Best first-line therapy for patients with advanced non-small cell lung cancer, performance status 2 without a targetable mutation or with an unknown mutation status

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View authors' declarations of interest

Abstract

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To identify the best first-line therapy for advanced lung cancer in patients with performance status 2 without a targetable mutation or with an unknown mutation status.

Background

Description of the condition

Lung cancer is the most frequent cause of cancer-related death worldwide, diagnosed in over 1.8 million patients annually (Ferlay 2015). Non-small cell lung cancer (NSCLC) accounts for 75% of all cases. At the time of diagnosis, most patients (> 50%) already have advanced disease and can be treated only with palliative systemic therapies or best supportive care (Driessen 2017). Unfortunately, despite these therapies, survival rates remain poor, with a median

survival of 8.8 months for patients with stage IV disease (Goldstraw 2016). Besides tumor stage, survival is determined by various patient- and tumor-related factors (eg, smoking status, age, gender, performance score [PS], histologic characteristics), of which PS is the most important prognostic factor (Sculier 2008).

The two most commonly used performance scores are the Karnofsky Index of Performance Status (KPS) and the Eastern Cooperative Oncology Group Scale of Performance Status (ECOG PS). These scores correlate strongly, although the ECOG PS shows better predictive performance - Buccheri 1996 - and has been adopted by the World Health Organization (WHO) (WHO 1979). The ECOG PS is a five-grade scale: 0 - fully active, able to carry on all pre-disease activities without restriction; 1 - restricted in physically strenuous activity but ambulatory and able to carry out work of light or sedentary nature; 2 - ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours; 3 - capable of only limited self-care, confined to bed or chair more than 50% of waking hours; 4 - completely disabled, cannot carry on any self-care, totally confined to bed or chair; and 5 - dead.

Evidence is clear that patients with a known targetable mutation (eg, epidermal growth factor receptor [EGFR] mutation, anaplastic lymphoma kinase [ALK] mutation) should be treated with targeted therapy, regardless of PS (Geffen 2013;Hanna 2017;Novello 2016). Patients with PS of 0 or 1 are usually treated with systemic therapies such as platinum-based doublet chemotherapy and/or checkpoint inhibitors, whereas patients with PS of 3 or 4 most often receive supportive care. However, treatment for patients with PS 2 without a targetable mutation remains unclear (Novello 2016). Historically, patients with a PS of 2 are frequently excluded from (important) clinical trials because of poorer outcomes and increased toxicity compared with patients with a PS of 0 or 1 (Borghaei 2015;Kogure 2018; Scagliotti 2008;Zinner 2016). As a consequence, trial populations often fail to represent the real-world population of patients with lung cancer, as 20% to 30% of all new patients with advanced NSCLC present with PS 2 (Kawachi 2018; Lilenbaum 2008). Subsets of patients with PS 2 can be distinguished in clinical practice: those who were in poor health due to comorbidities and developed lung cancer; those whose PS is (in part) a result of their lung cancer; and those who fall into both groups. Most trials do not distinguish between these groups.

Description of the intervention

To identify the best first-line treatment for patients with advanced NSCLC with PS of 2 and non-targetable or unknown mutation status, we will include trials assessing chemotherapy (platinum doublet-based regimens, single or combination cytotoxic agents), immunotherapy (anti-programmed cell death protein 1 [PD-1] or programmed death ligand [PD-L1]/cytotoxic T lymphocyte-associated antigen 4 [CTLA-4]), vascular endothelial growth factor (VEGF) inhibitors, and best supportive care (BSC).

Regardless of PS, a variety of single cytotoxic agents and combination regimens have been evaluated for the treatment of NSCLC. In 1995, the Non-Small Cell Lung Cancer Collaborative Group published a meta-analysis showing the benefits of chemotherapy added to BSC for overall survival (NSCLC Collaborative Group 2000). In 2008, a subsequent add-on meta-analysis by the same group showed overall improvement in one-year survival of 9% (from 20% to 29%), representing an absolute increase in median survival of 1.5 months (hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.71 to 0.83). The most commonly studied groups of agents are vinca alkaloid or etoposide with or without platinum agents as single- or doublet-agent regimens (NSCLC Collaborative Group 2010). Regimens using combinations of cytotoxic agents containing platinum agents show better results than are seen with single-agent treatment and BSC (D'Addario 2005). Guidelines therefore recommend standard first-line chemotherapy consisting of a platinum doublet regimen (Hanna 2017;Novello 2016). To date, the most commonly used agents are cisplatin or carboplatin plus docetaxel; gemcitabine; paclitaxel; vinorelbine; and pemetrexed. Adding bevacizumab to first-line chemotherapy regimens showed additional absolute survival of 26 days (Lima 2011).

In recent years, immunotherapy has emerged as a novel treatment. Since 2015, three immune checkpoint inhibitors - nivolumab and pembrolizumab (both PD-1 inhibitors) and atezolizumab (PD-L1 inhibitor) - have been approved by the US Food and Drug Administration (FDA) for the treatment of advanced lung cancer and have become standard therapies in first-line and/or second-line settings for patients with advanced disease. Compared to current chemotherapy regimens, these immune checkpoint inhibitors lead to better progression-free survival and one-year survival along with greater quality of life (Borghaei 2015;Brahmer 2015;Reck 2018). Results of studies combining chemotherapy and immunotherapy have been published (Paz-Ares 2018). Ipilimumab, a CTLA-4 inhibitor, is still under investigation as an addition to current regimens of chemotherapy and/or immunotherapy.

How the intervention might work

Currently used cytotoxic agents can be divided into four groups.

- Alkylating agents (platinum agents [cisplatin and carboplatin]): these agents cause cross-linking of DNA, thereby inhibiting DNA repair and/or synthesis.
- Antimetabolites (pyrimidine analogues [gemcitabine], folate antagonists [pemetrexed]): agents that interfere with DNA synthesis by disrupting processes essential to cell replication.
- Antimicrotubule agents (taxanes [docetaxel, paclitaxel] and vinca alkaloids [vinorelbine]): agents that block cell division by inhibiting formation or disassembly of microtubules.
- Topoisomerase inhibitors (ie, epipodophyllotoxins [etoposide]): agents that create DNA strand breaks and block DNA unwinding.

Bevacizumab is a monoclonal antibody that targets VEGF, thereby inhibiting angiogenesis. Immune checkpoint inhibitors (anti PD-1/L1, CTLA-4) affect the function of the immune system by stimulating or inhibiting regulatory feedback signaling of T cells, leading to a T cell response to tumor cells.

Why it is important to do this review

We identified a gap in the current overview literature about the best first-line treatment for patients with advanced NSCLC with performance status 2 and non-targetable or unknown mutation status. Guidelines from the American Society of Clinical Oncology (ASCO) or the European Society for Medical Oncology (ESMO) do not provide definitive answers (Hanna 2017; Novello 2016). We aim to address this knowledge gap, as this group of patients represents a significant proportion (20% to 30%) of the total population with newly diagnosed lung cancer.

Objectives

To identify the best first-line therapy for advanced lung cancer in patients with performance status 2 without a targetable mutation or with an unknown mutation status.

Methods

Criteria for considering studies for this review

Types of studies

Randomized clinical trials reporting at least one subset analysis of patients with performance score 2, with or without blinding. Cross-over studies will be excluded.

Types of participants

Patients aged 18 years and older who have not received previous therapy for pathological confirmed stage IIIB, IIIC, or IV NSCLC (Eighth Edition of TNM [tumor-node-metastasis] in Lung Cancer [Goldstraw 2016], or corresponding stages from previous editions) and with an ECOG PS of 2 or equivalent. Participants are considered for palliative systemic therapy only. We will include patients regardless of their histology (eg, squamous, non-squamous). Patients with confirmed targetable and treated mutations (eg, *EGFR, BRAF, ALK, MET, ROS1*) will be excluded.

Types of interventions

We will include in this review all types of platinum doublet-based regimens of chemotherapy and checkpoint-inhibiting immunotherapy. Chemotherapy is defined as cytotoxic drugs, for example (but not limited to), cisplatin, carboplatin, paclitaxel, pemetrexed, gemcitabine, vinorelbine, irinotecan, or docetaxel. Checkpoint-inhibiting immunotherapy is defined as drugs that target T cell suppressive pathways, for example, nivolumab, pembrolizumab (anti PD-1), atezolizumab, durvalumab (anti PD-L1), and ipilimumab (anti-CTLA-4). Other antitumor treatments such as bevacizumab (angiogenesis inhibitor) are allowed and will be categorized as subgroups.

We will investigate the following comparisons.

- Chemotherapy versus best supportive care.
- Chemotherapy versus chemotherapy.
- Chemotherapy versus immunotherapy.
- Chemotherapy plus immunotherapy versus chemotherapy or immunotherapy.
- Immunotherapy versus best supportive care.
- Immunotherapy versus immunotherapy.
- Interventions named above with the same intervention plus bevacizumab.

Types of outcome measures

Primary outcomes

- Overall survival (OS), defined as time from start of treatment until death by any cause
- Health-related quality of life (HRQoL), measured via validated international scales
- Toxicity/adverse events (Common Terminology Criteria for Adverse Events [CTCAE] grade 3 to 5, and Patient Reported Outcomes [PRO]-CTCAE if reported) (Kluetz 2016)

Secondary outcomes

- Tumor response rate, defined as the percentage of patients whose cancer shrinks or disappears after treatment based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (Eisenhauer 2009), or in cases of immunotherapy as reported via iRECIST criteria (Seymour 2017)
- Progression-free survival (PFS), defined as time from randomization until disease progression
- Survival rates at specified time points (6 and 12 months), defined as time from start of treatment until death by any cause

Search methods for identification of studies

Electronic searches

We will conduct searches in the following electronic databases.

- Lung Cancer Group Trials Register.
- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library (Appendix 1).
- MEDLINE, accessed via PubMed (Appendix 2).
- Embase (Appendix 3).

We will apply no restriction on language of publication.

Search strategies will be designed by the Information Specialists of the Cochrane Lung Cancer Group.

We will search all databases using both controlled vocabulary (namely, medical subject headings [MeSH] in MEDLINE and Emtree in Embase) and a wide range of free-text terms. We will perform the MEDLINE search using the Cochrane highly sensitive search strategy and the precision-maximizing version (2008 version), as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 6.4.11.1, and detailed in Box 6.4.b) (Higgins 2011b).

Searching other resources

We will use the following additional resources to identify studies eligible for inclusion.

- Reference lists of included trials.
- Meeting abstracts of conferences of the American Society of Clinical Oncology (ASCO) from 2016 to date.
- Meeting abstracts of conferences of the European Society for Medical Oncology (ESMO) from 2016 to date.
- Meeting abstracts of conferences of the International Association for the Study of Lung Cancer (IASLC) from 2016 to date.
- Clinical trials registries (www.clinicaltrials.gov, www.clinicaltrialsregister.eu) from 2016 to date.

Data collection and analysis

Selection of studies

We will transfer all retrieved titles and abstracts to a reference manager database (Rayyan 2016). Two review authors (RG and WG) will independently select studies for review that meet inclusion criteria, based on title and abstract. We will exclude duplicates and will obtain the full text of potentially relevant references. Any disagreement will be discussed to

achieve consensus. If this consensus is not achieved, a third review author (BV) will be consulted. Where appropriate, we will correspond with investigators to clarify study eligibility or to obtain raw data. If a study population combines multiple performance score groups (eg, PS 0 to 2), the whole group will be included. Where possible, we will recalculate Karnofsky and WHO performance scores as ECOG scores to enhance comparability. We will document reasons for exclusion.

Data extraction and management

Two review authors (RG and WG) will independently extract and document characteristics and outcome data from the included studies using an electronic data collection form. If we identify multiple published reports for an included study, we will collect data on separate data collection forms and will combine them after extraction. One review author (RG) will transfer data to the Cochrane Review Manager software (RevMan 2014), and a second review author (WG) will check the data. In cases of disagreement, a third review author will be consulted to reach consensus.

We will extract the following data.

- Author, year of publication, journal of origin, funding source.
- Methods (inclusion and exclusion criteria; type of analysis - intention-to-treat [ITT] or per-protocol [PP]; endpoints [with time points]; characteristics used to define subgroups).
- Participants (total number, baseline characteristics [if available: age, sex, smoking status, performance status, histology, mutation status, stage, country, ethnicity]).
- Intervention (agents used and control intervention).
- Outcomes (results on primary and secondary endpoints).

Assessment of risk of bias in included studies

We will assess the following types of bias using the Cochrane tool for assessing risk of bias.

- Selection bias (sequence generation, allocation concealment).
- Performance bias (blinding of participants and personnel).
- Detection bias (blinding of outcome assessment).
- Attrition bias (incomplete outcome assessment).
- Reporting bias (selective outcome reporting).
- Other sources of bias (as identified during analysis).

Measures of treatment effect

We will use the following measures of treatment effect.

- For time-to-event data, we will use hazard ratio (HR) and 95% confidence interval (CI), if possible. We will also present median survival and one-year survival if applicable.
- For dichotomous outcomes, we will use odds ratio (OR) or risk ratio (RR) and 95% CI, if possible.
- For continuous outcomes, we will use (standardized) mean difference (MD), if possible.

Unit of analysis issues

We do not expect to include trials using a non-standard design. For studies with more than one intervention arm, we will analyze these groups separately.

Dealing with missing data

If data are missing, we will try to contact the corresponding author of that study to obtain these results. If data are missing to such extent that the study cannot be included in the analysis, we will report this in the review.

Assessment of heterogeneity

We will assess the degree of heterogeneity using I^2 statistics and will consider a significance of heterogeneity test (X^2 test). An I^2 value > 30% or a low P value on the X^2 test ($P < 0.1$) will be considered to represent significant heterogeneity.

Assessment of reporting biases

We will use funnel plots to assess small study effects as publication bias if at least 10 studies are included in the analysis. We will visually inspect these plots and will consider publication bias as one of several possible explanations if we observe asymmetry, and we will conduct further exploration.

Data synthesis

If we identify a sufficient number of studies with a low degree of heterogeneity ($I^2 \leq 30\%$ or high P value on the X^2 test), we will conduct a meta-analysis using the fixed-effect model. If heterogeneity is substantial ($I^2 > 30\%$ or low P value on the X^2 test), we will conduct a meta-analysis using a random-effects model. For dichotomous outcomes, we will pool (calculated) risk ratios for an event or property. For continuous outcomes, we will pool (calculated) mean differences if all studies report outcomes using the same scale; otherwise, we will use the standardized mean difference approach. For time-to-event data, we will pool hazard ratios.

If we are unable to conduct a meta-analysis, we will summarize the results; we will display them using appropriate tables and images and will discuss them.

"Summary of findings" table

We intend to create a summary of findings table to report the following outcomes.

- Overall survival,
- Progression-free survival.
- 6/12-Month survival.
- Tumor response rate.
- Health-related quality of life.
- Toxicity/adverse events.

We will use GRADEpro software to prepare the summary of findings table (GradePRO 2015).

Subgroup analysis and investigation of heterogeneity

We consider the following factors as potential predictors of heterogeneity and will conduct a subgroup analysis to evaluate the effects of interventions in the following groups.

- Histology (squamous or non-squamous).
- PD-L1 status (tumor proportion score (TPS) < 1%, 1% to 49%, ≥ 50%).
- Patients aged < or ≥ 70 years.
- Combined performance status groups (eg, PS 0 to 2) versus performance status 2 only.
- Presence or absence of central nervous system metastasis.

Sensitivity analysis

If we identify issues suitable for sensitivity analysis, we will perform this analysis. If sufficient trials are included, we will exclude trials with potentially high risk of bias. If we perform a sensitivity analysis, we will report this by producing a summary table.

References

Additional references

Borghaei 2015

Borghaei H, Paz-Ares L, Horn L, Spigel R, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous nonsmall-cell lung cancer. *New England Journal of Medicine* 2015;373(17):1627-39.

PubMed | **Google Scholar**

Brahmer 2015

Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non small-cell lung cancer. *New England Journal of Medicine* 2015;373(2):123-35.

PubMed | **Google Scholar**

Buccheri 1996

Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. *European Journal of Cancer* 1996;32A(7):1135-41.

PubMed | **Google Scholar**

D'Addario 2005

D'Addario G, Pintilie M, Leighl NB, Feld R, Cerny T, Shepherd FA. Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. *Journal of Clinical Oncology* 2005;23(13):2926-36.

PubMed | **Google Scholar**

Driessen 2017

Driessen EJ, Aarts MJ, Bootsma GP, Loon JG, Janssen-Heijnen ML. Trends in treatment and relative survival among non-small cell lung cancer patients in the Netherlands (1990-2014): disparities between younger and older patients. *Lung Cancer* 2017;108:198-204.

PubMed | **Google Scholar**

Eisenhauer 2009

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European Journal of Cancer* 2009;45(2):228-47.

PubMed | **Google Scholar**

Ferlay 2015

Ferlay J, Soerjomataram I, Dikshit R, Sultan E, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International Journal of Cancer* 2015;136(5):E359-E86.

PubMed | **Google Scholar**

Geffen 2013

Geffen WH, Hiltermann TJ, Groen HJ. Surviving respiratory insufficiency with intensive care support in a pretreated, extensively metastasized patient with an EML4-ALK translocation. *Journal of Thoracic Oncology* 2013;8(1):e1-e2.

PubMed | **Google Scholar**

Goldstraw 2016

Goldstraw P, Chansky KA, Crowley J, Rami-Porta R, Asamura H, Eberhardt WiE, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *Journal of Thoracic Oncology* 2016;11(1):39-51.

PubMed | **Google Scholar**

GradePRO 2015 [Computer program]

McMaster University, Evidence Prime, Inc.. GRADEpro GDT. GRADEpro Guideline Development Tool. Hamilton (ON): McMaster University, Evidence Prime, Inc., 2015.

Hanna 2017

Hanna N, Johnson D, Temin S, Baker S, Brahmer J, Ellis PM, et al. Systemic therapy for stage IV non small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. *Journal of Clinical Oncology* 2017;35(30):3484-515.

PubMed | **Google Scholar**

Kawachi 2018

Kawachi H, Fujimoto D, Morimoto T, Ito M, Teraoka S, Sato Y, et al. Clinical characteristics and prognosis of patients with advanced non small-cell lung cancer who are ineligible for clinical trials. *Clinical Lung Cancer* 2018;19(5):e721-34.

PubMed | Google Scholar

Kluetz 2016

Kluetz PG, Chingos DT, Basch EM, Mitchell SA. Patient-reported outcomes in cancer clinical trials: measuring symptomatic adverse events with the National Cancer Institute's patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *American Society of Clinical Oncology Educational Book* 2016;35:67-73.

PubMed | Google Scholar

Kogure 2018

Kogure Y, Saka H, Takiguchi Y, Atagi S, Kurata T, Ebi N, et al. A randomized phase III study comparing carboplatin with nab-paclitaxel versus docetaxel for elderly patients with squamous-cell lung cancer: study protocol. *Clinical Lung Cancer* 2018;19(5):e711-5.

PubMed | Google Scholar

Lilenbaum 2008

Lilenbaum RC, Cashy J, Hensing TA, Young S, Cella D. Prevalence of poor performance status in lung cancer patients: implications for research. *Journal of Thoracic Oncology* 2008;3(2):125-9.

PubMed | Google Scholar

Lima 2011

Lima ABC, Macedo LT, Sasse AD. Addition of bevacizumab to chemotherapy in advanced non-small cell lung cancer: a systematic review and meta-analysis. *PLoS ONE* 2011;6(8):1-8.

Google Scholar

Novello 2016

Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Levra MG, et al. Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2016;27(Suppl 5):V1-V27.

PubMed | Google Scholar

NSCLC Collaborative Group 2000

Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy for non-small cell lung cancer. *Cochrane Database of Systematic Reviews* 2000, Issue 2. [DOI: 10.1002/14651858.CD002139]

NSCLC Collaborative Group 2010

Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung cancer. *Cochrane Database of Systematic Reviews* 2010, Issue 5. [DOI: 10.1002/14651858.CD007309.pub2]

Paz-Ares 2018

Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, et al. Pembrolizumab plus chemotherapy for squamous non small-cell lung cancer. *New England Journal of Medicine* 2018;379(21):2040-51.

PubMed | **Google Scholar**

Rayyan 2016

Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan - a web and mobile app for systematic reviews. *Systematic Reviews* 2016;5(1):210.

PubMed | **Google Scholar**

Reck 2018

Reck M, Taylor F, Penrod JR, DeRosa M, Morrissey L, Dastani H, et al. Impact of nivolumab versus docetaxel on health-related quality of life and symptoms in patients with advanced squamous non-small cell lung cancer: results from the CheckMate 017 study. *Journal of Thoracic Oncology* 2018;13(2):194-204.

PubMed | **Google Scholar**

RevMan 2014 [Computer program]

The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, 2014.

Scagliotti 2008

Scagliotti GV, Parikh P, Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *Journal of Clinical Oncology* 2008;26(21):3543-51.

PubMed | **Google Scholar**

Sculier 2008

Sculier JP, Chansky K, Crowley JJ, Meerbeeck J, Goldstraw P. The impact of additional prognostic factors on survival and their relationship with the anatomical extent of disease expressed by the 6th edition of the TNM classification of malignant tumors and the proposals for the 7th edition. *Journal of Thoracic Oncology* 2008;3(5):457-66.

PubMed | **Google Scholar**

Seymour 2017

Seymour L, Bogaerts J, Perrone A, Ford R, Mead B, Schwartz LH, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncology* 2017;18(3):73-9.

Google Scholar

WHO 1979

World Health Organization. WHO Handbook for Reporting Results of Cancer Treatment. WHO Offset Publication1979; Vol. 48, issue 4.

Zinner 2016

Zinner R, Visseren Grul C, Spigel DR, Obasaju C. Pemetrexed clinical studies in performance status 2 patients with non-small cell lung cancer (Review). *International Journal of Oncology* 2016;48(1):13-27.

PubMed | **Google Scholar**

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Contributions of authors

Drafting the protocol: all review authors listed.

Developing and running the search strategy: RG,WG, LCG Trial Search Coordinator.

Obtaining copies of studies: RG, WG, AW.

Selecting which studies to include: RG, WG.

Extracting data from studies: RG, WG.

Entering data into RevMan: RG.

Carrying out the analysis: RG, KJ, WG.

Interpreting the analysis: all review authors listed.

Drafting the final review: all review authors listed.

Updating the review: all review authors listed.

Declarations of interest

Rolof GP Gijtenbeek: none known.

Kim de Jong: none known.

Ben JW Venmans: none known.

Femke HM van Vollenhoven: none known.

Anneke Ten Brinke: none known

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Appendices

Appendix 1. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1MeSH descriptor: [Lung Neoplasms] explode all trees

#2MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees

#3lung carcinom*

#4lung neoplasm*

#5lung cancer*

#6nsclc

#7non small cell lung

#8#1 or #2 or #3 or #4 or #5 or #6 or #7

#9advanced

#10"stage 4"

#11"stage IV"

#12metasta*

#13#9 or #10 or #11 or #12

#14#8 and #13

#15PS2

#16PS of 2

#17"performance status 2"

#18performance status of 2

#19performance status (PS) of 2

#20#15 or #16 or #17 or #18 or #19

#21#14 and #20

#22MeSH descriptor: [Induction Chemotherapy] explode all trees

#23first line

#24MeSH descriptor: [Antineoplastic Agents] explode all trees

#25MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] explode all trees

#26carboplatin

#27cisplatin

#28deoxycytidine

#29erlotinib

#30gemcitabine

#31paclitaxel

#32pemetrexed

#33platinum based combination

#34MeSH descriptor: [Taxoids] explode all trees

#35taxanes

#36vinblastine

#37vinorelbine

#38#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37

#39#21 and #38

Appendix 2. MEDLINE search strategy

#41,"Search #23 AND #40"

#40,"Search #24 OR #25 OR #26OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39"

#39,"Search vinorelbine[Title/Abstract]"

#38,"Search Vinblastine[MeSH Terms] OR vinblastine[Title/Abstract]"

#37,"Search Taxoids[MeSH Terms] OR taxanes[Title/Abstract]"

#36,"Search platinum based combination[Title/Abstract]"

#35,"Search Pemetrexed[MeSH Terms] OR pemetrexed[Title/Abstract]"

#34,"Search Paclitaxel[MeSH Terms] OR paclitaxel[Title/Abstract]"

#33,"Search gemcitabine[Title/Abstract]"

#32,"Search Erlotinib Hydrochloride[MeSH Terms] OR erlotinib[Title/Abstract]"

#31,"Search docetaxel[Title/Abstract]"

#30,"Search Deoxycytidine[MeSH Terms] OR Deoxycytidine[Title/Abstract]"

#29,"Search Cisplatin[MeSH Terms] OR cisplatin[Title/Abstract]"

#28,"Search Carboplatin[MeSH Terms] OR carboplatin[Title/Abstract]"

#27,"Search Antineoplastic Combined Chemotherapy Protocols[MeSH Terms]"

#26,"Search Antineoplastic Agents[MeSH Terms]"

#25,"Search first line[Title/Abstract]"

#24,"Search Induction chemotherapy[MeSH Terms]"

#23,"Search #19 AND #22"

#22,"Search #20 OR #21"

#21,"Search performance status of 2[Title/Abstract] OR performance status 2[Title/Abstract]"

#20,"Search PS2[Title/Abstract] OR PS 2[Title/Abstract] OR PS of 2[Title/Abstract]"

#19,"Search #13 AND #18"

#18,"Search #14 OR #15 OR #16 OR #17"

#17,"Search metasta*[Title/Abstract]"

#16,"Search Stage IV[Title/Abstract]"

#15,"Search Stage 4[Title/Abstract]"

#14,"Search Advanced[Title/Abstract]"

#13,"Search #1 OR #2 OR #12"

#12,"Search #10 and #11"

#11,"Search #8 OR #9"

#10,"Search #3 OR #4 OR #5 OR #6 OR #7"

#9,"Search nonsmall cell*[Title/Abstract]"

#8,"Search non small cell*[Title/Abstract]"

#7,"Search lung tumour*[Title/Abstract]"

#6,"Search lung tumor*[Title/Abstract]"

#5,"Search lung neoplasm*[Title/Abstract]"

#4,"Search lung carcinoma*[Title/Abstract]"

#3,"Search lung cancer*[Title/Abstract]"

#2,"Search nsclc[Title/Abstract]"

#1,"Search Carcinoma, Non-Small-Cell Lung[MeSH Terms]"

Appendix 3. Embase search strategy

#50	#10 AND #15 AND #48 AND #49
#49	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47
#48	#16 OR #17 OR #18 OR #19 OR #20
#47	'navelbine':ab,ti
#46	'vinorelbine':ab,ti
#45	'navelbine'/exp
#44	'vinblastine':ab,ti
#43	'vinblastine'/exp
#42	'taxanes':ab,ti
#41	'taxoid'/exp

#40	'platinum based combination*':ab,ti
#39	'pemetrexed':ab,ti
#38	'pemetrexed'/exp
#37	'paclitaxel':ab,ti
#36	'paclitaxel'/exp
#35	'gemcitabine':ab,ti
#34	'gemcitabine'/exp
#33	'erlotinib':ab,ti
#32	'erlotinib'/exp
#31	'docetaxel':ab,ti
#30	'docetaxel'/exp
#29	'deoxycytidine':ab,ti
#28	'deoxycytidine'/exp
#27	'cisplatin':ab,ti
#26	'cisplatin'/exp
#25	'carboplatin':ab,ti
#24	'carboplatin'/exp
#23	'antineoplastic agent'/exp
#22	'first line':ab,ti
#21	'induction chemotherapy'/exp
#20	'performance status of 2':ab,ti
#19	'performance status 2':ab,ti
#18	'ps of 2':ab,ti
#17	'ps 2':ab,ti
#16	'ps2':ab,ti
#15	#11 OR #12 OR #13 OR #14
#14	'metasta*':ab,ti

#13	'stage iv':ab,ti
#12	'stage 4':ab,ti
#11	'advanced':ab,ti
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
#9	'nonsmall cell*':ab,ti
#8	'non small cell*':ab,ti
#7	'lung tumour*':ab,ti
#6	'lung tumor*':ab,ti
#5	'lung neoplasm*':ab,ti
#4	'lung carcinoma*':ab,ti
#3	'lung cancer*':ab,ti
#2	'nsclc':ab,ti
#1	'non small cell lung cancer'/exp