

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

Version 0.1 – Juni 2017

AWMF-Registernummer: 020/007OL

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Leitlinienreport

Bitte senden Sie Kommentare, Hinweise und Verbesserungsvorschläge zu dieser Leitlinie unter Verwendung des **Kommentierungsbogens** bis zum 13.08.2017 an: leitlinie.lungenkarzinom@pneumologie.de oder per Fax oder Post an:
Fax: 030/ 29 36 27 02
Post: Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e.V., Robert-Koch-Platz 9, 10115 Berlin

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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 Fachgesellschaft(en) der Leitlinie

Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e. V. (DGP), Deutsche Krebsgesellschaft e. V. (DKG)



1.4. Finanzierung der Leitlinie

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

1.5. Kontakt

Office Leitlinienprogramm Onkologie
c/o Deutsche Krebsgesellschaft e.V.
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 0.1 Konsultationsfassung, 2017, AWMF Registernummer 020/007 OL, <http://leitlinienprogramm-onkologie.de/Lungenkarzinom.98.0.html>, (Zugriff 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 2013-2017, 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, Hämatologen, 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 Selbsthilforganisationen)
- 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 (IQTG), 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: leitlinie.lungenkarzinom@pneumologie.de

Konsolidationsfassung

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 1 sind die an der Ersterstellung (Version 2010) und ersten Aktualisierung (Version 2017) beteiligten Fachgesellschaften und anderen Organisationen sowie die jeweils benannten Fachexperten/Fachexpertinnen aufgelistet¹. In Tabelle 2 sind die Mitglieder der Arbeitsgruppen für die Aktualisierung der Leitlinie (2013-2017) aufgeführt.

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*

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

Beteiligte Fachgesellschaften und Organisationen	Mandatsträger
	Thomas Gauler* Norbert Niederle* Ernst Späth-Schwalbe* Martin Wolf*
Arbeitsgruppe biologische Krebstherapie	Markus Horneber*
Berufsverband Deutscher Pathologen	Alfred Böcking*
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*
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**
Deutsche Gesellschaft für Hämatologie und Onkologie (DGHO)	Frank Griesinger*** Jürgen Wolf** Uwe Martens* Alexander Schmittel*

² Bei der Aktualisierung als Fachexperte ad personam beteiligt für die Aktualisierung der arbeitsmedizinischen Abschnitte

Beteiligte Fachgesellschaften und Organisationen	Mandatsträger
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 Bölkbas** 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	Jacqueline Müller-Nordhorn*

Beteiligte Fachgesellschaften und Organisationen	Mandatsträger
Gesundheitsökonomie, Charité Berlin	Thomas Reinhold*
Österreichische Gesellschaft für Pneumologie (ÖGP)	Otto Burghuber*** Maximilian Hochmair** Andrea Mohn-Staudner*** Klaus Kirchbacher*
Österreichische Gesellschaft für Radioonkologie (ÖGRO)	Thomas Auburger* Boris Pokrajac*
Zentralverband der Physiotherapeuten/Krankengymnasten (ZVK)	Michaela Franke*
Pneumologisch-onkologische onkologische Arbeitsgemeinschaft 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*
Krebsgesellschaft Nordrhein-Westfalen	Klaus-Michael Müller*
Selbsthilfe Lungenkrebs	Barbara Baysal*** Werner Kleinert**
Kompetenz-Centrum 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; ** = 2013-2017; *** = 2006-2017;	

Tabelle 2: Arbeitsgruppen des Aktualisierungsprozesses 2013-2017 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. Bölkbas, 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 2017)
- Dr. med. Simone Wesselmann, MBA (Aktualisierung der Qualitätsindikatoren)

4. Fragestellungen und Gliederung

Die Gliederung der Leitlinie kann der Langversion 1.0 (2017) 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/NEJMoa1102873].

Pathologie

Eine wichtige histologische Gruppe der nicht-kleinzeligen 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 Erkenntnissen war die sog. Erhaltungstherapie: 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 [Cappuzzo 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 verbesserte, 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:

Konsolidationsfassung

Tabelle 3: PICO-Fragen für die Aktualisierung der S3-Leitlinie Lungenkarzinom (2013-2017)

	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 / Bronchial-lavage 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 / Bronchial-lavage 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 Verringerung der	RCT

	Population	Intervention	Kontrolle	Outcome	Studien-typ
				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 patientenrelevante 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 patientenrelevante Endpunkte (für RCT)	SR, Querschnittsstudien, prospektive Kohortenstudien (delayed cross- sectional studies)
Prognostische Faktoren	Prognost. ungünstige, (G3L1V1[alternativ])	Adjuvante Chemotherapie	Keine Chemotherapie	OS, PFS, Lokalrezidiv	SR, RCT und prospektive Kohortenstudien.

	Population	Intervention	Kontrolle	Outcome	Studien-typ
	operierte NSCLC				
Resektionsränder	Operierte Patienten SCLC/ NSCLC St 1-3	R-Angabe, Completeness of resection Close margin, positive margin, microscopic 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

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

	Population	Intervention	Kontrolle	Outcome	Studien-typ
					explorative Subgruppenanalysen*
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	RCT, Systematische Übersichtsarbeiten
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	Population	Intervention	Kontrolle	Outcome	Studien-typ
				<p>entscheidend bewertet:</p> <ul style="list-style-type: none"> 1.Gesamt mortalität 2.Aggressiveitt der Therapie am ebens-ende 3.Anzahl Patientenverfgungen (resuscitation preferences?) <p>Als weniger wichtig bewertet:</p> <ul style="list-style-type: none"> 1.Verringerung der Anzahl erforderlicher Kriseninterventionen (Unplanned contacts/emergency contact) 2.Cost effectiveness 	
	Patienten mit Lungenkarzinom, aus anderen Grnden als PICO 1 nicht kurativ behandelbar	Strukturierte palliativmedizinische Intervention	Keine strukturierte/ spezifische palliativmedizinische Intervention	<p>Entscheidend:</p> <ul style="list-style-type: none"> 1.Lebensqualitt = Quality of Life (mehrere validierte Instrumente = FACT-L, TOI, LCSS, EORTCQ30 LC Symptom subscale) 2.Verbesserung Angst/Depression 3.Verschlechterung Angst/Suizidrate <p>Als wichtig, aber nicht entscheidend bewertet:</p>	RCT, Systematische bersichtsarbeit

	Population	Intervention	Kontrolle	Outcome	Studien-typ
				1. Anzahl Patientenverfügungen (resuscitation preferences?) Als weniger wichtig bewertet: 1. Cost effectiveness 2. Gesamt mortalität 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 rate

5. Methodisches Vorgehen

5.1. Leitlinienadaptation

Für den Aktualisierungsprozess 2013-2017 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 trial [TiAb])) NOT (animals [MeSH Terms] NOT

Thema (Recherchedatum)	Suchstrategie
	humans [MeSH Terms])
Pathologie	
Immunhistochemische Marker (12.05.2014)	<p>(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 k11[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]))</p>

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 (II[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

Thema (Recherchedatum)	Suchstrategie
	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])
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

Thema (Recherchedatum)	Suchstrategie
	four[tiab] OR 4[tiab])) AND (EGFR tyrosine kinase inhibitor 324674 [Supplementary Concept] OR TKI[tiab] OR tyrosine kinase inhibitor[tiab] OR erlotinib[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]

Thema (Recherchedatum)	Suchstrategie
	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])
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.

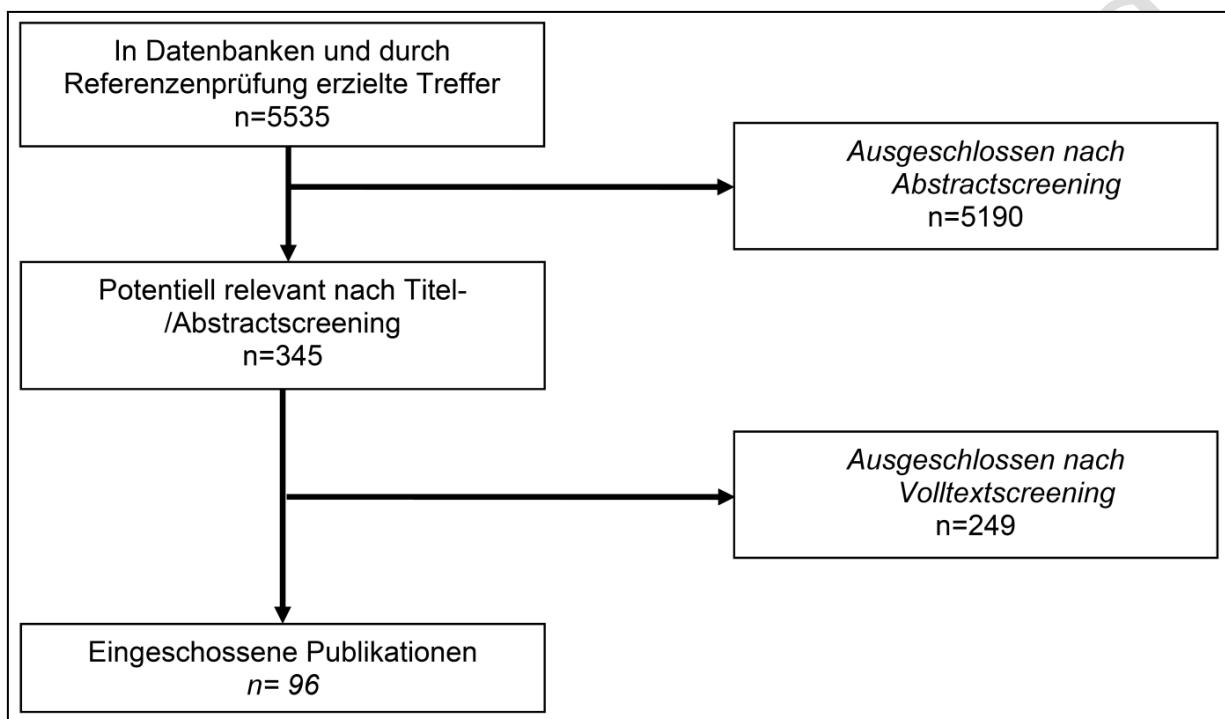


Abbildung 1: Flow-Chart zur Primärrecherche

Identifiziert durch Recherche Screening: n=438
<i>Pathologie</i>
Immunhistochemische Marker: n=1312
Molekular-pathologische Testung: n=431
Aufarbeitung LK: n=5
Prognostische Faktoren: n=602
Resektionsränder: n=169
<i>Therapie</i>
Molekular stratifizierte 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 angegeben 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.

Konsolidationsfassung

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 „2017“) 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 Aktualisierung 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 0 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).

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 Abstimmungsverhalten 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, Interessenkonfliktmanagement, externe Literaturrecherche, Ableitung von Qualitätsindikatoren, Erstellen einer Patientenleitlinie) Einteilung in Steuergruppe und Arbeitsgruppen (AGs). Weitere Organisation der Formulierung PICO-Fragen für die externe Recherche

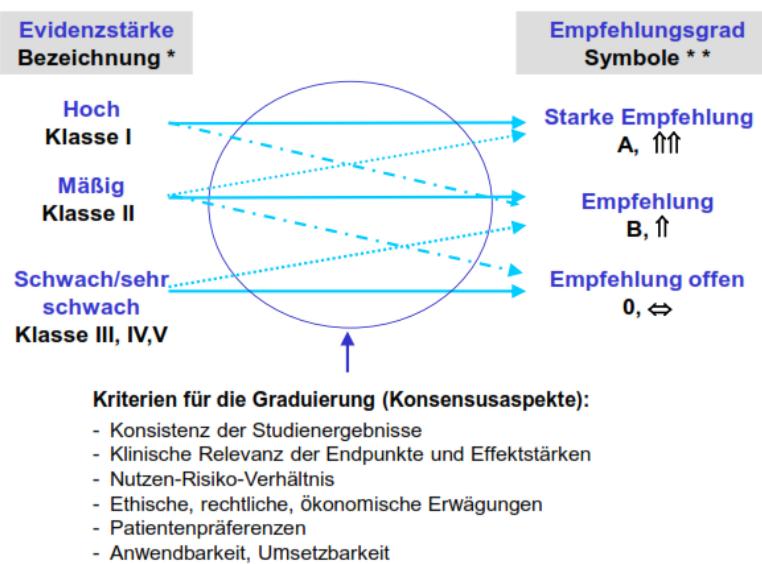
Prozess	Datum/ Zeitraum	Themen
Treffen der Steuergruppe und AG-Sprecher	18.11.2013	Konkretisierung der Schlüsselfragen nach dem PICO-Schema für die externe Literaturrecherche.
Telefonkonferenz der Steuergruppe	22. 01. 2014	Priorisierung der Schlüsselfragen zur Einholung einer Kostenkalkulation für die 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) Endobronchiale Elektroverfahren

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 könnte. 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) kann im Rahmen einer öffentlichen Konsultation durch die (Fach)Öffentlichkeit über einen Zeitraum von mindestens 6 Wochen begutachtet werden.

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	Eigentümerinteres- se (z. B. Patent, Urheberrecht, Verkaufs Lizenz) ⁴	Besitz von Geschäfts- anteilen, Aktien, Fonds ⁵	Persön- liche Beziehu- ngen ⁶	Mitgliedschaft Fachgesellschaf- ten/Berufsverb- ände, andere Leitlinien- gruppen ⁷	wissen- schaft- liche 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 Bölkbas	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	Ja Astra Zeneca, Roche Pharma, Eli Lilly, GSK,	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	Eigentümerinteres- se (z. B. Patent, Urheberrecht, Verkaufs Lizenz) ⁴	Besitz von Geschäfts- anteilen, Aktien, Fonds ⁵	Persön- liche Beziehu- ngen ⁶	Mitgliedschaft Fachgesellschaf- ten/Berufsverb- ände, andere Leitlinien- gruppen ⁷	wissen- schaft- liche oder persönliche Interessen ⁸	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
	Pharma, Eli Lilly, GSK, Boehringer Ingelheim, Teva Pharma, Bristol Myers Squibb, Novartis Pharma, Pfizer Pharma, Bayer, MerckSerono, Merck (USA)	Boehringer Ingelheim, 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

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit ¹	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co- Autorenschaften ²	Finanzielle Zuwendungen (Drittmittel) ³	Eigentümerinteres- se (z. B. Patent, Urheberrecht, Verkaufs Lizenz) ⁴	Besitz von Geschäfts- anteilen, Aktien, Fonds ⁵	Persön- liche Beziehu- ngen ⁶	Mitgliedschaft Fachgesellschaf- ten/Berufsverb- ände, andere Leitlinien- gruppen ⁷	wissen- schaft- liche oder persönliche Interessen ⁸	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
Dr. Fernando Gamarra	Nein	Nein	Nein	Nein	Nein	Nein	Ja DGP, DKG, European Respiratory Society (chair der „Lung Cancer Group“), American Thoracic Society	Nein	Klinikum der Ludwig- Maximilians Universität München
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 (Tumordoku- mentation)	Nein	Nein	Nein	Ja DGP, DKG	Nein	Paul-Gerhardt-Diakonie – EV. Lungenklinik Berlin
Dr. Andreas Gröschel	Ja Lilly, Roche, Boehringer, Amgen,	Ja Lilly, Roche, Boehringer, Merck Sorono	Nein	Nein	Nein	Nein	Ja DGP, DKG, AIO, POA, ERS	Nein	Ambulantes Aachener Lungenzentrum, Universitätsklinikum des Saarlandes

	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	Persön- liche Beziehu- ngen ⁶	Mitgliedschaft Fachgesellsc- haft/Berufsverb- ände, andere Leitlinien- gruppen ⁷	wissen- schaft- liche oder persönliche Interessen ⁸	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
	Merck Sorono								
Dr. Sylvia Gütz	Ja Boehringer Ingelheim	Ja Boehringer Ingelheim, Pierre Fabre, Roche, Lilly	Nein	Nein	Nein	Nein	Ja DGP, DKG	Nein	Ev. Diakonissenkranken- haus Leipzig, Klinikum St. Georg
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 Großhadern GmbH
Felix Herth	Ja Uptake Medical, Aeris, Olympus Medical, PneumRx, Boston Scientific, Roche Diagnetics, Intermune, Novartis, Lilly, Pulmonx, Astra Zeneca, Allmiral, Takeda, Pierre Fabre, Boehringer Ingelheim	Ja Uptake Medical, Aeris, PneumRx, Boston Scientific, Roche Diagnetics, 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	Ja	Nein	Nein	Nein	Nein	Ja	Ja	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	Persön- liche Beziehu- ngen ⁶	Mitgliedschaft Fachgesellschaf- ten/Berufsverb- ände, andere Leitlinien- gruppen ⁷	wissen- schaft- liche oder persönliche Interessen ⁸	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
	LL Immuno- therapy board GSK	Bezahlte Vorträge bei verschiedenen Industriegesponserten Symposien					DGT, DGP, DKG	Zertifizierungs- kommission Lungenkrebs- zentren DKG	
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 Thoraxchirurgie	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),	Ja Planungsgruppe NVL- Programm Lenkungsaus- schuss OL und KoQK wissenschaftl. Beirat AQUA AG Dokumentati	AWMF

	Berater-bzw. Gutachtertäti gkeit oder bezahlte Mitarbeit ¹	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co- Autorenschaften ²	Finanzielle Zuwendungen (Drittmittel) ³	Eigentümerinteres se (z. B. Patent, Urheberrecht, Verkaufs Lizenz) ⁴	Besitz von Geschäfts- anteilen, Aktien, Fonds ⁵	Persön- liche Beziehu ngen ⁶	Mitgliedschaft Fachgesellschaf ten/Berufsverb ände, andere Leitlinien- gruppen ⁷	wissen schaft liche oder persönliche Interessen ⁸	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
							Deutsche Gesellschaft für Chirurgie	on des NKP Gutachterin für DAkKS	
Dr. Christian Kugler	Nein	Ja Astra Zeneca, Lilly, Novartis, Roche	Nein	Nein	Nein	Nein	Ja Präsident Dt. Gesellschaft für Thoraxchirurgie, Vorstandsmitglie d 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 Klinikum Emil von Behring, Berlin
Dr. Frank Noack	Nein	Nein	Nein	Nein	Nein	Nein	Ja DGT, DGCH	Nein	Klinik für Thoraxchirurgie

	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	Persön- liche Beziehu- ngen ⁶	Mitgliedschaft Fachgesellschaf- ten/Berufsverb- ände, andere Leitlinien- gruppen ⁷	wissen- schaft- liche oder persönliche Interessen ⁸	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
									Mönchengladbach
Dr. Monika Nothacker, MPH	Nein	Nein	Nein	Nein	Nein	Nein	Ja DKG, DNebM	Nein	AWMF, ÄZQ (bis 6/12)
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, AstraZeneca, Boehringer	Ja Hoffmann-La Roche, Lilly, Pfizer, AstraZeneca, Boehringer Ingelheim, BMS	Nein	Nein	Nein	Nein	Ja ESMO, Guideline Group	Nein	LungenClinic Großhansdorf

	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	Persön- liche Beziehu- ngen ⁶	Mitgliedschaft Fachgesellsc- haft/Berufsverb- ände, andere Leitlinien- gruppen ⁷	wissen- schaft- liche oder persönliche Interessen ⁸	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
	Ingelheim, BMS								
Dr. S. Riha	Ja Boehringer Ingelheim Pharma GmbH, Lilly Deutschland GmbH	Ja Novartis Pharma GmbH	Nein	Nein	Nein	Nein	Ja DGP, DKG, DGP, DGNTF	Nein	Fachkrankenhaus Coswig 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 Geriatriegesundheit, 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)	Nein	Universitätsmedizin Greifswald

	Berater-bzw. Gutachtertäti- gkeit oder bezahlte Mitarbeit ¹	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co- Autorenschaften ²	Finanzielle Zuwendungen (Drittmittel) ³	Eigentümerinteres- se (z. B. Patent, Urheberrecht, Verkaufs Lizenz) ⁴	Besitz von Geschäfts- anteilen, Aktien, Fonds ⁵	Persön- liche Beziehu- ngen ⁶	Mitgliedschaft Fachgesellschaf- ten/Berufsverb- ände, andere Leitlinien- gruppen ⁷	wissen- schaft- liche oder persönliche Interessen ⁸	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
							befindlich)		
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
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 (unbezahlbar)	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.	Ja Roche, Pfizer	Nein	Nein	Nein	Nein	Ja DGP, AIO, POA	Nein	Lungenklinik Hemer

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit ¹	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co- Autorenschaften ²	Finanzielle Zuwendungen (Drittmittel) ³	Eigentümerinteres- se (z. B. Patent, Urheberrecht, Verkaufslizenz) ⁴	Besitz von Geschäfts- anteilen, Aktien, Fonds ⁵	Persön- liche Beziehu- ngen ⁶	Mitgliedschaft Fachgesellschaf- ten/Berufsverb- ände, andere Leitlinien- gruppen ⁷	wissen- schaft- liche oder persönliche Interessen ⁸	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
	Boehringer Ingelheim, Fa. Pfizer								
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 Amgen, multizentrische Studien in 2014	Nein	Nein	Nein	Ja DEGRO, Berufsverband deutscher Strahlenthera- peuten	Nein	Universität Duisburg- Essen
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	Nein	DKG

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit ¹	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co- Autorenschaften ²	Finanzielle Zuwendungen (Drittmittel) ³	Eigentümerinteres- se (z. B. Patent, Urheberrecht, Verkaufs Lizenz) ⁴	Besitz von Geschäfts- anteilen, Aktien, Fonds ⁵	Persön- liche Beziehu- ngen ⁶	Mitgliedschaft Fachgesellschaf- ten/Berufsverb- ände, andere Leitlinien- gruppen ⁷	wissen- schaft- liche oder persönliche Interessen ⁸	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
								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
Dag Wormanns	Ja Median Technologies	Ja Novartis, AstraZeneca	Nein	Ja Patent: Philips (kann ich nicht lesen)	Nein	Nein	Ja Deutsche Röntgengesellsc- haft	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, Verkaufs Lizenz)

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-/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
<p>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.</p> <p>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.</p> <p>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.</p>	<p>Region/Setting USA, 33 Screening centres</p> <p>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</p> <p>Exclusion criteria Metallic implants or devices in the chest or back, such as pacemakers or Harrington fixation</p>	<p>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</p> <p>Control Chest radiography (0.02 mSv, <40s) 3 rounds at 1-year intervals</p>	<p>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</p> <p>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</p> <p>Test of interaction for mortality due to lung neoplasm</p>	<p>Study type RCT (one arm of RCT for diagnostic accuracy [false positive results])</p> <p>Level of evidence 1b (2b for measures of diagnostic accuracy)</p> <p>Risk of bias Generation of allocation sequence: + Allocation concealment: ?</p> <p>Blinding of participants and personal:</p>

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 /CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
<p>N Engl J Med, 2013. 369(10): p. 920-31.</p> <p>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.</p> <p>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.</p>	<p>rods</p> <p>Treatment for, or evidence of, any cancer other than nonmelanoma skin cancer or carcinoma <i>in situ</i> (with the exception of transitional cell carcinoma <i>in situ</i> or bladder carcinoma <i>in situ</i>) in the 5 years prior to eligibility assessment</p> <p>History of lung cancer</p> <p>History of removal of any portion of the lung, excluding needle biopsy</p> <p>Requirement for home oxygen supplementation</p> <p>Unexplained weight loss of more than 15 pounds in the 12 months prior to eligibility assessment</p> <p>Recent hemoptysis</p> <p>Pneumonia or acute</p>	<p>Positive test was defined as the finding of a noncalcified nodule of any size or another abnormality potentially related to lung cancer</p> <p>Reference standard (only positive screening results)</p> <p>Medical records documenting diagnostic evaluation procedures. Beyond office visits and physical examinations, imaging examinations, including diagnostic chest CT and F-fluorodeoxyglucose- positron-emission tomography (FDG-PET), were the most commonly performed procedures</p> <p>Time interval between index and reference test</p> <p>Not specified (within one year)</p> <p>Included/randomised patients</p> <p><i>T1 (one year after randomization)</i></p>	<p>Former (RR=0.91) vs. current smokers (RR=0.81); >0.4</p> <p>Test of interaction for mortality due to lung neoplasm</p> <p>Age; >0.4</p> <p>Test of interaction for mortality due to lung neoplasm</p> <p>Women (RR=0.73) vs. men (RR=0.92); 0.08</p> <p>Overall mortality (within 7 years after first enrolment, median 6.5 years)</p> <p>1877/ 2000; RRR = 6.7%; 1.2 - 13.6</p> <p>Test of interaction for</p>	<p>-</p> <p>Blinding of outcome assessment:</p> <p>+</p> <p>Incomplete outcome data: +</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p> <p>QUADAS-II</p> <p>Selection of patients: +</p> <p>Conduct/interpretation of index test: +</p> <p>Conduct/interpretation of reference test: ?</p> <p>Patient flow: ?</p>

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 /CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	<p>respiratory infection treated with antibiotics in the 12 weeks prior to eligibility assessment</p> <p>Prior testing</p> <p>Patients with chest CT examination in the 18 months prior to eligibility assessment were excluded</p> <p>Patient characteristics</p> <p>Age at randomization</p> <ul style="list-style-type: none"> <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 <p>Female (%): 41.0/ 41.0</p>	<p>26,722/ 26,732 <i>T2 (two years after randomization)</i></p> <p>26,732/ 26,110</p> <p>Analysed patients</p> <p><i>T1</i></p> <p>24,715/ 24,089</p> <p><i>T2</i></p> <p>24,102/ 23,346</p> <p>Attrition</p> <p><i>T1</i></p> <p>2007/ 2643</p> <p><i>T2</i></p> <p>2620/ 3386</p> <p>Excluded from analysis (reason)</p> <p>ITT according to authors</p> <p>NR (false positive results)</p>	<p>overall mortality Former (RR=0.914) vs. current smokers (RR=0.944); NS</p> <p>Test of interaction for overall mortality</p> <p>Age; NS</p> <p>Test of interaction for overall mortality</p> <p>Women (RR=0.921) vs. men (RR=0.936); NS</p> <p>False positive results</p> <p>T1</p> <p>97.6%/ 95.6%; NR; NR</p> <p>T2</p> <p>94.8%/ 93.4%; NR; NR</p> <p><u>Adverse events from follow up procedure (within 6</u></p>	

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 /CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	<p>Race or ethnic group</p> <p>White (%): 90.9/ 90.8</p> <p>Black (%): 4.5/ 4.4</p> <p>Asian (%): 2.1/ 2.0</p> <p>American Indian/ Alaska Native(%): 0.3/ 0.4</p> <p>Native Hawaiian/ Pacific Islander(%): 0.3/ 0.4</p> <p>More than one race or ethnic group (%): 1.2/ 1.3</p> <p>Data missing(%): 0.6/ 0.8</p> <p>Hispanic ethnic group</p> <p>Hispanic or Latino (%): 1.8/ 1.7</p> <p>Neither Hispanic nor Latino (%): 97.6/ 97.4</p> <p>Data missing (%): 0.6/ 0.9</p> <p>Smoking status</p> <p>Current (%): 48.1/ 48.3</p> <p>Former (%): 51.9/ 51.7</p>		<p><u>years after first enrolment)</u></p> <p><i>Lung cancer confirmed</i></p> <p><i>Thoracotomy, Thoracoscopy, or Mediastinoscopy</i></p> <p>At least one complication (%): 32.4/ 31.2; NR</p> <p>Major complication (%): 13.9/ 11.6; NR</p> <p>Death (%): 1/ 2.1; NR</p> <p><i>Bronchoscopy</i></p> <p>At least one complication (%): 9.2/ 8.7; NR</p> <p>Major complication (%): 2.6/ 2.2; NR</p> <p>Death (%): 5.3/ 10.9; NR</p> <p><i>Needle Biopsy</i></p> <p>At least one complication (%): 21.2/ 3.4; NR</p> <p>Major complication (%): 0/ 0; NR</p>	

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 /CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
			<p>Death (%): 3.0/ 3.4 <i>No Invasive Procedure</i> At least one complication (%): 16.1/ 7.1; NR Major complication (%): 6.5/ 6.7; NR Death (%): 0/ 6.7</p> <p><i>Lung cancer not confirmed</i> <i>Thoracotomy, Thoracoscopy, or Mediastinoscopy</i> At least one complication (%): 15.9/ 15.6; NR Major complication (%): 5.5/ 2.2; NR Death (%): 1.2/ 0; NR <i>Bronchoscopy</i> At least one complication (%): 4.8/ 0; NR Major complication (%): 0.9/</p>	

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 /CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
			<p>0; NR</p> <p>Death (%): 1.8/ 0; NR</p> <p><i>Needle Biopsy</i></p> <p>At least one complication (%): 10.6/ 4.2; NR</p> <p>Major complication (%): 0/ 0; NR</p> <p>Death (%): 0/ 0; NR</p> <p><i>No Invasive Procedure</i></p> <p>At least one complication (%): 0.1/ 0.2; NR</p> <p>Major complication (%): <0.1/ 0.1; NR</p> <p>Death (%): <0.1/ 0.1</p>	
<p>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.</p>	<p>Region/setting USA, 6 screening centres</p> <p>Inclusion criteria 55 to 74 years Cigarette smoking history</p>	<p>Index test(s)</p> <p>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.)</p>	<p>False positive results (12 month) 33%/ 15%; NR; sign.</p>	<p>Study type RCT (one arm of RCT for diagnostic accuracy[false positive results])</p> <p>Level of evidence 1b (2b for measures of</p>

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 /CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	<p>of 30 pack-years or more, and were current smokers or had quit in the past 10 years</p> <p>Exclusion criteria</p> <p>Previous lung cancer</p> <p>Removal of part or all of a lung</p> <p>Current treatment of any cancer except nonmelanoma skin cancer</p> <p>Prior testing</p> <p>Patient with chest CT within 24 months of enrolment were excluded</p> <p>Patient characteristics</p> <p>Age</p> <p>65-74 y (%):32/ 32</p> <p>55-64 y (%):68/ 68</p>	<p>2 rounds at 1-year intervals</p> <p>Control</p> <p>Chest radiography (high-kilovolt equipment at a tube-to-receiver distance of 6 to 10 feet)</p> <p>2 rounds at 1-year intervals</p> <p>Reference standard</p> <p>No specific diagnostic algorithm for follow-up of positive results</p> <p>Center personnel abstracted medical records</p> <p>Results of record screening</p> <p>Imaging examinations: 308 / 110</p> <p>Minimally invasive procedure: 25 / 6</p> <p>Moderately invasive procedure: 20 / 7</p> <p>Major surgical procedure: 8 / 4</p>		<p>diagnostic accuracy)</p> <p>Risk of bias</p> <p>Generation of allocation sequence: +</p> <p>Allocation concealment: +</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome assessment: +</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting: +</p> <p>Other source of bias:</p>

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 /CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	<p>Female (%):42/ 40</p> <p>Current smoker (%):58/ 57</p> <p><i>Smoking history</i></p> <p>60 pack-years (%):42/ 43</p> <p>30-59 pack-years (%):58/ 57</p>	<p>Any invasive procedure: 33 / 9</p> <p>Time interval between index and reference test</p> <p>not specified (within one year)</p> <p>Included/randomised patients</p> <p>1660/ 1658</p> <p>Analysed patients</p> <p>1610/ 1580</p> <p>Attrition</p> <p>29/ 14</p> <p>Excluded from analysis (reason)</p> <p>50 (missed or declined all screenings)</p> <p>78 (missed or declined all screenings)</p>		<p>+</p> <p>QUADAS-II</p> <p>Selection of patients:</p> <p>+</p> <p>Conduct/interpretation of index test:</p> <p>+</p> <p>Conduct/interpretation of reference test::</p> <p>?</p> <p>Patient flow:</p> <p>+</p>
Infante, M., et al., A randomized study of lung cancer screening with spiral	<p>Region/Setting</p> <p>Italy, 2 centres</p>	<p>Intervention(s)</p> <p>Chest X-ray</p>	<p>Mortality due to lung neoplasm (5 years, median 33.7 months);1.6%/ 1.7%;</p>	<p>Study type</p> <p>RCT</p>

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 /CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
<p>computed tomography: three-year results from the DANTE trial. Am J Respir Crit Care Med, 2009. 180(5): p. 445-53.</p> <p>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.</p> <p>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.</p>	Inclusion criteria 60-74 years Active or quit < 10 years prior to accrual 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	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 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	NR; 0.84 Overall mortality (5 years, median 33.7); 2.0%/ 2.1%; NR; 0.93 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	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, setting inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG /CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	Other severe metabolic disturbances Dementia 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	Control Chest X-ray Sputum cytology testing Medical interview and physical examination (five yearly)	Included/randomised patients 1276/ 1196 Analysed patients 1276/ 1196 Attrition 3.4%/ 5.3%	+ 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 /CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	<p>45.5-49.0</p> <p>Age in years (mean, 95% CI): 64.3, 64.0-64.7/ 64.6, 64.3-64.9</p> <p><i>Co-morbid conditions</i></p> <p>Respiratory (%): 35.0/ 30.99</p> <p>Hypertension(%): 35.7/ 37.4</p> <p>Cardiac (%): 12.5/ 13.8</p> <p>Peripheral vascular (%):10.2/ 9.0</p> <p>Diabetes (%): 8.2/ 8.3</p> <p>Other (%): 35.4/ 35.6</p>			
<p>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.</p>	<p>Region/Setting Italy, hospitals</p> <p>Inclusion criteria 49 years and above Current or former smokers (having quit smoking within 10 years)</p>	<p>Intervention(s) Primary prevention (smoking cessation) with pulmonary function rest evaluation + blood sample collection</p> <p>Group 1. Biennial LDCT (120 kV, 30mAs, 0.75mm collimation, gantry rotation time 0.5s, pitch</p>	<p>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)</p>	<p>Study type RCT</p> <p>Level of evidence 1b</p> <p>Risk of bias</p>

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 /CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	<p>of recruitment) with at least 20 pack-years of smoking</p> <p>Exclusion criteria</p> <p>History of cancer within the previous 5 years</p> <p>Patient characteristics</p> <p>Age</p> <p><55 (%): 32.0/ 33.1/ 38.1</p> <p>55-59 (%): 30.6/ 28.4/ 27.7</p> <p>60-64 (%): 22.0/ 23.0/ 20.6</p> <p>65-69 (%): 12.1/ 11.3/ 10.1</p> <p>≥70 (%): 3.4/ 4.2/ 3.3</p> <p>Median: 58/ 57/ 57</p> <p>Female (%): 31.5/ 31.6/ 36.7</p> <p>Smoking Status</p>	<p>1.5, 16 slice)</p> <p>Group 2. Annual LDCT (120 kV, 30mAs, 0.75mm collimation, gantry rotation time 0.5s, pitch 1.5, 16 slice)</p> <p>Participants with nodules greater than 250.mm³ were referred for additional workup, including fluorine 18-fluorodeoxyglucose PETor lung biopsy.</p> <p>Control</p> <p>Primary prevention (smoking cessation) with pulmonary function rest evaluation + blood sample collection</p> <p>Included/randomised patients</p> <p>1186/ 1190/ 1723</p> <p>Analysed patients</p> <p>4097</p> <p>Attrition</p> <p>2</p>	<p>Overall mortality (5 years, median 4.4 years); 20/ 31/ 20; HR=1.39 (CT arms vs. control); 0.13 (p-value overall), 0.83-2.34 (95% CI for HR of CT arms vs. control)</p>	<p>Generation of allocation sequence: +</p> <p>Allocation concealment: +</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome assessment: +</p> <p>Incomplete outcome data: +</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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 /CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	<p>Former (%): 31.7/ 31.1/ 10.3</p> <p><i>Duration of smoking</i></p> <p><30 (%): 8.3/ 8.6/ 8.1</p> <p>30-39 (%): 49.2/ 50.8/ 49.7</p> <p>40-49 (%): 37.3/ 34.6/ 35.9</p> <p>≥ 50 (%): 5.2/ 6.1/ 6.3</p> <p><i>Cigarettes per day</i></p> <p><20 (%): 23.8/ 22.0/ 33.0</p> <p>20-29 (%): 51.8/ 52.0/ 42.4</p> <p>30-39 (%): 11.9/ 11.9/ 14.0</p> <p>≥ 40 (%): 12.6/ 14.0/ 10.6</p> <p><i>Pack years of cigarettes</i></p> <p>Median: 39/ 39/ 38</p> <p><i>FEV1 (predicted)</i></p> <p><90 (%): 27.7/ 28.2/ 19.2</p>	<p>Excluded from analysis (reason)</p> <p>NA</p>		

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 /CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
<p>Pedersen, J.H., et al., The Danish randomized lung cancer CT screening trial--overall design and results of the prevalence round. <i>J Thorac Oncol</i>, 2009. 4(5): p. 608-14.</p> <p>Petersen, R.H., et al., Lung cancer screening and video-assisted thoracic surgery. <i>J Thorac Oncol</i>, 2012. 7(6): p. 1026-31.</p> <p>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. <i>Thorax</i>, 2012. 67(4): p. 296-301.</p>	<p>Region/Setting Denmark, one center</p> <p>Inclusion criteria 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.</p> <p>Exclusion criteria Weight over 130 kg History of cancer</p>	<p>Intervention(s) CT scans of the study were performed on a MDCT scanner (16 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</p>	<p>Mortality due to lung neoplasm (5.5 years, median 4.81 years); 0.73%/0.54%; 0.428</p> <p>Overall mortality (5.5 years, median 4.81 years); 2.97%/2.05%; 0.059</p>	<p>Study type RCT</p> <p>Level of evidence 1b</p> <p>Risk of bias Generation of allocation sequence: + Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data: +</p>

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 /CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	<p>diagnosis and treatment</p> <p>Lung tuberculosis</p> <p>Illness that would shorten life expectancy to <10 years</p> <p>Chest CT received during the last year for any reason</p> <p>Patient characteristics (n)</p> <p>Age</p> <p>49: 8/ 6</p> <p>50-54: 586/ 586</p> <p>55-59: 676/ 699</p> <p>60-64: 604/ 571</p> <p>65-69: 169/ 184</p> <p>70-74: 9/ 6</p> <p>Female (%): 22.1/ 22.7</p> <p>FEV1 (Mean, SD)</p>	<p>for diagnostic investigation, in addition to nodules with suspicious morphology</p> <p>Nodules category 3, 4, or 5 regarded as screening test positive</p> <p>Five rounds annual</p> <p>Control</p> <p>Lung function tests (five annual)</p> <p>Included/randomised patients</p> <p>2052/ 2052</p> <p>Analysed patients</p> <p>NR</p> <p>Attrition</p> <p>15/ 14</p> <p>Excluded from analysis (reason)</p> <p>NA</p>		<p>Selective reporting:</p> <p>+ Other source of bias:</p> <p>+ </p>

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 /CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	<p>Male: 3.3 L, 0.7/ 3.3 L, 0.7 Female: 2.4 L, 0.5/ 2.4 L, 0.5</p> <p><i>Smoking status</i></p> <p>Current smoker: 1545/ 1579</p> <p>Former smoker: 507/ 473</p> <p><i>Smoking duration (years)</i></p> <p><i>Current smokers</i></p> <p><26: 22/ 24</p> <p>26-30: 81/ 85</p> <p>31-35: 303/ 307</p> <p>36-40: 504/ 511</p> <p>41-45: 395/ 400</p> <p>>45: 240/ 252</p> <p><i>Former smokers</i></p> <p><26: 19/ 12</p> <p>26-30: 53/ 56</p>			

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 /CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	<p>31-35: 143/ 130 36-40: 164/ 167 41-45: 96/ 76 >45: 31/ 32 Missing: 1/ 0</p> <p><i>Cigarettes/day</i></p> <p><i>Current smokers</i></p> <p><10: 158/ 170 10-20: 713/ 701 21-30: 419/ 412 >40: 111/ 103 None: 28/ 45 Missing: 117/ 148</p> <p><i>Former smokers</i></p> <p><10: 22/ 22 10-20: 257/ 239 21-30: 137/ 136 >40: 69/ 46</p>			

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 /CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	<p>None: 1 / 4</p> <p>Missing: 21 / 23</p> <p><i>Duration of smoking (former smokers)</i></p> <p><5: 386 / 353</p> <p>6–10: 110 / 111</p> <p>>10: 8 / 9</p> <p>Missing: 3 / 0</p>			

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.	<p><i>Included</i></p> <p>NR</p> <p><i>Attrition</i></p> <p>NR</p> <p><i>Analyzed</i></p> <p>308</p> <p><i>Excluded from analysis</i></p> <p>NR</p>	<p><i>Inclusion</i></p> <p>Clinical stage IIIB or IV</p> <p>Not undergone previous chemotherapy treatment</p> <p><i>Exclusion</i></p> <p>Two primary tumors at the time of diagnosis</p> <p><i>Patient characteristics</i></p> <p>Age (median, range): 60, 31–80</p> <p>Male (%): 83.8</p> <p>Female (%): 16.2</p> <p><i>Histology</i></p>	<p><i>Setting</i></p> <p>NR</p> <p><i>Country</i></p> <p>Spain</p>	KRAS (allelic discrimination method using fluorogenic RT-PCR, with a GeneAmp 7000 SDS)	<p>Median (month) PFS; mutated vs. wild type; 5.43 vs. 5.77; 0.277</p> <p>Median (month) OS; mutated vs. wild type; 9.07 vs. 10.03; 0.514</p>	Univariate	<p><i>Study type</i></p> <p>Cohort study</p> <p><i>Level of evidence</i></p> <p>4</p> <p><i>Risk of bias</i></p> <p>Participation: ?</p> <p>Attrition: ?</p> <p>PF measurement: +</p> <p>Outcome measurement: +</p> <p>Confounding: -</p> <p>Statistical analysis: -</p>

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 <i>Treatment</i> Cisplatin (75 mg/m ²) and docetaxel (75 mg/m ²) 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.	<p><i>Included</i> 67</p> <p><i>Attrition</i> NR</p> <p><i>Analyzed</i> 60 (EGFR) 62 (KRAS)</p> <p><i>Excluded from analysis</i> 7 (EGFR-FISH) 5 (KRAS)</p> <p><i>Exclusion</i> NR</p>	<p><i>Inclusion</i> Advanced stage lung adenocarcinoma Therapeutic or diagnostic surgery</p> <p>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</p>	<p><i>Setting</i> Hospital</p> <p><i>Country</i> Italy</p>	<p>EGFR (PCR, pre-sequencing kit, sequenced with both forward and reverse primers, automated sequencing)</p> <p>EGFR (FISH, classified Colorado scoring criteria)</p> <p>KRAS (PCR, pre-sequencing kit, sequenced with</p>	<p>Median (weeks) OS; EGFR mutated vs. EGFR wild type 99 vs. 92; 0.87</p> <p>Median OS; EGFR mutated vs. EGFR wild type: NR; NS</p> <p>Median (weeks) OS; FISH positive vs. FISH negative: 177 vs. 57; 0.048</p> <p>Median OS; FISH positive vs. FISH negative: NR; NS</p> <p>Median(weeks) OS; KRAS positive vs. KRAS negative ; 44 vs. 125; 0.03</p>	<p>Univariate</p> <p>Univariate</p> <p>Univariate</p> <p>Univariate</p> <p>Univariate</p>	<p><i>Study type</i> Cohort study</p> <p><i>Level of evidence</i> 4</p> <p><i>Risk of bias</i> Participation: - Attrition: ?</p> <p>PF measurement: +</p> <p>Outcome measurement: +</p> <p>Confounding: -</p> <p>Statistical analysis: -</p>

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
		<p><u>Patient characteristics</u></p> <p>Age (median, range): 64, 35-81</p> <p>Female (%): 48</p> <p>Male (%): 52</p> <p>Smoking status</p> <p>Never smoker (%): 57</p> <p>Former light smoker (%): 22</p> <p>Current smoker (%): 21</p> <p>Histology</p> <p>ADC (%): 78</p> <p>BAC features (%): 22</p> <p>Stage</p> <p>IIIB(%): 19</p>		both forward and reverse primers, automated sequencing)	<p>Median OS; KRAS positive vs. KRAS negative: HR=3.52; 1.39-8.9</p> <p>Median (weeks) PFS; KRAS positive vs. KRAS negative : 11 vs. 28; 0.001</p>	<p>Multivariate (factors NR)</p> <p>Univariate</p>	

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
		IV(%): 81 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					

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
		<p>Histology</p> <p>ADC (%), M+/WT: 25.5 / 74.5</p> <p>BAC features > 80% (%), M+/WT: 33.3 / 66.4</p> <p>Stage</p> <p>IIIB(%), M+/WT: 0 / 100</p> <p>IV(%), M+/WT: 34 / 66</p> <p>CNS metastasis</p> <p>No (%), M+/WT: 24.1 / 75.9</p> <p>Yes (%), M+/WT: 50 / 50</p> <p><i>EGFR FISH status</i> (positive: n=34/ negative: n=26)</p> <p>Age (median), +/-: 68 / 59</p>					

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 (%), +/-: 61.6/ 38.5 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/					

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
		<p>44.7 CNS metastasis No (%), +/-: 58.2/ 41.8</p> <p>Yes (%), M+/WT: 60/ 40</p> <p><i>KRAS mutation status</i> (M+: n=12/ WT: n=50) Age (median), M+/WT: 61/ 64</p> <p>Female (%), M+/WT: 9.7/ 90.3</p> <p>Male (%), M+/WT: 29/ 71</p> <p>Smoking status</p> <p>Never smoker (%), M+/WT: 12.5/ 88.8</p> <p>Former light smoker (%), M+/WT: 54.5/ 45.5</p>					

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
		<p>Current smoker (%), M+/WT: 15.4/ 84.6</p> <p>Histology</p> <p>ADC (%), M+/WT: 18.9/ 81.1</p> <p>BAC features > 80% (%), M+/WT: 22.2/ 77.8</p> <p>Stage</p> <p>IIIB(%), M+/WT: 15.4/ 84.6</p> <p>IV(%), M+/WT: 20.4/ 79.6</p> <p>CNS metastasis</p> <p>No (%), M+/WT: 17.9/ 82.1</p> <p>Yes (%), M+/WT: 33.3/ 66.7</p> <p><i>Treatment</i></p> <p>Chemo 1st line: 45</p>					

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 2 nd line: 16 Chemo 3 rd line: 8 TKIs 1 st line: 6 TKIs 2 nd line: 11 TKIs 3 rd line: 3					

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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 X., et al., Effect of gefitinib challenge to initial treatment with non-small cell lung cancer Biomedicine & Pharmacotherapy, 2011. 65: p. 542-6.	<p><i>Included</i> 61</p> <p><i>Attrition</i> NR</p> <p><i>Analyzed</i> 61</p> <p><i>Excluded from analysis</i> NR</p>	<p><i>Inclusion</i> 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</p> <p><i>Exclusion</i> NR</p> <p><i>Patient characteristics</i> 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</p>	<p><i>Setting</i> NR</p> <p><i>Country</i> China</p>	EGFR (NR)	<p>ORR (follow-up NR) mutation vs. unknown or wild type; 50% vs. 14.2%; 0.003</p> <p>Median (month) OS; mutation vs. unknown or wild type; 17 vs. 11; 0.000</p> <p>Median (month) PFS; mutation vs. unknown or wild type; 9 vs. 2.5; 0.000</p>	Univariate	<p><i>Study type</i> <i>Cohort study</i> <i>Level of evidence</i> 4</p> <p><i>Risk of bias</i> <i>Participation:</i> + <i>Attrition:</i> ?</p> <p><i>PF measurement:</i> ?</p> <p><i>Outcome measurement:</i> ?</p> <p><i>Confounding:</i> -</p> <p><i>Statistical analysis:</i> -</p>

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 EGFR-TKI treatment efficacy Anticancer research, 2013. 33: p. 1705-12.	<p><i>Included</i> 223</p> <p><i>Attrition</i> NR</p> <p><i>Analyzed</i> 179 EGFR 174 KRAS</p> <p><i>Excluded from analysis</i> 44 (EGFR) 49 (KRAS)</p>	<p><i>Inclusion</i> Stage IIIB and IV</p> <p><i>Exclusion</i> NR</p> <p><i>Patient characteristics</i> EGFR mutation status (M+[mutated]: n=16/ WT[wild type]: n=163) Age (median): 69/ 62</p> <p>Female (%): 31.3/ 16.6 Male (%): 68.8/ 83.4</p> <p>Smoking status Current or former smoker (%): 68.8/ 96.8 Never smoker (%): 31.3/ 3.2</p> <p>EGFR-TKI Gefitinib (n=91, %): 68.8/ 49.1</p> <p>Erlotinib (n=88, %): 31.3/ 50.9</p>	<p><i>Setting</i> Hospital</p> <p><i>Country</i> Czech Republic</p>	<p>EGFR (PCR processed with a special DNA extraction step or DNA was extracted with standard spin column procedure)</p> <p>KRAS (PCR processed with a special DNA extraction step or DNA was extracted with standard spin column procedure)</p>	<p>Median (month) PFS; EGFR mutated vs. EGFR wild type; 2.9 vs. 1.9; 0.425</p> <p>Median (month) OS; EGFR mutated vs. EGFR wild type; 6.8 vs. 7.8; 0.673</p> <p>Median (month) PFS; KRAS mutated vs. KRAS wild type; 1.3 vs. 2.0; 0.120</p> <p>Median (month) OS; KRAS mutated vs. KRAS wild type; 5.7 vs. 8.2; 0.039</p>	<p>Univariate</p>	<p><i>Study type</i> Cohort study <i>Level of evidence</i> 4</p> <p><i>Risk of bias</i> Participation: - Attrition: ? PF measurement: +</p> <p>Outcome measurement: ? Confounding: - Statistical analysis: -</p>

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
		<p>Stage IIIB (%): 50/ 36.2 IV (%): 50/ 63.8</p> <p>Treatment line 1 (%): 12.5/ 13.5 2 (%): 81.3/ 46 3 (%): 6.3/ 39.3 4 (%): 0/ 1.2</p> <p>ECOG PS 1 (%): 75/ 65 2 (%): 25/ 31.9 others (%): 0/ 3.1</p> <p><i>KRAS mutation status</i> (M+: n=14/ WT: n=160) Age (median): 56/ 63 Female (%): 35.7/ 16.3 Male (%): 64.3/ 83.8 Smoking status Current or former smoker (%): 85.7/ 94.4</p>					

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
		<p>Never smoker (%): 14.3/ 5.1</p> <p>EGFR-TKI Gefitinib (%): 50/ 49.4</p> <p>Erlotinib (%): 50/ 50.6</p> <p>Stage</p> <p>IIIB (%): 28.6/ 38.8</p> <p>IV (%): 71.4/ 61.3</p> <p>Treatment line</p> <p>1 (%): 0/ 2.5</p> <p>2 (%): 64.3/ 66.3</p> <p>3 (%): 35.7/ 30.6</p> <p>4 (%): 0/ 0.6</p> <p>ECOG PS</p> <p>0 (%): 7.1/ 13.8</p> <p>1 (%): 71.4/ 46.3</p> <p>2 (%): 21.4/ 38.8</p> <p>3 (%): 0/ 1.3</p> <p>ADC:43</p> <p>SLC: 16</p>					

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
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 oncology, 2008. 26 (20): p. 3351-57.	<p><i>Included</i> 76</p> <p><i>Attrition</i> NR</p> <p><i>Analyzed</i> NR</p> <p><i>Excluded from analysis</i> -</p>	<p><i>Inclusion</i> Not previously treated with chemotherapy or radiotherapy</p> <p><i>Setting</i> NR</p> <p><i>Country</i> USA</p> <p>Performance status of 0 or 1 Adequate organ function</p> <p>Sequential treatment arm: Paclitaxel 225 mg/m² and carboplatin every 3 weeks plus concurrent cetuximab 400 mg/m² by 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</p>		<p>EGFR (FISH: positive if tumors with ≥4 copies of the EGFR gene in ≥40% of cells or tumors with EGFR gene amplification)</p>	<p>Median (month) OS; positive vs. negative; 15 vs. 7 (HR=0.58); 0.046</p> <p>Median (month) PFS; positive vs. negative; 6 vs. 3 (HR=0.45); 0.0011</p> <p>Median (%) ORR; positive vs. negative; 45 vs. 26; NR</p> <p>FISH positive vs. FISH negative; NR; 0.049</p> <p>OS (follow-up NR)</p>	<p>Univariate</p>	<p><i>Study type</i> RCT</p> <p><i>Level of evidence</i> 4</p> <p><i>Risk of bias</i> Participation: - Attrition: ?</p> <p><i>PF measurement:</i> + <i>Outcome measurement:</i> ?</p> <p><i>Confounding:</i> - <i>Statistical analysis:</i> -</p>

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
		carboplatin for 4 cycles followed by cetuximab <i>Exclusion</i> NR <i>Patient characteristics</i> Female (%): 44 Male (%): 56 Age (median): 64 Race White (%): 84 Black (%): 9 Asian (%): 6 Unknown (%): 1 Smoking status Current smoker (%): 39 Former light smoker (%): 48 Never smoker (%): 12 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 (%): 57 Squamous cell carcinoma (%): 18 Other (%): 25 Stage IIIB (%): 9 IV (%): 91					
Kappers et al., Soluble epidermal growth factor receptor (sEGFR) and carcinoembryonic antigen (CEA) concentration in patients with non-small cell lung cancer: correlation with survival after erlotinib and gefitinib treatment. Ecancer 2010, 4:178: p: 1-11	<i>Included</i> 145 <i>Attrition</i> NR <i>Analyzed</i> 102 <i>Excluded from analysis</i> 43	<i>Inclusion</i> Advanced non-small cell lung cancer <i>Attrition</i> Not responding to conventional chemotherapy or unable to receive chemotherapy due to poor medical condition <i>Analyzed</i> Treated with gefitinib or erlotinib \geq 14 days <i>Excluded from analysis</i> Treated with gefitinib: daily dose of 250 mg or treated with erlotinib: daily dose of 150 mg Pre-treatment serum available for SEGFR	<i>Setting</i> Hospital <i>Country</i> Netherlands	Soluble EGFR determined by a sandwich quantitative enzyme-linked immunosorbent assay	Median (month) OS; sEGFR \geq 55 μ g/l/ sEGFR <55 μ g/l; 0.033 OS (median follow-up 161 days); per sEGFR μ g/l/ increment (not specified); HR = 1.044; 1.014-1.075	Univariate Multivariate (age, gender, smoking status, tumour stage, histology and treatment drug, CEA levels)	<i>Study type</i> Cohort study <i>Level of evidence</i> 4 <i>Risk of bias</i> Participation: ? Attrition: ? PF measurement: + Outcome 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
		<p>analysis</p> <p><i>Exclusion</i></p> <p>NR</p> <p><i>Patient characteristics</i></p> <p>Age (mean, SD): 59, 12.2</p> <p>Gender:</p> <p>Male: 54</p> <p>Female: 48</p> <p>Smoking status:</p> <p>Non: 21</p> <p>Former/Current: 78</p> <p>Tumour stage:</p> <p>III: 20</p> <p>IV: 81</p> <p>Histology:</p> <p>Adenocarcinoma: 66</p> <p>Non-small cell, undifferentiated: 20</p> <p>Squamous cell carcinoma: 13</p>					<p>Confounding: -</p> <p>Statistical analysis: -</p>

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
		Drug: Gefitinib: 67 Erlotinib: 35 sEGFR (μ g/l, mean): <55: 43 ≥55: 59					
Kelly et al., Evaluation of KRAS mutations, angiogenic biomarkers and DCE-MRI in patients with advanced non-small cell lung cancer receiving sorafenib; Clin. Cancer Research 2011, 17 (5): p.1190-1199	<p><i>Included</i> 37</p> <p><i>Attrition</i> NR</p> <p><i>Analyzed</i> 34 (KRAS) NR (EGFR)</p> <p><i>Excluded from analysis</i> 3 (KRAS) NR (EGFR)</p>	<p><i>Inclusion</i> 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 <i>Exclusion</i> Patients with symptomatic brain metastases (unless they had treatment and stable disease for at least 4 weeks)</p>	<p><i>Setting</i> NR</p> <p><i>Country</i> USA</p> <p><i>Setting</i> KRAS (Pyrosequencing technology on a PyroMark Q24 instrument and the PyroMark Q24 KRAS v2.0 kit)</p> <p><i>Setting</i> EGFR (pyrosequencing using a Genetic Analyzer 3130cl)</p>		<p>Median (month) OS; KRAS wildtype vs. KRAS mutant; 13.2 vs.7.2; p=0.59</p> <p>Median (month) PFS; KRAS wildtype vs. KRAS mutant; 3.6 vs.2.6; p=0.51</p> <p>Median ORR; KRAS wildtype vs. KRAS mutant; NR; no correlation (according authors)</p> <p>Median OS; EGFR wildtype vs. EGFR mutant; NR; no correlation (according authors)</p>	<p>Univariate</p>	<p><i>Study type</i> Cohort study</p> <p><i>Level of evidence</i> 4</p> <p><i>Risk of bias</i> Participation: - Attrition: ? PF measurement: + Outcome measurement: +</p> <p><i>Confounding:</i> - Statistical analysis: -</p>

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
		<p>least 3 month without steroids)</p> <p>Excluded in second protocol: patients with squamous cell carcinoma</p> <p><i>Patient characteristics</i></p> <p>Female (%): 49</p> <p>Male (%): 51</p> <p>Age (median): 61</p> <p>Histology</p> <p>ADC (%): 60</p> <p>Adenocarcinoma with BAC features: 24</p> <p>Squamous cell carcinoma (%): 8</p> <p>Poorly differentiated carcinoma (%): 5</p> <p>Others: 3</p> <p>Race</p> <p>White (%): 68</p> <p>African American (%):</p>			<p>authors)</p> <p>Median PFS; EGFR wildtype vs. EGFR mutant; NR; no correlation (according authors)</p> <p>Median ORR; EGFR wildtype vs. EGFR mutant; NR; no correlation (according authors)</p>		

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
		13 Asian (%): 11 Hispanic/Latino (%): 8 ECOG PS 0 (%): 14 PS 1 (%): 86 No. of prior chemotherapy and targeted regimens 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					

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
Kim et al., EGFR mutation: Significance as a stratification factor in the era of molecular-targeted therapy; Oncology letters 2011; 2; p: 383-387	<p><i>Included</i> 116</p> <p><i>Attrition</i> NR</p> <p><i>Analyzed</i> 83</p> <p><i>Excluded from analysis</i> 33</p>	<p><i>Inclusion</i> Stage IIIB/IV Received chemotherapy alone EGFR mutational status was known</p> <p><i>Exclusion</i> NR</p> <p><i>Patient characteristics</i> 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</p>	<p><i>Setting</i> NR</p> <p><i>Country</i> Japan</p>	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)	<p><i>Study type</i> Cohort study <i>Level of evidence</i> 2b</p> <p><i>Risk of bias</i> Participation: + Attrition: ?</p> <p><i>PF measurement:</i> + <i>Outcome measurement:</i> + <i>Confounding:</i> + <i>Statistical analysis:</i> ?</p>

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
		Large-cell carcinoma: 14 Tumour stage IIIB:16 IV: 67 Smoking status Current smoker: 20 Former smoker: 25 Never smoker: 38 EGFR Mutation: 28 Wild-type: 55 First-line chemotherapy Platinum based: 68 Single-agent: 15 No. of regimens (median, range): 3, 1-9 EGFR-TKI treatment yes: 52 no: 31					

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
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	<p><i>Included</i> 122</p> <p><i>Attrition</i> NR</p> <p><i>Analyzed</i> 105</p> <p><i>Excluded from analysis</i> 17</p>	<p><i>Inclusion</i> Patients who have archived tissue blocks for analysis of tumor EGFR gene</p> <p><i>Exclusion</i> NR</p> <p><i>Patient characteristics (Wild-type EGFR/ Mutated EGFR)</i> 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</p>	<p><i>Setting</i> Medical centres</p> <p><i>Country</i> China</p>	<p>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)</p>	<p>Median (months) OS; EGFR wild type vs. mutated mutation; 18.6 vs. 20.6; p=0.2159</p> <p>Median (months) PFS; EGFR wild type vs. mutated mutation; 6.6 vs. 6.1; p=0.2501</p> <p>Median (%) ORR; EGFR wild type vs. mutated; 30.6 vs. 44.6; p=0.162</p>	<p>Multivariate analysis (gender, smoking status, histology) Univariate</p>	<p><i>Study type</i> Cohort study</p> <p><i>Level of evidence</i> 2b</p> <p><i>Risk of bias</i> Participation: + Attrition: ?</p> <p><i>PF measurement:</i> +</p> <p><i>Outcome measurement:</i> +</p> <p><i>Confounding:</i> +</p> <p><i>Statistical analysis:</i> +</p>

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 (%): 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					

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

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
Mack et al., EGFR mutations detected in plasma are associated with patient outcome in erlotinib plus docetaxel-treated non-small cell lung carcinoma; Journal of thoracic oncology (2009); 4 (12); p: 1466-72,	<p><i>Included</i></p> <p>NR</p> <p><i>Attrition</i></p> <p>NR</p> <p><i>Analyzed</i></p> <p>49</p> <p><i>Excluded from analysis</i></p> <p>NR</p> <p><i>Exclusion</i></p> <p>NR</p> <p><i>Patient characteristics</i></p>	<p><i>Inclusion</i></p> <p>Patients with cytologically and histologically defined NSCLC</p> <p>Docetaxel 70 mg day 1 and erlotinib 600–800 mg days 2, 9, and 16 on a 21-d cycle (14.6% of patients)</p> <p>or Docetaxel 70–75 mg day 1 and erlotinib 150–300 mg days 2–16 on a 21-d cycle (25.0% of patients)</p> <p>or docetaxel 70 mg day 1 and erlotinib 200 mg days 2–16 on a 21-d cycle (60.4 % of patients)</p> <p><i>Exclusion</i></p> <p>NR</p>	<p><i>Setting</i></p> <p>NR</p> <p><i>Country</i></p> <p>USA</p>	<p>EGFR (DNA was extracted using QIAamp DNA Blood mini kit. Exons 19, 20 and 21 by allele-specific PCR assay using Scorpion-amplification refractory mutation system, patient was considered positive if a mutation was detected either in plasma or in tumor)</p>	<p>Median (months) PFS; EGFR wildtype vs. mutation; 18.3 vs. 4; 0.012</p> <p>Median (months) OS; EGFR wildtype vs. mutation; 39.6 vs. 17.8; ns</p> <p>Response rate; EGFR wildtype vs. mutation; NR; association (according authors)</p>	<p>Univariate</p>	<p><i>Study type</i></p> <p>Cohort study</p> <p><i>Level of evidence</i></p> <p>4</p> <p><i>Risk of bias</i></p> <p>Participation: ?</p> <p>Attrition: ?</p> <p>PF measurement: +</p> <p>Outcome measurement: ?</p> <p>Confounding: -</p> <p>Statistical analysis: -</p>

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
		<p><i>Characteristics</i></p> <p>Age (median, range): 59, 34-79</p> <p>Sex</p> <p>Female (%): 56.3</p> <p>Male (%): 43.7</p> <p>Smoking status</p> <p>Never-smoker (%): 33.3</p> <p>Former/current smoker (%): 66.7</p> <p>ECOG performance status</p> <p>0 (%): 50</p> <p>≥1 (%): 50</p> <p>Race</p> <p>African descent (%): 4.2</p> <p>White (%): 91.6</p> <p>East/ South East Asian (%): 4.2</p> <p>Histological type</p> <p>Adenocarcinoma (%): 66.6</p> <p>Squamous cell carcinoma (%): 14.6</p> <p>Other (%): 18.8</p>					
Pallis et al., A phase II trial of erlotinib as front-line treatment in clinically selected patients with non-small-	<p><i>Included</i></p> <p>49</p>	<p><i>Inclusion</i></p> <p>Chemotherapy-naïve nonsmokers (<100 cigarettes in life)</p>	<p><i>Setting</i></p> <p>NR</p>	<p>DNA sequencing of exons 18-21 of EGFR and exon 2 of KRAS (determined by direct forward and reverse)</p>	<p>ORR (18.9 months); EGFR mutated vs. wild type; 66.7% vs. 14.9%; 0.006</p>	<p>Univariate</p>	<p><i>Study type</i></p> <p>Cohort study</p> <p><i>Level of evidence</i></p>

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
cell lung cancer; Clinical lung cancer: 13 (2),p:129-35	<i>Attrition</i> NR <i>Analyzed</i> 36 <i>Excluded from analysis</i> 13	or histological or cytological confirmed inoperable locally advanced (stage IIIB) or metastatic (stage IV) NCSLC and histologic feature of adenocarcinoma ≥18 years At least 1 unidimensionally measurable 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	<i>Country</i> Greece	sequencing of the PCR).	Median (months) PFS; EGFR mutated vs. wild type; 12.4 vs. 5.8; 0.078 Median (months) OS; EGFR mutated vs. wild 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		4 <i>Risk of bias</i> <i>Participation:</i> ? <i>Attrition:</i> ? <i>PF measurement:</i> + <i>Outcome measurement:</i> ? <i>Confounding:</i> - <i>Statistical analysis:</i> -

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
		<p>No history of cardiac disease</p> <p>Erlotinib 150 mg per day orally</p> <p><i>Exclusion</i></p> <p>NR</p> <p><i>Patient characteristics</i></p> <p>Age (median, Range): 68, 36-81</p> <p>Sex</p> <p>Male (%): 34.7</p> <p>Female (%): 65.3</p> <p>Performance status</p> <p>0 (%): 22.4</p> <p>1 (%): 71.4</p> <p>2 (%): 6.1</p> <p>Stage</p> <p>IIIB (%): 14.3</p> <p>IV (%): 85.7</p> <p>Histologic type</p> <p>AdenoCA (%): 93.9</p> <p>Bronchoalveolar (%): 6.1</p> <p>Grade</p>					

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
		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; Chinese Medical Journal 2011; 124 (1); p: 19-25	<i>Included</i> 28 <i>Attrition</i> NR <i>Analyzed</i> 14 <i>Excluded from analysis</i> NR	<i>Inclusion</i> Histologically or cytologically confirmed to be with stage III or IV NSCLC <i>Country</i> Measurable tumors with Response Evaluation criteria in solid tumors 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 <i>Exclusion</i>	<i>Setting</i> NR <i>Country</i> 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. 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	Univariate	<i>Study type</i> <i>Cohort study</i> <i>Level of evidence</i> 4 <i>Risk of bias</i> <i>Participation:</i> ? <i>Attrition:</i> ? <i>PF measurement:</i> + <i>Outcome measurement:</i> ? <i>Confounding:</i> - <i>Statistical analysis:</i> -

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
		<p>NR</p> <p><i>Patient characteristics</i></p> <p>Sex</p> <p>Female: 8</p> <p>Male: 6</p> <p>Age (median, range): 53.5, 40-67</p> <p>Histologic type</p> <p>Adenocarcinoma: 11</p> <p>Bronchioles alveolar carcinoma: 1</p> <p>Squamous cell carcinoma: 2</p> <p>Stage</p> <p>III: 3</p> <p>IV: 11</p>			<p>Median (days) OS: KRAS mutated vs. wildtype: NR vs.not reached; NR</p>		
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;	<p><i>Included</i></p> <p>113</p> <p><i>Attrition</i></p> <p>NR</p> <p><i>Analyzed</i></p>	<p><i>Inclusion</i></p> <p>≥18 years</p> <p>Histological confirmed measurable stage III or IV nonsquamous NSCLC</p> <p>Eastern Cooperative Oncology Group 0-1</p>	<p><i>Setting</i></p> <p>NR</p> <p><i>Country</i></p> <p>Germany</p>	<p>KRAS (detected using the QIAGEN KRAS PCR Kit)</p>	<p>Median ORR; KRAS mutated vs. wild type; NR; no significant association (according authors)</p> <p>Median PFS; KRAS mutated vs. wild type; NR; no significant</p>	<p>Univariate</p>	<p><i>Study type</i></p> <p>Cohort study</p> <p><i>Level of evidence</i></p> <p>4</p> <p><i>Risk of bias</i></p> <p>Participation: -</p>

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
Lung Cancer (2013): 81; p: 428-34	47 <i>Excluded from analysis</i> 66	Tissue availability for detection of EGFR expression Estimated life expectancy of ≥ 12 weeks Treated with 4-6 cycles pemetrexed 500 mg/m ² IV plus cisplatin 75 mg /m ² IV on day 1 of each 21-day cycle; cetuximab 400 mg/m ² IV Cycle 1/ day 1 with subsequent doses of 250 mg/m ² IV weekly <i>Exclusion</i> Prior systemic chemotherapy, immunotherapy, targeted therapy or biological therapy for NSCLC Patients with symptomatic central nervous system metastasis < 1 year			association (according authors)		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
		<p>prior to enrollment</p> <p>Serious conditions within 6 months of study treatment</p> <p>Common Terminology Criteria for Adverse Events≥grade 1 peripheral neuropathy or major surgery within 4 weeks of study entry</p> <p>Unwilling or unable to take folic acid, vitamin B12 or corticosteroids</p> <p>Uncontrollable clinically significant third-space fluid</p> <p><i>Patient characteristics</i></p> <p>All treated</p> <p>Age (median, range): 59.7, 38.1-78.7</p> <p>Sex</p> <p>Male (%): 63.7</p> <p>Caucasian (%): 100</p> <p>ECOG PS</p>					

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
		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*	<i>Included</i> 393 <i>Attrition</i> - <i>Analyzed</i> 293 (EGFR ICH) 208 (EGFR FISH) 195 (KRAS/EGFR mutations) <i>Excluded from analysis</i>	<i>Inclusion</i> ≥18 years Histologically or cytologically confirmed, unresectable stage IIIB/IV NSCLC <i>Setting</i> NR <i>Country</i> Germany <i>Performance status</i> Eastern cooperative oncology group performance status 0-3 <i>Exclusion</i> 1 or 2 prior courses of standard chemotherapy or radiotherapy or were 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	<i>Setting</i> NR <i>Country</i> Germany	<i>EGFR protein expression (EGFR PharmDx immunohistochemistry kit)</i>	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 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;	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
	100 (EGFR ICH) 185 (EGFR FISH) 185 (KRAS/EGFR mutations) 195	<p>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</p> <p><i>Exclusion</i></p> <p>Evidence of unstable systemic disease Prior treatment with anti-EGFR agents Previous malignancies (last 5 years, other than successful treatment for cervical carcinoma/ skin cancer) Untreated brain metastasis or spinal cord compression</p>		EGFR FISH (samples with high gene copy number were classed as FISH-positive)	<p>0.46-9.34</p> <p>Response (maximum 800 days); EGFR (IHC any) vs. none; OR=2.41; 0.31-18.83</p> <p>Median (months) OS; FISH positive vs. FISH negative; 8.6 vs. 6.1; NR</p> <p>PFS (maximum 800 days); FISH negative vs. positive; HR = 0.58; 0.42-0.82</p> <p>OS (maximum 800 days); FISH negative vs. positive; HR = 0.63; 0.43-0.91</p> <p>Response (maximum 800 days); FISH positive vs. negative; OR=3.32, 1.09-10.14</p>		-

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
		<p>Significant ophthalmologic abnormalities</p> <p><i>Patient characteristics</i></p> <p>Age (median, range): 65, 31-90</p> <p>Gender</p> <p>Female (%): 41</p> <p>Male (%): 59</p> <p>Ethnic origin</p> <p>Caucasian (%): 99</p> <p>Oriental (%): 1</p> <p>Histology</p> <p>Adenocarcinoma (%): 51</p> <p>Squamous cell carcinoma (%): 32</p> <p>Other (%): 18</p> <p>Smoking status</p> <p>Never-smoker (%): 24</p> <p>Former or current smoker (%): 75</p> <p>ECOG PS</p> <p>0 (%): 22</p> <p>1 (%): 51</p> <p>2 (%): 21</p>		<p>EGFR exon 18-21 (nested primers PCR with Hot Star Taq)</p> <p>KRAS 2 and 3 (nested primers PCR with Hot Star Taq)</p>	<p>PFS (maximum 800 days); EGFR wildtype vs. mutation; HR= 0.31; 0.13-0.78</p> <p>OS (maximum 800 days); EGFR wildtype vs. mutation; HR = 0.33; 0.12-0.91</p> <p>Response (maximum 800 days); EGFR mutation vs. wildtype; OR=33.0, 2.96-370.4</p> <p>PFS (maximum 800 days); KRAS wildtype vs. mutation; HR=1.56; 0.92-2.65</p> <p>OS; KRAS wildtype vs. mutation; HR=1.64; 0.97-2.80</p> <p>Response (maximum 800 days); KRAS mutation vs.</p>		

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 (%): 5 Stage IIIB (%): 21 IV (%): 79 Line of therapy 1 st (%): 19 2 nd (%): 40 3 rd (%): 37 Tumor characteristics (positive) EGFR IHC ($\geq 10\%$, %): 81 EGFR IHC (%): 88 EGFR FISH (%): 24 EGFR mutations (%): 7 KRAS mutations (%): 15			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.	<p><i>Included</i> 85</p> <p><i>Attrition</i> NR</p> <p><i>Analyzed</i> 60</p> <p><i>Excluded from analysis</i> NR</p>	<p><i>Inclusion</i> Patients with miliary intrapulmonary carcinomatosis at initial diagnosis</p> <p><i>Exclusion</i> NR</p> <p><i>Patient characteristics (EGFR mutation/ wild-type)</i> 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/</p>	<p><i>Setting</i> University hospital</p> <p><i>Country</i> Taiwan</p>	<p>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)</p>	<p>Median (months) PFS; EGFR mutated vs. wild type: 9.2 vs. 2.7; <0.001</p> <p>Median (months) OS; EGFR mutated vs. wild type; 17.8 vs. 10.6; 0.008</p> <p>OS; EGFR mutated vs. wild type; HR=0.19; 0.08-0.44</p>	<p>Univariate</p> <p>Univariate</p> <p>Multivariate (adjusted for sex, age, smoking status, tumour type, extra pulmonary metastasis, EGFR mutation status, EGFR-TKI use and treatment order)</p>	<p><i>Study type</i> <i>Cohort study</i> <i>Level of evidence</i> 2b</p> <p><i>Risk of bias</i> <i>Participation:</i> ? <i>Attrition:</i> ?</p> <p><i>PF measurement:</i> + <i>Outcome measurement:</i> ? <i>Confounding:</i> + <i>Statistical analysis:</i> +</p>

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 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.	<p><i>Included</i> 100</p> <p><i>Attrition</i> NR</p> <p><i>Analyzed</i> NR</p> <p><i>Excluded from analysis</i> NR</p>	<p><i>Inclusion</i> Inoperable stage IIIB/IV NSCLC</p> <p><i>Attrition</i> Adults (≥ 20 years) with cytological or histological confirmation of locally advanced or metastatic NSCLC</p> <p><i>Analyzed</i> Underwent prospective screening for EGFR mutations</p> <p><i>Excluded from analysis</i> ≥1 measurable or assessable lesion according to Response Evaluation Criteria in Solid Tumors Gefitinib treatment or cytotoxic chemotherapy</p> <p><i>Exclusion</i> Pulmonary fibrosis, interstitial pneumonia or prior treatment with EGFR TKI or antibody</p>	<p><i>Setting</i> Cancer center</p> <p><i>Country</i> Japan</p>	EGFR (exon 19 deletion mutation determined by common fragment analyses using PCR with FAM-labeled primer set, PCR products were subjected to electrophoresis on an ABI PRISM 310 instrument)	<p>ORR first-line gefitinib (median 22.2 months); EGFR mutated vs. wild-type: 87% vs. 0; NR</p> <p>ORR after second-line gefitinib (median 22.2 months); EGFR mutated vs. wild-type: 80 vs. 0; NR</p> <p>ORR to first-line cytotoxic chemotherapy (median 22.2 months); EGFR mutated vs. wild-type; 32% vs. 28%; 0.7198</p> <p>ORR to second-line cytotoxic chemotherapy (%); EGFR mutated vs. wild-type; 20 vs. 6.9; 0.1690</p> <p>Median (months) PFS in patients treated with cytotoxic chemotherapy as first-line therapy;</p>	Univariate	<p><i>Study type</i> <i>Cohort study</i> <i>Level of evidence</i> 2b</p> <p><i>Risk of bias</i> <i>Participation:</i> + <i>Attrition:</i> ?</p> <p><i>PF measurement:</i> + <i>Outcome measurement:</i> ? <i>Confounding:</i> + <i>Statistical analysis:</i> +</p>

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
		<p><i>Patient characteristics (Mutation/ Wild-type)</i></p> <p>Sex Female: 33/ 14 Male: 15/ 38 $p<0.0001$</p> <p>Age ≤ 60: 18/ 23 >60: 30/29</p> <p>$p=0.4942$</p> <p>Histology Adenocarcinoma: 47/ 48 Non-adenocarcinoma: 1/ 4 $p=0.1985$</p> <p>Smoking status Never smoker: 32/ 11 Smoker: 16/ 41 $p<0.0001$</p> <p>Stage of initial diagnosis IIIB: 7/ 17 IV: 41/ 35 $p=0.0341$</p> <p>ECOG PS at initial diagnosis 0/1: 42/ 40 2: 2/ 7 3: 3/ 3</p>			<p>EGFR mutated vs. wild type; HR = 1.095; 0.668-1.794</p> <p>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</p> <p>OS after first-line treatment; EGFR mutation yes vs. no; HR=1.928; 1.048-3.545</p>	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
		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/ -					

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

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.	<p><i>Included</i></p> <p>79</p> <p><i>Attrition</i></p> <p>NR</p> <p><i>Analyzed</i></p> <p>17 biomarker analysis)</p> <p><i>Excluded from analysis</i></p> <p>62</p>	<p><i>Inclusion</i></p> <p>Histologically or cytological diagnosis of NSCLC</p> <p>Stage IIIB or IV</p> <p>Existence of measurable focus</p> <p>No prior use of anti-EGFR agents</p> <p>Erlotinib p.o. 150 mg per day</p> <p><i>Exclusion</i></p> <p>NR</p> <p><i>Patient characteristics</i></p> <p>Age (median, range)): 60.9, 35-83</p> <p>Sex</p> <p>Male (%): 63.3</p> <p>Female (%): 36.7</p> <p>ECOG Performance status</p> <p>0 (%): 38</p> <p>1 (%): 31.5</p>	<p><i>Setting</i></p> <p>NR</p> <p><i>Country</i></p> <p>China</p>	<p>EGFR exon 19/21/ KRAS gene mutations (mutant-enriched PCR assay and multiplex branched DANN assay, high expression defined as EGFR mRNA > 75% percentile)</p>	<p>ORR (minimum 3 months); EGFR mRNA expression high vs. mid-low; 16.7 vs. 36.4; 0.600</p> <p>ORR(minimum 3 months); EGFR mutation vs. wild-type; 50 vs. 11.1; 0.131</p> <p>ORR(minimum 3 months); KRAS mutation yes vs. no; 0 vs. 35.7; 0.515</p> <p>Median (weeks) PFS; EGFR mutation vs. wild-type; 66 vs. 12; 0.018</p> <p>Median (weeks) PFS: EGFR mRNA expression high vs. mid-low; 36 vs. 220.123</p> <p>Median (weeks) PFS; KRAS mutation yes vs. no; NR0.97</p>	<p>Univariate</p>	<p><i>Study type</i></p> <p>Cohort study</p> <p><i>Level of evidence</i></p> <p>4</p> <p><i>Risk of bias</i></p> <p>Participation: +</p> <p>Attrition: ?</p> <p>PF measurement: +</p> <p>Outcome measurement: ?</p> <p>Confounding: -</p> <p>Statistical analysis: -</p>

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
		<p>2 (%): 13.9 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</p> <p>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</p>					

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
		<p>Further chemotherapy Yes (%): 39.2 No (%): 60.8</p> <p>EGFR mRNA expression High (%): 35.3 Mid-low (%): 64.7</p> <p>EGFR gene mutation Exon 19 mutation (%): 29.4 Exon 21 mutation (%): 17.6 No (%): 52.9</p> <p>KRAS gene mutation Yes (%): 17.6 No (%): 82.4</p>					
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	<i>Included</i> 1NR	<i>Inclusion</i> Being diagnostically confirmed with the disease by pathologists	<i>Setting</i> NR	EGFR (Denaturing high performance liquid chromatography method)	ORR (follow-up NR); mutation vs. wild-type; 37% vs. 31.9%; 0.525	Univariate	<i>Study type</i> Cohort study <i>Level of evidence</i> 2b
	<i>Attrition</i> NR	Receiving confirmed first-line chemotherapy for at least two cycles	<i>Country</i> China		Median (months) PFS; EGFR mutation vs. wild-type; 4 vs. 3; ns		<i>Risk of bias</i> Participation: ?
	<i>Analyzed</i> 145	Having response data for chemotherapy and targeted therapy Availability of peripheral			OS (follow-up NR); EGFR wildtype vs. mutation; HR=0.187; 0.141-0.412	Multivariate (factors NR)	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
	<p><i>Excluded from analysis</i></p> <p>NR</p> <p><i>Exclusion</i></p> <p>NR</p> <p><i>Patient characteristics (EGFR mutation/ wild-type)</i></p> <p>Age (mean, range): 60.5, 27-76/ 62, 42-78</p> <p>Gender</p> <p>Male (%): 53.7/ 54.9</p> <p>Female (%): 46.3/ 45.1</p> <p>Histology</p> <p>Adenocarcinoma (%): 87/ 64.8</p> <p>Non-adenocarcinoma (%): 13/ 35.2</p> <p>Disease stage</p> <p>III (%): 33.3/ 25.3</p> <p>IV (%): 66.7/ 74.7</p> <p>ECOG</p> <p>0-1 (%): 88.9/ 87.9</p> <p>2 (%): 11.1/ 12.1</p> <p>Chemotherapy regimens</p>						<p>?</p> <p>PF measurement: +</p> <p>Outcome measurement: ?</p> <p>Confounding: ?</p> <p>Statistical analysis: ?</p>

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
		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]; I ² / 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 number of patients	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 A-priori design: ? Two reviewers: + Literature search: +

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
	<p>with KRAS should be more than five Hazard ration (HRs) for overall survival according to KRAS mutation status either had to be reported or could be calculated from the data presented</p> <p>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</p> <p>Published as a full text in English</p> <p>Exclusion criteria</p> <p>NR</p>			<p>Status of publication:</p> <ul style="list-style-type: none"> - <p>List of studies: +</p> <p>Study characteristics:</p> <ul style="list-style-type: none"> + <p>Critical appraisal:</p> <ul style="list-style-type: none"> + + <p>Conclusion:</p> <ul style="list-style-type: none"> + + <p>Combining findings:</p> <ul style="list-style-type: none"> + + <p>Publication bias:</p> <ul style="list-style-type: none"> + + <p>Conflict of interest:</p> <ul style="list-style-type: none"> - -

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-/CG) of study population	Intervention(s), control and patient flow (IG-/CG)	Outcomes (IG-/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Adverse events (IG-/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 Thoracic 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	Intervention(s) <i>Adjuvant chemotherapy</i> Erlotinib n=2 Cisplatin + gemcitabine n=1 Carboplatin + taxol n=1 Pemetrexed n=1 Erlotinib + pemetrexed n=1	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
	<p>at the time of surgery Death within 1 month of surgery Who did not receive postoperative radio therapy (PORT)</p> <p>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</p>	<p>Included patients 61</p> <p>Analysed patients 42/14</p> <p>Attrition NR</p> <p>Excluded from analysis (reason) NR</p>			<p>concealment: -</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome assessment: + Incomplete outcome data: ?</p> <p>Selective reporting: +</p> <p>Other source of bias: - (results are reported inconsistently)</p>

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
	<p>T2 (%): 54.1 T3 (%): 16.4 T4 (%): 11.5</p> <p>Clinical N status N0 (%): 1.6</p> <p>Clinical M status M0 (%): 100</p> <p>Level of N2 involvement at surgery Single station (%): 73.8 Multiple station (%): 26.2</p> <p>Tumor histology Moderate (%): 27.9 Poor (%): 62.3 unclear (%): 9.8</p> <p>RECIST response CR/RR (%): 47.5 SD/PD (%): 47.5</p> <p>Type of surgery Lobectomy/bilobectomy (%): 80.3 Wedge/segmentectomy (%):</p>				

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
	<p>6.6 Pneumonectomy (%): 13.1</p> <p><i>Pathologic T status</i> T1 (%): 29.5 T2 (%): 55.7 T3 (%): 8.2 T4 (%): 6.6</p> <p><i>Postoperative chemotherapy</i> Concurrent (%): 14.8 Adjuvant (%): 6.6 Both (%): 3.3 None (%): 75.4</p>				
<p>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.</p>	<p>Region USA</p> <p>Inclusion criteria ≥18 years Completely resected T2N0, T1N1 or T2N1 non-small-cell lung cancer</p> <p>Acceptable baseline</p>	<p>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</p>	<p>OS (median 9.3 years) 47.1% / 40.4%; HR= 1.28; 1.01-1.64</p> <p>Disease specific survival (median 9.3 years); 63.6/56.2; HR= 1.37; 1.04-1.81</p>	<p>Drug-related adverse events among patients who received at least one dose of vinorelbine plus cisplatin</p> <p>Fatigue (%): 81 Anorexia (%): 55 Alopecia (%): 32 Local toxicity (%): 35 Diarrhea (%): 23</p>	<p>Study type RCT</p> <p>Level of evidence 2b</p> <p>Risk of bias Generation of allocation sequence:</p>

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
<p>Journal of clinical oncology (2010), 28 (1); p.: 29-34.</p> <p>Winton T. et al., Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer, NEJM (2005), 352 (25), p: 2586-2597.</p>	<p>characteristics ECOG performance status of 0 or 1</p> <p>Mandatory: Preoperative computed computer tomographic scan and intraoperative mediastinal lymph-node resection or biopsy of nodes that were 1.5 cm or larger</p> <p>Exclusion criteria Incomplete preoperative or intraoperative staging Incomplete resection, wedge or segmental resection Involvement of tracheobronchial angle nodes (station 10) or more central</p>	<p>Control Observation</p> <p>Included/randomised patients 240/ 242</p> <p>Analysed patients 240/ 242</p> <p>Attrition 18/15</p> <p>Excluded from analysis (reason) NR (received at least one dose)</p>		<p>Nausea (%): 80 Vomiting (%): 48 Constipation (%): 47 Infection (%): 22 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</p>	<p>?</p> <p>Allocation concealment: ?</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome assessment: +</p> <p>Incomplete outcome data: +</p> <p>Selective reporting: +</p> <p>Other source of bias: ?</p>

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
	<p>mediastinal nodes</p> <p>Mixed histologic features</p> <p>A T3 tumor, or diffuse lobar or multifocal bronchioalveolar carcinoma, melanoma, or other cancer treated within the previous five years</p> <p>Clinically significant cardiac dysfunction, active infection, or neurologic or psychiatric disorders</p> <p>Patient characteristics</p> <p>Age (median): 60.5/ 61</p> <p>Female (%):34/ 36</p> <p>ECOG PS</p> <p>0 : 120/ 116</p> <p>1 : 122/123</p>				

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
	<p><i>Smoking status</i> ever smoked (%): 96/ 91 No longer smoking (%): 84/ 85</p> <p><i>Postsurgical stage</i> T2N0 (%): 46/ 45 T1N1 (%): 16/ 13 T2N1 (%): 38/ 42</p> <p><i>Histology</i> Adenocarcinoma (%): 53/ 53 Squamous (%): 37/38 Other (%): 10/ 9</p> <p><i>Comorbidity</i> None (%): 66.5 / 77 Present (%): 33.5 / 32</p> <p><i>RAS mutation</i> Absent (%): 68/ 71 Present (%): 24/ 24 Unknown (%): 8/ 5</p> <p><i>Tumor diameter (stage IB)</i> <4 cm : 45/ 54 ≥4 cm : 66/ 54</p>				
Douillard J-Y. et al.;	Region	Intervention(s)	Progression free	WHO grade >0	Study type

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
<p>Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International trial Association [ANITA]: a randomized controlled trial Lancet Oncol 2006; 7: p. 719-27.</p>	<p>Europe</p> <p>Inclusion criteria Stage I (T2N0 only), stage II and stage IIIA NSCLC</p> <p>Complete resection of the primary tumor (all margins free of disease: R0)</p> <p>Age 18-75 years</p> <p>WHO performance status ≤2</p> <p>Adequate biological functions</p> <p>Exclusion criteria History of concurrent malignant disease (apart from adequately treated non-melanoma skin cancer or in-situ cervical cancer) Previous primary</p>	<p>Vinorelbine 30 mg/m² on days 1, 8, 15 and 22 (cycles repeated every 4 weeks) for maximum of 16 doses and cisplatin 100 mg/m² on days 1, 29, 57 and 85</p> <p>Control Observation</p> <p>Included/randomised patients 407/ 433</p> <p>Analysed patients 407/ 433</p> <p>Attrition NR</p> <p>Excluded from analysis (reason) NA</p>	<p>survival (median 76/ 77 months) 14%/8%; HR= 1.316; 1.099-1.563</p> <p>Median progression free survival (months) 36.3/20.7; NR; NR</p> <p>OS (median 76/77 months)</p> <p>Difference between groups 8.4%; HR= 1.25; 1.042-1.515</p> <p>Median survival (months) 65.7/43.7; NR; ns</p> <p>The test of interaction for survival</p>	<p>Neutropenia (%): 92/ 4</p> <p>Anaemia (%): 78/ 6</p> <p>Thrombocytopenia (%): 14/ 1</p> <p>Febrile neutropenia (%): 9/ 0</p> <p>Infection (%): 32/ 10</p> <p>Nausea or vomiting (%): 80/ 7</p> <p>Diarrhoea (%): 16/ 2</p> <p>Constipation (%): 45/ 5</p> <p>Anorexia (%): 71/ 17</p> <p>Asthenia (%): 82/ 32</p> <p>Peripheral neuropathy (%): 28/ 1</p> <p>Alopecia (%): 57/ 0</p>	<p>RCT</p> <p>Level of evidence</p> <p>2b</p> <p>Risk of bias</p> <p>Generation of allocation sequence: ?</p> <p>Allocation concealment: -</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome assessment: +</p> <p>Incomplete outcome data: +</p>

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
	<p>tumors</p> <p>Patient characteristics</p> <p>Age (median, range): 59, 32-75/ 59, 18-75</p> <p>< 55 years (%): 33/35</p> <p>≥ 55 years (%): 67/ 65</p> <p>Sex</p> <p>Female (%): 14/ 13</p> <p>Time from surgery to randomization (days, median, range): 34 , 6-5/ 33, 7-53</p> <p>Type of surgery</p> <p>Pneumonectomy (%): 38/ 36</p> <p>Lobectomy (%): 57/ 58</p> <p>Other (%): 4/ 5</p> <p>Postoperative stage</p> <p>I (%): 36/ 36</p> <p>II (%): 22/ 26</p> <p>IIIA (%): 41/ 37</p> <p>Lymph nodal status</p> <p>NO (%): 44/ 43</p>		<p>Nodal status positive vs. negative; 0.004</p> <p>Local relapse (median 76/ 77 months)</p> <p>12% vs. 18%; NR; 0.025</p>		<p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	<p>N1 (%): 26/ 31 N2 (%): 29/ 24</p> <p>Histology Squamous-cell carcinoma (%): 59/ 58 Non squamous cell carcinoma (%): 40/ 41</p> <p>WHO-performance status 0 (%):48/ 52 1 (%): 47/ 44 2 (%): 3/ 3</p>				
<p>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.</p>	<p>Region Europe</p> <p>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-</p>	<p>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)</p> <p>Treatment was repeated every 3 weeks for three cycles</p>	<p>Disease free survival (5 years) 36.6%/34.1%; HR=1.042; 0.82-1.33</p> <p>OS (5 years) 45.5/44%; HR = 0.99; 0.606-1.613</p>	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	<p>Study type RCT</p> <p>Level of evidence 2b</p> <p>Risk of bias Generation of allocation sequence: ? Allocation concealment:</p>

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
	<p>2</p> <p>Absence of previous chemotherapy or radiotherapy</p> <p>Adequate hematologic, hepatic and renal function</p> <p>Deemed fit for chemotherapy and proposed surgical resection</p> <p>Exclusion criteria</p> <p>Previous cancer other than nonmelanoma skin cancer or carcinoma in situ to the cervix</p> <p>Clinically significant cardiac dysfunction, active infection or neurologic or psychiatric disorders</p>	<p>Control</p> <p>Surgery alone + observation</p> <p>Included/randomised patients</p> <p>211/ 212</p> <p>Analysed patients</p> <p>210/ 210</p> <p>Attrition</p> <p>NR</p> <p>Excluded from analysis (reason)</p> <p>0/0</p>		<p>Sensory neuropathy (%): 32.4/ NR</p> <p>Allergic reaction (%): 2.2/ NR</p>	<p>+ Blinding of participants and personal:</p> <p>-</p> <p>Blinding of outcome assessment:</p> <p>+ Incomplete outcome data:</p> <p>+ Selective reporting:</p> <p>+ Other source of bias:</p>

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
	<p>Patient characteristics</p> <p>Age (median, range): 64, 33-81/ 64 36-89,</p> <p>Sex</p> <p>Female (%): 13.8/ 12.4</p> <p>ECOG performance status</p> <p>0 (%):45.2/ 48.6</p> <p>1 (%):52.9/ 50</p> <p>Histological features</p> <p>Squamous-cell carcinoma (%):49/ 50</p> <p>Adenocarcinoma (%):32.9/ 33.8</p> <p>Large-cell carcinoma (%):11.4/ 10</p> <p>Others (%):6.7/ 6.2</p> <p>Clinical stage</p> <p>T1N0 (%):14.3/ 9.5</p> <p>T2N0 (%):63.3/ 63.8</p> <p>T2N1 (%): 11.9/ 11.9</p> <p>T3N0 (%):8.6/ 12.4</p>				
Gottfried M. et al.,	Region	Intervention(s)	Median survival	Adjuvant/ Control	Study type

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
<p>Cisplatin-based three drugs combination (NIP) as induction and adjuvant treatment in locally advanced non-small cell lung cancer, Journal of thoracic oncology (2008), 3 (2), p: 152- 57.</p>	<p>Europe</p> <p>Inclusion criteria</p> <p>Present histologic and/or cytologic evidence of NSCLC</p> <p>Locally advanced disease (T3/T4 or IIIA tumors) without any previous treatment</p> <p>Aged ≥18</p> <p>Eastern Cooperative Oncology Group performance status ≤2</p> <p>Life expectancy ≥3 months</p> <p>At least one assessable lesion, with blood and biochemical parameters within normal ranges</p>	<p>Adjuvant cisplatin-based three drugs combination (NIP) chemotherapy (two cycles): vinorelbine 25 mg/ m² IV in days 1 and 5, ifosamide/ 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.</p> <p>Control</p> <p>Observation</p> <p>Included/randomised patients 37/ 42</p> <p>Analysed patients</p>	<p>(months)</p> <p>31.8/ 32.3; NR; NR</p> <p>Median disease-free survival (months)</p> <p>16.8/ 16.8; NR; NR</p>	<p>Nausea/vomiting (%): 12.5/ 0</p> <p>Alopecia (%): 19/ 0</p> <p>Infection (%): 6/ 3</p> <p>Asthenia (%): 6/ 3</p> <p>Pain (%): 0/ 6</p> <p>Anorexia (%): 0/ 3</p>	<p>RCT</p> <p>Level of evidence</p> <p>2b</p> <p>Risk of bias</p> <p>Generation of allocation sequence: ?</p> <p>Allocation concealment: ?</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome assessment: +</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting:</p>

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
	<p>Exclusion criteria</p> <p>Superior vena cava syndrome</p> <p>Central nervous system metastasis</p> <p>Second malignancy (except adequately treated basal cell carcinoma of the skin and carcinoma in situ of the uterine cervix)</p> <p>Active infectious disease</p> <p>Pregnancy</p> <p>Neurologic disorders which could interfere with the evaluation of neurologic toxicity and mentally incapacitated patients</p> <p>Family, social or environmental conditions impairing</p>	<p>37 / 42</p> <p>Attrition NR</p> <p>Excluded from analysis (reason) NR</p>			<p>+</p> <p>Other source of bias: +</p>

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
	<p>adequate follow-up and protocol compliance</p> <p>Breast-feeding</p> <p>Patient characteristics</p> <p>Age (median, range): 59, 35-75</p> <p>Sex</p> <p>Female (%): 15</p> <p>Histology</p> <p>Squamous cell (%): 52</p> <p>Adenocarcinoma (%): 31</p> <p>Large cell carcinoma (%): 6</p> <p>NSCLC (NOS) (%): 11</p> <p>Stage at diagnosis</p> <p>IIB (%): 28</p> <p>IIIA (%): 65</p> <p>IIIB (%): 7</p> <p>Performance status</p> <p>0-1 (%): 99</p>				

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 (%): 1 T diameter (cm, median, range): 5.5, 1.2–10.6 N0 (%): 34 N1 (%): 1 N2 (%): 65				
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	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	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: -

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
	<p>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 Adequate organ function</p> <p>Exclusion criteria Serious concurrent conditions</p> <p>Patient characteristics <u>Group B/ A Sex</u> Male : 49/ 49 Female : 36/ 38 Age (average): 60.2/ 60.9 PS</p>	<p>at 400 mg day⁻¹ for at least 1 year</p> <p>Control Group A (Stage I): observation Group C (Stages II and IIIA): observation</p> <p>Included/ randomised patients A / B: 87/ 85 C /D: 48/ 47</p> <p>Analysed patients A/B: 87/ 85 C/D: 48/ 47</p> <p>Attrition NR</p> <p>Excluded from analysis (reason) NR</p>			<p>Blinding of outcome assessment: + Incomplete outcome data: ? Selective reporting: + Other source of bias: - (no adjustment for multiple comparisons)</p>

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
	<p>0: 66/ 66 1: 19/19 2: 0/ 2</p> <p>pT 1: 45/41 2 : 40/ 46</p> <p>Stage I: 85 / 87</p> <p>Histology Adenocarcinoma: 68/ 67 Squamous cell carcinoma: 15/ 17 Large cell carcinoma: 2/ 3</p> <p>DNA pattern Diploidy: 17/ 18 Aneuploidy: 68/ 69</p> <p>Group D/ C</p> <p>Sex Male: 35/ 35 Female: 12/ 13 Age (average): 60.5/ 59.3</p>				

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 0: 35 / 36 1: 10/12 2: 2 / 0 pT 1: 13/ 12 2: 24/ 24 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	Region China	Intervention(s) Surgery plus adjuvant vinorelbine (25 mg/m ²) administered as a 10-	Median OS (months) 33/ 24; NR; ns	Vinorelbine/Paclitaxel/CG Severe adverse events (%): 5.3/ 2.4/ NR	Study type RCT Level of evidence

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non-small cell lung cancer; Journal of thoracic oncology (2010), 5 (7); p: 1033-41.	Inclusion criteria Age 18 to 75 Eastern Cooperative Performance status ≤1 No significant weight loss Adequate bone marrow reserves CT scans for chest, abdomen, and magnetic resonance imaging or CT scans of brain to exclude any systematic involvement	minute infusion on days 1 and 8)/ carboplatin OR paclitaxel (175 mg/m ² given as a 3-hour infusion in day 1) /carboplatin (AUC=5) doublets Control surgery plus observation	OS (median 35/ 28 months) NR/NR; HR=1.505; 1.040-2.178 Median disease free survival (months) 32/ 20; NR; NR Disease free survival (median 35/ 28 months) NR/ NR; HR=1.560; 1.064-2.287	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	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
	<p>Received previous chemotherapy, immunotherapy or thoracic irradiation</p> <p>Underwent sleeve or wedge resection of the tumor</p> <p>Patient characteristics</p> <p>Age (median, range): 54, 31-73/ 59, 24-75</p> <p>p=0.629</p> <p>Sex</p> <p>Male (%): 70.8/ 76.1</p> <p>Female (%): 29.2/ 23.9</p> <p>p=0.475</p> <p>Histologic features</p> <p>Squamous (%): 22.8/ 33.8</p> <p>Nonsquamous (%): 79.2/ 69.2</p> <p>p=0.133</p> <p>T stage</p>	<p>Excluded from analysis (reason)</p> <p>NR</p>			<p>Other source of bias: +</p>

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
	<p>T1 (%): 10.1/ 12.7 T2 (%): 69.6/ 52.1 T3 (%): 20.3/ 35.2 p=0.076</p> <p>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</p> <p>Metastatic level of LN F1 (%): 63.3/ 77.5 F2 (%): 32.9/ 19.7 F3 (%): 3.8/ 2.8 p=0.164</p> <p>Extent of resection Lobectomy (%): 86.1/ 76.1 Pneumonectomy (%): 13.9/ 23.9 p=0.116</p>				

+ 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
<p>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.</p>	<p>Inclusion criteria Randomized trials performed after the NSCLC meta-analysis published in 1995 Included only patients with completely resected NSCLC Compared cisplatin-based chemotherapy versus no chemotherapy Squamous cell: 48.5%</p> <p>Exclusion criteria Trials using concomitant radiochemotherapy or preoperative chemotherapy Incompletely resected patients Included in the 1995 meta-analysis</p> <p>Search period 1995-2003</p>	<p>Intervention(s) Cisplatin-vinorelbine adjuvant chemotherapy</p> <p>Control Observation</p>	<p>OS (median 5.2 years) Chemotherapy vs. observation; HR= 1.25 [1.099-1.429]; n = 2823</p> <p>Disease-free survival (median 5.2 years); Chemotherapy vs. observation; HR= 1.333 [1.176-1.493]; n=2965</p>	<p>Level of evidence 2a</p> <p>Methodological quality NA (individual patient data meta-analysis)</p>

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.	<p><i>Included</i> 28</p> <p><i>Attrition</i> 2</p> <p><i>Analyzed</i> 26</p> <p><i>Excluded from analysis</i> 2 (tumour was not completely resected surgically due to its invasion of the thoracic</p>	<p><i>Inclusion</i> Pulmonary resection for pleomorphic carcinoma</p> <p><i>Exclusion</i> -</p> <p><i>Patient characteristics</i> Age (median range): 69,49-83 Gender Male: 24 Female: 2 Presenting symptoms Yes: 15 No: 11 CEA levels High (\geq 5ng/ml): 6 Low (< 5ng/ml): 20</p>	<p><i>Setting</i> Hospital</p> <p><i>Country</i> Japan</p>	Microscopically complete/incomplete resection (determining the extent of resection by intraoperative frozen tissue examinations)	<p>OS (2 year); complete resection yes vs. no; 86.5% vs. NR; 0.037</p> <p>OS (5 year); complete resection yes vs. no; 51.9% vs. NR; 0.037</p> <p>OS (NR); invasion to the visceral pleural surface yes vs. no; yes > no; 0.048</p>	Univariate	<p><i>Study type</i> Cohort study</p> <p><i>Level of evidence</i> 4</p> <p><i>Risk of bias</i> Participation: + Attrition: ? PF measurement: + Outcome measurement: + Confounding: -</p>

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
	aorta [n=1] and small-cell carcinoma was also detected in the resected lung [n=1])	<p>Smoking habits Yes: 22 No: 4</p> <p>Tumour location Upper lobe: 22 Lower lobe: 4</p> <p>Tumour size (mm) range (median): 14-100 (45)</p> <p>P-T stage 1: 2 2: 15 3: 7 4: 2</p> <p>PI factor 0: 5 1: 7 2: 4 3: 10</p> <p>P-N stage 0: 19 1: 5 2: 2</p> <p>P-staging I: 12 II: 9 III: 5</p>					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
		Microscopically 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.	<p><i>Included</i> 292</p> <p><i>Attrition</i> NR</p> <p><i>Analyzed</i> 292</p> <p><i>Excluded from analysis</i> -</p>	<p><i>Inclusion criteria</i> 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</p>	<p><i>Setting</i> Hospital</p> <p><i>Country</i> Australia</p>	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)	<p><i>Study type</i> Cohort study</p> <p><i>Level of evidence</i> 2b</p> <p><i>Risk of bias</i> Participation: + Attrition: ? PF measurement: +</p>

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
		<p>Any extrathoracic disease was planned for resection either synchronously or as a staged procedure</p> <p>Pathologic features consistent with melanoma in preoperative biopsy</p> <p>Primary lesion controlled</p> <p><i>Exclusion criteria</i> NR</p> <p><i>Patient characteristics</i> Sex Male (%): 71 Female (%): 29 Age (mean, SD): 58, 14</p>				<p>diagnosis of primary tumor; Disease-free interval; histologic subtype of primary melanoma; positive lymph node)</p>	<p>Outcome measurement: ?</p> <p>Confounding: +</p> <p>Statistical analysis: +</p>

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
		<p>Median (range): 59 (19-84)</p> <p>Primary melanoma site</p> <ul style="list-style-type: none"> Extremity (%): 35 Trunk (%): 26 Head and neck (%): 26 Unknown (%): 11 <p>Histologic subtype of primary melanoma</p> <ul style="list-style-type: none"> Nodular (%): 31 Superficial spreading (%): 25 Occult (%): 16 Desmoplastic (%): 9 Not classified (%): 16 <p>American joint committee on cancer stage of primary tumor</p> <ul style="list-style-type: none"> I (%): 23 II (%): 47 III (%): 17 IV (%): 13 					

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
		<p>No. of pulmonary metastasis (mean, SD): 2, 3 Median (range): 1 (1-40) 1 (%): 59 2-3 (%): 32 >3 (%): 9</p> <p>Size of largest metastasis (cm, mean, SD): 3, 2 Median (range): 2 (1.15) ≤2cm (%): 52 >2cm (%): 48</p> <p>Extent of lung involvement Unilateral (%): 94 Bilateral (%): 6</p> <p>Time from diagnosis of primary tumor (month) Median (range): 44 (0-479)</p> <p>Disease-free interval (month)</p>					

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
		Median (range): 22 (0-479) Prior treatment of nonpulmonary recurrences No (%): 62 Yes (%): 38					

Konsultativ

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.	<p><i>Included</i> 48</p> <p><i>Attrition</i> NR</p> <p><i>Analyzed</i> 48</p> <p><i>Excluded from analysis</i> NR</p>	<p><i>Inclusion criteria</i> Underwent en bloc surgical resection of NSCLC invading the pulmonary sulcus and spine without evidence of distant metastasis</p> <p><i>Exclusion criteria</i> Tumor infiltration into the spinal canal or into the brachial plexus at C7 nerve root and above were generally considered to be inoperable</p> <p><i>Patient characteristics</i> Age (median, range): 62, 32 – 78</p>	<p><i>Setting</i> Hospital</p> <p><i>Country</i> Canada</p>	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)	<p><i>Study type</i> Cohort study</p> <p><i>Level of evidence</i> 2b</p> <p><i>Risk of bias</i> Participation: + Attrition: ? PF measurement: + Outcome measurement: + Confounding: + Statistical analysis:</p>

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
		Sex Female: 17 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.	<p><i>Included</i> 328</p> <p><i>Attrition</i> NR</p> <p><i>Analyzed</i> 328</p> <p><i>Excluded from analysis</i> NR</p>	<p><i>Inclusion criteria</i> Clinical stage IA NSCLC</p> <p>Undergone segmentectomy or wedge resection</p> <p><i>Exclusion criteria</i> Nonperipherally located carcinoma</p> <p>Multiple lung carcinomas, Pleural dissemination, positive pleural effusion or lavage cytology Planned an adjuvant therapy after surgical resection Adenocarcinoma in situ.</p>	<p><i>Setting</i> Hospital</p> <p><i>Country</i> Japan</p>	Microscopic surgical margin	<p>Locoregional recurrence (median: 58 months); negative vs. positive surgical margin; HR=3.888; 1.634-9.255</p> <p>Disease-specific survival (median: 62 months); negative vs. positive surgical margin; HR=3.211; 1.427-7.255</p> <p>Locoregional recurrence (median: 58 months); visceral pleura invasion absent vs. present; 2.272; 1.282-4.027</p> <p>Disease-specific survival (median: 62 months); visceral pleura invasion absent vs. present; 2.553; 1.503-4.338</p>	Multivariate (sex, tumor location, reason for sublobar resection, pulmonary resection extent, lymphadenectomy 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,	<p><i>Study type</i> Cohort study</p> <p><i>Level of evidence</i> 2b</p> <p><i>Risk of bias</i> Participation: + Attrition: ? PF measurement: + Outcome measurement: ? Confounding: +</p>

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
		<p><i>Patient characteristics</i></p> <p>Age</p> <p>≤ 71 y (%): 54</p> <p>> 71 y (%): 46</p> <p>Sex</p> <p>Male (%): 60</p> <p>Female (%): 40</p> <p>Smoking status</p> <p>0 (%): 42</p> <p><0-600 (%): 10</p> <p>>600 (%): 48</p> <p>CEA</p> <p>Within normal range (%): 84</p> <p>Elevated (%): 16</p> <p>Tumor location</p> <p>Right upper or middle lobe (%): 35</p> <p>Right lower lobe (%): 21</p> <p>Left upper lobe (%): 27</p> <p>Left lower lobe (%): 17</p> <p>Tumor size</p> <p>≤2.0 cm (%): 76</p>				tumor size in the resected lung specimens).	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
		<p>2,1-2.0 cm (%): 24 Cons/Tumor ratio ≤75% (%): 27 > 75% (%): 63</p> <p>Reason for sublobar resection Compromised (%): 49 Intentional (%): 51</p> <p>Pulmonary resection extent Sampling only (%): 74 Systematic mediastinal node dissection (%): 26</p> <p>Tumor histology Adenocarcinoma (%): 82 Squamous cell carcinoma (%): 14</p> <p>Tumor size, pathologic ≤2.0 cm (%): 75 2.1-3.0 cm (%): 20</p> <p>Microscopic surgical margin</p>					

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
		Positive (%): 3 Negative (%): 97 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.	<i>Included</i> 83 <i>Attrition</i> NR <i>Analyzed</i> 83 <i>Excluded from analysis</i>	<i>Inclusion criteria</i> Resection consisting of a lobectomy or pneumonectomy <i>Setting</i> Hospital <i>Country</i> USA <i>Exclusion criteria</i> Pathological confirmation of pN2 NSCLC Complete information on tumor size, tumor location, extent of disease/ lymph node involvement, surgical margin	<i>Setting</i> Hospital <i>Country</i> 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 survival): multivariate (radiotherapy, chemotherapy, age at diagnosis and gender) Other comparisons: univariate	<i>Study type</i> Cohort study <i>Level of evidence</i> 2b <i>Risk of bias</i> 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
	NA	<p>status, ECE status, cause of death</p> <p><i>Exclusion criteria</i> Received neoadjuvant chemotherapy/radiation therapy</p> <p>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</p>			<p>Local recurrence-free survival (2 years); negative vs. positive margin; 59%(45-73) vs. NA; 0.753</p>		<p>?</p> <p>PF measurement: ?</p> <p>Outcome measurement: ?</p> <p>Confounding: +</p> <p>Statistical analysis: +</p>

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.	<i>Included</i> 37 <i>Attrition</i> NR <i>Analyzed</i> 37 <i>Excluded from analysis</i> NR	<i>Inclusion criteria</i> NSCLC <i>Exclusion criteria</i> NR <i>Patients characteristics</i> Age (median, range): 71, 50- 82 Sex Male (%): 54 Tumor size (mm, median, range): 15, 5-35 Histology Adenocarcinoma (%): 86	<i>Setting</i> Hospital <i>Country</i> 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	<i>Study type</i> Cohort study <i>Level of evidence</i> 2b <i>Risk of bias</i> Participation: + Attrition: ? <i>PF measurement:</i> +

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.	<i>Included</i> 496	<i>Inclusion criteria</i> ≥18 years <i>Attrition</i> NR	<i>Setting</i> Hospital	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	Multivariate (age, gender, lymph node status)	<i>Study type</i> Cohort study <i>Level of evidence</i> 2b <i>Risk of bias</i> Participation: + Attrition:
	<i>Analyzed</i> 496	<i>Exclusion criteria</i> Previous surgical resection of pulmonary malignancies	<i>Country</i> USA		OS (mean 35.2); margin length ≤ 20mm vs. > 20mm; HR=1.16; 0.91-1.48		
	<i>Excluded</i>	Died within 30					

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
	<i>from analysis</i> NR	<p>days of surgery</p> <p>Multiple tumor site of the same histology or of different histology with unknown histologic origin of the recurrence</p> <p><i>Patients' characteristics</i></p> <p>Gender</p> <p>Male (%): 68.5</p> <p>Female (%): 31.5</p> <p>Age at resection (mean, SD): 65.9, 10.6</p> <p>Smoking status at resection</p> <p>Never smokers (%): 12.1</p> <p>Former smoker (%): 66.9</p> <p>Active smoker (%): 21</p> <p>Chemo- or</p>			<p>OS (mean 35.2); 1 mm decrease in bronchial margin resection length; HR=1.01; 0.997-1.01</p>		<p>?</p> <p>PF measurement: ?</p> <p>Outcome measurement: +</p> <p>Confounding: +</p> <p>Statistical analysis: +</p>

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
		<p>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 Pneumonectomy (%): 21.2</p>					

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
		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 standard chemotherapy Histologically or cytologically confirmed locally advanced or metastatic NSCLC Completion 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	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)	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	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
	<p>Maximum interval between the last day of the final 4th chemotherapy cycle and randomization was 21 days</p> <p>Exclusion criteria</p> <p>Prior treatment with EGFR-targeted or angiogenesis-targeted treatment</p> <p>Any unresolved toxicity greater than NCI CTCAE grade 2 from previous anticancer therapy</p> <p>Patient characteristics</p> <p>Age (median): 61/60.5</p> <p>Men (%): 62.7/66.7</p> <p>Women (%): 37.3/33.3</p>	<p>Excluded from analysis (reason)</p> <p>1/0 (not received treatment)</p>	<p>[Vandetanib], 17.0 month [placebo], RECIST criteria 28/ 7; HR=1.50; 0.99-2.27</p> <p>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</p>	<p>Insomnia (%): 18.7/4.8</p> <p>Hypertension (%): 17.3/0</p> <p>Nausea (%): 17.3/14.3</p> <p>Chest pain (%): 16/11.9</p> <p>Dry skin (%): 13.3/0</p>	<p>Blinding of outcome assessment: +</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	<p>WHO PS</p> <p>0 (%): 26.7/23.8</p> <p>1 (%): 73.3/76.2</p> <p>Histology</p> <p>Adenocarcinoma (%): 74.7/73.8</p> <p>Squamous cell carcinoma (%): 14.7/21.4</p> <p>Other (%): 10.7/4.8</p> <p>Smoking habits</p> <p>Non-smoker (%): 37.3/33.3</p> <p>Ex-smoker (%): 25.3/31</p> <p>Smoker (%): 37.3/35.7</p> <p>Disease stage</p> <p>IIIB (%): 20/28.6</p>				

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
	<p>IV (%): 80/71.4</p> <p><i>Response to previous therapy</i></p> <p>Partial response (%): 58.7/71.4</p> <p>Stable disease (%): 41.3/28.6</p>				
<p>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). <i>J Thorac Oncol</i>, 2013. 8(8): p. 1075-83.</p>	<p>Region United States</p> <p>Inclusion criteria Primary or recurrent, advanced (stage IIIB or IV) NSCLC measurable by RECIST</p> <p>Any histologic subtype were eligible, including</p>	<p>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</p>	<p>Median overall survival (months) 9.8/9.4; NA; ns (CIs overlap)</p> <p>Overall survival (median follow-up: 13.5 months) 37.5%/33%; NR; 0.68</p>	<p>Grade 1 Allergy/immunology: 4/3 Auditory/ear: 2/1 Blood/bone marrow: 4/1 Cardiac arrhythmia: 4/3</p> <p>Cardiac general:</p>	<p>Study type RCT</p> <p>Level of evidence 1b</p> <p>Risk of bias Generation of allocation sequence:</p>

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	<p>squamous cell carcinoma</p> <p>ECOG PS of 0 or 1</p> <p>Age ≥18 years</p> <p>Adequate organ function, normal calcium and magnesium</p> <p>Exclusion criteria</p> <p>Previous cytotoxic chemotherapy or targeted therapy for advanced or metastatic disease</p> <p>Cardiac dysfunction</p> <p>Greater than 1 grade neuropathy</p> <p>Known sensitivity to carboplatin</p>	<p>Control</p> <p>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</p> <p>Included/randomised patients</p> <p>80/82</p> <p>Analysed patients</p> <p>80/82 (efficacy)</p>	<p>Median progression-free survival (months)</p> <p>4.5/4.2; NA; ns (CIs overlap)</p> <p>Progression-free survival (median follow-up: 13.5 months, RECIST criteria)</p> <p>89%/95%; NR; 0.07</p> <p>Overall response (median follow-up: 13.5 months, RECIST criteria)</p> <p>15/15; NR; NR</p>	<p>3/7</p> <p>Constitutional symptoms: 9/18</p> <p>Dermatology/skin: 12/11</p> <p>Endocrine: 2/3</p> <p>Gastrointestinal: 17/17</p> <p>Bleeding: 15/7</p> <p>Infection: 0/2</p> <p>Lymphatics: 5/9</p> <p>Metabolic/laboratory: 18/9</p> <p>Musculoskeletal/soft tissue: 1/4</p> <p>Neurology: 14/13</p>	<p>+ Allocation concealment: -</p> <p>Blinding of participants and personal: +</p> <p>Blinding of outcome assessment: +</p> <p>Incomplete outcome data: +</p> <p>Selective reporting: +</p> <p>Other source of</p>

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	<p>Patient characteristics</p> <p>Age (median): 63.5/63</p> <p><50 (%): 12.5/7.3</p> <p>50-59 (%): 20/31.7</p> <p>60-69 (%): 42.5/28.1</p> <p>≥70 (%): 25/32.9</p> <p>Male (%): 52.5/51.2</p> <p>Female (%): 47.5/48.8</p> <p>Ethnicity</p> <p>White, non-Hispanic (%): 82.5/87.8</p> <p>White, Hispanic (%): 0/2.4</p> <p>Black, non-Hispanic (%): 11.3/9.8</p> <p>Black, Hispanic (%): 1.3/0</p>	<p>77/81 (safety)</p> <p>Attrition</p> <p>NR</p> <p>Excluded from analysis (reason)</p> <p>3/1 (safety, not received induction)</p>		<p>Ocular/visual: 3/7</p> <p>Pain: 15/10</p> <p>Pulmonary/upper respiratory: 19/12</p> <p>Renal/genitourinary: 4/2</p> <p>Sexual/reproductive function: 0/1</p> <p>Syndromes: 1/0</p> <p>Vascular: 1/4</p> <p>Worst degree: 1/2</p> <p>Grade 2</p> <p>Allergy/immuno</p>	bias: +

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	<p>Asian (%): 1.3/0</p> <p>Native Hawaiian/Pacific Islander (%): 1.3/0</p> <p>Other (%): 2.5/0</p> <p>Stage</p> <p>IIIB with malignant effusion (%): 6.3/11</p> <p>IV (%): 85/80.5</p> <p>Recurrent (%): 8.8/8.5</p> <p>ECOG PS</p> <p>0 (%): 33.8/41.5</p> <p>1 (%): 66.3/58.5</p> <p>Histology</p> <p>Adenocarcinoma (%): 57.5/58.5</p> <p>Squamous cell carcinoma</p>			<p>logy: 5/3</p> <p>Auditory/ear: 1/1</p> <p>Blood/bone marrow: 4/3</p> <p>Cardiac arrhythmia: 3/6</p> <p>Cardiac general: 3/8</p> <p>Constitutional symptoms: 27/17</p> <p>Dermatology/skin: 23/28</p> <p>Endocrine: 0/1</p> <p>Gastrointestinal: 29/20</p> <p>Bleeding: 4/3</p>	

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	<p>(%): 23.8/19.5</p> <p>Large cell carcinoma (%): 5.0/0</p> <p>Bronchialveolar (%): 0/3.7</p> <p>Adenosquamos (%): 2.5/2.4</p> <p>NSCLC, NOS (%): 11.3/14.6</p> <p>Other (%): 0/1.2</p> <p><i>Smoking history</i></p> <p>Ever smoker (%): 92.5/93.8</p> <p>Current smoker (%): 20.3/27.6</p>			<p>Infection: 10/16</p> <p>Lymphatics: 6/4</p> <p>Metabolic/laboratory: 5/7</p> <p>Musculoskeletal /soft tissue: 3/7</p> <p>Neurology: 11/6</p> <p>Ocular/visual: 1/3</p> <p>Pain: 16/19</p> <p>Pulmonary/upper respiratory: 6/8</p> <p>Renal/genitourinary: 0/2</p> <p>Sexual/reproductive function: 1/0</p>	

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				Syndromes: 0/2 Vascular: 2/7 Worst degree: 8/8 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	

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				Dermatology/skin: 13/5 Endocrine: 1/0 Gastrointestinal: 15/25 Bleeding: 1/1 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	

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				Pulmonary/upper respiratory: 8/12 Renal/genitourinary: 1/3 Secondary malignancy: 17/0 Syndromes: 1/0 Vascular: 5/3 Worst degree: 23/25 Grade 4 Allergy/immunology: 2/0 Blood/bone marrow: 31/28	

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				Cardiac arrhythmia: 1/0 Cardiac general: 1/1 Constitutional symptoms: 1/1 Dermatology/skin: 1/2 Gastrointestinal: 2/1 Infection: 4/4 Metabolic/laboratory: 0/3 Musculoskeletal /soft tissue: 1/0 Pain: 2/0 Pulmonary/uppe	

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				r respiratory: 0/1 Vascular: 3/5 Worst degree: 34/35 Grade 5 Blood/bone marrow: 0/1 Cardiac general: 2/0 Constitutional symptoms: Death: 5/6 Bleeding: 0/2 Hepatobiliary/pancreas: Infection: 0/3	

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				Metabolic/laboratory: 1/1 Neurology: 1/0 Pulmonary/upper respiratory: 1/1 Renal/genitourinary: 1/0 Worst degree: 10/	
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	Intervention(s) 15 doses of 1 mg of racotumomab-alum Induction phase consisted on 5 doses, administered every 2 weeks After induction,	Median overall survival (months) 8.23/6.80; NA; ns (CIs overlap) Overall survival (2 years) 18.4%/6.7%; HR=1.59;	Burning in injectionsite (%): 41.9/31.3 Pain in injectionsite (%): 33.7/24.7 Bonepain (%): 18.6/19.1	Study type RCT Level of evidence 1b

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	<p>Achievement CR, PR or SD after the standard first-line therapy</p> <p>Measurable disease</p> <p>ECOG PS ≤2</p> <p>Adequate renal, hepatic and haematological functions</p> <p>First-line chemotherapy with regimens included vinblastine or etoposide combined with cisplatin or carboplatin.</p> <p>Exclusion criteria</p> <p>Immunotherapy or other investigational drugs</p> <p>Hypersensitivity to any</p>	<p>vaccination every 4 weeks, for one year (10 doses)</p> <p>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.</p> <p>Control</p> <p>Placebo</p> <p>Included/randomised patients</p>	<p>1.15-2.17</p> <p>Median progression-free survival (months)</p> <p>5.33/3.90; NA; ns (CIs overlap)</p> <p>Progression-free survival (max 84 months, RECIST criteria)</p> <p>NR; HR=1.37; 1.01-1.89</p>	<p>Cough (%): 8.1/12.4</p> <p>Dyspnea (%): 5.8/5.6</p> <p>Asthenia (%): 16.3/11.2</p> <p>Anorexia (%): 7/7.9</p> <p>Expectoration (%): 1.2/3.4</p> <p>Induration (%): 11.6/10.1</p> <p>Headache (%): 9.3/10.1</p> <p>Pruritus (%): 10.5/5.6</p> <p>Fever (%): 9.3/13.5</p>	<p>Risk of bias</p> <p>Generation of allocation sequence: +</p> <p>Allocation concealment: ?</p> <p>Blinding of participants and personal: +</p> <p>Blinding of outcome assessment: +</p> <p>Incomplete outcome data:</p>

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	<p>component of the formulation</p> <p>Pregnancy or lactating</p> <p>Uncontrolled chronic diseases</p> <p>History of severe allergic reactions</p> <p>Brain metastases or other primary neoplastic lesion</p> <p>Active infections, symptomatic congestive heart failure, unstable angina, cardiac arrhythmia or psychiatric disorders</p> <p>Receiving systemic corticosteroids at the time of inclusion</p> <p>Positive serology Hepatitis</p>	<p>87/89</p> <p>Analysed patients</p> <p>87/89 (efficacy)</p> <p>86/89 (safety)</p> <p>Attrition</p> <p>NR</p> <p>Excluded from analysis (reason)</p> <p>1/0 (safety: received treatment)</p>		<p>Increased volume in injection site (%): 10.5/3.4</p> <p>Local erythema (%): 12.8/12.4</p> <p>Myalgia (%): 5.8/7.9</p> <p>Arthralgia (%): 5.8/5.6</p>	<p>?</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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	<p>B, C or HIV</p> <p>Patient characteristics</p> <p>Age ≤ 60 years (%): 43.7/46.1</p> <p>Age ≥ 60 years (%): 56.3/53.9</p> <p>Female (%): 32.3/33.7</p> <p>Male (%): 67.8/66.3</p> <p>ECOG PS</p> <p>0 (%): 46/44.9</p> <p>1 (%): 51.7/50.6</p> <p>2 (%): 2.3/4.5</p> <p>Race</p> <p>White (%): 80.5/79.8</p> <p>Afro-Caribbean (%):</p>				

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	<p>12.6/14.6</p> <p>Other (%): 6.9/5.6</p> <p><i>Smoking history</i></p> <p>Current smoker (%): 18.45/21.3</p> <p>Former smoker (%): 77/73</p> <p>Non smoker (%): 4.6/5.6</p> <p><i>Tumor histology</i></p> <p>Squamos cell carcinoma (%): 37.9/37.1</p> <p>Adenocarcinoma (%): 28.7/34.8</p> <p>Large cell carcinoma (%): 20.7/15.7</p> <p>NSCLC NOS (%): 12.6/12.4</p> <p><i>Disease stage</i></p>				

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	<p>IIIB (%): 55.2/57.3 IV (%): 44.8/42.7</p> <p><i>First-line treatment</i></p> <p>CT (%): 100/100 RT (%): 57.5/57.3</p> <p><i>First line chemotherapy</i></p> <p>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</p>				

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	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	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	Intervention(s) Four cycles of platinum-based induction therapy Pemetrexed (500 mg/m ² , Eli Lilly, Indianapolis, IN, USA) intravenously on day 1 plus best supportive care in 21-day cycles. Control Placebo (0.9% sodium chloride) intravenously	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	Drug related Anaemia (%): 15/5 Leucopenia (%): 6/1 Neutropenia (%): 6/0 Thrombocytopenia (%): 4/1 ALT (%): 10/4 AST (%): 8/4	Study type RCT Level of evidence 1b Risk of bias Generation of allocation sequence: +

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<p>plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet, 2009; 374(9699): p. 1432-40.</p>	<p>Estimated life expectancy of at least 12 weeks 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</p>	<p>on day 1 plus best supportive care in 21-day cycles. Four cycles of platinum-based induction therapy</p>	<p>4.0/ 2.0; NA; ns (CIs overlap) Progression-free survival (median follow-up: 11.2 months, RECIST criteria) NR; HR=1.67; 1.37- 2.04</p>	<p>Fatigue (%): 24/10 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 (%):</p>	<p>Allocation concealment: + Blinding of participants and personal: + Blinding of outcome assessment: + Incomplete outcome data: ? Selective reporting: + Other source of bias:</p>

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
	<p>breastfeeding</p> <p>Patient characteristics</p> <p>Age (mean): 60.6/60.4</p> <p>Male (%): 73/73</p> <p>Female (%): 27/27</p> <p>Ethnic origin</p> <p>White (%): 63/67</p> <p>East/west Asian (%): 32/30</p> <p>Other (%): 4/3</p> <p>Disease stage</p> <p>IIIB (%): 18/21</p> <p>IV (%): 82/79</p> <p>Smoking status</p>	<p>-</p>	<p>Median time to worsening of Symptoms (month, LCSS)</p> <p>5.75/3.71; NA; ns (CIs overlap)</p> <p>Time to worsening of Symptoms (follow-up NR, LCSS)</p> <p>5.75/3.71; HR=0.86; 0.66-1.12</p>	<p>7/2</p> <p>Pruritus (%): 3/<1</p> <p>Sensory neuropathy (%): 9/4</p> <p>Alopecia (%): 4/<1</p> <p>Any infection (%): 5/2</p> <p>Creatinine clearance (%): 4/<1</p>	

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	<p>Smoker (%): 73/71 Never-smoker (%): 26/28 Unknown (%): <1/<1</p> <p>ECOG PS</p> <p>0 (%): 40/38 1 (%): 60/62</p> <p>Histology</p> <p>Non squamous (%): 74/70 Adenocarcinoma (%): 50/48 Large cell (%): 2/5 Other or indeterminate (%): 21/18 Squamos (%): 26/30</p> <p>Best response to induction treatment</p>				

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
	<p>CP+PR (%): 47/52</p> <p>Stable disease (%): 52/48</p> <p><i>Induction regimen</i></p> <p>Docetaxel-carboplatin (%): 5/3</p> <p>Docetaxel-cisplatin (%): 2/2</p> <p>Paclitaxel-carboplatin (%): 30/27</p> <p>Paclitaxel-cisplatin (%): 6/9</p> <p>Carboplatin plus taxane (%): 35/30</p> <p>Carboplatin plus gemcitabine (%): 24/22</p> <p>Cisplatin plus taxane (%): 8/11</p>				

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
	<p>Cisplatin plus gemcitabine (%): 33/38</p> <p><i>LCSS item (mean)</i></p> <p>Loss of appetite: 23/23.5; 14/19</p> <p>Fatigue: 33.5/33.9; 30/28</p> <p>Cough: 19.9/19.6; 9/9</p> <p>Dyspnoea: 21.4/20.1; 10/8</p> <p>Haemoptysis: 2.8/3.5; 0/0</p> <p>Pain: 14.8/22.8; 4/5</p> <p>Symptom distress: 20.9/23.2; 11/14</p> <p>Interference with activity level: 32.9/33.3; 25.5/27</p> <p>Overall quality of life: 33.5/33.3; 30/31</p>				

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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 Completion of four cycles of standard platinum-doublet chemotherapy without disease progression ECOG PS 0 or 1 Adequate renal, hepatic, and haematological function	Intervention(s) Oral erlotinib 150 mg/day Control Placebo Included/randomised patients 438/451 Analysed patients 437/447 Attrition NR Excluded from analysis (reason)	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 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	Treatment-related All grades One or more (%): 65/20 Rash (%): 60/8 Pruritus (%): 6/2 Diarrhoea (%): 18/3 General disorders and administration site conditions (%): 9/3 Anorexia (%): 5/2 Infections and infestations (%):	Study type RCT Level of evidence 1b Risk of bias Generation of allocation sequence: + Allocation concealment: + Blinding of participants and

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	<p>Negative pregnancy test for females of childbearing age</p> <p>Exclusion criteria</p> <p>Previous exposure to anti-EGFR agents</p> <p>Uncontrolled, symptomatic brain metastases</p> <p>Any other malignancies within the previous 5 years</p> <p>Patient characteristics</p> <p>Age (median): 60/60</p> <p>Male (%): 73/75</p> <p>Female (%): 27/25</p>	<p>1/4 (efficacy [PFS], progressed before randomisation)</p> <p>0/0 (safety)</p>	<p>criteria) NR; HR=1.40; 1.22-1.61</p> <p>Progression-free survival (6 months, RECIST criteria) 25%/15%; NR; statistical significant (CIs not overlapping)</p> <p>ORR (median follow-up: 11.4 months [erlotinib], 11.5 [placebo], RECIST criteria) 11.9%/5.4%; NR; 0.0006</p> <p>Diseases control rate (12</p>	<p>5/<1</p>	<p>personal: + Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +</p>

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	<p>Stage</p> <p>IIIB (%): 26/24</p> <p>IV (%): 74/76</p> <p>Ethnic origin</p> <p>Caucasian (%): 84/83</p> <p>Asian (%): 14/15</p> <p>Other (%): 1/1</p> <p>ECOG PS</p> <p>0 (%): 31/32</p> <p>1 (%): 69/68</p> <p>Smoking status</p> <p>Current smoker (%): 55/56</p> <p>Former smoker (%): 28/27</p> <p>Never smoker (%): 18/17</p> <p>Histology</p>		<p>weeks, RECIST criteria)</p> <p>40.8%/27.4; NR; 0. 0001</p> <p>Time to deterioration in quality life (median follow-up: 11.4 months [erlotinib], 11.5 [placebo], FACT-L)</p> <p>NR; HR=0.96; 0.79–1.16;</p>		

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	<p>Adenocarcinoma/broncho alveolar carcinoma (%): 47/44</p> <p>Squamos-cell carcinoma (%): 38/43</p> <p>Other (%): 15/13</p> <p><i>Response to previous chemotherapy</i></p> <p>Complete response (%): <1/<1</p> <p>Partial response (%): 42/47</p> <p>Stable disease (%): 58/52</p> <p>Other/unknown (%): <1/1</p> <p><i>EGFR IHC status</i></p> <p>Positive (%): 70/69</p> <p>Negative (%): 14/13</p>				

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	<p>Indeterminate (%): 4/5</p> <p>Missing (%): 12/12</p> <p><i>EGFR mutation status</i></p> <p>Activating mutation (%): 5/6</p> <p>Other mutation (%): 2/<1</p> <p>Wild-type (%): 45/42</p> <p>Missing (%): 40/43</p>				
<p>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</p>	<p>Region United States and Europe</p> <p>Inclusion criteria Histologically or cytologically confirmed stage IIIB or IV NSCLC Not amenable to local</p>	<p>Intervention(s) Gefitinib (250 mg daily)</p> <p>Control Placebo</p>	<p>Median overall survival (months) 10.9/9.4; NA; NR</p> <p>Overall survival (median follow up: 41 months) NR; HR=1.23; 0.89-1.69</p>	<p>Treatment related non-haematological Grade 3 Cardiovascular/general (%): 0/2.3 Fatigue (%): 4.7/1.2</p>	<p>Study type RCT</p> <p>Level of evidence 1b</p> <p>Risk of bias</p>

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01/03)." Eur J Cancer 47(15): 2331-2340	<p>therapy</p> <p>Non-progressing after prior platinum based chemotherapy (2-6 cycles)</p> <p>Without unacceptable toxicity</p> <p>Age ≥ 18years</p> <p>WHO PS 2 or less</p> <p>Adequate renal, hepatic and haematological functions</p> <p>Exclusion criteria</p> <p>Previous EGFR therapy, symptomatic brain metastasis, other malignancies, pregnancy or breast-feeding and interstitial pulmonary disease</p>	<p>Included/randomised patients</p> <p>86/87</p> <p>Analysed patients</p> <p>87/86</p> <p>Attrition</p> <p>9/15</p> <p>Excluded from analysis (reason)</p> <p>86/85 (safety, started treatment)</p>	<p>Median progression-free survival (months)</p> <p>4.1/2.9; NA; NR</p> <p>Progression-free survival (median follow up: 41months, RECIST criteria)</p> <p>NR; HR=1.64; 1.20-2.22</p> <p>ORR (time point NR, RECIST criteria)</p> <p>12%/1%; NR; 0.004</p> <p>Diseases Control rate (time point NR, RECIST criteria)</p> <p>79%/66%; NR; 0.07</p>	<p>Rash/desquamation (%): 1.2/0</p> <p>Dermatology/skin (%): 1.2/0</p> <p>Anorexia (%): 0/1.2</p> <p>Diarrhoea (%): 1.2/0</p> <p>Vomiting (%): 1.2/0</p> <p>Gastrointestinal (%): 0/1.2</p> <p>Hepatic-other (%): 8.2/0</p> <p>Infection without neutropenia (%): 1.2/1.2</p>	<p>Generation of allocation sequence: +</p> <p>Allocation concealment: +</p> <p>Blinding of participants and personal: +</p> <p>Blinding of outcome assessment: +</p> <p>Incomplete outcome data: +</p> <p>Selective reporting: +</p>

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
	<p>Patient characteristics</p> <p>Age (median): 61/62</p> <p>Male (%): 78/76</p> <p>Female (%): 22/24</p> <p>Clinical stage</p> <p>IIIB (%): 19/15</p> <p>IV (%): 81/85</p> <p>PS</p> <p>0 (%): 36/35</p> <p>1 (%): 57/61</p> <p>2 (%): 7/5</p> <p>Prior platinum chemotherapy</p> <p>Cisplatin-based (%): 45/56</p>			<p>Dizziness/light headedness (%): 0/1.2</p> <p>Neurology (%): 0/3.5</p> <p>Pain (%): 4.7/7</p> <p>Cough (%): 1.2/3.5</p> <p>Dyspnoea (%): 4.7/5.8</p> <p>Pulmonary (%): 0/1.2</p> <p>Renal/genitourinary (%): 2.4/0</p> <p>Other toxicity (%): 4.7/3.5</p> <p>Grade 4</p>	<p>Other source of bias: +</p>

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	Carboplatin-based (%): 55/44 Cis/Carbo-platin based (%): 1/0 <i>Response to chemotherapy</i> Complete/partial response (%): 40/40 Stable disease (%): 61/60 <i>Histological type</i> Squamos (%): 17/22 Adenomacarcinoma (%): 57/46 Undifferentiated (%): 15/17 Large cell carcinoma (%): 11/15			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 <i>Treatment related haematological/biochemical Grade 3</i>	

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	<p><i>Smoking status</i></p> <p>Non-smoker (%): 21/23</p> <p>Current smoker (%): 29/26</p> <p>Former smoker (%): 49/48</p> <p>Missing (%): 1/2</p>			<p>Absolute neutrophil count (%): 1.2/0</p> <p>Platelets (%): 1.2/0</p> <p>Haemoglobin (%): 0/2.3</p> <p>Bilirubin (%): 1.2/1.2</p> <p>Hypernatraemia (%): 1.2/0</p> <p>Hyponatraemia (%): 8.2/8.1</p> <p>Hyperkalaemia (%): 1.2/0</p> <p>Hypokalaemia (%): 1.2/1.2</p> <p>Alkaline</p>	

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				<p>phosphatase (%): 1.2/0</p> <p>SGPT, ALAT (%): 8.2/0</p> <p>SGOT, ASAT (%): 8.2/1.2</p> <p>Grade 4</p> <p>Hypernatraemia (%): 0/1.2</p> <p>Hypocalcaemia (%): 1/1.2</p> <p>SGPT, ALAT (%): 2.4/1.2</p>	
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	<p>Region USA</p> <p>Inclusion criteria Age ≥18 years</p>	<p>Intervention(s) Oral carboxyaminoimidazole (CAI) at a dose of 250 mg daily</p>	<p>Median overall survival (months) 11.4/10.5; NA; NR</p> <p>Overall survival (median follow-up: 29.6 [CAI],</p>	<p>Grade 1/2</p> <p>Fatigue (%): 46.7/26.1</p> <p>Anorexia (%): 31.1/13</p>	<p>Study type RCT</p> <p>Level of evidence 1b</p>

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completion of initial therapy (NCCTG 97-24-51). Lung Cancer, 2008. 60(2): p. 200-7.	<p>Histologically or cytologically confirmed stage III or IV NSCLC</p> <p>Completion of only one chemotherapy regimen (with or without thoracic radiation) within the previous 6 weeks</p> <p>Complete response, partial response or stable disease</p> <p>Initial chemotherapy minimum of 3 and a maximum of 6 months</p> <p>ECOG PS 0,1 or 2</p> <p>Adequate bone marrow, hepatic and renal function</p> <p>Expected survival of at least 3 months</p>	<p>Control Placebo</p> <p>Included/randomised 94/92</p> <p>Analysed patients 94/92 (efficacy) 65%/79% (quality of life)</p> <p>Attrition 7/14 (survival analyses)</p> <p>Excluded from analysis (reason) NR (safety, received treatment, in at least 25% of patients in either arm)</p>	<p>28.3 [placebo] NR; NA; 0.54</p> <p>Median progression-free survival (months) 2.8/ 2.4; NA; NR</p> <p>Progression-free survival (median follow-up: 29.6 [CAI], 28.3 [placebo], WHO criteria) NR; NR; 0.50</p> <p>Patients with 10 points decline in quality life (8 weeks, FACT-L) 63%/49%; NR; 0.18</p>	<p>Nausea (%): 60/30.4</p> <p>Vomiting (%): 28.9/14.1</p> <p>Ataxia (%): 22.2/13</p> <p>Neuro-sensory (%): 51.1/44.6</p> <p>Anemia (%): 48.9/55.4</p> <p>Grade 3</p> <p>Fatigue (%): 7.8/3.3</p> <p>Nausea (%): 2.2/0</p> <p>Vomiting (%): 3.3/0</p>	<p>Risk of bias</p> <p>Generation of allocation sequence: +</p> <p>Allocation concealment: ?</p> <p>Blinding of participants and personal: +</p> <p>Blinding of outcome assessment: +</p> <p>Incomplete outcome data: +</p>

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	Exclusion criteria Woman who were pregnant, nursing or not 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	25%/21% (quality of life, not completed questionnaire)		Ataxia (%): 11.1/3.3 Neuro-sensory (%): 8.9/0	Selective reporting: + Other source of bias: +

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	<p>0 (%): 41/39</p> <p>1 (%): 52/50</p> <p>2 (%): 7/11</p> <p>Race</p> <p>White (%): 97/97</p> <p>Black or African American (%): 1/0</p> <p>American Indian or Alaska Native (%): 1/1</p> <p>Not reported (%): 2/1</p> <p>Prior response</p> <p>Complete (%): 5/4</p> <p>Partial (%): 40/49</p> <p>Regression (%): 10/9</p> <p>Stable (%): 45/38</p>				

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	<p>Platinum based initial therapy (%): 76/79</p> <p><i>Smoking status</i></p> <p>Never (%): 12/11</p> <p>Former (%): 57/62</p> <p>Current (%): 21/16</p> <p>Not reported (%): 10/11</p> <p><i>Stage</i></p> <p>IIIA/IIIB (%): 23/21</p> <p>IV (%): 77/79</p> <p><i>Histology</i></p> <p>Bronchoalveolar/large cell (%): 6/14</p> <p>NOS NSCLC/not available (%): 17/12</p> <p>Adenocarcinoma (%):</p>				

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	54/60 Squamos (%): 22/14				
<p>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 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.</p> <p>Paz-Ares LG, de Marinis F, Dediu M, et al. PARAMOUNT: Final overall survival results of the phase</p>	Region Primarily European Inclusion criteria Advanced nonsquamous NSCLC stage IIIB to IV 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	Intervention(s) Four cycles of pemetrexed (500 mg/m ² intravenously and cisplatin (75 mg/m ² IV) on day 1 of 21-day cycles Maintenance pemetrexed (500 mg/m ² on day 1 of 21-day cycles) plus BSC Control Four cycles of pemetrexed (500 mg/m ² intravenously and cisplatin (75	Median overall survival (months) 16.9/14.0; NA; ns (CIs overlap) Overall survival (2 years) 32%/21%; HR=1.28; 1.04-1.56 Median progression-free survival (months) 4.4/2.8; NA; statistical significant (CIs not overlapping)	All grades Patients with ≥1 laboratory adverse event (%): 24/7 Anemia (%): 14/4 Neutropenia (%): 8/1 Leukopenia (%): 4/0 Thrombocytopenia (%): 3/1 Alanine aminotransferase (%): 3/1 Fatigue (%):	Study type RCT Level of evidence 1b Risk of bias Generation of allocation sequence: + Allocation concealment: +

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<p>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.</p> <p>Pujol JL, Paz-Ares L, de Marinis F, Dedi M, et al Long-term and low-grade safety results of a phase III study (PARAMOUNT): maintenance 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</p>	<p>therapy and tumour histology</p> <p>CNS metastases were eligible if the metastases were stable and successfully treated with local therapy (that is, stable treated metastases), and the patient was off corticosteroids for at least 4 weeks</p> <p>Patient characteristics</p> <ul style="list-style-type: none"> Age (median): 61/62 <65 (%): 66/62 ≥65 (%): 34/38 Male (%): 56/62 Female (%): 44/38 	<p>mg/m² IV) on day 1 of 21-day cycles</p> <p>Maintenance Placebo plus BSC</p> <p>Included/randomised patients</p> <p>359/180</p> <p>Analysed patients</p> <p>359/180</p> <p>Attrition</p> <p>4/0</p> <p>Excluded from analysis (reason)</p> <p>≤20% (quality of life, not completed)</p>	<p>Progression-free survival (median follow up: 24.3 months, RECIST criteria)</p> <p>NR; HR=1.67; 1.38-2.00</p> <p>ORR (median follow up: 5.0 months, RECIST criteria)</p> <p>3%/0.6%; NR; 0.18</p> <p>Diseases Control rate (median follow up: 5.0 months, RECIST criteria)</p> <p>71%/60%; NR; 0.009</p> <p>Quality of life (after treatment, EQ-5D index)</p>	<p>16/11</p> <p>Nausea (%): 11/2</p> <p>Vomiting (%): 6/2</p> <p>Mucositis/stomatitis (%): 5/2</p> <p>Oedema (%): 5/3</p> <p>Anorexia (%): 4/1</p> <p>Pain (%): 4/2</p> <p>Infection (%): 3/2</p> <p>Diarrhoea (%): 3/2</p> <p>Neuropathy (%): 3/6</p>	<p>Blinding of participants and personal:</p> <p>+ Blinding of outcome assessment:</p> <p>+ Incomplete outcome data:</p> <p>+ Selective reporting:</p> <p>+ Other source of bias:</p> <p>+ </p>

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. 2014 Nov;15(6):418-25.	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 1 (%): 68/66 2-3 (%): 0.3/1 Disease stage before maintenance therapy IIIB (%): 9/10	questionnaire)	score) 0.77/0.79; NR; ns Quality of life (after treatment, EQ-5D VAS) 71.08/ 71.02; NR; ns	Watery eye (%): 3/<1 Constipation (%): 2/3	

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
	<p>IV (%): 91/90</p> <p>Best tumor response to induction therapy</p> <p>Complete/partial response (%): 44/42</p> <p>Stable disease (%): 53/53</p> <p>Progressive disease (%): 0.3/1</p> <p>Unknown (%): 3/4</p> <p>Time from start of induction therapy to randomisation (months)</p> <p>Median: 2.96/2.96</p> <p>Histology</p> <p>Bronchialveolar (%): 2/1</p> <p>Adenocarcinoma (%): 85/88</p>				

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 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. <i>Neoplasma</i> , 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 PS <2 Wild-type EGFR	Intervention(s) Cisplatin (80-120 mg/m ² body surface area) and Paclitaxel injection (Ta..xol, 135-250 mg/m ² body surface area), once every three weeks (group Gefitinib maintenance) Gefitinib maintenance therapy of 250 mg/day by oral administration (group 3) until disease progression or the development of	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: - Allocation concealment: - Blinding of participants and

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
	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	intolerable side effect Control Cisplatin (80-120 mg/m ² body surface area) and Paclitaxel injection (Ta..xol, 135-250 mg/m ² body surface area), once every three weeks (group Gefitinib maintenance Placebo) Included/randomised patients NR Analysed patients 7/7 Attrition NR			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
		Excluded from analysis (reason)			
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	Intervention(s) Maintenance Belagenpumatucel-L (2.5×10^7 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	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)	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

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
	<p>age</p> <p>ECOG performance status of 0, 1 or 2</p> <p>Estimated life expectancy of at least 12 weeks</p> <p>No other antitumour therapies within four weeks of randomisation.</p> <p>Exclusion criteria</p> <p>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</p>	<p>270/262</p> <p>Analysed patients</p> <p>270/262</p> <p>Attrition</p> <p>NR</p> <p>Excluded from analysis (reason)</p> <p>NR</p>	<p>criteria)</p> <p>NR; HR=1.01; 0.83-1.22</p> <p>ORR (max 48 months, RECIST criteria)</p> <p>2.5%/0.4%; NR; 0.123</p>	<p>Headache: 48/28</p> <p>Induration: 22/4</p> <p>Injection site reaction: 260/62</p> <p>Musculoskeletal pain: 34/21</p> <p>Nasopharyngitis: 26/11</p> <p>Nausea: 40/36</p> <p>Non-cardiac chest pain: 23/9</p> <p>Pyrexia: 25/17</p> <p>Rash: 23/10</p>	<p>personal: +</p> <p>Blinding of outcome assessment: +</p> <p>Incomplete outcome data: +</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	<p>Patient characteristics</p> <p>Age (mean): 61.5/60.5</p> <p>Men (%): 58/58</p> <p>Women (%): 42/42</p> <p>Race</p> <p>White (%): 88/90</p> <p>Black (%): 2/2</p> <p>Asian (%): 8/8</p> <p>Not specified (%): 2/1</p> <p>Ethnicity</p> <p>Hispanic (%): 2/1</p> <p>Non-hispanic (%): 98/99</p> <p>Stage</p> <p>Stage IIIA (%): 8/8</p> <p>Stage IIIB/IV (%): 92/92</p>				Respiratory tract infection: 33/28

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
	<p>Histology</p> <p>Adenocarcinoma (%): 60/54</p> <p>Squamos (%): 24/31</p> <p>Large Cell (%): 6/5</p> <p>Adenosquamos carcinoma (%): 2/2</p> <p>Undifferentiated (%): 4/2</p> <p>Other/not specified (%): 4/3</p> <p>Brain metastases</p> <p>Positive (%): 7/7</p> <p>Negative (%): 93/93</p> <p>Pre-randomisation therapies</p> <p>Prior chemoRT (%): 29/27</p>				

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
	<p>Non prior chemoRT (%): 71/73</p> <p>Prior bevacizumab (%): 11/10</p> <p>Non prior bevacizumab (%): 89/90</p> <p>Enrolment by region</p> <p>North America (%): 42/41</p> <p>Rest of the World (%): 58/59</p> <p>PS (ECOG)</p> <p>0 (%): 44/50</p> <p>1 (%): 51/45</p> <p>2 (%): 3/2</p>				
Zhang, L., et al., Gefitinib versus placebo as maintenance therapy in	Region China	Intervention(s) Gefitinib (250 mg/day)	Median overall survival (months)	NR	Study type RCT

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
<p>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.</p> <p>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-</p>	Inclusion criteria Chinese patients Locally advanced/metastatic NSCLC Disease control after first-line platinum-based doublet chemotherapy Exclusion criteria Patient characteristics Age(median): 55/55 Men (%): 56/62 Women (%): 44/38 Histology Adenocarcinoma(%): 71/70	orally) administered 3-6 weeks postchemotherapy Control Placebo (orally) administered 3-6 weeks postchemotherapy. Included/randomised patients 296 Analysed patients 148/148 Attrition 147/148	18.97%/16.00 %; NA; NR Overall survival (median follow-up 17.83 month) 112/118; HR=1.14; 0.88-1.47 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		Level of evidence 1b Risk of bias Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: +

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TONG 0804), on behalf of the INFORM investigators.	<p>Squamous (%): 18/20 Others (%): 11/10</p> <p>Disease stage IIIB (%): 39/30 IV (%): 61/70</p> <p>WHO PS 0 (%): 47/49 1 (%): 51/49 2 (%): 2/3</p> <p>Smoking history Nonsmoker (%): 53/55 Ex-smoker (%): 39/37 Current smoker (%): 8/8</p> <p>Type of first chemotherapy</p>	<p>1/1 (progression free survival) 21/12 (overall survival) 123/116 (FACT-L)</p> <p>Excluded from analysis (reason) 1/0 (safety, not received treatment) 25/32 (FACT-L, no assessable results)</p> <p>Sustained clinically relevant improvement in cancer symptoms (time point NR, FACT-L)</p> <p>28%/10%; OR = 3.41; 1.65–7.06</p>	<p>ORR (median follow-up 15.9 month, RECIST criteria) 24/1%; OR=54.10; 7.17–408</p> <p>Diseases control rate (median follow-up 15.9 month, RECIST criteria) 72%/51%; 2.69; 1.62–4.46</p>		<p>Blinding of outcome assessment: +</p> <p>Incomplete outcome data: +</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	Taxane (%): 41/45 Nontaxane (%): 59/55 Response to first chemotherapy PR or CR (%): 39/34 SD (%): 61/66				

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
<p>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.</p>	<p>Region NR</p> <p>Inclusion criteria 18 years of age or older Histologically or cytologically confirmed, inoperable, stage IIIB or IV NSCLC One bidimensionally measurable indicator lesion that had not been previously irradiated Performance status had to be 0 to 2 Life expectancy of ≥ 12 weeks and adequate hematologic, renal and hepatic function Fully recovered patient from all adverse effects if prior radiation therapy or major</p>	<p>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</p> <p>Control</p>	<p>Median time to progression (weeks) 38/29; NA; 0.124</p> <p>Median survival time (weeks) 75/60; NA; 0.243</p> <p>Overall survival (2 years) 32%/26%; NR; NR</p>	<p>At least one AE 86%/NR</p> <p>At least one Grade 3 or 4 AE 45%/NR</p>	<p>Study type RCT</p> <p>Level of evidence 2b</p> <p>Risk of bias Generation of allocation sequence: ?</p> <p>Allocation concealment: ?</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome assessment: ?</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting: +</p>

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
	<p>surgery (had to be completed at least 3 weeks before enrollment)</p> <p>Stable disease or better on initial therapy</p> <p>Exclusion criteria</p> <p>Prior chemotherapy</p> <p>Measurable neuropathy, active serious infection, or other serious underlying medical conditions</p> <p>Patient characteristics</p> <p>Age (median): 66/65</p> <p>Male (%): 63/62</p> <p>Stage</p> <p>IIIB (%): 28/22</p> <p>IV (%): 72/78</p>	<p>Observation</p> <p>Included/randomised patients</p> <p>NR</p> <p>Analysed patients</p> <p>65/65</p> <p>Attrition</p> <p>NR</p> <p>Excluded from analysis (reason)</p> <p>NA (not received treatment, patients were removed from the study for grade 3 or greater neuropathy)</p>			<p>Other source of bias: +</p>

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
	<p><i>Performance status (ECOG)</i></p> <p>0-1 (%): 91 / 92</p> <p>2 (%): 9/8</p>				
<p>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.</p>	<p>Region NR</p> <p>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</p>	<p>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</p>	<p>Response rate (median 20.5/17) 50.7% / 45.6%; NR; 0.554</p> <p>Median overall survival (months) 10.2/8.1; NR; 0.172</p> <p>Median time to progression or death (month) 3.6/2.0; NA; < 0.001</p>	<p>Neutropenia (% of cycles): 14.9/NR</p> <p>Thrombocytopenia (% of cycles): 1.7/NR</p> <p>Anemia (% of cycles): 2.6/NR</p> <p>Leukopenia (% of cycles): 2.3/NR</p> <p>Nausea/vomiting (% of cycles): 0.8/NR</p> <p>Alopecia (% of cycles): 4.3/NR</p> <p>Hemorrhage (% of cycles): 0//NR</p> <p>Pulmonary (% of cycles):</p>	<p>Study type RCT</p> <p>Level of evidence 2b</p> <p>Risk of bias</p> <p>Generation of allocation sequence: ?</p> <p>Allocation concealment: +</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome</p>

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
	<p>(KPS) ≥70</p> <p>Measurable disease Age≥19 years</p> <p>Estimated life expectancy of at least 12 weeks</p> <p>Adequate bone marrow reserve Childbearing potential</p> <p>Patients who demonstrated complete response, partial response, or stable disease within 1 month after the fourth cycles gemcitabine</p> <p>Exclusion criteria</p> <p>Prior chemotherapy</p> <p>Prior radiotherapy (up to 60 Gy) was permitted if the irradiated area was not the only source of measurable disease</p>	<p>Control</p> <p>Best supportive care</p> <p>Included/randomised patients</p> <p>215 (ratio 2:1)</p> <p>Analysed patients</p> <p>99 in total (progression)</p> <p>NR for other outcomes</p> <p>Attrition</p> <p>NR</p> <p>Excluded from analysis (reason)</p> <p>116 in total (NR, outcome progression)</p>	<p>Progression or death (median 20.5/17)</p> <p>NR; HR=1.429; 1.11-2.00</p>	<p>0.5/NR</p> <p>Hepatic</p> <p>ALT/AST (% of cycles): 0.2//NR</p> <p>Bilirubin (% of cycles): 0//NR</p>	<p>assessment: ?</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	<p>Active infection</p> <p>Presence of symptomatic central nervous system metastases</p> <p>Inadequate liver function</p> <p>Inadequate renal function</p> <p>Serious concomitant systemic disorder incompatible with the study</p> <p>Second primary malignancy</p> <p>Patient characteristics</p> <p>Age (median): 58/68</p> <p>Male (%): 70.3/79.4</p> <p>Stage</p> <p>IIIB (%): 27.5/26.5</p> <p>IV (%): 72.5/73.5</p> <p>KPS</p> <p>> 80 (%): 47.8/48.5</p>	NR for other outcomes			

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
	<p>≤ 80 (%): 52.2/51.5</p> <p>Histology</p> <p>Squamous cell carcinoma (%): 42.0/38.2</p> <p>Adenocarcinoma (%): 44.9/39.7</p> <p>Large cell (%): 4.3/2.9</p> <p>Other (%): 8.7/9.1</p> <p>Prior therapy</p> <p>Radiation (%): 13.0/7.4</p> <p>Surgery (%): 19.6/20.6</p> <p>Metastatic sites of disease</p> <p>Lung (%): 42.0/42.6</p> <p>Lymph node (%): 65.2/61.8</p> <p>Liver (%): 13.8/19.1</p> <p>Bone (%): 15.2/11.8</p> <p>Adrenal (%): 8.7/10.3</p> <p>Visceral tumor sites positive</p>				

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
	<p>(%): 91.3/88.2</p> <p>< 3 organs involved (%): 79.7/72.1</p> <p>≥ 3 organs involved (%): 20.3/27.9</p>				
<p>Mubarak, N. A randomized, phase 2 study 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</p>	<p>Region</p> <p>Egypt, Lebanon, and Saudi Arabia</p> <p>Inclusion criteria</p> <p>≥18 years</p> <p>Estimated life expectancy of ≥12 weeks</p> <p>Performance status of 0 or 1</p> <p>Histologic or cytologic diagnosis of stage IIIB (with pleural effusion and/or positive supraclavicular nodes) or stage IV NSCLC with nonsquamous histology that</p>	<p>Pemetrexed (500 mg/m² every 21 days) and best supportive care</p> <p>Maintenance therapy commenced on day 1 of the fifth cycle and continued until disease progression, unacceptable toxicity, or another permitted reason for discontinuation</p> <p>Median number of cycles of pemetrexed given was 4.0</p>	<p>Response rate (time period)</p> <p>0/0; NA, NA</p> <p>Median overall survival (months)</p> <p>12.2/11.8; NR; ns</p> <p>Overall survival (1 year)</p> <p>54.4%/49.5%; HR=1.053; 0.508-2.174</p> <p>Median progression-</p>	<p>Dyspnea (%): 7.1/14.8</p> <p>Anemia (%): 10.7/3.7</p> <p>Chest/thorax pain (%): 10.7/11.1</p> <p>Neutropenia (%): 7.1/0.0</p> <p>Abnormal alanine aminotransferase (%): 7.1/3.7</p> <p>Fatigue (%): 3.6/7.4</p> <p>Nausea (%): 7.1/0.0</p> <p>Vomiting (%): 7.1/0.0</p>	<p>Study type</p> <p>RCT</p> <p>Level of evidence</p> <p>2b- (single results with wide confidence interval)</p> <p>Risk of bias</p> <p>Generation of allocation sequence:</p> <p>+</p> <p>Allocation concealment:</p> <p>?</p> <p>Blinding of participants and personal: -</p>

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
24;12:423.	<p>was not amenable to curative therapy</p> <p>No prior systemic anticancer therapy for lung cancer</p> <p>Creatinine clearance (CrCl) ≥45 mL/min</p> <p>Serum creatinine <1.5 x ULN</p> <p>Adequate bone marrow reserve and liver function</p> <p>Atleast one unidimensionally measurable lesion</p> <p>Prior surgery and radiotherapy were allowed if patients had recovered at least 4 weeks before the initiation of induction therapy</p> <p>No disease progression</p> <p>Exclusion criteria</p> <p>Any serious concomitant</p>	<p>Control</p> <p>Best supportive care</p> <p>Included/randomised patients</p> <p>28/27</p> <p>Analysed patients</p> <p>28/27</p> <p>Attrition</p> <p>5/2</p> <p>Excluded from analysis (reason)</p> <p>-</p>	<p>free survival (months)</p> <p>3.2/3.2; NA; ns</p> <p>Progression-free survival</p> <p>NR; HR=1.539; 0.833 – 2.857 (adjusted for best tumour response, sex, baseline disease stage performance status)</p>		<p>Blinding of outcome assessment: -</p> <p>Incomplete outcome data: +</p> <p>Selective reporting: +</p> <p>Other source of bias: - (groups not balanced)</p>

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
	<p>systemic disorder</p> <p>Brain metastasis</p> <p>Clinically significant third-space fluid collections</p> <p>Significant weight loss (>10%) during the 6 weeks before study entry</p> <p>Pregnancy or breast-feeding</p> <p>Inability to interrupt aspirin or other nonsteroidal anti-inflammatory agents for a 5-day period (or 8-day period for long-acting agents such as piroxicam)</p> <p>Inability or unwillingness to take folic acid, dexamethasone (or equivalent) or vitamin B12 supplementation</p> <p>Patient characteristics</p> <p>Age (median): 61/59</p>				

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
	<p>Male (%): 71.4/63.0</p> <p>Smoking status</p> <p>Current (%): 28.6/22.2</p> <p>Former (%): 28.6/40.7</p> <p>Never (%): 42.9/37.0</p> <p>Stage</p> <p>IIIB (%): 32.1/37.0</p> <p>IV (%): 67.9/63.0</p> <p>Performance status</p> <p>0 (%): 28.6/22.2</p> <p>1 (%): 71.4/77.8</p> <p>Histology</p> <p>Adenocarcinoma (%): 67.9/77.8</p> <p>Large cell (%): 28.6/18.5</p> <p>Mixed cell (%): 3.6/3.7</p> <p>Prior response</p>				

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
	<p>Complete (%): 0.0/3.7</p> <p>Partial (%): 35.7/40.7</p> <p>Stable (%): 60.7/48.1</p> <p>Unknown (%): 3.6/7.4</p> <p>Race</p> <p>Caucasian (%): 92.9/96.3</p> <p>African (%): 7.1/3.7</p> <p>Prior therapy</p> <p>Radiotherapy (%): 7.1/3.7</p> <p>Curative surgery (%): 0.0/7.4</p>				
Pérol, M. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line	<p>Region</p> <p>France</p> <p>Inclusion criteria</p> <p>Age 18 to 70 years</p> <p>Histologically or cytologically documented stage IV NSCLC or</p>	<p>Intervention(s)</p> <p>1) Continuation maintenance with gemcitabine (1,250mg/m² day 1, day 8 of a 3-week cycle); median number of treatment cycles was four</p>	<p>Median overall survival (months)</p> <p>1) 12.1/10.8; NA; NR</p> <p>2) 11.4/10.8; NA; NR</p> <p>Overall survival (median 25.6)</p>	<p>≥ 1 serious AE unrelated to disease progression (%): 22.7/23.2/18.7</p> <p>≥ 1 grade 3/4 AE related to treatment (%): 27.9/15.5/2.6</p> <p>Anemia (%): 38.3/15.5/7.7</p>	<p>Study type RCT</p> <p>Level of evidence 1b</p> <p>Risk of bias</p> <p>Generation of allocation</p>

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
treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol. 2012;30(28):3516-24. Bylicki, O., et al., Efficacy of pemetrexed as second-line therapy in advanced NSCLC after either treatment-free interval or maintenance therapy with gemcitabine or	<p>stage IIIB NSCLC with documented pleural involvement Measurable disease Performance status (PS) of 0 or 1 Exclusion criteria Prior therapy with an EGFR inhibitor</p> <p>Concurrent radiotherapy except for bone metastasis Pre-existing interstitial lung disease 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</p>	<p>(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 Subgroup analysis subsequent pemetrexed At the occurrence of disease progression, all patients were</p>	<p>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) NR/NR; HR=1.786; 1.388-2.272 2) NR/NR; HR=1.440; 1.136-1.851 Subgroup analysis</p>	<p>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 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</p>	<p>sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +</p>

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
erlotinib in IFCT-GFPC 05-02 phase III study. J Thorac Oncol, 2013; 8(7): p. 906-14.	<p>Patient characteristics</p> <p>Age (median): 58/56/60</p> <p>Male (%): 73.4/72.9/72.9</p> <p>Smoking status</p> <p>Current and former (%): 89.0/89.0/92.3</p> <p>Never (%): 11.0/11.0/7.7</p> <p>Stage</p> <p>IIIB (%): 9.3/7.4/9.2</p> <p>IV (%): 90.7/92.6/90.8</p> <p>Unknown (%): 1.9/4.5/1.3</p> <p>Performance status</p> <p>0 (%): 40.1/37.9/44.2</p> <p>1 (%): 53.9/55.6/52.6</p> <p>2 (%): 4.6/5.2/2.6</p> <p>3 (%): 1.3/1.3/0.6</p>	<p>being proposed second-line chemotherapy with pemetrexed</p> <p>Pemetrexed was administered by a 10 minutes intravenous perfusion the first day of each 21-day cycle</p> <p>Subsequent treatments after second-line pemetrexed were selected at the discretion of each investigator</p> <p>Control</p> <p>Observation</p> <p>Included/randomised</p>	<p>subsequent pemetrexed</p> <p>Median progression-free survival (months)</p> <p>4.2/3.9; NA; NR</p> <p>4.2/3.9; NA; NR</p> <p>Progression-free survival (time period NR)</p> <p>1) NR/NR; HR = 1.235; 0.943-1.613</p> <p>2) NR/NR; HR = 1.205; 0.917-1.563</p> <p>Median overall survival (months from beginning of second-line pemetrexed)</p> <p>1) 8.3/7.5; NA; NR</p> <p>2) 9.1/7.5; NA; NR</p>	<p>Treatment-related deaths (absolute number): 2/0/0</p> <p>Subgroup analysis subsequent pemetrexed</p> <p>Anemia (%): 7.0/4.3/5.4</p> <p>Neutropenia (%): 19.3/9.5/13.1</p> <p>Thrombocytopenia (%): 8.8/3.4/6.2</p> <p>Fatigue (%): 2.6/9.5/10.8</p> <p>Infection (%): 2.6/3.4/2.3</p> <p>Pain (%): 4.4/3.4/3.1</p>	

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
	<p>Unknown (%): 1.3/1.3/0.6</p> <p>Brain metastases (%): 3.2/1.3/0.6</p> <p>Histology</p> <p>Adenocarcinoma (%): 65.6/62.6/66.5</p> <p>Squamous cell carcinoma (%): 22.1/17.4/19.4</p> <p>Unknown (%): 12.3/20.0/14.2</p> <p>Response to induction chemotherapy</p> <p>Objective response (%): 52.6/52.9/52.9</p> <p>Stable disease (%): 47.4/47.1/47.1</p> <p>Patient characteristics (subgroup analysis subsequent pemetrexed)</p>	<p>patients 154/155/155</p> <p>Analysed patients 149/153/152</p> <p>Attrition 144/145/148</p> <p>Excluded from analysis (reason) 5/2/3 (no adequate data on progression)</p> <p>Analysed patients (subgroup analysis subsequent pemetrexed) 114/116/130</p>	<p>Overall survival (time period NR)</p> <p>1) NR/NR; HR =1.235; 0.935-1.630</p> <p>2) NR/NR; HR=1.25; 0.952-1.630</p> <p>Objective response rate (time period NR)</p> <p>1) 6.0%/14.6%; NR; ns</p> <p>2) 12.3%/14.6%; NR; ns</p>		

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
	<p>Age (median): 58/59/56</p> <p>Male (%): 70.2/73.3/72.3</p> <p>Smoking status</p> <p>Never-smoker (%): 12.3/12.9/6.2</p> <p>Current/former smoker (%): 87.7/87.1/93.8</p> <p>Stage</p> <p>IIIB (%): 9.0/8.2/9.4</p> <p>IV (%): 91.0/91.8/90.6</p> <p>Performance status</p> <p>0 (%): 41.6/36.0/44.2</p> <p>1 (%): 54.9/59.6/54.3</p> <p>2 (%): 3.5/3.5/0.8</p> <p>Histologic types</p> <p>Squamous cell carcinoma (%): 20.2/15.5/21.5</p> <p>Adenocarcinoma (%):</p>				

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
	<p>67.5/65.5/63.1</p> <p>Other: NSCLC, NOS (%): 12.2/19.0/15.3.</p> <p>Response after CT induction</p> <p>Stable disease (%): 44.7/43.1/43.1</p> <p>Complete/partial response (%): 55.3/56.9/56.9</p>				
<p>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.</p>	<p>Region</p> <p>France</p> <p>Inclusion criteria</p> <p>Histologically confirmed stage IIIB and IV NSCLC</p> <p>Performance status ≤2 ≤ 75 years</p> <p>Patients with stage IIIB disease were required to have no contraindications to thoracic</p>	<p>Intervention(s)</p> <p>Vinorelbine</p> <p>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 the first MIC cycle in patients treated with</p>	<p>Median overall survival (months)</p> <p>12.3/12.3; NA; NR</p> <p>Overall survival (2 years)</p> <p>20%/20%; NR; NR</p> <p>Overall survival (median 10.4/11.9)</p> <p>NR/NR; HR =0.926;</p>	<p>Anemia (%): 9.2/NR</p> <p>Leukopenia (%): 46.9/NR</p> <p>Thrombocytopenia (%): 3.4/NR</p> <p>Infection (%): 12.6/NR</p> <p>Hemorrhage (%): 1.1/NR</p> <p>Ileus (%): 3.4/NR</p> <p>Pulmonary (%): 6.9/NR</p> <p>Peripheral neuropathy (%): 6.9/NR</p>	<p>Study type</p> <p>RCT</p> <p>Level of evidence</p> <p>2b</p> <p>Risk of bias</p> <p>Generation of allocation sequence:</p> <p>+</p> <p>Allocation concealment:</p> <p>+</p>

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
	<p>radiotherapy Leukocyte count above 3000/μL Neutrophil count above 1500/μL Platelet count above 150 000/μL Serum creatinine level below 130 μmol/L</p> <p>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 Interstitial pneumonitis</p>	<p>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</p> <p>Control Observation Vinorelbine treatment was not allowed in patients</p>	<p>0.680-1.266</p> <p>Median progression-free survival (months) 5/3; NR; NR</p> <p>Progression-free survival (median follow-up 10.4/11.9) HR=1.299; 0.935-1.786</p> <p>Progression-free survival (2 years) 13%;15%; NR; NR</p>	<p>Cardiac (%): 1.1/NR Others (%): 9.2/NR</p>	<p>Blinding of participants and personal: - Blinding of outcome assessment: + Incomplete outcome data: ? Selective reporting: + Other source of bias: +</p>

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
	<p>Severe cardiac disease</p> <p>Cirrhosis</p> <p>Responders to induction chemotherapy</p> <p>Patient characteristics</p> <p>Age (median): 62/63</p> <p>Male (%): 95.6/90.0</p> <p>Stage</p> <p>IIIB (%): 47.3/56.7</p> <p>IV (%): 52.7/43.3</p> <p>Performance status</p> <p>0 (%): 33.0/33.3</p> <p>1 (%): 51.6/57.8</p> <p>2 (%): 15.4/8.9</p> <p>Histology</p> <p>Squamous (%): 60.4/58.9</p>	<p>assigned to the observation group at any time</p> <p>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</p> <p>Included/randomised patients</p> <p>91/90</p> <p>Analysed patients</p> <p>91/90</p> <p>87/0 (for safety)</p>			

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
	<p>Adenocarcinoma (%): 30.8/28.9</p> <p>Large cell (%): 8.8/12.2</p> <p>Response to induction treatment at random assignment</p> <p>Complete (%): 13.2/6.7</p> <p>Partial (%): 86.8/93.3</p>	<p>Attrition NR</p> <p>Excluded from analysis (reason) 4/90 (not received any treatment, no available data)</p>			

+ 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	<p>Region Korea, USA</p> <p>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</p>	<p>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</p> <p>Control Pemetrexed 500 mg/m² was administered intravenously over 10 minutes on day 1 of every 21-day cycle Cycles were repeated until disease progression,</p>	<p>Median overall survival (months) 8.5/8,5; NA; NR</p> <p>Overall survival (median follow-up: 60.6 months)</p> <p>90%/89%; NR; NR</p> <p>Median progression-free survival (months) 2.0/2.0 ; NA; ns</p> <p>Progression-free survival (6 months, RECIST criteria) 15%/22%; NR; 0.35</p>	<p>Hematologic toxicity Anemia (%): 21/51 Leukocytopenia (%): -/4 Neutropenia (%): -/6 Thrombocytopenia (%): -/6</p> <p>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</p>	<p>Study type RCT</p> <p>Level of evidence 2b</p> <p>Risk of bias Generation of allocation sequence: + Allocation concealment: ? Blinding of participants and personal: -</p> <p>Blinding of</p>

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
	<p>if treated with radiation therapy and clinically stable</p> <p>Exclusion criteria</p> <p>Chronic diarrhea of any grade, inflammatory bowel disease, uncontrolled comorbid illness, or other malignancies</p> <p>Squamous cell histology or activating <i>EGFR</i> mutations</p> <p>Patient characteristics</p> <p>Age (mean): 67/64</p> <p>Men (%): 73/70</p> <p>PS (ECOG)</p> <p>0 (%): 10/11</p> <p>1 (%): 54/57</p> <p>2 (%): 35/32</p> <p>Histology</p>	<p>unacceptable toxicity</p> <p>Included/randomised patients</p> <p>48/47</p> <p>Analysed patients</p> <p>48/47</p> <p>NR (efficacy)</p> <p>Attrition</p> <p>NR</p> <p>Excluded from analysis (reason)</p> <p>-</p>	<p>ORR (median follow-up: 60.6 months, RECIST criteria)</p> <p>8%/13%; NR; 0.52</p> <p>Diseases control rate (median follow-up: 60.6 months, RECIST criteria)</p> <p>8%/13%; NR; 0.36</p>	<p>(%): -/4</p>	<p>outcome assessment: -</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	<p>Adenocarcinoma (%): 65/62</p> <p>Squamous cell carcinoma (%): 19/21</p> <p>LCNEC (%): 2/2</p> <p>NSCLC not otherwise specified (%): 15/15</p> <p><i>Stage at treatment</i></p> <p>IIIB (%): 4/6</p> <p>IV (%): 96/94</p> <p><i>Metastatic sites</i></p> <p>Lung to lung (%): 44/38</p> <p>Pleura (%): 54/34</p> <p>Brain (%): 8/15</p> <p>>2 sites (%): 48/38</p> <p><i>Treatment sequence</i></p> <p>2nd- line (%): 63/68</p> <p>3rd - line (%): 38/32</p> <p><i>Smoking habits</i></p> <p>Current and former smokers</p>				

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
	<p>(%): 69/70</p> <p>Never smokers (%): 31/30</p> <p><i>Previous chemotherapy</i></p> <p>Platinum-based combinations (%): 83/87</p> <p>Non-platinum combinations (%): 8/6</p> <p>Monotherapy without platinum (%): 8/6</p> <p><i>Previous best response to first-line treatment</i></p> <p>Complete response (%): 2/0</p> <p>Partial response (%): 52/68</p> <p>Stable disease (%): 29/26</p> <p>Progressive disease (%): 17/6</p> <p><i>EGFR mutation</i></p> <p>Mutant (%): 2/2</p> <p>Wild- Type (%): 48/28</p> <p>Unknown (%): 50/70</p>				

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
<p>Paz-Ares, L., et al., Necitumumab plus pemetrexed and cisplatin as first-line therapy 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.</p>	<p>Region 20 countries</p> <p>Inclusion criteria Age of 18 or older 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</p> <p>Exclusion criteria Symptomatic brain metastases Clinically significant third-space fluid retention requiring repeated drainage4 Peripheral neuropathy of</p>	<p>Intervention(s) 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 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</p> <p>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</p>	<p>Median overall survival (months) 11.3/11.5; NA; ns (CIs overlapping)</p> <p>Overall survival (median follow-up: 24.5 months [necitumumab], 25.6 months [9]) 75%/77%; HR= 1.01; 0.84-1.21</p> <p>Median progression-free survival (months) 5.6/5.6; NA; ns</p> <p>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</p>	<p>Neutropenia (%): 32/32 Anaemia (%): 26/31 Fatigue (%): 56/51 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</p>	<p>Study type RCT</p> <p>Level of evidence 1b</p> <p>Risk of bias Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of outcome</p>

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
	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 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	cycles 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)	ORR (median follow-up: 24.5 months [necitumumab], 25.6 months [9], RECIST criteria) 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)		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
	<p>hypersensitivity reaction to any of the treatment components</p> <p>Concurrent active malignancy other than adequately treated basal-cell carcinoma of the skin or preinvasive carcinoma of the cervix</p> <p>History of drug abuse</p> <p>Patient characteristics</p> <p>Age (mean): 61/60</p> <p>Men (%): 68/66</p> <p>Age group (years)</p> <p><65 (%): 63/68</p> <p>>65 (%): 37/32</p> <p><70 (%): 83/84</p> <p>>70 (%): 17/16</p> <p>PS (ECOG)</p> <p>0 (%): 37/42</p> <p>1 (%): 58/52</p>				

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
	<p>2 (%): 5/6 Missing (%): <1/0</p> <p><i>Smoking habits</i></p> <p>Current smoker (%): 76/75 Ex- light smoker (%): 8/8 Never smokers (%): 16/17</p> <p><i>Disease histology</i></p> <p>Adenocarcinoma (%): 89/90 Large- cell carcinoma (%): 8/8 Other (%): 2/2 Missing (%): <1/0</p> <p><i>Ethnic origin</i></p> <p>White (%): 93/94 Asian (%): <1/0 Other (%): 7/6</p> <p><i>Previous anticancer therapy</i></p> <p>Surgery (%): 26/29 Radiotherapy (%): 10/13</p>				

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
	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 Investigators (Phase III Studie: Crizo vs. Chemo)	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 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	Intervention(s) Oral crizotinib, at a dose of 250 mg twice daily Administered every 3 weeks for a maximum of six cycles 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	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) 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-	Vision disorder (%): 71/9 Diarrhea (%): 61/13 Edema (%): 49/12 Vomiting (%): 46/36 Constipation (%): 43/30 Elevated aminotransferases (%): 36/13 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	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
	<p>neurologically stable for at least 2 weeks before enrollment and the patient had no ongoing requirement for glucocorticoids</p> <p>Exclusion criteria</p> <p>NR</p> <p>Patient characteristics</p> <p>Age (mean): 52/54</p> <p>Men (%): 40/37</p> <p>PS (ECOG)</p> <p>0 or 1 (%): 94/95</p> <p>2 (%): 6/5</p> <p>Histology</p> <p>Adenocarcinoma (%): 94/94</p> <p>Nonadenocarcinoma (%): 6/6</p> <p>Smoking habits</p> <p>Current smoker (%): 6/3</p>	<p>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</p> <p>Administered every 3 weeks for a maximum of six cycles</p> <p>Treatment was continued until RECIST-defined disease progression, development of unacceptable toxic effects</p> <p>Included/randomised patients</p> <p>172/171</p> <p>Analysed patients</p> <p>172/171 (efficacy)</p>	<p>up: 17.4 months [crizotinib], 16.7 months [9], RECIST criteria)</p> <p>74%/45%; NR; <0.001</p> <p>Change from baseline in quality of life (time point NR, EQ-5D)</p> <p>NR; Crizotinib>control; 0.002</p> <p>Change from baseline in quality of life (time point NR, QLQ-C30)</p> <p>NR; Crizotinib>control; <0.001</p> <p>Reduction in symptoms (time point</p>	<p>Neutropenia (%): 21/30</p> <p>Stomatitis (%): 12/20</p> <p>Asthenia (%): 13/24</p> <p>Anemia (%): 9/32</p> <p>Leukopenia (%): 7/15</p> <p>Thrombocytopenia (%): 1/18</p> <p>Nausea (%): 56/59</p> <p>Decreased appetite (%): 30/34</p> <p>Cough (%): 23/20</p> <p>Neuropathy (%): 20/22</p> <p>Dyspnea (%): 18/15</p>	<p>-</p> <p>Incomplete outcome data: +</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	<p>Former smoker (%): 33/32</p> <p>Never smokers (%): 62/65</p> <p>Ethnic origin</p> <p>White (%): 53/50</p> <p>Asian (%): 45/47</p> <p>Other (%): 2/4</p> <p>Extent of disease</p> <p>Locally advanced (%): 2/2</p> <p>Metastatic (%): 98/98</p> <p>Time since first diagnosis-mo</p> <p>Median: 1.2/1.2</p> <p>Range: 0- 114.0/ 0-93.6</p> <p>Brain metastases present - no.(%): 26/27</p>	<p>NR (quality of life)</p> <p>171/169 (safety)</p> <p>Attrition</p> <p>8/8</p> <p>Excluded from analysis (reason)</p> <p>0/2 (events before cross-over)</p> <p>NR (quality of life and symptoms, at least one post baseline)</p>	<p>NR, QLQ-C30)</p> <p>NR; Crizotinib>control, <0.05 (pain, dyspnea, fatigue, insomnia, nausea and vomiting); Crizotinib>control, $p>0.05$ (constipation); Control> Crizotinib, $p<0.05$ (diarrhea)</p> <p>Reduction in symptoms (time point NR, QLQ-LC13)</p> <p>NR; Crizotinib>control, $p<0.05$ (dyspnea, cough, chest pain, arm or shoulder pain, alopecia, and pain in other parts of the body); Crizotinib>control,</p>		

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
			p>0.05 (hemoptysis, sore mouth); Control> Crizotinib, p<0.05 (peripheral neuropathy); Control> Crizotinib, 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, randomized, open-label, ENSURE study. Ann Oncol, 2015. 26(9): p. 1883-9.	Region China, Malaysia, Philipines Inclusion criteria ≥18 years Histologically or cytologically confirmed stage IIIB/IV EGFR mutation-positive NSCLC ECOG PS of 0-2 Exclusion criteria Prior chemotherapy or agents targeting HER receptors Inability to take oral medication	Intervention(s) Erlotinib (oral; 150 mg once daily until progression/ unacceptable toxicity Control Gemcitabine 1250 mg/m ² i.v. days 1 and 8 plus cisplatin 75 mg/m ² i.v. day 1, every 3 weeks for up to four cycles Included/randomised patients	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 Median progression-free survival (months) 11.0/5.6; NA; NR	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 Dry skin (%): 9.1/1.9 Dermatitis acneiform (%): 8.2/0 Leukopenia (%): 6.4/49 Neutropenia (%): 4.5/51	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 (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
	<p>≥grade 2 peripheral neuropathy Brain metastases History of any malignancies within 5 years Surgery within 4 weeks of the study</p> <p>Patient characteristics Age (mean): 57.5/56 Men (%): 38.2/39.3</p> <p>PS (ECOG) 0 (%): 14.7/14.4 1 (%): 78.9/79.8 2 (%): 6.4/5.8</p> <p>Histology Adenocarcinoma (%): 94.5/94.4 Squamous cell carcinoma (%): 1.8/1.9</p>	<p>110/107 Analysed patients 110/107 (efficacy) Attrition 0/2 Excluded from analysis (reason) 0/3 (safety not received treatment)</p>	<p>Progression-free survival (median follow-up: 28.9 months [Erlotinib], 27.1 months [Gemcitabine], RECIST criteria) NR; HR=2.38; 1.51-3.70</p> <p>ORR (median follow-up: 28.9 months [Erlotinib], 27.1 months [Gemcitabine], RECIST criteria) 62.7% / 33.6%; NR; NR</p> <p>Diseases control rate (median follow-up: 28.9 months [Erlotinib], 27.1</p>	<p>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 Chest discomfort (%): 5.5/2.9 Cough (%): 17.3/8.7 Dyspnea (%): 5.5/2.9</p>	<p>- Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +</p>

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
	<p>Other (%): 3.6/3.6</p> <p><i>Smoking habits</i></p> <p>Current smoker (%): 24.5/29</p> <p>Former smoker (%): 3.6/1.9</p> <p>Never smokers (%): 71.8/69.2</p> <p><i>Stage of disease</i></p> <p>IIIB (%): 9.1/6.5</p> <p>IV (%): 90.9/93.5</p> <p><i>Tissue-assessed EGFR mutation</i></p> <p>type</p> <p>Exon 19 deletion (%): 52.3/57</p> <p>Exon 21 L858R mutation (%): 47.7/43</p> <p><i>Country</i></p> <p>China (%): 79.1/82.2</p> <p>Non China (%): 20.9/17.8</p>		<p>months [Gemcitabine], RECIST criteria)</p> <p>89.1%/76.6%; NR; NR</p>	<p>Decreased appetite (%): 12.7/28.8</p> <p>Hypokalemia (%): 5.5/6.7</p> <p>Paronychia (%): 15.5/0</p> <p>Dizziness (%): 6.4/13.5</p> <p>Headache (%): 4.5/6.7</p> <p>Backpain (%): 7.3/5.8</p> <p>Insomnia (%): 4.5/7.7</p> <p>Neutropenia (%): 0.9/25</p> <p>Leukopenia (%): 0.9/14.4</p> <p>Anemia (%): 0.9/12.5</p> <p>Thrombocytopenia (%): 0/6.7</p> <p>Decreased white blood cell count (%): 0/6.7</p> <p>Decreased neutrophil count (%): 0/5.8</p> <p>Rash (%): 6.4/1</p>	

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
<p>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.</p> <p>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.</p>	<p>Region China</p> <p>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</p> <p>Exclusion criteria Uncontrolled brain metastases</p>	<p>Intervention(s) Oral erlotinib 150 mg once daily until disease progression or unacceptable toxic effects</p> <p>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 cycle (up to four cycles)</p> <p>Included/randomised patients 83/82</p>	<p>Median overall survival (months) 22.8/27.2; NA; NR</p> <p>Overall survival (median follow-up 15.6 month) 80%/83%; NR; NR</p> <p>Overall survival (median follow-up 25.9 month) 37%/37%; NR; NR</p> <p>Progression free survival (median follow-up 15.6 month)</p> <p>NR/NR; HR= 6.25; 3.847-10.00</p>	<p>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</p>	<p>Study type RCT</p> <p>Level of evidence 1b</p> <p>Risk of bias Generation of allocation sequence: +</p> <p>Allocation concealment: + Blinding of participants and personal: - Blinding of outcome assessment: -</p>

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
<p>Lancet Oncol, 2011. 12(8): p. 735-42.</p> <p>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.</p>	<p>Previous systemic anticancer therapy for advanced disease</p> <p>Patient characteristics</p> <p>Age (median): 57/59</p> <p>Male (%): 41/40</p> <p>PS (ECOG)</p> <p>0-1 (%): 91/96</p> <p>2 (%): 9/4</p> <p>Smoking status</p> <p>Present or former smoker (%): 28/31</p> <p>Non-smoker (%): 72/69</p> <p>Histology</p> <p>Adenocarcinoma (%): 88/86</p> <p>Non-adenocarcinoma (%): 12/14</p> <p>EGFR mutation</p> <p>Exon 19 deletion (%): 52/54</p>	<p>Analysed patients</p> <p>82/72</p> <p>71/54 (quality of life)</p> <p>Attrition</p> <p>61/82</p> <p>Excluded from analysis (reason)</p> <p>1/10 (not received treatment)</p> <p>12/28 (quality of life: not received treatment, not completed questionnaire)</p>	<p>Median progression free survival (months)</p> <p>13.1/4.6; NA; statistical significant</p> <p>Response rate (median follow-up 15.6 month)</p> <p>83/36; NR; 0.0001</p> <p><i>Mean change in functioning (baseline to cycle 2, FACT-L)</i></p> <p>Physical well-being</p> <p>NR/NR; NR; 0.003</p> <p>Social/family well-being</p> <p>NR/NR; NR; 0.303</p> <p>Emotional well-being</p>		<p>Incomplete outcome data: +</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	<p>L858R mutation (%): 48/46</p> <p>Disease stage</p> <p>IIIB (%): 13/7</p> <p>IV (%): 87/93</p>		<p>NR/NR; NR; 0.036</p> <p>Functional well-being</p> <p>NR/NR; NR; 0.093</p> <p>Lung cancer subscale</p> <p>NR/NR; NR; 0.004</p>		

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
<p>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.</p>	<p>Region Italia</p> <p>Inclusion criteria Wild-type EGFR Recurrence or progression after failing platinum-based chemotherapy.</p> <p>ECOG performance status of 2 or less</p> <p>Adequate vital functions</p> <p>Exclusion criteria Previous treatment with taxanes or anti-EGFR drugs</p> <p>Patient characteristics Age (mean): 66/67 Men (%): 71/66</p>	<p>Intervention(s) Erlotinib 150 mg was given orally every day. Received a median of two cycles, with a median dose of 137 mg/day.</p> <p>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.</p> <p>Median of three cycles, with a median dose per cycle of 91 mg/m² for the weekly schedule and 75 mg/m² for the 3-weekly schedule</p>	<p>Median overall survival (months) 5.4/8.2; NR; ns (CIs overlap)</p> <p>Overall survival (1 year) 31.8%/39.6%; HR= 0.73; 0.53-1.00</p> <p>Median progression-free survival (months) 2.4/2.9; NR; ns</p> <p>Progression-free survival (6 months) 16.5%/27.3%; HR= 0.71; 0.53 -0.95</p> <p>ORR</p>	<p>Febrile neutropenia (%): 0 / 5</p> <p>Neutropenia (%): 3/30</p> <p>Diarrhoea (%): 30/21</p> <p>Alopecia (%): 2/33</p> <p>Asthenia (%): 37/49</p> <p>Neurological (%): 5/16</p> <p>Nausea or vomiting (%): 10/23</p> <p>Dermatological (%): 58/4</p>	<p>Study type RCT</p> <p>Level of evidence 1b</p> <p>Risk of bias</p> <p>Generation of allocation sequence: +</p> <p>Allocation concealment: +</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome assessment: -</p> <p>Incomplete outcome data: +</p> <p>Selective reporting: +</p>

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
	<p><i>PS (ECOG)</i></p> <p>0 (%): 48/48</p> <p>1 (%): 44/45</p> <p>2 (%): 8/6</p> <p><i>Histology</i></p> <p>Squamous (%): 28/21</p> <p>Adenocarcinoma (%): 63/75</p> <p>Large-cell carcinoma (%): 1 /1</p> <p>Bronchoalveolar (%): 3/0</p> <p>Others (%): 5/3</p> <p><i>Smoking habits</i></p> <p>Current and former smokers (%): 83/73</p> <p>Never smokers (%): 17/27</p> <p><i>Ethnic origin</i></p> <p>White (%): 99/99</p> <p>Asian (%): 1 /1</p>	<p>Included/randomised patients</p> <p>112/110</p> <p>Analysed patients</p> <p>109/110 (efficacy)</p> <p>97/100 (ORR)</p> <p>107/104 (safety)</p> <p>Attrition</p> <p>NR</p> <p>Excluded from analysis (reason)</p> <p>3/0 (efficacy, ineligible for genotyping)</p> <p>5/6 (safety, not received allocated intervention)</p>	<p>3.0/15.5; NR; 0.003</p>		<p>Other source of bias: +</p>

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
	<p><i>Previous chemotherapy</i></p> <p>First line (%): 92/93</p> <p>Adjuvant (%): 8/6</p> <p>Unknown (%): 0/1</p> <p>Previous best response to first-line treatment</p> <p>Complete response (%): 1/0</p> <p>Partial response (%): 44/35</p> <p>Stable disease (%): 24/35</p> <p>Progressive disease (%): 31/29</p>	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. <i>J Clin Oncol</i> , 2012. 30(10):	<p>Region</p> <p>Korea</p> <p>Inclusion criteria</p> <p>Chemotherapy-naïve never-smokers older than age 18 years</p>	<p>Intervention(s)</p> <p>Gefitinib 250 mg/d orally until disease progression</p> <p>Median duration of treatment for gefitinib was 163 days</p>	<p>Median overall survival (months)</p> <p>27.2/25.6; NR; NR</p> <p>Overall survival (50 months)</p> <p>NR; NR; HR= 1.043;</p>	NR	<p>Study type</p> <p>RCT</p> <p>Level of evidence</p> <p>2b</p> <p>Risk of bias</p>

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
p. 1122-8. (subgroup EGFR mutation)	<p>Stage IV adenocarcinoma of the lung with measurable or nonmeasurable disease</p> <p>Performance status of 0 to 2</p> <p>Adequate bone marrow, liver, and renal function</p> <p>EGFR mutation</p> <p>Exclusion criteria</p> <p>Known severe hypersensitivity to gefitinib or any constituents of this product</p> <p>Any evidence of clinically active interstitial lung disease</p> <p>Severe or uncontrolled systemic disease</p> <p>Concomitant use of</p>	<p>Control</p> <p>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</p> <p>Median number of GP cycles was six</p> <p>Included/randomised patients</p> <p>NR/NR</p> <p>Analysed patients</p> <p>26/16</p> <p>Attrition</p>	<p>0.498 – 2.182</p> <p>Median progression free survival (months)</p> <p>8.0/6.3; NR; NR</p> <p>Progression-free survival (30 months)</p> <p>NR/NR; HR= 1.838; 0.909 – 3.717</p> <p>ORR (time period NR)</p> <p>94.6%/37.5%; NR; 0.002</p> <p>Median change in quality of Life (baseline to week 21,QLQ-C30)</p> <p>NR;NR; 0.513</p> <p><i>Median change in</i></p>		<p>Generation of allocation sequence: +</p> <p>Allocation concealment: ?</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome assessment: +</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting: +</p> <p>Other source of bias: - (subgroup analysis)</p>

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
	<p>phenytoin, carbamazepine, rifampin, barbiturate, or St John's wort</p> <p>Nonstable brain metastasis</p> <p>Patient characteristics</p> <p>NR</p>	<p>NR/NR</p> <p>Excluded from analysis (reason)</p> <p>NR/NR</p>	<p><i>quality of Life (baseline to week 21, LC13)</i></p> <p>Dyspnea: NR; NR; 0.95</p> <p>Coughing: NR; NR; 0.199</p> <p>Hemoptysis: NR; NR; 0.006 (in favour of Gefitinib)</p> <p>Sore mouth: NR; NR; 0.007 (in favour of Gefitinib)</p> <p>Dysphagia: NR; NR; 0.004 (in favour of Gefitinib)</p> <p>Peripheral neuropathy: NR; NR; 0.789</p> <p>Alopecia: NR; NR; 0.004 (in favour of Gemcitabine)</p> <p>Pain in chest: NR; NR; 0.214</p> <p>Pain in arm or</p>		

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
			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)	<p>Region NR</p> <p>Inclusion criteria Pemetrexed-naive and TKI-naive patients with documented stage IV NSCLC who experience disease progression after 1 or 2 chemotherapy lines</p> <p>Patients aged <65 years must have received a platinum-based regimen, which was not mandatory for older patients</p> <p>Performance status (PS)</p>	<p>Intervention(s) Erlotinib (150 mg/day orally; median duration 3.2 months)</p> <p>Control Pemetrexed (500 mg/m² over a 1-hour as an intravenous infusion on day 1, every 3 weeks; median, 3 cycles)</p> <p>Included/randomised patients</p>	<p>Overall survival (median 27.3/29.0) NR/NR; HR= 0.52; 0.10 - 2.69</p> <p>ORR (median 27.3/29.0) No differences</p>	NR	<p>Study type RCT</p> <p>Level of evidence 2b-</p> <p>Risk of bias</p> <p>Generation of allocation sequence: +</p> <p>Allocation concealment: +</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome</p>

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
	<p>from 0 to 2</p> <p>Adequate bone marrow tests Life expectancy ≥ 3 months</p> <p>Clinically stable with irradiated brain metastases</p> <p>EGFR mutation</p> <p>Exclusion criteria</p> <p>Squamous cell histology (Amendment after July 2008)</p> <p>Second primary tumor</p> <p>Active infection</p> <p>Severe heart disease</p> <p>Uncontrolled diabetes mellitus</p> <p>Patient characteristics</p> <p>NR</p>	<p>NR</p> <p>Analysed patients 5/6</p> <p>Attrition NR</p> <p>Excluded from analysis (reason) NR</p>			<p>assessment: ?</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting: +</p> <p>Other source of bias: - (subgroup analysis)</p>

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
<p>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)</p>	<p>Region Japan</p> <p>Inclusion criteria</p> <p>Age 20 years or older</p> <p>NSCLC with stage IV disease</p> <p>Previous treatment with one or two chemotherapy regimens, including at least one platinum agent</p> <p>Evaluable or measurable disease by computed tomography (CT) or magnetic resonance imaging</p> <p>Performance status of 0 to 2</p> <p>EGFR mutation</p>	<p>Intervention(s) Erlotinib (150 mg per day) was administered orally</p> <p>Control Docetaxel was administered every 3 weeks as a 1-hour intravenous infusion of 60mg/m²</p> <p>Included/randomised patients NR</p> <p>Analysed patients 5/6</p> <p>Attrition NR</p> <p>Excluded from Progression free</p>	<p>Median overall survival (months) Not reached/27.8 months; NA; NR</p> <p>Overall survival (40 months) HR=NR/NR; HR= 2.632; 0.909 –10.00</p> <p>Test of interaction for survival EGFR positive vs. EGFR negative; 0.20</p> <p>Median progression free survival (months) 9.3/7.0; NA; NR</p>	<p>NR</p>	<p>Study type RCT</p> <p>Level of evidence 2b</p> <p>Risk of bias</p> <p>Generation of allocation sequence: +</p> <p>Allocation concealment: ?</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome assessment: ?</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting: +</p>

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	analysis (reason) NR	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		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	Region Japan Inclusion criteria Confirmed stage IV NSCLC Harbouing activating EGFR mutations (either exon 19 deletion or L858R in exon	Intervention(s) Gefitinib (250 mg/day, administered orally) Continued until progression of the disease, development of unacceptable toxic	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	Study type RCT Level of evidence 2b Risk of bias Generation of 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
(WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol, 2010; 11(2): p. 121-8.	<p>21) Aged 75 years or younger WHO performance status 0-1</p> <p>Measurable or non-measurable disease according to the Response Evaluation Criteria in Solid Tumours (RECIST)</p> <p>Adequate organ function</p> <p>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</p>	<p>effects, a request by the patient to discontinue treatment, serious non-compliance with the protocol, or completion of three to six chemotherapy cycles</p> <p>Control</p> <p>Docetaxel (60 mg/m², administered intravenously over a 1 h period) followed by cisplatin (80 mg/m², administered intravenously over a 90-min period)</p> <p>Continued until progression of the disease, development of unacceptable toxic</p>	<p>Progression free survival (median 81 days)</p> <p>NR/NR; HR= 2.045; 1.41-2.976</p> <p>Objective response rate (median 81 days)</p> <p>62.1%/32.2%; NR; <0.0001</p>	<p>Diarrhoea (%): 54/40</p> <p>Fatigue (%): 39/83</p> <p>Paronychia (%): 32/1</p> <p>Stomatitis (%): 22/15</p> <p>Nausea (%): 17/94</p> <p>Constipation (%): 16/44</p> <p>Alopecia (%): 9/76</p> <p>Sensory disturbance (%): 8/26</p> <p>Leucocytopenia (%): 15/49</p> <p>Thrombocytopenia (%): 14/0</p> <p>Neutropenia (%): 8/84</p> <p>Anemia (%): 38/17</p>	<p>sequence: +</p> <p>Allocation concealment: +</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome assessment: ?</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	<p>Exclusion criteria</p> <p>Previous drug therapy that had targeted EGFR</p> <p>History of interstitial lung disease</p> <p>Severe drug allergy</p> <p>Active infection or other serious disease condition</p> <p>Symptomatic brain metastases</p> <p>Poorly controlled pleural effusion, pericardial effusion or ascites necessitating drainage, active double cancer, or severe hypersensitivity to drugs containing polysolvate 80</p> <p>Patients in pregnancy or lactation, or whose participation in the trial</p>	<p>eff ects, a request by the patient to discontinue treatment, serious ,non-compliance with the protocol, or completion of three to six chemotherapy cycles</p> <p>Included/randomised patients 88/89</p> <p>Analysed patients 87/88 (for safety) 86/86 (for efficacy)</p> <p>Attrition NR</p> <p>Excluded from analysis (reason) 1/1 (safety, not</p>			

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
	<p>was judged to be inappropriate by the attending doctor</p> <p>Patient characteristics</p> <p>Age (median): 64.0/64.0</p> <p>Male (%): 27/26</p> <p><i>PS (ECOG)</i></p> <p>0 (%): 56/52</p> <p>1 (%): 30/34</p> <p><i>Histological type</i></p> <p>Adenocarcinoma (%): 83/84</p> <p>Adenosquamous carcinoma (%): 0/1</p> <p>Squamous-cell carcinoma (%): 1/0</p> <p>Non-small-cell-lung cancer; not otherwise specified (%): 2/1</p>	<p>received therapy)</p> <p>2/3 (efficacy, not received therapy, exon 18 mutation, allergic reaction, insufficient consent)</p>			

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
	<p><i>Smoking history</i></p> <p>Never (%): 61/57</p> <p>Former/current (%): 25/29</p> <p><i>Stage</i></p> <p>Postoperative recurrence (%): 35/36</p> <p>With postoperative adjuvant chemotherapy (%): 19/23</p> <p>Without postoperative adjuvant chemotherapy (%): 16/13</p> <p>IIIB (%): 10/9</p> <p>IV (%): 41/41</p> <p><i>EGFR mutation</i></p> <p>Exon 19 detection (%): 50/37</p> <p>L858R (%): 36/49</p>				
Mok, T. S. "Gefitinib or carboplatin-	Region	Intervention(s)	Overall survival (time period NR)	NR	Study type

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
<p>paclitaxel in pulmonary adenocarcinoma." N Engl J Med, 2009. 361(10): 947-957. (subgroup analysis)</p>	<p>Hong Kong, China, Indonesia, Japan, Malaysia, the Philippines, Singapore, Taiwan, and Thailand</p> <p>Inclusion criteria</p> <p>18 years of age or older</p> <p>Confirmed stage IIIB or IV non-small-cell lung cancer with histologic features of adenocarcinoma (including bronchoalveolar carcinoma)</p> <p>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)</p> <p>Performance status 0 to 2</p>	<p>Gefitinib (250 mg per day, administered orally)</p> <p>Median treatment duration 6.4 months</p> <p>Control</p> <p>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</p>	<p>NR/NR; HR= 1.28; 0.833-2.00</p> <p>Progression free survival (median follow-up 5.6)</p> <p>NR/NR; HR= 2.08; 1.56-2.78 -</p> <p>Test of interaction for progression free survival</p> <p>EGFR positive vs. EGFR negative ; <0.001)</p> <p>Objective response rate (time period NR)</p> <p>71.2%/47.3%; NR; 0.001</p>		<p>RCT</p> <p>Level of evidence 2b</p> <p>Risk of bias</p> <p>Generation of allocation sequence: +</p> <p>Allocation concealment: ?</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome assessment: ?</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting: +</p> <p>Other source of bias:</p>

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
	<p>Measurable disease according to RECIST</p> <p>At least 1 measurable lesion not previously irradiated, adjuvant chemotherapy permitted if not platinum-based and completed > 6 months previously, adequate hepatic function</p> <p>EGFR mutation positive</p> <p>Exclusion criteria</p> <p>Previous chemotherapy or biologic or immunologic therapy</p> <p>Patient characteristics</p> <p>Age < 65 years (%): 72.0/69.8</p> <p>Male (%): 18.2/20.2</p>	<p>period of 15 to 60 minutes) in cycles of once every 3 weeks for up to 6 cycles.</p> <p>Median treatment duration 3.4 months</p> <p>Included/randomised patients</p> <p>132/129 (baseline characteristics)</p> <p>Analysed patients</p> <p>NR (survival outcomes)</p> <p>131/128 (FACT-L)</p> <p>Attrition</p> <p>NR</p> <p>Excluded from analysis (reason)</p> <p>NR</p>	<p>Clinical relevant sustained improvement in functioning (time period NR, FACT-L)</p> <p>70.2%/44.5%; HR = 3.01; 1.79-5.07</p>		+

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	<p>PS (ECOG) 0 or 1 (%): 90.2/94.6</p> <p><i>Smoking history</i> Never smoker (%): 93.9/94.6</p>	1/1 (FACT-L)			
<p>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.</p>	<p>Region France, Italy, and Spain</p> <p>Inclusion criteria Stage IIIB (with pleural effusion) or stage IV NSCLC</p> <p>Measurable or evaluable disease</p> <p>Activating EGFR mutations (exon 19 deletion or L858R mutation in exon 21)</p> <p>Age older than 18 years</p>	<p>Intervention(s) Oral erlotinib (150 mg per day)</p> <p>Median duration of treatment was 8.2 months (range 0.3–32.9, IQR 3.1–12.0)</p> <p>Control 3 week cycles of standard intravenous chemotherapy (75 mg/m² cisplatin plus 75 mg/m² docetaxel)</p>	<p>Median overall survival (months) 19.3/19.5; NA; ns</p> <p>Overall survival (median follow-up 18.9 /14.4 months) 56/64; HR= 0.96; 0.60-1.54</p> <p>Median progression free survival (months) 9.7/5.2; NA; sign.</p>	<p>Fatigue (%): 57/72</p> <p>Rash (%): 80/5</p> <p>Diarrhoea (%): 57/18</p> <p>Appetite loss (%): 31/34</p> <p>Anaemia (%): 12/49</p> <p>Neutropenia (%): 0/40</p> <p>Alopecia (%): 14/18</p> <p>Neuropathy (%): 9/14</p> <p>Arthralgia (%): 11/6</p> <p>Thrombocytopenia (%): 1/15</p> <p>Aminotransferase rise</p>	<p>Study type RCT</p> <p>Level of evidence 1b</p> <p>Risk of bias</p> <p>Generation of allocation sequence: +</p> <p>Allocation concealment: +</p> <p>Blinding of participants</p>

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
	<p>Exclusion criteria History of chemotherapy for metastatic disease (neoadjuvant or adjuvant chemotherapy was allowed if it ended \geq6 months before entry to study)</p> <p>Patient characteristics Age (median): 65/65 Male (%): 33/22 <i>PS (ECOG)</i> 0 (%): 31/34 1 (%): 55/52 2 (%): 14/14 <i>Smoking status</i> Never smoked (%): 66/72 Previous smoker (%): 26/14 Current smoker (%): 8/14</p>	<p>on day 1 or 75 mg/m² cisplatin on day 1 plus 1250 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)</p> <p>Included/randomised patients 86/87</p> <p>Analysed patients 86/87 (efficacy) 84/82 (safety)</p> <p>Attrition NR/NR</p> <p>Excluded from</p>	<p>Progression free survival (median follow-up 18.9 /14.4 months) NR/NR; HR= 2.70; 1.85-4</p> <p>Progression free survival (2 years) 11%/0%; NA; NR</p> <p>Response rate (median follow-up 18.9 /14.4 months, per protocol) 56%/15%; NR; NR</p>	<p>(%): 6/6 Febrile neutropenia (%): 0/4 Pneumonitis (%): 1/1</p>	<p>and personal: - Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +</p>

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
	<p><i>Histological diagnosis</i></p> <p>Adenocarcinoma (%): 95/90</p> <p>Bronchoalveolar adenocarcinoma (%): 0/2</p> <p>Large-cell carcinoma (%): 3/1</p> <p>Squamous-cell carcinoma (%): 1/0</p> <p>Other (%): 0/7</p> <p><i>EGFR mutation</i></p> <p>Exon 19 deletion (%): 66/67</p> <p>L858R mutation in exon 21 (%): 34/33</p> <p><i>Clinical stage</i></p> <p>N3 (not candidate for thoracic radiotherapy) (%): 1/0</p> <p>IIIA (%): 1/0</p>	<p>analysis (reason) 0/0 (intention to treat)</p>			

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
	IIIB (malignant pleural effusion) (%): 7/6 IV (%): 91/94 <i>Bone metastasis</i> Yes (%): 33/33 No (%): 67/67 <i>Brain metastasis</i> 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	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	Overall survival (median follow-up 16.4 months) NR/NR; HR= 1.12; 0.73 – 1.73 Median overall survival not reached Median progression	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	Study type RCT Level of evidence 1b 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
	<p>Treatment-naive advanced lung adenocarcinoma</p> <p>Performance status 0 or 1</p> <p>Adequate end-organ function</p> <p>Measurable disease according to RECIST</p> <p>Exclusion criteria</p> <ul style="list-style-type: none"> - <p>Patient characteristics</p> <p>Age (median): 61.5/61.0</p> <p>Male (%): 36.1/33.0</p> <p>PS (ECOG)</p> <p>0 (%): 40.0/35.7</p> <p>1 (%): 60.0/63.5</p> <p>2 (%): 0.0/0.9</p> <p><i>Smoking history</i></p>	<p>Intravenous cisplatin (75 mg/m²) and pemetrexed (500 mg/m²) once every 21 days up to a maximum of six cycles</p> <p>Median number of chemotherapy cycles was six</p> <p>Treatment continued until investigator-assessed progression</p> <p>Included/randomised patients 230/115</p> <p>Analysed patients 230/115 (efficacy) 229/111 (safety)</p>	<p>free survival (months) 11.1/6.9; NA; NR</p> <p>Progression free survival (median follow-up 16.4 months)</p> <p>20%/3%; HR= 1.72; 1.28 – 2.33</p> <p>HR=</p> <p>Objective response rate (median follow-up 16.4 months)</p> <p>56%/23%; NR; 0.001</p> <p>Clinically meaningful worsening of cough (patient reported, time period NR)</p>	<p>Nausea (%): 17.9/65.8</p> <p>Fatigue (%): 17.5/46.8</p> <p>Vomiting (%): 17.9/42.3</p> <p>Epistaxis (%): 13.1/0.9</p> <p>Cheilitis (%): 12.2/0.9</p> <p>Anemia (%): 3.1/27.9</p> <p>Constipation (%): 2.6/18.9</p> <p>Leukopenia (%): 1.7/18.9</p> <p>Neutropenia (%): 0.9/31.5</p>	<p>Allocation concealment: ?</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome assessment: +</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	<p>Never (%): 67.4/70.4</p> <p>Former (%): 30.4/27.8</p> <p>Current (%): 2.2/1.7</p> <p><i>Adenocarcinoma stage</i></p> <p>IIIB with pleural effusion (%): 8.7/14.8</p> <p>IV (%): 91.3/85.2</p> <p><i>EGFR mutation</i></p> <p>Exon 19 deletion (%): 49.1/49.6</p> <p>L858R (%): 39.6/40.9</p> <p>Other (%): 11.3/9.6</p> <p><i>Race</i></p> <p>White (%): 26.5/26.1</p> <p>East Asian (%): 71.7/72.2</p> <p>Other (%): 1.7/1.7</p>	<p>Attrition</p> <p>NR</p> <p>Excluded from analysis (reason)</p> <p>1/4 (safety; not received treatment)</p>	<p>NR/NR; HR= 0.60; 0.41 – 0.87</p> <p>Clinically meaningful worsening of dyspnea (patient reported, time period NR)</p> <p>NR/NR; HR= 0.68; 0.50 – 0.93</p> <p>Deterioration of pain (patient reported, time period NR)</p> <p>NR/NR; HR= 0.83; 0.62 – 1.10</p>		
Wu, Y. Afatinib versus cisplatin plus gemcitabine for first-	Region China, Thailand, and South	Intervention(s) Oral continuous	Median overall survival (months)	Diarrhoea (%): 88.3/10.6	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; primary outcome marked bold)	Adverse events (IG _n /CG)	Study type, level of evidence and risk of bias
<p>line treatment of 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.</p>	<p>Korea</p> <p>Inclusion criteria</p> <p>Untreated stage IIIB (with pleural effusion) or IV lung adenocarcinoma</p> <p>Performance status of 0 or 1</p> <p>Measurable disease according to RECIST</p> <p>Adequate organ function</p> <p>EGFR mutation-positive tumor tissue at the screening stage</p> <p>Exclusion criteria</p> <p>-</p> <p>Patient characteristics</p> <p>Age (median): 58/58</p>	<p>afatinib (40 mg per day)</p> <p>Median duration of treatment with afatinib was 398 days (IQR 173–537).</p> <p>Control</p> <p>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</p> <p>Median number of treatment cycles was four</p> <p>Included/randomised patients</p>	<p>22.1/22.2; NA, ns</p> <p>Overall survival (median follow-up 16.6 months)</p> <p>NR/NR; HR= 0.95; 0.68 – 1.33</p> <p>Median progression free survival (months)</p> <p>11.0/5.6; NA; sign.</p> <p>Progression free survival (median follow-up 16.6 months)</p> <p>NR/NR; HR= 3.57; 2.564 – 5.00</p> <p>Objective response rate (time period NR)</p> <p>66.9%/23.0%; OR =</p>	<p>Rash or acne (%): 80.8/8.8</p> <p>Stomatitis or mucositis (%): 51.9/5.3</p> <p>Paronychia (%): 32.6/0.0</p> <p>Epistaxis (%): 12.6/0.9</p> <p>Pruritus (%): 10.9/0.0</p> <p>Decreased appetite (%): 10.0/40.7</p> <p>Fatigue (%): 10.0/36.3</p> <p>Vomiting (%): 9.6/80.5</p> <p>Nausea (%): 7.5/75.2</p> <p>Constipation (%): 1.7/12.4</p> <p>Bone marrow failure (%): 0.0/4.4</p> <p>Alanine aminotransferase concentration increase</p>	<p>Level of evidence 2b</p> <p>Risk of bias</p> <p>Generation of allocation sequence: +</p> <p>Allocation concealment: +</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome assessment: -</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	<p>Male (%): 36.0/32.0</p> <p><i>PS (ECOG)</i></p> <p>0 (%): 19.8/33.6</p> <p>1 (%): 80.2/66.4</p> <p><i>Smoking history</i></p> <p>Never smoked (%): 74.8/81.1</p> <p>Other current or ex-smoker (%): 21.9/15.6</p> <p>< 15 pack-years and stopped > 1 year ago (%): 3.3/3.3</p> <p><i>Adenocarcinoma stage</i></p> <p>IIIB with pleural effusion (%): 6.6/4.9</p> <p>IV (%): 93.4/95.1</p> <p><i>EGFR mutation</i></p> <p>Exon 19 deletion (%): 51.2/50.8</p>	<p>242/122</p> <p>Analysed patients</p> <p>242/122 (efficacy)</p> <p>239/113 (safety)</p> <p>Approx. 85% (patient reported outcomes)</p> <p>Attrition</p> <p>NR</p> <p>Excluded from analysis (reason)</p> <p>0/0 (efficacy)</p> <p>3/9 (safety, not received treatment)</p>	<p>7.28; 4.36 – 12.18</p> <p><i>Patient reported outcomes (time period NR)</i></p> <p>Improvement in overall health status (QLQ-C30)</p> <p>62.7%/32.7%; NR; 0.0001</p> <p>Deterioration in overall health status (QLQ-C30)</p> <p>NR/NR; HR 0.56; 0.41 – 0.77</p> <p>Improvement in cough</p> <p>NR/NR; in favour of intervention; <0.0001</p> <p>Deterioration in cough</p> <p>NR/NR; HR = 0.45; 0.30–0.68</p>	<p>(%): 20.1/15.9</p> <p>Aspartate aminotransferase concentration increase (%): 15.1/10.6</p> <p>Anaemia (%): 5.4/27.4</p> <p>Hypokalaemia (%): 5.4/13.3</p> <p>Leucopenia (%): 3.3/51.3</p> <p>Neutropenia (%): 2.1/54.0</p> <p>Hyponatraemia (%): 1.7/8.8</p> <p>Haemoglobin concentration decreased (%): 1.7/17.7</p> <p>Neutrophil count decreased (%): 0.8/25.7</p> <p>White blood cell count decreased (%): 0.8/23.9</p>	

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
	<p>L858R (%): 38.0/37.7 Uncommon (%): 10.7/11.5</p> <p><i>Race</i></p> <p>South-east Asian (%): 5.8/8.2</p> <p>South Korean (%): 4.5/1.6</p> <p>Chinese (%): 89.7/90.2</p>		<p>Improvement in dyspnoea</p> <p>NR/NR; in favour of intervention; <0.0001</p> <p>Improvement in dyspnoea (rested)</p> <p>NR/NR; in favour of intervention; 0.594</p> <p>Improvement in dyspnoea (walked)</p> <p>NR/NR; in favour of intervention; <0.0001</p> <p>Improvement in dyspnoea (climbed stairs)</p> <p>NR/NR; in favour of intervention; <0.0001</p> <p>Deterioration in dyspnoea</p> <p>NR/NR; HR = 0.54; 0.40–0.73</p>	<p>Thrombocytopenia (%): 0.8/18.6</p> <p>Platelet count decreased (%): 0.8/10.6</p>	

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
			<p>Improvement in shortness of breath NR/NR; in favour of intervention; 0.006</p> <p>Improvement in pain NR/NR; in favour of intervention; 0.003</p> <p>Improvement in have pain NR/NR; in favour of intervention; 0.015</p> <p>Improvement in pain affecting daily activities NR/NR; in favour of intervention; 0.079</p> <p>Improvement in pain in chest NR/NR; in favour of intervention; 0.021</p> <p>Improvement in pain in arm or shoulder</p>		

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
			<p>NR/NR; in favour of intervention; 0.14</p> <p>Improvement in pain in other parts</p> <p>NR/NR; in favour of intervention; 0.092</p> <p>Deterioration in pain</p> <p>NR/NR; HR = 0.70; 0.51–0.96</p>		
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.	<p>Region China</p> <p>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</p>	<p>Intervention(s) Oral erlotinib 150 mg once daily until disease progression or unacceptable toxic effects</p> <p>Median duration of treatment was 55.5 weeks (range 3.1 – 93.0)</p> <p>Control</p>	<p>Overall survival (median follow-up 15.6 month) 80%/83%; NR; NR</p> <p>Progression free survival (median follow-up 15.6 month) NR/NR; HR= 6.25; 3.847-10.00</p>	<p>Neutropenia (%): 6/69</p> <p>Thrombocytopenia (%): 4/64</p> <p>Anaemia (%): 5/72</p> <p>Infection (%): 17/10</p> <p>Skin rash (%): 73/19</p> <p>Diarrhoea (%): 25/6</p> <p>Stomatitis (%): 13/1</p> <p>Paronychia (%): 4/0</p> <p>Vomiting or nausea (%):</p>	<p>Study type RCT</p> <p>Level of evidence 2b</p> <p>Risk of bias</p> <p>Generation of allocation sequence: +</p> <p>Allocation concealment: +</p>

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
<p>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.</p>	<p>Measurable disease according to RECIST ECOG performance status of 0-2, and adequate haematological, biochemical, and organ function</p> <p>Exclusion criteria Uncontrolled brain metastases Previous systemic anticancer therapy for advanced disease</p> <p>Patient characteristics Age (median): 57/59 Male (%): 41/40 PS (ECOG) 0-1 (%): 91/96</p>	<p>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))</p> <p>Median duration of treatment 10.4 weeks (range 1.0 – 18.9)</p> <p>Included/randomised patients 83/82</p> <p>Analysed patients 82/72</p>	<p>Median progression free survival (months) 13.1/4.6; NA; sign.</p> <p>Response rate (median follow-up 15.6 month) 83/36; NR; 0.0001</p> <p><i>Mean change in functioning (baseline to cycle 2, FACT-L)</i></p> <p>Physical well-being NR/NR; NR; 0.003</p> <p>Social/family well-being NR/NR; NR; 0.303</p> <p>Emotional well-being NR/NR; NR; 0.036</p> <p>Functional well-being NR/NR; NR; 0.093</p>	<p>1/46 Constipation (%): 9/15 Increased ALT (%): 37/33 Fatigue (%): 5/24</p>	<p>Blinding of participants and personal: -</p> <p>Blinding of outcome assessment: -</p> <p>Incomplete outcome data: +</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	<p>2 (%): 9/4</p> <p><i>Smoking status</i></p> <p>Present or former smoker (%): 28/31</p> <p>Non-smoker (%): 72/69</p> <p><i>Histology</i></p> <p>Adenocarcinoma (%): 88/86</p> <p>Non-adenocarcinoma (%): 12/14</p> <p><i>EGFR mutation</i></p> <p>Exon 19 deletion (%): 52/54</p> <p>L858R mutation (%): 48/46</p> <p><i>Disease stage</i></p> <p>IIIB (%): 13/7</p> <p>IV (%): 87/93</p>	<p>71/54 (quality of life)</p> <p>Attrition</p> <p>61/82</p> <p>Excluded from analysis (reason)</p> <p>1/10 (not received treatment)</p> <p>12/28 (quality of life: not received treatment, no complete questionnaire)</p>	<p>Lung cancer subscale</p> <p>NR/NR; NR; 0.004</p>		

+ 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. <i>Cancer</i> , 2015. 121(6): p. 883-92.	Region Sydney, Australia Inclusion criteria Patients ≥18 years Histologically or cytologically 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/m ² 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	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	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	administered at a dose of 75 mg/m ² 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. Pemetrexed was administered at a dose of 500 mg/m ² 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	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	Diarrhea (%): 28.4/30.4 Headache (%): 28.4/11.6 Epistaxis (%): 25.4/7.2 Back pain (%): 23.9/13 Dyspnea (%): 22.4/21.4 Insomnia (%): 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	- 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
	<p>Clinically relevant coronary artery disease</p> <p>Myocardial infarction within 6 months before randomization</p> <p>Uncontrolled congestive heart failure</p> <p>Chronic daily treatment with aspirin (<325 mg/day)</p> <p>Other known inhibitors of platelet function</p> <p>History of gross hemoptysis within 2 months of trial entry</p> <p>Any grade 3 or 4 gastrointestinal bleeding within 3 months before study entry</p>	<p>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.</p> <p>Included/randomised patients 69/71</p> <p>Analysed patients 69/71 (efficacy) 67/69 (safety)</p> <p>Attrition 3/3</p> <p>Excluded from analysis (reason) 2/2 (safety, patients with at least 1 adverse event)</p> <p>Patient characteristics</p>		<p>Arterial thrombotic events (%): 10.4/4.3</p> <p>Acute myocardial infarction (%): 1.5/0</p> <p>Angina pectoris (%): 3/1.4</p> <p>Cardiorespiratory arrest (%): 0/1.4</p> <p>Intestinal ischemia (%): 1.5/0</p> <p>Ischemic cerebral infarction (%): 1.5/0</p> <p>Myocardial infarction (%): 3.0/1.4</p> <p>Peripheral vascular disorder (%): 1.5/0</p> <p>Congested heart failure (%): 1.5/0</p> <p>Gastrointestinal perforation (%): 1.5/0</p> <p>Healing complication</p>	

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
	<p>Treated: safety population (%): 97.1/97.2</p> <p>Age 18 to <65y (%): 53.6/52.1</p> <p>Age ≥65y (%): 46.4/47.9</p> <p>Male (%): 52.2/63.4</p> <p>Female (%): 47.8/36.6</p> <p>ECOG performance status</p> <p>0-1 (%): 92.8/91.5</p> <p>2 (%): 4.3/5.6</p> <p>Missing (%): 2.9/2.8</p> <p>Histology</p> <p>Adenocarcinoma (%): 87/87.3</p> <p>Large cell carcinoma (%): 1.4/4.2</p> <p>Squamos cell carcinoma (%): 0/0</p>			<p>(%): 3/0</p> <p>Proteinuria (%): 6/4.3</p> <p>Venous thrombotic events (%): 11.9/7.2</p>	

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
	<p>Adenosquamous (%): 0/2.8</p> <p>NSCLC, NOS (%): 8.7/4.2</p> <p>Other (%): 2.9/1.4</p> <p><i>Smoking habits</i></p> <p><100 cigarettes in lifetime</p> <p>No (%): 84.1/77.5</p> <p>Yes (%): 15.9/22.5</p> <p><i>Ethnic origin</i></p> <p>White (%): 87/91.5</p> <p>Asian (%): 1.4/5.6</p> <p>Black (%): 11.4/2.8</p> <p><i>Carboplatin therapy: patients treated (%): 70.1/69.6</i></p> <p><i>Cisplatin therapy: patients treated (%): 29.9/30.4</i></p>				

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
<p>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 on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet. 2014 Aug 23;384(9944):665-73..</p>	<p>Region 26 countries on 6 continents</p> <p>Inclusion criteria Aged ≥18 years Squamous or non-squamous stage IV NSCLC who had progressed during or after a first-line platinum-based 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</p>	<p>Intervention(s) Intravenous docetaxel 75 mg/m² plus intravenous ramucirumab 10 mg/kg on day 1 of a 21 day cycle.</p> <p>Control Intravenous docetaxel 75 mg/m² plus placebo on day 1 of a 21 day cycle.</p> <p>Included/randomised patients 628/625</p> <p>Analysed patients 628/625 (efficacy) 47%/49% (quality of life) 627/618 (safety)</p> <p>Attrition 9/10</p> <p>Excluded from analysis (reason)</p>	<p>Median overall survival (months) 10.5 / 9.1; NA; ns (CIs overlap)</p> <p>Overall survival (median follow-up: 9.5 month [ramucirumab], 8.8 month [placebo])</p> <p>NR; HR=1.16; 1.02-1.33</p> <p>Median progression-free survival (months) 4.5/3.0 ; NA; NA; ns (CIs overlap)</p> <p>Progression-free survival (median</p>	<p>Any (%): 98/ 95 Fatigue (%): 55/49 Decreased appetite (%): 29/25 Diarrhoea (%): 32/27 Nausea (%): 27/27 Alopecia (%): 26/25 Stomatitis (%): 23/13 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</p>	<p>Study type RCT</p> <p>Level of evidence 1b</p> <p>Risk of bias Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: +</p>

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
	<p>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</p> <p>Measurable or non-measurable disease with ECOG 0-1</p> <p>Exclusion criteria</p> <p>Previous therapy for advanced or metastatic disease was EGFR tyrosine kinase inhibitor monotherapy</p> <p>Major blood vessel involvement, intratumour cavitation, poorly</p>	<p>1/7 (safety, not received one dose) 53%/51% (quality of life, not responded questionnaire)</p>	<p>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) 23%/14%; OR=1.89; 1.41-2.54</p> <p>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</p>	<p>Lacrimation increased (%): 13/4 Myalgia (%): 12/10 Arthralgia (%): 11/8 Back pain (%): 11/8 Abdominal pain (%): 11/10 Dysgeusia (%): 11/7 Insomnia (%): 11/8 Headache (%): 11/11</p> <p>Haematological adverse events Neutropenia (%): 55/45 Leucopenia (%): 21/19 Anaemia (%): 21/28 Febrile neutropenia (%): 16/10 Thrombocytopenia (%): 13/5</p>	<p>Blinding of outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +</p>

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
	<p>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</p> <p>Patient characteristics</p> <p>Age (median): 62/61</p> <p>Men (%): 67/66</p> <p>Histology</p> <p>Non- Squamous (%): 74/72</p> <p>Squamous (%): 25/27</p> <p>Unknown (%): 1/1</p> <p>Smoking Habits</p> <p>Ever (%): 74/72</p> <p>Never (%): 25/27</p>		<p>Patients with >15mm increase in quality life (30 days, LCSS)</p> <p>NR ; HR=1.00; 0.84-1.19</p>	<p>Adverse events of special interest</p> <p>Bleeding or haemorrhage (%): 29/15</p> <p>Epistaxis (%): 19/6</p> <p>Gastrointestinal haemorrhage (%): 3/2</p> <p>Pulmonary haemorrhage (%): 8/7</p> <p>Haemoptysis (%): 6/5</p> <p>Hypertension (%): 11/5</p> <p>Infusion-related reaction (%): 4/4</p> <p>Proteinuria (%): 3/1</p> <p>Venous thromboembolic (%): 3/6</p> <p>Renal failure (%): 2/2</p>	

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
	<p>Unknown (%): <1/<1</p> <p>Ethnic Origin</p> <p>White(%): 84/80</p> <p>Asian(%): 12/14</p> <p>Black(%): 3/3</p> <p>Other(%): 2/3</p> <p>ECOG performance status</p> <p>0 (%): 33/32</p> <p>1 (%): 67/68</p> <p>Region of origin</p> <p>East Asia (South Korea or Taiwan) (%): 7/7</p> <p>Other (%): 93/93</p> <p>Disease</p> <p>Measurable (%): 96/96</p> <p>Non - measurable (%): 4/4</p>			<p>Arterial thromboembolic (%): 2/2</p> <p>Congestive heart failure (%): 1/1</p> <p>Gastrointestinal perforation (%): 1/<1</p>	

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
	<p>EGFR status</p> <p>Wild type (%): 33/32</p> <p>Mutant (%): 2/3</p> <p>Unknown or missing (%): 65/66</p> <p>Best response to platinum- based chemotherapy</p> <p>CR,PR,or SD(%): 67/67</p> <p>PD(%): 28/29</p> <p>Missing(%): 5/4</p> <p>Previous maintenance treatment</p> <p>No (%): 79/77</p> <p>Yes (%): 21/23</p> <p>Previous taxane</p> <p>No (%): 76/76</p> <p>Yes (%): 24/24</p> <p>Previous bevacizumab</p>				

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
	<p>treatment</p> <p>No (%): 86/85</p> <p>Yes (%): 14/15</p> <p>Time since previous therapy</p> <p>< 9 months (%): 64/60</p> <p>> 9 months (%): 36/40</p> <p>Missing (%): <1/0</p>				
<p>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.</p>	<p>Region 32 countries</p> <p>Inclusion criteria Patients \geq18 years Histologically confirmed unresectable stage IIIB with pericardial/pleural effusion or stage IV/recurrent NSCLC</p>	<p>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 experienced disease progression, had unacceptable</p>	<p>Median overall survival (months) 11.1/ 10.7; NA; ns (CIs overlap)</p> <p>Overall survival (2 years) 21%/12%; HR=1.12; 0.89-1.41</p>	<p>Serious occurring within 6 months of treatment initiation Patients with any (%): 46/28</p> <p>Any serious adverse events Diarrhea (%): 7/<1 Dehydration (%): 5/2 Dyspnea (%): 4/3</p>	<p>Study type RCT</p> <p>Level of evidence 1b</p> <p>Risk of bias Generation of allocation</p>

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
	<p>Measurable or non-measurable disease</p> <p>Exclusion criteria</p> <p>Life expectancy less than 3 months</p> <p>ECOG PS greater than or equal to 2</p> <p>Untreated or symptomatic central nervous system metastases</p> <p>Prior chemotherapy, including adjuvant chemotherapy within 52 weeks of randomization</p> <p>Prior targeted therapy central or peripheral radiation within 28 or 14 days</p> <p>Arterial or venous thrombosis within 12 months</p>	<p>toxicity, or withdrew consent, for a maximum of 36 months.</p> <p>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</p> <p>Control</p> <p>Placebo</p> <p>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.</p> <p>Treatment was planned to continue until patients experienced disease progression, had unacceptable toxicity, or withdrew consent, for a maximum of 36 months.</p>	<p>Median progression-free survival (months) 4.9/5.1; NA; ns (CIs overlap)</p> <p>Progression-free survival (2 years, RECIST criteria) 68/57; HR=1.18; 0.90-1.54</p> <p>ORR (2 years, RECIST criteria) 38% / 35%; 2.6%; - 7.4 - 12.6</p>	<p>Neutropia (%): 4/3 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 Fatigue (%): 2/<1 Nausea (%): 2/<1 Pleural effusion (%): 2/0 Hypotension (%): 2/1 Abdominal pain (%): 2/<1</p>	<p>sequence: +</p> <p>Allocation concealment: +</p> <p>Blinding of participants and personal: +</p> <p>Blinding of outcome assessment: +</p> <p>Incomplete outcome data: +</p> <p>Selective reporting: +</p>

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
	<p>Pulmonary haemorrhage or gross hemoptysis within 6 months of randomization</p> <p>Bleeding diastasis or bleeding within 14 days</p> <p>Uncontrolled hypertension</p> <p>Inadequate renal cardiac, hepatic, or hematologic function</p> <p>Patient characteristics</p> <p>Age (mean): 62/59.5</p> <p>Men (%): 80/84</p> <p>ECOG performance status</p> <p>0 (%): 35/37</p> <p>1 (%): 65/62</p> <p>Missing: 0/<1</p>	<p>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</p> <p>Included/randomised patients 182/178</p> <p>Analysed patients 182/178 (efficacy) 181/173 (safety)</p> <p>Attrition Lost to follow-up: 1/0</p> <p>Excluded from analysis (reason) 1/5 (safety, not received treatment)</p>		<p>Decreased appetite (%): 2/0</p> <p>Sepsis (%): 2/0</p> <p>Pyrexia (%): <1/2</p> <p>Troughout the study</p> <p>Patients with any (%): 95/91</p> <p>Worst grade 3 (%): 33/27</p> <p>Worst grade 2 (%): 10/9</p> <p>Worst grade 1 (%): 20/12</p> <p>Adverse events with ≥5% difference in incidence between arms</p> <p>Diarrhea (%): 38/16</p> <p>Alopecia (%): 34/40</p> <p>Nausea (%): 28/21</p>	<p>Other source of bias: +</p>

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
	<p>Histology</p> <p>Adenocarcinoma (%): 0/1</p> <p>Squamos cell carcinoma (%): 96/97</p> <p>Undifferentiated (%): <1/0</p> <p>Other (%): 4/2</p> <p>Smoking habits</p> <p>Past or present smoker (%): 84/89</p> <p>Ethnic origin</p> <p>White (%): 73/74</p> <p>Asian (%): 21/16</p> <p>Hispanic (%): 5/6</p> <p>Black (%): <1/3</p> <p>Other (%): <1/<1</p> <p>Disease stage at study entry</p> <p>Stage IIIB with pericardial/pleural</p>			<p>Hypertension (%): 26/9</p> <p>Vomiting (%): 22/17</p> <p>Decreased appetite (%): 22/14</p> <p>Anemia (%): 18/25</p> <p>Weight decreased (%): 17/8</p> <p>Thrombocytopenia (%): 15/8</p> <p>Headache (%): 13/6</p> <p>Abdominal pain (%): 11/5</p> <p>Arthralgia (%): 10/17</p> <p>Dehydration (%): 9/3</p> <p>Depression (%): 7/2</p> <p>Chest pain 6/14</p> <p>Patients with serious (%): 47/29</p>	

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
	<p>effusion (%): 15/14</p> <p>Stage IV/recurrent (%): 85/86</p> <p>Weight loss</p> <p><5% in previous 6months (%): 76/76</p> <p>Brain metastases</p> <p>Yes (%): 5/5</p> <p>No (%): 95/95</p> <p>No information (%): <1/1</p> <p>Previous chemotherapy</p> <p>Adjuvant (%): 1/2</p> <p>Previous best response to first-line treatment</p> <p>Complete response (%): 1/0</p> <p>Partial response (%): 44/35</p> <p>Stable disease (%): 24/35</p>			<p>Serious grade ≥3 adverse events in ≥2% of patients in either treatment arm (%): 45/27</p> <p>Diarrhea (%): 5/0</p> <p>Neutropenia (%): 4/3</p> <p>Dyspnea (%): 4/4</p> <p>Dehydration (%): 4/1</p> <p>Pneumonia (%): 3/4</p> <p>Pulmonary haemorrhage (%): 3/0</p> <p>Non-small-cell lung cancer (%): 3/2</p> <p>Anemia (%): 2/2</p> <p>Vomiting (%): 2/1</p> <p>Febrile neutropenia (%): 2/<1</p> <p>Pleural effusion (%): 2/0</p>	

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
	Progressive disease (%): 31/29			Abdominal pain (%): 2/<1 Nausea (%): 2/<1 Fatigue (%): 2/0 Decreased appetite (%): 2/0 Sepsis (%): 2/0 Thrombocytopenia (%): 2/<1	
Ramalingam, S.S., et al., Randomized 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.	Region USA and non US countries Inclusion criteria Patients ≥18 years Cytologically or histologically confirmed recurrent stage IIIB (pleural or pericardial effusion) or IV	Intervention(s) Linifanib 12.5 mg (intervention group 1), or linifanib 7.5 mg (intervention group 2) Carboplatin (AUC 6 mg/mL/min) and paclitaxel (200mg/m ²) 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.	Median overall survival (months) 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)	Linifanib 12.5/linifanib 7.5/placebo Any (%): 100/97.6/97.9 Diarrhea (%): 44.7/31/21.3 Thrombocytopenia (%): 40.4/31/14.9 Anemia (%):	Study type RCT Level of evidence 1b Risk of bias Generation of

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
	(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 Radiation therapy or major surgery ≤21 days before study entry Untreated brain or meningeal metastases Full therapeutic dose of anticoagulation therapy Central thoracic tumor	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/m ²) 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 Included/randomised patients 47/44/47 Analysed patients	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) 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,	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 % (%): 72.3/85.7/57.4 Diarrhea (%): 8.5/2.4/2.1 Thrombocytopenia (%): 29.8/16.7/2.1 Anemia (%):	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	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
	<p>lesion as defined by location within the hilar structures</p> <p>History of significant cancer-related bleeding</p> <p>Proteinuria (grade >1)</p> <p>Uncontrolled hypertension</p> <p>Left ventricular ejection fraction less than 50%</p> <p>History of myocardial infarction, stroke, or transient ischemic attack ≤6 months before study entry</p> <p>Antiretroviral therapy for HIV disease</p> <p>Another active malignancy within the past 5 years</p> <p>Severe GI disease that could interfere with drug</p>	<p>47/44/47 (efficacy)</p> <p>47/42/47 (safety)</p> <p>Attrition</p> <p>0/0/1</p> <p>Excluded from analysis (reason)</p> <p>0/2/0 (safety, at least one dose linifanib)</p>	<p>RECIST)</p> <p>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)</p>	<p>4.3/11.9/8.5</p> <p>Hypertension (%): 10.6/4.8/2.1</p> <p>Dysphonia (%): 2.1/0/0</p> <p>Weight decrease (%): 2.1/2.4/0</p> <p>PPE (%): 8.5/0/0</p> <p>Hypothyroidism (%): 0/0/0</p> <p>Pneumothorax (%): 2.1/0/0</p> <p>Oral candidiasis (%): 0/0/0</p> <p>Any serious (%): 53.2/59.5/34</p>	<p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	<p>absorption</p> <p>Pregnancy or breastfeeding</p> <p>Patient characteristics</p> <p>(linifanib 12.5/linifanib 7.5/placebo)</p> <p>Age (mean): 60/61.5/61</p> <p><65 (%): 72.3/70.5/63.8</p> <p>≥65 (%): 27.7/29.5/36.2</p> <p>Men (%): 57.4/56.8/57.4</p> <p>ECOG performance status</p> <p>0 (%): 34/29.5/31.9</p> <p>1 (%): 66/70.5/68.1</p> <p>Histology</p> <p>Adenocarcinoma (%): 85.1/95.2/89.4</p> <p>Large cell (%): 6.4/5.3/0</p>				

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
	<p>Other (%): 8.5/0/10.6</p> <p><i>Smoking habits</i></p> <p>Smoker (%): 80.9/88.6/83.0</p> <p><i>Country</i></p> <p>US (%): 23.4/29.5/27.7</p> <p>Outside US (%): 76.6/70.5/72.3</p> <p><i>Ethnic origin</i></p> <p>White (%): 87.2/93.2/89.4</p> <p>Asian (%): 4.3/6.8/4.3</p> <p>Black (%): 4.3/0/4.3</p> <p>Other (%): 4.3/0/2.1</p> <p><i>Disease</i></p> <p>Locally advanced (%): 4.3/4.8/8.5</p> <p>Metastatic (%): 95.7/95.2/91.5</p>				
Reck M, Kaiser R,	Region	Intervention(s)	Median overall	Any serious AE (%):	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
<p>Mellegaard A, Douillard JY, Orlov S, Krzakowski M, von Pawel J, Gottfried M, Bondarenko I, Liao M, Gann CN, Barreco 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.</p>	<p>27 countries, (23 European countries, China, South Korea, India and South Africa)</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> ≥18 years Patients with histologically or cytologically confirmed 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 	<p>Docetaxel 75 mg/m² by intravenous infusion on day 1 plus nintedanib 200 mg twice daily orally on days 2–21, every 3 weeks</p> <p>Until unacceptable adverse events or disease progression</p> <p>Control</p> <p>Patients were assigned to docetaxel 75 mg/m² by intravenous infusion on day 1 plus placebo on days 2–21, every 3 weeks</p> <p>Until unacceptable adverse events or disease progression</p> <p>Treatment was continued until unacceptable adverse events or disease progression</p> <p>Included/randomised patients</p> <p>655/659</p> <p>Analysed patients</p>	<p>survival (months)</p> <p>10.1/9.1; NA; ns (CIs not overlapping)</p> <p>Overall survival (median follow-up: 31.7 months)</p> <p>NR; HR=1.06; 0.95-1.20</p> <p>Median progression-free survival (months)</p> <p>3.5/2.7; NA; statistical significant (CIs not overlapping)</p> <p>Progression-free survival (median follow-up: 31.7 month, RECIST criteria)</p>	<p>34.4/31.5</p> <p>Any AE (%): 93.6/93</p> <p>Diarrhoea (%): 42.3/21.8</p> <p>Decreased neutrophils (%): 37.1/35.9</p> <p>Fatigue (%): 30.4/26.9</p> <p>Increased ALT (%): 28.5/8.4</p> <p>Decreased white blood cell count (%): 24.5/24.4</p> <p>Nausea (%): 24.2/18</p> <p>Increased AST (%): 22.5/6.6</p> <p>Decreased appetite (%): 22.2/15.6</p> <p>Dyspnoea (%): 19/16.8</p> <p>Vomiting (%): 16.9/9.3</p> <p>Alopecia (%):</p>	<p>RCT</p> <p>Level of evidence</p> <p>1b</p> <p>Risk of bias</p> <p>Generation of allocation sequence: +</p> <p>Allocation concealment: +</p> <p>Blinding of participants and personal: +</p> <p>Blinding of</p>

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
	<p>allowed for adjuvant, neoadjuvant, or neoadjuvant plus adjuvant therapy</p> <p>Eligibility criteria included ECOG performance status of 0 or 1</p> <p>At least one target lesion measurable</p> <p>Exclusion criteria</p> <p>Active brain metastases</p> <p>Patients with previous docetaxel or VEGFR inhibitors with the exception of bevacizumab</p> <p>Radiographic evidence of cavitary or necrotic tumours, centrally located tumours with radiographic evidence of</p>	<p>655/659 (efficacy) 652/655 (safety)</p> <p>Attrition 5/5</p> <p>Excluded from analysis (reason) 3/4 (safety, not received treatment)</p>	<p>NR; HR=1.18; 1.04-1.33</p> <p>ORR (median follow-up: 31.7 month, RECIST criteria)</p> <p>4.4%/3.3%; OR=1.34; 0.76-2.39</p> <p>Diseases control rate (median follow-up: 31.7 month, RECIST criteria)</p> <p>54% / 41.3%; OR=1.68; 1.35-2.09</p>	<p>16.4/18.2 Cough (%): 15.2/16.8 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 Anaemia (%): 5.4/7.5 Pneumonia (%): 5.1/5.5 Hypokalaemia (%): 4.1/3.1 Increased GGT (%):</p>	<p>outcome assessment: + Incomplete outcome data: + Selective reporting: + Other source of bias: +</p>

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
	<p>local invasion of major blood vessels, or a recent history (<3 months) of clinically significant haemoptysis or a major thrombotic or clinically relevant major bleeding event in the past 6 months</p> <p>Patient characteristics</p> <p>Age (mean): 60/60</p> <p>Men (%): 72.7/72.7</p> <p>PS (ECOG)</p> <p>0 (%): 28.5/28.7</p> <p>1 (%): 71.3/71.3</p> <p>Histology</p> <p>Squamous- cell carcinoma (%): 42.1/42.3</p> <p>Adenocarcinoma (%): 49.2/51</p>			<p>4/0.9</p> <p>Leucopenia (%): 4/5.2</p> <p>Hyperglycaenia (%): 3.7/4.6</p> <p>Hypnoatraenia (%): 3.4/2</p> <p>Pleural effusion (%): 2.3/2.9</p> <p>Increased hepatic enzyme (%): 1.5/0</p>	

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
	<p>Large – cell carcinoma (%): 3.8/2.4</p> <p>Combination (%): 0.6/0.8</p> <p>Other (%): 4.3/3.5</p> <p><i>Clinical stage at diagnosis</i></p> <p>Stage < IIIB (%): 16/15.9</p> <p>Stage IIIB (%): 22.6/22.2</p> <p>Stage IV (%): 60.9/61.9</p> <p>Missing (%): 0.5/0</p> <p><i>Metastases at screening</i> (%): 89.8/91.8</p> <p><i>Brain metastases at baseline</i> (%): 5.8/5.8</p> <p><i>Baseline sum of longest diameters (mm)</i>: 49-123.4/ 48.5-121</p> <p><i>Months since first diagnosis (median)</i>: 8.8/8.6</p>				

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
	<p>Previous surgery (%): 21.8/21.5</p> <p>Previous radiotherapy (%): 29.2/28.5</p> <p>Smoking habits</p> <p>Current and former smokers (%): 74.8/75.6</p> <p>Never smokers (%): 25.2/24.4</p> <p>Ethnic origin</p> <p>White (%): 81.4/80.4</p> <p>Asian (%): 17.7/18.7</p> <p>Black or African American (%): 0.6/0.8</p> <p>American Indian or Alaskan native (%): 0.3/0.2</p> <p>Previous first line therapy (%): 98.6/98.8</p>				

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
	<p>Platinum- based therapy (%): 97.2/97.7</p> <p>Non- platinum based therapy (%): 2.8/2.3</p> <p><i>First - line bevacizumab</i> (%): 4.1/3.5</p> <p>Previous best response to first-line treatment</p> <p>Complete response (%): 2/2.9</p> <p>Partial response (%): 33.1/27.2</p> <p>Stable disease (%): 38.5/38.2</p> <p>Progressive disease (%): 19.7/21.4</p> <p>Not known or unavailable (%): 6.7/10.3</p>				
Seto, T., et al., Erlotinib alone or with bevacizumab as first-	Region Japan	Intervention(s) Erlotinib plus bevacizumab group	Overall survival (median follow-up was 20.4 months)	Erlotinib plus bevacizumab / Erlotinib alone	Study type RCT

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
<p>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.</p>	<p>Inclusion criteria Histologically or cytologically confirmed stage 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 One or more measurable lesion based on RECIST 1.1</p> <p>Exclusion criteria Confirmation of Thr790Met mutation</p>	<p>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</p> <p>Control Erlotinib alone group received erlotinib orally once a day at 150 mg/day. Patients remained on treatment until disease progression or unacceptable toxicity</p> <p>Included/randomised patients 77/77</p> <p>Analysed patients 75/77</p> <p>Attrition NR</p>	<p>17%/23%; NR; NR</p> <p>Median progression-free survival (months) 16/9.7; NA; significant (CIs not overlapping)</p> <p>Progression-free survival (median follow-up was 20.4 months, RECIST) NR; HR=1.85; 1.27-2.78</p> <p>ORR (median follow-up was 20.4 months, RECIST) 69%/64%; NR; 0.495</p>	<p>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 Hypertension (%): 76/13 Pruritus (%): 45/42 Weight decreased (%): 44/25 Decreased appetite (%): 35/34 Proteinuria (%): 52/4</p>	<p>Level of evidence 1b</p> <p>Risk of bias Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of</p>

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
	<p>Presence of brain metastases</p> <p>History or presence of haemoptysis or bloody sputum</p> <p>Any coagulation disorder, tumor invading or abutting major blood vessels</p> <p>Coexistence or history of interstitial lung disease</p> <p>Previous receipt of EGFR inhibitors or VEGF receptor inhibitors</p> <p>Patient characteristics</p> <p>Erlotinib plus group/Erlotinib alone</p> <p>Age (mean): 67/67</p> <p><75 (%): 84/81</p> <p>≥75 (%): 16/19</p>	<p>Excluded from analysis (reason)</p> <p>2/0 (received treatment)</p>	<p>DCR (median follow-up was 20.4 months)</p> <p>99%/88%; NR; 0.0177</p> <p>Quality of life (FACT-L, till treatment discontinuation [115 days])</p> <p>Intervention<control; NR; ns</p>	<p>Dysgeusia (%): 27/22</p> <p>Nasopharyngitis (%): 27/19</p> <p>Constipation (%): 23/19</p> <p>Alopecia (%): 17/18</p> <p>Nausea (%): 16/19</p> <p>Vomiting (%): 19/9</p> <p>Malaise (%): 13/13</p> <p>Insomnia (%): 11/10</p> <p>Pyrexia (%): 9/12</p> <p>Upper respiratory tract infection (%): 12/9</p> <p>Conjunctivitis (%): 11/9</p> <p>Peripheral oedema (%): 11/8</p> <p>Fatigue (%): 13/4</p> <p>Nail disorder (%): 12/5</p>	<p>outcome assessment: -</p> <p>Incomplete outcome data: +</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	<p>Men (%): 40/34</p> <p>Female (%): 60/66</p> <p><i>ECOG performance status</i></p> <p>0 (%): 57/53</p> <p>1 (%): 43/47</p> <p><i>Histology</i></p> <p>Adenocarcinoma (%): 85.1/95.2/89.4</p> <p>Large cell (%): 6.4/5.3/0</p> <p>Other (%): 8.5/0/10.6</p> <p><i>Smoking habits</i></p> <p>Never smoker (%): 56/58</p> <p>Former light smoker (%): 12/8</p> <p>Other (%): 32/34</p> <p><i>Clinical stage at screening</i></p> <p>IIIB (%): 1/0</p>			<p>Dry eye (%): 11/4</p> <p>Dyphonia (%): 11/1</p>	

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
	<p>IV (%): 80/81</p> <p>Postoperative recurrence (%): 19/19</p> <p>EGFR mutation type</p> <p>Exon 19 detection (%): 53/52</p> <p>Exon 21 Leu858Erf mutation (%): 47/48</p>				
<p>Zinner, R.G., et al., PRONOUNCE: randomized, open-label, phase III study of first-line pemetrexed + carboplatin followed by maintenance pemetrexed versus paclitaxel + carboplatin + bevacizumab followed by maintenance bevacizumab in</p>	<p>Region USA</p> <p>Inclusion criteria Chemotherapy naïve adults Patients ≥18 years Cytologically or histologically confirmed stage IV nonsquamous NSCLC ECOG PS 0 or 1</p>	<p>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 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.</p>	<p>Median overall survival (months) 11.7/10.5; NA; ns (CIs overlap)</p> <p>Overall survival (2 year) 17.6%/18.0%; HR=1.07; 0.83 - 1.36</p> <p>Median progression-</p>	<p>Grad 3</p> <p>Anemia (%): 5.4/18.1</p> <p>Neutropenia (%): 22.3/21.1</p> <p>Thrombocytoenia (%): 4.2/15.2</p> <p>Febrile neutropenia (%): 1.2/0</p> <p>Hypertension (%): 2.4/0</p> <p>Thrombosis/embolism (%): 1.8/1</p>	<p>Study type RCT</p> <p>Level of evidence 1b</p> <p>Risk of bias Generation of allocation sequence:</p>

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
patients with advanced nonsquamous non-small-cell lung cancer. J Thorac Oncol, 2015. 10(1): p. 134-42.	<p>Measurable disease by RECIST</p> <p>Adequate organ function</p> <p>Exclusion criteria</p> <p>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</p> <p>Use of an investigational agent within 30 days of randomization</p> <p>Any serious concomitant disorder that could compromise the ability to</p>	<p>Control</p> <p>Pemetrexed+carboplatin followed by pemetrexed</p> <p>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.</p> <p>Included/randomised patients</p> <p>179/182</p> <p>Analysed patients</p> <p>179/182 (efficacy)</p>	<p>free survival (follow-up: 1-41 months) 5.49/4.44; NA; NR</p> <p>Progression-free survival (follow-up: 1-41 months) NR; HR= 1.06; 0.84 - 1.35</p> <p>ORR (follow-up: 1-41 months) 27.4%/23.6%; NR; 0.414</p> <p>DCR (follow-up: 1-41 months) 57%/59.9%; NR; 0.575</p>	<p>Any hemorrhagic events (%): 0/1.2</p> <p>Sensory neuropathy (%): 2.4/0</p> <p>Grad 4</p> <p>Anemia (%): 0/0.6</p> <p>Neutropenia (%): 26.5/3.5</p> <p>Thrombocytoenia (%): 5.4/8.8</p> <p>Febrile neutropenia (%): 0.6/0</p> <p>Thrombosis/embolism (%): 0.6/0</p>	<p>+</p> <p>Allocation concealment: ?</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome assessment: -</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting: +</p>

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
	<p>adhere to the protocol</p> <p>Patient characteristics</p> <p>Age (mean): 65.4/65.8</p> <p>>70 (%): 28.5/32.4</p> <p>Female (%): 41.9/42.3</p> <p>ECOG performance status</p> <p>0 (%): 46.9/46.7</p> <p>1 (%): 53.1/52.7</p> <p>Histology</p> <p>Adenocarcinoma (%): 76.5/83.5</p> <p>Large cell (%): 5.0/0.5</p> <p>Other or indeterminate (%): 18.4/15.4</p> <p>Smoking habits</p> <p>Ever (%): 96.1/90.1</p> <p>Ethnic origin</p>	<p>166/171 (safety)</p> <p>Attrition</p> <p>NR</p> <p>Excluded from analysis (reason)</p> <p>11/11 (safety, one dose of study)</p>			<p>Other source of bias:</p> <p>+ </p>

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
	<p>White (%): 87.7/90.7</p> <p>African American (%): 11.2/6.0</p> <p>Asian (%): 0.0/2.2</p> <p>American Indian (%): 1.1/0.0</p> <p>Multiple (%): 0.0/1.1</p> <p>Disease stage IV</p> <p>M1a (%): 29.6/28.6</p> <p>No previously treated brain metastasis (%): 82.1/87.4</p>				
<p>Zhou C, Wu YL, Chen G, Liu X et al.</p> <p>BEYOND: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase III Study of First-Line Carboplatin/Paclitaxel</p>	<p>Region</p> <p>China</p> <p>Inclusion criteria</p> <p>>18 years</p> <p>Histologically or cytologically confirmed,</p>	<p>Intervention(s)</p> <p>Carboplatin intravenously and paclitaxel (175 mg/m²) 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</p>	<p>Median overall survival (months)</p> <p>24.3/17.7 ; NA; NR</p> <p>Overall survival (follow-up: 1-2 years)</p> <p>NR; HR=1.47; 1.08-</p>	<p>AEs of special interest (%): 49/23</p> <p>Grade > 3 AES of special interest (%): 11/2</p> <p>Hypertension (%): 5/1</p> <p>Proteinuria (%): 4/0</p> <p>GI perforations (%):</p>	<p>Study type</p> <p>RCT</p> <p>Level of evidence</p> <p>1b</p>

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
<p>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.</p>	<p>locally advanced, metastatic, or recurrent nonsquamous NSCLC Eastern Cooperative Oncology Group performance status of 0 to 1</p> <p>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</p>	<p>Control Carboplatin intravenously and paclitaxel (175 mg/m²) IV (on day 1 of each 3-week cycle for up to six cycles plus placebo)</p> <p>Included/randomised patients 138/138</p> <p>Analysed patients 138/138 (efficacy) 140/134 (safety)</p> <p>Attrition NR</p> <p>Excluded from analysis (reason) +2/4 (safety, not received treatment or wrong treatment)</p>	<p>2.00</p> <p>Median progression-free survival (months) 9.2/6.5; NA; NR</p> <p>Progression-free survival (follow-up: 1-2 years) NR ; HR=2.5; 1.85-3.45</p> <p>ORR (follow-up: 1-2 years, RECIST criteria) 54%/26%; NR; <0.001</p> <p>Diseases control rate (follow-up: 1-2</p>	<p>1/1</p> <p>Bleeding (%): 1/1 Cerebral hemorrhage (%): <1/0 Hernaturia (%): 0/>1 Upper GI hemorrhage (%): <1/0</p> <p>Congestive heart failure (%): 1/0 Thromboembolic events (%): 0/1</p> <p>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</p>	<p>Risk of bias Generation of allocation sequence: +</p> <p>Allocation concealment: +</p> <p>Blinding of participants and personal: +</p> <p>Blinding of outcome assessment: +</p> <p>Incomplete outcome data: ?</p>

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
	<p>bevacizumab dose) use of Full-dose anticoagulants or a thrombolytic agent for therapeutic purposes</p> <p>Patient characteristics</p> <p>Age (mean): 57/56</p> <p>Men (%): 54/56</p> <p>ECOG PS</p> <p>0 (%): 25/20</p> <p>1 (%): 75/80</p> <p>Histology</p> <p>Adenocarcinoma (%): 99/98</p> <p>Large – cell carcinoma (%): 1/1</p> <p>Mixed cell carcinoma (%): 0/1</p> <p>Smoking Habits</p>		<p>years, RECIST criteria) 94%/89%; NR; ns (CIs overlapping)</p>	<p>difference in Incidence of >2% between treatment arms</p> <p>Neutropenia (%): 23/28</p> <p>Anemia (%): 7/11</p> <p>Thrombocytopenia (%): 7/9</p> <p>Bone marrow failure (%): 11/3</p> <p>Febrile neutropenia (%): 3/5</p> <p>WBC count decreased (%): 11/5</p> <p>Hypertension (%): 5/1</p> <p>Diarrhea (%): 1/3</p> <p>Prostelnuria (%): 4/0</p> <p>Back pain (%): 0/2</p>	<p>Selective reporting: + Other source of bias: +</p>

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
	<p>Non-smoker/former smoke (%): 50/56</p> <p>Smoker (%): 50/44</p> <p>Disease stage</p> <p>Recurrent (%): 3/2</p> <p>IIIB (%): 6/7</p> <p>IV (%): 91/91</p> <p>Unknown (%): 0/1</p> <p>EGFR mutation status assessment (%): 85/66</p> <p>EGFR mutation positive (%): 27/26</p> <p>EGFR wild type (%): 73/74</p>				

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.	<p>Region 118 centers in 21 countries</p> <p>Inclusion criteria</p> <p>Age ≥ 18 years</p> <p>Locally advanced or metastatic (stage IIIB to IV) NSCLC after failure of first-line anticancer treatment</p> <p>Performance status 0 to 2</p> <p>Life expectancy ≥ 12 weeks</p> <p>Adequate hematologic, hepatic, renal, and cardiac function.</p> <p>Patients with squamous cell histology were permitted (recruitment was completed before labeling of pemetrexed)</p>	<p>Intervention(s) Once-daily oral vandetanib 100 mg plus pemetrexed</p> <p>Pemetrexed 500 mg/m² was administered as an intravenous infusion every 21 days (maximum of six cycles)</p> <p>Median number of pemetrexed cycles was 5.0</p> <p>The median duration of treatment was 102</p> <p>Control Oral placebo plus pemetrexed</p> <p>Pemetrexed 500 mg/m² was administered as an intravenous infusion every 21 days</p>	<p>Median overall survival (months) 10.5/9.2; NA; NR</p> <p>Overall survival (minimum 12 month) NR/NR; HR = 1.12; 0.92 – 1.37</p> <p>Median progression free survival (weeks) 17.6/11.9; NA; NR</p> <p>Progression free survival (minimum 6 month) NR/NR; HR = 1.16; 0.94 – 1.45 (97.58% CI)</p> <p>Objective response rate</p>	<p>Fatigue (%): 39/45</p> <p>Nausea (%): 29/37</p> <p>Rash (%): 38/26</p> <p>Cough (%): 25/22</p> <p>Anorexia (%): 22/24</p> <p>Dyspnea (%): 21/24</p> <p>Diarrhea (%): 26/18</p> <p>Constipation (%): 20/20</p> <p>Vomiting (%): 15/22</p> <p>Anemia (%): 8/22</p>	<p>Study type RCT</p> <p>Level of evidence 1b</p> <p>Risk of bias</p> <p>Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: + Blinding of outcome assessment:</p>

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
	<p>for nonsquamous histology only) as were patients with pretreated clinically stable brain metastases</p> <p>Exclusion criteria</p> <p>Chemotherapy or other anticancer therapy < 3 weeks before study entry</p> <p>Radiation therapy within 4 weeks before study entry</p> <p>Prior treatment with pemetrexed or VEGFR tyrosine kinase inhibitors (TKIs)</p> <p>Patient characteristics</p> <p>Age (median): 60/60</p> <p>Male (%): 62/62</p> <p>Performance status</p>	<p>(maximum of six cycles)</p> <p>Median number of pemetrexed cycles was 4.0</p> <p>The median duration of treatment was 85</p> <p>Included/randomised patients 256/278</p> <p>Analysed patients 256/278 (efficacy) 260/273 (safety)</p> <p>Attrition None</p> <p>Excluded from analysis (reason)</p> <p>None (efficacy)</p> <p>0/1 (safety: not received treatment)</p>	<p>(minimum 6 month)</p> <p>19%/8%; NR; <0.001</p> <p>DCR (minimum 6 month)</p> <p>57%/46%; NR; 0.0116</p> <p>Time to deterioration of symptoms (Lung Cancer Symptom Scale, minimum 6 month)</p> <p>NR/NR; HR = 1.41; 1.06-1.85</p>		<p>?</p> <p>Incomplete outcome data: +</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	<p>0 (%): 41/41</p> <p>1 (%): 52/54</p> <p>2 (%): 7/5</p> <p><i>Histology</i></p> <p>Adenocarcinoma (%): 61/65</p> <p>Squamous cell (%): 21/22</p> <p>Other (%): 18/13</p> <p><i>Stage</i></p> <p>IIIB (%): 14/17</p> <p>IV (%): 86/83</p> <p>Number of prior chemotherapy regimes</p> <p>1 (%): 85/86</p> <p>2 (%): 13/11</p> <p>3 (%): 0.4/0.4</p> <p>Race/ethnicity</p> <p>White (%): 77/78</p> <p>East Asian (%): 11/12</p>				

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 (%): 12/9 Smoking history 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	Intervention(s) Docetaxel (75 mg/m ² 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/m ² Median of 4 docetaxel cycles Exposure to vandetanib 12.1 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)	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	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
	<p>Criteria in Solid Tumours</p> <p>Adequate cardiac, haematopoietic, hepatic, and renal function</p> <p>Exclusion criteria</p> <p>Previous therapy with docetaxel or a VEGFR TKI</p> <p>Previous treatment with bevacizumab or paclitaxel</p> <p>Squamous-cell histology or brain metastases if treated within 4 weeks before study entry or not clinically stable without steroids for 10 days</p> <p>Patient characteristics</p> <p>Age (mean): 59/59</p> <p>Male (%): 72/68</p> <p><i>Ethnic origin</i></p> <p>Caucasian (%): 59/60</p>	<p>Control</p> <p>Docetaxel (75 mg/m² in a 1-h intravenous infusion every 3 weeks; maximum six cycles) with placebo</p> <p>Median of 4 docetaxel cycles</p> <p>Exposure to placebo 13.0 weeks</p> <p>Included/randomised patients 694/697</p> <p>Analysed patients 694/697 (efficacy) 689/690 (safety)</p> <p>Attrition 432/458</p> <p>Excluded from analysis</p>	<p>Median progression free survival 4.0/3.2; NR; NR</p> <p>ORR (median 12.8 month) 17%/10%; NR; 0.0001</p> <p>DCR (median 12.8 month) 60%/55%; NR; 0.06</p> <p>Deterioration (FACT-L LCS, median 12.8 month)</p> <p>NR/NR; HR= 1.30; 1.09-1.54 (97.5% CI)</p> <p>Median time to</p>	<p>Leukopenia (%): 18/16</p> <p>Asthenia (%): 16/13</p> <p>Anaemia (%): 10%15</p> <p>Myalgia (%): 13/11</p> <p>Insomnia (%):13/11</p> <p>Stomatitis (%): 12/12</p>	<p>Blinding of participants and personal: +</p> <p>Blinding of outcome assessment: +</p> <p>Incomplete outcome data: +</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	<p>East Asian (%): 37/36</p> <p>Other (%): 4/4</p> <p><i>Smoking history</i></p> <p>Current smoker (%): 37/35</p> <p>Former smoker (%): 40/40</p> <p>Non-smoker (%): 23/25</p> <p><i>WHO performance status</i></p> <p>0 (%): 36/34</p> <p>1 (%): 63/65</p> <p>Other (%): 1/1</p> <p><i>Histology</i></p> <p>Adenocarcinoma (%): 59/60</p> <p>Squamous (%): 27/23</p> <p>Other (%): 14/17</p> <p><i>Stage of disease</i></p> <p>Stage IIIb (%): 14/15</p> <p>Stage IV (%): 86/85</p>	<p>(reason)</p> <p>5/7 (safety, not treated)</p>	<p>deterioration (FACT-L LCS) 3.5/2.7;NR;NR</p>		

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
	<p>Brain metastases (%): 9/11</p> <p><i>Previous chemotherapy</i></p> <p>Platinum compound (%): 95/95</p> <p>Pyrimidine analogue (%): 44/45</p> <p>Taxane (%): 31/30</p> <p>Vinca alkaloid or analogue (%): 18/18</p> <p><i>Best response to first-line chemotherapy</i></p> <p>Complete response (%): 2/2</p> <p>Partial response (%): 31/31</p> <p>Stable disease (%): 36/37</p> <p>Progressive disease (%): 24/24</p> <p>Non-evaluable (%): 2/2</p>				

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	Intervention(s) All patients initially received two cycles of chemotherapy with docetaxel 100 mg/m ² 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	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
	<p>Exclusion criteria</p> <p>Hemoptysis</p> <p>History of documented hemorrhagic diathesis or coagulopathy</p> <p>Therapeutic anticoagulation</p> <p>Radiation therapy within 21 days before enrolment or major surgery within 28 days before enrolment</p> <p>Clinically significant cardiovascular disease</p> <p>Medically uncontrolled hypertension</p> <p>Prior systemic chemotherapy for NSCLC</p> <p>Symptomatic or untreated brain metastases</p> <p>Tumors invading or</p>	<p>plus erlotinib administered orally at 150 mg/dL per day beginning on the first day of the third cycle and continued with erlotinib monotherapy thereafter until progression</p> <p>Bevacizumab in combination with chemotherapy (docetaxel and carboplatin chemotherapy + bevacizumab</p> <p>Four cycles of docetaxel-carboplatin plus bevacizumab 7.5 mg/kg by intravenous infusion every 28 days and continued with bevacizumab every 21</p>	<p>Objective Response rate (median follow-up 440 days)</p> <p>48%/39%/44%/31%; NR; NR</p>		<p>-</p> <p>Blinding of outcome assessment: ?</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	<p>abutting major blood vessels (based on radiologist assessment)</p> <p>Patient characteristics</p> <p>Age (median): 62.5/62.5/60/65</p> <p>Male (%): 77/80/83/85</p> <p>Histologic type</p> <p>Adenocarcinoma (%): 92/89/87/92</p> <p>Large cell (%): 8/11/13/8</p> <p>Stage of disease</p> <p>Stage IIIb (%): 25/27/17/16</p> <p>Stage IV (%): 75/73/83/84</p> <p>Smoking history</p> <p>Never (%): 15/16/3/8</p> <p>Previous (%):</p>	<p>days until disease progression</p> <p>Bevacizumab in combination with erlotinib and chemotherapy (docetaxel and carboplatin chemotherapy + bevacizumab + erlotinib)</p> <p>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</p> <p>Control</p>			

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
	<p>75/80/88/64</p> <p>Current (%): 10/4/8/23</p> <p><i>EGFR Status</i></p> <p>Immunohistochemistry (+) (%): 73/22/40/65</p> <p>Immunohistochemistry (-) (%): 27/73/60/35</p> <p><i>VEGF status</i></p> <p>Immunohistochemistry (+) (%): 37/31/53/60</p> <p>Immunohistochemistry (-) (%): 63/69/47/40</p>	<p>Docetaxel and carboplatin chemotherapy alone</p> <p>Further four cycles of docetaxel-carboplatin and continued with observation until disease progression</p> <p>Included/randomised patients</p> <p>62/62/62/62 Analysed patients</p> <p>52/56/60/61</p> <p>Attrition</p> <p>10/6/2/1</p> <p>Excluded from analysis (reason)</p> <p>10/6/2/1 (attrition)</p>			
Heist, R.S. CALGB 30704 (Alliance): A	Region NR	Intervention(s) Sunitinib alone at 37.5	Median overall survival (months)	Overall AEs (%): 67/80/29	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; primary outcome marked bold)	Adverse events (IG _n /CG)	Study type, level of evidence and risk of bias
<p>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 Oncol, 2014; 9(2): p. 214-21.</p>	<p>Inclusion criteria Patients aged 18 years or older Advanced NSCLC (stage IIIB or IV) with evidence of progression after first-line therapy 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.</p>	<p>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 Included/randomised patients 47/41/42 Analysed patients 47/41/42 Attrition NR Excluded from analysis (reason) 0/0/0</p>	<p>8.0/6.7/10.5; NA; p=0.03 Overall survival (median 36 month) NR/NR; HR = 0.714; 0.435 – 1.111 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</p>	<p>Hematologic AEs (%): 23/47/17 Low haemoglobin (%): 7/8/2 Low absolute neutrophil count (%): 7/28/5 Low platelets (%): 7/17/4 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</p>	<p>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:</p>

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
	<p>Exclusion criteria</p> <p>Symptomatic congestive heart failure</p> <p>Active coronary artery disease defined as myocardial infarction or unstable angina in the past year</p> <p>Cerebrovascular accident or transient ischemic accident in the past year</p> <p>Uncontrolled hypertension</p> <p>Hemoptysis</p> <p>Cavitary pulmonary lesions</p> <p>History of thromboembolism</p> <p>Requirement for full-dose therapeutic anticoagulation</p>		<p>survival (median 26 month)</p> <p>1) NR/NR; HR = 0.714; 0.455 – 1.111</p> <p>2) NR/NR; HR = 0.768; 0.476 – 1.111</p> <p>Response rate (median 36 month)</p> <p>17%/22%/14%; NR; 0.34</p>	<p>Elevated aspartate aminotransferase (%): 5/0/2</p> <p>Rash (hand-foot) (%): 7/0/0</p> <p>Cardiac ischemia (%): 2/0/0</p> <p>Hypertension (%): 5/5/2</p> <p>Pulmonary haemorrhage (%): 2/0/0</p> <p>Other haemorrhage (%): 0/3/0</p> <p>Thrombosis/embolism (%): 0/6/0</p>	<p>+ Selective reporting: + Other source of bias: - (multiple testing without adjustment)</p>

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
	<p>Patient characteristics</p> <p><i>Age</i></p> <p>< 60 (%): 32/37/38</p> <p>60 – 70 (%): 51/32/36</p> <p>> 70 (%): 17/32/26</p> <p>Male (%): 53/54/52</p> <p><i>Race</i></p> <p>White (%): 91/78/86</p> <p>Black (%): 6/20/12</p> <p>Asian (%): 2/2/0</p> <p>More than one race (%): 0/0/2</p> <p><i>Ethnicity</i></p> <p>Non-Hispanic (%): 100/88/93</p> <p>Hispanic (%): 0/2/5</p> <p>Unknown (%): 0/10/2</p> <p><i>Performance status</i></p>				

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
	<p>0 (%): 36/34/31</p> <p>1 (%): 64/66/69</p> <p><i>Histology</i></p> <p>Adenocarcinoma (%): 69/66/67</p> <p>Squamous cell (%): 15/15/10</p> <p>Large cell (%): 9/0/5</p> <p>Undifferentiated NSC (%): 13/2/7</p> <p>Other (%): 4/17/7</p> <p>Missing (%): 0/0/5</p> <p><i>Stage of disease</i></p> <p>Stage IIIb (%): 17/7/12</p> <p>Stage IV (%): 83/93/88</p> <p><i>Prior surgery</i></p> <p>No (%): 72/73/57</p> <p>Yes (%): 26/27/38</p> <p>Missing (%): 2/0/5</p>				

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
	<p><i>Prior XRT</i></p> <p>No (%): 55/51/52</p> <p>Yes (%): 45/49/40</p> <p>Missing (%): 0/0/7</p> <p><i>No. of prior chemo regimens</i></p> <p>1 (%): 91/95/90</p> <p>2+ (%): 9/0/2</p> <p>Missing (%): 0/5/7</p>				
<p>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.</p>	<p>Region</p> <p>12 centers in North America</p> <p>Inclusion criteria</p> <p>Stage IIIB (with pleural effusion), stage IV, or recurrent NSCLC</p> <p>Age ≥ 18 years</p> <p>Bi-dimensionally</p>	<p>Intervention(s)</p> <p>carboplatin/paclitaxel plus low-dose (7.5 mg/kg) bevacizumab</p> <p>Median number of bevacizumab doses 8</p> <p>Median of six cycles of carboplatin plus paclitaxel</p> <p>carboplatin/paclitaxel plus high-dose (15</p>	<p>Median overall survival (months)</p> <p>11.6/14.9; NA; 0.84</p> <p>17.7/14.9; NA; 0.63</p> <p>Median time to progression (months)</p> <p>4.1/7.0/5.9; NR; 0.185</p> <p>Response rate (time</p>	<p>Chills (%): 12.5/11.8/9.4</p> <p>Diarrhea (%): 28.1/41.2/18.8</p> <p>Epistaxis (%): 31.3/44.1/6.3</p> <p>Fever (%): 34.4/32.4/12.5</p> <p>Headache (%): 31.3/47.1/9.4</p> <p>Hemorrhage (%): 12.5/0.0/0.0</p>	<p>Study type</p> <p>RCT</p> <p>Level of evidence</p> <p>2b</p> <p>Risk of bias</p> <p>Generation of allocation sequence:</p> <p>+</p>

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
2184-91.	<p>measurable disease</p> <p>Performance status ≤ 2</p> <p>Life expectancy ≥ 3 months</p> <p>Availability for regular follow-up</p> <p>Exclusion criteria</p> <p>Small-cell or mixed histologies</p> <p>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</p> <p>Absolute neutrophil count ≤ 1,500/ µL</p> <p>Hemoglobin less than 9</p>	<p>mg/kg) bevacizumab</p> <p>Median number of bevacizumab doses 10</p> <p>Median of six cycles of carboplatin plus paclitaxel</p> <p>Bevacizumab was administered by intravenous infusion over 90 minutes, 1 hour after each cycle of chemotherapy</p> <p>Control</p> <p>Carboplatin/paclitaxel alone</p> <p>Up to six cycles of carboplatin/paclitaxel</p> <p>Paclitaxel (200 mg/m²) was administered over 3 hours every 3 weeks</p> <p>Carboplatin dosing was</p>	<p>period NR)</p> <p>21.9%/40.0%/31.3%; NR; NR</p>	<p>Hypertension (%): 15.6/17.6/3.1</p> <p>Hemoptysis (%): 28.1/11.8/6.3</p> <p>Infection (%): 31.3/35.3/25.0</p> <p>Leukopenia (%): 46.9/55.9/31.3</p> <p>Nausea (%): 50.0/50.0/46.9</p> <p>Neuropathy (%): 12.5/14.7/28.1</p> <p>Paresthesia (%): 28.1/35.3/21.9</p> <p>Peripheral neuritis (%): 25.0/38.2/28.1</p> <p>Rash (%): 34.4/23.5/9.4</p> <p>Stomatitis (%): 15.6/23.5/9.4</p> <p>Thrombocytopenia (%): 6.3/20.6/15.6</p>	<p>Allocation concealment: +</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome assessment: +</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	<p>gm/dL</p> <p>Platelet count ≤ 100,000/μL</p> <p>Bilirubin > 2.0 mg/dL</p> <p>AST or ALT ≥ 5 times upper limit of normal (ULN) for subjects with metastases</p> <p>> 2.5 X ULN for those without metastases</p> <p>Serum creatinine > 1.8 mg/dL.</p> <p>Nonhealing wounds, ulcers, or bone fractures</p> <p>Significant cardiovascular disease</p> <p>Significant peripheral vascular disease, CNS metastasis, active secondary malignancies (other than basal cell carcinoma of the skin), an active infection, or</p>	<p>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)</p> <p>For females, a correction factor of 0.85 was used</p> <p>Carboplatin was administered over 15 to 30 minutes, beginning 60 minutes after completion of the paclitaxel</p> <p>Median of six cycles of carboplatin plus paclitaxel</p> <p>Included/randomised patients</p>		<p>Thrombotic events (%): 12.5/17.6/9.4</p> <p>Vomiting (%): 18.8/23.5/18.8</p>	

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
	<p>pregnancy</p> <p>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</p> <p>Recent or current use of aspirin or oral and/or parenteral anticoagulants (except low-dose Coumadin 1 mg)</p> <p>Patient characteristics</p> <p>Male (%): 20/16/24</p> <p><i>Performance status</i></p> <p>0 (%): 16/19/15</p> <p>1 (%): 15/12/15</p> <p>2 (%): 1/4/2</p>	<p>32/35/32</p> <p>Analysed patients</p> <p>32/34/32</p> <p>Attrition</p> <p>Excluded from analysis (reason)</p> <p>0/1/0</p>			

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
	<p><i>Histology</i></p> <p>Adenocarcinoma (%): 29/23/17</p> <p>Large cell anaplastic (%): 1/5/4</p> <p>Squamous cell (%): 10/3/7</p> <p>Other (%): 1/4/4</p> <p><i>Stage</i></p> <p>IIIB (%): 2/7/6</p> <p>IV (%): 30/28/26</p> <p>Duration of current cancer</p> <p>< 1 year (%): 24/28/22</p> <p>1 year (%): 2/4/4</p> <p>2 years (%): 2/1/2</p> <p>≥ 3 years (%): 4/2/4</p> <p>Prior cancer therapy</p> <p>Any (%): 10/10/13</p>				

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
	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 Performance status of 0 or 1 Life expectancy of at least 12 weeks Normal end organ function Patients with squamous	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 intravenous infusion over 1 hour on day 1 of each 21-day) cycle Control Placebo and docetaxel (75mg/m ² intravenous	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 (300mg docetaxel vs. control) Progression free survival (minimum 18 month) NR/NR; HR = 1.56; 0.95	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 Nausea/vomiting (%): 31/34/24 Hypertension (%): 7/9/2 Dizziness (%): 7/4/5	Study type RCT Level of evidence 2b Risk of bias Generation of allocation sequence: ? Allocation concealment: ? Blinding of participants and personal: + Blinding of

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
	<p>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</p> <p>Exclusion criteria</p> <p>Previous treatment with docetaxel or EGFR/VEGFR signaling inhibitors</p> <p>Chemotherapy within the last 4 to 6 weeks</p> <p>Radiation therapy within the last 4 weeks</p> <p>Patient characteristics</p> <p>Age (median): 61/60/58</p> <p>Male (%): 50/57/66</p> <p>Performance status</p>	<p>infusion over 1 hour on day 1 of each 21-day cycle)</p> <p>Included/randomised patients 42/44/41</p> <p>Analysed patients 0/0/0</p> <p>Attrition NR/NR/NR</p> <p>Excluded from analysis (reason) None</p>	<p>- 2.63 NR/NR; HR = 1.20; 0.74 - 2.00</p> <p>Median progression free survival (weeks) 18.7/17.0;12.0; NA; 0.074 (100mg docetaxel vs. control), 0.461 (300mg docetaxel vs. control)</p> <p>Response rate 26%/18%/12%; NR; NR</p>		<p>outcome assessment: ?</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting: +</p> <p>Other source of bias: - (multiple testing without adjustment)</p>

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
	<p>0 (%): 33.3/36.4/36.6</p> <p>1 (%): 64.3/61.4/63.4</p> <p><i>Smoking status</i></p> <p>Current smoker (%): 26.2/36.4/26.8</p> <p>Previous smoker (%): 57.1/54.5/63.4</p> <p>Nonsmoker (%): 16.7/9.1/9.8</p> <p><i>Histology</i></p> <p>Adenocarcinoma (%): 54.8/45.5/48.8</p> <p>Squamous (%): 28.6/31.8/26.8</p> <p>Other histologies (%): 16.7/22.7/24.4</p> <p>Brain metastases (%): 16.7/4.5/9.8</p> <p><i>Stage</i></p> <p>IIIB (%): 31.0/20.5/31.7</p>				

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 (%): 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.	<p>Region 19 sites in Japan</p> <p>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) Performance Status 0 or 1 life expectancy of \geq 3 months Adequate bone marrow, hepatic, and renal function</p>	<p>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 Chemotherapy was repeated every 21 days for a total of 6 cycles unless there was evidence of disease</p>	<p>Overall survival (minimum 16 month) NR/NR; HR = 1.01; 0.67 - 1.54</p> <p>Median overall survival (months) 22.8/23.4; NA; ns (CIs overlap)</p> <p>Progression free survival (minimum 16 month) NR/NR; HR = 1.64; 1.12 - 2.38</p> <p>Median progression free survival (months)</p>	<p>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 Nasal bleeding (%): 72/12 Venous thromboembolism (%): 4/3 Arterial thromboembolism (%):</p>	<p>Study type RCT Level of evidence 2b</p> <p>Risk of bias Generation of allocation sequence: + Allocation concealment: + Blinding of participants and personal: - Blinding of</p>

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
	<p>Exclusion criteria</p> <p>Prior chemotherapy for NSCLC</p> <p>Central nervous system metastases or spinal cord compression</p> <p>Tumor invading major blood vessels or with cavitation</p> <p>Hemoptysis (≥ 2.5 mL per event)</p> <p>History of coagulation disorders or therapeutic anticoagulation</p> <p>Uncontrolled hypertension</p> <p>History of a symptomatic lung disorder</p> <p>Patient characteristics</p>	<p>progression or unacceptable toxicity</p> <p>Median number of chemotherapy cycles was 6</p> <p>Control</p> <p>Carboplatin-paclitaxel alone</p> <p>Same treatment for carboplatin and paclitaxel as in the intervention group</p> <p>Median number of chemotherapy cycles was 4.5</p> <p>Included/randomised patients</p> <p>121/59</p>	<p>6.9/5.9; NA; ns (CIs overlap)</p> <p>Objective Response rate (minimum 16 month)</p> <p>60.7%/31.0%; NR; 0.0013</p> <p>DCR (minimum 16 month)</p> <p>94.0%/70.7%; NR; 0.0002</p>	<p>1/0</p> <p>Congestive heart disease (%): 1/2</p> <p>Proteinuria (%): 52/17</p> <p>Fatigue (%): 52/53</p> <p>Vomiting (%): 36/31</p> <p>Neuropathy (%): 88/86</p> <p>Muscle pain (%): 70/71</p> <p>Joint pain (%): 82/79</p> <p>Elevated aspartate aminotransferase (%): 47/36</p> <p>Elevated alanine aminotransferase (%): 48/41</p> <p>Hyponatremia (%): 14/3</p> <p>Treatment-related death (%): <1/0</p>	<p>outcome assessment: ?</p> <p>Incomplete outcome data: +</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	<p>Age (median): 61/60</p> <p>Male (%): 64/64</p> <p><i>Performance status</i></p> <p>0 (%): 51/49</p> <p>1 (%): 49/51</p> <p><i>Smoking status</i></p> <p>Never smoker (%): 31/32</p> <p>Current or previous smoker (%): 69/68</p> <p><i>Tumor histology</i></p> <p>Adenocarcinoma (%): 93/92</p> <p>Large cell carcinoma (%): 2/3</p> <p>Other (%): 7/3</p> <p><i>Stage</i></p> <p>IIIB (%): 23/20</p> <p>IV (%): 69/71</p> <p>Recurrent (%): 8/8</p>	<p>Analysed patients</p> <p>119/58 (safety)</p> <p>117/58 (efficacy)</p> <p>Attrition</p> <p>4/1</p> <p>Excluded from analysis (reason)</p> <p>2/1 (safety, did not start treatment))</p> <p>4/1 (efficacy, ineligible)</p>			

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
<p>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.</p>	<p>Region 93 centers in 16 countries</p> <p>Inclusion criteria Chemotherapy-naïve 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.</p> <p>Performance status of 0 or 1</p> <p>At least one measurable lesion</p> <p>Adequate bone marrow, liver, and renal function as assessed</p>	<p>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)</p> <p>Up to six cycles, each of 21 days</p> <p>Median duration of treatment 17.0 weeks</p> <p>Control Gemcitabine (1,250 mg/m² per day intravenously on days 1 and 8), cisplatin (75 mg/m² intravenously on day 1), and placebo</p> <p>Up to six cycles, each of 21 days</p>	<p>Median overall survival (months) 12.4/12.5; NA; ns (CIs overlap)</p> <p>Overall survival (minimum 1 year) NR/NR; HR = 0.98; 0.83 – 1.16</p> <p>Median progression free survival (months) 6.0/5.5; NA; ns (CIs overlap)</p> <p>Progression free survival (minimum 1 year) (NR/NR; HR = 1.20; 1.03 – 1.41)</p> <p>Response rate</p>	<p>All treatment-emergent drug-related AEs (%): 86.0/69.3</p> <p>Thrombocytopenia (%): 15.8/11.5</p> <p>Anemia (%): 8.8/9.1</p> <p>Neutropenia (%): 8.1/8.9</p> <p>Leukopenia (%): 6.5/3.4</p> <p>Rash/desquamation (%): 33.5/15.1</p> <p>Diarrhea (%): 31.4/10.9</p> <p>Fatigue (%): 29.4/24.7</p> <p>Hand-foot skin reaction (%): 28.8/3.1</p> <p>Nausea (%): 24.4/20.1</p> <p>Anorexia (%): 15.8/11.5</p> <p>Hypertension (%): 14.5/6.3</p> <p>Oral mucositis (%): 14.5/5.2</p>	<p>Study type RCT</p> <p>Level of evidence 1b</p> <p>Risk of bias</p> <p>Generation of allocation sequence: +</p> <p>Allocation concealment: +</p> <p>Blinding of participants and personal: +</p> <p>Blinding of outcome assessment:</p>

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
	<p>Life expectancy of at least 12 weeks.</p> <p>Exclusion criteria</p> <p>Patients with grade ≥ 2 pulmonary hemorrhage/bleeding or grade ≥ 3 other hemorrhage/bleeding events within 4 weeks of the first dose of study drug</p> <p>Cardiac disease (congestive heart failure, unstable angina, cardiac arrhythmia requiring antiarrhythmic therapy, active coronary artery disease, or history of myocardial infarction within the previous 6 months)</p> <p>Uncontrolled hypertension</p>	<p>Median duration of treatment 18.0 weeks</p> <p>Included/randomised patients 452/452</p> <p>Analysed patients 385/384 (safety) 385/387 (efficacy)</p> <p>Attrition 379/381</p> <p>Excluded from analysis (reason) 67/68 (safety: squamous cell NSCLC not treated) 67/65 (efficacy: squamous cell NSCLC)</p>	<p>(minimum 1 year) 27.8%/25.8%; NR; 0.27</p> <p>DCR (minimum 1 year) 62.1%/63.1%; NR; 0.39</p>	<p>Alopecia (%): 11.2/5.7</p> <p>Nose haemorrhage (%): 10.9/2.9</p> <p>Vomiting (%): 10.4/12.5</p> <p>Dry skin (%): 6.8/3.1</p> <p>Pruritus (%): 6.8/2.3</p> <p>Abdominal pain not otherwise specified (%): 6.5/2.1</p> <p>Constipation (%): 6.2/6.0</p> <p>Sensory neuropathy (%): 4.9/6.0</p> <p>Constitutional (other) (%): 2.1/0.5</p> <p>Gastrointestinal perforation (%): 0.3/0.0</p> <p>Central nervous system haemorrhage (%): 0.3/0.3</p> <p>Lung haemorrhage (%): 0.5/1.0</p>	<p>+ Incomplete outcome data: + Selective reporting: + Other source of bias: +</p>

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
	<p>History of HIV infection or chronic hepatitis B or C</p> <p>Active clinically serious infection</p> <p>Seizure disorder requiring medication</p> <p>Known brain metastasis</p> <p>History of bleeding diathesis or coagulopathy</p> <p>History of a thrombotic or embolic event (including a transient ischemic attack) within the previous 6 months</p> <p>Serious, nonhealing wound, ulcer, or bone fracture</p> <p>Uncorrected dehydration</p> <p>Pregnancy or lactation</p> <p>Therapeutic anticoagulation</p>			<p>Abdominal haemorrhage not otherwise specified (%): 0.3/0.0</p> <p>Vascular (thrombotic) (%): 3.6/3.4</p>	

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
	<p>Patient characteristics</p> <p>Age (median): 60/58</p> <p>Male (%): 59.2/63.3</p> <p><i>Performance status</i></p> <p>0 (%): 37.9/37.0</p> <p>1 (%): 62.1/63.0</p> <p><i>Smoking status</i></p> <p>Past or present smoker (%): 72.1/74.2</p> <p>Nonsmoker (%): 27.3/25.3</p> <p>Passive smoker (%): 0.5/0.5</p> <p><i>NSCLC classification</i></p> <p>Adenocarcinoma (%): 78.4/80.4</p> <p>Large cell carcinoma (%): 12.2/10.9</p> <p>Undifferentiated</p>				

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
	<p>carcinoma (%): 5.2/5.7</p> <p>Bronchoalveolar (%): 1.8/1.3</p> <p>Other (%): 2.3/1.8</p> <p><i>Disease stage</i></p> <p>IIIB (%): 12.2/12.1</p> <p>IV (%): 87.8/87.9</p> <p><i>Race/ethnicity</i></p> <p>White (%): 69.0/69.5</p> <p>Black (%): 0.9/0.0</p> <p>Asian (%): 27.5/27.6</p> <p>Hispanic (%): 2.6/2.1</p> <p>Other (%): 0.0/0.9</p> <p>Median time since diagnosis (weeks): 2.6/2.9</p>				
Ritzwoller, D.P., et al., Comparative effectiveness of adjunctive	Region USA	Intervention(s) Carboplatin/paclitaxel + bevacizumab (between 2005 and 2010)	Overall survival (90 month, multivariable-adjusted model) NR/NR; HR = 1.32; 1.09	NR	Study type Register-based cohort study

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
bevacizumab for advanced lung cancer: the cancer research network experience. J Thorac Oncol, 2014. 9(5): p. 692-701.	<p>Inclusion criteria</p> <p>Patients from Virtual Tumor Registry (VTR)</p> <p>Aged 21 years and older</p> <p>Stage IIIB/IV NSCLC</p> <p>Health plan enrollment at the time of cancer diagnosis</p> <p>First cancer diagnosis</p> <p>Survival of at least 1 month after cancer diagnosis</p> <p>Pathologically confirmed diagnosis</p> <p>Exclusion criteria</p> <p>Squamous cell types or if they were receiving concurrent radiation and chemotherapy</p>	<p>Control</p> <p>Carboplatin/paclitaxel (between 2005 and 2010)</p> <p>Carboplatin/paclitaxel (between 2002 and 2004)</p> <p>Included/randomised patients</p> <p>NA</p> <p>Analysed patients</p> <p>198/911/496</p> <p>Attrition</p> <p>NA</p> <p>Excluded from analysis (reason)</p> <p>NA</p>	<p>- 1.59</p> <p>NR/NR; HR = 1.67; 1.35 – 2.00</p> <p>Overall median survival (months)</p> <p>12.3/8.8; NA; ns (CIs overlap)</p> <p>12.3/7.5; NA; ns (CIs overlap)</p>		<p>Level of evidence 2c</p> <p>Risk of bias</p> <p>Generation of allocation sequence:</p> <p>-</p> <p>Allocation concealment:</p> <p>-</p> <p>Blinding of participants and personal:</p> <p>-</p> <p>Blinding of outcome assessment:</p> <p>-</p> <p>Incomplete</p>

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
	<p>Patient characteristics</p> <p>Age <65 at diagnosis (%): 63.6/48.7/51.2</p> <p>Age 65+ at diagnosis (%): 36.4/51.3/48.8</p> <p>Male (%): 51.5/50.8/49.0</p> <p><i>AJCC stage at diagnosis</i></p> <p>IIIB (%): 15.2/20.7/27.2</p> <p>IV (%): 84.8/79.3/72.8</p> <p>Race/ethnicity</p> <p>White (%): 78.3/75.9/71.0</p> <p>Hispanic (%): <1/4.2/7.3</p> <p>Black (%): 5.6/7.6/7.9</p> <p>Asian/Pacific Islander (%): 11.1/10.3/10.7</p> <p>Other race (%): <1/2.1/3.2</p> <p><i>Modified Charlson comorbidity score</i></p>				<p>outcome data: ?</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	<p>0 (%): 61.1/55.4/66.3</p> <p>1 (%): 24.7/24.9/22.6</p> <p>2+ (%): 14.1/19.6/11.1</p> <p><i>Level of differentiation</i></p> <p>Well/moderately (%): 22.2/12.1/13.5</p> <p>Poor/undifferentiated (%): 16.2/22.1/23.8</p> <p>Unknown (%): 61.6/65.9/62.7</p>				
<p>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.</p> <p>Brahmer, J.R. Sex differences in outcome with bevacizumab therapy: analysis of</p>	<p>Region NR</p> <p>Inclusion criteria Newly diagnosed stage IIIB (malignant pleural effusion) or stage IV cancer or recurrent non-small-cell lung cancer for</p>	<p>Paclitaxel and carboplatin plus bevacizumab at a dose of 15 mg per kilogram given intravenously on day 1</p> <p>Chemotherapy was repeated every 21 days for a total of six cycles</p>	<p>Median overall survival (months) 12.3/10.3; NA; NR</p> <p>Overall survival (median 19 month) NR/NR; HR = 1.27; 1.09 - 1.49</p>	<p>Neutropenia (%): 25.5/16.8</p> <p>Thrombocytopenia (%): 1.6/0.2</p> <p>Anemia (%): 0.0/0.9</p> <p>Febrile neutropenia (%): 5.2/2.0</p> <p>Hyponatremia (%): 3.5/1.1</p>	<p>Study type RCT</p> <p>Level of evidence 2b</p> <p>Risk of bias</p> <p>Generation of allocation</p>

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
<p>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.</p> <p>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 Clin Oncol, 2008. 26(1): p. 60-5.</p>	<p>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 History of documented hemorrhagic diathesis or coagulopathy Therapeutic</p>	<p>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 curve of 6.0 mg per</p>	<p>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 Test of interaction for</p>	<p>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 Other haemorrhage (%):</p>	<p>sequence: + Allocation concealment: ? Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data: + Selective reporting: + Other source of bias: - (interim analysis)</p>

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
	<p>anticoagulation</p> <p>Regular use of aspirin (>325 mg per day), nonsteroidal antiinflammatory agents, or other agents known to inhibit platelet function</p> <p>Radiation therapy within 21 days before enrolment or major surgery within 28 days before enrolment</p> <p>Clinically significant cardiovascular disease</p> <p>Medically uncontrolled hypertension</p> <p>Patient characteristics</p> <p>Age ≥ 65 years (%): 42/44</p> <p>Male (%): 50/58</p> <p><i>Race</i></p> <p>White (%): 90/91</p>	<p>milliliter per minute, administered intravenously on day 1</p> <p>The median number of cycles of therapy was five</p> <p>Included/randomised patients 434/444</p> <p>Analysed patients 417/433</p> <p>111/113 (subgroup)</p> <p>Attrition 2/2</p> <p>Excluded from analysis (reason) 17/11 (deemed to be ineligible on central review)</p>	<p>overall survival > age 70 (HR = 1.15) vs. age < 70 (NR); 0.34</p> <p>Test of interaction for overall survival males (HR = 1.37) vs. females (HR = 1.03); 0.09</p>		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
	<p>Black (%): 6/6</p> <p>Other (%): 4/3</p> <p><i>ECOG performance status</i></p> <p>0 (%): 40/40</p> <p>1 (%): 60/60</p> <p>Measurable Disease (%): 91/91</p> <p>Prior weight loss ($\geq 5\%$): 28/28</p> <p><i>Histology</i></p> <p>Adenocarcinoma or not otherwise specified (%): 88/88</p> <p>Large-cell cancer (%): 4/7</p> <p>Bronchioloalveolar carcinoma (%): 3/3</p> <p>Other histologic findings (%): 5/3</p> <p><i>Stage of disease</i></p>				

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
	<p>Stage IIIb (%): 12/13</p> <p>Stage IV (%): 74/78</p> <p>Recurrent disease (%): 14/9</p> <p>Prior radiation therapy (%): 8/9</p>				
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.	<p>Region 150 centers in 20 countries</p> <p>Inclusion criteria Chemotherapy-naïve patients Age ≥18 years Stage IIIB (limited to malignant pleural or pericardial effusion) or stage IV NSCLC Life expectancy ≥ 12 weeks</p>	<p>Sorafenib plus carboplatin and paclitaxel</p> <p>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</p> <p>Paclitaxel (200 mg/m² intravenously over 2.5</p>	<p>Median overall survival (months) 10.7/10.6; NA; ns (CIs overlap)</p> <p>Overall survival (20 month) NR/NR; HR = 0.87; 0.71 – 1.06</p> <p>Median progression free survival (months) 4.6/5.4; NA; ns (CIs overlap)</p>	<p>Any drug-related AE (%): 84/68</p> <p>Any drug-related SAE (%): 17/9</p> <p>Neutropenia (%): 9/7</p> <p>Thrombocytopenia (%): 8/3</p> <p>Anemia (%): 8/9</p> <p>Rash/desquamation (%): 46/13</p> <p>Diarrhea (%): 28/13</p> <p>Hand-foot skin reaction (%): 23/5</p> <p>Fatigue (%): 20/21</p>	<p>Study type RCT</p> <p>Level of evidence 2b</p> <p>Risk of bias</p> <p>Generation of allocation sequence: +</p> <p>Allocation concealment: ?</p>

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
	<p>Performance status of 0 or 1</p> <p>Adequate bone marrow, liver, and renal function</p> <p>Exclusion criteria</p> <p>National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; version 3) grade ≥ 2 pulmonary hemorrhage/bleeding</p> <p>CTCAE grade ≥ 3 other hemorrhage/ bleeding, or CTCAE grade more than 2 serious infections within 4 weeks of the first dose of study drug</p> <p>Active severe cardiac disease</p> <p>Relevant cardiac ventricular arrhythmias requiring antiarrhythmic</p>	<p>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</p> <p>Sorafenib (400 mg orally twice a day) on days 2 through 19</p> <p>Median number of CP treatment cycles was four</p> <p>Median duration of treatment was 16.6 weeks</p> <p>Control</p> <p>Placebo plus carboplatin and paclitaxel</p> <p>Paclitaxel (200 mg/m²)</p>	<p>Progression free survival (time period NR)</p> <p>NR/NR; HR = 1.01; 0.86 – 1.19</p> <p>Response rate (time period NR)</p> <p>27.4%/24.0%; NR; 0.102</p> <p>DCR (time period NR)</p> <p>50%/56%; NR; NR</p>	<p>Nausea (%): 15/17</p> <p>Sensory neuropathy (%): 14/13</p> <p>Hypertension (%): 12/6</p> <p>Pruritus (%): 12/6</p> <p>Alopecia (%): 11/12</p> <p>Anorexia (%): 9/6</p> <p>Vomiting (%): 9/7</p> <p>Oral mucositis (%): 8/2</p> <p>Dry skin (%): 7/3</p> <p>Constipation (%): 7/5</p> <p>Muscle pain (%): 6/7</p> <p>Nose haemorrhage (%): 5/2</p>	<p>Blinding of participants and personal: +</p> <p>Blinding of outcome assessment: ?</p> <p>Incomplete outcome data: +</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	<p>therapy</p> <p>Uncontrolled hypertension</p> <p>Known brain metastases</p> <p>HIV infection or chronic hepatitis B or C</p> <p>Thromboembolic events within the past 6 months</p> <p>History of bleeding diathesis or coagulopathy</p> <p>Serious nonhealing wound, ulcer, or bone fracture</p> <p>Patient characteristics</p> <p>Age (median): 62.0/63.0</p> <p>Male (%): 63/62</p> <p><i>Performance status</i></p> <p>0 (%): 41/41</p> <p>1 (%): 59/59</p>	<p>intravenously over 2.5 to 4 hours) first and carboplatin (area under the curve = 6</p> <p>intravenously over 15 to 60 minutes)</p> <p>immediately after on day 1 of a 21-day cycle during the chemotherapy phase</p> <p>Placebo (oral placebo tablets twice a day) on days 2 through 19</p> <p>Median number of CP treatment cycles was five</p> <p>Median duration of treatment was 16.6 weeks</p> <p>Median duration of treatment was 17.9 weeks</p> <p>Included/randomised</p>			

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
	<p><i>Smoking status</i></p> <p>Past or present smoker (%): 84/86</p> <p><i>NSCLC classification</i></p> <p>Adenocarcinoma (%): 57/59</p> <p>Large cell carcinoma (%): 5/6</p> <p>Squamous cell carcinoma (%): 23/25</p> <p>Other (%): 15/10</p> <p><i>Stage at study entry</i></p> <p>IIIB (%): 9/10</p> <p>IV (%): 91/90</p> <p>Race</p> <p>White (%): 88/86</p> <p>Black (%): 4/3</p> <p>Asian (%): 5/5</p> <p>Hispanic (%): 2/5</p>	<p>patients</p> <p>464/462</p> <p>Analysed patients</p> <p>463/459 (safety)</p> <p>None (efficacy)</p> <p>Attrition</p> <p>NR</p> <p>Excluded from analysis (reason)</p> <p>1/3 (safety, not treated)</p>			

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	Intervention(s) Bevacizumab 15 mg/kg, ixabepilone 30 mg/m ² 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/m ² 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)	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	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

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
	<p>protein/creatinine ratio of <1.0; absence of non-healing wounds or hemoptysis.</p> <p>Exclusion criteria</p> <p>Prior systemic therapy for advanced</p> <p>Disease</p> <p>Significant cardiovascular disease (including unstable angina, myocardial infarction, or stroke within 6 months of enrolment)</p> <p>Uncontrolled hypertension</p> <p>Untreated central nervous system (CNS) metastases (patients with CNS metastases treated with radiation or surgery were eligible provided there</p>	<p>were 4</p> <p>Included/randomised patients</p> <p>NRAnalysed patients</p> <p>40/42</p> <p>Attrition</p> <p>NR</p> <p>Excluded from analysis (reason)</p> <p>4/4 (not evaluable)</p>		<p>reaction (%): 5/NR</p> <p>Cough (%): 10/NR</p> <p>Hemorrhagic events (all) (%): 3/NR</p> <p>Vomiting (%): 10/NR</p>	<p>outcome assessment:</p> <p>-</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting:</p> <p>+</p> <p>Other source of bias:</p> <p>- (no to control for confounding, statistical significance of results not reported)</p>

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
	<p>was no evidence of CNS disease progression following treatment)</p> <p>Sufficient recovery from any major surgery</p> <p><i>Patient characteristics</i></p> <p>Age (median): 63/63</p> <p>Male (%): 48/57</p> <p><i>Performance status</i></p> <p>0 (%): 65/33</p> <p>1 (%): 35/67</p> <p><i>Smoking status</i></p> <p>Current smoker (%): 18/36</p> <p>Former smoker (%): 66/62</p> <p>Never smoker (%): 18/2</p> <p><i>Histology</i></p> <p>Adenocarcinoma (%): 80/31</p>				

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
	<p>Squamous (%): 3/47</p> <p>Large cell (%): 5/7</p> <p>Not otherwise specified (%): 12/14</p> <p><i>Stage</i></p> <p>IIIB (%): 15/24</p> <p>IV (%): 67/69</p> <p>Recurrent (%): 18/7</p> <p>Race</p> <p>Caucasian (%): 93/100</p> <p>African-American (%): 7/0</p>				
<p>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.</p>	<p>Region</p> <p>Inclusion criteria</p> <p>Aged 65 years or older</p> <p>Stage IIIB or IV non-squamous cell NSCLC (diagnosed</p>	<p>First-line bevacizumab-carboplatin-paclitaxel</p> <p>Diagnoses in 2006-2007</p> <p>Control</p>	<p>Overall survival (multivariable-36 month, adjusted model)</p> <p>NR/NR; HR = 0.99; 0.88 - 1.14</p> <p>NR/NR; HR = 1.06; 0.94 - 1.20</p>	<p>NR</p>	<p>Study type</p> <p>Register-based cohort study</p> <p>Level of evidence</p> <p>2c</p>

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
	<p>between 2002 and 2007)</p> <p>First-line chemotherapy with bevacizumabcarboplatin-paclitaxel or carboplatinpaclitaxel within 4 months of diagnosis</p> <p>Exclusion criteria</p> <p>Other primary cancers diagnosed either before or after NSCLC</p> <p>Death within 30 days of NSCLC diagnosis</p> <p>Patient characteristics</p> <p>Age 65-69 at diagnosis (%): 39.9/33.5/34.2</p> <p>Age 70-74 at diagnosis (%): 26.4/30.1/32.3</p> <p>Age 75-79 at diagnosis</p>	<p>First-line carboplatin-paclitaxel</p> <p>Diagnoses in 2006-2007</p> <p>First-line carboplatin-paclitaxel</p> <p>Diagnoses in 2002-2005</p> <p>Included/randomised patients</p> <p>318/1844/2666</p> <p>Analysed patients</p> <p>318/1182/2664</p> <p>Attrition</p> <p>NA</p> <p>Excluded from analysis (reason)</p> <p>0/2/2 (NR)</p>	<p>Median Survival (months)</p> <p>9.7/8.9/8.0; NA; NR</p> <p>Survival (1 year)</p> <p>39.6%/40.1%/35.6%; NR; ns (CIs overlap)</p>		<p>Risk of bias</p> <p>Generation of allocation sequence:</p> <p>-</p> <p>Allocation concealment:</p> <p>-</p> <p>Blinding of participants and personal:</p> <p>-</p> <p>Blinding of outcome assessment:</p> <p>-</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting:</p>

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
	<p>(%): 24.5/23.5/23.0</p> <p>Age ≥ 80 at diagnosis (%): 9.1/12.9/10.5</p> <p>Male (%): 50.9/55.2/52.9</p> <p><i>AJCC stage at diagnosis</i></p> <p>IIIB (%): 17.6/29.1/30.6</p> <p>IV (%): 82.4/70.9/69.4</p> <p>Race/ethnicity</p> <p>Non-Hispanic white (%): 87.7/83.0/85.1</p> <p>Non-Hispanic black (%): 4.7/8.3/6.3</p> <p>Other (%): 7.5/8.7/8.6</p> <p><i>Modified Charlson comorbidity score</i></p> <p>0 (%): 66.0/56.3/62.3</p> <p>1 (%): 27.7/27.4/24.7</p> <p>≥ 2 (%): 6.3/16.3/13.0</p> <p><i>Level of differentiation</i></p>				<p>+</p> <p>Other source of bias: +</p>

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
	<p>(tumor grade)</p> <p>Well/moderately (%): 15.7/10.8/10.4</p> <p>Poorly/undifferentiated (%): 26.7/29.2/30.8</p> <p>Unknown (%): 57.5/60.0/58.8</p>				

+ 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
<p>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.</p>	<p><i>Inclusion criteria</i> 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 <i>Un-confounded trials</i>, i.e. treatment arms that differed only with regard to bevacizumab administration <i>Exclusion criteria</i> - <i>Search period</i> Date of search 24 April 2009</p>	<p><i>Intervention(s)</i> Bevacizumab 7.5 mg/kg + carboplatin and paclitaxel (or + cisplatin and gemcitabine) Bevacizumab 15 mg/kg + carboplatin and paclitaxel (or + cisplatin and gemcitabine)</p> <p><i>Control</i> Carboplatin and paclitaxel (or Cisplatin and gemcitabine and placebo (low or high dose))</p>	<p>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); I²=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); I²=36%; 6; 2573 <i>Toxicity</i> Proteinurea 2.4%/0.2%; HR=4.81 (2.28-10.1); I²=0%; 3; NR Hypertension 8.1%/1.3%; HR=3.69 (2.49-</p>	<p><i>Level of evidence</i> 1a <i>Methodological quality</i> 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: -</p>

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
			<p>5.47); I²=16%; 4; NR</p> <p>Thrombosis</p> <p>8.2%/7.4%; HR=1.03 (0.74-1.43); I²=36%; 4; NR</p> <p>Haemorrhagic events</p> <p>4.6%/1.4%; HR=2.67 (1.63-4.39); I²=0%; 4; NR</p> <p>Neuropathy</p> <p>4.6%/7.3%; HR=0.84 (0.57-1.23); I²=0%; 4; NR</p> <p>Neutropenia</p> <p>40.7%/28.4%; HR=1.53 (1.25-1.87); I²=0%; 4; NR</p> <p>Febrile neutropenia</p> <p>3.5%/2.1%; HR=1.72 (1.01-2.95); I²=0%; 3; NR</p> <p>Thrombocytopenia</p> <p>24.1%/21.5%; HR=1.17 (0.88-1.55); I²=0%; 3; NR</p> <p>Anemia</p> <p>11.5%/12.4%; HR=0.92 (0.64-1.33); I²=0%; 3; NR</p>	

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

Konsultationsfassung

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
<p>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.</p>	<p>Region NR</p> <p>Inclusion criteria Oligometastatic disease (<5 metastases) at diagnosis Receipt of a biologically equivalent dose of 60 Gy in 2-Gy fractions.</p> <p>Exclusion criteria Prior thoracic surgery or radiation therapy Prior or concurrent other malignancy</p> <p>Patient characteristics Age (median): 64 Female (%): 53</p>	<p><i>Brain</i> Whole-brain irradiation (30 Gy, %): 10 Stereotactic radiosurgery (12-20 Gy, %): 22 Surgery + whole-brain irradiation (%): 6</p> <p><i>Adrenal</i> Surgery (%): 1 EBRT (45 Gy, %): 1</p> <p><i>Bone</i> Surgery + EBRT (30 Gy, %): 1 EBRT (30-45 Gy, %): 5</p>	<p><i>Overall survival (median 35 months)</i> 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</p> <p><i>Disease free survival (median 35 months)</i> 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</p>	<p>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</p>	<p>Study type Registry based prospective cohort study</p> <p>Level of evidence 2c</p> <p>Risk of bias Generation of allocation sequence: - Allocation concealment: - Blinding of participants and personal: - Blinding of outcome assessment: ? Incomplete outcome data: ? Selective reporting: +</p>

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
	<p><i>Race</i></p> <p>White (%): 86</p> <p>African American (%): 12</p> <p>Asian (%): 2</p> <p><i>Smoking status</i></p> <p>Never (%): 5</p> <p>Former (%): 71</p> <p>Current (%): 24</p> <p>Cardiovascular disease history (%): 28</p> <p>Respiratory disease history (%): 23</p> <p><i>Karnofsky performance status</i></p> <p>≤80 (%): 77</p> <p>>80 (%): 23</p> <p><i>Primary tumor location</i></p> <p>Left lower lobe (%): 17</p> <p>Left upper lobe (%): 27</p> <p>Right lower lobe (%): 17</p>	<p><i>Lung</i></p> <p>EBRT (45-70 Gy, %): 13</p> <p>Stereotactic radiosurgery (50 Gy, %): 3</p> <p><i>Liver</i></p> <p>Radiofrequency ablation (%): 1</p> <p><i>Skin</i></p> <p>Surgery (%): 1</p> <p>EBRT (45 Gy, %): 1</p> <p><i>Axillary nodes or subcutaneous nodules</i></p> <p>EBRT (63-70 Gy, %): 8</p> <p><i>Concurrent chemoradiation</i></p> <p>No (%): 33</p>			<p>Other source of bias: +</p>

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
	<p>Right middle lobe (%): 5 Right upper lobe (%): 34 <i>Metastasis location</i> 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 <i>T category</i></p>	<p>Yes (%): 67 <i>Radiation technique</i> 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</p>			

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
	<p>T0 (%): 3</p> <p>T1 (%): 21</p> <p>T2 (%): 32</p> <p>T3 (%): 19</p> <p>T4 (%): 26</p> <p><i>N category</i></p> <p>N0 (%): 13</p> <p>N1 (%): 5</p> <p>N2 (%): 48</p> <p>N3 (%): 33</p> <p>Gross tumor volume (cm³, median): 124</p> <p><i>No. of metastases</i></p> <p>1 (%): 78</p> <p>2 (%): 13</p> <p>3 (%): 8</p> <p>4 (%): 1</p>	<p>64 (OMD treatment)/14(no OMD treatment)</p> <p>Attrition</p> <p>NR</p> <p>Excluded from analysis (reason)</p> <p>NR</p>			

+ 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 µmol/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 etoposide 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 cyclophosphamide, doxorubicin, and vincristine (CAV). In the EV group, each cycle was administered over 3 days, day 1, etoposide 120 mg/m ² by infusion over	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

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
	<p>Exclusion criteria</p> <p>-</p> <p>Patient characteristics</p> <p>Age (median): 67/68</p> <p>Male (%): 63/61</p> <p><i>Extent of disease</i></p> <p>Limited (%): 42/45</p> <p>Extensive (%): 58/55</p> <p>Unknown (%): 3/0</p> <p>PS</p> <p>II (%): 62/63</p> <p>III(%): 35/36</p> <p>IV(%): 4/2</p> <p>Unknown (%): 2/0</p>	<p>30 min, 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 day</p> <p>cyclophosphamide 750 mg/m², doxorubicin 40 mg/m², and vincristine 1.3 mg/m²(maximum dose 2.0 mg)</p> <p>Included/randomised patients 171/168</p> <p>Analysed patients 110/101 (per protocol)</p>		<p>Thrombocytopenia (%): 3/2</p>	<p>assessment: ?</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
		120/121 (safety) 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	Intervention(s) 1250 mg/m ² 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	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-	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

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
	<p>at least 4 weeks before chemotherapy and to have a life expectancy of at least 12 weeks</p> <p>Measurable or assessable disease in nonirradiated fields, unless subsequent disease was documented</p> <p>Patients with stable brain metastases were eligible</p> <p>Patients must have had adequate bone marrow reserve, kidney, and liver functions</p> <p>Exclusion criteria</p> <p>Active infection or a history of other neoplasms (except for basal cell carcinoma of</p>	<p>Same gemcitabine regimen plus carboplatin area under the curve of 3 (Calvert formula) as a 1-hour infusion on days 1 and 14</p> <p>Repeated every 28 days for two cycles; if patients had partial response, stable disease, or clinical benefit, they received two more cycles.</p> <p>Included/randomised patients</p> <p>47/43</p> <p>Analysed patients</p> <p>Attrition</p> <p>NR</p> <p>Excluded from analysis</p>	<p>free survival (months) 2.98/4.07; NA; 0.36</p> <p>Improved general feeling (measure NR) 52%/41%; NR; 0.53</p> <p>Improved (Lung Cancer Symptom Scale) pain 43%/50%; NR; 1.0</p> <p>Improved cough (Lung Cancer Symptom Scale) 69%/71%; NR; 1.0</p> <p>Improved fatigue 58%/50%; NR; 1.0</p>		<p>concealment: ?</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome assessment: ?</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	<p>the skin or <i>in situ</i> carcinoma of the cervix)</p> <p>Active cardiac disease or preexisting grade 3 or 4 motor or sensory neuropathy</p> <p>Women of childbearing age were required to have a negative pregnancy test within 48 hours of study enrolment</p> <p>Patient characteristics</p> <p>Age (median): 73/70.5</p> <p>Male (%): 83/72</p> <p><i>Stage</i></p> <p>IIIb-IIIb (%): 36/26</p> <p>IV (%): 64/74</p> <p><i>Prior radiotherapy</i></p> <p>Yes (%): 23/28</p>	<p>(reason) 3/4 (NR)</p>	<p>Improved dyspnea (Lung Cancer Symptom Scale) 75%/33%; NR; 0.24</p> <p>Improved anorexia (Lung Cancer Symptom Scale) 67%/100%; NR; 0.46</p> <p>Improved weight loss (Lung Cancer Symptom Scale) 71%/25%; NR; 0.24</p>		

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
	<p><i>Histology</i></p> <p>Squamous cell (%): 28/30</p> <p>Adenocarcinoma (%): 57/56</p> <p>Undifferentiated (%): 9/9</p> <p>Unclassified (%): -/2</p> <p>Unknown (%): 6/2</p> <p><i>Metastatic sites</i></p> <p>Lymph nodes (%): 51/63</p> <p>Pleural effusion (%): 45/26</p> <p>Liver (%): 19/23</p> <p>Bones (%): 34/33</p> <p>Brain (%): 13/9</p> <p>Adrenal glands (%): 4/12</p> <p><i>Number of metastatic sites</i></p> <p>1 (%): 38/35</p>				

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 (%): 32/42 ≥ 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;26(6):863-9	<p>Region NR</p> <p>Inclusion criteria</p> <p>Cytologic or histologic confirmation of stage IIIIB (malignant effusion) and IV NSCLC</p> <p>Measurable or assessable disease</p> <p>PS of 2 by Eastern Cooperative Oncology Group criteria</p> <p>Prior radiation was allowed and toxicities had to be resolved</p>	<p>Intervention(s) Treatment with erlotinib 150 mg orally once daily until progression</p> <p>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.</p> <p>Patients who experienced progression or did not tolerate or refused</p>	<p>Objective response rate (time period NR) 4%/12%; NR; NR</p> <p>Median overall survival (months) 6.6/9.7; NA; ns</p> <p>Overall survival (time period NR) NR; HR = 0.58; 0.37 - 0.92</p> <p>Median progression-free survival</p>	<p>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</p>	<p>Study type RCT</p> <p>Level of evidence 2b</p> <p>Risk of bias</p> <p>Generation of allocation sequence: +</p> <p>Allocation concealment: +</p> <p>Blinding of participants and</p>

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
	<p>before study entry</p> <p>Brain metastases were eligible if neurologically stable and no longer receiving corticosteroids after appropriate therapy</p> <p>Adequate organ function was required</p> <p>Exclusion criteria</p> <p>Prior chemotherapy or prior EGFR inhibitor therapy</p> <p>Locally advanced disease amenable to combined-modality therapy</p> <p>Patients with gastrointestinal illness that may affect oral absorption, or any other</p>	<p>further chemotherapy were allowed to cross over to erlotinib</p> <p>Included/randomised patients 52/51</p> <p>Analysed patients 52/51</p> <p>Attrition 47/49</p> <p>Excluded from analysis (reason) 0/0</p>	<p>(months) 1.9/3.5; NA; ns</p> <p>Progression-free survival (time period NR) NR; HR = 0.67; 0.47 - 1.02</p> <p>Worsening of peripheral neuropathy (EORTC QLQ-LC13) (end of study) 59%/16%; NR; 0.003</p> <p>Worsening of alopecia (EORTC QLQ-LC13) (end of study) 85%/29%; NR; <0.001</p>	<p>Anemia (%): 4/20</p>	<p>personal: -</p> <p>Blinding of outcome assessment: -</p> <p>Incomplete outcome data: -</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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
	<p>serious medical condition that might impair their ability to receive protocol therapy</p> <p>Patients with concurrent active malignancies, except <i>in situ</i> carcinoma of the cervix and basal cell carcinoma of the skin</p> <p>Patient characteristics ≥ 70 years (%): 46/47 Male (%): 44/55</p> <p><i>Race</i> White (%): 67/65 African American (%): 23/20 Other (%): 10/15</p> <p><i>Extend of disease</i> Stage IIIB (%): 13/14</p>		<p>Worsening in chest pain (EORTC QLQ-LC13) (end of study) 15%/37%; NR; 0.004</p> <p>Worsening of hemoptysis (EORTC QLQ-LC13) (end of study) 0%/24%; NR; 0.078</p> <p>Worsening of pain in arm/shoulder (EORTC QLQ-LC13) (end of study) 38%/13%; NR; 0.024</p>		

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
	<p>Stage IV (%): 87/86</p> <p><i>Histology</i></p> <p>Adenocarcinoma, BAC (%): 17/6</p> <p>Adenocarcinoma, no BAC (%): 6/10</p> <p>Adenocarcinoma, BAC unknown (%): 27/NR</p> <p>Nonadenocarcinoma (%): 50/37</p> <p><i>Smoking history</i></p> <p>Never stopped (%): 12/8</p> <p>Stopped ≤ 1 year (%): 35/49</p> <p>Stopped > year (%): 54/43</p>				
Lilenbaum, R. Single-Agent Versus Combination Chemotherapy in	<p>Region</p> <p>NR</p>	<p>Intervention(s)</p> <p>Paclitaxel alone</p> <p>Paclitaxel was administered</p>	<p>Objective response rate (time period NR)</p> <p>10%/24%; NR; ns</p>	<p>Toxicities comparable to general study population (according authors)</p> <p>Toxicities of general study</p>	<p>Study type</p> <p>RCT</p> <p>Level of evidence</p>

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
Advanced Non-Small-Cell Lung Cancer: The Cancer and Leukemia Group B (study 9730). J Clin Oncol. 2005 Jan 1;23(1):190-6. (PS2 subgroup)	<p>Inclusion criteria</p> <p>Cytological or histological confirmation of stage IIIB (malignant effusion) and IV NSCLC</p> <p>At least 18 years of age</p> <p>Measurable or evaluable disease</p> <p>Adequate hematological, hepatic, and renal function</p> <p>Performance status (PS) of 2 as assessed by standard CALGB criteria</p> <p>Prior radiation therapy was allowed if it did not encompass the index lesion(s) and was completed 2 or more weeks before protocol enrolment</p>	<p>intravenously over 3 hours at a dose of 225 mg/m², on day 1</p> <p>Repeated every 3 weeks for a maximum of six cycles</p> <p>Patients who developed febrile neutropenia or grade 4 neutropenia lasting more than 5 days received filgrastim in all subsequent cycles</p> <p>Control</p> <p>Paclitaxel in combination with carboplatin</p> <p>Paclitaxel was administered intravenously over 3 hours at a dose of 225 mg/m², on day 1</p> <p>Carboplatin was administered</p>	<p>Median overall Survival (months) 2.4/4.7; NA; 0.016</p> <p>Overall survival (1 year) 10%/18%; HR = 0.60; 0.40 – 0.91</p> <p>Test of interaction for survival PS0-1 vs. PS2; p = 0.019</p>	<p>population</p> <p>Absolute neutrophil count (%): 32/62</p> <p>Thrombocytopenia (%): 1/12</p> <p>Anemia (%): 3/12</p> <p>Infection (%): 5/8</p> <p>Nausea/vomiting (%): 4/9</p> <p>Diarrhea (%): 1/4</p> <p>Neuropathy (%): 14/15</p> <p>Renal toxicity (%): 0/0</p> <p>Cardiac toxicity (%): 0/0</p> <p>Hyperglycemia (%): 18/18</p> <p>Fatigue (%): 5/7</p> <p>Any grade 3-4 (%): 73/90</p> <p>Grade 5 (death) (%): 1/1</p>	<p>2b</p> <p>Risk of bias</p> <p>Generation of allocation sequence: +</p> <p>Allocation concealment: +</p> <p>Blinding of participants and personal: ?</p> <p>Blinding of outcome assessment: ?</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting:</p>

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
	<p>Exclusion criteria</p> <p>Prior chemotherapy</p> <p>Locally advanced NSCLC</p> <p>Known brain metastases</p> <p>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</p> <p>HIV positive</p> <p>Patient characteristics</p> <p><i>For general population (NR for subgroup)</i></p>	<p>intravenously over 30 minutes, after paclitaxel, at a dose calculated to produce an area under the concentration-time curve (AUC) of 6.0 mg/mL/min</p> <p>Repeated every 3 weeks for a maximum of six cycles</p> <p>Patients who developed febrile neutropenia or grade 4 neutropenia lasting more than 5 days received filgrastim in all subsequent cycles</p> <p>Second-line chemotherapy was given at the physician's discretion, and the regimens used were documented as part of the follow-up</p>			<p>+</p> <p>Other source of bias:</p> <ul style="list-style-type: none"> - (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
	<p>Age (median): 63/64</p> <p>Male (%): 69/68</p> <p><i>Disease stage</i></p> <p>IIIB: 17/21</p> <p>IV/recurrent: 83/87</p> <p><i>Performance status</i></p> <p>0-1 (%): 82/83</p> <p>2 (%): 18/17</p> <p><i>Histologic type</i></p> <p>Adenocarcinoma: 54/51</p> <p>Others: 46/45</p>	<p>Included/randomised patients</p> <p>NR/NR</p> <p>Analysed patients</p> <p>50/49</p> <p>Attrition</p> <p>NR/NR</p> <p>Excluded from analysis (reason)</p> <p>NR/NR</p>			
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. J Clin Oncol 2000; 18(15): 3131-3137.	<p>Region</p> <p>45 European centers</p> <p>Inclusion criteria</p> <p>Age ≤ 75 years</p> <p>Histologically or cytologically proven</p>	<p>Intervention(s)</p> <p>1) Vinorelbine alone at a dose of 30 mg/m² weekly</p> <p>2) Vinorelbine 30 mg/m² plus cisplatin 120 mg/m² on days 1 and 29 and then every 6 weeks</p>	<p>Median overall survival (months)</p> <p>17/18/18; NA; ns</p> <p>Overall Survival (1 year)</p> <p>15%/17%/13%; NR;</p>	<p>NR for subgroup</p>	<p>Study type RCT</p> <p>Level of evidence 2b</p> <p>Risk of bias</p>

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
Cell Lung Cancer. Oncologist 2001;6 Suppl 1:8-11. (PS2 subgroup)	<p>squamous cell carcinoma, adenocarcinoma, or large-cell carcinoma of the lung</p> <p>WHO performance status (PS) 2 or 3</p> <p>Inoperability at the time of trial entry, ie, stage III or IV</p> <p>Exclusion criteria</p> <p>Prior malignancy except adequately controlled basal cell carcinoma of the skin</p> <p>Prior chemotherapy</p> <p>Symptomatic brain metastases</p> <p>Preexisting hearing loss</p> <p>Uncontrolled infection</p>	<p>Control</p> <p>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</p> <p>Included/randomised patients</p> <p>NR for subgroup Analysed patients</p> <p>NR for subgroup Attrition</p> <p>NR</p> <p>Excluded from analysis (reason)</p> <p>NR</p>	<p>ns</p> <p>Test of interaction for survival</p> <p>PS0-1 vs. PS2 (platinum containing regimes); ns</p>		<p>Generation of allocation sequence: +</p> <p>Allocation concealment: +</p> <p>Blinding of participants and personal: ?</p> <p>Blinding of outcome assessment: +</p> <p>Incomplete outcome data: ?</p> <p>Selective reporting: +</p> <p>Other source of bias: - (subgroup analysis)</p>

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
	<p>Normal blood count</p> <p>Normal liver and renal function</p> <p>at least one unirradiated measurable lesion</p> <p>Patient characteristics</p> <p>PS2: 46/42/33</p> <p>PS3: 1/0/4</p> <p>No others reported for subgroup</p>				
<p>Reynolds, C. Randomized phase III trial of gemcitabine-based chemotherapy with <i>in situ</i> RRM1 and ERCC1 protein levels for response prediction in non-small-cell lung cancer. J Clin Oncol. 2009</p>	<p>Region NR</p> <p>Inclusion criteria Histologically or cytologically newly diagnosed NSCLC Stage IIIB or stage IV</p>	<p>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</p>	<p>Response rate (time period NR) 21.1%/6.3%; NR; 0.01 (but CIs overlap)</p> <p>Median overall survival (months) 6.7/5.1; NA; 0.24</p>	<p>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</p>	<p>Study type RCT</p> <p>Level of evidence 2b</p> <p>Risk of bias Generation of allocation</p>

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;27(34):5808-15.	<p>PS2</p> <p>Measurable disease by Response Evaluation Criteria in Solid Tumors Group</p> <p>Age ≥ 18 years</p> <p>Adequate organ function</p> <p>Exclusion criteria</p> <p>Prior chemotherapy</p> <p>Patient characteristics</p> <p>Age (median): 72.9/75.0</p> <p>Male (%): 55.3/56.5</p> <p><i>Stage</i></p> <p>IIIB (%): 15.3/5.9</p> <p>IV (%): 83.4/94.1</p> <p>Unknown (%): 2.4 / 0</p>	<p>Control</p> <p>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 evidence for disease progression or intolerable toxicity</p> <p>Included/randomised patients</p> <p>85/85</p> <p>Analysed patients</p> <p>85/85</p> <p>Attrition</p> <p>18/16</p> <p>Excluded from analysis (reason)</p>	<p>Overall survival (1 year) 31.3%/21.2%; NR; NR</p> <p>Median progression-free survival (months) 3.8/2.7; NR; 0.14</p>	<p>Anorexia (%): 15.2/19.8</p> <p>Nausea (%): 11.4/12.3</p> <p>Pneumonia (%): 6.3/11.1</p> <p>Dehydration (%): 6.3/9.9</p> <p>Diarrhea (%): 3.8/8.6</p> <p>Vomiting (%): 5.1/6.2</p> <p>Pleural effusion (%): 6.3/3.7</p> <p>Dizziness (%): 6.3/2.5</p> <p>Rash (%): 3.8/1.2</p> <p>Chest pain (%): 2.5/4.9</p> <p>Alopecia (%): 2.5/0</p>	<p>sequence: ?</p> <p>Allocation concealment: ?</p> <p>Blinding of participants and personal: ?</p> <p>Blinding of outcome assessment: +</p> <p>Incomplete outcome data: +</p> <p>Selective reporting: +</p> <p>Other source of bias: - results for response rate inconsistently</p>

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
	<p>Histology</p> <p>Adenocarcinoma (%): 62.3/52.9</p> <p>Squamous carcinoma (%): 16.5/25.9</p> <p>Other (%): 21.2/21.2</p>	0/0			
<p>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;31(23):2849-53</p>	<p>Region</p> <p>Eight centers in Brazil and one in the United States</p> <p>Inclusion criteria</p> <p>Cytologic or histologic confirmation of stages IIIB (malignant effusion) and IV NSCLC</p> <p>ECOG PS of 2</p> <p>Toxicities had to be resolved before study entry if there was prior</p>	<p>Intervention(s)</p> <p>Pemetrexed 500 mg/m²</p> <p>All patients received premedications with dexamethasone, vitamin B12, and folic acid according to the pemetrexed label</p> <p>Control</p> <p>Combination of carboplatin at an area under the curve of 5 and pemetrexed 500 mg/m², both administered</p>	<p>Objective response rate (time period NR)</p> <p>6.9%/18.4%; NR; NR</p> <p>Median overall survival (months)</p> <p>5.3/9.3; NA; 0.001</p> <p>Overall survival (36 month)</p> <p>NR; HR=0.62; 0.46 - 0.83</p>	<p>Anemia (%): 3.9/11.7</p> <p>Thrombocytopenia (%): 0.0/1.0</p> <p>Neutropenia (%): 1.0/6.8</p> <p>Febrile neutropenia (%): 2.9/1.0</p> <p>Nausea/emasis (%): 1.0/4.9</p> <p>Diarrhea (%): 2.0/1.0</p> <p>Dyspnea (%): 10.8/5.8</p> <p>Grade 5 event (%): 0.0/3.9</p>	<p>Study type</p> <p>2b</p> <p>Level of evidence</p> <p>RCT</p> <p>Risk of bias</p> <p>Generation of allocation sequence:</p> <p>+</p> <p>Allocation concealment:</p> <p>+</p>

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
	<p>irradiation Neurologically stable condition and no longer receiving of corticosteroids after appropriate therapy if patients had brain metastases Adequate organ function, including glomerular filtration rate ≥ 45 mL/min</p> <p>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</p>	<p>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 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</p>	<p>Median progression-free survival (months) 2.8/5.8; NA; 0.35 – 0.63</p> <p>Progression-free survival (1 year) 2%/17%; NR; NR</p>		<p>Blinding of participants and personal: ? Blinding of outcome assessment: + Incomplete outcome data: - Selective reporting: + Other source of bias: +</p>

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
	<p>combined-modality therapy</p> <p>Concurrent active malignancies, except <i>in situ</i> carcinoma of the cervix and basal cell carcinoma of the skin</p> <p>Patient characteristics</p> <p>Age (median): 65/65</p> <p>Male (%): 58.8/63.1</p> <p>Disease stage</p> <p>IIIB (%): 4.9/5.8</p> <p>IV (%): 95.1/94.2</p> <p>Weight loss ≥ 5% (%): 53.9/58.3</p> <p>Histology</p> <p>Adenocarcinoma (%): 80.4/82.5</p> <p>Squamous cell (%):</p>	<p>Included/randomised patients 109/108</p> <p>Analysed patients 102/103</p> <p>Attrition 33/19</p> <p>Excluded from analysis (reason) 7/5 (not received any treatment)</p>			

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
	<p>10.8/2.9</p> <p>Unknown (%): 4.9/4.9</p> <p>Smoking status</p> <p>Current (%): 10.8/17.3</p> <p>Former (%): 66.7/60.2</p> <p>Never (%): 22.5/22.5</p> <p>Comorbidities</p> <p>Hypertension (%): 45.1/44.7</p> <p>COPD (%): 17.6/11.7</p> <p>Diabetes mellitus (%): 7.8/12.6</p>				

+ 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
<p>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.</p>	<p><i>Inclusion criteria</i></p> <p>Randomized trial</p> <p>Evaluation of the administration of combination versus single-agent chemotherapy in untreated patients with advanced NSCLC and PS 2 (Eastern Cooperative Oncology Group scale)</p> <p>Trials dedicated to PS2 patients</p> <p>Trials performed a subset analysis according to PS</p> <p><i>Exclusion criteria</i></p> <p>Non-randomized trials</p> <p>Combination chemotherapy in both treatment arms</p>	<p><i>Intervention(s)</i></p> <p>Combination platinum-based chemotherapy</p> <p>Combination non-platinum-based chemotherapy</p> <p><i>Control</i></p> <p>Single-agent chemotherapy</p>	<p>Overall survival</p> <p>HR 0.71 (0.61 – 0.81); 2%; 8; 862</p> <p>HR 0.96 (0.80 – 1.15); 0%; 3; 252</p> <p>Progression-free survival</p> <p>1) HR 0.61 (0.45 – 0.84); NR; 4; 522</p> <p>Objective response rate</p> <p>OR 3.10 (1.85 – 5.21); NR; 6; 651</p> <p>OR 0.63 (0.23 – 1.72); NR; 2; 207</p> <p>Toxicity (grade II and IV)</p> <p>Hematologic anemia OR 3.12 (1.55 – 6.27); NR; 4; 519</p>	<p><i>Level of evidence</i></p> <p>1a</p> <p><i>Methodological quality</i></p> <p>A-priori design: +</p> <p>Two reviewers: ?</p> <p>Literature search: ?</p> <p>Status of publication: +</p> <p>List of studies: -</p> <p>Study characteristics: +</p> <p>Critical appraisal: -</p> <p>Conclusion: +</p> <p>Combining findings: +</p> <p>Publication bias:</p>

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
	<p>Trials that included patients with PS 3 or pretreated patients</p> <p><i>Search period</i> Last search was updated in July 2013 without year restriction</p>		<p>Trombocytopenia OR 12.81 (4.65 – 33.10); NR; 4; 519</p> <p>Neutropenia OR 7.91 (3.97 – 15.78); NR; 4; 519</p> <p>Non-hematologic febrile neutropenia OR 0.32 (0.05-2.06); NR; 3; 432</p> <p>Fatigue OR 0.75 (0.40-1.40); NR; 3; 349</p> <p>Nausea OR 1.21 (0.05-29.34); NR; 3; 432</p>	<p>-</p> <p>Conflict of interest: +</p>

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

Konsult

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-/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. <i>Cancer</i> , 2014. 00: p. 1-9.	<p>Region/Setting USA, single center, home based care</p> <p>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</p> <p>Exclusion criteria NR</p>	<p>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</p>	<p>Depression (Patient Reported Outcomes Measurement Information System, 8 weeks); $11.65/16.00$; SMD= -1.8; $<.0001$</p> <p>Anxiety (Patient Reported Outcomes Measurement Information System, 8 weeks); $12.35/14.84$; SMD= -1.3; $<.0001$</p>	<p>Study type RCT</p> <p>Level of evidence 2b</p> <p>Risk of bias</p> <p>Generation of allocation sequence: ?</p> <p>Allocation concealment: ?</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome assessment: ?</p> <p>Incomplete outcome data:</p>

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

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/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	<p>Length of marriage (mean, SD): 36.20, 8.70</p> <p><i>Type of lung cancer</i></p> <p>SCLC (%): 16</p> <p>NSCLC (%): 84</p> <p><i>Stage of cancer</i></p> <p>Stage 3 NSCLC (%): 26</p> <p>Stage 4 NSCLC (%): 58</p> <p>Extensive-stage SCLC (%): 16</p>	<p>Analysed patients 20/19 dyads</p> <p>Attrition 0/1</p> <p>Excluded from analysis (reason) NA</p>		
<p>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.</p>	<p>Region/Setting USA, two sites</p> <p>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 epidermal growth factor receptor</p>	<p>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</p>	<p>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</p>	<p>Study type RCT Level of evidence 2b Risk of bias Generation of allocation sequence: + Allocation concealment:</p>

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/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	<p>2 positive) cancer</p> <p>Exclusion criteria</p> <p>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</p> <p>Patient characteristics</p> <p>Age (mean, SD): 65.47, 10.3/65.2, 11.7</p> <p>Male (%): 62.1/58.2</p> <p><i>Marital status</i></p> <p>Never married (%): 6.9/8.2</p> <p>Married or living with partner (%): 73.1/67.2</p> <p>Divorced or separated (%): 11.0/13.4</p> <p>Widowed (%): 9.0/11.2</p> <p><i>Education</i></p> <p>< High school graduate (%): 11.7/14.9</p>	<p>support 3) symptom management, 4) advance care planning and unfinished business,</p> <p>Appendix listing supportive care resources</p> <p>Caregivers also were invited and encouraged to participate in these sessions</p> <p>Follow up until patient died or study ended</p> <p>Control</p> <p>All oncology and supportive services without restrictions including referral to the institutions' interdisciplinary palliative care service.</p> <p>Included/randomised patients</p> <p>161/161</p> <p>Analysed patients</p>	<p>Depressed mood (Center for Epidemiological Studies Depression Scale, 13 month); 78/73; MD= -2.7; 0.03</p> <p>Median survival (months, median follow-up 10.7); 14/8.5; NR; NR</p> <p>Survival (median follow-up 10.7); 30.4/26.1; NR; 0.14</p>	<p>?</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome assessment: ?</p> <p>Incomplete outcome data: +</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	<p>High school graduate (%): 57.2/55.2</p> <p>College graduate (%): 29.7/28.4</p> <p>Missing (%): 1.4/1.5</p> <p><i>Race (no Hispanic or black)</i></p> <p>White (%): 98.6/98.5</p> <p>Other (%): 0.7/0.7</p> <p>Missing (%): 0.7/0.7</p> <p><i>Religion</i></p> <p>Protestant (%): 46.9/44.8</p> <p>Catholic (%): 30.3/31.3</p> <p>Jewish (%): 2.1/0.7</p> <p>Other (%): 17.2/21.6</p> <p>Missing (%): 3.4/1.5</p> <p><i>Work status</i></p> <p>Employed (%): 20.0/16.4</p> <p>Retired (%): 51.7/52.2</p> <p>Not employed (%): 26.2/30.6</p> <p>Missing (%): 2.1/0.7</p>	<p>145/134</p> <p>Attrition</p> <p>16/9</p> <p>Excluded from analysis (reason)</p> <p>16/ 27 (not received intervention)</p>		

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

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/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	<p>Referral to hospice (%): 2.8/1.5</p> <p>Referral to palliative care (%): 23.4/29.1</p> <p><i>Resource use in prior 3 months (mean)</i></p> <p>Hospital days: 2.6/2.8</p> <p>Intensive care unit days: 0.03/0.05</p> <p>Emergency department visits: 0.28/0.38</p>			
<p>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. <i>J Clin Oncol</i>, 2012. 30(4): p. 394-400.</p>	<p>Region/Setting</p> <p>USA, cancer center</p> <p>Inclusion criteria</p> <p>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)</p> <p>Exclusion criteria</p> <p>NR</p>	<p>Intervention(s)</p> <p>Adapted guidelines from the National Consensus Project for Quality Palliative Care</p> <p>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</p>	<p>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)</p> <p>Median time to switch from first to second line chemotherapy (18 months); 7.4/7.5; NA; 0.79</p> <p>Median time to switch</p>	<p>Study type</p> <p>RCT</p> <p>Level of evidence</p> <p>2b</p> <p>Risk of bias</p> <p>Generation of allocation sequence:</p> <p>?</p> <p>Allocation concealment:</p> <p>?</p> <p>Blinding of participants and personal:</p>

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/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	<p>Patient characteristics</p> <p>Age (mean, SD): 64.98, 9.73/64.87, 9.41</p> <p>Female (%): 54.5/48.6</p> <p><i>Race</i></p> <p>White (%): 100.0/94.6</p> <p>Black (%): 0.0/4.0</p> <p>Asian (%): 0.0/1.4</p> <p><i>Ethnicity</i></p> <p>Hispanic/Latino (%): 1.3/1.4</p> <p><i>Marital status</i></p> <p>Married (%): 62.3/60.8</p> <p>Single (%): 11.7/12.2</p> <p>Divorced/separated (%): 15.6/16.2</p> <p>Widowed (%): 10.4/10.8</p> <p><i>ECOG PS</i></p> <p>0 (%): 33.8/40.5</p> <p>1 (%): 59.7/47.3</p> <p>2 (%): 6.5/12.2</p>	<p>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</p> <p>Control</p> <p>Patients met with the palliative care service on request from the patient, family or oncologist</p> <p>Included/randomised patients 77/74</p> <p>Analysed patients 77/74</p> <p>Attrition 2/2</p> <p>Excluded from analysis (reason) NA</p>	<p>from second to third chemotherapy (18 months); 5.0/5.3; NA; 0.53</p>	<p>- Blinding of outcome assessment: ?</p> <p>Incomplete outcome data: + Selective reporting: + Other source of bias: +</p>

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/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	<p><i>Initial anticancer therapy</i></p> <p>Platinum-based combined chemotherapy (%): 45.5/47.3</p> <p>Single agent (%): 11.7/4.1</p> <p>Oral EGFR-TKI (%): 7.8/8.1</p> <p>Radiation (%): 35.1/35.1</p> <p>Combined chemoradiotherapy (%): 0.0/4.1</p> <p>No treatment (%): 0.0/1.4</p>			
<p>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.</p> <p>Pirl, W.F., et al., Depression and survival in metastatic non-</p>	<p>Region/Setting</p> <p>USA, single center</p> <p>Inclusion criteria</p> <p>Confirmed metastatic NSCLC, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2</p> <p>Service were not eligible to participate in the study.</p> <p>77 to EPC integrated with standard care and 74 to standard care alone.</p>	<p>Intervention(s)</p> <p>Early Palliative Care</p> <p>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.</p> <p>Following general guidelines for the ambulatory palliative care visits, adapted from the National consensus Project for Quality Palliative Care.</p>	<p>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)</p> <p>Quality of life (Trial outcome index (FACT-L), 12 weeks); 59.0/53.0, adjusted MD= - 5.2; 1.6 - 8.9 (adjusted for</p>	<p>Study type RCT</p> <p>Level of evidence 2b</p> <p>Risk of bias</p> <p>Generation of allocation sequence: ?</p> <p>Allocation concealment:</p>

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/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
small-cell lung cancer: effects of early palliative care. J Clin Oncol, 2012. 30(12): p. 1310-5.	<p>Exclusion criteria Patients who were already receiving care from the palliative care</p> <p>Patient characteristics Age (mean, SD): 64.98, 9.73/64.87, 9.41 Female (%): 55/49 <i>Race</i> White (%): 77/95 Black (%): 0/4 Asian (%): 0/1 Hispanic or Latino ethnic group (%): 1/1 <i>Marital status</i> Married (%): 62/61 Single (%): 12/12 Divorced or separated (%): 12/12 Widowed (%): 10/11 <i>ECOG performance status</i></p>	<p>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</p>	<p>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 Unplanned contact (Mental Health visits, 12 weeks);</p>	<p>?</p> <p>Blinding of participants and personal: -</p> <p>Blinding of outcome assessment: ?</p> <p>Incomplete outcome data: +</p> <p>Selective reporting: +</p> <p>Other source of bias: +</p>

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/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of evidence and risk of bias
	<p>0 (%): 34/41 1 (%): 60/47 2 (%): 6/12 Presence of brain metastases (%): 31/26</p> <p><i>Initial anticancer therapy</i></p> <p>Platinum-based combination chemotherapy (%): 45/47</p> <p>Single agent (%): 12/4</p> <p>Oral EGFR tyrosine kinase inhibitor (%): 6/6</p> <p>Radiotherapy (%): 35/35</p> <p>Chemoradiotherapy (%): 0/4</p> <p>No chemotherapy (%): 0/1</p> <p>Receipt of initial chemotherapy as part of a clinical trial (%): 21/27</p> <p>Never smoked or smoked ≤10 packs/year (%): 24/22</p> <p><i>Assessment of mood symptoms</i></p> <p>Anxiety subscale (HADS, %): 36/33</p> <p>Depression subscale (HADS, %): 22/25</p>		25%/35%; NR; 0.16	

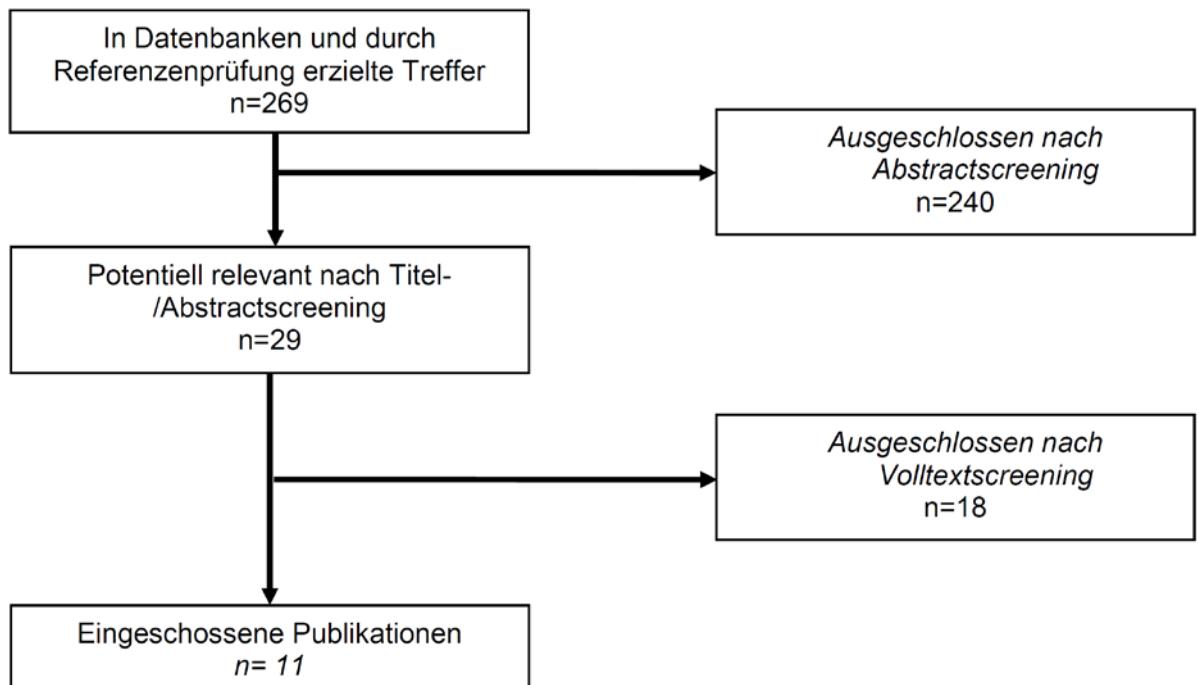
Study/Reference	Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population	Intervention(s), control and patient flow (IG/CG)	Outcomes (IG/CG; relative effect measure or mean difference; 95% CI or p; primary outcome marked bold)	Study type, level of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

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 Maintenance Palcetb-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, Qualitätsindikatoren-datenbank 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>

12.4.3. Literaturdatenbanken

- 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.cihi.conferences.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/#.UIJ9iW25OH4
- 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.ncbi.nlm.nih.gov/pmc/articles/>
- 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/ergebnisse/leistungsbereiche/index.html	0
	QISA - Qualitätsindikatorensystem für die ambulante http://www.aok-gesundheitspartner.de/bund/qisa/themen/index.html	0
BQS-Institut	Qualitätsindikatordatenbank über http://www.bqs-qualitaetsindikatoren.de/	0
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

12.5.3. Homepages von Leitlinienorganisationen

Institution	Quelle	Treffer
d		
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.cihi.conferences.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/#.UIJ9iW25OH4	3
Healthcare Improvement	http://www.healthcareimprovementscotland.org/our_work/cancer_care_improvement/cancer_qpis.aspx	13

12.5.3. Homepages von Leitlinienorganisationen

Institution	Quelle	Treffer
Scotland		
JCAHO (Joint Commission on Accrediation of Healthcare Organizations)	http://www.jointcommission.org/accountability_measures.aspx	0
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 (with homogeneity*) 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 a single 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 (with homogeneity*) 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 (with homogeneity*) 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 Incorporating clinically 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 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 <i>Assessments should be made for each main outcome (or class of outcomes)</i>	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 <i>Assessments should be made for each main outcome (or class of outcomes)</i>	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†	<p>a. Adequate participation in the study by eligible persons</p> <p>b. Description of the source population or population of interest</p> <p>c. Description of the baseline study sample</p> <p>d. Adequate description of the sampling frame and recruitment</p> <p>e. Adequate description of the period and place of recruitment</p> <p>f. Adequate description of inclusion and exclusion criteria</p>	<p>a. Adequate response rate for study participants</p> <p>b. Description of attempts to collect information on participants who dropped out</p> <p>c. Reasons for loss to follow-up are provided</p> <p>d. Adequate description of participants lost to follow-up</p> <p>e. There are no important differences between participants who completed the study and those who did not</p>	<p>a. A clear definition or description of the PF is provided</p> <p>b. Method of PF measurement is adequately valid and reliable</p> <p>c. Continuous variables are reported or appropriate cut points are used</p> <p>d. The method and setting of measurement of PF is the same for all study participants</p> <p>e. Adequate proportion of the study sample has complete data for the PF</p> <p>f. Appropriate methods of imputation are used for missing PF data</p>	<p>a. A clear definition of the outcome is provided</p> <p>b. Method of outcome measurement used is adequately valid and reliable</p> <p>c. The method and setting of outcome measurement is the same for all study participants</p>
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

12.5.3. Homepages von Leitlinienorganisationen

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. | <input type="checkbox"/> Yes
<input type="checkbox"/> No
<input type="checkbox"/> Can’t answer
<input type="checkbox"/> 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. | <input type="checkbox"/> Yes
<input type="checkbox"/> No
<input type="checkbox"/> Can’t answer
<input type="checkbox"/> 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. | <input type="checkbox"/> Yes
<input type="checkbox"/> No
<input type="checkbox"/> Can’t answer
<input type="checkbox"/> 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 | <input type="checkbox"/> Yes
<input type="checkbox"/> No
<input type="checkbox"/> Can’t answer
<input type="checkbox"/> Not applicable |
| 5. Was a list of studies (included and excluded) provided?
A list of included and excluded studies should be provided. | <input type="checkbox"/> Yes
<input type="checkbox"/> No
<input type="checkbox"/> Can’t answer
<input type="checkbox"/> 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
<p>1. Were the studies included in a systematic review conducted in the same setting or were the findings consistent across settings or time periods?</p> <p>2. Are there important differences in on-the-ground realities and constraints that might substantially alter the feasibility and acceptability of an option?</p> <ul style="list-style-type: none"> • 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? <p>3. Are there important differences in health system arrangements^b that may mean an option could not work in the same way?</p> <ul style="list-style-type: none"> • 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? <p>4. Are there important differences in the baseline conditions that might yield different absolute effects even if the relative effectiveness was the same?</p> <ul style="list-style-type: none"> • 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? <p>5. What insights can be drawn about options, implementation, and monitoring and evaluation?</p> <ul style="list-style-type: none"> • 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? 	<ul style="list-style-type: none"> • Descriptions of study settings (geographic, health system, etc) and time periods • 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 <ul style="list-style-type: none"> • Organizational context of the interventions • Factors affecting implementation that were identified in the included studies <ul style="list-style-type: none"> • Baseline prevalence in the study populations/settings • Descriptions of study populations • Any evidence of differential effects across sociodemographic or other groupings <ul style="list-style-type: none"> • 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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