia (%):0/0.6 Neutropenia (%): 26.5/3.5 Thrombocytoenia (%): 5.4/8.8 Febrile neutropenia (%): 0.6/0 Thrombosis/embolism (%): 0.6/0	Generation of allocation sequence: + Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: ? Selective reporting: + Other source of bias:

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Any serious concomitant disorder that could compromise the ability to adhere to the protocol **Patient characteristics** Age (mean): 65.4/65.8 >70 (%): 28.5/32.4 Female (%):41.9/42.3 ***ECOG performance status*** 0 (%):46.9/46.7 1 (%): 53.1/52.7 ***Histology*** Adenocarcinoma (%): 76.5/83.5 Large cell (%): 5.0/0.5 Other or indeterminate (%):18.4/15.4 ***Smoking habits*** Ever (%): 96.1/90.1	**Included/randomised patients** 179/182 **Analysed patients** 179/182 (efficacy) 166/171 (safety) **Attrition** NR **Excluded from analysis (reason)** 11/11 (safety, one dose of study)	57%/59.9%; NR; 0.575		+

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Ethnic origin White (%): 87.7/90.7 African American (%): 11.2/6.0 Asian (%): 0.0/2.2 American Indian (%): 1.1/0.0 Multiple (%): 0.0/1.1 ***Disease stage IV*** M1a (%):29.6/28.6 ***No previously treated brain metastasis (%): 82.1/87.4***				
Zhou C, Wu YL, Chen G, Liu X et al. BEYOND: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase III Study of First-Line Carboplatin/Paclitaxel	**Region** China **Inclusion criteria** >18 years Histologically or cytologically confirmed, locally	**Intervention(s)** Carboplatin intravenously and paclitaxel (175 mg/m^2) IV (on day 1 of each 3-week cycle for up to six cycles plus bevacizumab 15 mg/kg IV on day 1 of each cycle until disease progression, unacceptable toxicity	Median overall survival (months) 24.3/17.7 ; NA; NR Overall survival (follow-up: 1-2 years) NR; HR=1.47; 1.08-2.00	**AEs of special interest (%):** 49/23 Grade > 3 AES of special interest (%): 11/2 Hypertension (%): 5/1 Protelnuria (%): 4/0 GI perforations (%): 1/1	**Study type** RCT **Level of evidence** 1b **Risk of bias**

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
Plus Bevacizumab or Placebo in Chinese Patients With Advanced or Recurrent Nonsquamous Non-Small-Cell Lung Cancer J Clin Oncol. 2015 Jul 1;33(19):2197-204.	advanced, metastatic, or recurrent nonsquamous NSCLC Eastern Cooperative Oncology Group performance status of 0 to 1 **Exclusion criteria** Mixed non–small-cell and small-cell histology or mixed adenocarcinoma with predominant squamous histology History of hemoptysis Tumors invading major blood vessels, CNS metastases, and uncontrolled hypertension Current or recent (within 10 days of first bevacizumab dose) use of	**Control** Carboplatin intravenously and paclitaxel (175 mg/m²) IV (on day 1 of each 3-week cycle for up to six cycles plus placebo **Included/randomised patients** 138/138 **Analysed patients** 138/138 (efficacy) 140/134 (safety) **Attrition** NR **Excluded from analysis (reason)**	**Median progression-free survival (months)** 9.2/6.5; NA; NR **Progression-free survival (follow-up: 1-2 years)** NR ; HR=2.5; 1.85-3.45 ORR (follow-up: 1-2 years, RECIST criteria) 54%/26%; NR; <0.001 Diseases control rate (follow-up: 1-2 years, RECIST criteria) 94%/89%; NR; ns (CIs overlapping)	**Bleeding (%):** 1/1 Cerebral hemorrhage (%): <1/0 Hernaturia (%): 0/>1 Upper GI hemorrhage (%): <1/0 Congestive heart failure (%): 1/0 Thromboembolic events (%): 0/1 **Overviews of AES** Grade >3 (%): 67/62 Serious AEs (%): 14/12 AEs leading to death (%): 2/1 AEs leading to study withdrawal (%): 19/15 **Grade > 3 AEs with a difference in Incidence of >2% between treatment arms**	Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: + Blinding of outcome assessment: + Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Full-dose anticoagulants or a thrombolytic agent for therapeutic purposes **Patient characteristics** Age (mean): 57/56 Men (%): 54/56 ***ECOG PS*** 0 (%): 25/20 1 (%): 75/80 ***Histology*** Adenocarcinoma (%): 99/98 Large – cell carcinoma (%): 1/1 Mixed cell carcinoma (%): 0/1 ***Smoking Habits*** Nonsmoker/former smoke (%): 50/56 Smoker (%): 50/44	+2/4 (safety, not received treatment or wrong treatment)		Neutropenia (%): 23/28 Anemia (%): 7/11 Thrombocytopenia (%): 7/9 Bone marrow failure (%): 11/3 Febrile neutropenia (%): 3/5 WBC count decreased (%): 11/5 Hypertension (%): 5/1 Diarrhea (%): 1/3 Prostelnuria (%): 4/0 Back pain (%): 0/2	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IGn/CG) of study population	Intervention(s), control and patient flow (IGn/CG)	Outcomes (IGn/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IGn/CG)	Study type, level of evidence and risk of bias
	Disease stage Recurrent (%): 3/2 IIIB (%): 6/7 IV (%): 91/91 Unknown (%): 0/1 ***EGFR mutation status assessment (%):*** 85/66 EGFR mutation positive (%): 27/26 EGFR wild type (%): 73/74				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
de Boer, R.H., et al., Vandetanib plus pemetrexed for the second-line treatment of advanced non-small-cell lung cancer: a randomized, double-blind phase III trial. J Clin Oncol, 2011. 29(8): p. 1067-74.	Region 118 centers in 21 countries Inclusion criteria Age ≥ 18 years Locally advanced or metastatic (stage IIIB to IV) NSCLC after failure of first-line anticancer treatment Performance status 0 to 2 Life expectancy ≥ 12 weeks Adequate hematologic, hepatic, renal, and cardiac function. Patients with squamous cell histology were permitted (recruitment was completed before labeling of pemetrexed for nonsquamous histology	Intervention(s) Once-daily oral vandetanib 100 mg plus pemetrexed Pemetrexed 500 mg/m² was administered as an intravenous infusion every 21 days (maximum of six cycles) Median number of pemetrexed cycles was 5.0 The median duration of treatment was 102 Control Oral placebo plus pemetrexed Pemetrexed 500 mg/m² was administered as an intravenous infusion every 21 days (maximum of six cycles)	Median overall survival (months) 10.5/9.2; NA; NR Overall survival (minimum 12 month) NR/NR; HR = 1.12; 0.92 – 1.37 Median progression free survival (weeks) 17.6/11.9; NA; NR Progression free survival (minimum 6 month) NR/NR; HR = 1.16; 0.94 – 1.45 (97.58% CI) Objective response rate (minimum 6 month)	Fatigue (%): 39/45 Nausea (%): 29/37 Rash (%): 38/26 Cough (%): 25/22 Anorexia (%): 22/24 Dyspnea (%): 21/24 Diarrhea (%): 26/18 Constipation (%): 20/20 Vomiting (%): 15/22 Anemia (%): 8/22	Study type RCT Level of evidence 1b Risk of bias Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: + Blinding of outcome assessment: ?

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	only) as were patients with pretreated clinically stable brain metastases Exclusion criteria Chemotherapy or other anticancer therapy < 3 weeks before study entry Radiation therapy within 4 weeks before study entry Prior treatment with pemetrexed or VEGFR tyrosine kinase inhibitors (TKIs) Patient characteristics Age (median): 60/60 Male (%): 62/62 *Performance status* 0 (%): 41/41 1 (%): 52/54	Median number of pemetrexed cycles was 4.0 The median duration of treatment was 85 Included/randomised patients 256/278 Analysed patients 256/278 (efficacy) 260/273 (safety) Attrition None Excluded from analysis (reason) None (efficacy) 0/1 (safety: not received treatment)	19%/8%; NR; <0.001 DCR (minimum 6 month) 57%/46%; NR; 0.0116 Time to deterioration of symptoms (Lung Cancer Symptom Scale, minimum 6 month) NR/NR; HR = 1.41; 1.06-1.85		Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	2 (%): 7/5 *Histology* Adenocarcinoma (%): 61/65 Squamous cell (%): 21/22 Other (%): 18/13 *Stage* IIIB (%): 14/17 IV (%): 86/83 Number of prior chemotherapy regimes 1 (%): 85/86 2 (%): 13/11 3 (%): 0.4/0.4 Race/ethnicity White (%): 77/78 East Asian (%): 11/12 Other (%): 12/9 Smoking history				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Smoker (%): 78/81 Nonsmoker (%): 22/19 Prior bevacizumab (%): 8/8				
Herbst, R.S., et al., Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small-cell lung cancer (ZODIAC): a double-blind, randomised, phase 3 trial. Lancet Oncol, 2010. 11(7): p. 619-26.	Region Multinational Inclusion criteria Age 18 years or older Histological or cytological confirmation of locally advanced or metastatic stage IIIB–IV NSCLC after failure of first-line platinum-based therapy WHO performance status of 0 or 1 Measurable disease by Response Evaluation Criteria in Solid Tumours	Intervention(s) Docetaxel (75 mg/m² in a 1-h intravenous infusion every 3 weeks; maximum six cycles) in combination with vandetanib (100 mg/day orally). The docetaxel dose in Japan was 60 mg/m² Median of 4 docetaxel cycles Exposure to vandetanib 12.1 weeks Control Docetaxel (75 mg/m² in a 1-h intravenous infusion every 3 weeks;	Overall survival (minimum 16 month) 78%/77%; HR = 1.05; (97.52% CI: 0.93 - 1.19) Median overall survival 10.3/9.9; NR; NR Progression free survival (median 12.8 month) 28%/22%; HR = 1.27; (97.58% CI: 1.11 - 1.43) Median progression free survival	Diarrhoea (%): 42/33 Alopecia (%): 33/35 Rash (%): 42/24 Fatigue (%): 30/31 Neutropenia (%): 32/27 Anorexia (%): 29/30 Nausea (%): 23/32 Cough (%): 19/19 Dyspnoea (%): 17/21 Constipation (%):17/20 Pyrexia (%): 20/17 Vomiting (%): 16/21 Leukopenia (%): 18/16 Asthenia (%): 16/13 Anaemia (%): 10%15	Study type RCT Level of evidence 1b Risk of bias Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Adequate cardiac, haematopoietic, hepatic, and renal function Exclusion criteria Previous therapy with docetaxel or a VEGFR TKI Previous treatment with bevacizumab or paclitaxel Squamous-cell histology or brain metastases if treated within 4 weeks before study entry or not clinically stable without steroids for 10 days Patient characteristics Age (mean): 59/59 Male (%): 72/68 *Ethnic origin* Caucasian (%): 59/60 East Asian (%):37/36	maximum six cycles) with placebo Median of 4 docetaxel cycles Exposure to placebo 13.0 weeks Included/randomised patients 694/697 Analysed patients 694/697 (efficacy) 689/690 (safety) Attrition 432/458 Excluded from analysis (reason) 5/7 (safety, not treated)	4.0/3.2; NR; NR ORR (median 12.8 month) 17%/10%; NR; 0.0001 DCR (median 12.8 month) 60%/55%; NR; 0.06 Deterioration (FACT-L LCS, median 12.8 month) NR/NR; HR= 1.30; 1.09-1.54 (97.5% CI) Median time to deterioration (FACT-L LCS) 3.5/2.7;NR;NR	Myalgia (%): 13/11 Insomnia (%):13/11 Stomatitis (%): 12/12	Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Other (%): 4/4 *Smoking history* Current smoker (%): 37/35 Former smoker (%): 40/40 Non-smoker (%): 23/25 *WHO performance status* 0 (%): 36/34 1 (%): 63/65 Other (%): 1/1 *Histology* Adenocarcinoma (%): 59/60 Squamous (%):27/23 Other (%): 14/17 *Stage of disease¶* Stage IIIb (%): 14/15 Stage IV (%): 86/85				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Brain metastases (%): 9/11 *Previous chemotherapy* Platinum compound (%): 95/95 Pyrimidine analogue (%): 44/45 Taxane (%): 31/30 Vinca alkaloid or analogue (%): 18/18 *Best response to first-line chemotherapy* Complete response (%): 2/2 Partial response (%): 31/31 Stable disease (%): 36/37 Progressive disease (%): 24/24 Non-evaluable (%): 2/2				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Not applicable or not recorded (%): 4/3 Prior bevacizumab (%): 3/3				
Boutsikou, E. Docetaxel-carboplatin in combination with erlotinib and/or bevacizumab in patients with non-small cell lung cancer. Onco Targets Ther, 2013. 6: p. 125-34.	Region NR Inclusion criteria Confirmed newly diagnosed stage IIIb or stage IV non-squamous NSCLC Age ≥ 18 years Performance status of 0 or 1 Adequate hematologic, hepatic, and renal function (including urinary excretion of ≤ 500 mg of protein per day) Two cycles chemotherapy Exclusion criteria	Intervention(s) All patients initially received two cycles of chemotherapy with docetaxel 100 mg/m² and carboplatin at a dose of area under the concentration-time curve of 5.5 every 28 days Erlotinib in combination with chemotherapy (docetaxel and carboplatin chemotherapy + erlotinib) Four cycles of docetaxel-carboplatin plus erlotinib administered orally at 150 mg/dL per	Median overall survival (days) 491/754/663/460; NA; 0.381 Overall survival (median 440 days) 27%/16%; HR = 1.24; 0.59 – 2.56 39%/16%; HR = 1.30; 0.63 -2.63 18%/16%; HR = 1.53; 0.67 - 3.70 Progression free survival NR; NR; NS	Anemia: 2/3/8/10 Neutropenia: 3/3/6/14 Thrombocytopenia: 2/4/4/4 Hypertension: 0/3/2/0 Rash: 7/0/12/0 Diarrhea: 4/0/8/0 Hemoptysis: 0/2/5/0 Proteinuria: 0/4/4/0 Renal failure: 0/0/0/5 Cardiotoxicity: 0/0/0/2 Pulmonary embolism: 0/1/0/0	Study type RCT Level of evidence 2b Risk of bias Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: -

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Hemoptysis History of documented hemorrhagic diathesis or coagulopathy Therapeutic anticoagulation Radiation therapy within 21 days before enrolment or major surgery within 28 days before enrolment Clinically significant cardiovascular disease Medically uncontrolled hypertension Prior systemic chemotherapy for NSCLC Symptomatic or untreated brain metastases Tumors invading or abutting major blood vessels (based on radiologist assessment)	day beginning on the first day of the third cycle and continued with erlotinib monotherapy thereafter until progression Bevacizumab in combination with chemotherapy (docetaxel and carboplatin chemotherapy + bevacizumab Four cycles of docetaxel-carboplatin plus bevacizumab 7.5 mg/kg by intravenous infusion every 28 days and continued with bevacizumab every 21 days until disease progression Bevacizumab in combination with erlotinib and	Objective Response rate (median follow-up 440 days) 48%/39%/44%/31%; NR; NR		Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Patient characteristics Age (median): 62.5/62.5/60/65 Male (%): 77/80/83/85 *Histologic type* Adenocarcinoma (%): 92/89/87/92 Large cell (%): 8/11/13/8 *Stage of disease* Stage IIIb (%): 25/27/17/16 Stage IV (%): 75/73/83/84 *Smoking history* Never (%): 15/16/3/8 Previous (%): 75/80/88/64 Current (%): 10/4/8/23 *EGFR Status*	chemotherapy (docetaxel and carboplatin chemotherapy + bevacizumab + erlotinib Four cycles of chemotherapy plus bevacizumab 7.5 mg/kg every 28 days and erlotinib 150 mg/dL, and continued with bevacizumab every 21 days and erlotinib until disease progression Control Docetaxel and carboplatin chemotherapy alone Further four cycles of docetaxel-carboplatin and continued with observation until disease progression			

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Immunohistochemistry (+) (%): 73/22/40/65 Immunohistochemistry (-) (%): 27/73/60/35 *VEGF status* Immunohistochemistry (+) (%): 37/31/53/60 Immunohistochemistry (-) (%): 63/69/47/40	Included/randomised patients 62/62/62/62 Analysed patients 52/56/60/61 Attrition 10/6/2/1 Excluded from analysis (reason) 10/6/2/1 (attrition)			
Heist, R.S. CALGB 30704 (Alliance): A randomized phase II study to assess the efficacy of pemetrexed or sunitinib or pemetrexed plus sunitinib in the second-line treatment of advanced non-small-cell lung cancer. J Thorac	Region NR Inclusion criteria Patients aged 18 years or older Advanced NSCLC (stage IIIB or IV) with evidence of progression after first-line therapy	Intervention(s) Sunitinib alone at 37.5 mg/day Pemetrexed 500 mg/m² on day 1 with sunitinib 37.5 mg daily Control Pemetrexed alone at 500 mg/m² on day 1	Median overall survival (months) 8.0/6.7/10.5; NA; p=0.03 Overall survival (median 36 month) NR/NR; HR = 0.714; 0.435 – 1.111	Overall AEs (%): 67/80/29 Hematologic AEs (%): 23/47/17 Low haemoglobin (%): 7/8/2 Low absolute neutrophil count (%): 7/28/5 Low platelets (%): 7/17/4	Study type RCT Level of evidence 2b Risk of bias Generation of allocation sequence:

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
Oncol, 2014. 9(2): p. 214-21.	Performance status (PS) of 0 or 1 Prior bevacizumab was allowed No restrictions regarding histologic subtype of NSCLC, and central review was not required Adequate hematologic, liver, and kidney function Treated, asymptomatic brain metastases were allowed. Exclusion criteria Symptomatic congestive heart failure Active coronary artery disease defined as myocardial infarction or unstable angina in the past year	Included/randomised patients 47/41/42 Analysed patients 47/41/42 Attrition NR Excluded from analysis (reason) 0/0/0	NR/NR: HR = 0.5; 0.313 – 0.833 Progression free survival (18 weeks) 37.0%/48.1%/53.7%; NR; 0.88 Median progression free survival (months) 3.3/3.7/4.9; NA; 0.18 Progression free survival (median 26 month) 1) NR/NR; HR = 0.714; 0.455 – 1.111 2) NR/NR; HR = 0.768; 0.476 – 1.111	Febrile neutropenia (%): 0/3/0 Nonhematologic AEs (%): 59/62/19 Fatigue (%): 27/23/9 Infection (%): 4/6/2 Nausea (%): 2/8/0 Vomiting (%): 0/5/0 Mucositis (%): 2/8/0 Diarrhea (%): 0/0/2 Elevated alanine aminotransferase (%): 2/3/0 Elevated aspartate aminotransferase (%): 5/0/2 Rash (hand-foot) (%): 7/0/0 Cardiac ischemia (%): 2/0/0 Hypertension (%): 5/5/2 Pulmonary haemorrhage (%): 2/0/0	+ Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: + Other source of bias: - (multiple testing without adjustment)

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Cerebrovascular accident or transient ischemic accident in the past year Uncontrolled hypertension Hemoptysis Cavitary pulmonary lesions History of thromboembolism Requirement for full-dose therapeutic anticoagulation Patient characteristics *Age* < 60 (%): 32/37/38 60 – 70 (%): 51/32/36 > 70 (%): 17/32/26 Male (%): 53/54/52		Response rate (median 36 month) 17%/22%/14%; NR; 0.34	Other haemorrhage (%): 0/3/0 Thrombosis/embolism (%): 060	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Race White (%): 91/78/86 Black (%): 6/20/12 Asian (%): 2/2/0 More than one race (%): 0/0/2 *Ethnicity* Non-Hispanic (%): 100/88/93 Hispanic (%): 0/2/5 Unknown (%): 0/10/2 *Performance status* 0 (%): 36/34/31 1 (%): 64/66/69 *Histology* Adenocarcinoma (%): 69/66/67 Squamous cell (%): 15/15/10 Large cell (%): 9/0/5				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Undifferentiated NSC (%): 13/2/7 Other (%): 4/17/7 Missing (%): 0/0/5 *Stage of disease* Stage IIIb (%): 17/7/12 Stage IV (%): 83/93/88 *Prior surgery* No (%): 72/73/57 Yes (%): 26/27/38 Missing (%): 2/0/5 *Prior XRT* No (%): 55/51/52 Yes (%): 45/49/40 Missing (%): 0/0/7 *No. of prior chemo regimens* 1 (%): 91/95/90 2+ (%): 9/0/2				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Missing (%): 0/5/7				
Johnson, D.H., et al., Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol, 2004. 22(11): p. 2184-91.	Region 12 centers in North America Inclusion criteria Stage IIIB (with pleural effusion), stage IV, or recurrent NSCLC Age ≥ 18 years Bi-dimensionally measurable disease Performance status ≤ 2 Life expectancy ≥ 3 months Availability for regular follow-up Exclusion criteria Small-cell or mixed histologies	Intervention(s) carboplatin/paclitaxel plus low-dose (7.5 mg/kg) bevacizumab Median number of bevacizumab doses 8 Median of six cycles of carboplatin plus paclitaxel carboplatin/paclitaxel plus high-dose (15 mg/kg) bevacizumab Median number of bevacizumab doses 10 Median of six cycles of carboplatin plus paclitaxel Bevacizumab was administered by intravenous infusion over 90 minutes, 1 hour after	Median overall survival (months) 11.6/14.9; NA; 0.84 17.7/14.9; NA; 0.63 Median time to progression (months) 4.1/7.0/5.9; NR; 0.185 Response rate (time period NR) 21.9%/40.0%/31.3%; NR; NR	Chills (%): 12.5/11.8/9.4 Diarrhea (%): 28.1/41.2/18.8 Epistaxis (%):31.3/44.1/6.3 Fever (%): 34.4/32.4/12.5 Headache (%): 31.3/47.1/9.4 Hemorrhage (%): 12.5/0.0/0.0 Hypertension (%): 15.6/17.6/3.1 Hemoptysis (%): 28.1/11.8/6.3 Infection (%): 31.3/35.3/25.0 Leukopenia (%): 46.9/55.9/31.3 Nausea (%): 50.0/50.0/46.9	Study type RCT Level of evidence 2b Risk of bias Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment:

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Prior chemotherapy or biotherapy, radiotherapy to an area of measurable disease (unless disease progression had been documented following completion of therapy), or radiotherapy within 2 weeks preceding day 0 Absolute neutrophil count ≤ 1,500/ µL Hemoglobin less than 9 gm/dL Platelet count ≤ 100,000/ µL Bilirubin > 2.0 mg/dL AST or ALT ≥ 5 times upper limit of normal (ULN) for subjects with metastases > 2.5 X ULN for those without metastases Serum creatinine > 1.8 mg/dL.	each cycle of chemotherapy Control Carboplatin/paclitaxel alone Up to six cycles of carboplatin/paclitaxel Paclitaxel (200 mg/m2) was administered over 3 hours every 3 weeks Carboplatin dosing was based on the Calvert formula with a target area under the curve of 6 mg/mL X min and glomerular filtration rate (GFR) estimated for males as GFR (140 – age) X weight/72 X (serum creatinine) For females, a correction factor of 0.85 was used		Neuropathy (%): 12.5/14.7/28.1 Paresthesia (%): 28.1/35.3/21.9 Peripheral neuritis (%): 25.0/38.2/28.1 Rash (%): 34.4/23.5/9.4 Stomatitis (%): 15.6/23.5/9.4 Thrombocytopenia (%): 6.3/20.6/15.6 Thrombotic events (%): 12.5/17.6/9.4 Vomiting (%): 18.8/23.5/18.8	+ Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Nonhealing wounds, ulcers, or bone fractures Significant cardiovascular disease Significant peripheral vascular disease, CNS metastasis, active secondary malignancies (other than basal cell carcinoma of the skin), an active infection, or pregnancy major surgery within 4 weeks before day 0, a fine needle biopsy or an open biopsy within 1 week before day 0, a significant recent traumatic injury, or the anticipation of a major surgical procedure Recent or current use of aspirin or oral and/or parenteral anticoagulants (except low-dose Coumadin 1 mg)	Carboplatin was administered over 15 to 30 minutes, beginning 60 minutes after completion of the paclitaxel Median of six cycles of carboplatin plus paclitaxel Included/randomised patients 32/35/32 Analysed patients 32/34/32 Attrition Excluded from analysis (reason) 0/1/0			

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Patient characteristics Male (%): 20/16/24 *Performance status* 0 (%): 16/19/15 1 (%): 15/12/15 2 (%): 1/4/2 *Histology* Adenocarcinoma (%): 29/23/17 Large cell anaplastic (%): 1/5/4 Squamous cell (%): 10/3/7 Other (%): 1/4/4 *Stage* IIIB (%): 2/7/6 IV (%): 30/28/26 Duration of current cancer				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	< 1 year (%):24/28/22 1 year (%): 2/4/4 2 years (%): 2/1/2 ≥ 3 years (%): 4/2/4 Prior cancer therapy Any (%): 10/10/13 Radiation (%): 9/7/8 Other (%): 7/9/11				
Heymach, J.V. Randomized, placebo-controlled phase II study of vandetanib plus docetaxel in previously treated non small-cell lung cancer. J Clin Oncol, 2007. 25(27): p. 4270-7.	Region 27 centers in the United States, the Czech Republic, and Hungary Inclusion criteria Locally advanced or metastatic stage IIIB/IV NSCLC after failure of first-line platinum-based therapy Age at least 18 years	Intervention(s) Once-daily oral vandetanib (100 mg; continuous 21-day treatment periods) and docetaxel (75mg/m^2 intravenous infusion over 1 hour on day 1 of each 21-day) cycle Once-daily oral vandetanib (300 mg; continuous 21-day treatment periods) and docetaxel (75mg/m^2	Overall survival (minimum 24 month) NR/NR; HR = 1.10; 0.66 – 1.82 NR/NR; HR = 0.78; 0.48 - 1.28 Median overall survival (months) 13.1/7.9/13.4; NA; 0.723 (100mg docetaxel vs. control), 0.334	Diarrhea (%): 38/50/24 Fatigue (%): 40/46/27 Neutropenia (%): 26/32/20 Nausea (%): 26/30/17 Alopecia (%): 29/35/17 Cough (%): 24/20/15 Diarrhea and related events (%): 38/50/27 Rash (%): 40/46/24	Study type RCT Level of evidence 2b Risk of bias Generation of allocation sequence: ?

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Performance status of 0 or 1 Life expectancy of at least 12 weeks Normal end organ function Patients with squamous cell histology were eligible, and brain metastases were permitted if treated at least 4 weeks before study entry and clinically stable without steroid treatment for 1 week Exclusion criteria Previous treatment with docetaxel or EGFR/VEGFR signaling inhibitors Chemotherapy within the last 4 to 6 weeks Radiation therapy within the last 4 weeks	intravenous infusion over 1 hour on day 1 of each 21-day) cycle Control Placebo and docetaxel (75mg/m^2 intravenous infusion over 1 hour on day 1 of each 21-day cycle) Included/randomised patients 42/44/41 Analysed patients 0/0/0 Attrition NR/NR/NR Excluded from analysis (reason) None	(300mg docetaxel vs. control) Progression free survival (minimum 18 month) NR/NR; HR = 1.56; 0.95 – 2.63 NR/NR; HR = 1.20; 0.74 – 2.00 Median progression free survival (weeks) 18.7/17.0;12.0; NA; 0.074 (100mg docetaxel vs. control), 0.461 (300mg docetaxel vs. control) Response rate 26%/18%/12%; NR; NR	Nausea/vomiting (%): 31/34/24 Hypertension (%): 7/9/2 Dizziness (%): 7/4/5	Allocation concealment: ? Blinding of participants and personal: + Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: - (multiple testing without adjustment)

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Patient characteristics Age (median): 61/60/58 Male (%): 50/57/66 *Performance status* 0 (%): 33.3/36.4/36.6 1 (%): 64.3/61.4/63.4 *Smoking status* Current smoker (%): 26.2/36.4/26.8 Previous smoker (%): 57.1/54.5/63.4 Nonsmoker (%): 16.7/9.1/9.8 *Histology* Adenocarcinoma (%): 54.8/45.5/48.8 Squamous (%): 28.6/31.8/26.8				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Other histologies (%): 16.7/22.7/24.4 Brain metastases (%): 16.7/4.5/9.8 *Stage* IIIB (%): 31.0/20.5/31.7 IV (%): 66.7/79.5/68.3				
Niho, S., et al., Randomized phase II study of first-line carboplatin-paclitaxel with or without bevacizumab in Japanese patients with advanced non-squamous non-small-cell lung cancer. Lung Cancer, 2012. 76(3): p. 362-7.	Region 19 sites in Japan Inclusion criteria 20 - 74 years Stage IIIB with pleural and/or pericardial effusion and/or pleural dissemination, IV or recurrent non-squamous NSCLC Measurable lesions (RECIST)	Intervention(s) Bevacizumab and carboplatin-paclitaxel All treatments were administered on day 1 of a 21-day cycle Carboplatin was administered at a dose calculated to produce an area-under-the-curve (AUC) of 6 mg/(mL min), paclitaxel was administered at a dose of 200 mg/m² and bevacizumab at a dose of 15 mg/kg	Overall survival (minimum 16 month) NR/NR; HR = 1.01; 0.67 – 1.54 Median overall survival (months) 22.8/23.4; NA; ns (CIs overlap) Progression free survival (minimum 16 month)	Leukopenia (%): 94/90 Neutropenia (%): 96/94 Decreased haemoglobin (%): 85/84 Thrombocytopenia (%): 72/67 Febrile neutropenia (%): 8/7 Hypertension (%): 48/10 Bleeding (%): 78/31 Hemoptysis (%): 22/5	Study type RCT Level of evidence 2b Risk of bias Generation of allocation sequence: + Allocation concealment: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Performance Status 0 or 1 life expectancy of ≥ 3 months Adequate bone marrow, hepatic, and renal function Exclusion criteria Prior chemotherapy for NSCLC Central nervous system metastases or spinal cord compression Tumor invading major blood vessels or with cavitation Hemoptysis (≥2.5 mL per event) History of coagulation disorders or therapeutic anticoagulation	Chemotherapy was repeated every 21 days for a total of 6 cycles unless there was evidence of disease progression or unacceptable toxicity Median number of chemotherapy cycles was 6 Control Carboplatin-paclitaxel alone Same treatment for carboplaitin and paclitaxel as in the intervention group Median number of chemotherapy cycles was 4.5	NR/NR; HR = 1.64; 1.12 - 2.38 Median progression free survival (months) 6.9/5.9; NA; ns (CIs overlap) Objective Response rate (minimum 16 month) 60.7%/31.0%; NR; 0.0013 DCR (minimum 16 month) 94.0%/70.7%; NR; 0.0002	Nasal bleeding (%): 72/12 Venous thromboembolism (%): 4/3 Arterial thromboembolism (%): 1/0 Congestive heart disease (%): 1/2 Proteinuria (%): 52/17 Fatigue (%): 52/53 Vomiting (%): 36/31 Neuropathy (%): 88/86 Muscle pain (%): 70/71 Joint pain (%): 82/79 Elevated aspartate aminotransferase (%): 47/36 Elevated alanine aminotransferase (%): 48/41 Hyponatremia (%): 14/3 Treatment-related death (%): <1/0	Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Uncontrolled hypertension History of a symptomatic lung disorder Patient characteristics Age (median): 61/60 Male (%): 64/64 *Performance status* 0 (%): 51/49 1 (%): 49/51 *Smoking status* Never smoker (%): 31/32 Current or previous smoker (%): 69/68 *Tumor histology* Adenocarcinoma (%): 93/92 Large cell carcinoma (%): 2/3	Included/randomised patients 121/59 Analysed patients 119/58 (safety) 117/58 (efficacy) Attrition 4/1 Excluded from analysis (reason) 2/1 (safety, did not start treatment)) 4/1 (efficacy, ineligible)			

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Other (%): 7/3 *Stage* IIIB (%): 23/20 IV (%): 69/71 Recurrent (%): 8/8				
Paz-Ares, L.G., et al., Phase III, randomized, double-blind, placebo-controlled trial of gemcitabine/cisplatin alone or with sorafenib for the first-line treatment of advanced, nonsquamous non-small-cell lung cancer. J Clin Oncol, 2012. 30(25): p. 3084-92.	Region 93 centers in 16 countries Inclusion criteria Chemotherapy-naive patients age ≥ 18 years Stage IIIB (malignant pleural or pericardial effusion) or IV nonsquamous NSCLC and for whom treatment with gemcitabine/cisplatin was considered medically acceptable. Performance status of 0 or 1	Intervention(s) Gemcitabine (1,250 mg/m² per day intravenously on days 1 and 8), cisplatin (75 mg/m² intravenously on day 1), and sorafenib (400 mg per day as two 200-mg tablets) Up to six cycles, each of 21 days Median duration of treatment 17.0 weeks Control Gemcitabine (1,250 mg/m2 per day	Median overall survival (months) 12.4/12.5; NA; ns (CIs overlap) Overall survival (minimum 1 year) NR/NR; HR = 0.98; 0.83 – 1.16 Median progression free survival (months) 6.0/5.5; NA; ns (CIs overlap)	All treatment-emergent drug-related AEs (%): 86.0/69.3 Thrombocytopenia (%): 15.8/11.5 Anemia (%): 8.8/9.1 Neutropenia (%): 8.1/8.9 Leukopenia (%): 6.5/3.4 Rash/desquamation (%): 33.5/15.1 Diarrhea (%): 31.4/10.9 Fatigue (%): 29.4/24.7 Hand-foot skin reaction (%): 28.8/3.1 Nausea (%): 24.4/20.1	Study type RCT Level of evidence 1b Risk of bias Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal:

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	At least one measurable lesion Adequate bone marrow, liver, and renal function as assessed Life expectancy of at least 12 weeks. Exclusion criteria Patients with grade ≥ 2 pulmonary hemorrhage/bleeding or grade ≥ 3 other hemorrhage/bleeding events within 4 weeks of the first dose of study drug Cardiac disease (congestive heart failure, unstable angina, cardiac arrhythmia requiring antiarrhythmic therapy, active coronary artery disease, or history of	intravenously on days 1 and 8), cisplatin (75 mg/m2 intravenously on day 1), and placebo Up to six cycles, each of 21 days Median duration of treatment 18.0 weeks Included/randomised patients 452/452 Analysed patients 385/384 (safety) 385/387 (efficacy) Attrition 379/381 Excluded from analysis (reason) 67/68 (safety: squamous cell NSLC not treated)	Progression free survival (minimum 1 year) (NR/NR; HR = 1.20; 1.03 – 1.41 Response rate (minimum 1 year27.8%/25.8%; NR; 0.27 DCR (minimum 1 year) 62.1%/63.1%; NR; 0.39	Anorexia (%): 15.8/11.5 Hypertension (%): 14.5/6.3 Oral mucositis (%): 14.5/5.2 Alopecia (%): 11.2/5.7 Nose haemorrhage (%): 10.9/2.9 Vomiting (%): 10.4/12.5 Dry skin (%): 6.8/3.1 Pruritus (%): 6.8/2.3 Abdominal pain not otherwise specified (%): 6.5/2.1 Constipation (%): 6.2/6.0 Sensory neuropathy (%): 4.9/6.0 Constitutional (other) (%): 2.1/0.5 Gastrointestinal perforation (%): 0.3/0.0	+ Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	myocardial infarction within the previous 6 months) Uncontrolled hypertension History of HIV infection or chronic hepatitis B or C Active clinically serious infection Seizure disorder requiring medication Known brain metastasis History of bleeding diathesis or coagulopathy History of a thrombotic or embolic event (including a transient ischemic attack) within the previous 6 months Serious, nonhealing wound, ulcer, or bone fracture	67/65 (efficacy: squamous cell NSLC)		Central nervous system haemorrhage (%): 0.3/0.3 Lung haemorrhage (%): 0.5/1.0 Abdominal haemorrhage not otherwise specified (%): 0.3/0.0 Vascular (thrombotic) (%): 3.6/3.4	

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Uncorrected dehydration Pregnancy or lactation Therapeutic anticoagulation Patient characteristics Age (median): 60/58 Male (%): 59.2/63.3 *Performance status* 0 (%): 37.9/37.0 1 (%): 62.1/63.0 *Smoking status* Past or present smoker (%): 72.1/74.2 Nonsmoker (%): 27.3/25.3 Passive smoker (%): 0.5/0.5 *NSCLC classification*				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Adenocarcinoma (%): 78.4/80.4 Large cell carcinoma (%): 12.2/10.9 Undifferentiated carcinoma (%): 5.2/5.7 Bronchoalveolar (%): 1.8/1.3 Other (%): 2.3/1.8 *Disease stage* IIIB (%): 12.2/12.1 IV (%): 87.8/87.9 *Race/ethnicity* White (%): 69.0/69.5 Black (%): 0.9/0.0 Asian (%): 27.5/27.6 Hispanic (%): 2.6/2.1 Other (%): 0.0/0.9 Median time since diagnosis (weeks): 2.6/2.9				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
Ritzwoller, D.P., et al., Comparative effectiveness of adjunctive bevacizumab for advanced lung cancer: the cancer research network experience. J Thorac Oncol, 2014. 9(5): p. 692-701.	Region USA Inclusion criteria Patients from Virtual Tumor Registry (VTR) Aged 21 years and older Stage IIIB/IV NSCLC Health plan enrollment at the time of cancer diagnosis First cancer diagnosis Survival of at least 1 month after cancer diagnosis Pathologically confirmed diagnosis Exclusion criteria	Intervention(s) Carboplatin/paclitaxel + bevacizumab (between 2005 and 2010) Control Carboplatin/paclitaxel (between 2005 and 2010) Carboplatin/paclitaxel (between 2002 and 2004) Included/randomised patients NA Analysed patients 198/911/496 Attrition NA	Overall survival (90 month, multivariable-adjusted model) NR/NR; HR = 1.32; 1.09 – 1.59 NR/NR; HR = 1.67; 1.35 – 2.00 Overall median survival (months) 12.3/8.8; NA; ns (CIs overlap) 12.3/7.5; NA; ns (CIs overlap)	NR	Study type Register-based cohort study Level of evidence 2c Risk of bias Generation of allocation sequence: - Allocation concealment: - Blinding of participants and personal: - Blinding of outcome assessment: -

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Squamous cell types or if they were receiving concurrent radiation and chemotherapy Patient characteristics Age <65 at diagnosis (%): 63.6/48.7/51.2 Age 65+ at diagnosis (%): 36.4/51.3/48.8 Male (%): 51.5/50.8/49.0 *AJCC stage at diagnosis* IIIB (%): 15.2/20.7/27.2 IV (%): 84.8/79.3/72.8 Race/ethnicity White (%): 78.3/75.9/71.0 Hispanic (%): <1/4.2/7.3 Black (%): 5.6/7.6/7.9 Asian/Pacific Islander (%): 11.1/10.3/10.7	Excluded from analysis (reason) NA			Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Other race (%): <1/2.1/3.2 *Modified Charlson comorbidity score* 0 (%): 61.1/55.4/66.3 1 (%): 24.7/24.9/22.6 2+ (%): 14.1/19.6/11.1 *Level of differentiation* Well/moderately (%): 22.2/12.1/13.5 Poor/undifferentiated (%): 16.2/22.1/23.8 Unknown (%): 61.6/65.9/62.7				
Sandler, A., et al., Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med, 2006. 355(24): p. 2542-50.	Region NR Inclusion criteria	Intervention(s) Paclitaxel and carboplatin plus bevacizumab at a dose of 15 mg per kilogram given intravenously on day 1	Median overall survival (months) 12.3/10.3; NA; NR Overall survival (median 19 month)	Neutropenia (%): 25.5/16.8 Thrombocytopenia (%): 1.6/0.2 Anemia (%): 0.0/0.9	Study type RCT Level of evidence 2b

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
Brahmer, J.R. Sex differences in outcome with bevacizumab therapy: analysis of patients with advanced-stage non-small cell lung cancer treated with or without bevacizumab in combination with paclitaxel and carboplatin in the Eastern Cooperative Oncology Group Trial 4599. J Thorac Oncol, 2011. 6(1): p. 103-8. Ramalingam, S.S., et al., Outcomes for elderly, advanced-stage non small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of Eastern Cooperative Oncology Group Trial 4599. J	Newly diagnosed stage IIIB (malignant pleural effusion) or stage IV cancer orrecurrent non–small-cell lung cancer for without prior chemotherapy Measurable or nonmeasurable disease as defined by the RECIST Performance status of 0 or 1 Adequate hematologic, hepatic, and renal function Exclusion criteria Histologic evidence of predominantly squamous-cell cancer; hemoptysis Central nervous system metastases Pregnancy or lactation	Chemotherapy was repeated every 21 days for a total of six cycles unless there was evidence of disease progression or intolerance of the study treatment Bevacizumab monotherapy every 3 weeks until evidence of disease progression or unacceptable toxic effects developed The median number of cycles of therapy was seven Control Paclitaxel at a dose of 200 mg per square meter of body-surface area and carboplatin at a dose calculated to produce an area under the concentration– time	NR/NR; HR = 1.27; 1.09 - 1.49 Overall survival (2 years) 23%/15%; NR; NR Median progression free survival (months) 6.2/4.5; NR; NR Progression free survival (median 19 month) NR/NR; HR = 1.52; 1.30 – 1.75 Response rate (median 19 month) 35%/15%; NR; < 0.001	Febrile neutropenia (%): 5.2/2.0 Hyponatremia (%): 3.5/1.1 Hypertension (%): 7.0/0.7 Proteinuria (%): 3.1/0.0 Headache (%): 3.0/0.5 Rash or desquamation (%): 2.3/0.5 Bleeding events (all) (%): 4.4/0.7 Central nervous system haemorrhage (%): 0.7/0.0 Epistaxis (%): 0.7/0.2 Hematemesis (%): 0.5/0.0 Hemoptysis (%): 1.9/0.2 Melena or gastrointestinal bleeding (%): 0.9/0.4	Risk of bias Generation of allocation sequence: + Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: + Other source of bias: -

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
Clin Oncol, 2008. 26(1): p. 60-5.	History of documented hemorrhagic diathesis or coagulopathy Therapeutic anticoagulation Regular use of aspirin (>325 mg per day), nonsteroidal antiinflammatory agents, or other agents known to inhibit platelet function Radiation therapy within 21 days before enrolment or major surgery within 28 days before enrolment Clinically significant cardiovascular disease Medically uncontrolled hypertension Patient characteristics Age ≥ 65 years (%): 42/44 Male (%): 50/58	curve of 6.0 mg per milliliter per minute, administered intravenously on day 1 The median number of cycles of therapy was five Included/randomised patients 434/444 Analysed patients 417/433 111/113 (subgroup) Attrition 2/2 Excluded from analysis (reason) 17/11 (deemed to be ineligible on central review)	Test of interaction for overall survival > age 70 (HR = 1.15) vs. age < 70 (NR); 0.34 Test of interaction for overall survival males (HR = 1.37) vs. females (HR = 1.03); 0.09	Other haemorrhage (%):	(interim analysis without adjustment)

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Race White (%): 90/91 Black (%): 6/6 Other (%): 4/3 *ECOG performance status* 0 (%): 40/40 1 (%): 60/60 Measurable Disease (%): 91/91 Prior weight loss (≥5%): 28/28 *Histology* Adenocarcinoma or not otherwise specified (%): 88/88 Large-cell cancer (%): 4/7 Bronchioloalveolar carcinoma (%): 3/3				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Other histologic findings (%): 5/3 *Stage of disease* Stage IIIb (%): 12/13 Stage IV (%): 74/78 Recurrent disease (%): 14/9 Prior radiation therapy (%): 8/9				
Scagliotti, G., et al., Phase III study of carboplatin and paclitaxel alone or with sorafenib in advanced non-small-cell lung cancer. J Clin Oncol, 2010. 28(11): p. 1835-42.	Region 150 centers in 20 countries Inclusion criteria Chemotherapy-naïve patients Age ≥18 years Stage IIIB (limited to malignant pleural or pericardial effusion) or stage IV NSCLC	Intervention(s) Sorafenib plus carboplatin and paclitaxel Paclitaxel (200 mg/m² intravenously over 2.5 to 4 hours) first and carboplatin (area under the curve = 6 intravenously over 15 to 60 minutes) immediately after on day 1 of a 21-day cycle during the chemotherapy phase	Median overall survival (months) 10.7/10.6; NA; ns (CIs overlap) Overall survival (20 month) NR/NR; HR = 0.87; 0.71 – 1.06 Median progression free survival (months)	Any drug-related AE (%): 84/68 Any drug-related SAE (%): 17/9 Neutropenia (%): 9/7 Thrombocytopenia (%): 8/3 Anemia (%): 8/9 Rash/desquamation (%): 46/13 Diarrhea (%): 28/13	Study type RCT Level of evidence 2b Risk of bias Generation of allocation sequence: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Llife expectancy ≥ 12 weeks Performance status of 0 or 1 Adequate bone marrow, liver, and renal function Exclusion criteria National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; version 3) grade ≥ 2 pulmonary hemorrhage/bleeding CTCAE grade ≥ 3 other hemorrhage/ bleeding, or CTCAE grade more than 2 serious infections within 4 weeks of the first dose of study drug Active severe cardiac disease	Paclitaxel (200 mg/m² intravenously over 2.5 to 4 hours) first and carboplatin (area under the curve = 6 intravenously over 15 to 60 minutes) immediately after on day 1 of a 21-day cycle during the chemotherapy phase Sorafenib (400 mg orally twice a day) on days 2 through 19 Median number of CP treatment cycles was four Median duration of treatment was 16.6 weeks Control Placebo plus carboplatin and paclitaxel	4.6/5.4; NA; ns (CIs overlap) Progression free survival (time period NR) NR/NR; HR = 1.01; 0.86 – 1.19 Response rate (time period NR) 27.4%/24.0%; NR; 0.102 DCR (time period NR) 50%/56%; NR; NR	Hand-foot skin reaction (%): 23/5 Fatigue (%): 20/21 Nausea (%): 15/17 Sensory neuropathy (%): 14/13 Hypertension (%): 12/6 Pruritus (%): 12/6 Alopecia (%): 11/12 Anorexia (%): 9/6 Vomiting (%): 9/7 Oral mucositis (%): 8/2 Dry skin (%): 7/3 Constipation (%): 7/5 Muscle pain (%): 6/7 Nose haemorrhage (%): 5/2	Allocation concealment: ? Blinding of participants and personal: + Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Relevant cardiac ventricular arrhythmias requiring antiarrhythmic therapy Uncontrolled hypertension Known brain metastases HIV infection or chronic hepatitis B or C Thromboembolic events within the past 6 months History of bleeding diathesis or coagulopathy Serious nonhealing wound, ulcer, or bone fracture Patient characteristics Age (median): 62.0/63.0 Male (%): 63/62 *Performance status* 0 (%): 41/41	Paclitaxel (200 mg/m² intravenously over 2.5 to 4 hours) first and carboplatin (area under the curve = 6 intravenously over 15 to 60 minutes) immediately after on day 1 of a 21-day cycle during the chemotherapy phase Placebo (oral placebo tablets twice a day) on days 2 through 19 Median number of CP treatment cycles was five Median duration of treatment was 16.6 weeks Median duration of treatment was 17.9 weeks			

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	1 (%): 59/59 *Smoking status* Past or present smoker (%): 84/86 *NSCLC classification* Adenocarcinoma (%): 57/59 Large cell carcinoma (%): 5/6 Squamous cell carcinoma (%): 23/25 Other (%): 15/10 *Stage at study entry* IIIB (%): 9/10 IV (%): 91/90 Race White (%): 88/86 Black (%): 4/3 Asian (%): 5/5 Hispanic (%): 2/5	Included/randomised patients 464/462 Analysed patients 463/459 (safety) None (efficacy) Attrition NR Excluded from analysis (reason) 1/3 (safety, not treated)			

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Other (%): 2/2				
Spigel, D.R., et al., Phase II trial of ixabepilone and carboplatin with or without bevacizumab in patients with previously untreated advanced non-small-cell lung cancer. Lung Cancer, 2012. 78(1): p. 70-5.	Region NR Inclusion criteria Unresectable stage III or IV NSCLC (cohort A: all non-small-cell histologies; cohort B: non-squamous tumors only) Measurable disease by radiologic evaluation (RECIST) Adequate organ function Performance status of 0 or 1 Additionally for cohort B: No major surgical procedure <1 month, no primary thoracic radiation <3 months, urine protein/creatinine ratio of	Intervention(s) Bevacizumab 15 mg/kg, ixabepilone 30 mg/m2 and carboplatin AUC = 6 on day 1 of each 21-day treatment cycle Median number of treatment cycles (chemotherapy only) were 6 Control Intravenous ixabepilone 30 mg/m2 over 3-h and carboplatin AUC = 6 calculated by the Calvert formula on day 1 of each 21-day treatment cycle Median number of treatment cycles (chemotherapy only) were 4	Median overall survival (months) 13.2/9.3; NA; ns (CIs overlap) Overall survival (median 15.7 month/17.5 month) 47%/31%; NR; NR Median progression free survival (months) 6.7/5.3; NA; ns (CIs overlap) Response rate (NR) 48%/29%; NR; ns (CIs overlap)	Anemia (%): 27/10 Leukopenia (%): 22/14 Neutropenia (%): 48/31 Febrile neutropenia (%):3/2 Thrombocytopenia (%): 20/19 Cardiac arrhythmia (%): NR/5 Dehydration (%): 8/7 Diarrhea (%): 8/8 Dyspnea (%):10/10 Fatigue (%): 23/10 Hyponatremia (%): 8/5 Infection (%): 20/5 Pain (all types) (%): 28/10 Allergic/hypersensitivity reaction (%): 5/NR	Study type Prospective cohort study Level of evidence 2b- Risk of bias Generation of allocation sequence: - Allocation concealment: - Blinding of participants and personal: - Blinding of outcome assessment:

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	<1.0; absence of non-healing wounds or hemoptysis. Exclusion criteria Prior systemic therapy for advanced Disease Significant cardiovascular disease (including unstable angina, myocardial infarction, or stroke within 6 months of enrolment) Uncontrolled hypertension Untreated central nervous system (CNS) metastases (patients with CNS metastases treated with radiation or surgery were eligible provided there was no evidence of CNS disease progression following treatment)	Included/randomised patients NRAnalysed patients 40/42 Attrition NR Excluded from analysis (reason) 4/4 (not evaluable)		Cough (%): 10/NR Hemorrhagic events (all) (%): 3/NR Vomiting (%): 10/NR	- Incomplete outcome data: ? Selective reporting: + Other source of bias: - (no to control for confounding, statistical significance of results not reported)

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Sufficient recovery from any major surgery Patient characteristics Age (median): 63/63 Male (%): 48/57 *Performance status* 0 (%): 65/33 1 (%): 35/67 *Smoking status* Current smoker (%): 18/36 Former smoker (%): 66/62 Never smoker (%): 18/2 *Histology* Adenocarcinoma (%): 80/31 Squamous (%): 3/47 Large cell (%): 5/7				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Not otherwise specified (%): 12/14 *Stage* IIIB (%): 15/24 IV (%): 67/69 Recurrent (%):18/7 Race Caucasian (%): 93/100 African-American (%): 7/0				
Zhu, J., et al., Carboplatin and paclitaxel with vs without bevacizumab in older patients with advanced non-small cell lung cancer. JAMA, 2012. 307(15): p. 1593-601.	Region Inclusion criteria Aged 65 years or older Stage IIIB or IV non−squamous cell NSCLC (diagnosed between 2002 and 2007) First-line chemotherapy with	Intervention(s) First-line bevacizumab-carboplatin-paclitaxel Diagnoses in 2006-2007 Control First-line carboplatin-paclitaxel Diagnoses in 2006-2007	Overall survival (multivariable-36 month, adjusted model) NR/NR; HR = 0.99; 0.88 – 1.14 NR/NR; HR = 1.06; 0.94 – 1.20 Median Survival (months)	NR	Study type Register-based cohort study Level of evidence 2c Risk of bias Generation of allocation sequence:

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	bevacizumabcarboplatin-paclitaxel or carboplatinpaclitaxel within 4 months of diagnosis Exclusion criteria Other primary cancers diagnosed either before or after NSCLC Death within 30 days of NSCLC diagnosis Patient characteristics Age 65-69 at diagnosis (%): 39.9/33.5/34.2 Age 70-74 at diagnosis (%): 26.4/30.1/32.3 Age 75-79 at diagnosis (%): 24.5/23.5/23.0 Age ≥ 80 at diagnosis (%): 9.1/12.9/10.5	First-line carboplatin-paclitaxel Diagnoses in 2002-2005 Included/randomised patients 318/1844/2666 Analysed patients 318/1182/2664 Attrition NA Excluded from analysis (reason) 0/2/2 (NR)	9.7/8.9/8.0; NA; NR Survival (1 year) 39.6%/40.1%/35.6%; NR; ns (CIs overlap)		- Allocation concealment: - Blinding of participants and personal: - Blinding of outcome assessment: - Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Male (%): 50.9/55.2/52.9 *AJCC stage at diagnosis* IIIB (%): 17.6/29.1/30.6 IV (%): 82.4/70.9/69.4 Race/ethnicity Non-Hispanic white (%): 87.7/83.0/85.1 Non-Hispanic black (%): 4.7/8.3/6.3 Other (%): 7.5/8.7/8.6 *Modified Charlson comorbidity score* 0 (%): 66.0/56.3/62.3 1 (%): 27.7/27.4/24.7 ≥ 2 (%): 6.3/16.3/13.0 *Level of differentiation (tumor grade)* Well/moderately (%): 15.7/10.8/10.4				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Poorly/undifferentiated (%): 26.7/29.2/30.8 Unknown (%): 57.5/60.0/58.8				

+ low risk of bias; - high risk of bias, ? unclear risk of bias, CG: control group; CI: confidence interval; IG: intervention groups; NR: not reported; ns: not statistical significant

Review/reference	Inclusion, exclusion criteria search period	Intervention (IG), control (CG)	Outcomes (HR (CI); I^2 or test of heterogeneity; N; n)	Level of evidence and methodological quality
Soria et al., Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer. Ann Oncol. 2013 Jan;24(1):20-30. doi: 10.1093/annonc/mds590. Epub 2012 Nov 23.	*Inclusion criteria* Randomised, clinical trials comparing bevacizumab plus platinum-based chemotherapy with chemotherapy alone as first-line therapy for inoperable locally advanced (stage IIIB), recurrent or metastatic (stage IV) NSCLC Un-confounded trials, i.e. treatment arms that differed only with regard to bevacizumab administration *Exclusion criteria* - *Search period* Date of search 24 April 2009	*Intervention(s)* Bevacizumab 7.5 mg/kg + carboplatin and paclitaxel (or + cisplatin and gemcitabine) Bevacizumab 15 mg/kg + carboplatin and paclitaxel (or + cisplatin and gemcitabine) *Control* Carboplatin and paclitaxel (or Cisplatin and gemcitabine and placebo (low or high dose))	Overall survival HR = 0.93 (0.76 – 1.14); NR; 2; 756 HR = 0.88 (0.79 – 0.99); NR; 4; 1817 Total HR = 0.90 (0.81 – 0.99); I^2=0%; 6; 2573 Progression free survival (2) HR = 0.75 (0.63 – 0.89); NR; 2; 756 (4) HR = 0.71 (0.63 – 0.79); NR; 4; 1817 Total HR = 0.72 (0.66 – 0.79); I^2=36%; 6; 2573 *Toxicity* Proteinurea 2.4%/0.2%; HR=4.81 (2.28-10.1); I^2=0%; 3; NR Hypertension 8.1%/1.3%; HR=3.69 (2.49-5.47); I^2=16%; 4; NR	*Level of evidence* 1a *Methodological quality* A-priori design: + Two reviewers: + Literature search: + Status of publication: + List of studies: + Study characteristics: + Critical appraisal: + Conclusion: + Combining findings: + Publication bias: - Conflict of interest: -

Review/reference	Inclusion, exclusion criteria search period	Intervention (IG), control (CG)	Outcomes (HR (CI); I^2 or test of heterogeneity; N; n)	Level of evidence and methodological quality
			Thrombosis 8.2%/7.4%; HR=1.03 (0.74-1.43); I^2=36%; 4; NR Haemorrhagic events 4.6%/1.4%; HR=2.67 (1.63-4.39); I^2=0%; 4; NR Neuropathy 4.6%/7.3%; HR=0.84 (0.57-1.23); I^2=0%; 4; NR Neutropenia 40.7%/28.4%; HR=1.53 (1.25-1.87); I^2=0%; 4; NR Febrile neutropenia 3.5%/2.1%; HR=1.72 (1.01-2.95); I^2=0%; 3; NR Thrombocytopenia 24.1%/21.5%; HR=1.17 (0.88-1.55); I^2=0%; 3; NR Anemia 11.5%/12.4%; HR=0.92 (0.64-1.33); I^2=0%; 3; NR	

+ yes; - no, ? can't answer; O not applicable, CG: control group; CI: confidence interval; IG: intervention groups; NR: not reported; ns: not statistical significant

12.2.8. Thema: OMD

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
Lopez Guerra, J.L., et al., Prognostic impact of radiation therapy to the primary tumor in patients with non-small cell lung cancer and oligometastasis at diagnosis. Int J Radiat Oncol Biol Phys, 2012. 84(1): p. e61-7.	Region NR Inclusion criteria Oligometastatic disease (<5 metastases) at diagnosis Receipt of a biologically equivalent dose of 60 Gy in 2-Gy fractions. Exclusion criteria Prior thoracic surgery or radiation therapy Prior or concurrent other malignancy Patient characteristics Age (median): 64 Female (%): 53	Intervention(s) *Brain* Whole-brain irradiation (30 Gy, %): 10 Stereotactic radiosurgery (12-20 Gy, %): 22 Surgery + whole-brain irradiation (%): 6 *Adrenal* Surgery (%): 1 EBRT (45 Gy, %): 1 *Bone* Surgery + EBRT (30 Gy, %): 1 EBRT (30-45 Gy, %): 5	*Overall survival (median 35 months)* NR; HR (no OMD treatment vs. OMD treatment, unadjusted model) = 1.70; 0.041 NR; NR (no OMD treatment vs. OMD treatment, adjusted model); ns *Disease free survival (tmedian 35 months)* NR; HR (no OMD treatment vs. OMD treatment, unadjusted model) = 1.55; 0.099 NR; NR (no OMD treatment vs. OMD treatment, adjusted model); ns	Grade 2 radiation pneumonitis (%): 16.7 Grade 2 esophagitis (%): 39.7 Grade >2 severe pulmonary toxicity (%): 6.4 Grade >2 severe esophageal toxicity (%): 19.4	Study type Registry based prospective cohort study Level of evidence 2c Risk of bias Generation of allocation sequence: - Allocation concealment: - Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Race White (%): 86 African American (%): 12 Asian (%): 2 *Smoking status* Never (%): 5 Former (%): 71 Current (%): 24 Cardiovascular disease history (%): 28 Respiratory disease history (%): 23 *Karnofsky performance status* ≤80 (%): 77 >80 (%): 23 *Primary tumor location* Left lower lobe (%): 17 Left upper lobe (%): 27 Right lower lobe (%): 17	*Lung* EBRT (45-70 Gy, %): 13 Stereotactic radiosurgery (50 Gy, %): 3 *Liver* Radiofrequency ablation (%): 1 *Skin* Surgery (%): 1 EBRT (45 Gy, %): 1 *Axillary nodes or subcutaneous nodules* EBRT (63-70 Gy, %): 8 *Concurrent chemoradiation* No (%): 33			Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Right middle lobe (%): 5 Right upper lobe (%): 34 *Metastasis location* Adrenal (%): 15 Bone (%): 15 Brain (%): 42 Contralateral (%): 15 Axillary lymph nodes (%): 8 Skin (%): 4 Subcutaneous nodules (%): 4 Liver (%): 2 Pancreas (%): 1 Pleural effusion (%): 1 Soft tissue histology (%): 2 Squamous cell (%): 10 Adenocarcinoma (%): 58 NSCLC, not specified (%): 32 *T category*	Yes (%): 67 *Radiation technique* 3-dimensional conformal radiation therapy (%): 27 Intensity modulated radiation therapy (%): 69 Proton beam therapy (%): 4 Radiation dose to the primary tumor (Gy or GyE for protons, median): 63 Included 78 Analysed patients			

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	T0 (%): 3 T1 (%): 21 T2 (%): 32 T3 (%): 19 T4 (%): 26 *N category* N0 (%): 13 N1 (%): 5 N2 (%): 48 N3 (%): 33 Gross tumor volume (cm^3, median): 124 *No. of metastases* 1 (%): 78 2 (%): 13 3 (%): 8 4 (%): 1	64 (OMD treatment)/14(no OMD treatment) Attrition NR Excluded from analysis (reason) NR			

+ yes; - no, ? can't answer; O not applicable, CG: control group; CI: confidence interval; IG: intervention groups; NR: not reported; RT: radio therapy; ns: not statistical significant

12.2.9. Thema: Performance Status 2

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
Girling, D.J., Comparison of oral etoposide and standard intravenous multidrug chemotherapy for small-cell lung cancer: a stopped multicentre randomised trial. Medical Research Council Lung Cancer Working Party. Lancet, 1996. 348(9027): p. 563-6.	Region UK and Ireland Inclusion criteria Previously untreated Microscopically confirmed SCLC WHO performance status 2–4 No contraindication to either treatment Normal renal function Plasma bilirubin below 35 _mol/L Patients with grade 4 performance status had to be likely to benefit from chemotherapy	Intervention(s) Patients received control therapy + four cycles of oral etopside 50 mg twice daily for 10 days every 3 weeks. Control Clinicians chose whether to use four cycles every 3 weeks of intravenous regimen of etoposide and vincristine (EV) or yclophosphamide, doxorubicin, and vincristine (CAV). In the EV group, each cycle was adminstered over 3 days, day 1, etoposide 120 mg/m² by infusion over 30 min,	ORR (1 year) 45%/51%; NR; NR Overall survival (1 year) 11%/13%; HR = 0.74; 0.56 - 0.97 Median Survival (days) 130/183; NA; NR Palliation pf major symptoms score improved (3 month) 41%/46%; NR; similar (according authors)	Alopecia (%): 58/79 Anorexia (%): 42/38 Nausea (%):23/21 Vomiting (%): 13/12 Dysphagia (%):10/8 Sore mouth/mucositis (%): 15/16 Numbness/paraesthesia (%): 5/12 Fever (%): 12/16 Septicaemia (%): 4/7 Bronchopneumonia (%): 5/12 Bleeding (%): 4/1 Anaemia (%): 15/7 Leucopenia (%): 15/13 Neutropenia (%): 14/12	Study type RCT Level of evidence 2b Risk of bias Generation of allocation sequence: + Allocation concealment: - Blinding of participants and personal: - Blinding of outcome assessment: ?

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Exclusion criteria - Patient characteristics Age (median): 67/68 Male (%): 63/61 *Extend of disease* Limited (%): 42/45 Extensive (%): 58/55 Unknown (%): 3/0 PS II (%): 62/63 III(%): 35/36 IV(%): 4/2 Unknown (%): 2/0	vincristine 1.3 mg/m2 by intravenous injection (maximum dose 2.0 mg); days 2 and 3, etoposide 240 mg/m² orally or 120 mg/m² by infusion. In the CAV group, each cycle was administered by intravenous injection on a single daycyclophosphamide 750 mg/m², doxorubicin 40 mg/m², and vincristine 1.3 mg/m² (maximum dose 2.0 mg) Included/randomised patients 171/168 Analysed patients 110/101 (per protocol) 120/121 (safety)		Thrombocytopenia (%): 3/2	Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
		Attrition NR Excluded from analysis (reason) 42/49 (no data available)			
Kosmidis, P.A., Gemcitabine versus Gemcitabine–Carboplatin for Patients with Advanced Non-small Cell Lung Cancer and a Performance Status of 2: A Prospective Randomized Phase II Study of the Hellenic Cooperative Oncology Group. J Thorac Oncol. 2007 Feb;2(2):135-40	Region NR Inclusion criteria At least 18 years of age Histologically confirmed, inoperable, recurrent,or metastatic stage IIIb NSCLC with pleural effusion or stage IV NSCLC ECOG PS of 2 Required to have completed radiotherapy at least 4 weeks before chemotherapy and to	Intervention(s) 1250 mg/m² of gemcitabine via 30-minute infusion with normal saline on days 1 and 14 Repeated every 28 days for two cycles; if patients had partial response, stable disease, or clinical benefit, they received two more cycles Control Same gemcitabine regimen plus carboplatin area under the curve of 3 (Calvert formula) as a 1-	Objective response rate (time period NR) 4%/14%; NR; 0.14 Overall survival (1 year) 17.8%/20%; NR; NR Median survival (months) 4.8/6.7; NA; 0.49 Median progression-free survival (months)	Hospitalizations or deaths (%): 0/0 Neutropenia (%): 8.5/32.5 Severe neutropenia (%): 2/7.5 Thrombocytopenia (%): 0/25 Severe Thrombocytopenia (%): 0/7.5 Anemia (%): 2/7.5 Bleeding (%): 0/0 Infection (%): 0/0	Study type RCT Level of evidence 2b Risk of bias Generation of allocation sequence: ? Allocation concealment: ?

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	have a life expectancy of at least 12 weeks Measurable or assessable disease in nonirradiated fields, unless subsequent disease was documented Patients with stable brain metastases were eligible Patients must have had adequate bone marrow reserve, kidney, and liver functions Exclusion criteria Active infection or a history of other neoplasms (except for basal cell carcinoma of the skin or in situ carcinoma of the cervix)	hour infusion on days 1 and 14 Repeated every 28 days for two cycles; if patients had partial response, stable disease, or clinical benefit, they received two more cycles. Included/randomised patients 47/43 Analysed patients 44/39 Attrition NR Excluded from analysis (reason) 3/4 (NR)	2.98/4.07; NA; 0.36 Improved general feeling (measure NR) 52%/41%; NR; 0.53 Improved (Lung Cancer Symptom Scale) pain 43%/50%; NR; 1.0 Improved cough (Lung Cancer Symptom Scale) 69%/71%; NR; 1.0 Improved fatigue 58%/50%; NR; 1.0		Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Active cardiac disease or preexisting grade 3 or 4 motor or sensory neuropathy Women of childbearing age were required to have a negative pregnancy test within 48 hours of study enrolment Patient characteristics Age (median): 73/70.5 Male (%): 83/72 *Stage* IIIb-IIIb (%): 36/26 IV (%): 64/74 *Prior radiotherapy* Yes (%): 23/28 *Histology*		Improved dyspnea (Lung Cancer Symptom Scale) 75%/33%; NR; 0.24 Improved anorexia (Lung Cancer Symptom Scale) 67%/100%; NR; 0.46 Improved weight loss (Lung Cancer Symptom Scale) 71%/25%; NR; 0.24		

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Squamous cell (%): 28/30 Adenocarcinoma (%): 57/56 Undifferentiated (%): 9/9 Unclassified (%): -/2 Unknown (%): 6/2 *Metastatic sites* Lymph nodes (%): 51/63 Pleural effusion (%): 45/26 Liver (%): 19/23 Bones (%): 34/33 Brain (%): 13/9 Adrenal glands (%): 4/12 *Number of metastatic sites* 1 (%): 38/35 2 (%): 32/42				

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	≥ 3 (%): 26/21 Unknown (%): 4/2				
Lilenbaum, R. Randomized Phase II Trial of Erlotinib or Standard Chemotherapy in Patients With Advanced Non–Small-Cell Lung Cancer and a Performance Status of 2. J Clin Oncol. 2008 20;26(6):863-9	Region NR Inclusion criteria Cytologic or histologic confirmation of stage IIIB (malignant effusion) and IV NSCLC Measurable or assessable disease PS of 2 by Eastern Cooperative Oncology Group criteria Prior radiation was allowed and toxicities had to be resolved before study entry	Intervention(s) Treatment with erlotinib 150 mg orally once daily until progression Control Combination of carboplatin at an area under the curve (AUC) of 6 and paclitaxel at a dose of 200 mg/m², both administered IV on day 1 every 21 days for up to four cycles. Patients who experienced progression or did not tolerate or refused further chemotherapy were	Objective response rate (time period NR) 4%/12%; NR; NR Median overall survival (months) 6.6/9.7; NA; ns Overall survival (time period NR) NR; HR = 0.58; 0.37 - 0.92 Median progression-free survival (months) 1.9/3.5; NA; ns	All (%): 85/98 Rash (%): 65/6 Diarrhea (%): 44/20 Nausea/vomiting (%): 27/55 Anorexia (%): 13/20 Fatigue (%): 13/33 Stomatitis (%): 12/2 Constipation (%): 8/10 Alopecia (%): 6/49 Myalgia/arthralgia (%): 4/20 Neuropathy peripheral (%): 2/37 Anemia (%): 4/20	Study type RCT Level of evidence 2b Risk of bias Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: -

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Brain metastases were eligible if neurologically stable and no longer receiving corticosteroids after appropriate therapy Adequate organ function was required Exclusion criteria Prior chemotherapy or prior EGFR inhibitor therapy Locally advanced disease amenable to combined-modality therapy Patients with gastrointestinal illness that may affect oral absorption, or any other serious medical condition that might impair their	allowed to cross over to erlotinib Included/randomised patients 52/51 Analysed patients 52/51 Attrition 47/49 Excluded from analysis (reason) 0/0	Progression-free survival (time period NR) NR; HR = 0.67; 0.47 - 1.02 Worsening of peripheral neuropathy (EORTC QLQ-LC13) (end of study) 59%/16%; NR; 0.003 Worsening of alopecia (EORTC QLQ-LC13) (end of study) 85%/29%; NR; <0.001 Worsening in chest pain (EORTC QLQ-		Blinding of outcome assessment: - Incomplete outcome data: - Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	ability to receive protocol therapy Patients with concurrent active malignancies, except in situ carcinoma of the cervix and basal cell carcinoma of the skin Patient characteristics ≥ 70 years (%): 46/47 Male (%): 44/55 *Race* White (%): 67/65 African American (%): 23/20 Other (%): 10/15 *Extend of disease* Stage IIIB (%): 13/14 Stage IV (%): 87/86 *Histology*		LC13) (end of study) 15%/37%; NR; 0.004 Worsening of hemoptysis (EORTC QLQ-LC13) (end of study) 0%/24%; NR; 0.078 Worsening of pain in arm/shoulder (EORTC QLQ-LC13) (end of study) 38%/13%; NR; 0.024		

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Adenocarcinoma, BAC (%): 17/6 Adenocarcinoma, no BAC (%): 6/10 Adenocarcinoma, BAC unknown (%): 27/NR Nonadenocarcinoma (%): 50/37 *Smoking history* Never stopped (%): 12/8 Stopped ≤ 1 year (%): 35/49 Stopped > year (%): 54/43				
Lilenbaum, R. Single-Agent Versus Combination Chemotherapy in Advanced Non–Small-Cell Lung Cancer: The Cancer and Leukemia Group B (study 9730).	Region NR Inclusion criteria Cytological or histological confirmation of	Intervention(s) Paclitaxel alone Paclitaxel was administered intravenously over 3 hours at a dose of 225 mg/m², on day 1	Objective response rate (time period NR) 10%/24%; NR; ns Median overall Survival (months)	Toxicities comparable to general study population (according authors) Toxicities of general study population Absolute neutrophil count (%): 32/62	Study type RCT Level of evidence 2b Risk of bias

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
J Clin Oncol. 2005 Jan 1;23(1):190-6. (PS2 subgroup)	stage IIIB (malignant effusion) and IV NSCLC At least 18 years of age Measurable or evaluable disease Adequate hematological, hepatic, and renal function Performance status (PS) of 2 as assessed by standard CALGB criteria Prior radiation therapy was allowed if it did not encompass the index lesion(s) and was completed 2 or more weeks before protocol enrolment Exclusion criteria Prior chemotherapy Locally advanced NSCLC	Repeated every 3 weeks for a maximum of six cycles Patients who developed febrile neutropenia or grade 4 neutropenia lasting more than 5 days received filgrastim in all subsequent cycles Control Paclitaxel in combination with carboplatin Paclitaxel was administered intravenously over 3 hours at a dose of 225 mg/m^2, on day 1 Carboplatin was administered intravenously over 30 minutes, after paclitaxel, at a dose calculated to produce an area under the	2.4/4.7; NA; 0.016 Overall survival (1 year) 10%/18%; HR = 0.60; 0.40 – 0.91 Test of interaction for survival PS0-1 vs. PS2; p = 0.019	Thrombocytopenia (%): 1/12 Anemia (%): 3/12 Infection (%): 5/8 Nausea/vomiting (%): 4/9 Diarrhea (%): 1/4 Neuropathy (%): 14/15 Renal toxicity (%): 0/0 Cardiac toxicity (%): 0/0 Hyperglycemia (%): 18/18 Fatigue (%): 5/7 Any grade 3-4 (%): 73/90 Grade 5 (death) (%): 1/1	Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: ? Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: + Other source of bias: - (subgroup analysis)

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Known brain metastases Previous or concomitant malignancy except for curatively treated carcinoma-in-situ of the cervix or breast, nonmelanoma skin cancer, and nonrecurrent primary tumor treated surgically more than 5 years before enrolment HIV positive Patient characteristics *For general population (NR for subgroup)* Age (median): 63/64 Male (%): 69/68 *Disease stage* IIIB: 17/21 IV/recurrent: 83/87	concentration-time curve (AUC) of 6.0 mg/mL/min Repeated every 3 weeks for a maximum of six cycles Patients who developed febrile neutropenia or grade 4 neutropenia lasting more than 5 days received filgrastim in all subsequent cycles Second-line chemotherapy was given at the physician's discretion, and the regimens used were documented as part of the follow-up Included/randomised patients NR/NR Analysed patients 50/49			

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Performance status 0-1 (%): 82/83 2 (%): 18/17 *Histologic type* Adenocarcinoma: 54/51 Others: 46/45	Attrition NR/NR Excluded from analysis (reason) NR/NR			
Le Chevalier, T. Long Term Analysis of Survival in the European Randomized Trial Comparing Vinorelbine/ Cisplatin to Vindesine/ Cisplatin and Vinorelbine Alone in Advanced Non-Small Cell Lung Cancer. Oncologist 2001;6 Suppl 1:8-11. (PS2 subgroup)	Region 45 European centers Inclusion criteria Age ≤ 75 years Histologically or cytologically proven squamous cell carcinoma, adenocarcinoma, or large-cell carcinoma of the lung WHO performance status (PS) 2 or 3	Intervention(s) 1) Vinorelbine alone at a dose of 30 mg/m² weekly 2) Vinorelbine 30 mg/m² plus cisplatin 120 mg/m² on days 1 and 29 and then every 6 weeks Control Vindesine 3 mg/m² per week for six weeks and then every other week plus cisplatin 120 mg/m² on days 1 and 29 and then every 6 weeks	Median overall survival (months) 17/18/18; NA; ns Overall Survival (1 year) 15%/17%/13%; NR; ns Test of interaction for survival PS0-1 vs. PS2 (platinum containing regimes); ns	NR for subgroup	Study type RCT Level of evidence 2b Risk of bias Generation of allocation sequence: + Allocation concealment: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Inoperability at the time of trial entry, ie, stage III or IV Exclusion criteria Prior malignancy except adequately controlled basal cell carcinoma of the skin Prior chemotherapy Symptomatic brain metastases Preexisting hearing loss Uncontrolled infection Normal blood count Normal liver and renal function at least one unirradiated measurable lesion	Included/randomised patients NR for subgroup Analysed patients NR for subgroup Attrition NR Excluded from analysis (reason) NR			Blinding of participants and personal: ? Blinding of outcome assessment: + Incomplete outcome data: ? Selective reporting: + Other source of bias: - (subgroup analysis)

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Patient characteristics PS2: 46/42/33 PS3: 1/0/4 No others reported for subgroup				
Reynolds, C. Randomized phase III trial of gemcitabine-based chemotherapy with in situ RRM1 and ERCC1 protein levels for response prediction in non-small-cell lung cancer. J Clin Oncol. 2009 1;27(34):5808-15.	Region NR Inclusion criteria Histologically or cytologically newly diagnosed NSCLC Stage IIIB or stage IV PS2 Measurable disease by Response Evaluation Criteria in Solid Tumors Group Age ≥ 18 years	Intervention(s) Gemcitabine and carboplatin was given every 3 weeks at doses of 1,000 mg/m² of gemcitabine on days 1 and 8 and of carboplatin at an area under the curve of 5 on day 1 Control Gemcitabine was given every 3 weeks at a dose of 1,250 mg/m² on days 1 and 8. Up to six cycles of therapy were planned unless there was	Response rate (time period NR) 21.1%/6.3%; NR; 0.01 (but CIs overlap) Median overall survival (months) 6.7/5.1; NA; 0.24 Overall survival (1 year) 31.3%/21.2%; NR; NR	Neutropenia (%): 69.6/18.5 Anemia (%): 39.3/30.8 Thrombocytopenia (%): 50.6/7.4 Febrile neutropenia (%): 0/0 Fatigue (%): 27.8/37.0 Dyspnea (%): 26.6/30.8 Anorexia (%): 15.2/19.8 Nausea (%): 11.4/12.3 Pneumonia (%): 6.3/11.1 Dehydration (%): 6.3/9.9 Diarrhea (%): 3.8/8.6	Study type RCT Level of evidence 2b Risk of bias Generation of allocation sequence: ? Allocation concealment: ?

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Adequate organ function Exclusion criteria Prior chemotherapy Patient characteristics Age (median): 72.9/75.0 Male (%): 55.3/56.5 *Stage* IIIB (%): 15.3/5.9 IV (%): 83.4/94.1 Unknown (%):2.4 /0 Histology Adenocarcinoma (%): 62.3/52.9 Squamous carcinoma (%): 16.5/25.9 Other (%): 21.2/21.2	evidence for disease progression or intolerable toxicity Included/randomised patients 85/85 Analysed patients 85/85 Attrition 18/16 Excluded from analysis (reason) 0/0	Median progression-free survival (months) 3.8/2.7; NR; 0.14	Vomiting (%): 5.1/6.2 Pleural effusion (%): 6.3/3.7 Dizziness (%): 6.3/2.5 Rash (%): 3.8/1.2 Chest pain (%): 2.5/4.9 Alopecia (%): 2.5/0	Blinding of participants and personal: ? Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: - results for response rate inconsistently

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
Zukin, M. Randomized phase III trial of single-agent pemetrexed versus carboplatin and pemetrexed in patients with advanced non-small-cell lung cancer and Eastern Cooperative Oncology Group performance status of 2. J Clin Oncol. 2013 10;31(23):2849-53	Region Eight centers in Brazil and one in the United States Inclusion criteria Cytologic or histologic confirmation of stages IIIB (malignant effusion) and IV NSCLC ECOG PS of 2 Toxicities had to be resolved before study entry if there was prior irradiation Neurologically stable condition and no longer receiving of corticosteroids after appropriate therapy if patients had brain metastases	Intervention(s) Pemetrexed 500 mg/m² All patients received premedications with dexamethasone, vitamin B12, and folic acid according to the pemetrexed label Control Combination of carboplatin at an area under the curve of 5 and pemetrexed 500 mg/m², both administered intravenously on day 1 every 21 days for up to four cycles All patients received premedications with dexamethasone, vitamin B12, and folic acid according to the pemetrexed label	Objective response rate (time period NR) 6.9%/18.4%; NR; NR Median overall survival (months) 5.3/9.3; NA; 0,001 Overall survival (36 month) NR; HR=0.62; 0.46 – 0.83 Median progression-free survival (months) 2.8/5.8; NA; 0.35 – 0.63	Anemia (%): 3.9/11.7 Thrombocytopenia (%): 0.0/1.0 Neutropenia (%): 1.0/6.8 Febrile neutropenia (%): 2.9/1.0 Nausea/emesis (%): 1.0/4.9 Diarrhea (%): 2.0/1.0 Dyspnea (%): 10.8/5.8 Grade 5 event (%): 0.0/3.9	Study type 2b Level of evidence RCT Risk of bias Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: ? Blinding of outcome assessment: + Incomplete outcome data: -

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Adequate organ function, including glomerular filtration rate ≥ 45 mL/min Exclusion criteria Squamous cell histology (by protocol amendment in May 2009, when 14 such patients had been enrolled) Prior chemotherapy Locally advanced disease amenable to combined-modality therapy Concurrent active malignancies, except in situ carcinoma of the cervix and basal cell carcinoma of the skin Patient characteristics	Dose reductions of chemotherapy according to prespecified guidelines based on episodes of febrile neutropenia, grade 4 thrombocytopenia and/or bleeding, and any grade 3 or 4 nonhematologic toxicity except nausea/emesis Treatment delays of up to 3 weeks were allowed Included/randomised patients 109/108 Analysed patients 102/103 Attrition 33/19 Excluded from analysis (reason)	**Progression-free survival (1 year)** 2%/17%; NR; NR		Selective reporting: + Other source of bias: +

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Age (median): 65/65 Male (%): 58.8/63.1 Disease stage IIIB (%): 4.9/5.8 IV (%): 95.1/94.2 Weight loss ≥ 5% (%) 53.9/58.3 Histology Adenocarcinoma (%): 80.4/82.5 Squamous cell (%): 10.8/2.9 Unknown (%): 4.9/4.9 Smoking status Current (%): 10.8/17.3 Former (%): 66.7/60.2 Never (%): 22.5/22.5 Comorbidities	7/5 (not received any treatment)			

Study/Reference	Region, inclusion criteria, exclusion criteria and baseline characteristics (IG_n/CG) of study population	Intervention(s), control and patient flow (IG_n/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG_n/CG)	Study type, level of evidence and risk of bias
	Hypertension (%): 45.1/44.7 COPD (%): 17.6/11.7 Diabetes mellitus (%): 7.8/12.6				

+ low risk of bias; - high risk of bias, ? unclear risk of bias, CG: control group; CI: confidence interval; IG: intervention groups; NR: not reported; not statistical significant

Review/reference	Inclusion, exclusion criteria search period (patients marked bold)	Intervention (IG), control (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; I^2/ Q; N; n) or (effect direction; number of studies showing effect direction; number of significant studies showing effect direction; total number of studies)	Level of evidence and methodological quality
Mörth, C. Single-agent versus combination chemotherapy as first-line treatment for patients with advanced non-small cell lung cancer and performance status 2: a literature-based meta-analysis of randomized studies. Lung Cancer. 2014 84(3):209-14.	*Inclusion criteria* Randomized trial Evaluation of the administration of combination versus single-agent chemotherapy in untreated patients with advanced NSCLC and PS 2 (Eastern	*Intervention(s)* Combination platinum-based chemotherapy Combination non-platinum-based chemotherapy *Control*	Overall survival HR 0.71 (0.61 – 0.81); 2%; 8; 862 HR 0.96 (0.80 – 1.15); 0%; 3; 252 Progression-free survival	*Level of evidence* 1a *Methodological quality* A-priori design: +

Review/reference	Inclusion, exclusion criteria search period (patients marked bold)	Intervention (IG), control (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; I^2/ Q; N; n) or (effect direction; number of studies showing effect direction; number of significant studies showing effect direction; total number of studies)	Level of evidence and methodological quality
	Cooperative Oncology Group scale) Trials dedicated to PS2 patients Trials performed a subset analysis according to PS *Exclusion criteria* Non-randomized trials Combination chemotherapy in both treatment arms Trials that included patients with PS 3 or pretreated patients *Search period* Last search was updated in July 2013 without year restriction	Single-agent chemotherapy	1) HR 0.61 (0.45 – 0.84); NR; 4; 522 Objective response rate OR 3.10 (1.85 – 5.21); NR; 6; 651 OR 0.63 (0.23 – 1.72); NR; 2; 207 Toxicity (grade II and IV) Hematologic anemia OR 3.12 (1.55 – 6.27); NR; 4; 519 Trombocytopenia OR 12.81 (4.65 – 33.10); NR; 4; 519 Neutropenia OR 7.91 (3.97 – 15.78); NR; 4: 519 Non-hematologic febrile neutropenia OR 0.32 (0.05–2.06); NR; 3; 432	Two reviewers: ? Literature search: ? Status of publication: + List of studies: - Study characteristics: + Critical appraisal: - Conclusion: + Combining findings: + Publication bias: - Conflict of interest: +

Review/reference	Inclusion, exclusion criteria search period (patients marked bold)	Intervention (IG), control (CG)	Outcomes (RR [CI] / OR [CI] / MD [CI] / SDM [CI]; I^2/ Q; N; n) or (effect direction; number of studies showing effect direction; number of significant studies showing effect direction; total number of studies)	Level of evidence and methodological quality
			Fatigue OR 0.75 (0.40–1.40); NR; 3; 349 Nausea OR 1.21 (0.05–29.34); NR; 3; 432	

+ yes; - no, ? can't answer; O not applicable, CG: control group; CI: confidence interval; IG: intervention groups; NR: not reported

12.2.10. Thema: Palliativmedizin

Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
Badr, H., et al., Dyadic psychosocial intervention for advanced lung cancer patients and their family caregivers: Results of a randomized pilot trial. Cancer, 2014. 00: p. 1-9.	Region/Setting USA, single center, home based care Inclusion criteria Patients with advanced LC and were within 1 month of treatment initiation (any line of therapy) Spending more than 50% of their time out of bed on a daily basis, as measured by an Eastern Cooperative Oncology Group performance status ≤2 Spouse/partner or other close family member whom they identified as their primary caregiver Both patients and caregivers had to ≥18 years Ability to read and understand English Exclusion criteria NR	Intervention(s) Manual with six items: Self-care, stress and coping, symptom management, effective communication, problem solving, maintaining and enhancing relationships. Approximately half the content of each item was the same for patients and caregivers, and half was tailored to the person's role (patient or caregiver). Tailored content for patients included strategies for balancing autonomy with soliciting/accepting support, disclosing care/support needs, and supporting/acknowledging the caregiver. Tailored content for caregivers included strategies for minimizing overprotection and negative interaction patterns (eg,	Depression (Patient Reported Outcomes Measurement Information System, 8 weeks); 11.65/16.00; SMD= -1.8; <.0001 Anxiety (Patient Reported Outcomes Measurement Information System, 8 weeks); 12.35/14.84; SMD= -1.3; <.0001	Study type RCT Level of evidence 2b Risk of bias Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data:

Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	Patient characteristics Female (%): 74 Age (mean, SD): 68.17, 10.30 White (non-Hispanic) (%): 85 *Employment status* Employed full-time (%): 15 Employed part-time (%): 23 Unemployed/retired (%): 62 *Education* High school diploma or less (%): 14 At least some college (%): 38 College degree (%): 48 *Caregiver relationship to the patient* Spouse/partner (%): 51 Son/daughter (%): 31 Other family member (ie, sibling, cousin, or parent) (%): 18 Married (%): 59	nagging and criticizing) and for supporting the patient's self-care goals. 6 weekly 60-minute telephone counselling sessions with a trained interventionist During sessions, the interventionist reviewed homework and manual content, guided participants through in-session activities, and assigned the next week's homework Control Usual palliative care Management of pain, distress, anxiety through oncology practice and psychiatry, social work and home based visiting nurse Included/randomised patients 20 / 19 Analysed patients		+ Selective reporting: + Other source of bias: +

Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	Length of marriage (mean, SD): 36.20, 8.70 *Type of lung cancer* SCLC (%): 16 NSCLC (%): 84 *Stage of cancer* Stage 3 NSCLC (%): 26 Stage 4 NSCLC (%): 58 Extensive-stage SCLC (%): 16	20/19 dyads Attrition 0/1 Excluded from analysis (reason) NA		
Bakitas, M., et al., Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. JAMA, 2009. 302(7): p. 741-9.	Region/Setting USA, two sites Inclusion criteria 8 to 12 weeks of a new diagnosis of gastrointestinal tract (unresectable stage III or IV), lung (stage IIIB or IV non-small cell or extensive small cell), genitourinary tract (stage IV), or breast (stage IV and visceral crisis, lung or liver metastasis, estrogen receptor negative , human	Intervention(s) Advanced practice nurses with palliative care specialty training conducted 4 initial structured educational and problem- solving sessions Manual for: 1) problem solving 2) communication and social	Quality of life (Functional Assessment of Chronic Illness Therapy for Palliative Care scores, 13 month); 78/72; MD= 8.6; 0.02 Symptom intensity (Edmonton Symptom Assessment Scale, 13 month); 80/74; MD= −24.2; 0.24	Study type RCT Level of evidence 2b Risk of bias Generation of allocation sequence: + Allocation concealment:

Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	epidermal growth factor receptor 2 positive) cancer Exclusion criteria Patients with impaired cognition (<17 on a modified Mini-Mental State Examination),18 an Axis I psychiatric disorder (schizophrenia, bipolar disorder), or active substance use Patient characteristics Age (mean, SD): 65.47, 10.3/65.2, 11.7 Male (%): 62.1/58.2 *Marital status* Never married (%): 6.9/8.2 Married or living with partner (%): 73.1/67.2 Divorced or separated (%): 11.0/13.4 Widowed (%): 9.0/11.2 *Education* < High school graduate (%): 11.7/14.9	support 3) symptom management, 4) advance care planning and unfinished business, Appendix listing supportive care resources Caregivers also were invited and encouraged to participate in these sessions Follow up until patient died or study ended Control All oncology and supportive services without restrictions including referral to the institutions' interdisciplinary palliative care service. Included/randomised patients 161/161 Analysed patients	Depressed mood (Center for Epidemiological Studies Depression Scale, 13 month); 78/73; MD= −2.7; 0.03 Median survival (months, median follow-up 10.7); 14/8.5; NR; NR Survival (median follow-up 10.7); 30.4/26.1; NR; 0.14	? Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	High school graduate (%): 57.2/55.2 College graduate (%): 29.7/28.4 Missing (%): 1.4/1.5 *Race (no Hispanic or black)* White (%): 98.6/98.5 Other (%): 0.7/0.7 Missing (%): 0.7/0.7 *Religion* Protestant (%): 46.9/44.8 Catholic (%): 30.3/31.3 Jewish (%): 2.1/0.7 Other (%): 17.2/21.6 Missing (%): 3.4/1.5 *Work status* Employed (%): 20.0/16.4 Retired (%): 51.7/52.2 Not employed (%): 26.2/30.6 Missing (%): 2.1/0.7	145/134 Attrition 16/9 Excluded from analysis (reason) 16/ 27 (not received intervention)		

Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	VA medical center enrollment site (%): 27.6/27.6 Lives in rural area (%): 52.4/60.5 Caregiver enrolled (%): 77.2/68.7 *Primary disease site* Gastrointestinal tract (%): 42.1/43.3 Lung (%): 34.5/32.1 Genitourinary tract (%): 13.1/13.4 Breast (%): 10.3/11.2 *Anticancer treatment at enrollment* Chemotherapy (%): 73.8/71.6 Radiation therapy (%): 20.7/22.4 Karnofsky Performance Status (mean, SD): 78.4, 11.1/77.4, 12.8 *Type of advance directive* Living will (%): 43.4/49.2 Durable power of attorney for health care (%): 42.8/50.0 Do not resuscitate order (%): 7.6/5.2			

Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	Referral to hospice (%): 2.8/1.5 Referral to palliative care (%): 23.4/29.1 *Resource use in prior 3 momths (mean)* Hospital days: 2.6/2.8 Intensive care unit days: 0.03/0.05 Emergency department visits: 0.28/0.38			
Greer, J.A., et al., Effect of early palliative care on chemotherapy use and end-of-life care in patients with metastatic non-small-cell lung cancer. J Clin Oncol, 2012. 30(4): p. 394-400.	Region/Setting USA, cancer center Inclusion criteria Pathologically confirmed metastatic NSCLC diagnosed within the previous 8 weeks, an Eastern Cooperative Oncology Group performance status ranging from 0 (asymptomatic) to 2 (symptomatic and in bed < 50% of day) Exclusion criteria NR	Intervention(s) Adapted guidelines from the National Consensus Project for Quality Palliative Care Consulted with a member of the palliative care team, consisting of board-certified palliative care physicians and advanced-practice nurses, within 3 weeks of enrollment and at least monthly thereafter in the outpatient setting until death. Clinicians and patients could schedule additional palliative care consultations at their discretion	Chemotherapy use within 60 days of death (18 months); 52.5%/ 70.1%; OR=0.47; 0.23 - 0.99; (adjusted for age, sex, and baseline performance status) Median time to switch from first to second line chemotherapy (18 months); 7.4/7.5; NA; 0.79	Study type RCT Level of evidence 2b Risk of bias Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal:

Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	Patient characteristics Age (mean, SD): 64.98, 9.73/64.87, 9.41 Female (%): 54.5/48.6 *Race* White (%): 100.0/94.6 Black (%): 0.0/4.0 Asian (%): 0.0/1.4 *Ethnicity* Hispanic/Latino (%): 1.3/1.4 *Marital status* Married (%): 62.3/60.8 Single (%): 11.7/12.2 Divorced/separated (%): 15.6/16.2 Widowed (%): 10.4/10.8 *ECOG PS* 0 (%): 33.8/40.5 1 (%): 59.7/47.3 2 (%): 6.5/12.2	Palliative care clinicians assessed physical and psychosocial symptoms, helped to clarify the disease process, established goals of care, assisted with treatment decisions, and coordinated care Control Patients met with the palliative care service on request from the patient, family or oncologist Included/randomised patients 77/74 Analysed patients 77/74 Attrition 2/2 Excluded from analysis (reason) NA	Median time to switch from second to third chemotherapy (18 months); 5.0/5.3; NA; 0.53	- Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	Initial anticancer therapy Platinum-based combined chemotherapy (%): 45.5/47.3 Single agent (%): 11.7/4.1 Oral EGFR-TKI (%): 7.8/8.1 Radiation (%): 35.1/35.1 Combined chemoradiotherapy (%): 0.0/4.1 No treatment (%): 0.0/1.4			
Temel, J.S., et al., Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med, 2010. 363(8): p. 733-42. Pirl, W.F., et al., Depression and survival in metastatic non-small-	Region/Setting USA, single center Inclusion criteria Confirmed metastatic NSCLC, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2 Service were not eligible to participate in the study. 77 to EPC integrated with standard care and 74 to standard care alone.	Intervention(s) Early Palliative Care At least monthly meetings with palliative care team, which consisted of board-certified palliative care physicians and advanced practice nurses in the ambulatory setting until death. Following general guidelines for the ambulatory palliative care visits, adapted from the National consensus Project for Quality Palliative Care.	Quality of life (total Functional Assessment of Cancer Therapy–Lung, 12 weeks); 98.0/91.5; adjusted MD= 5.4; 0.7 - 10.0 (adjusted for baseline) Quality of life (Trial outcome index (FACT-L), 12 weeks);	Study type RCT Level of evidence 2b Risk of bias Generation of allocation sequence: ? Allocation concealment:

Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
cell lung cancer: effects of early palliative care. J Clin Oncol, 2012. 30(12): p. 1310-5.	Exclusion criteria Patients who were already receiving care from the palliative care Patient characteristics Age (mean, SD): 64.98, 9.73/64.87, 9.41 Female (%): 55/49 *Race* White (%): 77/95 Black (%): 0/4 Asian (%): 0/1 Hispanic or Latino ethnic group (%): 1/1 *Marital status* Married (%): 62/61 Single (%): 12/12 Divorced or separated (%): 12/12 Widowed (%): 10/11 *ECOG performance status*	Routine oncology care 6 Participants randomly assigned to the standard Control Standard care Only meet palliative care team when meeting was requested by the patient, the family, or the oncologist Routine oncology care Included/randomised patients 77/74 Analysed patients 77/74 Attrition 0 Excluded from analysis (reason) NA	59.0/53.0, adjusted MD= -5.2; 1.6 - 8.9 (adjusted for baseline) Quality of life (Lung cancer subscale (FACT-L), 12 weeks); 21.0/19.3; adjusted MD= -1.0; -0.2 - 2.3 (adjusted for baseline) Depression (Patient Health Questionnaire 9, change from baseline to 12 weeks); -0.96/ 0.06; NR; <.001 Overall mortality (12 weeks); 12.99%/22.97%; NR; NR	? Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: + Other source of bias: +

Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	0 (%): 34/41 1 (%): 60/47 2 (%): 6/12 Presence of brain metastases (%): 31/26 *Initial anticancer therapy* Platinum-based combination chemotherapy (%): 45/47 Single agent (%): 12/4 Oral EGFR tyrosine kinase inhibitor (%): 6/6 Radiotherapy (%): 35/35 Chemoradiotherapy (%): 0/4 No chemotherapy (%): 0/1 Receipt of initial chemotherapy as part of a clinical trial (%): 21/27 Never smoked or smoked ≤10 packs/year (%): 24/22 *Assessment of mood symptoms* Anxiety subscale (HADS, %): 36/33 Depression subscale (HADS, %): 22/25		Unplanned contact (Mental Health visits, 12 weeks); 25%/35%; NR; 0.16	

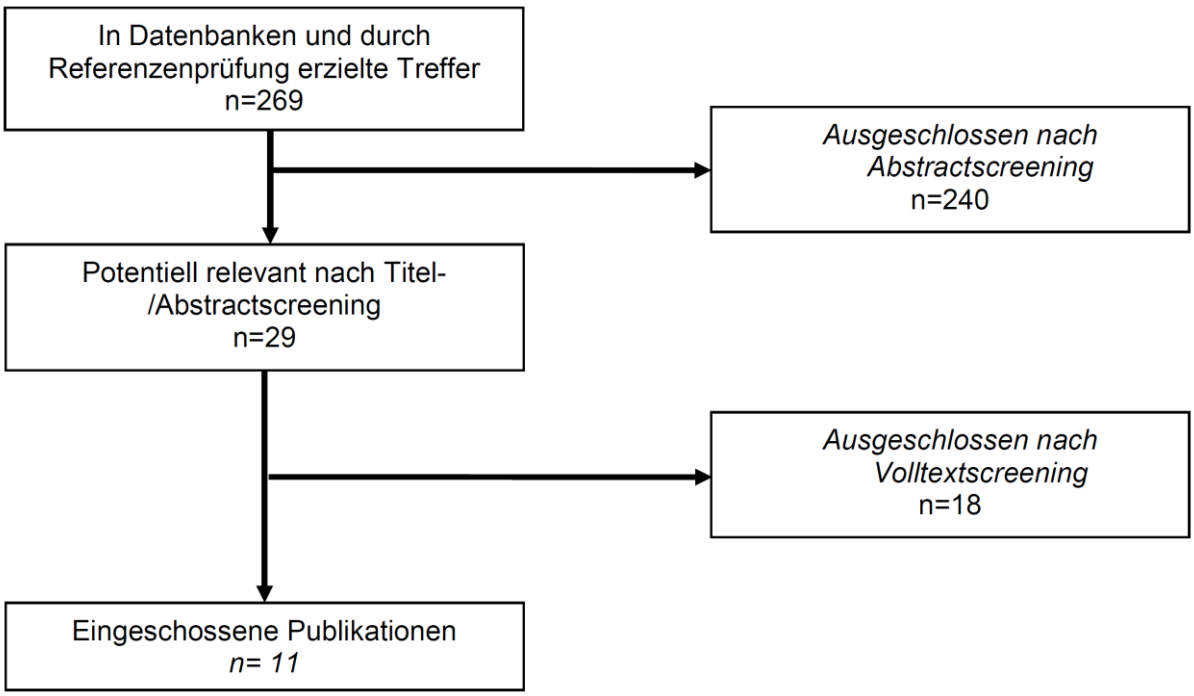
Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG_n/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	PHQ-9 major depressive syndrome (%): 12/17 *Scores on quality-of-life measures* FACT-L scale (mean, SD): 93.6, 16.5 /91.7, 16.7 Lung-cancer subscale (mean, SD): 20.1, 4.4 /18.7, 4.4 Trial Outcome Index (mean, SD): 56.2,13.4 /55.3, 13.1			

12.3. Studienselektion

Nachgereicht Kliniker

Eingeschlossen: 11 Publikationen (teilweise in Updaterecherche enthalten)

Update Recherche Maintenance, molekular stratifizierte Therapie und Anti-VEGF



Maintenance

3 Studien (4 Publikationen)

Molekular stratifiziert

5 Studien (7 Publikationen)

Anti-VEGF

8 Studien (8 Publikationen)

Nachscreening Maintence Palceb-Kontrolle

Eingeschlossen: 8 Studien (11 Publikationen)

12.4. Recherche nach bestehenden Qualitätsindikatoren zum Lungenkarzinom

Die Recherche wurde vom OL-Office (Thomas Langer) am 31. August 2016 durchgeführt.

Als Recherchevokabular wurden folgende Begriffe verwendet:

Population: lung cancer

Intervention: quality/health/performance/outcome/process und indicator(s)/ measure* / criterion/ assessment/

Qualitätsindikator; Qualitätsindikatoren

Bei der Suche erfolgte keine Einschränkung des Suchzeitraums oder bzgl. der Sprache. Die Suche wurde in den folgenden Quellen durchgeführt.

12.4.1. Nationale Qualitätsindikatorenprojekte/-programme

- AQUA-Institut, Internetseite zur Sektorenübergreifenden Qualitätssicherung über http://www.sqg.de/ergebnisse/leistungsbereiche/index.html
- AQUA-Institut, QISA – Qualitätsindikatorensystem für die ambulante Versorgung über Ordner im Büro DR (nicht online verfügbar)
- BQS-Institut, Qualitätsindikatorendatenbank über http://www.bqs-qualitaetsindikatoren.de/
- GKV-Spitzenverband, Qualitätsindikatoren-Thesaurus über http://quinth.gkv-spitzenverband.de/content/suche.php
- GKV-Spitzenverband, Qualitätssicherung Medizinische Rehabilitation über http://www.qs-reha.de/indikationen/indikationen.jsp
- KBV, AQUIK Ambulante Qualitätsindikatoren und Kennzahlen über http://www.kbv.de/23546.html

12.4.2. Internationale Qualitätsindikatorenprojekte/-programme

- AHRQ (Agency for Health Research and Quality) Quality Indicators über http://www.qualityindicators.ahrq.gov/
- AHRQ (Agency for Health Research and Quality) National Quality Measures Clearinghouse über http://www.qualitymeasures.ahrq.gov/
- AMA (American Medical Association) Set of Indicators http://www.ama-assn.org/ama/pub/physician-resources/physician-consortium-performance-improvement.page?
- ASCO (American Society of Clinical Oncology) National Initiative for Cancer Care Quality http://www.asco.org/institute-quality/national-initiative-cancer-care-quality-niccq

- ASCO (American Society of Clinical Oncology)Quality Oncology Practice Initiative http://qopi.asco.org/index.html
- ASCO (American Society of Clinical Oncology) + NCCN (National Comprehensive Cancer Network) Set of quality indicators http://www.asco.org/institute-quality/asco-nccn-quality-measures
- CIHI (Canadian Institute for Health Information) Health Indicators über http://www.cihiconferences.ca/indicators/2012/definitions12_e.html
- CQCO (Cancer Quality Council of Ontario) Cancer System Quality Index – set of indicators http://www.csqi.on.ca/all_indicators/#.UlJ9iW25OH4
- ISD Scotland Health Indicators über http://www.indicators.scot.nhs.uk/Reports/Main.htm
- Healthcare Improvement Scotland
- http://www.healthcareimprovementscotland.org/programmes/cancer_care_improvement/cancer_resources/cancer_qpis.aspx
- JCAHO (Joint Commission on Accrediation of Healthcare Organizations) über http://www.jointcommission.org/accountability_measures.aspx
- NHS (National Health Services) Indicators for Quality Improvement über https://mqi.ic.nhs.uk/
- NQF (National Quality Forum) Performance Measures über http://www.qualityforum.org/QPS/ → Find Measures
- OECD Health Care Quality Indicators über http://www.oecd.org/health/healthpoliciesanddata/healthcarequalityindicators.htm
- RAND Corporation Quality of Care Assessment Tools (QA Tools) über http://www.rand.org/health/surveys_tools/qatools.html
- Niederländisches onkologisches Leitlinienprogramm – Oncoline über www.oncoline.nl
- Belgisches HTA- und Leitlinieninstitut -KCE über www.kce.fgov.be

12.4.3. Literaturdatenbanken

- Medline über http://www.pubmed.org
- The Cochrane Library über http://www.thecochranelibrary.com

Recherchestrategie und -vokabular richten sich nach den Möglichkeiten der jeweiligen Recherchequelle, wurden entsprechend modifiziert und unter „Recherchestrategien“ dargelegt.

12.4.4. Freie Internetrecherche

Mit den unter Kapitel 12.4 aufgeführten Begriffen wurde unter Verwendung von Suchmaschinen im Internet gesucht.

Die Recherche national und international bereits bestehender Qualitätsindikatoren in den genannten Quellen erfolgte mit folgender Recherchestrategie:

12.5. Recherchestrategien

12.5.1. PubMed (31. August 2016)

Search	Query	Items found
	((lung neoplasm[mesh]) OR ((lung OR pulmonary OR bronchial OR respiratory) AND (cancer* OR carcinoma* OR neoplasm* OR tumour* OR tumor*))) AND (("quality indicator" OR "quality indicators" OR "quality measure" OR "quality measures" OR "performance measure" OR "performance measures" OR "performance indicator" OR "performance indicators" OR "indicator of quality" OR "indicators of quality") AND ("last 10 years"[PDat])))	606

Anzahl der Treffer nach Titel- und Abstractsichtung: 20

12.5.2. Cochrane (31. August 2016)

Nr.	Suchfrage	Anzahl
#1	(quality or performance or health):ti	41157
#2	(indicator or indicators or measure or measures):ti	4662
#3	#1 and #2	706
#4	cancer* or carcinoma* or neoplasm* or tumour* or tumor*	124413
#5	lung or pulmonary or bronchial or respiratory	95429
#6	#4 and #5	17644
#7	#3 and #6	6

Anzahl der Treffer nach Titel und Abstraktsichtung: 0

12.5.3. Homepages von Leitlinienorganisationen

Institution	Quelle	Treffer
AQUA-Institut	Internetseite zur Sektorenübergreifenden Qualitätssicherung über http://www.sqg.de/ergebvnisse/leistungsbereiche/index.html	0
	QISA – Qualitätsindikatorensystem für die ambulante http://www.aok-gesundheitspartner.de/bund/qisa/themen/index.html	0
BQS-Institut	Qualitätsindikatorendatenbank über http://www.bqs-qualitaetsindikatoren.de/	0

Institution	Quelle	Treffer
GKV-Spitzenverband	Qualitätsindikatoren-Thesaurus über http://quinth.gkv-spitzenverband.de/content/suche.php	11
GKV-Spitzenverband	Qualitätssicherung Medizinische Rehabilitation über http://www.qs-reha.de/indikationen/indikationen.jsp	0
KBV	AQUIK Ambulante Qualitätsindikatoren und Kennzahlen über http://www.kbv.de/23546.html	0
AHRQ (Agency for Health Research and Quality) Quality Indicators	über http://www.qualityindicators.ahrq.gov/	0
AHRQ (Agency for Health Research and Quality) National Quality Measures Clearinghouse	http://www.qualitymeasures.ahrq.gov/	7
AMA (American Medical Association)	http://www.ama-assn.org/ama/pub/physician-resources/physician-consortium-performance-improvement.page	0
ASCO (American Society of Clinical Oncology)Quality Oncology Practice Initiative	http://qopi.asco.org/index.html	4
CIHI (Canadian Institute for Health Information) Health Indicators	http://www.cihiconferences.ca/indicators/2012/definitions12_e.html	0
CQCO (Cancer Quality Council of Ontario) Cancer System Quality Index – set of indicators	http://www.csqi.on.ca/all_indicators/#.UlJ9iW25OH4	3
Healthcare Improvement Scotland	http://www.healthcareimprovementscotland.org/our_work/cancer_care_improvement/cancer_qpis.aspx	13
JCAHO (Joint Commission	http://www.jointcommission.org/accountability_measures.aspx	0

Institution	Quelle	Treffer
on Accreditation of Healthcare Organizations)		
NQF (National Quality Forum) Performance Measures	http://www.qualityforum.org/QPS/	1
OECD Health Care Quality Indicators	http://www.oecd.org/health/healthpoliciesanddata/healthcarequalityindicators.htm	0
RAND Corporation Quality of Care Assessment Tools (QA Tools) über	http://www.rand.org/health/surveys_tools/qatools.html	12
Oncoline (Niederlande)	http://oncoline.nl/index.php	0
KCE (Belgien)	https://kce.fgov.be/	23

Die Recherche führte zu keinen nationalen QI, aber einer Reihe internationaler QI, die in einem Dokument zusammengefasst wurden. Diese kann auf Anfrage beim OL-Office eingesehen werden.

12.6. Levels of Evidence

Level 1A	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	1a SR (with homogeneity*)of RCTs SR (withhomogeneity*) of inception cohort studies; CDR† validated in different populations SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres SR (with homogeneity*) of prospective cohort studies SR (with homogeneity*) of Level 1 economic studies
Level 1b	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Individual RCT (with narrow Confidence Interval‡) Individual inception cohort study with > 80% follow-up; CDR† validated in asingle population Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre Prospective cohort study with good follow-up**** Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
Level 1c	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	All or none§ All or none case series Absolute SpPins and SnNouts†† All or none case-series Absolute better-value or worse-value analyses ††††
Level 2a	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	SR (with homogeneity*) of cohort studies SR (withhomogeneity*) of either retrospective cohort studies or untreated control groups in RCTs SR (with homogeneity*) of Level >2 diagnostic studies SR (with homogeneity*) of 2b and better studies SR (withhomogeneity*) of Level >2 economic studies
Level 2b	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Individual cohort study (including low quality RCT; e.g., <80% followup) Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split sample §§§ only Exploratory** cohort study with good††† reference standards; CDR† after derivation, or validated only on split-sample§§§ or databases Retrospective cohort study, or poor follow-up Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
Level 2c	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	"Outcomes" Research; Ecological studies "Outcomes" Research Ecological studies Audit or outcomes research
Level 3a	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	SR (with homogeneity*) of case-control studies SR (with homogeneity*) of 3b and better studies SR (with homogeneity*) of 3b and better studies SR (with homogeneity*) of 3b And better studies
Level 3b	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Individual Case-Control Study Non-consecutive study; or without consistently applied reference standards Non-consecutive cohort study, or very limited population Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses IIncorporatingclinically sensible variations.
Level 4	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Case-series (and poor quality cohort and casecontrol studies§§) Case-series (and poor quality prognostic cohort studies***) Case-control study, poor or nonindependent reference standard Case-series or superseded reference standards Analysis with no sensitivity analysis
Level 5	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

12.7. Cochrane Risk of Bias Tool

Domain	Description	Review authors' judgement
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors *Assessments should be made for each main outcome (or class of outcomes)*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes)*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcome data adequately addressed?
Selective outcome reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Was the study apparently free of other problems that could put it at a high risk of bias?

12.8. QUADAS II

Domain	Patient Selection	Index Test	Reference Standard	Flow and Timing
Description	Describe methods of patient selection Describe included patients (previous testing, presentation, intended use of index test, and setting)	Describe the index test and how it was conducted and interpreted	Describe the reference standard and how it was conducted and interpreted	Describe any patients who did not receive the index tests or reference standard or who were excluded from the 2 × 2 table (refer to flow diagram) Describe the interval and any interventions between index tests and the reference standard
Signaling questions (yes, no, or unclear)	Was a consecutive or random sample of patients enrolled? Was a case–control design avoided? Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard? If a threshold was used, was it prespecified?	Is the reference standard likely to correctly classify the target condition? Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between index tests and reference standard? Did all patients receive a reference standard? Did all patients receive the same reference standard? Were all patients included in the analysis?
Risk of bias (high, low, or unclear)	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns about applicability (high, low, or unclear)	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or its interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

12.9. QUIPS

Variable	Bias Domains			
	1. Study Participation	**2. Study Attrition**	**3. Prognostic Factor Measurement**	**4. Outcome Measurement**
Optimal study or characteristics of unbiased study	The study sample adequately represents the population of interest	The study data available (i.e., participants not lost to follow-up) adequately represent the study sample	The PF is measured in a similar way for all participants	The outcome of interest is measured in a similar way for all participants
Prompting items and considerations†	a. Adequate participation in the study by eligible persons	a. Adequate response rate for study participants	a. A clear definition or description of the PF is provided	a. A clear definition of the outcome is provided
	b. Description of the source population or population of interest	b. Description of attempts to collect information on participants who dropped out	b. Method of PF measurement is adequately valid and reliable	b. Method of outcome measurement used is adequately valid and reliable
	c. Description of the baseline study sample	c. Reasons for loss to follow-up are provided	c. Continuous variables are reported or appropriate cut points are used	c. The method and setting of outcome measurement is the same for all study participants
	d. Adequate description of the sampling frame and recruitment	d. Adequate description of participants lost to follow-up	d. The method and setting of measurement of PF is the same for all study participants	
	e. Adequate description of the period and place of recruitment	e. There are no important differences between participants who completed the study and those who did not	e. Adequate proportion of the study sample has complete data for the PF	
	f. Adequate description of inclusion and exclusion criteria		f. Appropriate methods of imputation are used for missing PF data	
Ratings‡				
High risk of bias	The relationship between the PF and outcome is very likely to be different for participants and eligible nonparticipants	The relationship between the PF and outcome is very likely to be different for completing and noncompleting participants	The measurement of the PF is very likely to be different for different levels of the outcome of interest	The measurement of the outcome is very likely to be different related to the baseline level of the PF
Moderate risk of bias	The relationship between the PF and outcome may be different for participants and eligible nonparticipants	The relationship between the PF and outcome may be different for completing and noncompleting participants	The measurement of the PF may be different for different levels of the outcome of interest	The measurement of the outcome may be different related to the baseline level of the PF
Low risk of bias	The relationship between the PF and outcome is unlikely to be different for participants and eligible nonparticipants	The relationship between the PF and outcome is unlikely to be different for completing and noncompleting participants	The measurement of the PF is unlikely to be different for different levels of the outcome of interest	The measurement of the outcome is unlikely to be different related to the baseline level of the PF

Bias Domains	
5. Study Confounding	**6. Statistical Analysis and Reporting**
Important potential confounding factors are appropriately accounted for	The statistical analysis is appropriate, and all primary outcomes are reported
a. All important confounders are measured	a. Sufficient presentation of data to assess the adequacy of the analytic strategy
b. Clear definitions of the important confounders measured are provided	b. Strategy for model building is appropriate and is based on a conceptual framework or model
c. Measurement of all important confounders is adequately valid and reliable	c. The selected statistical model is adequate for the design of the study
d. The method and setting of confounding measurement are the same for all study participants	d. There is no selective reporting of results
e. Appropriate methods are used if imputation is used for missing confounder data	
f. Important potential confounders are accounted for in the study design	
g. Important potential confounders are accounted for in the analysis	
The observed effect of the PF on the outcome is very likely to be distorted by another factor related to PF and outcome	The reported results are very likely to be spurious or biased related to analysis or reporting
The observed effect of the PF on outcome may be distorted by another factor related to PF and outcome	The reported results may be spurious or biased related to analysis or reporting
The observed effect of the PF on outcome is unlikely to be distorted by another factor related to PF and outcome	The reported results are unlikely to be spurious or biased related to analysis or reporting

12.10. AMSTAR

1. Was an "a priori" design provided? The research question and inclusion criteria should be established before the conduct of the review.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated, and where feasible, the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.[a]	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

6. Were the characteristics of the included studies provided?
   In an aggregated form, such as a table, data from the original studies should be provided on the participants, interventions, and outcomes. The ranges of characteristics in all the studies analyzed, e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.
   ☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

7. Was the scientific quality of the included studies assessed and documented?
   "A priori" methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo-controlled studies, or allocation concealment as inclusion criteria); for other types of studies, alternative items will be relevant.
   ☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
   The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.
   ☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

9. Were the methods used to combine the findings of studies appropriate?
   For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I^2). If heterogeneity exists, a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).
   ☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

10. Was the likelihood of publication bias assessed?
    An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).
    ☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

11. Was the conflict of interest included?
    Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.
    ☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

12.11. Applicability checklist

End user question	Data that can be provided in the review to address these questions
1. Were the studies included in a systematic review conducted in the same setting or were the findings consistent across settings or time periods?	• Descriptions of study settings (geographic, health system, etc) and time periods
2. Are there important differences in on-the-ground realities and constraints that might substantially alter the feasibility and acceptability of an option? • Are there any political, social, or cultural factors that may affect the implementation of this intervention? • Would the general population and/or the targeted population accept this intervention? • Is the intervention ethically acceptable? • Does the target population in the local setting have sufficient means (e.g., educational, financial, social, geographical) to receive/implement the intervention? • Can the intervention be tailored to suit the implementation setting?	• Descriptions of study settings and populations • Standardized description of intervention components, including whether these were tailored for specific settings • Factors affecting implementation that were identified in the included studies
3. Are there important differences in health system arrangements[b] that may mean an option could not work in the same way? • Which organization will be responsible for the provision of the intervention in the local setting? Are there barriers to implement this intervention because of the structure of that organization? • Is the capacity to implement the intervention comparable between the study settings and the local setting in such matters as political environment, social acceptability, resources, organizational structure, and the skills of the local providers?	• Organizational context of the interventions • Factors affecting implementation that were identified in the included studies
4. Are there important differences in the baseline conditions that might yield different absolute effects even if the relative effectiveness was the same? • What is the baseline prevalence of the health issue of interest in the local setting? What is the difference in prevalence between the study setting(s) and the local setting? • Are the characteristics of the target population comparable between the study setting(s) and the local setting?	• Baseline prevalence in the study populations/settings • Descriptions of study populations • Any evidence of differential effects across sociodemographic or other groupings
5. What insights can be drawn about options, implementation, and monitoring and evaluation? • Are there sufficient resources (e.g., educational, financial) to implement the intervention? • Do the providers or implementers of the intervention have the skills to deliver this intervention? If not, will training be available?	• Standardized description of intervention implementation • Factors affecting implementation that were identified in the included studies • Data from the included studies on the resources required to implement the intervention

13. Literatur

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