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

Gijtenbeek RGP, de Jong K, Venmans BJW, van Vollenhoven FHM, Ten Brinke A, Van der Wekken AJ, van Geffen WH

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[Intervention Review]

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

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ABSTRACT

Background

Most people who are newly diagnosed with non-small cell lung cancer (NSCLC) have advanced disease. For these people, survival is determined by various patient- and tumor-related factors, of which the performance status (PS) is the most important prognostic factor. People with PS 0 or 1 are usually treated with systemic therapies, whereas people with PS 3 or 4 most often receive supportive care. However, treatment for people with PS 2 without a targetable mutation remains unclear. Historically, people with a PS 2 cancer are frequently excluded from (important) clinical trials because of poorer outcomes and increased toxicity. We aim to address this knowledge gap, as this group of people 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 people with performance status 2 without a targetable mutation or with an unknown mutation status.

Search methods

We used standard, extensive Cochrane search methods. The latest search date was 17 June 2022.

Selection criteria

We included randomized controlled trials (RCTs) that compared different chemotherapy (with or without angiogenesis inhibitor) or immunotherapy regimens, specifically designed for people with PS 2 only or studies including a subgroup of these people.

Data collection and analysis

We used standard Cochrane methods. Our primary outcomes were 1. overall survival (OS), 2. health-related quality of life (HRQoL), and 3. toxicity/adverse events. Our secondary outcomes were 4. tumor response rate, 5. progression-free survival, and 6. survival rates at six and 12 months' treatment. We used GRADE to assess certainty of evidence for each outcome.

Main results

We included 22 trials in this review and identified one ongoing trial. Twenty studies compared chemotherapy with different regimens, of which 11 compared non-platinum therapy (monotherapy or doublet) versus platinum doublet. We found no studies comparing best supportive care with chemotherapy and only two abstracts analyzing chemotherapy versus immunotherapy.

We found that platinum doublet therapy showed superior OS compared to non-platinum therapy (hazard ratio [HR] 0.67, 95% confidence interval [CI] 0.57 to 0.78; 7 trials, 697 participants; moderate-certainty evidence). There were no differences in six-month survival rates (risk ratio [RR] 1.00, 95% CI 0.72 to 1.41; 6 trials, 632 participants; moderate-certainty evidence), whereas 12-month survival rates were improved for treatment with platinum doublet therapy (RR 0.92, 95% CI 0.87 to 0.97; 11 trials, 1567 participants; moderate-certainty evidence). PFS and tumor response rate were also better for people treated with platinum doublet therapy, with moderate-certainty evidence (PFS: HR 0.57, 95% CI 0.42 to 0.77; 5 trials, 487 participants; tumor response rate: RR 2.25, 95% CI 1.67 to 3.05; 9 trials, 964 participants).

When analyzing toxicity rates, we found that platinum doublet therapy increased grade 3 to 5 hematologic toxicities, all with low-certainty evidence (anemia: RR 1.98, 95% CI 1.00 to 3.92; neutropenia: RR 2.75, 95% CI 1.30 to 5.82; thrombocytopenia: RR 3.96, 95% CI 1.73 to 9.06; all 8 trials, 935 participants).

Only four trials reported HRQoL data; however, the methodology was different per trial and we were unable to perform a meta-analysis.

Although evidence is limited, there were no differences in 12-month survival rates or tumor response rates between carboplatin and cisplatin regimens. With an indirect comparison, carboplatin seemed to have better 12-month survival rates than cisplatin compared to non-platinum therapy.

The assessment of the efficacy of immunotherapy in people with PS 2 was limited. There might be a place for single-agent immunotherapy, but the data provided by the included studies did not encourage the use of double-agent immunotherapy.

Authors' conclusions

This review showed that as a first-line treatment for people with PS 2 with advanced NSCLC, platinum doublet therapy seems to be preferred over non-platinum therapy, with a higher response rate, PFS, and OS. Although the risk for grade 3 to 5 hematologic toxicity is higher, these events are often relatively mild and easy to treat. Since trials using checkpoint inhibitors in people with PS 2 are scarce, we identified an important knowledge gap regarding their role in people with advanced NSCLC and PS 2.

PLAIN LANGUAGE SUMMARY

Best therapy for people with advanced non-small cell lung cancer who have not been treated without a targetable mutation and moderately impaired performance status

Key messages

– The preferred chemotherapy for people with moderately impaired performance status (PS) with advanced non-small cell lung cancer (NSCLC) and that have never received any treatment before should contain two medicines, one of which is a platinum-based medicine.

– Although the risk for bone marrow damage is higher with a platinum-based medicine, these events are often relatively mild and easy to treat.

– We were unable to assess the effects of immunotherapy on moderately impaired people.

What is non-small cell lung cancer?

Lung cancer is the most frequent cause of cancer-related death worldwide and NSCLC is the most common subtype. At the time of diagnosis, the disease has already spread in more than half of all cases. In the tumors of a minority of people diagnosed with NSCLC that has spread to other parts of the body specific mutations can be found, which are treated distinct from the majority of people without such mutations.

How can non-small cell lung cancer be treated?

NSCLC can only be treated with life-prolonging medicines such as chemotherapy (a medicine used to destroy cancer cells) or immunotherapy (a medicine that boosts the person's immune system and helps the body find and destroy cancer cells). Selecting the best treatment depends on the health condition of the person. That condition is determined using a scale from 0 (no symptoms) to 5 (dead). There is no discussion on the treatment of relatively fit people (scoring 0 or 1), as they often tolerate these treatments relatively well. People with a low health condition (scoring 3 or 4) receive only supportive care in most cases. However, although representing 20% to 30% of all people, the best treatment for moderately impaired people (PS 2) is not clear, as they often do not participate in trials.

What did we want to find out?

Our objective was to investigate the best therapy for people with advanced NSCLC without a specific mutation with PS 2.

What did we do?

We searched medical databases for clinical trials comparing treatments for advanced NSCLC with best supportive care or other treatments.

What did we find?

We found 22 trials; 20 compared different types of chemotherapy and two compared chemotherapy versus immunotherapy.

Main results

People treated with chemotherapy regimens using two medicines, including a platinum-based medicine, had longer survival than people treated with chemotherapies without a platinum-based medicine. However, these people did have more side effects, especially with a negative influence on the bone marrow (matter found in the center of bones), resulting in a temporary lack of red and white blood cells, and platelets. The few studies that analyzed health-related quality of life all used different methods of measurement. We found no difference in quality of life when we looked at those studies individually. We found two partly published trials studying immunotherapy, which found no survival benefit compared to chemotherapy.

What are the limitations of the evidence?

We are moderately confident in our results that chemotherapies with a platinum-based medicine increases survival. We are also moderately confident in the evidence evaluating the time to progression of disease because in all included studies, both investigators and trial participants were fully aware of which treatment the participants received. This might lead to substantial bias. In addition, we have little confidence in the evidence regarding toxicities because the evidence is based on a small number of studies with conflicting outcomes.

How up to date is this evidence?

The evidence is up to date to 17 June 2022.

SUMMARY OF FINDINGS

Summary of findings 1. Platinum doublet compared to non-platinum therapy for people with advanced non-small cell lung cancer, performance status 2 without a targetable mutation or with an unknown mutation status

Platinum doublet compared to non-platinum therapy for people with advanced non-small cell lung cancer, performance status 2 without a targetable mutation or with an unknown mutation status

Patient or population: people with advanced non-small cell lung cancer, performance status 2 without a targetable mutation or with an unknown mutation status
Setting: –
Intervention: platinum doublet
Comparison: non-platinum therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with non-platinum therapy	Risk with platinum doublet				
Overall survival	**Study population**		**HR 0.67** (0.57 to 0.78)	697 (7 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	Platinum doublet increases overall survival.
	Not applicable					
12-month survival rates	**Study population**		**RR 0.92** (0.87 to 0.97)	1567 (11 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	Platinum doublet increases 12 months survival rates.
	824 per 1000	767 per 1000 (726 to 808)				
Progression-free survival	**Study population**		**HR 0.57** (0.42 to 0.77)	487 (5 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	Platinum doublet likely increases progression-free survival.
	Not applicable					
Tumor response rate	**Study population**		**RR 2.25** (1.67 to 3.05)	964 (9 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	Platinum doublet likely increases tumor response rate.
	103 per 1000	231 per 1000 (172 to 314)				
Toxicity – anemia grade 3–5	**Study population**		**RR 1.98** (1.00 to 3.92)	935 (8 RCTs)	⊕⊕⊖⊖ **Low**[a,b]	Platinum doublet may result in an increase of anemia grade 3–5.
	63 per 1000	126 per 1000 (63 to 249)				
	Study population		**RR 2.75** (1.30 to 5.82)	935 (8 RCTs)	⊕⊕⊖⊖ **Low**[a,b]	Platinum doublet may result in an increase of neutropenia grade 3–5.

Toxicity – neutropenia grade 3–5	123 per 1000	337 per 1000 (159 to 714)				
Toxicity – thrombocytopenia grade 3–5	**Study population**		**RR 3.96** (1.73 to 9.06)	935 (8 RCTs)	⊕⊕⊝⊝ **Low**[a,b]	Platinum doublet may result in an increase of thrombocytopenia grade 3–5.
	30 per 1000	117 per 1000 (51 to 268)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard ratio; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level. All studies were open-label and, therefore, considered high risk for outcome bias and allocation concealment was unclear.
[b]Downgraded one level due to high heterogeneity.

BACKGROUND

Description of the condition

Lung cancer is the most frequent cause of cancer-related death worldwide, diagnosed in over 2.2 million people annually (Sung 2021). Non-small cell lung cancer (NSCLC) accounts for 75% of all cases. At the time of diagnosis, more than 50% of people already have advanced disease and can be treated only with palliative systemic therapies or best supportive care (BSC) (Driessen 2017). Unfortunately, despite these therapies, survival rates remained poor, with a median survival of 8.8 months for people with Stage IV disease (Goldstraw 2016). More recently, after the introduction of checkpoint inhibitors and targeted therapies, the prognosis of selected patients improved (Gijtenbeek 2020; Howlader 2020; Noordhof 2021). However besides tumor stage and driver mutation status, survival is determined by various patient- and tumor-related factors (e.g. smoking status, age, gender, performance status [PS], histologic characteristics), of which PS is the most important prognostic factor (Sculier 2008).

The two most commonly used PSs are the Karnofsky 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 predisease 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 people with known molecular targets (e.g. epidermal growth factor receptor [EGFR] mutation, anaplastic lymphoma kinase [ALK] rearrangement or fusion) should be treated with targeted therapy, regardless of PS (Gijtenbeek 2023; Hendriks 2023; Inoue 2009; Iwama 2017; Owen 2022). People with PS of 0 or 1 are usually treated with systemic therapies such as platinum-based doublet chemotherapy or checkpoint inhibitors (or both), whereas people with PS of 3 or 4 most often receive supportive care (except for patients eligible for target therapy). However, treatment for people with PS 2 without a targetable mutation remains unclear (Hendriks 2023). Historically, people with a PS of 2 were included in clinical trials (Finkelstein 1986). However, in the last decades they were frequently excluded from (important) clinical trials because of poorer outcomes and increased toxicity compared with people with a PS of 0 or 1 (Borghaei 2015; Gijtenbeek 2022; Kogure 2018; Scagliotti 2008; Schiller 2002; Zinner 2016). As a consequence, trial populations often fail to represent the real-world population of people with lung cancer, as 20% to 30% of all newly diagnosed people with advanced NSCLC present with PS 2 (Kawachi 2018; Lilenbaum 2008). Due to developments over time and real-world evidence, study protocols are slowly migrating to re-include people with PS 2 (Lee 2022; Lena 2022). Also, subsets of people 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 people with advanced NSCLC with PS of 2 and non-targetable or unknown mutation status, we included 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 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 (OS) (NSCLC Collaborative Group 1995; 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 those with single-agent treatment and BSC (D'Addario 2005). Guidelines, therefore, recommend standard first-line chemotherapy consisting of a platinum doublet regimen (Hendriks 2023; Owen 2022). 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, multiple immune checkpoint inhibitors (e.g. 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 or second-line (or both) settings for people with advanced disease. Compared to current chemotherapy regimens, these immune checkpoint inhibitors lead to better progression-free survival (PFS) and one-year survival along with improved quality of life (QoL) (Borghaei 2015; Brahmer 2015; Reck 2018). Results of studies combining chemotherapy and immunotherapy have been published (Paz-Ares 2018). Therapies combining different types of immunotherapy such as ipilimumab, a CTLA-4 inhibitor, and nivolumab, are now being introduced as an addition to current regimens of chemotherapy or immunotherapy (or both) (Hellmann 2019).

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 or synthesis (or both).

- 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 (i.e. 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 people with advanced NSCLC with PS 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 (Hendriks 2023; Owen 2022). We aimed to address this knowledge gap, as this group of people 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 people with performance status 2 without a targetable mutation or with unknown mutation status.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) reporting at least one subset analysis of people with PS 2, with or without blinding. We excluded cross-over studies.

Types of participants

People aged 18 years and older who had not received previous therapy for pathologically 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 were considered for palliative systemic therapy only. We included people regardless of their histology (e.g. squamous, non-squamous). We excluded people with confirmed targetable and treated mutations (e.g. EGFR, BRAF, ALK, MET, ROS1).

Types of interventions

We included all types of chemotherapy and checkpoint-inhibiting immunotherapy. Chemotherapy was defined as cytotoxic drugs, for example (but not limited to), cisplatin, carboplatin, paclitaxel, pemetrexed, gemcitabine, vinorelbine, irinotecan, or docetaxel. Checkpoint-inhibiting immunotherapy was defined as drugs that targeted 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) were allowed and categorized as subgroups.

We investigated the following comparisons.

- Chemotherapy versus BSC
- Chemotherapy versus chemotherapy
- Chemotherapy versus immunotherapy
- Chemotherapy plus immunotherapy versus chemotherapy or immunotherapy
- Immunotherapy versus BSC
- 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 people whose cancer shrank or disappeared 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 (six and 12 months), defined as time from start of treatment until death by any cause

Search methods for identification of studies

Electronic searches

We conducted searches in the following electronic databases from inception to 17 June 2022.

- Cochrane 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, accessed via Elsevier (Appendix 3)

We applied no restriction on the language of publication.

The Information Specialists of the Cochrane Lung Cancer Group designed the search strategies.

We searched 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 performed 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* (Section 6.4.11.1, and detailed in Box 6.4.b) (Higgins 2022).

Searching other resources

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

- Reference lists of included trials
- Meeting abstracts of conferences of the ASCO from 2016 to 13 September 2022
- Meeting abstracts of conferences of the ESMO from 2016 to 13 September 2022
- Meeting abstracts of conferences of the International Association for the Study of Lung Cancer (IASLC) from 2016 to 13 September 2022
- Clinical trials registries (www.clinicaltrials.gov, www.clinicaltrialsregister.eu) from 2016 to 17 June 2022

Data collection and analysis

Selection of studies

We transferred all retrieved titles and abstracts to a reference manager database (Rayyan 2016), and excluded duplicates. Two review authors (RG and WG) independently selected studies for review that meet inclusion criteria, based on titles and abstracts, and obtained the full-text of potentially relevant references. We discussed any disagreements to achieve consensus. If there was no consensus, we consulted a third review author (BV). Where appropriate, we corresponded with investigators to clarify study eligibility or to obtain raw data. If a study population combined multiple PS groups (e.g. PS 0 to 2), we included the whole group. Where possible, we recalculated KPS and WHO PSs as ECOG PSs to enhance comparability. We documented reasons for exclusion at the full-text stage in the Characteristics of excluded studies table.

Data extraction and management

Two review authors (RG and WG) independently extracted and documented characteristics and outcome data from the included studies using an electronic data collection form. If we identified multiple published reports for an included study, we collected data on separate data collection forms and combined them after extraction. One review author (RG) transferred data to the Review Manager 5 (Review Manager 2020), and a second review author (WG) checked the data. In cases of disagreement, we consulted a third review author (BV) to reach consensus.

We extracted 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, PS, 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 assessed the following types of bias using the Cochrane RoB 1 tool (as reported in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Intervention* [Higgins 2022]).

- 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)

We rated each domain of the tool at 'low', 'high', or 'unclear' risk of bias at study level and for each outcome where possible. We supported the rating of each domain with a brief description.

Measures of treatment effect

We used the following measures of treatment effect.

- For time-to-event data, we used hazard ratio (HR) and 95% confidence interval (CI), if possible. We also presented median survival and six- or 12-month survival if applicable.
- For dichotomous outcomes, we used risk ratio (RR) and 95% CI, if possible.
- For continuous outcomes, we used mean difference (MD) where studies used the same scale or standardized mean difference (SMD) where studies used difference scales, if possible.

Unit of analysis issues

We did not include trials using a non-standard design. For studies with more than one intervention arm, we analyzed these groups separately.

Dealing with missing data

If data were missing, we tried to contact the corresponding author of that study to obtain these results. If data were missing to such an extent that the study could not be included in the analysis, we reported this.

Assessment of heterogeneity

We assessed the degree of heterogeneity using I^2 statistics and considered a significance of heterogeneity test (Chi^2 test). An I^2 value greater than 30% or a low P value on the Chi^2 test ($P < 0.1$) was considered to represent at least moderate heterogeneity.

Assessment of reporting biases

We used funnel plots to assess small-study effects as publication bias if at least 10 studies were included in the analyses. We visually inspected these plots and considered publication bias as one of several possible explanations when we observed asymmetry, and we conducted further exploration.

Data synthesis

When we identified a sufficient number of studies with a low degree of heterogeneity (I^2 of 30% or less or $P \geq 0.1$ on the Chi^2 test), we conducted a meta-analysis using the fixed-effect model. If there was substantial heterogeneity (I^2 greater than 30% or $P \leq 0.1$ on the Chi^2 test), we conducted a meta-analysis using a random-effects

model. For dichotomous outcomes, we pooled (calculated) RRs for an event or property. For time-to-event data, we pooled HRs.

If we were unable to conduct a meta-analysis, we summarized the results narratively and use appropriate tables and images.

Subgroup analysis and investigation of heterogeneity

We considered the following factors as potential predictors of heterogeneity and planned a subgroup analysis to evaluate the effects of interventions in the following groups, if there were sufficient data.

- Histology (squamous or non-squamous)
- PD-L1 status (tumor proportion score (TPS) less than 1%, 1% to 49%, 50% or greater)
- People aged less than 70 years or 70 years or greater
- Presence or absence of central nervous system metastasis
- Chemotherapy monotherapy versus doublet (post-hoc)

Sensitivity analysis

When we identified issues suitable for sensitivity analysis, we performed this analysis. When there were sufficient trials, we excluded trials with potentially high risk of bias, with the exception of blinding. If we performed a sensitivity analysis, we reported this by producing a summary table.

Summary of findings and assessment of the certainty of the evidence

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

- OS
- HRQoL
- Toxicity/adverse events
- Tumor response rate
- PFS
- Survival rates

When creating the summary of findings table, we applied the GRADE approach as suggested in Chapters 11 and 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022) and used GRADEpro GDT software (GRADEpro GDT).

RESULTS

Description of studies

Results of the search

We identified 4128 records (2602 from CENTRAL, 553 from MEDLINE, and 973 from Embase), which reduced to 3661 after the removal of duplicates.

Initial screening of titles and abstracts excluded 3538 manuscripts, resulting in 164 manuscripts requiring full-text analysis (Figure 1). Of these, 67 were eligible, 20 manuscripts were added by additional sources. After exclusion of 62 articles for various reasons (see Excluded studies), we included 22 trials in this systematic review (Flotten 2012; Gridelli 2007; Gronberg 2009; Hainsworth 2007; Karampeazis 2011; Kosmidis 2007; Kosmidis 2012; Langer 2007; Le Chevalier 2001; Lee 2022; Lena 2022; Lilenbaum 2005; Morabito 2013; Morere 2010; Quoix 2011; Reynolds 2009; Saito 2012; Schuette 2017; Spigel 2018; Sweeney 2001; Yadav 2021; Zukin 2013). One trial was still ongoing (NCT02581943).

Figure 1. PRISMA flow diagram.

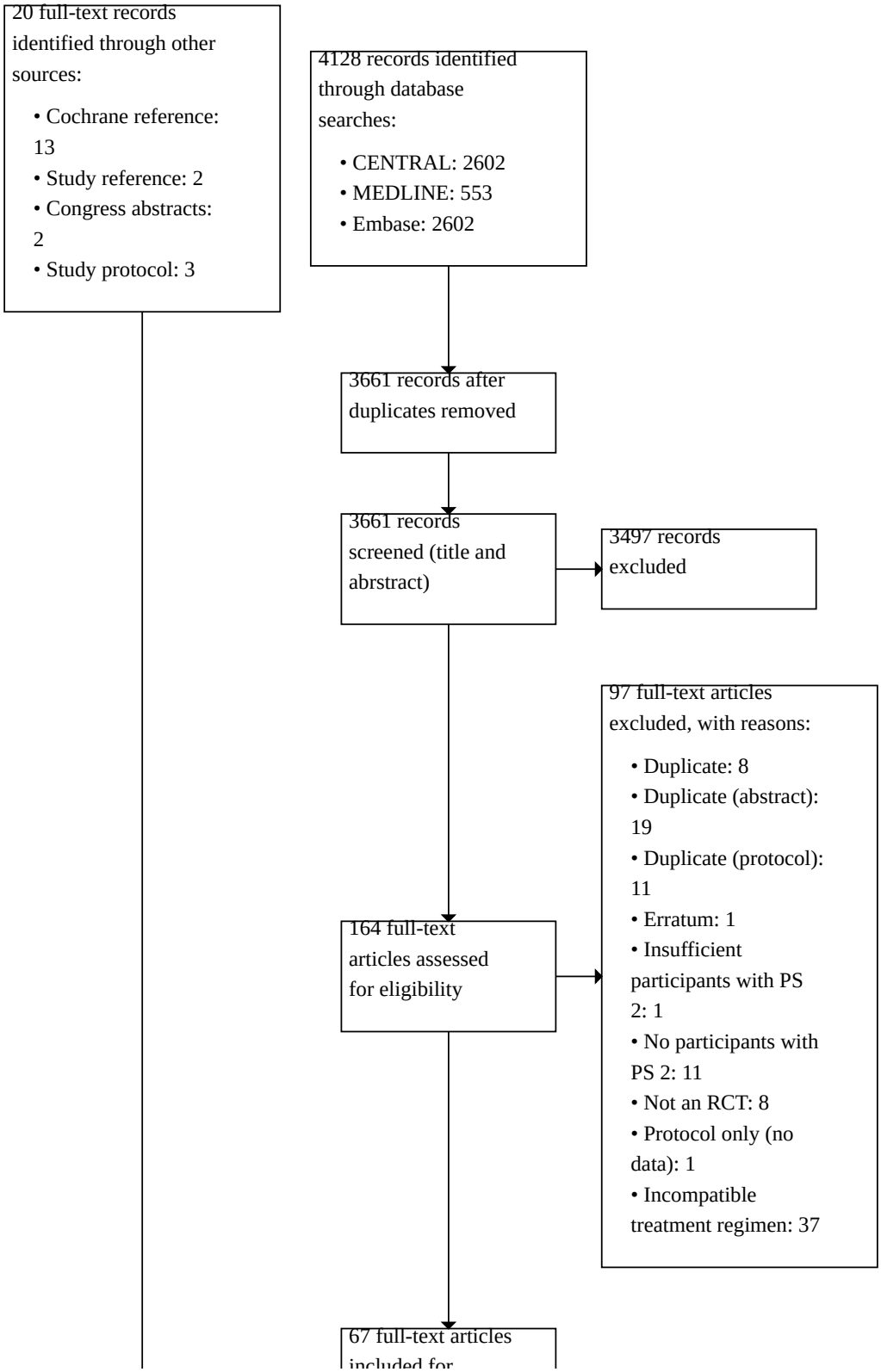
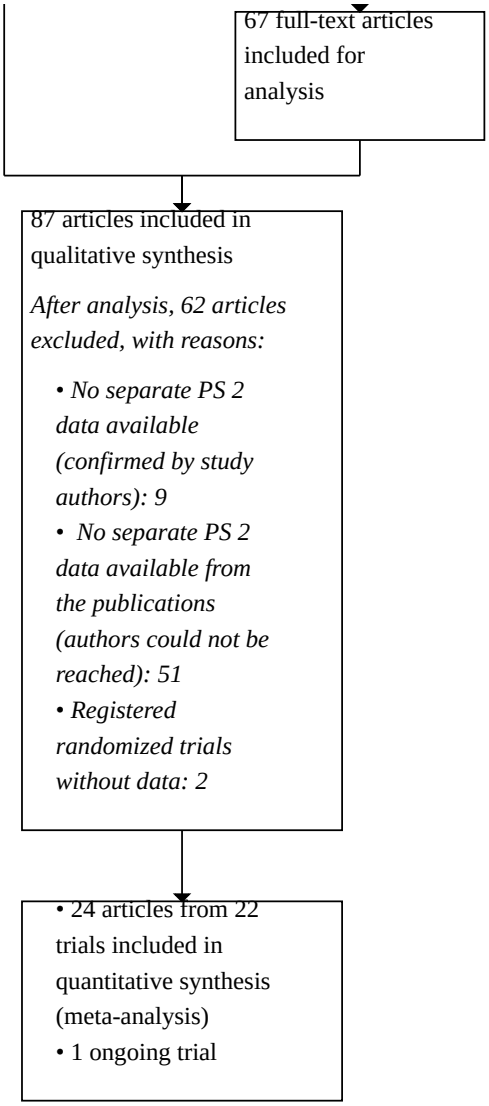


Figure 1. (Continued)



Except for two trials presented as congress abstract only (Lee 2022; Lena 2022), all other studies compared chemotherapy with different regimens, of which 11 compared non-platinum therapy versus platinum doublet. There were no studies comparing BSC with chemotherapy.

Of those 20 chemotherapy trials, nine were designed especially for or reported outcomes of people with PS 2 only, of which six compared non-platinum therapy versus platinum doublet (Kosmidis 2007; Morabito 2013; Reynolds 2009; Saito 2012; Spigel 2018; Zukin 2013). The other three trials used various non-comparable chemotherapy regimens (Kosmidis 2012; Langer 2007; Sweeney 2001).

We obtained full subgroup data from five studies (Flotten 2012; Gronberg 2009; Morere 2010; Quoix 2011; Yadav 2021). We were unable to obtain additional data from the six other studies and only incomplete subgroup data were available (Gridelli 2007; Hainsworth 2007; Karampeazis 2011; Le Chevalier 2001; Lilenbaum 2005; Schuette 2017). We did not identify any imbalances in recruitment of people with PS 2 between treatment arms, in any included study (Table 1; Table 2).

Chemotherapy versus chemotherapy

Non-platinum therapy versus platinum doublet regimens

We included 11 trials in this subgroup, involving 1244 people with PS 2. Nine trials compared non-platinum monotherapy with a platinum doublet regimen (Kosmidis 2007; Le Chevalier 2001; Lilenbaum 2005; Morabito 2013; Quoix 2011; Reynolds 2009; Schuette 2017; Spigel 2018; Zukin 2013), and two trials used non-platinum doublet therapy (Flotten 2012; Saito 2012). The data of these studies are summarized and analyzed in Table 1 and Table 3.

Flotten 2012 conducted an open-label, randomized, multicenter phase III trial in Norway comparing treatment with oral vinorelbine 60 mg/m^2 and gemcitabine 1000 mg/m^2 versus carboplatin area

under the curve (AUC) 5 and vinorelbine in people with PS 0 to 2. A total of 444 participants were randomized, stratified by WHO PS 0 or 1 versus 2, Stage IIIB versus IV, and age under 75 years versus 75 years or older, including 111 people with PS 2. The primary endpoint was OS; secondary endpoints were QoL, toxicity, and use of palliative radiation therapy. The study was not designed to assess response rates or time to progression (TTP). The study authors provided additional data on the PS 2 subgroup upon request.

Kosmidis 2007 evaluated single-agent gemcitabine 1250 mg/m^2 versus carboplatin AUC 3 and gemcitabine in 90 participants with PS 2 only in a prospective randomized phase II trial in Greece. Their primary outcome was clinical benefit, based on three measures: Lung Cancer Symptom Scale (LCSS), which consists of six symptoms (dyspnea, cough, hemoptysis, fatigue, anorexia, and pain); general feeling (very good, good, or poor); and the participant's weight. Secondary outcomes were OS, PFS, and toxicity. We contacted the study authors for additional information; however, this was no longer available.

Le Chevalier 2001 reported the long-term analysis of survival in a European multicenter randomized phase III study (Le Chevalier 1994), comparing cisplatin 120 mg/m^2 and vinorelbine 30 mg/m^2 (on days one and 29, then every six weeks) to cisplatin and vindesine 3 mg/m^2 (on days one and 29, then every six weeks) and vinorelbine 30 mg/m^2 weekly alone. A total of 612 participants were randomized, stratified by center and stage; 121 people had PS 2. Their primary endpoint was OS, with response rate and tolerance as secondary endpoints. Not all our endpoints regarding participants with PS 2 could be retrieved from the publication, and we were unable to retrieve additional data.

Lilenbaum 2005 (CALGB 9730) analyzed the effect of single-agent paclitaxel 225 mg/m^2 versus combination therapy of carboplatin AUC 6 and paclitaxel in a US population. Randomization was stratified by stage, PS (0 or 1 versus 2), and age (under 70 years versus 70 years or older) and the primary endpoint was OS. Secondary endpoints were PFS and response rate, not defined according to RECIST. A total of 99/561 (18%) randomized participants had a PS of 2. Not all data of participants with PS 2 were reported and we were unable to retrieve additional data.

Morabito 2013 (NCT00526643) performed an open-label randomized multicenter phase III study in Italy dedicated to people with PS 2 younger than 70 years, comparing gemcitabine 1200 mg/m^2 monotherapy with cisplatin 60 mg/m^2 and gemcitabine. Randomization was stratified by gender, center, and stage (IIIB versus IV). The primary outcome was OS and the secondary outcomes were PFS, response, toxicity, and QoL. A total of 57 participants were randomized. This publication reported all our endpoints.

Quoix 2011 (IFCT-0501) included 451 participants aged 70 years or older in an open-label multicenter randomized phase III trial from France, comparing carboplatin AUC 6 and weekly paclitaxel 90 mg/m^2 with monotherapy (vinorelbine 25 mg/m^2 or gemcitabine 1150 mg/m^2). Randomization was performed centrally and stratified participants by center, PS (0 or 1 versus 2), stage (III versus IV), and age (80 years or younger versus older than 80 years). The study was designed with an estimate of 520 required participants, but in view of the highly positive results of the second interim analysis, the independent data monitoring committee recommended that participant recruitment be stopped after the inclusion of 451 participants, containing 123 people with PS 2. As only the HR of OS of people with PS 2 was reported, we contacted the Intergroupe Francophone de Cancérologie Thoracique (IFCT) to obtain additional information and received a full analysis of the PS 2 subgroup data.

Fiteni 2016 published QoL data; however, they did not report the QoL data of people with PS 2 separately. We were unable to retrieve additional data.

Reynolds 2009 evaluated the efficacy of gemcitabine 1250 mg/m^2 versus carboplatin AUC 5 and gemcitabine 1000 mg/m^2 in people with PS 2, primarily on OS and secondarily on PFS, response rate, and two biomarkers. They randomized 170 of the targeted 220 people to both arms, but as participant accrual was 50% of the expected rate, the trial was terminated prematurely. Not all data of participants with PS 2 were reported and we were unable to retrieve additional data. The biomarker data provided were beyond the scope of this meta-analysis.

Saito 2012 investigated the one-year survival rate of people with PS 2 treated with carboplatin AUC 6 and paclitaxel 200 mg/m^2 compared to those treated with vinorelbine 25 mg/m^2 and gemcitabine 1000 mg/m^2. Secondary endpoints were response rate, PFS, symptom improvement, and toxicity. After randomization with disease stage (IIIB versus IV) and bodyweight loss in the previous six months (less than 5% versus 5% or greater) as stratification factors, 84 people were assessable for analysis. Not all the endpoints of this meta-analysis were reported, but we were unable to retrieve additional data.

Schuette 2017 compared pemetrexed 500 mg/m^2 and bevacizumab 7.5 mg/kg with carboplatin AUC 5, pemetrexed, and bevacizumab for at least four to a maximum of six cycles, in an open-label, multicenter, randomized phase III study from Germany. The primary outcome was PFS, and secondary outcomes were OS, objective response rate, and safety profile. A total of 271 participants were randomized without stratification by PS, containing only 13 participants with PS 2 (six and seven per arm). In the total study group, a higher rate of people discontinued the study due to adverse events with platinum therapy compared to the non-platinum arm. Also, in the platinum arm, reduction of study medication occurred twice as often. Not all endpoints were reported for participants with PS 2 only and we were unable to retrieve additional data.

Spigel 2018 performed an open-label, multicenter, randomized phase II trial in the US, dedicated to participants with PS 2. They compared three arms, pemetrexed 500 mg/m^2; pemetrexed and bevacizumab 15 mg/kg; and pemetrexed, bevacizumab, and carboplatin AUC 5, with PFS as their primary outcome and objective response rate (ORR), TTP, OS, and six- to 12-month survival as secondary outcomes. They included 172 participants; 48 in the pemetrexed arm, 63 in the pemetrexed and bevacizumab arm, and 61 in the pemetrexed, bevacizumab, and carboplatin arm, after randomization stratified by age (under 75 years versus 75 years or older) and albumin (less than 3.5 g/dL versus 3.5 g/dL or greater). During the trial, inclusion in the single-agent pemetrexed arm was discontinued after publication of the study performed by Zukin 2013. In our analysis, we decided to compare pemetrexed plus bevacizumab with pemetrexed plus bevacizumab plus carboplatin.

We did not include the pemetrexed alone arm. This publication reported almost all our endpoints and could be supplemented using data published in NCT00892710.

Zukin 2013 performed a trial dedicated to people with PS 2 only. They studied the effect of single-agent pemetrexed 500 mg/m^2 versus carboplatin AUC 5 and pemetrexed on OS, ORR, PFS, and toxicity in an open-label, multicenter, randomized phase III trial in the US and Brazil. A total of 217 participants were randomized, stratified by stage (IIIB versus IV), weight loss (less than 5% versus 5% or greater), and age (under 70 years versus 70 years or older). Best response could not be determined in 34% of the pemetrexed arm versus 23% of the carboplatin and pemetrexed arm. This publication reported all our endpoints.

Other studies

Nine other studies used different treatment regimens. See also Table 2 for an overview of treatment regimens and outcome measurements.

Gridelli 2007 studied the differences in TTP, ORR, OS, and toxicity between single-agent pemetrexed or sequential pemetrexed plus gemcitabine in a European open-label, multicenter phase II study in elderly people or people with poor PS, ineligible for platinum therapy. A total of 92 participants were randomized, stratified by stage (IIIB versus IV) and PS (0 or 1 versus 2), with 14 participants with PS 2 in the pemetrexed arm and 17 participants with PS 2 in the pemetrexed plus gemcitabine arm. Only aggregated data on OS and PFS were reported for participants with PS 2. We attempted to contact the authors but were unable to retrieve additional data.

Gronberg 2009 conducted an open-label, multicenter phase III trial in Norway. They compared pemetrexed 500 mg/m^2 plus carboplatin AUC 5 with gemcitabine 1000 mg/m^2 plus carboplatin, with HRQoL (European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire [EORTC QLQ-C30]/ European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer [EORTC QLQ-LC13]) as the primary outcome. Secondary outcomes were OS and toxicity. Randomization was stratified by PS (0 or 1 versus 2), stage (IIIB versus IV), and age (under 75 years versus 75 years or over). There were 47 (22%) participants with PS 2 in the pemetrexed plus carboplatin arm and 49 (23%) participants with PS 2 in the gemcitabine plus carboplatin arm. As the primary publication of this trial provided the OS analysis in people with PS 2 only, we contacted the study authors and subsequently received all data required for this review.

Hainsworth 2007 performed a multicenter phase III trial in the US, comparing docetaxel 36 mg/m^2 with gemcitabine 800 mg/m^2 plus docetaxel 30 mg/m^2. All drugs were administered on days one, eight, and 15 of a 28-day cycle for a recommended 6 courses of therapy. People included were older than 65 years or poor candidates for platinum therapy due to comorbidity or poor performance. There was no stratification in randomization reported. The primary endpoint was OS, and secondary endpoints were ORR, PFS, and toxicity. Except for OS, there was no full PS 2 analysis. We contacted the study authors, but the data necessary for our analysis were no longer available.

Karampeazis 2011 evaluated OS, ORR, TTP, and safety profile in people aged 65 years or older treated with either docetaxel 38 mg/m^2 or vinorelbine 25 mg/m^2, both administered on days one and eight of a three-week cycle, in an open-label, multicenter, phase III trial from Greece. They randomized 138 participants, stratifying according to PS (0 or 1 versus 2) and stage (IIIB versus IV). Among them were 26 participants with PS 2; 19 treated with docetaxel and six with vinorelbine. The study reported aggregated data on OS and ORR for the subgroup of participants with PS 2. Therefore, we attempted to contact the study authors but were unable to retrieve additional data.

Kosmidis 2012 randomized people to vinorelbine 60 mg/m^2 or paclitaxel 90 mg/m^2 on days one, eight, and 15 of a four-week cycle for a maximum of four cycles. They included people with PS 2 only and were primarily focused on clinical benefits. There was no stratification in randomization provided. Secondary endpoints were ORR, OS, TTP, and toxicity. The total number of participants was estimated to be 92, but due to low accrual, the study was prematurely terminated after randomization of 75 participants. Not all our endpoints could be retrieved from the publication. We contacted the study authors but no further data were available.

Langer 2007 (ECOG 1599) conducted an open-label phase II trial in the US comparing carboplatin AUC 6 plus paclitaxel 200 mg/m^2 with cisplatin 60 mg/m^2 plus gemcitabine 1000 mg/m^2 in participants with PS 2. Stratification factors included weight loss in preceding six months (less than 5% versus 5% or greater) and stage (IIIb versus IV/recurrent). The primary endpoint was one-year survival rate, other endpoints were ORR, PFS, and toxicities. As a result of power calculations based on previous studies, they randomized 103 participants, which proved to be underpowered to detect the reported improvement in one-year OS. As this publication presented almost all our endpoints, we contacted the study authors but were unable to retrieve additional data.

Morere 2010 (IFCT-0301) presented the results of an open-label multicenter, phase II trial from France. People with PS 2 or 3 were randomized to gefitinib, gemcitabine 1250 mg/m^2, or docetaxel 75 mg/m^2, stratifying by PS (2 versus 3) and pathologic diagnosis (adenocarcinoma versus non-adenocarcinoma). They assessed PFS, ORR, OS, and toxicities. The gefitinib arm was not included in this review. A total of 42 participants were randomized: 30 participants with PS 2 received gemcitabine and 28 participants with PS 2 received docetaxel. The study was set up as exploratory, therefore it was underpowered to make definite conclusions. We contacted the IFCT to obtain additional information and received a complete analysis of the PS 2 subgroup.

Sweeney 2001 reported the results of the ECOG 1594 trial, which compared four platinum doublet regimens, cisplatin 75 mg/m^2 plus paclitaxel 135 mg/m^2, cisplatin 100 mg plus gemcitabine 1000 mg/m^2, cisplatin 75 mg/m^2 plus docetaxel 75 mg/m^2, and carboplatin AUC 6 plus paclitaxel 225 mg/m^2. Stratification variables used in randomization were PS (0 or 1 versus 2), weight loss in preceding six months (less than 5% versus 5% or greater), stage (IIIB versus IV/recurrent), and presence or absence of brain metastases. After 66 participants with a PS of 2 had been enrolled, the study design was amended to include only participants with a PS of 0 or 1 because of the high rate of serious adverse events in the people with a PS of 2 (Schiller 2002). A later conclusion was that these events were related to disease progression rather than treatment-related adverse events. This publication reported all our endpoints.

Yadav 2021 performed a single center open-label randomized trial with a superiority design in India. A total of 44 participants were randomized to carboplatin AUC 5 plus pemetrexed 500 mg/m^2 or carboplatin AUC 5 plus paclitaxel 80 mg/m^2, without stratification by any factor. Participants in both treatment arms were allowed to receive maintenance pemetrexed 500 mg/m^2. The primary endpoint was six-month PFS rate, and secondary endpoints were ORR, disease control rates, OS, and toxicity. We contacted the study authors and received a full analysis of the PS 2 subgroup.

Chemotherapy versus immunotherapy

We identified two studies comparing chemotherapy versus immunotherapy.

Lee 2022 designed a global, multicenter, open-label phase III trial for people not eligible for platinum chemotherapy, randomizing participants between single-agent atezolizumab 1200 mg or single-agent non-platinum chemotherapy (vinorelbine or gemcitabine at investigators choice, dose per relevant local guidelines), without reported stratification factors. Most participants were not eligible for any platinum-doublet chemotherapy due to poor PS (ECOG PS 2 or 3), or participants aged 70 years or older with PS 0 or 1 with substantial comorbidities or contraindication(s) for any platinum-doublet chemotherapy. The primary endpoint was OS, and secondary endpoints were OS rates at six, 12, 18 and 24 months; ORR; PFS; duration of response; toxicity; and QoL. Data were presented at the 2022 ESMO congress only, and we were unable to obtain additional data from the authors.

Lena 2022 conduced a randomized phase III trial in France, randomizing participants stratified by age (under 70 years versus 70 years or older), PS (0 or 1 versus 2), and histology (squamous versus non-squamous), to either nivolumab 240 mg every two weeks plus ipilimumab 1 mg/kg every six weeks, or doublet chemotherapy with carboplatin AUC 5 plus pemetrexed 500 mg/m^2 or carboplatin AUC 6 plus paclitaxel 90 mg/m^2, and the possibility to use maintenance with pemetrexed. The primary endpoint was OS, and secondary endpoints were one-year OS, ORR, PFS, safety rate, tolerability rate, and QoL. A preplanned interim analysis carried out after observation of 33% of deaths, out of 174 randomized participants (of planned 242 participants), showed a risk of futility especially for participant with PS 2. This led to a halt in randomization. As this study was only accessed by abstract from the 2022 ASCO annual congress, we were unable to obtain additional data.

Excluded studies

After full-text analysis, we excluded 97 manuscripts as they did not match our inclusion criteria (Figure 1). The main reasons for exclusion were the use of an incompatible treatment regimen (37/97) or duplicate items (38/97).

We excluded 60 studies as they did not provide separate PS 2 data. We attempted to contact study authors, and in nine cases it was confirmed that there was no possibility of obtaining aggregated PS 2 data only (Al-Gizawy 2014; Doebele 2015; Ferry 2017; Giaccone 1998; Kosmidis 1994; Kumar 2015; Perol 2002; Rodrigues-Pereira 2011; Wachters 2003). We could not contact the authors from the other 51 studies, probably because many studies were performed decades ago (Anderson 1985; Anderson 2000; Atagi 2017; Belani 2006; Cartei 1993; Cellerino 1991; Comella 2004; Crino 1990; Crino 1995; Cullen 1999; Danson 2003; ELVIS 1999; Esteban 2006; Fossella 2003; Ganz 1989; Gebbia 2002; Gebbia 2003; Georgoulias 2001; Greco 2007; Gridelli 1996; Gridelli 2003a; Gridelli 2003b; Grigorescu 2002; Helbekkmo 2007; Helsing 1998; Hillerdal 2011; Jang 2017; Jelić 2001; Kaasa 1991; Karampeazis 2017; Leong 2007; Manegold 1997; Masutani 1996; Paccagnella 2006; Quoix 1991; Ranson 2000; Rapp 1988; Rosell 1987; Rosell 2002; Rosso 1990; Roszkowski 2000; Ruckdeschel 1985; Ruckdeschel 1986; Shinkai 1985; Sorensen 2012; Spiro 2004; Stathopoulos 2004; ten Bokkel Huinink 1999; Thongprasert 1999; Veronesi 1988; Woods 1990).

Two trials were registered on Clinicaltrials.gov; however, we were unable to obtain any data (NCT00004887; NCT01593293).

Ongoing studies

Chemotherapy plus immunotherapy versus immunotherapy

We identified one ongoing clinical trial designed for people with PS 2, randomizing people between single-agent pembrolizumab or pembrolizumab plus paclitaxel plus carboplatin (NCT02581943). Results from this study are expected in 2023.

Risk of bias in included studies

See Figure 2 and Figure 3 for an overview of risk of bias in all included studies.

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

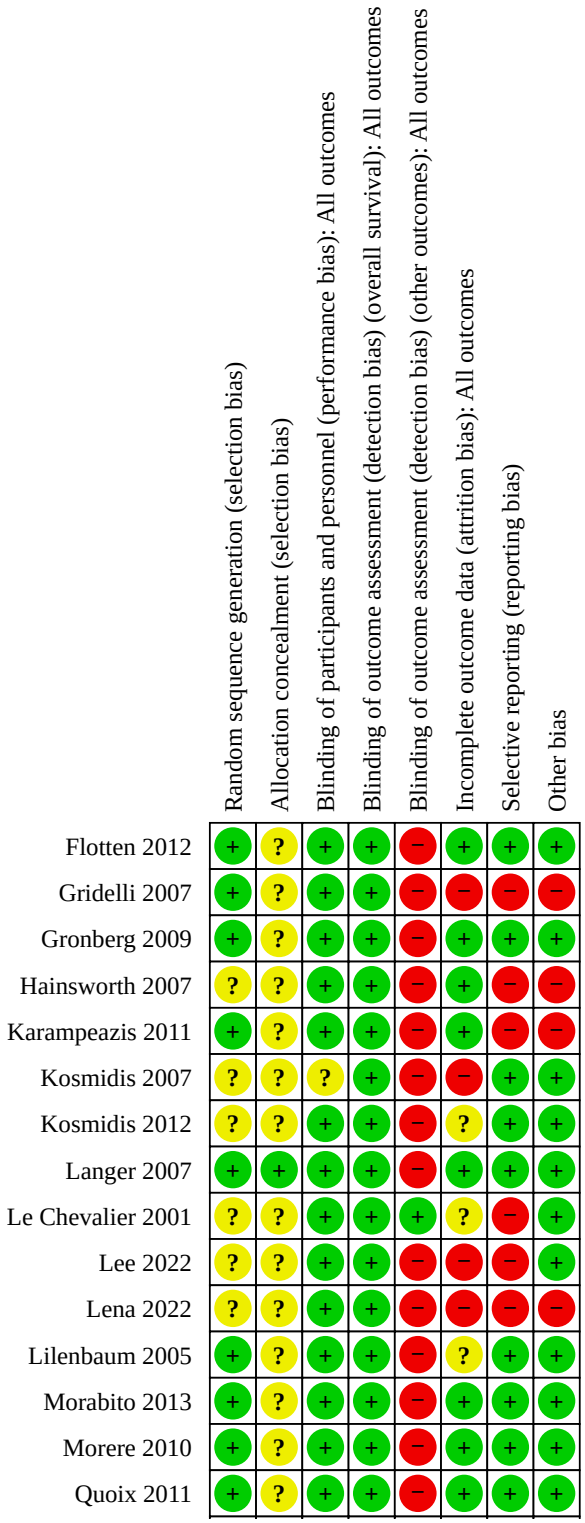


Figure 2. (Continued)

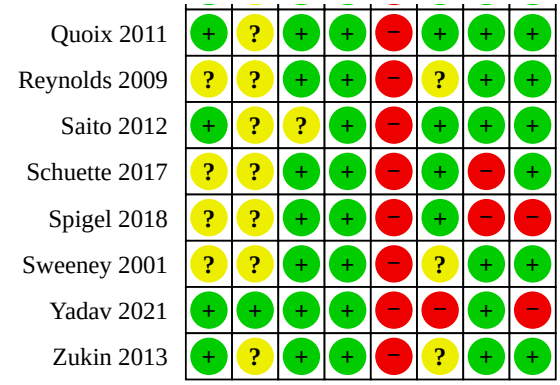
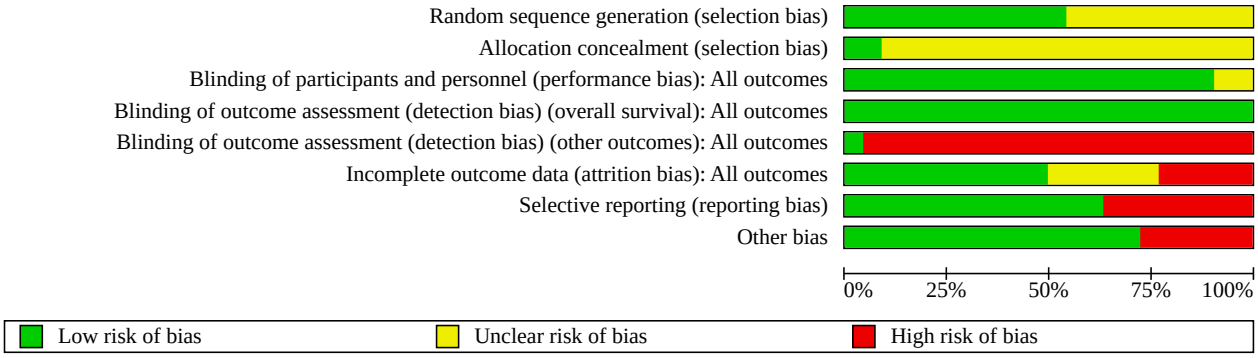


Figure 3. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.



Allocation

Flotten 2012, Gridelli 2007, Gronberg 2009, Karampeazis 2011, Langer 2007, Lilenbaum 2005, Morabito 2013, Morere 2010, Quoix 2011, Saito 2012, Yadav 2021, and Zukin 2013 had a low risk of bias for random sequence generation. Hainsworth 2007, Kosmidis 2007, Kosmidis 2012, Le Chevalier 2001, Lee 2022, Lena 2022, Reynolds 2009, Schuette 2017, Spigel 2018, and Sweeney 2001 had an unclear risk of bias for random sequence generation. No studies were at high risk of random sequence generation.

We considered Langer 2007 and Yadav 2021 to have a low risk of bias for allocation concealment. All other included trials were at unclear risk.

Blinding

Almost all included studies were reported as open-label trials. In Kosmidis 2007, we were unable to retrieve the blinding status of participants and investigators and Saito 2012 provided no information on blinding (it was probably an open-label trial as treatment days between arms were different); therefore, this was at unclear risk of performance blinding.

We considered that an open-label trial is unlikely to influence OS; therefore, we considered this outcome at low risk of detection bias. However, the bias for the other outcomes in terms of PFS, ORR, and toxicity are considered high risk in all but one of the included studies. Le Chevalier 2001 used a panel of at least three experts, who were blinded to the treatment assignment, verified eligibility criteria, staging, and toxicity, and reviewed original x-rays to evaluate response in all cases and it was, therefore, considered at low risk of detection bias.

Incomplete outcome data

We classified five studies at high risk for incomplete outcome reporting (Gridelli 2007; Hainsworth 2007; Lee 2022; Lena 2022; Yadav 2021). Gridelli 2007 did change their outcome measures after data analysis as 44/87 included people had censored times for time to progressive disease, whereas only 14/87 people had censored times for PFS, therefore adding PFS as outcome measurement. Next, best overall response was not assessable in 17 (38.6%) versus four (9.3%) of the people and therefore considered as high risk. Kosmidis 2007 had high rates of missing QoL data on the LCSS, which was the primary outcome measure. After enrollment of 102 people, 12 people were not included in the analysis. Two people were excluded from the analysis and 10 people were considered ineligible. Seven people were inadvertently randomized (PS less than 2), two received protocol treatment as second line, and one had another cancer. Two people randomized in the platinum doublet arm received gemcitabine only but were included in the survival analysis. Lee 2022 and Lena 2022 were only reported as congress abstracts and did not provide a full detailed analysis. Yadav 2021 included 180 of planned 362 people before study

termination. However, nine people did not start study treatment due to various reasons, four were lost to follow-up, and three switched to target therapy. Next, radiologic response evaluation was not possible in 18 people.

Six studies were classified at unclear risk. Kosmidis 2012 was unable to include all people in the toxicity analysis with an unknown effect. Le Chevalier 2001 was classified at unclear risk, as in the primary study a small number of people were not treated according to protocol but were included in the analysis (Le Chevalier 1994). Reynolds 2009 and Zukin 2013 did not have data available for all people when analyzing response, with unclear risk. Sweeney 2001 was classified at unclear risk for incomplete outcome bias. Accrual of participants with PS 2 was discontinued because of a perception of excess adverse events. Lilenbaum 2005 was considered at unclear risk as 23 (3.9%) participants either withdrew from the study before receiving protocol therapy or were later found to be ineligible.

Flotten 2012, Gronberg 2009, Hainsworth 2007, Karampeazis 2011, Langer 2007, Morabito 2013, Morere 2010, Quoix 2011, Saito 2012, Spigel 2018, and Schuette 2017 were at low risk of attrition bias.

Selective reporting

Eight studies were at high risk for reporting bias (Gridelli 2007; Hainsworth 2007; Karampeazis 2011; Le Chevalier 2001; Lee 2022; Lena 2022; Schuette 2017; Spigel 2018).

Gridelli 2007 was considered high risk for selective reporting, as PFS was retrospectively added as an outcome measurement. Hainsworth 2007 did not perform a full separate analysis of participants with PS 2 except for OS, although this group of participants was a different subgroup compared to the PS 0 or 1, elderly group. Karampeazis 2011 did not perform all analyses in participants with PS 2, whereas this was one of the study aims. Le Chevalier 2001 only reported the one-year survival rates of participants with PS 2, the other outcomes were not assessed in participants with PS 2 only. Lee 2022 and Lena 2022 only reported limited data in congress abstracts, not providing all required data for this review. Schuette 2017 did not report all outcomes in participants with PS 2. Also, they provided insufficient information on severity grade of toxicities. Spigel 2018 reported treatment-related toxicities only if the incidence was greater than 10% of at least one study arm, thereby considered at high risk for reporting bias.

The other included studies were considered at low risk for selective reporting, as no evidence of selective reporting bias was found and all outcomes were provided (Flotten 2012; Gronberg 2009; Kosmidis 2007; Kosmidis 2012; Langer 2007; Lilenbaum 2005; Morabito 2013; Morere 2010; Quoix 2011; Reynolds 2009; Saito 2012; Sweeney 2001; Yadav 2021; Zukin 2013).

Other potential sources of bias

Karampeazis 2011 had a slow accrual rate because of the reluctance of investigators to prescribe chemotherapy in people with a PS of 2, and a further slowdown of accrual occurred after 2006 when Kudoh 2006 reported their randomized trial in elderly people. Because of these reasons, the data monitoring committee decided to close the study after including 138/176 planned participants, resulting in an underpowered study. Due to a change in the standard of care and slow accrual, Yadav 2021 was terminated early after randomizing 180 people while the estimated sample size was 364 (182 in each arm).

While Spigel 2018 was ongoing, a randomized phase 3 trial demonstrated the superiority of platinum doublet (Lilenbaum 2005). As a result, the accrual of people to single-agent pemetrexed (arm one) was stopped, and subsequent randomization (1:1) was continued to arms two and three only.

Hainsworth 2007 included both people with PS 2 or elderly people, however, a separate analysis was not performed and therefore considered at high risk of bias.

Lena 2022 showed partly incorrect data in their congress abstract, therefore considered at high risk of bias.

Gridelli 2007 was at high risk as they performed complete subgroup analysis including both people with PS 2 or elderly people.

All other trials were at low risk of other bias.

Effects of interventions

See: **Summary of findings 1** Platinum doublet compared to non-platinum therapy for people with advanced non-small cell lung cancer, performance status 2 without a targetable mutation or with an unknown mutation status

We summarized the effects of interventions in the Summary of findings 1, Table 2, and Table 3.

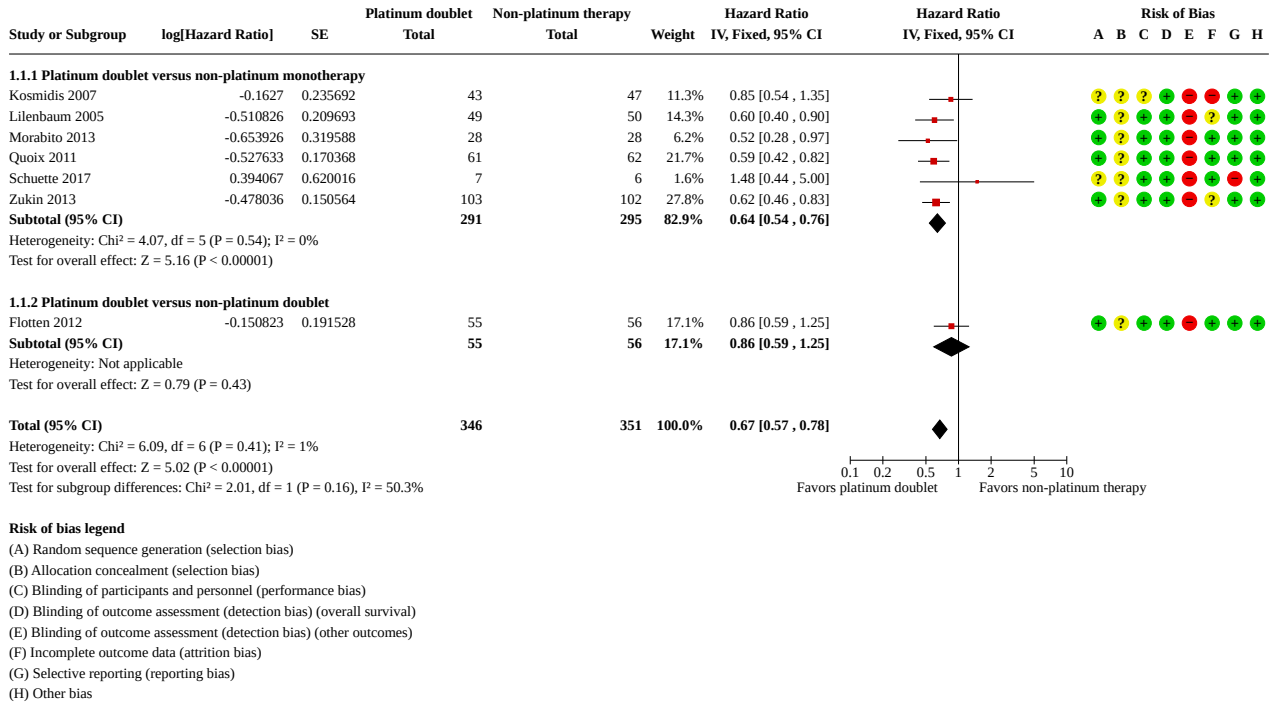
Chemotherapy versus chemotherapy: non-platinum therapy versus platinum doublet regimens

Overall survival

All 11 RCTs included in this analysis evaluated OS as an endpoint (Table 3). However, we excluded four studies from the analysis as they presented no HRs (Le Chevalier 2001; Reynolds 2009; Saito 2012; Spigel 2018).

Meta-analysis of the seven remaining studies included 697 people showed the superiority of platinum doublet therapy over non-platinum therapy with low heterogeneity (HR 0.67, 95% CI 0.57 to 0.78; I^2 = 1%; moderate-certainty evidence; Analysis 1.1; Figure 4). Although there was significant heterogeneity between non-platinum monotherapy and non-platinum doublet subgroups (I^2 = 50.3%), excluding the only study using non-platinum doublet (Flotten 2012) did not influence the pooled results (HR 0.64, 95% CI 0.54 to 0.76; I^2 = 0%). Analyzing only the studies designed for participants with PS 2 (Kosmidis 2007; Morabito 2013; Zukin 2013), and excluding the studies performing PS 2 subgroup analysis (Flotten 2012; Lilenbaum 2005; Quoix 2011; Schuette 2017), did not influence the results (HR 0.66, 95% CI 0.52 to 0.83; I^2 = 0%).

Figure 4. Forest plot of comparison of platinum doublet versus non-platinum therapy on overall survival



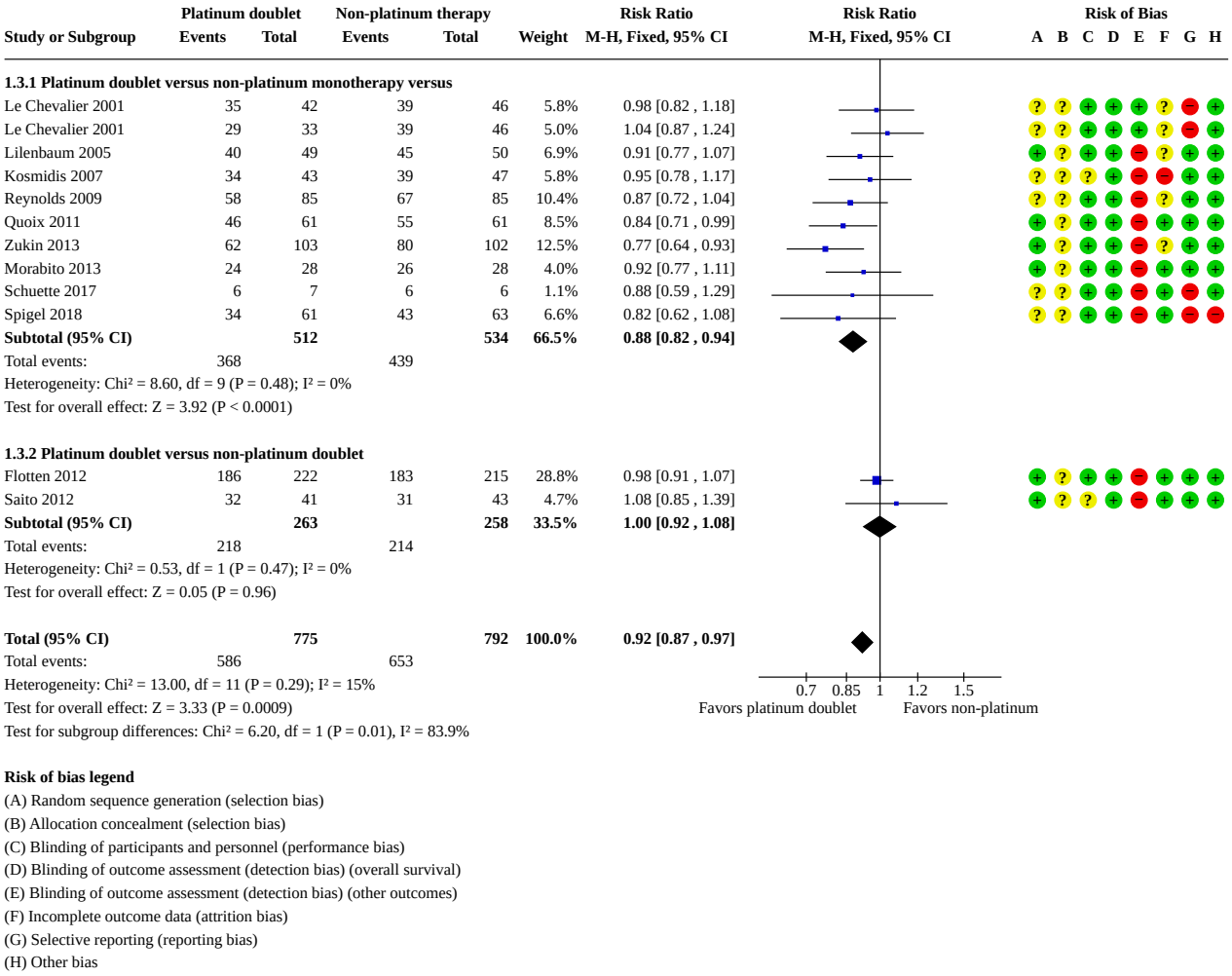
Six- and 12-month survival rates

Of the 11 trials included in this analysis, only six reported six-month survival rates. In contrast, all trials reported 12-month survival rates (Table 3).

There was no difference in six-month survival between treatment regimens (random-effects model; RR 1.00, 95% CI 0.72 to 1.41; I^2 = 76%; moderate-certainty evidence; Analysis 1.2). The reason for heterogeneity was unclear. Exclusion of the only study using non-platinum doublet (Flotten 2012) did not influence the pooled results (RR 1.03, 95% CI 0.64 to 1.63; I^2 = 80%). When including only studies designed especially for participants with PS 2 (Morabito 2013; Spigel 2018; Zukin 2013), heterogeneity decreased and there was a trend towards the superiority of platinum therapy, but did not reach a significance level (RR 0.75, 95% CI 0.53 to 1.04; I^2 = 57%).

In the meta-analysis of 1567 participants from 11 studies, 12-month survival rates were improved with platinum doublet therapy (RR 0.92, 95% CI 0.87 to 0.97; I^2 = 15%; moderate-certainty evidence; Analysis 1.3; Figure 5). However, there was clear subgroup heterogeneity between the non-platinum monotherapy and non-platinum doublet therapy arms (I^2 = 83.9%). The treatment effect of platinum doublet was higher in the subgroup compared with non-platinum monotherapy (RR 0.88, 95% CI 0.82 to 0.94; I^2 = 0%; 9 trials, 1046 participants), whereas there was no difference between treatment arms in the non-platinum doublet subgroup (RR 1.00, 95% CI 0.92 to 1.08; I^2 = 0%; 2 trials, 521 participants). When analyzing only the studies designed for participants with PS 2 (Kosmidis 2007; Morabito 2013; Reynolds 2009; Saito 2012; Spigel 2018; Zukin 2013), and thus excluding those performing PS 2 subgroup analysis (Flotten 2012; Le Chevalier 2001; Lilenbaum 2005; Quoix 2011; Schuette 2017), we found no changes in treatment effect or heterogeneity (HR 0.87, 95% CI 0.80 to 0.95; I^2 = 18%), but there was lower heterogeneity when excluding the only remaining study comparing to non-platinum doublet therapy (Saito 2012) (HR 0.85, 95% CI 0.77 to 0.93; I^2 = 0%).

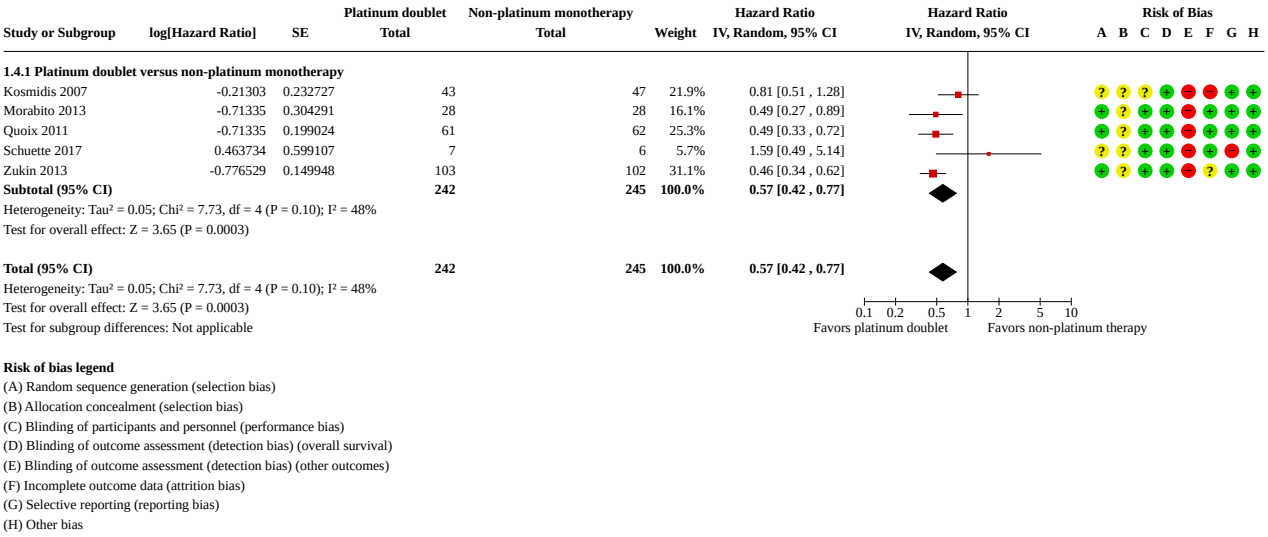
Figure 5. Forest plot of comparison of platinum doublet versus non-platinum therapy on 12 months survival rates



Progression-free survival

Five trials including 487 participants contributed to the meta-analysis of PFS (Kosmidis 2007; Morabito 2013; Quoix 2011; Schuette 2017; Zukin 2013); all compared platinum doublet to non-platinum monotherapy. PFS of people treated with platinum doublet therapy was superior compared to people treated with non-platinum monotherapy, with substantial heterogeneity (random-effects model; HR 0.57, 95% CI 0.42 to 0.77; I^2 = 48%; moderate-certainty evidence; Analysis 1.4; Figure 6). When analyzing only the studies designed for people with PS 2 (Kosmidis 2007; Morabito 2013; Zukin 2013), there was no change in treatment effect and higher heterogeneity (HR 0.56, 95% CI 0.39 to 0.80; I^2 = 53%). However, when excluding the two studies with a high risk of bias on domains other than blinding (as all studies were open-label) (Kosmidis 2007; Schuette 2017), the heterogeneity disappeared (HR 0.47, 95% CI 0.38 to 0.59; I^2 = 0%).

Figure 6. Forest plot of comparison of platinum doublet versus non-platinum therapy on progression free survival

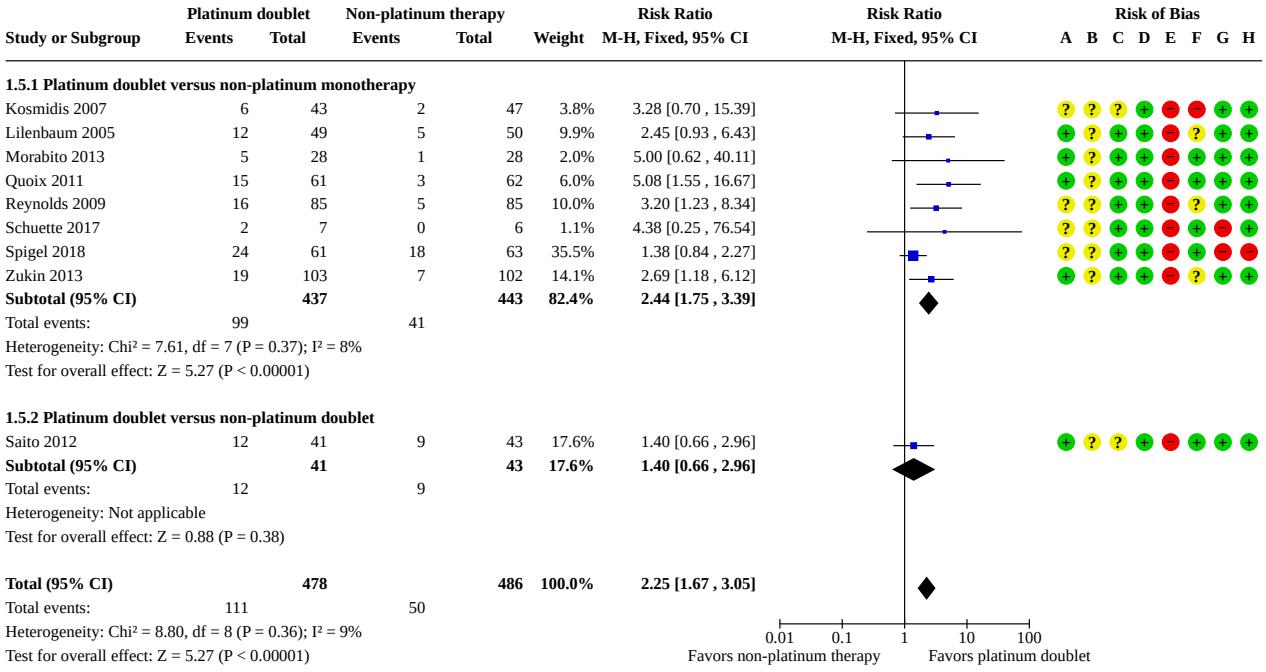


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias) (overall survival)
(E) Blinding of outcome assessment (detection bias) (other outcomes)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Tumor response rate

Nine studies including 964 participants found a higher tumor response rate for people treated with platinum therapy (RR 2.25, 95% CI 1.67 to 3.05; I^2 = 9%; moderate-certainty evidence; Analysis 1.5; Figure 7). This did not change after excluding Saito 2012 (RR 2.44, 95% CI 1.75 to 3.39; I^2 = 8%), or when excluding studies evaluating PS 2 subgroups only (RR 2.16, 95% CI 1.49 to 3.14; I^2 = 19%).

Figure 7. Forest plot of comparison of platinum doublet versus non-platinum therapy on tumor response rate



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias) (overall survival)
(E) Blinding of outcome assessment (detection bias) (other outcomes)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Toxicity

Of the 11 included studies in this analysis, three did not report any adverse event analysis in participants with PS 2 only (Le Chevalier 2001; Lilenbaum 2005; Schuette 2017).

Five studies reported all-grade adverse events (Kosmidis 2007; Morabito 2013; Quoix 2011; Schuette 2017; Spigel 2018), whereas 11 studies reported hematologic adverse events, but there was considerable heterogeneity in the publication of non-hematologic adverse events and, therefore, we were only able to meta-analyze nausea/vomiting, asthenia, and fatigue.

Eight studies reported data for adverse events with grade 3 or higher, with low heterogeneity among the hematologic adverse events and high heterogeneity in reporting of non-hematologic adverse events.

Except for febrile neutropenia (moderate-certainty evidence), all other toxicity outcomes were of low-certainty evidence.

All grades hematologic adverse events

There was no difference in risk of anemia (any grade) (RR 1.13, 95% CI 0.92 to 1.39; I^2 = 28%; 4 studies, 304 participants; Analysis 1.6). However, there was increased risk of any-grade neutropenia and thrombocytopenia in people treated with platinum doublet therapy in a pooled analysis of five studies including 391 participants (neutropenia: RR 2.22, 95% CI 1.58 to 3.11; Analysis 1.7; thrombocytopenia: RR 3.05, 95% CI 2.08 to 4.48; Analysis 1.8).

All grades non-hematologic adverse events

There were no differences in risk for nausea/vomiting, asthenia, or fatigue (nausea/vomiting: RR 1.23, 95% CI 0.94 to 1.60; I^2 = 0%; 4 studies, 304 participants; Analysis 1.9; asthenia: RR 1.30, 95% CI 0.92 to 1.85; I^2 = 0%; 3 studies, 250 participants; Analysis 1.10; fatigue: RR 1.16, 95% CI 0.86 to 1.56; I^2 = 0%; 2 studies, 168 participants; Analysis 1.11).

Grade 3 or higher hematologic adverse events

We assessed the risk for grade 3 or higher hematologic adverse events in eight studies including 935 participants (Flotten 2012; Kosmidis 2007; Morabito 2013; Quoix 2011; Reynolds 2009; Saito 2012; Spigel 2018; Zukin 2013). In the pooled analysis, people treated with platinum doublet therapy were at higher risk for severe anemia (random-effects model; RR 1.98, 95% CI 1.00 to 3.92; I^2 = 46%; Analysis 1.12). The high heterogeneity was due to the inclusion of Flotten 2012 and Saito 2012, as they compared to non-platinum doublet therapy. When we excluded these studies, the risk difference was enhanced and there was no heterogeneity (RR 2.78, 95% CI 1.58 to 4.89; I^2 = 0%).

People treated with platinum doublet therapy were at higher risk for severe neutropenia and thrombocytopenia (neutropenia: RR 2.75, 95% CI 1.30 to 5.82; I^2 = 82%; Analysis 1.13; thrombocytopenia: RR 3.96, 95% CI 1.73 to 9.06; I^2 = 42%; Analysis 1.14). When we excluded Flotten 2012 and Saito 2012, the risk differences were increased and there was no heterogeneity (neutropenia: RR 4.31, 95% CI 2.80 to 6.64; I^2 = 0%; Analysis 1.13; thrombocytopenia: RR 7.69, 95% CI 3.74 to 15.80; I^2 = 0%; Analysis 1.14).

Seven studies including 821 participants found no difference in the risk for febrile neutropenia (RR 1.63, 95% CI 0.85 to 3.12; I^2 = 27%; Analysis 1.15).

Grade 3 or higher non-hematologic adverse events

There were no differences in risk for grade 3 to 5 nausea/vomiting (RR 2.74, 95% CI 0.83 to 9.04; I^2 = 44%; 7 studies, 850 participants; Analysis 1.16). This did not change after exclusion of the non-platinum doublet studies of Flotten 2012 and Saito 2012 (RR 1.41, 95% CI 0.32 to 6.27; I^2 = 41%). However, when pooling only those two studies, there was a difference (RR 8.72, 95% CI 2.07 to 36.71; I^2 = 0%).

Four studies including 439 participants assessed grade 3 to 5 fatigue. There was no difference between arms (RR 0.81, 95% CI 0.35 to 1.90; I^2 = 62%; Analysis 1.17). Excluding Flotten 2012 did not result in a change. There was no difference in grade 3 to 5 asthenia between arms (RR 2.06, 95% CI 0.97 to 4.38; I^2 = 0%; 2 studies, 237 participants; Analysis 1.18).

Health-related quality of life

Four trials reported HRQoL data. Of those, three were performed in a trial including participants with PS 2 only (Kosmidis 2007; Morabito 2013; Saito 2012). One included participants with PS 2 as a subgroup, and did not report on this subgroup in their primary report but provided the data following our request (Flotten 2012). However, the used methodology was different in each trial and, therefore, we were unable to perform a meta-analysis on these data.

Flotten 2012 compared the results of the EORTC QLQ-C30 with LC13 lung cancer subscale from baseline to week 17 in people randomized to vinorelbine plus gemcitabine or carboplatin plus vinorelbine. They found no difference between arms in general HRQoL, nausea/vomiting, dyspnea, pain, or fatigue subscales during the study period. A formal calculation analyzing changes overtime was not performed, although numerically, the global QoL score (on a scale from 0 to 100) was not clinically relevant (less than 10 points).

Morabito 2013 also reported the outcomes of the EORTC QLQ-C30 and LC13 subscale; however, they only evaluated QoL on days one and eight of cycles one and two in people randomized to gemcitabine monotherapy or cisplatin plus gemcitabine. There was no evidence of a negative impact of platinum doublet compared to gemcitabine monotherapy in terms of general HRQoL; however, compliance to the questionnaires was low with a 32% completion rate for gemcitabine monotherapy and 46% for platinum doublet.

Kosmidis 2007 used the LCSS to assess clinical benefit after cycles two and four in 90 people randomized to gemcitabine monotherapy or carboplatin plus gemcitabine. Regarding general feeling and symptoms, there was no difference between the two arms at each timepoint, or when compared to baseline values. There was a high rate of missing values, varying per item, ranging from 37% to 93% missing data.

Saito 2012 analyzed disease-related symptoms using the Lung Cancer Subscale of the Functional Assessment of Cancer Therapy – Lung Cancer Subscale (FACT-LCS) at baseline and after cycles one and two in people randomized between carboplatin plus paclitaxel or gemcitabine plus vinorelbine. With a completion rate of 81% at the end of cycle two, there was an improvement of the summed score compared to baseline in both arms, above minimal important difference but no difference between arms.

Chemotherapy versus chemotherapy: carboplatin versus cisplatin therapy

For direct comparison, two studies including 131 participants provided sufficient data for analysis of 12-month survival and tumor response rates (Langer 2007 (PS 2 only); Sweeney 2001 (subgroup analysis)). For comparability, we included only the cisplatin plus gemcitabine arm from Sweeney 2001 in this analysis.

Twelve-month survival rate

There was no difference in 12-month survival rates (random-effects model; RR 1.08, 95% CI 0.73 to 1.60; I^2 = 59%; Analysis 2.1), or in tumor response rate (RR 0.64, 95% CI 0.64 to 1.34; I^2 = 0%; Analysis 2.3).

We also performed an indirect comparison, comparing subgroups. Two studies including 223 participants used cisplatin as the platinum compound (Le Chevalier 2001 (subgroup analysis); Morabito 2013 (PS 2 only)) versus nine trials including 1344 participants using carboplatin (Flotten 2012; Kosmidis 2007; Lilenbaum 2005; Quoix 2011; Reynolds 2009; Saito 2012; Schuette 2017; Spigel 2018; Zukin 2013). In the carboplatin subgroup, 12-month survival rates were better for the carboplatin group compared to the non-platinum group (RR 0.91, 95% CI 0.86 to 0.96; I^2 = 28%), while cisplatin showed no survival benefit (RR 0.98, 95% CI 0.89 to 1.09; I^2 = 0%; Analysis 2.2).

Tumor response rate

There was no difference in tumor response rate (RR 0.64, 95% CI 0.31 to 1.34; I^2 = 0%; Analysis 2.3).

Chemotherapy versus immunotherapy

We included only two trials comparing immunotherapy with chemotherapy (Lee 2022; Lena 2022). Both were published as congress abstract only, providing only limited data and, therefore, we were unable to perform a meta-analysis using these data.

After inclusion of 344 people with PS 2, Lee 2022 found that atezolizumab was not superior to non-platinum chemotherapy (vinorelbine or gemcitabine) on median OS (12-month OS rate: 43.7% with atezolizumab versus 38.6% with non-platinum chemotherapy; HR 0.86, 95% CI 0.67 to 1.10). In a cohort of (estimated) 64 participants with PS 2, Lena 2022 found a median OS of 2.9 months (95% CI 1.4 to 4.8) in people treated with nivolumab plus ipilimumab compared to 6.1 months (95% CI 3.5 to 10.4) in those treated with platinum doublet therapy (P = 0.22). Other endpoints were not specified or reported. There might be an

inclusion bias in this trial, as there were fewer participants included with PD-L1 expression of 50% or greater than expected.

DISCUSSION

Summary of main results

Historically, people with a PS of 2 are frequently excluded from (important) clinical trials because of poorer outcomes and increased toxicity compared with people with a PS of 0 or 1 (Borghaei 2015; Kogure 2018; Scagliotti 2008; Zinner 2016). This is reflected in the fact that of 3661 unique screened records, only 67 articles were included in our analysis, whereas only the data of 22 trials were reported or retrieved sufficient to be included in the meta-analysis. These studies included 6759 participants, including only 2395 participants with PS 2 (35.4%). As there was high heterogeneity between treatment regimens, we were only able to perform a full meta-analysis of platinum doublet versus non-platinum therapy.

From the analysis of 11 studies comparing non-platinum therapy versus platinum doublet, we found that the use of platinum doublet therapy resulted in superior OS, 12-month survival rate, PFS, and tumor response rate compared with non-platinum monotherapy. There were no changes in the outcomes when we restricted the analysis to only including studies specifically designed for people with PS 2.

There were no differences in the comparison with platinum doublet versus non-platinum doublet therapy. However, these advantages were associated with a greater risk of grade 3 or 4 adverse events compared to non-platinum therapy for anemia, neutropenia, and thrombocytopenia. There was no difference in risk for febrile neutropenia, neither were there differences in non-hematologic toxicity such as fatigue, asthenia, nausea, and vomiting. Although evidence was limited, carboplatin seemed to give better 12-month survival rates than cisplatin when compared to non-platinum therapy.

Although checkpoint inhibitors with or without platinum doublet became first-line treatment in people with PS 0 and 1 (NICE 2023; Hendriks 2023), we identified an important knowledge gap as data from randomized trials of its use in people with PS 2 were limited. In this analysis with limited supporting data, whereas use of double-agent immunotherapy is not encouraged in people with PS 2, there might be a place for single-agent immunotherapy.

Overall completeness and applicability of evidence

We were unable to include randomized trials comparing chemotherapy with BSC. Although such studies were performed in participants with PS 2, no data were available to date for use in this review as the studies were performed decades ago.

Our analysis included only studies using cytotoxic chemotherapy, with or without the addition of an angiogenesis inhibitor. As there were too many various treatment regimens, we could not specify the effect size by type of cytotoxic agent other than platinum doublet versus non-platinum therapies, and we were unable to select the preferred platinum doublet regimen. People with PS 2 could benefit more from platinum doublet chemotherapy, whereas for people who are ineligible for platinum chemotherapy, non-platinum (mono or doublet) therapies could be beneficial.

The group of people with PS 2 is heterogeneous and the results of our study should be interpreted with caution as the cause of the deterioration of the PS might be due to comorbidity or the disease itself. The latter might benefit more from systemic therapy than the first group (Sculier 2007). Of note, most included studies were performed before the introduction of immunotherapy and most targeted therapies, therefore PD-L1 status and availability of targetable mutations were not assessed in these people. Also, as the ECOG PS is a subjective score, different healthcare providers may report different PS (Chow 2016).

There were only two partially published randomized trials using immune checkpoint inhibitors in people with PS 2, showing disappointing results in OS in people treated with immunotherapy compared to chemotherapy. They did not report toxicity rates specified to people with PS 2. As the OS might be similar between single-agent chemotherapy and single-agent immunotherapy, the decision might be based on the adverse events people experience. One prospective phase II trial evaluating first-line immunotherapy in people with PS 2 with advanced NSCLC found that pembrolizumab can be safely administered, with no increase in the risk of immune-related or other toxicities, with OS of 7.9 months (95% CI 2.6 to unlimited) (PePS2 trial, Middleton 2020). A virtual International Expert Panel was established in July 2021 with the aim of reviewing the available evidence on the use of immunotherapy in NSCLC people with ECOG PS 2, both in clinical practice and in a research setting. The panelists agreed that, though limited, the available data support the safety of single-agent immunotherapy in NSCLC people with PS 2 (Gridelli 2022).

Quality of the evidence

All studies were open-label and therefore considered high risk for outcome bias, except OS. Therefore, we downgraded the certainty of evidence of these outcomes (PFS, response rate, toxicities). Also, due to high heterogeneity, we downgraded the certainty of evidence of the toxicity outcomes, except for febrile neutropenia. Finally, because the number of studies reporting asthenia was sparse, we downgraded the certainty of evidence.

Potential biases in the review process

This review contains, to our knowledge, the largest dataset on people with advanced NSCLC with PS 2 and first-line therapy. However, a few limitations should be stated.

From a high number of included studies, we were unable to retrieve some data to analyze in our study. In most studies including people with PS 2, the main endpoints were not reported for this subgroup only and were subsequently excluded.

Also, the treatment regimens used in the analysis of platinum doublet versus non-platinum therapy were varied. We were unable to perform an analysis to evaluate each therapy separately due to the limited number of trials.

All included studies were open-label, which enhances detection bias for response rates, PFS, and toxicities. We do not expect that OS and six- and 12-month rates were influenced by this study methodology.

Agreements and disagreements with other studies or reviews

In 1995, the NSCLC Collaborative Group published an analysis comparing chemotherapy with BSC based on individual patient data, including people with PS 2 (NSCLC Collaborative Group 1995). This study was later adapted by Cochrane and found a survival benefit of chemotherapy over BSC in people with PS of 2 or greater in a pooled analysis of 2714 people from 16 RCTs, including 594 participants with PS 2 or greater (NSCLC Collaborative Group 2010). Whereas they did not suggest a specific treatment regimen and they included a minority of people with PS 3, it is clear that people with declined PS benefit from chemotherapy compared to BSC only.

Vasconcellos 2020 performed a Cochrane Review comparing cisplatin versus carboplatin in combination with a third-generation drug for advanced NSCLC. They showed equivalent OS, 12-month OS, and response rate. Regarding adverse events, carboplatin caused more thrombocytopenia, and cisplatin caused more nausea/vomiting. They did not include a subgroup of participants with PS 2. One Cochrane Review in people with advanced NSCLC aged greater than 70 years without significant comorbidities found that survival increased with platinum combination therapy when compared with non-platinum therapy, with a higher risk of major adverse events (Santos 2015). Although the performance of older people is often reduced, this review also did not include a PS 2 subgroup.

The results of this systemic meta-analysis support the recommendations made by ESMO (Hendriks 2023) for the treatment of people with PS 2 with advanced NSCLC, based on a meta-analysis performed by Bronte 2015. This review included six RCTs, which are also included in our review.

AUTHORS' CONCLUSIONS

Implications for practice

This review showed that platinum doublet chemotherapy as a first-line treatment for people with performance status (PS) 2 with advanced non-small cell lung cancer (NSCLC) results in a higher response rate, progression-free survival, and overall survival, compared to non-platinum chemotherapy. Although the risk for especially grade 3 or 4 hematologic toxicity is higher, these events are often relatively mild and easy to treat. However, a few studies compared quality of life during the study period and observed no difference between the treatment arms, suggesting that platinum doublet therapy is tolerated well.

We did not find a beneficial effect of cisplatin over carboplatin. However, this analysis should be interpreted with care as the direct comparison of cisplatin with carboplatin contained a small number of people. The assessment of the efficacy of immunotherapy in people with PS 2 is limited. There might be a place for single-agent immunotherapy, but the use of double-agent immunotherapy in people with PS 2 is not encouraged.

Implications for research

Our results showed a significant advantage of platinum doublet therapy over non-platinum therapies. However, many of the included studies were not designed for people with PS 2 only and reported only subgroup analysis, thus lacking power. Only when this population is represented in prospective randomized controlled trials can definitive conclusions be drawn.

Presently, the first-line treatment for people with advanced NSCLC without a targetable mutation is immunotherapy or chemo-immunotherapy, stratified by PD-L1 status. As the use of immunotherapy is emerging, people with PS 2 are generally not included in randomized controlled trials (Borghaei 2015; Kogure 2018; Scagliotti 2008; Zinner 2016), and data are not sufficient to create general conclusions. Evidence from non-randomized trials show that people with PS 2 can be treated safely and effectively with immunotherapy or chemo-immunotherapy, but trials performed and published to date do not compare immunotherapy with regimens used in general practice.

Planned subgroups were based on histology (squamous or non-squamous), PD-L1 status, people aged under 70 years or 70 years or over, and the presence or absence of central nervous system metastasis. There were insufficient data to conduct these subgroup analyses, as the included trials did not sufficiently report our outcomes.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

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* Indicates the major publication for the study

Flotten 2012

Study characteristics	
Methods	Study design: open, randomized, multicenter phase III trial Location and number of centers: 35, Norway
Participants	Inclusion criteria • NSCLC Stage IV or Stage IIIB not eligible for curative treatment • WHO PS 0–2 • Adequate bone marrow and liver function • No other active malignancy and no gastrointestinal disease • Affecting absorption of vinorelbine Exclusion criteria: none stated Baseline imbalances: none N screened: 444 N randomized: • N vinorelbine + gemcitabine: 221 • N carboplatin + vinorelbine: 223 N completed: 215/222 N PS 2: 55/56
Interventions	Type of analysis: PP Treatment group 1: vinorelbine capsules 60 mg/m^2 + intravenous gemcitabine 1000 mg/m^2, on days 1 and 8 Control arm/treatment arm 2: carboplatin AUC 5 on day 1 + vinorelbine capsules 60 mg/m^2 on days 1 and 8 Both groups were planned for 3 cycles of chemotherapy in 3-week cycles The oral dose of vinorelbine 60 mg/m^2 is comparable with the commonly used intravenous dose of 25 mg/m^2. People aged ≥ 75 years had their doses reduced by 25%.
Outcomes	Primary endpoint: OS Secondary endpoints: HRQoL, toxicity, and use of palliative radiation therapy
Notes	Included people with Stage III NSCLC, who will be classified as Stage IV in current TNM.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	After the participants had signed the informed consent form and completed the baseline HRQoL form, they were randomized by telephone to the central study office at Haukeland University Hospital, Bergen, Norway. Randomization was stratified by WHO PS 0–1 vs 2, Stage IIIB vs IV, and age < 75 vs ≥ 75 years.

Flotten 2012 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study, although the outcome was unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (overall survival) All outcomes	Low risk	Open-label study, this was unlikely to influence survival.
Blinding of outcome assessment (detection bias) (other outcomes) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	We analyzed 437 participants for survival, HRQoL, and use of palliative radiation therapy, and 434 for toxicity. Study therapy was discontinued due to toxicity in 9 (4%) vs 7 (3%) people, and due to progressive disease in 24 (11%) vs 25 (11%) people. Study therapy on day 8 was omitted in 44/551 (8%) cycles vs 37/593 (6%) cycles. Alive participants completed, vinorelbine + gemcitabine and carboplatin + vinorelbine, respectively, 89% (850 forms) and 90% (910 forms), of the expected HRQoL questionnaires during the first 17 weeks.
Selective reporting (reporting bias)	Low risk	PS 2 data not reported in primary article. Additional information received from the authors upon request.
Other bias	Low risk	None.

Gridelli 2007

Study characteristics	
Methods	Study design: open-label phase II study Location and number of centers: unknown
Participants	Inclusion criteria • People with histologic or cytologic confirmation of Stage IIIB NSCLC (with supraclavicular lymph node metastases or pleural effusion) or Stage IV NSCLC not amenable to surgery or curative radiation therapy • No prior chemotherapy (prior surgery and radiation therapy were permitted as long as relapse or disease progression had occurred after the procedure or therapy) • Measurable disease according to RECIST criteria • Age ≥ 70 years or < 70 years for people who, in the investigator's opinion, were ineligible for platinum-based chemotherapy because of poor PS or comorbidities • ECOG PS 0–2 • Estimated life expectancy ≥ 12 weeks • Adequate bone marrow, renal, and hepatic function Exclusion criteria

Gridelli 2007 *(Continued)*

- Symptomatic brain metastases
- Uncontrolled pleural effusions
- Inability or unwillingness to take steroids or vitamin supplementation

Baseline imbalances: arms were well balanced for all demographic and stratification factors

N screened: NR

N randomized: 92

- N pemetrexed: 47
- N pemetrexed/gemcitabine: 45

N completed: 44/43

N PS 2: 14/17

Interventions	Type of analysis: PP Treatment arm 1: pemetrexed 500 mg/m^2 on day 1 every 3 weeks for a maximum of 8 cycles Control arm/treatment arm 2: pemetrexed at same dosage for cycles 1 and 2 and then gemcitabine 1200 mg/m^2 on days 1 and 8 every 3 weeks for cycles 3 and 4. This 4-cycle schedule was repeated once, for a total of 8 cycles.
Outcomes	Primary: time to progressive disease. PFS was added retrospectively Secondary: toxicity, response rate, and OS Tumor response assessed using the RECIST criteria Toxicity evaluations, performed at the end of each cycle, were based on the National Cancer Institute common toxicity criteria, version 2 Time to progressive disease defined as the time from the date of randomization to the first date of documented disease progression and was censored on the date of last tumor assessment for people without documented progressive disease at the time of analysis. Because many people died without documented progressive disease, there was a high rate of censoring for time to progressive disease. Therefore, PFS was added retrospectively as a similar measure that would have less censoring. PFS was defined as the time from the date of randomization to the first date of documented disease progression or death from any cause and was censored on the date of last follow-up for people not known to have died at the time of the analysis. OS was defined as the time from the date of randomization to the date of death from any cause and was censored on the date of last follow-up for people not known to have died at the time of analysis.
Notes	Response not assessable/unknown 17 (38.6%) vs 4 (9.3%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was controlled by a computerized voice response unit at a central location for all study sites and was stratified according to disease stage (Stage IIIB vs Stage IV) and PS (0–1 vs 2).
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study, although the outcome was unlikely to be influenced by lack of blinding.

Gridelli 2007 *(Continued)*

Blinding of outcome assessment (detection bias) (overall survival) All outcomes	Low risk	Open-label study, this was unlikely to influence survival.
Blinding of outcome assessment (detection bias) (other outcomes) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	High risk	All 87 participants were evaluable for efficacy and toxicity. 44/87 participants had censored times for time to progressive disease, whereas only 14/87 people had censored times for PFS. Therefore, PFS was retrospectively added as an outcome measure. Best overall response was not assessable/unknown in 17 (38.6) vs 4 (9.3) people.
Selective reporting (reporting bias)	High risk	PFS was retrospective added as outcome measure.
Other bias	High risk	No complete subgroup analysis as the study included both people with PS 2 or elderly people.

Gronberg 2009

Study characteristics	
Methods	Study design: open-label, randomized, multicenter phase III trial Location and number of centers: 35 hospitals in Norway
Participants	Inclusion criteria • Stage IIIB (ineligible for curative radiation therapy) or Stage IV NSCLC • Chemotherapy naive • Aged > 18 years • WHO PS 0–2 • Adequate bone marrow and liver function • Creatinine clearance ≥ 45 mL/minute (Cockroft-Gault formula) • Provided written informed consent Exclusion criteria: none specified Baseline imbalances: none. Baseline characteristics were well balanced between the treatment arms for all people and in the subgroups. N screened: NR N randomized: 446 • N pemetrexed + carboplatin: 225 • N gemcitabine + carboplatin: 221 N completed: 219/217

Gronberg 2009 *(Continued)*

	N PS 2: 47/49
Interventions	Type of analysis: ITT Treatment arm 1: pemetrexed 500 mg/m^2 + carboplatin AUC 5 (Calvert's formula) on day 1 Control arm/treatment arm 2: gemcitabine 1000 mg/m^2 on days 1 and 8 + carboplatin AUC 5 on day 1 People aged ≥ 75 years received a 25% lower dose of the study therapy. Chemotherapy cycles were repeated every 3 weeks for up to 4 cycles.
Outcomes	Primary: HRQOL: global QoL, nausea/vomiting, fatigue, and dyspnea (EORTC QLQ-C30/LC13) Secondary: OS and toxicity Participants underwent laboratory tests and completed HRQoL questionnaires before each chemotherapy cycle (weeks 0, 3, 6, and 9) and at follow-up visits (weeks 12, 20, 28, 36, 44, and 52). Toxicity was graded using the CTCAE version 3.0. Survival was defined as time from random assignment until death. The mean scores and AUCs for the first 20 weeks were compared between groups. The clinically relevant minimum difference in mean HRQoL scores has been defined as 10.
Notes	Stage IIIB (ineligible for curative radiation therapy), most people will be Stage IV in current TNM. Additional data provided by authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned by telephone to the study office. Block random assignment was used to stratify for PS (0 or 1 vs 2), stage (IIIB vs IV), and age (< versus ≥ 75 years).
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study, the outcomes were unlikely to be influenced.
Blinding of outcome assessment (detection bias) (overall survival) All outcomes	Low risk	Open-label study, this was unlikely to influence survival.
Blinding of outcome assessment (detection bias) (other outcomes) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	10 ineligible people were excluded from all analyses. 9 people did not complete the baseline HRQoL questionnaire, and 13 people received no study treatment. Thus, 427 people were eligible for the HRQoL analyses, 436 people were eligible for the survival analyses, and 423 people were eligible for the toxicity analyses.

Gronberg 2009 *(Continued)*

Selective reporting (reporting bias)	Low risk	Unreported PS 2 data received from study authors.
Other bias	Low risk	None.

Hainsworth 2007

Study characteristics	
Methods	Study design: randomized phase III study Location and number of centers: 39 in US
Participants	Inclusion criteria • Stage IIIB (malignant pleural effusion) or Stage IV, biopsy-confirmed NSCLC (adenocarcinoma, squamous cell carcinoma, large cell carcinoma, or mixtures of these histologies) • Aged > 65 years or poor candidates for standard platinum-based chemotherapy regimens because of either coexistent medical illness or poor PS • Previously untreated with chemotherapy • ECOG PS 0–2 • Measurable or evaluable disease • Adequate bone marrow and liver function • Serum creatinine ≤ 2.0 mg/dL Exclusion criteria • Parenchymal brain metastases or meningeal metastases. The single exception was the patient with a solitary brain metastasis, previously treated with definitive resection or radiation therapy (or both), with no residual metastasis on CT scanning or MRI • Major surgical procedure within 4 weeks • Pre-existing peripheral neuropathy > grade 1 • Other invasive cancers treated within 5 years • Pregnant or lactating women Baseline imbalances: none N screened: NR N randomized: 350 N docetaxel: NR N docetaxel + gemcitabine: NR N completed: 171/174 N PS 2: 57/65
Interventions	Type of analysis: both ITT and PP Treatment arm 1: docetaxel 36 mg/m^2 by 30-minute intravenous infusion on days 1, 8, and 15 of a 28-day cycle Control arm/treatment arm: gemcitabine 800 mg/m^2, 30-minute intravenous infusion, followed by docetaxel 30 mg/m^2, 30-minute intravenous infusion; both drugs were administered on days 1, 8, and 15 of a 28-day cycle

Hainsworth 2007 *(Continued)*

	Participants continued treatment until disease progression or for a recommended 6 courses (24 weeks) of therapy
Outcomes	Primary: OS Secondary: ORR, PFS, toxicity OS was measured from the date of first treatment until the date of death. All participants who received ≥ 1 dose of treatment were included in the toxicity comparisons. Toxicity was measured by Common Toxicity Criteria, Version 2.0
Notes	Stage IIIB with malignant pleural effusion, all Stage IV according to current TNM.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization methods not reported.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study, although the outcome was unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (overall survival) All outcomes	Low risk	Open-label study, this was unlikely to influence survival.
Blinding of outcome assessment (detection bias) (other outcomes) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No documented withdrawals from the study, all people included in the analysis.
Selective reporting (reporting bias)	High risk	There was no full separate PS 2 analysis except for OS, although this was a different subgroup compared to the PS 0 or 1, elderly group.
Other bias	High risk	No complete subgroup analysis as the study included both people with PS 2 or elderly people.

Karampeazis 2011

Study characteristics

Methods	Study design: multicenter randomized phase III trial Location and number of centers: unknown number in Greece
Participants	Inclusion criteria

Karampeazis 2011 *(Continued)*

- Chemotherapy- and radiation therapy-naive people aged ≥ 65 years
- Histologically or cytologically confirmed Stage IIIB (with pleural effusion) and Stage IV NSCLC
- PS 0–2
- Adequate bone marrow, renal, and liver
- Life expectancy ≥ 3 months
- Brain metastases were allowed provided that they were irradiated and the patient was clinically stable

Exclusion criteria

- Second active primary tumor
- Active infection
- Severe heart disease or ≥ grade 2 electrocardiographic abnormality
- Uncontrolled diabetes mellitus
- Bleeding tendency

Baseline imbalances: NR

N screened: NR

N randomized: 138

- N docetaxel: 72
- N vinorelbine: 66

N completed: 66/64

N PS 2: 19/7

Interventions	Type of analysis: ITT Treatment arm 1: docetaxel 38 mg/m^2 over a 1-hour intravenous infusion on days 1 and 8 every 3 weeks Control arm/treatment arm 2: vinorelbine 25 mg/m^2 over a 30-minute intravenous infusion on days 1 and 8 every 3 weeks
Outcomes	Primary: OS Secondary: ORR, safety profile, and TTP Response assessment was evaluated every 2 chemotherapy cycles and every month after treatment completion. Objective tumor responses were evaluated according to RECIST. Duration of tumor response was measured from the date that the first objective response (complete or partial) was observed to the first date of tumor progression or death from any cause. The TTP was measured from study entry until the day of the first evidence of disease progression or death, whereas OS was measured from the date of study entry to death or last contact.
Notes	Prematurely terminated due to low accrual after inclusion of 138/176 planned people All Stage IIIB people are probably Stage IV in current TNM.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	People were centrally randomized by computer software to a 1:1 ratio to receive either docetaxel or vinorelbine. The randomization to each arm was done by stratification according to PS (0 or 1 vs 2) and stage of disease (IIIB vs IV).

Karampeazis 2011 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study, the outcome was unlikely to be influenced.
Blinding of outcome assessment (detection bias) (overall survival) All outcomes	Low risk	Open-label study, this was unlikely to influence survival.
Blinding of outcome assessment (detection bias) (other outcomes) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 participants in the docetaxel arm and 2 participants in the vinorelbine arm did not receive the allocated treatment because of either early death during the period of disease assessment (5 participants in the docetaxel arm and 1 participant in the vinorelbine arm) or requirement for radiation therapy to urgently control deteriorating symptoms (1 participant with hemoptysis in the docetaxel arm and 1 participant with superior vena cava syndrome in the vinorelbine arm). 1 participant in the docetaxel arm and 10 participants in the vinorelbine arm were lost to follow-up; these people were considered to have disease that progressed in the ITT analysis.
Selective reporting (reporting bias)	High risk	Not all analyses were performed in participants with PS 2, whereas this was 1 of the study aims.
Other bias	High risk	The trial had a slow accrual rate because of the reluctance of investigators to prescribe chemotherapy in people with a PS of 2, and a further slowdown of accrual occurred after 2006 when Kudoh 2006 reported their randomized trial in elderly people. Because of these reasons, the data monitoring committee decided to close the study.

Kosmidis 2007

Study characteristics	
Methods	Study design: prospective randomized open-label phase II Location and number of centers: unknown number in Greece
Participants	Inclusion criteria • Chemo-naive people aged > 18 years with histologically confirmed, inoperable, recurrent, or metastatic Stage IIIb NSCLC with pleural effusion or Stage IV NSCLC • ECOG PS 2 • Prior radiation therapy was allowed when completed ≥ 4 weeks before chemotherapy • Life expectancy > 12 weeks • Measurable or assessable disease in non-irradiated fields, unless subsequent disease was documented • People with stable brain metastases were eligible • Adequate bone marrow reserve, kidney, and liver functions

Kosmidis 2007 *(Continued)*

	Exclusion criteria • Active infection or a history of other neoplasms (except for basal cell carcinoma of the skin or in situ carcinoma of the cervix) • Active cardiac disease or pre-existing grade 3 or 4 motor or sensory neuropathy • Women of childbearing age were required to have a negative pregnancy test within 48 hours of study enrollment Baseline imbalances: none (basic characteristics and health status) N screened: 102 N randomized: 90 • N gemcitabine: 47 • N gemcitabine/carboplatin: 43 N completed: 44/39 N PS 2: all 2 participants with incomplete medical records were excluded from the analysis. 10 participants were considered ineligible (7 ECOG < 2, 2 second-line therapy, 1 other cancer)
Interventions	Type of analysis: ITT Treatment arm 1: gemcitabine 1250 mg/m^2 via 30-minute infusion with normal saline on days 1 and 14 Control arm/treatment arm 2: gemcitabine 1250 mg/m^2 via 30-minute infusion with normal saline + carboplatin AUC 3 (Calvert formula) as a 1-hour infusion on days 1 and 14
Outcomes	In both arms, the treatment was repeated every 28 days for 2 cycles; if people had PR, stable disease, or clinical benefit, they received 2 additional cycles. All eligible participants who received ≥ 2 cycles of chemotherapy were evaluated for efficacy. Response was evaluated according to standard WHO criteria. All eligible people who received ≥ 1 cycle of chemotherapy were evaluable for toxicity. Toxicity was evaluated according to WHO criteria. Primary: clinical benefit, based on 3 measures: • LCSS, which consists of 6 symptoms: dyspnea, cough, hemoptysis, fatigue, anorexia, and pain • General feeling (very good, good, or poor) • Participant's weight Secondary: OS, survival, time to disease progression, toxicity
Notes	Stage IIIB (with pleural effusion) and Stage IV, according to TNM8, now probably all Stage IV. Carboplatin AUC 3 (low dose) High rate of missing LCSS values.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.

Kosmidis 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding or incomplete blinding, the outcome was unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (overall survival) All outcomes	Low risk	Open-label study, this was unlikely to influence survival.
Blinding of outcome assessment (detection bias) (other outcomes) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	High risk	High rate of missing QoL data (LCSS), which was the primary outcome measure. 2 people with incomplete medical records were excluded from the analysis. 10 people were considered ineligible. 7 people were inadvertently randomized (PS 2), 2 received protocol treatment as second line, and 1 had another cancer. 2 people randomized in the platinum doublet arm received gemcitabine only, but were included in the survival analysis.
Selective reporting (reporting bias)	Low risk	All endpoints reported.
Other bias	Low risk	None.

Kosmidis 2012

Study characteristics	
Methods	Study design: prospective randomized phase II Location and number of centers: unknown number in Greece
Participants	Inclusion criteria • Chemo-naive people aged > 18 years with histologically confirmed, inoperable, recurrent, or metastatic Stage IIIb NSCLC with pleural effusion or Stage IV NSCLC • ECOG PS 2 • Prior radiation therapy was allowed when completed ≥ 4 weeks before chemotherapy • Life expectancy > 12 weeks • Measurable or assessable disease in non-irradiated fields, unless subsequent disease was documented • People with stable brain metastases were eligible • Adequate bone marrow reserve, kidney, and liver functions Exclusion criteria • Active infection or a history of other neoplasms (except for basal cell carcinoma of the skin or in situ carcinoma of the cervix) • Active cardiac disease or pre-existing grade 3 or 4 motor or sensory neuropathy • Women of childbearing age were required to have a negative pregnancy test within 48 hours of study enrollment

Kosmidis 2012 *(Continued)*

	Baseline imbalances: none (basic characteristics and health status) N screened: 102 N randomized: 90 • N gemcitabine: 47 • N gemcitabine/carboplatin: 43 N completed: 44/39 N PS 2: all 2 people with incomplete medical records were excluded from the analysis. 10 people were considered ineligible (7 ECOG < 2, 2 second line, 1 other cancer)
Interventions	Type of analysis: ITT Treatment arm 1: gemcitabine 1250 mg/m^2 via 30-minute infusion with normal saline on days 1 and 14 Control arm/treatment arm 2: gemcitabine 1250 mg/m^2 via 30-minute infusion with normal saline + carboplatin AUC 3 (Calvert formula) as a 1-hour infusion on days 1 and 14 In both arms, the treatment was repeated every 28 days for 2 cycles; if people had PR, stable disease, or clinical benefit, they received 2 more cycles. All eligible people who received ≥ 2 cycles of chemotherapy were evaluated for efficacy. Response was evaluated according to standard WHO criteria. All eligible people who received ≥ 1 cycle of chemotherapy were evaluable for toxicity.
Outcomes	Primary: clinical benefit, based on 3 measures: • LCSS, which consists of 6 symptoms: dyspnea, cough, hemoptysis, fatigue, anorexia, and pain • General feeling (very good, good, or poor) • Participant's weight Secondary: OS, survival, time to disease progression, toxicity (evaluated according to WHO criteria)
Notes	Stage IIIB (with pleural effusion) and Stage IV, according to TNM8, now all Stage IV. Carboplatin AUC 3 (low dose)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization methods not described.
Allocation concealment (selection bias)	Unclear risk	Randomization methods not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study, but the outcome was unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (overall survival) All outcomes	Low risk	Open-label study, this was unlikely to influence survival.

Kosmidis 2012 *(Continued)*

Blinding of outcome assessment (detection bias) (other outcomes) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In group 1, 1 participant had missing data whereas in group 2, 1 participant did not start treatment and 1 also had missing data. Toxicity: percentages were calculated on the 65 participants (32 navelbine, 33 paclitaxel) for whom we had data on toxicities.
Selective reporting (reporting bias)	Low risk	All endpoints provided.
Other bias	Low risk	None.

Langer 2007

Study characteristics	
Methods	Study design: randomized phase II trial Location and number of centers: number unknown in US
Participants	Inclusion criteria • Advanced, incurable, chemotherapy-naive NSCLC • ECOG PS 2 • Aged ≥ 18 years • Adequate physiologic indices, including absolute neutrophil count ≥ 2000; platelets ≥ 100,000; creatinine ≤ 1.5 mg/dL; bilirubin ≤ 1.5 mg/dL • Signed informed consent Exclusion criteria • Prior radiation to assessable disease (unless disease progression was confirmed at that site by physical examination, radiography, or pathology) • Pre-existing ≥ grade 2 sensory neuropathy • CNS metastases untreated or actively growing despite prior radiation or surgery • Other active concurrent malignancies • Pregnancy • Allergies to polyoxyethylate castor oil • Significant comorbidities precluding chemotherapy, including active congestive heart failure and recent myocardial infarction Baseline imbalances: none significant N screened: NR N randomized: 103 • N carboplatin/paclitaxel: 54 • N cisplatin/gemcitabine: 49 N completed: 51/47 N PS 2: all

Langer 2007 *(Continued)*

Interventions	Type of analysis: PP Treatment arm 1: paclitaxel 200 mg/m^2 intravenously day 1 over 3 hours. Carboplatin at a dose targeting ≥ AUC 6, over 30 minutes immediately after paclitaxel. Treatment was cycled at 3-week intervals. Treatment arm 2: gemcitabine 1000 mg/m^2 intravenous over 30 minutes on days 1 and 8 and cisplatin 60 mg/m^2 intravenous day 1 over 1 hour. Cycles were repeated every 3 weeks. Standard ECOG response criteria were used. Participants with CR, PR, or stable disease were allowed to continue treatment for up to 6 cycles, or until disease progression or unacceptable toxicity.
Outcomes	Primary: 1-year OS Secondary: response rate, TTP, toxicities
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	At study entry, participants were randomly assigned to arm 1 or 2 using permuted blocks within strata with dynamic balancing within main institutions and their affiliate networks. Stratification factors included weight loss in preceding 6 months (< 5% vs ≥ 5%) and disease stage (Stage IIIb with pleural or pericardial effusion by CT or chest x-ray or pleural implants documented pathologically, on CT or chest x-ray vs Stage IV/recurrent).
Allocation concealment (selection bias)	Low risk	Insufficient information.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study, the outcome was unlikely to be influenced.
Blinding of outcome assessment (detection bias) (overall survival) All outcomes	Low risk	Open-label study, this was unlikely to influence survival.
Blinding of outcome assessment (detection bias) (other outcomes) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant deemed ineligible had Stage IIIb disease without pleural effusion. 4 eligible people also never started protocol therapy. 2 experienced rapid decline in PS; 1 required emergency treatment for ventricular arrhythmia; 1 died as a result of cardiopulmonary arrest before treatment was initiated.
Selective reporting (reporting bias)	Low risk	All endpoints reported.
Other bias	Low risk	None.

Le Chevalier 2001

Study characteristics	
Methods	Study design: multicenter randomized phase III trial Location and number of centers: 45 European centers
Participants	Inclusion criteria • Aged ≤ 75 years • Histologically or cytologically confirmed squamous cell carcinoma, adenocarcinoma, or large-cell carcinoma of the lung • WHO PS 0, 1, or 2 • Inoperability at the time of trial entry, i.e. Stage III or IV disease according to the International Union Against Cancer classification • No prior malignancy except adequately controlled basal cell carcinoma of the skin; no prior chemotherapy • No symptomatic brain metastases • No pre-existing hearing loss • No uncontrolled infection • Normal blood count; normal liver and renal function • ≥ 1 unirradiated measurable lesion Exclusion criteria: none stated Baseline imbalances: none N screened: NR N randomized: 612 • N vinorelbine + cisplatin (group 1): 206 • N vindesine + cisplatin (group 2): 200 • N vinorelbine: 206 N completed: all N PS 2: 42/33/46
Interventions	Type of analysis: ITT Treatment arm 1: vinorelbine 30 mg/m^2 weekly Treatment arm 2: vinorelbine 30 mg/m^2 + cisplatin 120 mg/m^2 on days 1 and 29 and then every 6 weeks Treatment arm 3: control treatment consisting of vindesine 3 mg/m^2 per week for 6 weeks and then every other week + cisplatin 120 mg/m^2 on days 1 and 29 and then every 6 weeks People received treatment for ≥ 10 weeks unless progression was documented after ≥ 4 weeks of treatment. People with stable disease continued treatment for ≥ 18 weeks. People who achieved an objective response continued treatment until progression or toxicity.
Outcomes	Primary: OS Secondary: response and tolerance Response was evaluated according to WHO criteria, at 10 and 18 weeks of treatment. CR defined as the complete disappearance of all objective disease. A PR was defined as a ≥ 50% decrease in the sum of the products of the 2 longest perpendicular diameters of all measurable lesions initially selected as targets, without progression in any other site. CR and PR had to be confirmed by a

Le Chevalier 2001 *(Continued)*

second evaluation after ≥ 4 weeks. No change was defined as < 50% decrease or < 25% increase in the sum of the products of the 2 longest perpendicular diameters of all measurable lesions initially selected as targets. Progressive disease corresponded to an increase of ≥ 25% in the sum of the products of the 2 longest perpendicular diameters of all measurable lesions initially selected as targets or any new lesion not previously identified.

The duration of objective responses was calculated from the start of treatment until documented disease progression.

Survival was defined as the interval from the date of randomization until the date of death or last follow-up. Toxicities were graded according to WHO criteria, except neurotoxicity for which the Gralla scale was used.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Eligible people were randomly allocated to receive vinorelbine + cisplatin, vindesine + cisplatin, or vinorelbine alone.
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study, although the outcome was unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (overall survival) All outcomes	Low risk	A panel of ≥ 3 experts, who were blinded to the treatment assignment, verified eligibility criteria, staging, and toxicity and reviewed original x-rays to evaluate response in all cases.
Blinding of outcome assessment (detection bias) (other outcomes) All outcomes	Low risk	A panel of ≥ 3 experts, who were blinded to the treatment assignment, verified eligibility criteria, staging, and toxicity and reviewed original x-rays to evaluate response in all cases.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	From the primary report (Le Chevalier 1994): "Eight participants received no treatment (two on NVB-P, four on VDS-P, two on NVB) and three people, randomized to the VDS-P arm, received NVB-P; these three people were included in the VDS-P group for the analysis of survival and in the NVB-P group for toxicity, but were excluded from the analysis of response."
Selective reporting (reporting bias)	High risk	Except for 1-year OS, no separate PS 2 analysis.
Other bias	Low risk	None.

Lee 2022

Study characteristics

Methods	Study design: phase III, multicenter, open-label, randomized, controlled study

Lee 2022 *(Continued)*

	Location and number of centers: 91 centers globally
Participants	Inclusion criteria • Histologically or cytologically confirmed diagnosis of advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC as per the AJCC 7th edition • No sensitizing EGFR mutation (L858R or exon 19 deletions) or ALK fusion oncogene detected • No prior systemic treatment for advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC as per the AJCC 7th edition • Life expectancy ≥ 8 weeks • Deemed unsuitable by the investigator for any platinum-doublet chemotherapy due to poor PS (ECOG PS 2–3). However, participants aged ≥ 70 years who had an ECOG PS of 0 or 1 may have been included due to: substantial comorbidities or contraindication(s) for any platinum-doublet chemotherapy • Representative FFPE tumor tissue block obtained during course of disease (archival tissue) or at screening • Participants with treated, asymptomatic CNS metastases were eligible, provided they meet all the following criteria: measurable disease outside CNS; only supratentorial and cerebellar metastases allowed; no ongoing requirement for corticosteroids as therapy for CNS disease; no stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to randomization; no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study • Adequate hematologic and end organ function • Women of childbearing potential randomized to the atezolizumab treatment arm agree to use protocol defined methods of contraception Cancer-specific exclusion criteria • Participants aged < 70 years who had ECOG PS 0 or 1 • Active or untreated CNS metastases as determined by CT or MRI evaluation of the brain during screening and prior radiographic assessments • Uncontrolled tumor-related pain • Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently) • Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L or calcium > 12 mg/dL or corrected serum calcium > ULN) • History of other malignancy within 5 years prior to screening, except those with a negligible risk of metastasis or death treated with expected curative outcome • NCI CTCAE version 4.0 Grade 3 or higher toxicities due to any prior therapy (e.g. radiation therapy) (excluding alopecia), which have not shown improvement and are strictly considered interfering with current study medication • Participants who had received prior neoadjuvant, adjuvant chemotherapy, radiation therapy, or chemoradiation therapy with curative intent for non-metastatic disease must have experienced a treatment-free interval ≥ 6 months from randomization since the last chemotherapy, radiation therapy, or chemoradiation therapy General medical exclusion criteria • History of autoimmune disease except autoimmune-related hypothyroidism and controlled type I diabetes mellitus • History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g. bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis • Known positivity for HIV • Known active hepatitis B or hepatitis C • Active tuberculosis • Severe infections within 4 weeks prior to randomization • Significant cardiovascular disease, such as NYHA cardiac disease (≥ Class II), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina

Lee 2022 *(Continued)*

- Major surgical procedure other than for diagnosis within 4 weeks prior to randomization or anticipation of need for a major surgical procedure during the course of the study
- Prior allogeneic bone marrow transplantation or solid organ transplant
- Participants with an illness or condition that may interfere with capacity or compliance with the study protocol, as per investigator's judgment
- Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 28 days prior to randomization

Exclusion criteria related to atezolizumab

- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- Oral or intravenous antibiotic treatment
- Administration of a live, attenuated vaccine within 4 weeks before randomization or anticipation that such a live attenuated vaccine will be required during the study
- Prior treatment with cluster of differentiation 137 (CD137) agonists or immune checkpoint blockade therapies, anti-programmed death-1 (anti-PD-1), and anti-PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to randomization
- Treatment with systemic corticosteroids or other immunosuppressive medications
- Participants not willing to stop treatment with traditional herbal medicines

Exclusion criteria related to chemotherapy

- Known sensitivity and contraindications to the 2 comparative chemotherapy agents (i.e. oral or intravenous vinorelbine, and intravenous gemcitabine)

Baseline imbalances: NR

N screened: unknown

N randomized: 453

- N: atezolizumab 302
- N: chemotherapy 151

N completed: NR

N PS 2: 228/116

Interventions	Type of analysis: ITT or PP Treatment arm 1: atezolizumab 1200 mg intravenous infusion on day 1 of each 21-day cycle until loss of clinical benefit, unacceptable toxicity, participant or physician decision to discontinue, or death. Control arm/treatment arm 2: single-agent chemotherapy; either vinorelbine oral or intravenous, or gemcitabine intravenous, according to the label based on investigator's choice, per relevant local guidelines and Summary of Product Characteristics management.
Outcomes	Primary: OS Secondary: percentage of participants who are alive at specified time points (6, 12, 18, and 24 months); percentage of participants with objective response, as determined by the investigator using RECIST Version 1.1 (objective response defined as PR + CR); PFS; duration of response; percentage of participants with adverse events; change from baseline in EORTC-QLQ-C30 score; change from baseline in EORTC QLQ-LC13 score; time to deterioration in patient-reported lung cancer symptoms as assessed by EORTC QLQ-C30 Score; time to deterioration in patient-reported lung cancer symptoms assessed by EORTC QLQ-LC13 score; OS in participants with PD-L1-positive status; PFS in participants with PD-L1-positive status

Lee 2022 *(Continued)*

Notes	Presented at ESMO 2022 Slides included

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study, although the outcome was unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (overall survival) All outcomes	Low risk	Open-label study, this was unlikely to influence survival.
Blinding of outcome assessment (detection bias) (other outcomes) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	High risk	Presented as an abstract, no full PS 2 analysis, only HR provided for OS without median/range.
Selective reporting (reporting bias)	High risk	All outcomes in the protocol were reported for the total study population.
Other bias	Low risk	None.

Lena 2022

Study characteristics

Methods	Study design: randomized phase III, open label Location and number of centers: 37 in France
Participants	Inclusion criteria • Signed written informed consent • Cytologically or histologically confirmed NSCLC (adenocarcinoma, squamous cell carcinoma, large-cell carcinoma) • Stage IV or non-treatable by radiation therapy or surgery Stage III (7th classification) • No previous systemic chemotherapy for lung cancer, except in case of relapse after adjuvant treatment for localized disease with ≥ 6 months between end of previous chemotherapy and relapse • People aged < 70 years and PS 2 or ≥ 70 years and PS 0–2 • Judged fit enough to receive a carboplatin-based doublet according to ESMO guidelines

Lena 2022 *(Continued)*

- Presence of ≥ 1 measurable target lesion (RECIST 1.1 rules) in a non-irradiated region and analyzable by CT
- Life expectancy superior at 12 weeks
- Prior radiation therapy was authorized if it involved < 25% of the total bone marrow volume and finished 14 days before day 1 of planned treatment
- Screening laboratory values must have met the following criteria and should have been obtained within 14 days prior to randomization/registration white blood cell ≥ 2000/µL, neutrophils ≥ 1500/µL, platelets ≥ 100 × 10^3/µL, hemoglobin ≥ 10.0 g/dL, serum creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 45 mL/minute (if using the Cockcroft-Gault formula), AST/ALT ≤ 3 × ULN, total bilirubin ≤ 1.5 × ULN (except people with Gilbert syndrome, who can have total bilirubin inferior at 3.0 mg/dL)
- Availability of adequate FFPE tumor-derived material (tumor blocks or slides) from a biopsy, surgery, or fine needle aspirate for analysis of PD-L1 testing by immunohistochemistry
- Women of childbearing potential used appropriate method(s) of contraception during treatment

Exclusion criteria

- People with other severe concurrent disorders that occurred during the prior 6 months before enrollment (myocardial infection, severe or unstable angina, coronarian or peripheric arterial bypass operation, NYHA class 3 or 4 congestive heart failure, transient or constituted cerebral ischemic attack, ≥ grade 2 peripheral neuropathy, psychiatric or neurologic disorders preventing the patient from understanding the trial, uncontrolled infections)
- Serious or uncontrolled systemic disease judged as incompatible with the protocol by the investigator
- Another previous or concomitant cancer, except for basocellular cancer of the skin or treated cervical cancer in situ, or appropriately treated localized low-grade prostate cancer (Gleason score inferior at 6), unless the initial tumor was diagnosed and definitively treated > 5 years previously, with no evidence of relapse
- Known activating mutation of EGFR (exon 19 deletion, mutation L858R or L861X of exon 21, mutation G719A/S in exon 18) or EML4-ALK or ROS-1 translocation
- Superior vena cava syndrome
- Uncontrolled infectious status
- All concurrent radiation therapy
- Concurrent administration of ≥ 1 other antitumor therapies
- Psychological, familial, social, or geographic difficulties preventing follow-up as defined by the protocol
- Protected person (adults legally protected [under judicial protection, guardianship or supervision], person deprived of their liberty, pregnant woman, lactating woman, and minor)
- Concurrent participation in another clinical trial
- With active brain metastases or leptomeningeal metastases. Patients with brain metastases were eligible if metastases had been treated and there was no MRI evidence of progression for (lowest minimum ≥ 4 weeks) after treatment was complete and within 28 days prior to the first dose of nivolumab and ipilimumab administration. There must also have been no requirement for immunosuppressive doses of systemic corticosteroids (superior at 10 mg/day prednisone equivalents) for ≥ 2 weeks prior to study drug administration
- Had active, known, or suspected autoimmune disease. Patients were permitted to enroll if they had vitiligo, type 1 diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger
- Condition requiring systemic treatment with either corticosteroids (superior at 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses superior at 10 mg daily prednisone equivalents were permitted in the absence of active autoimmune disease
- Positive test for hepatitis B virus surface antigen or hepatitis C virus ribonucleic acid (hepatitis C virus antibody) indicating acute or chronic infection
- History of testing positive for HIV or known AIDS
- Lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity
- Allergies and adverse drug reaction

Lena 2022 *(Continued)*

- History of allergy to study drug components
- Severe spinal hypoplasia or hemorrhagic tumors, or both

Baseline imbalances: unknown

N screened: unknown

N randomized: 204

N per group NR

N completed: 204

N PS 2: 36.6%

Interventions	Type of analysis: ITT Treatment arm 1: nivolumab dosed intravenously over 30 minutes at 240 mg every 2 weeks combined with Ipilimumab dosed intravenously over 30 minutes at 1 mg/kg every 6 weeks until disease progression, unacceptable toxicity, or other reasons specified in the protocol. Control arm/treatment arm 2: doublet of chemotherapy according to standard of care carboplatin (AUC 5) with a dose that will be capped to 700 mg and pemetrexed (500 mg/m^2) over 4–6 hours every 3 weeks (restricted to non-squamous histology) *or* carboplatin (AUC 6) with a dose that will be capped to 700 mg and paclitaxel (90 mg/m^2) days 1, 8, and 15 over 4–6 hours every 4 weeks, with a maximum of 4 cycles of carboplatin-based doublet, and the possibility to use maintenance with pemetrexed.
Outcomes	Primary: OS Secondary: 1-year OS, ORR, PFS, safety rate, tolerability rate, HRQoL (EQ5D, EORTC ELD14), PD-L1, geriatric evaluation
Notes	242 people had to be randomized to detect a treatment effect HR on OS of 0.65, with an 85% power at a 2-sided alpha level of 5%. A preplanned interim analysis carried out after observation of 33% of deaths, out of 174 randomized people, showed a risk of futility especially for people with PS 2 (HR 1.8, 95% confidence interval 0.99 to 3.3). This led to a halt in randomization.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study, although the outcome was unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	Open-label study, this was unlikely to influence survival.

Lena 2022 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) (other outcomes) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	High risk	Presented as abstract, no full PS 2 analysis, very limited information provided, not all outcomes reported.
Selective reporting (reporting bias)	High risk	Not all outcomes in protocol were provided.
Other bias	High risk	Incorrect data in abstract, e.g. all PS groups = 104.1%.

Lilenbaum 2005

Study characteristics	
Methods	Study design: randomized phase III trial Location and number of centers: 35 in US
Participants	Inclusion criteria • People with cytologic or histologic confirmation of Stage IIIB (malignant effusion) • Aged > 18 years • Measurable or evaluable disease • PS 0–2 Exclusion criteria • Locally advanced NSCLC • Prior chemotherapy • Prior radiation < 2 weeks or on index lesion(s) • Known brain metastasis • Previous or concomitant malignancy (except carcinoma in situ of cervix or breast, non-melanoma skin cancer a non-recurrent primary tumor treated surgically > 5 years) • HIV-positive Baseline imbalances: none Randomization was centralized at the CALGB data management center in Durham, North Carolina. Patient randomization was stratified by Stage (IIIB vs IV vs recurrent), PS (0–1 vs 2), and age (< 70 years vs ≥ 70 years). N screened: NR N randomized: 584 N paclitaxel: 277 N carboplatin/paclitaxel: 284 N completed: 561 N PS 2: 50/49

Lilenbaum 2005 *(Continued)*

Interventions	Type of analysis: ITT Treatment arm 1: paclitaxel monotherapy Control arm/treatment arm 2: paclitaxel + carboplatin Paclitaxel was administered intravenously over 3 hours at a dose of 225 mg/m^2, on day 1, in both arms. Carboplatin was administered intravenously over 30 minutes, after paclitaxel, at a dose calculated to produce an AUC of 6.0 mg/mL/minute. Both treatments were repeated every 3 weeks for a maximum of 6 cycles.
Outcomes	Primary: OS calculated from the date of randomization to the date of death Secondary: response rate: CR was defined as the absence of disease at all known sites; a PR was defined as a ≥ 50% reduction in the sum of the perpendicular diameters of all measurable lesions, with no new lesions or enlargement of existing lesions; stable disease was defined as < 50% reduction or < 25% increase in all measurable lesions with the appearance of no new lesions; progressive disease was defined as a 25% increase in the product of 2 perpendicular diameters of any measured lesion or the development of new lesions. Failure-free survival calculated from the date of randomization to the date of progression, relapse, or death.
Notes	Response rate not defined according to RECIST.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to treatment with paclitaxel alone or in combination with carboplatin. Randomization was centralized at the CALGB data management center in Durham, North Carolina. Patient randomization was stratified by stage (IIIB vs IV vs recurrent), PS (0–1 vs 2), and age (< 70 years vs ≥ 70 years).
Allocation concealment (selection bias)	Unclear risk	Central allocation, concealment not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label, unclear effect on mortality.
Blinding of outcome assessment (detection bias) (overall survival) All outcomes	Low risk	Open-label study, this was unlikely to influence survival.
Blinding of outcome assessment (detection bias) (other outcomes) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Twenty-three people (3.9%) either withdrew from the study before receiving protocol therapy or were later found to be ineligible."
Selective reporting (reporting bias)	Low risk	Only main statement noted regarding toxicity among people with PS 2 noted, not all data presented.

Lilenbaum 2005 *(Continued)*

Other bias	Low risk	None.

Morabito 2013

Study characteristics	
Methods	Study design: multicenter randomized, open-label, 2-arm phase 3 study Location and number of centers: 9 institutions in Italy
Participants	Inclusion criteria • Age 18–70 years • Cytologically or histologically confirmed NSCLC, Stage IV or Stage IIIB with malignant pleural effusion or metastatic supraclavicular nodes • Adequate organ function Exclusion criteria • Symptomatic brain metastases • History of prior invasive malignancy • People who had received previous chemotherapy Baseline imbalances: only significant imbalance due to higher prevalence of chronic obstructive pulmonary disease in gemcitabine arm N screened: NR N randomized: 57 • N gemcitabine: 28 • N cisplatin gemcitabine: 29 N completed: 28/28 N PS 2: all
Interventions	Type of analysis: ITT Treatment arm 1: gemcitabine 1200 mg/m^2 in 30 minutes intravenous on days 1 and 8 Control arm/treatment arm 2: cisplatin 60 mg/m^2 intravenous on day 1 + gemcitabine 1000 mg/m^2 in 30 minutes intravenous on days 1 and 8 All treatments were repeated every 3 weeks, for a maximum of 4 cycles
Outcomes	Primary: OS Secondary: PFS, objective tumor response, toxicity, and HRQoL Tumor response was assessed at the end of the second and fourth cycle of chemotherapy using RECIST; confirmation of response was not required. Toxicity was assessed before each cycle of chemotherapy, according to the NCI CTCAE version 3.0. The EORTC QLQ-C30 questionnaire and EORTC QLQ-LC13 were used to evaluate QoL. In both arms, 4 questionnaires were planned: at baseline, at day 8 of cycle 1, and at days 1 and 8 of cycle 2. OS was calculated from the date of randomization to the date of death, or the date of last follow-up for alive people. PFS was defined as the time from the date of randomization to the date of progression of

Morabito 2013 *(Continued)*

	disease, or the date of death for people died without progression, or the date of last follow-up for people alive and without progression at the end of the study
Notes	All Stage III people are Stage IV in current TNM.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were centrally randomized to the 2 treatment arms (1:1 ratio), through a centralized automated minimization procedure, using gender, center, and stage (IIIB vs IV) as strata.
Allocation concealment (selection bias)	Unclear risk	Not specified by the study authors.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study, although the outcome was unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (overall survival) All outcomes	Low risk	Open-label study, this was unlikely to influence survival.
Blinding of outcome assessment (detection bias) (other outcomes) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant, randomized to cisplatin + gemcitabine, withdrew consent immediately after randomization and was excluded from the analysis. Information about toxicity was available for 54/55 people who started the assigned first-line; there was 1 participant with missing data in the gemcitabine arm.
Selective reporting (reporting bias)	Low risk	1 participant, randomized to cisplatin + gemcitabine, withdrew consent immediately after randomization and was excluded from the analysis. Information about toxicity was available for 54/55 people who started the assigned first-line; there was 1 participant with missing data in the gemcitabine arm.
Other bias	Low risk	None.

Morere 2010

Study characteristics

Methods	Study design: multicenter, randomized phase II open-label trial Location and number of centers: 29 centers in France
Participants	Inclusion criteria

Morere 2010 *(Continued)*

- Aged 18–80 years with Stage IIIB, IV NSCLC
- Have measurable or assessable disease
- ECOG PS 2 or 3
- Adequate organ function

Exclusion criteria

- Prior chemotherapy, EGFR inhibitor therapy, or thoracic radiation therapy
- Any other serious medical condition that might impair their ability to receive protocol therapy
- Prior or concurrent active malignancies

Baseline imbalances: smoking history was different between the arms, 14.3% of people in the docetaxel arm were never-smokers vs 0% of people in the gemcitabine arm and 4.7% of people in the gefitinib arm

N screened: NR

N randomized: 128

- N gefitinib: 43 (not included in further items)
- N gemcitabine: 42
- N docetaxel: 42

N completed: 125

N PS 2: 30/28

Interventions	Type of analysis: PP Treatment arm 1: gemcitabine 1250 mg/m^2 days 1 and 8 every 3 weeks Control arm/treatment arm 2: docetaxel 75 mg/m^2 day 1 every 3 weeks Treatment was given until progression or toxicity. People who experienced progression, did not tolerate or refused further chemotherapy were allowed to cross over to gefitinib provided that they still met the initial eligibility criteria. People who progressed after gefitinib were treated with docetaxel.
Outcomes	Primary: PFS Secondary: response rate, OS, and toxicities Toxicity was assessed every cycle using the NCI CTC Criteria version 3.0 Response was assessed by imaging studies every 9 weeks and evaluated by RECIST
Notes	Gefitinib arm not included in analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patient random assignment was block-stratified by PS (PS 2 vs PS 3) and pathologic diagnosis (adenocarcinoma vs non-adenocarcinoma).
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study, although the outcome was unlikely to be influenced by lack of blinding.

Morere 2010 *(Continued)*

Blinding of outcome assessment (detection bias) (overall survival) All outcomes	Low risk	Open-label study, this was unlikely to influence survival.
Blinding of outcome assessment (detection bias) (other outcomes) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 person ineligible (unsigned consent form), 2 people died before starting treatment.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	None.

Quoix 2011

Study characteristics	
Methods	Study design: multicenter, open-label, randomized, phase 3 trial Location and number of centers: 61 institutions in France
Participants	Inclusion criteria • Aged 70–89 years • Histologically or cytologically confirmed unresectable Stage IV NSCLC, or had Stage III disease unsuitable for radical radiation therapy. • PS 0–2 • Adequate hematologic, renal, and hepatic functions • Life expectancy ≥ 12 weeks • Previous radiation therapy at symptomatic sites was allowed if it had been completed ≥ 3 weeks before inclusion • People with asymptomatic brain metastases were eligible Exclusion criteria • Active malignancy within the past 5 years • Any previous chemotherapy • Peripheral neuropathy ≥ grade 2 • Comorbidities that impaired administration of chemotherapy • Respiratory impairment that required chronic oxygen delivery Baseline imbalances: more people in the monotherapy group presented with weight loss > 5% in the 3 months before randomization. As a consequence, people in the monotherapy group had lower body-mass index values than people in the doublet chemotherapy group N screened: NR N randomized: 451 • N monotherapy: 226 • N doublet therapy: 225

Quoix 2011 *(Continued)*

	N completed: 225/223 N PS 2: 62/61
Interventions	Type of analysis: ITT Treatment arm 1: carboplatin AUC 6 on day 1 and paclitaxel 90 mg/m^2 on days 1, 8, and 15 Control arm/treatment arm 2: vinorelbine 25 mg/m^2 on days 1 and 8 *or* gemcitabine 1150 mg/m^2 on days 1 and 8 The choice between vinorelbine and gemcitabine was made by each center at the beginning of the study. Cycles were repeated every 4 weeks (3 weeks of treatment + 1 week without) for doublet chemotherapy and every 3 weeks (2 weeks of treatment + 1 week without) for monotherapy, with planned maximums of 4 and 5 cycles, respectively.
Outcomes	Primary: OS, defined as the time from randomization to death from any cause Secondary: PFS, defined as the time from randomization to documented disease progression or death, whichever occurred first; response to first-line therapy at 6 weeks, Grade 3–4 toxic effects; QoL Tumors were assessed every 6 weeks until week 18 and every 3 months thereafter, according to WHO criteria. Toxic effects were assessed after each cycle, according to the NCI CTCAE (version 3.0). QoL was assessed with the EORTC QLQ-C-30 questionnaire + the QLQ-LC13 lung cancer module, at baseline, week 6, and week 18.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization centrally by computer using minimization method and stratified people by study center, WHO PS score (0–1 vs 2), stage (III vs IV), and age (≤ 80 years vs > 80 years).
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study, although the outcome was unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (overall survival) All outcomes	Low risk	Open-label study, this was unlikely to influence survival.
Blinding of outcome assessment (detection bias) (other outcomes) All outcomes	High risk	Treatment response was reviewed through investigator panels. Review of QoL and toxicity results were not specified.
Incomplete outcome data (attrition bias)	Low risk	Before treatment was started, 1 participant was excluded from the monotherapy and 2 from the doublet chemotherapy group; 18 people did not meet the

Quoix 2011 *(Continued)*

All outcomes		inclusion criteria but started first-line treatment and were included in the survival analysis.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting bias.
Other bias	Low risk	None.

Reynolds 2009

Study characteristics	
Methods	Study design: randomized open-label phase III clinical trial Location and number of centers: 84 community-based oncology practices in the US
Participants	Inclusion criteria • Histologic or cytologic new diagnosis of NSCLC, Stage IIIB with a cytologically positive pleural or pericardial effusion or Stage IV • No prior chemotherapy, including adjuvant or neoadjuvant therapy, for the treatment of NSCLC • ECOG PS 2 • People must have been ≥ 3 weeks since major surgery • People must have been ≥ 1 week since surgery, such as mediastinoscopy, pleuroscopy, or thoracostomy • People must have had measurable disease, defined as lesions that could be accurately measured in ≥ 1 dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or > 10 mm with spiral CT scan Exclusion criteria • Any prior radiation therapy to the thoracic area • Active and ongoing systemic infection • Prior radiation to > 25% of the bone marrow • ECOG PS other than 2 • People with a known hypersensitivity to gemcitabine and carboplatin Baseline imbalances: none N screened: 202 N randomized: 170 • N gemcitabine and carboplatin: 85 • N gemcitabine: 85 N completed: 81/79 N PS 2: all
Interventions	Type of analysis: ITT Treatment arm 1: gemcitabine 1000 mg/m^2 of on days 1 and 8 + carboplatin AUC 5 on day 1 every 3 weeks Control arm/treatment arm 2: gemcitabine 1250 mg/m^2 on days 1 and 8 every 3 weeks Up to 6 cycles of therapy was given

Reynolds 2009 *(Continued)*

Outcomes	Primary: OS Secondary: PFS, TRR, biomarkers RRM1 and ERCC1
Notes	202 people from 84 community-based oncology practices consented between March 2004 and December 2006. Participant accrual was 50% of the expected rate, and the trial was terminated. 32 people withdrew consent before randomization. Power calculation was 220 people. All people Stage IV in current TNM8

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "One hundred seventy patients were randomly assigned." Insufficient information on randomization methods provided.
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study, although the outcome was unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (overall survival) All outcomes	Low risk	Open-label study, this was unlikely to influence survival.
Blinding of outcome assessment (detection bias) (other outcomes) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Patient accrual was 50% of the expected rate, and the trial was terminated. Thirty-two people withdrew consent before randomization. Best measurable response by CT was available in 66 people treated with gemcitabine and carboplatin and 61 people treated with gemcitabine. Best confirmed response was available in 70 people treated with gemcitabine and carboplatin and 68 people treated with gemcitabine."
Selective reporting (reporting bias)	Low risk	All outcomes provided.
Other bias	Low risk	None.

Saito 2012

Study characteristics

Methods	Study design: randomized phase II study

Saito 2012 *(Continued)*

	Location and number of centers: unknown number in Japan
Participants	Inclusion criteria • Chemotherapy-naive people • PS 2 • Cytologically or histologically confirmed diagnosis of NSCLC stage of IIIB with malignant effusion or Stage IV, relapse after surgery or radiation therapy • Measurable or evaluable disease • Life expectancy ≥ 3 months • No concomitant malignancy • Aged > 18 years • Adequate baseline organ function • People with brain metastases were eligible if they had been treated with surgery or radiation therapy and were stable Exclusion criteria • Active and serious infections • Massive pleural or pericardial effusion that required drainage • Concomitant serious cardiovascular disease • Neuropathy ≥ Grade 2 • Pregnant or lactating Baseline imbalances: none significant N screened: NR N randomized • N paclitaxel + carboplatin: 44 • N vinorelbine + gemcitabine: 45 N completed: 41/43 N PS 2: all
Interventions	Type of analysis: ITT Treatment arm 1: paclitaxel 200 mg/m^2 intravenous on day 1 and carboplatin AUC 6 on day 1 Control arm/treatment arm 2: vinorelbine 25 mg/m^2 intravenous and gemcitabine 1000 mg/m^2 on days 1 and 8 Treatment was repeated every 3 weeks for up to 6 cycles unless there was evidence of disease progression, unacceptable toxicity, or withdrawal of consent. Continuation of the chemotherapy beyond 6 cycles was permitted at the discretion of the treating physician.
Outcomes	Primary: 1-year survival rate Secondary: response rate, TTP, symptom improvement, and toxicity. Duration of treatment response and survival was measured from the day of registration. Used WHO criteria were used for response assessment. Toxicity was evaluated according to the NCI Common Toxicity Criteria version 2.0. Disease-related symptoms were assessed according to the Lung Cancer Subscale of the Functional Assessment of Cancer Therapy – Lung QoL instrument (version 4.0) at the time of enrollment as well as at 3 and 6 weeks after the initiation of treatment. An increase of ≥ 2 points from the baseline score was defined as clinically meaningful symptom improvement.

Saito 2012 *(Continued)*

Notes	Almost all people had Stage IV disease in current TNM

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible participants were randomly assigned to 1 of the 2 treatment arms by a minimization method with disease stage (IIIB vs IV) and bodyweight loss in the previous 6 months (< 5% vs ≥ 5%) as stratifying variables. Randomization was performed at the West Japan Thoracic Oncology Group (now known as the West Japan Oncology Group) Data Center.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding (probably open-label trial as treatment days between arms are different).
Blinding of outcome assessment (detection bias) (overall survival) All outcomes	Low risk	Lack of blinding was unlikely to influence OS.
Blinding of outcome assessment (detection bias) (other outcomes) All outcomes	High risk	No information on blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 people were subsequently considered to be ineligible and 3 did not receive the protocol treatment.
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting.
Other bias	Low risk	None.

Schuette 2017

Study characteristics

Methods	Study design: phase III, randomized, open-label study Location and number of centers: 27 centers in Germany
Participants	Inclusion criteria • Aged ≥ 65 years • Histologically or cytologically documented inoperable, locally advanced (Stage IIIB with supraclavicular lymph-node metastases or malignant pleural or pericardial effusion), metastatic (Stage IV) or recurrent NSCLC other than squamous NSCLC • ≥ 1 measurable lesion according to RECIST • ECOG PS ≤ 2 • Adequate hematologic, blood-clotting, hepatic, and renal function

Schuette 2017 *(Continued)*

	Exclusion criteria • Mixed non-small cell and small cell tumors or mixed adenosquamous carcinomas with a predominantly squamous component • People who had received prior platinum-based or other chemotherapy regimens for advanced disease were ineligible for the study (except neoadjuvant or adjuvant therapy for early-stage disease and completed ≥ 6 months prior to diagnosis of advanced-stage disease) • History of hemoptysis, tumors invading major blood vessels, radiation therapy, major surgery, significant traumatic injury within 28 days prior to enrollment, anticipation of the need for major surgery during study treatment, minor surgery within 24 hours prior to the first bevacizumab infusion, history of inherited bleeding diathesis or coagulopathy with the risk of bleeding, use of full-dose anticoagulants or thrombolytic agents for therapeutic purposes, inability to interrupt salicylates or other nonsteroidal anti-inflammatory drugs (with the exception of low-dose aspirin), uncontrolled hypertension or clinically significant cardiovascular disease, nonhealing wounds, active peptic ulcers or bone fractures, history of abdominal fistulae, gastrointestinal perforation or intra-abdominal abscess within 6 months of enrollment, presence of clinically significant third-space fluid collections that could not be controlled by drainage or other procedures, history of diverticulitis, and yellow-fever vaccination within 30 days of enrollment Baseline imbalances: none reported N screened: NR N randomized: 271 • N: bevacizumab + pemetrexed + carboplatin 135 • N: bevacizumab + pemetrexed 136 N completed: 119/134 N PS 2: 6/7
Interventions	Type of analysis: ITT Treatment arm 1: bevacizumab 7.5 mg/kg + pemetrexed 500 mg/m^2 as a 10-minute intravenous infusion on day 1 of each 3-week cycle Control arm/treatment arm 2: bevacizumab 7.5 mg/kg + pemetrexed 500 mg/m^2 as a 10-minute intravenous infusion and carboplatin AUC 5 as a 30- to 60-minute intravenous infusion People should have received study medication for ≥ 4 cycles to a maximum of 6 cycles.
Outcomes	Primary: PFS Secondary: OS, ORR, safety Tumor assessments were performed every second cycle. Measurements were done according to RECIST criteria. Safety was evaluated as the incidence of adverse events graded using NCI CTCAE (version 3.0) and changes in laboratory tests or vital signs PFS defined as the number of days from the day of the first treatment until day of death (from any cause) or progression, whichever occurs earlier, or until the day of the last response assessment, if no progression or death (from any cause) is observed during the study OS defined as the number of days from the day of first treatment to death (from any cause), or until the last day if we know that the patient is alive
Notes	Higher rate of people discontinued the study due to adverse events under bevacizumab + pemetrexed + carboplatin compared to bevacizumab + pemetrexed. While study treatment was delayed in almost

Schuette 2017 *(Continued)*

a third of people in both treatment arms, reduction of study medication occurred twice as often in people treated with bevacizumab + pemetrexed + carboplatin.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Eligible participants were randomly assigned to 1 of 2 parallel treatment arms. No further information provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study, although the outcome was unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (overall survival) All outcomes	Low risk	Open-label study, unlikely to influence OS.
Blinding of outcome assessment (detection bias) (other outcomes) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	In arm A, 16 people were excluded from the ITT set. "Screening failure" was the most common reason for the exclusion of people from the ITT set, which was complemented by "patient received no study medication." In arm B, 2 people were excluded from the different analysis sets. The PP set excluded major protocol violations and consisted of 252 people. 1 participant was excluded from the PP set in arm A. The reason for the exclusion of that participant was a reduced bevacizumab dose for several cycles. Unclear if all reasons of exclusions in arm A are reported, judged as low risk of bias.
Selective reporting (reporting bias)	High risk	Insufficient information on severity grade of toxicities is provided. Not all outcomes were reported in people with PS 2 only.
Other bias	Low risk	None.

Spigel 2018

Study characteristics

Methods	Study design: randomized, open-label, phase 2 trial Location and number of centers: 27 in the US
Participants	Inclusion criteria • Aged ≥ 18 years

Spigel 2018 *(Continued)*

- Non-squamous NSCLC (adenocarcinoma or large cell carcinoma). Mixed tumors with small cell anaplastic elements are not eligible. Mixed tumors with squamous histology were acceptable as long as the squamous element was not the dominant histology
- Unresectable Stage IIIB or Stage IV disease. Stage IIIB disease should be ineligible for combined modality therapy (i.e. pleural effusions, pericardial effusions)
- ECOG PS 2
- No prior systemic therapy for Stage IIIB or Stage IV lung cancer
- Life expectancy ≥ 12 weeks
- People must have measurable disease per RECIST version 1.1
- Laboratory values as follows
  - Absolute neutrophil count ≥ 1500/µL
  - Hemoglobin ≥ 10 g/dL
  - Platelets ≥ 100,000/µL (≤ 7 days prior to treatment)
  - AST or ALT and alkaline phosphatase must have been < 2.5 × ULN, or < 5 × ULN in people with liver metastases
  - Total bilirubin < 1.5 × the institutional ULN
  - Calculated creatinine clearance ≥ 45 mL/minute
- Ability to take folic acid, vitamin B_{12}, and dexamethasone according to protocol
- Women of childbearing potential must have had a negative serum or urine pregnancy test performed within 7 days prior to start of treatment

Exclusion criteria

- Squamous cell histology
- Active brain metastases. People who had received radiation or surgery for brain metastases were eligible if there was no evidence of CNS disease progression, and ≥ 2 weeks had elapsed since treatment
- Major surgical procedure (not including mediastinoscopy), open biopsy, or significant traumatic injury within 4 weeks of beginning treatment; or the anticipation of the need for major surgical procedure during the course of the study.
- Minor surgical procedures (except for the placement of portacath or other central venous access) must have been completed ≥ 7 days prior to beginning protocol treatment
- Hypersensitivity to active or inactive excipients of any component of treatment (pemetrexed, bevacizumab, carboplatin, or a combination of these)
- Pulmonary carcinoid tumors
- Proteinuria
- Serious non-healing wound, active ulcer, or untreated bone fracture
- Evidence of bleeding diathesis or significant coagulopathy
- Hematemesis or hemoptysis within 1 month prior to study enrollment
- History of myocardial infarction or unstable angina within 6 months of beginning treatment
- Inadequately controlled (NYHA ≥ grade II congestive heart failure)
- Serious cardiac arrhythmia requiring medication
- Significant vascular disease within 6 months prior to day 1 of treatment
- History of stroke or transient ischemic attack ≤ 6 months prior to beginning treatment
- Any prior history of hypertensive crisis or hypertensive encephalopathy
- History of abdominal fistula or gastrointestinal perforation ≤ 6 months prior to day 1 of beginning treatment
- Concurrent severe, intercurrent illness including, but not limited to, ongoing or active infection, or psychiatric illness/social situations that would limit compliance with study requirements
- Mental condition that would prevent patient comprehension of the nature of, and risk associated with, the study
- Use of any non-approved or investigational agent ≤ 30 days of administration of the first dose of study drug. People may not have received any other investigational or anticancer treatments while participating in this study

Spigel 2018 *(Continued)*

- Past or current history of neoplasm other than the entry diagnosis except for treated non-melanoma skin cancer or carcinoma in situ of the cervix, or other cancers cured by local therapy alone and a disease-free survival ≥ 5 years

Baseline imbalances: none reported

N screened: NR

N randomized: 172

- N arm 1: 48
- N arm 2: 63
- N arm 3: 61

N completed: 48/59/55

N PS 2: all

Interventions	Type of analysis: ITT Treatment arm 1: pemetrexed 500 mg/m^2 intravenous Treatment arm 2: pemetrexed 500 mg/m^2 intravenous + bevacizumab 15 mg/kg intravenous Treatment arm 3: pemetrexed 500 mg/m^2 intravenous + bevacizumab 15 mg/kg intravenous + carboplatin AUC 5 intravenous All regimens were administered in 21-day cycles. In arm 3, carboplatin was administered only during the first 4 cycles. All regimens were continued until disease progression or unacceptable toxicity.
Outcomes	Primary: PFS Secondary: ORR, TTP, TTTF, OS, 6-/12-month survival PFS: the length of time, in months, that people were alive from their first date of protocol treatment until worsening of their disease. Responses were assessed by the investigators and characterized according to RECIST version 1.1 Adverse events and laboratory measurements were graded according to the NCI CTCAE (version 3.0)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Before randomization, participants were stratified for the following clinical characteristics: age (< 75 years vs ≥ 75 years) and albumin (< 3.5 g/dL vs ≥ 3.5 g/dL). People were then randomized (1:1:1) to 1 of 3 treatment arms. Randomization method unknown.
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study, although the outcome was unlikely to be influenced by lack of blinding.

Spigel 2018 *(Continued)*

Blinding of outcome assessment (detection bias) (overall survival) All outcomes	Low risk	Open-label study, this was unlikely to influence survival.
Blinding of outcome assessment (detection bias) (other outcomes) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	–
Selective reporting (reporting bias)	High risk	Toxicities < 10% in incidence are not reported.
Other bias	High risk	While this study was ongoing, a randomized phase 3 trial demonstrated the superiority of combination chemotherapy (paclitaxel and carboplatin) vs single-agent paclitaxel in the first-line treatment of people with Stage IV NSCLC and a poor PS (Lilenbaum 2005). As a result, the accrual of people to single-agent pemetrexed (arm 1) was stopped, and subsequent randomization (1:1) was continued to arms 2 and 3 only. Therefore, this study was underpowered.

Sweeney 2001

Study characteristics	
Methods	Study design: randomized open-label multicenter phase III trial Location and number of centers: unknown
Participants	Inclusion criteria • Stage IIIB* or Stage IV NSCLC • Measurable or evaluable disease • ECOG PS 0–2 • Adequate hematologic and renal function • Normal bilirubin • AST/ALT < 5 times ULN Exclusion criteria • Prior chemotherapy • Prior radiation therapy to area of measurable disease unless site has had subsequent progression • Other active malignancies • Significant cardiac disease Baseline imbalances: only descriptive, no statistics. Median ages were 60.6 years (range 43–78 years) for people in the paclitaxel + cisplatin arm, 68.5 years (range 47–78 years) for people in the cisplatin + gemcitabine arm, 65.2 years (range 42–79 years) for people in the cisplatin + docetaxel, and 61.6 years (range 44–73 years) for people in the paclitaxel + carboplatin arms. Gender distribution revealed that the paclitaxel + cisplatin and cisplatin + docetaxel arms were comprised of 67% and 61% males, respectively, whereas the cisplatin + gemcitabine and paclitaxel + carboplatin arms had 46% and 47% males, respectively (Table 3). > 80% of people had Stage IV disease except for the cisplatin + gemcitabine arm,

Sweeney 2001 *(Continued)*

	in which 69% of people had Stage IV disease. Weight loss > 10% was noted in 28% of people in the paclitaxel + cisplatin arm, in 23% of people in the cisplatin + gemcitabine arm, in 22% of people in the cisplatin + docetaxel arm and 33% of people in the paclitaxel + carboplatin arm. N screened: NR N randomized: 64 • N paclitaxel + cisplatin: 14 • N cisplatin + gemcitabine: 13 • N cisplatin + docetaxel: 18 • N paclitaxel + carboplatin: 15 N completed: all N PS 2: all
Interventions	Type of analysis: ITT Treatment arm 1: paclitaxel 135 mg/m^2 over 24 hours followed by cisplatin 75 mg/m^2 on day 2 every 21 days Treatment arm 2: cisplatin 100 mg/m^2 on day 1 + gemcitabine 1 g/m^2 on days 1, 8, and 15 on a 28-day cycle Treatment arm 3: cisplatin 75 mg/m^2 on day 1 + docetaxel 75 mg/m^2 on day 1 of a 21-day cycle Treatment arm 4: paclitaxel 225 mg/m^2 on day 1 administered over 3 hours + carboplatin AUC 6
Outcomes	Primary: OS Secondary: response rate, TTP, and toxicity Grading of toxicities was according to the NCI Common Toxicity Criteria CR defined as the complete disappearance of all clinically detectable disease measured by physical exam or radiographic studies (or both) for ≥ 4 weeks. PR defined as a decrease ≥ 50% in the sum of the products of the 2 longest perpendicular dimensions of all measurable lesions for ≥ 4 weeks without an increase > 25% in the size of any area known to contain malignant disease and without the appearance of any new areas of malignancy. Progressive disease defined as an increase ≥ 25% in the size of measurable lesions.
Notes	Primary publication: Schiller 2002 (not included in this review)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomized, method unknown. People were stratified according to ECOG PS (0 or 1 vs 2, with higher scores indicating greater impairment), weight loss in the previous 6 months (< 5% vs ≥ 5%), the stage of disease (IIIB vs IV or recurrent disease), and the presence or absence of brain metastases.
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided.
Blinding of participants and personnel (performance bias)	Low risk	Open-label study, although the outcome was unlikely to be influenced by lack of blinding.

Sweeney 2001 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) (overall survival) All outcomes	Low risk	Open-label study, this was unlikely to influence survival.
Blinding of outcome assessment (detection bias) (other outcomes) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study E1594 opened in October 1996 and closed in May 1999. Given recent improvements in supportive care and the sense that newer regimens were less toxic and more effective, people with a PS of 2 were considered eligible. This was a departure from the previous ECOG policy, which confined participation to people with a PS of 0 or 1. However, this trial was designed to assess separately the toxicity in people with a PS of 2 after the first 50 people were enrolled. In March 1997, the Data Monitoring Committee observed a substantial rate of toxicity in the people with a PS of 2 and recommended continued, close monitoring. By August 1997, 66 people with a PS of 2 had been enrolled, and accrual was discontinued because of a perception of excess adverse events. The determination of excess adverse events was based on the rate of toxicities and the 5/66 (7.6%) people who died on study. This report represents a final analysis of this subgroup. 1 participant withdrew consent before randomization, another participant had a myocardial infarction after registration, and a third participant died before chemotherapy was administered. A fourth participant was entered after people with a PS of 2 were no longer being accrued.
Selective reporting (reporting bias)	Low risk	All outcomes provided.
Other bias	Low risk	None.

Yadav 2021

Study characteristics	
Methods	Study design: open-label randomized trial with a superiority design Location and number of centers: single center in India
Participants	Inclusion criteria • Treatment-naive people • Aged 18–65 years • Tissue diagnosis of non-squamous NSCLC Stage 3B disease not amenable for definite chemoradiation, or Stage 4 disease (as per AJCC 7th edition) • ECOG PS 0, 1, or 2 • Adequate hematologic, renal (creatinine clearance > 45 mL/minute), and hepatic functions • People with treated and asymptomatic brain metastasis were allowed Exclusion criteria

Yadav 2021 *(Continued)*

- Known EGFR mutations or ALK gene rearrangement. People in which the EGFR and ALK status was unknown at the time of enrollment were included
- People on immunosuppressive medications or HIV disease and people having pre-existing symptomatic peripheral neuropathy were excluded

Cases that turned out to have EGFR mutations or ALK rearrangement after randomization were switched to TKIs either as maintenance (after 4 cycles of chemotherapy) or as second-line treatment as per the physician's discretion.

Baseline imbalances: all the features were well matched in both treatment arms except for the fact that 5% of people had NSCLC-NOS in the paclitaxel arm, while all people in the pemetrexed arm had adenocarcinoma

N screened: 180

N randomized: 171

- N carboplatin/pemetrexed: 85
- N carboplatin/paclitaxel: 86
- N completed: 83/81

N PS 2: 23/21

Interventions	Type of analysis: PP Treatment arm 1: pemetrexed 500 mg/m^2 + carboplatin AUC 5 every 3 weeks for 4 cycles Control arm/treatment arm 2: paclitaxel 80 mg/m^2 on day 1, day 8, and day 15 + carboplatin AUC 5 on day 1 every 4 weeks for 4 cycles Participants in both treatment arms were allowed to receive maintenance pemetrexed 500 mg/m^2 every 3 weeks until disease progression or intolerance in the absence of progressive disease after 4 cycles
Outcomes	Primary: 6-month PFS rate Secondary: ORR, disease control rates, OS, toxicities
Notes	Dose modifications and interruptions were required in 13.3% of people in the pemetrexed arm and 16.0% of the paclitaxel arm (P = 0.55). There were 3 toxicity-related deaths in the study, 1 in the pemetrexed group and 2 in the paclitaxel group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was conducted in a 1:1 ratio by block randomization using a computer-generated table of random numbers.
Allocation concealment (selection bias)	Low risk	Allocation concealment was performed through sealed envelopes that were opened by an independent person who was not involved in the study design or analysis.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study, although the outcome was unlikely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	Open-label study, this was unlikely to influence survival.

Yadav 2021 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) (other outcomes) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	High risk	Due to a change in the standard of care and slow accrual, the trial was terminated early after randomizing 180 people between 26 April 2016 and 9 January 2019. The estimated sample size was 364 (182 in each arm). 6 people withdrew consent before treatment initiation. 1 participant had squamous cell carcinoma on histology review and 2 participants received treatment before randomization. Out of 85 people allocated to the pemetrexed arm, 1 was lost to follow-up immediately after randomization and 1 opted to switch to EGFR TKI before the first dose of chemotherapy since his EGFR mutation was positive. In the paclitaxel arm, 86 people were allocated but 3 were lost to follow-up after randomization and 2 were switched to EGFR TKI before chemotherapy. Radiologic response evaluation was not available in 7 people in the pemetrexed arm and 11 people in the paclitaxel arm.
Selective reporting (reporting bias)	Low risk	All outcomes provided including extra statistical calculations provided by the authors.
Other bias	High risk	Due to a change in the standard of care and slow accrual, the trial was terminated early after randomizing 180 participants between 26 April 2016 and 9 January 2019. The estimated sample size was 364 (182 in each arm).

Zukin 2013

Study characteristics	
Methods	Study design: prospective randomized phase III trial Location and number of centers: 1 in the US; 8 in Brazil
Participants	Inclusion criteria • Cytologic or histologic confirmation of Stages IIIB (malignant effusion) and IV NSCLC by the 6th edition of AJCC manual were eligible if they had measurable disease and an ECOG PS of 2 • Initially, people with all histologic subtypes were eligible. A protocol amendment was implemented to exclude people with squamous cell histology in May 2009, when 14 such people had been enrolled. Exclusion criteria • Squamous histology (later) • Prior chemotherapy • Symptomatic brain metastasis • Concurrent active malignancy except cervix (in situ) or basal cell carcinoma of the skin • Inadequate organ function (laboratory results) Baseline imbalances: more people with squamous cell carcinoma in the pemetrexed arm (10.8%) than in the carboplatin + pemetrexed arm (2.9%) N screened: unknown

Zukin 2013 *(Continued)*

	N randomized: 217 N pemetrexed alone: 102 N carboplatin + pemetrexed: 103 N completed: 54/74 N PS 2: all
Interventions	Type of analysis: ITT Treatment arm 1: pemetrexed 500 mg/m^2 Control arm/treatment arm 2: carboplatin AUC 5 + pemetrexed 500 mg/m^2 Both administered intravenously on day 1 every 21 days for up to 4 cycles. Maintenance therapy was not allowed.
Outcomes	Primary: OS Secondary: response rate, PFS, and toxicity Response and progression were evaluated in this study using RECIST criteria, which take into account changes in only the largest diameter of the tumor lesions. PFS was measured from the date of first treatment dose to either the date the participant was first recorded as having disease progression or the date of death if the participant died as a result of any cause before progression. OS was measured from the date of first treatment dose to the date of death or the last date the participant was known to be alive, in which case the participant was censored as of that date. The study was designed with 80% power and a 2-sided type I error of 0.05, assuming that pemetrexed + carboplatin would result in a median survival of ≥ 4.3 months and pemetrexed alone would result in a median survival of ≥ 2.9 months (HR 0.67), which required a total of 208 eligible people.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An independent provider not involved in the study performed random assignment and stratified participants by stage (IIIB vs IV), weight loss (≥ 5% vs < 5%), and age (70 years vs 70 years).
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label, unclear effect on mortality.
Blinding of outcome assessment (detection bias) (overall survival) All outcomes	Low risk	Open-label study, this was unlikely to influence survival.

Zukin 2013 *(Continued)*

Blinding of outcome assessment (detection bias) (other outcomes) All outcomes	High risk	Open-label study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	12 people (7 in the pemetrexed arm and 5 in the carboplatin + pemetrexed arm) were deemed ineligible because of Stage IIIB disease without a malignant pleural effusion (4 people), uncontrolled CNS disease (2 people), non-measurable disease (1 person), glomerular filtration rate < 45 mL/minute (2 people), transaminases > 5 × ULN (2 people), and prior chemotherapy. Best response could not be determined in 34.4% of people in the pemetrexed arm and 23.3% of people in the carboplatin + pemetrexed arm, primarily because of lack of confirmation by RECIST.
Selective reporting (reporting bias)	Low risk	All outcomes provided.
Other bias	Low risk	None.

AJCC: American Joint Committee on Cancer; ALK: anaplastic lymphoma kinase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AUC: area under the curve; CALGB: Cancer and Leukemia Group B; CNS: central nervous system; CR: complete response; CT: computerized tomography; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; EORTC QLQ-ELD14: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Elderly Cancer Patients Module; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; EORTC QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer; EQ5D: EuroQol-5D; ESMO: European Society for Medical Oncology; FFPE: formalin-fixed paraffin-embedded; HR: hazard ratio; HRQoL: health-related quality of life; ITT: intention to treat; LCSS: Lung Cancer Symptom Scale; MRI: magnetic resonance imaging; N: number; NCI CTCAE: National Cancer Institute – Common Terminology Criteria for Adverse Events; NR: not reported; NSCLC: non-small cell lung cancer; NYHA: New York Heart Association; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PP: per-protocol; PR: partial response; PS: performance status; QoL: quality of life; RECIST: Response Evaluation Criteria in Solid Tumors; TKI: tyrosine kinase inhibitor; TNM: tumor-node-metastasis; TRR: tumor response rate; TTP: time to progression; ULN: upper limit of normal; WHO: World Health Organization.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Al-Gizawy 2014	No PS 2 data available, confirmed by the study authors.
Anderson 1985	No PS 2 data available, study authors could not be reached.
Anderson 2000	No PS 2 data available, study authors could not be reached.
Atagi 2017	No PS 2 data available, study authors could not be reached.
Belani 2006	No PS 2 data available, study authors could not be reached.
Cartei 1993	No PS 2 data available, study authors could not be reached.
Cellerino 1991	No PS 2 data available, study authors could not be reached.
Comella 2004	No PS 2 data available, study authors could not be reached.
Crino 1990	No PS 2 data available, study authors could not be reached.
Crino 1995	No PS 2 data available, study authors could not be reached.

Study	Reason for exclusion
Cullen 1999	No PS 2 data available, study authors could not be reached.
Danson 2003	No PS 2 data available, study authors could not be reached.
Doebele 2015	No PS 2 data available, confirmed by the study authors.
ELVIS 1999	No PS 2 data available, study authors could not be reached.
Esteban 2006	No PS 2 data available, study authors could not be reached.
Ferry 2017	No PS 2 data available, confirmed by the study authors.
Fossella 2003	No PS 2 data available, study authors could not be reached.
Ganz 1989	No PS 2 data available, study authors could not be reached.
Gebbia 2002	No PS 2 data available, study authors could not be reached.
Gebbia 2003	No PS 2 data available, study authors could not be reached.
Georgoulias 2001	No PS 2 data available, study authors could not be reached.
Giaccone 1998	No PS 2 data available, confirmed by the study authors.
Greco 2007	No PS 2 data available, study authors could not be reached.
Gridelli 1996	No PS 2 data available, study authors could not be reached.
Gridelli 2003a	No PS 2 data available, study authors could not be reached.
Gridelli 2003b	No PS 2 data available, study authors could not be reached.
Grigorescu 2002	No PS 2 data available, study authors could not be reached.
Helbekkmo 2007	No PS 2 data available, study authors could not be reached.
Helsing 1998	No PS 2 data available, study authors could not be reached.
Hillerdal 2011	No PS 2 data available, study authors could not be reached.
Jang 2017	No PS 2 data available, study authors could not be reached.
Jelić 2001	No PS 2 data available, study authors could not be reached.
Kaasa 1991	No PS 2 data available, study authors could not be reached.
Karampeazis 2017	No PS 2 data available, study authors could not be reached.
Kosmidis 1994	No PS 2 data available, confirmed by the study authors.
Kumar 2015	No PS 2 data available, study authors could not be reached.
Leong 2007	No PS 2 data available, study authors could not be reached.
Manegold 1997	No PS 2 data available, study authors could not be reached.

Study	Reason for exclusion
Masutani 1996	No PS 2 data available, study authors could not be reached.
NCT00004887	Registered on ClinicalTrials.gov; however, we were unable to obtain any data.
NCT01593293	Registered on ClinicalTrials.gov; however, we were unable to obtain any data.
Paccagnella 2006	No PS 2 data available, study authors could not be reached.
Perol 2002	No PS 2 data available, confirmed by the study authors.
Quoix 1991	No PS 2 data available, study authors could not be reached.
Ranson 2000	No PS 2 data available, study authors could not be reached.
Rapp 1988	No PS 2 data available, study authors could not be reached.
Rodrigues-Pereira 2011	No PS 2 data available, confirmed by the study authors.
Rosell 1987	No PS 2 data available, study authors could not be reached.
Rosell 2002	No PS 2 data available, study authors could not be reached.
Rosso 1990	No PS 2 data available, study authors could not be reached.
Roszkowski 2000	No PS 2 data available, study authors could not be reached.
Ruckdeschel 1985	No PS 2 data available, study authors could not be reached.
Ruckdeschel 1986	No PS 2 data available, study authors could not be reached.
Shinkai 1985	No PS 2 data available, study authors could not be reached.
Sorensen 2012	No PS 2 data available, study authors could not be reached.
Spiro 2004	No PS 2 data available, study authors could not be reached.
Stathopoulos 2004	No PS 2 data available, study authors could not be reached.
ten Bokkel Huinink 1999	No PS 2 data available, study authors could not be reached.
Thongprasert 1999	No PS 2 data available, study authors could not be reached.
Veronesi 1988	No PS 2 data available, study authors could not be reached.
Wachters 2003	No PS 2 data available, confirmed by the study authors.
Woods 1990	No PS 2 data available, study authors could not be reached.

Characteristics of ongoing studies *[ordered by study ID]*

NCT02581943

Study name	Effect of pembrolizumab with or without carboplatin and paclitaxel on immune response in people with recurrent or Stage IIIB-IV non-small cell lung cancer
Methods	Randomized open-label, single-center trial in the US

Participants	Inclusion criteria
	• People must have histologically or cytologically confirmed non-small cell lung cancer that is advanced/metastatic (Stage IIIB/IV) or recurrent (progression after surgery or radiation or chemo-radiation treatment for loco-regional disease)
	• Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion; newly obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on day 1; people for whom newly obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the sponsor; ≥ 4 mm of tumor tissue will be needed for programmed cell death-ligand (PD-L1) staining
	• People who have received up to 2 previous lines of systemic chemotherapy
	• ≥ 1 measurable lesion as defined by RECIST version 1.1 on screening computed tomography or magnetic resonance imaging
	• Eastern Cooperative Oncology Group performance status 2
	• White blood cell count > 2500 cells/µL
	• Absolute neutrophil count ≥ 1500/µL
	• Platelets ≥ 100,000/µL
	• Hemoglobin ≥ 9 g/dL
	• Total bilirubin ≤ 2.0 × ULN
	• Aspartate aminotransferase/alanine aminotransferase ≤ 2.5 × ULN or ≤ 5 × ULN in presence of liver metastases
	• Creatinine within normal institutional limits or creatinine clearance > 50 mL/minute for people with creatinine levels above institutional normal
	• Potassium ≥ lower limit of normal
	• Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) for the duration of study participation and for 4 weeks after the final administration of study drugs; should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately
	• Ability to understand and the willingness to sign an Institutional Review Board-approved informed consent document
	
	Exclusion criteria
	• Known active (untreated) CNS metastases that require steroids; people with CNS metastases who have completed a course of therapy would be eligible for the study provided they are clinically stable for ≥ 4 weeks before study entry, defined as:
	  ◦ no evidence of new or enlarging CNS metastasis or new neurologic symptoms attributable to CNS metastases
	  ◦ asymptomatic and receiving either no or stable doses of anticonvulsants and no corticosteroids for the 4 weeks prior to study entry
	• Current or previous other malignancy within 2 years of study entry, except cured basal or squamous cell skin cancer, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in situ of the cervix, or other non-invasive or indolent malignancy without sponsor approval
	• History of previous exposure to an anti-programmed cell death 1 (PD-1)/PD-L1 agent
	• People receiving any other investigational agents or > 2 different chemotherapy regimens (or both) for treatment of metastatic disease
	• Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study day 1 or who has not recovered (i.e. ≤ grade 1 or at baseline) from adverse events due to a previously administered agent
	• Note: people with ≤ grade 2 neuropathy are an exception to this criterion and may qualify for the study

NCT02581943 *(Continued)*

	• Note: if subject received major surgery, they must have recovered adequately from the toxicity or complications (or both) from the intervention prior to starting therapy • History of allergic reactions attributed to compounds of similar chemical or biologic composition to pembrolizumab, paclitaxel, or carboplatin • Current uncontrolled cardiac disease such as angina or myocardial infarction, congestive heart failure including New York Heart Association functional classification 3, or arrhythmia requiring treatment • History of pneumonitis or active lung infection • Chronic or current active infectious disease requiring systemic antibiotics, antifungals, or antivirals • People receiving chronic steroids or immunosuppression, or both • Known HIV infection, HBV or HCV viremia or at risk for HBV reactivation; HBV DNA and testing for HCV ribonucleic acid must be undetectable; at risk for HBV reactivation is defined as hepatitis B surface antigen positive or anti-hepatitis B core antibody-positive • History of autoimmune disease(s) • Psychiatric illness/social situations that would limit compliance with study requirements • Any other condition or circumstance that could interfere with adherence to the study's procedures or requirements, or otherwise compromise the study's objectives such as history of, or any evidence of active, non-infectious pneumonitis • Has an active infection requiring systemic therapy • Pregnant women are excluded; breastfeeding should be discontinued prior to study entry
Interventions	Treatment arm 1: pembrolizumab intravenous over 30 minutes on day 1. Courses repeat every 3 weeks for 2 years in the absence of disease progression or unacceptable toxicity. Treatment arm 2: pembrolizumab intravenous over 30 minutes on day 1, paclitaxel intravenous over 1 hour and carboplatin intravenous over 1 hour on days 1, 7, and 14. Courses repeat every 3 weeks for 2 years in the absence of disease progression or unacceptable toxicity. Dose not specified
Outcomes	Primary endpoints: duration of response, effect of treatment on immune markers, objective response rate, overall survival, progression-free survival Secondary endpoints: toxicity, quality of life, association between immune response and clinical response
Starting date	17 June 2016
Contact information	Unknown
Notes	Estimated study completion date: November 2022.

CNS: central nervous system; HBV: hepatitis B virus; HCV: hepatitis C virus; RECIST: Response Evaluation Criteria in Solid Tumors; ULN: upper limit of normal.

DATA AND ANALYSES

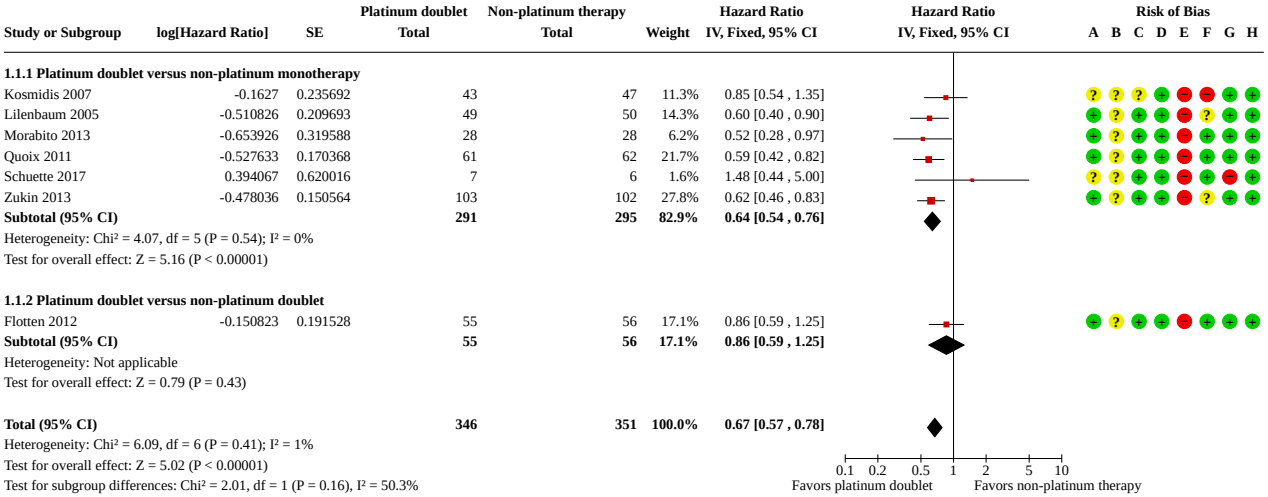
Comparison 1. Platinum doublet versus non-platinum therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Overall survival	7	697	Hazard Ratio (IV, Fixed, 95% CI)	0.67 [0.57, 0.78]
1.1.1 Platinum doublet versus non-platinum monotherapy	6	586	Hazard Ratio (IV, Fixed, 95% CI)	0.64 [0.54, 0.76]
1.1.2 Platinum doublet versus non-platinum doublet	1	111	Hazard Ratio (IV, Fixed, 95% CI)	0.86 [0.59, 1.25]
1.2 6-month survival rates	6	632	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.72, 1.41]
1.2.1 Platinum doublet versus non-platinum monotherapy	5	521	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.64, 1.63]
1.2.2 Platinum doublet versus non-platinum doublet	1	111	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.82, 1.30]
1.3 12-month survival rates	11	1567	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.87, 0.97]
1.3.1 Platinum doublet versus non-platinum monotherapy versus	9	1046	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.82, 0.94]
1.3.2 Platinum doublet versus non-platinum doublet	2	521	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.92, 1.08]
1.4 Progression-free survival	5	487	Hazard Ratio (IV, Random, 95% CI)	0.57 [0.42, 0.77]
1.4.1 Platinum doublet versus non-platinum monotherapy	5	487	Hazard Ratio (IV, Random, 95% CI)	0.57 [0.42, 0.77]
1.5 Tumor response rate	9	964	Risk Ratio (M-H, Fixed, 95% CI)	2.25 [1.67, 3.05]
1.5.1 Platinum doublet versus non-platinum monotherapy	8	880	Risk Ratio (M-H, Fixed, 95% CI)	2.44 [1.75, 3.39]
1.5.2 Platinum doublet versus non-platinum doublet	1	84	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.66, 2.96]
1.6 Toxicity – anemia (any grade)	4	304	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.92, 1.39]
1.7 Toxicity – neutropenia (any grade)	5	391	Risk Ratio (M-H, Fixed, 95% CI)	2.22 [1.58, 3.11]
1.8 Toxicity – thrombocytopenia (any grade)	5	391	Risk Ratio (M-H, Fixed, 95% CI)	3.05 [2.08, 4.48]
1.9 Toxicity – nausea/vomiting (any grade)	4	304	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.94, 1.60]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.10 Toxicity – asthenia (any grade)	3	250	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.92, 1.85]
1.11 Toxicity – fatigue (any grade)	2	168	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.86, 1.56]
1.12 Toxicity – anemia grade 3–5	8	935	Risk Ratio (M-H, Random, 95% CI)	1.98 [1.00, 3.92]
1.12.1 Platinum doublet versus non-platinum monotherapy	6	741	Risk Ratio (M-H, Random, 95% CI)	2.78 [1.58, 4.89]
1.12.2 Platinum doublet versus non-platinum doublet	2	194	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.17, 3.46]
1.13 Toxicity – neutropenia grade 3–5	8	935	Risk Ratio (M-H, Random, 95% CI)	2.75 [1.30, 5.82]
1.13.1 Platinum doublet versus non-platinum monotherapy	6	741	Risk Ratio (M-H, Random, 95% CI)	4.31 [2.80, 6.64]
1.13.2 Platinum doublet versus non-platinum doublet	2	194	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.70, 2.24]
1.14 Toxicity – thrombocytopenia grade 3–5	8	935	Risk Ratio (M-H, Random, 95% CI)	3.96 [1.73, 9.06]
1.14.1 Platinum doublet versus non-platinum monotherapy	6	741	Risk Ratio (M-H, Random, 95% CI)	7.69 [3.74, 15.80]
1.14.2 Platinum doublet versus non-platinum doublet	2	194	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.35, 2.97]
1.15 Toxicity – febrile neutropenia	7	821	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [0.85, 3.12]
1.15.1 Platinum doublet versus non-platinum monotherapy	5	627	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [0.61, 4.80]
1.15.2 Platinum doublet versus non-platinum doublet	2	194	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.68, 3.62]
1.16 Toxicity – nausea/vomiting grade 3–5	7	850	Risk Ratio (M-H, Random, 95% CI)	2.74 [0.83, 9.04]
1.16.1 Platinum doublet versus non-platinum monotherapy	5	656	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.32, 6.27]
1.16.2 Platinum doublet versus non-platinum monotherapy doublet	2	194	Risk Ratio (M-H, Random, 95% CI)	8.72 [2.07, 36.71]
1.17 Toxicity – fatigue grade 3–5	4	439	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.35, 1.90]

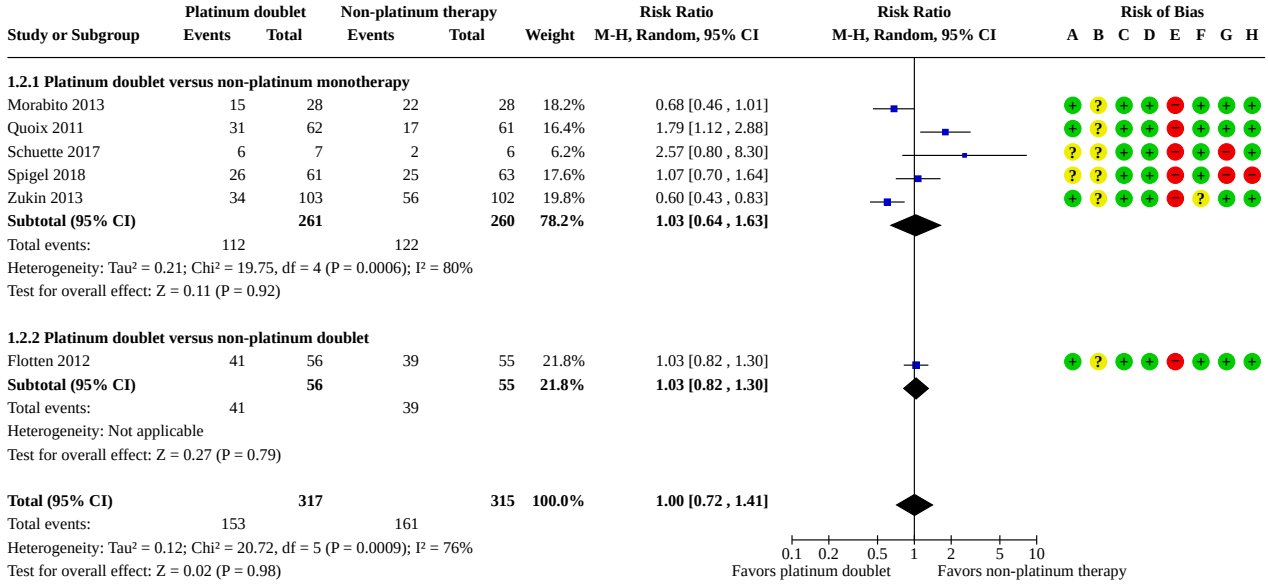
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.17.1 Platinum doublet versus non-platinum monotherapy	3	328	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.18, 3.45]
1.17.2 Platinum doublet versus non-platinum doublet	1	111	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.43, 1.87]
1.18 Toxicity – asthenia grade 3–5	2	237	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.97, 4.38]

Analysis 1.1. Comparison 1: Platinum doublet versus non-platinum therapy, Outcome 1: Overall survival



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias) (overall survival)
(E) Blinding of outcome assessment (detection bias) (other outcomes)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.2. Comparison 1: Platinum doublet versus non-platinum therapy, Outcome 2: 6-month survival rates

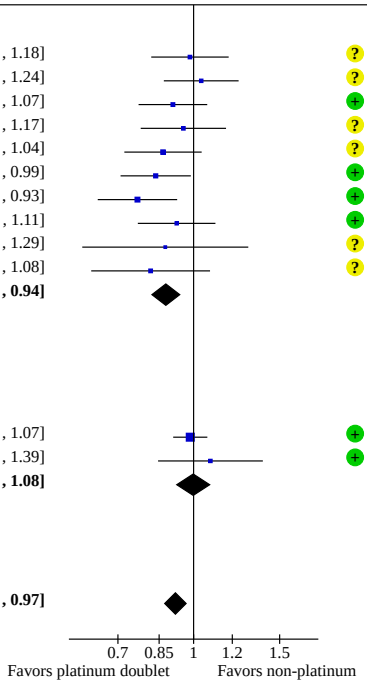


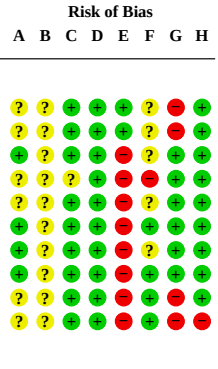
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias) (overall survival)
(E) Blinding of outcome assessment (detection bias) (other outcomes)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.3. Comparison 1: Platinum doublet versus non-platinum therapy, Outcome 3: 12-month survival rates

Study or Subgroup	Platinum doublet Events	Total	Non-platinum therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Platinum doublet versus non-platinum monotherapy versus						
Le Chevalier 2001	35	42	39	46	5.8%	0.98 [0.82 , 1.18]
Le Chevalier 2001	29	33	39	46	5.0%	1.04 [0.87 , 1.24]
Lilenbaum 2005	40	49	45	50	6.9%	0.91 [0.77 , 1.07]
Kosmidis 2007	34	43	39	47	5.8%	0.95 [0.78 , 1.17]
Reynolds 2009	58	85	67	85	10.4%	0.87 [0.72 , 1.04]
Quoix 2011	46	61	55	61	8.5%	0.84 [0.71 , 0.99]
Zukin 2013	62	103	80	102	12.5%	0.77 [0.64 , 0.93]
Morabito 2013	24	28	26	28	4.0%	0.92 [0.77 , 1.11]
Schuette 2017	6	7	6	6	1.1%	0.88 [0.59 , 1.29]
Spigel 2018	34	61	43	63	6.6%	0.82 [0.62 , 1.08]
Subtotal (95% CI)		**512**		**534**	**66.5%**	**0.88 [0.82 , 0.94]**
Total events:	368		439			
Heterogeneity: Chi² = 8.60, df = 9 (P = 0.48); I² = 0%						
Test for overall effect: Z = 3.92 (P < 0.0001)						
1.3.2 Platinum doublet versus non-platinum doublet						
Flotten 2012	186	222	183	215	28.8%	0.98 [0.91 , 1.07]
Saito 2012	32	41	31	43	4.7%	1.08 [0.85 , 1.39]
Subtotal (95% CI)		**263**		**258**	**33.5%**	**1.00 [0.92 , 1.08]**
Total events:	218		214			
Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.05 (P = 0.96)						
Total (95% CI)		**775**		**792**	**100.0%**	**0.92 [0.87 , 0.97]**
Total events:	586		653			
Heterogeneity: Chi² = 13.00, df = 11 (P = 0.29); I² = 15%						
Test for overall effect: Z = 3.33 (P = 0.0009)						
Test for subgroup differences: Chi² = 6.20, df = 1 (P = 0.01), I² = 83.9%						

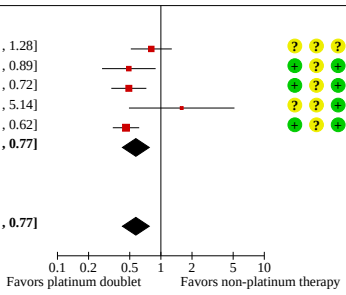




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias) (overall survival)
(E) Blinding of outcome assessment (detection bias) (other outcomes)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.4. Comparison 1: Platinum doublet versus non-platinum therapy, Outcome 4: Progression-free survival

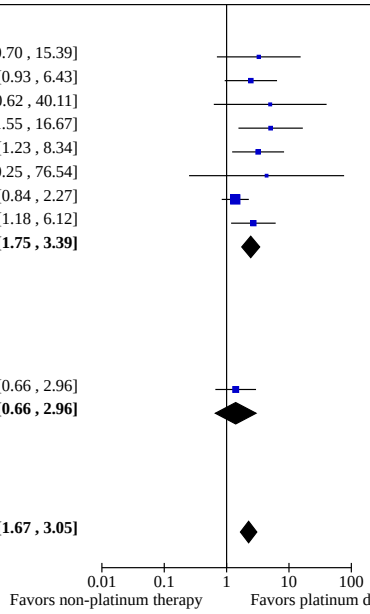
Study or Subgroup	log[Hazard Ratio]	SE	Platinum doublet Total	Non-platinum monotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
1.4.1 Platinum doublet versus non-platinum monotherapy						
Kosmidis 2007	-0.21303	0.232727	43	47	21.9%	0.81 [0.51 , 1.28]
Morabito 2013	-0.71335	0.304291	28	28	16.1%	0.49 [0.27 , 0.89]
Quoix 2011	-0.71335	0.199024	61	62	25.3%	0.49 [0.33 , 0.72]
Schuette 2017	0.463734	0.599107	7	6	5.7%	1.59 [0.49 , 5.14]
Zukin 2013	-0.776529	0.149948	103	102	31.1%	0.46 [0.34 , 0.62]
Subtotal (95% CI)			**242**	**245**	**100.0%**	**0.57 [0.42 , 0.77]**
Heterogeneity: Tau² = 0.05; Chi² = 7.73, df = 4 (P = 0.10); I² = 48%						
Test for overall effect: Z = 3.65 (P = 0.0003)						
Total (95% CI)			**242**	**245**	**100.0%**	**0.57 [0.42 , 0.77]**
Heterogeneity: Tau² = 0.05; Chi² = 7.73, df = 4 (P = 0.10); I² = 48%						
Test for overall effect: Z = 3.65 (P = 0.0003)						
Test for subgroup differences: Not applicable						

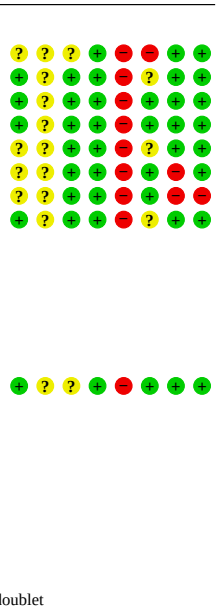


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias) (overall survival)
(E) Blinding of outcome assessment (detection bias) (other outcomes)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.5. Comparison 1: Platinum doublet versus non-platinum therapy, Outcome 5: Tumor response rate

Study or Subgroup	Platinum doublet Events	Total	Non-platinum therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Platinum doublet versus non-platinum monotherapy						
Kosmidis 2007	6	43	2	47	3.8%	3.28 [0.70 , 15.39]
Lilenbaum 2005	12	49	5	50	9.9%	2.45 [0.93 , 6.43]
Morabito 2013	5	28	1	28	2.0%	5.00 [0.62 , 40.11]
Quoix 2011	15	61	3	62	6.0%	5.08 [1.55 , 16.67]
Reynolds 2009	16	85	5	85	10.0%	3.20 [1.23 , 8.34]
Schuette 2017	2	7	0	6	1.1%	4.38 [0.25 , 76.54]
Spigel 2018	24	61	18	63	35.5%	1.38 [0.84 , 2.27]
Zukin 2013	19	103	7	102	14.1%	2.69 [1.18 , 6.12]
Subtotal (95% CI)		**437**		**443**	**82.4%**	**2.44 [1.75 , 3.39]**
Total events:	99		41			
Heterogeneity: Chi² = 7.61, df = 7 (P = 0.37); I² = 8%						
Test for overall effect: Z = 5.27 (P < 0.00001)						
1.5.2 Platinum doublet versus non-platinum doublet						
Saito 2012	12	41	9	43	17.6%	1.40 [0.66 , 2.96]
Subtotal (95% CI)		**41**		**43**	**17.6%**	**1.40 [0.66 , 2.96]**
Total events:	12		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.88 (P = 0.38)						
Total (95% CI)		**478**		**486**	**100.0%**	**2.25 [1.67 , 3.05]**
Total events:	111		50			
Heterogeneity: Chi² = 8.80, df = 8 (P = 0.36); I² = 9%						
Test for overall effect: Z = 5.27 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.76, df = 1 (P = 0.19), I² = 43.1%						

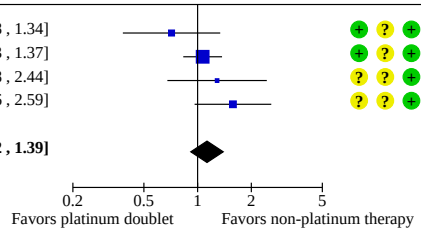


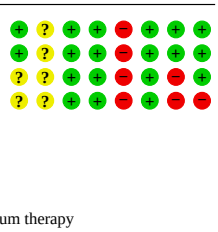


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias) (overall survival)
(E) Blinding of outcome assessment (detection bias) (other outcomes)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.6. Comparison 1: Platinum doublet versus non-platinum therapy, Outcome 6: Toxicity – anemia (any grade)

Study or Subgroup	Platinum doublet Events	Total	Non-platinum therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Morabito 2013	10	28	13	26	18.3%	0.71 [0.38 , 1.34]
Quoix 2011	42	61	40	62	53.7%	1.07 [0.83 , 1.37]
Schuette 2017	6	7	4	6	5.8%	1.29 [0.68 , 2.44]
Spigel 2018	25	55	17	59	22.2%	1.58 [0.96 , 2.59]
Total (95% CI)		**151**		**153**	**100.0%**	**1.13 [0.92 , 1.39]**
Total events:	83		74			
Heterogeneity: Chi² = 4.15, df = 3 (P = 0.25); I² = 28%						
Test for overall effect: Z = 1.13 (P = 0.26)						
Test for subgroup differences: Not applicable						



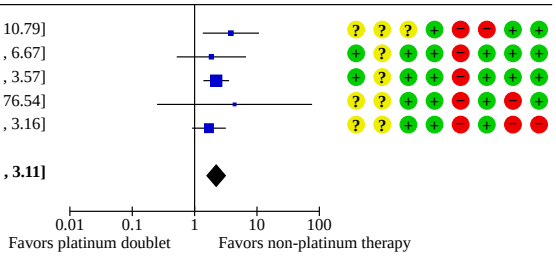


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias) (overall survival)
(E) Blinding of outcome assessment (detection bias) (other outcomes)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.7. Comparison 1: Platinum doublet versus non-platinum therapy, Outcome 7: Toxicity – neutropenia (any grade)

Study or Subgroup	Platinum doublet Events	Total	Non-platinum therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kosmidis 2007	13	40	4	47	10.6%	3.82 [1.35 , 10.79]
Morabito 2013	6	28	3	26	8.9%	1.86 [0.52 , 6.67]
Quoix 2011	35	61	16	62	45.6%	2.22 [1.38 , 3.57]
Schuette 2017	2	7	0	6	1.5%	4.38 [0.25 , 76.54]
Spigel 2018	19	55	12	59	33.3%	1.70 [0.91 , 3.16]
Total (95% CI)		**191**		**200**	**100.0%**	**2.22 [1.58 , 3.11]**
Total events:	75		35			

Heterogeneity: Chi² = 2.05, df = 4 (P = 0.73); I² = 0%
Test for overall effect: Z = 4.59 (P < 0.00001)
Test for subgroup differences: Not applicable

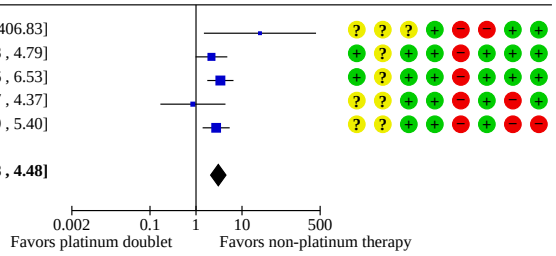


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias) (overall survival)
(E) Blinding of outcome assessment (detection bias) (other outcomes)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.8. Comparison 1: Platinum doublet versus non-platinum therapy, Outcome 8: Toxicity – thrombocytopenia (any grade)

Study or Subgroup	Platinum doublet Events	Total	Non-platinum therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kosmidis 2007	10	40	0	47	1.7%	24.59 [1.49 , 406.83]
Morabito 2013	14	28	6	26	23.5%	2.17 [0.98 , 4.79]
Quoix 2011	30	61	9	62	33.8%	3.39 [1.76 , 6.53]
Schuette 2017	2	7	2	6	8.1%	0.86 [0.17 , 4.37]
Spigel 2018	23	55	9	59	32.8%	2.74 [1.39 , 5.40]
Total (95% CI)		**191**		**200**	**100.0%**	**3.05 [2.08 , 4.48]**
Total events:	79		26			

Heterogeneity: Chi² = 5.37, df = 4 (P = 0.25); I² = 25%
Test for overall effect: Z = 5.69 (P < 0.00001)
Test for subgroup differences: Not applicable

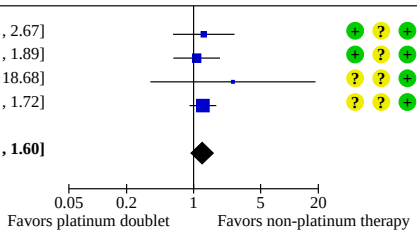


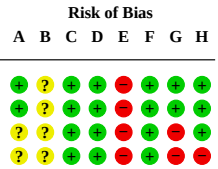
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias) (overall survival)
(E) Blinding of outcome assessment (detection bias) (other outcomes)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.9. Comparison 1: Platinum doublet versus non-platinum therapy, Outcome 9: Toxicity – nausea/vomiting (any grade)

Study or Subgroup	Platinum doublet Events	Total	Non-platinum therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Morabito 2013	11	28	8	26	15.0%	1.28 [0.61 , 2.67]
Quoix 2011	18	61	17	62	30.6%	1.08 [0.61 , 1.89]
Schuette 2017	3	7	1	6	2.0%	2.57 [0.35 , 18.68]
Spigel 2018	35	55	30	59	52.5%	1.25 [0.91 , 1.72]
Total (95% CI)		**151**		**153**	**100.0%**	**1.23 [0.94 , 1.60]**
Total events:	67		56			

Heterogeneity: Chi² = 0.77, df = 3 (P = 0.86); I² = 0%
Test for overall effect: Z = 1.51 (P = 0.13)
Test for subgroup differences: Not applicable



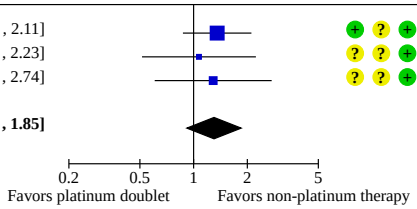


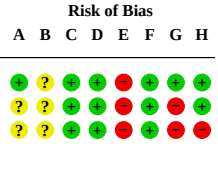
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias) (overall survival)
(E) Blinding of outcome assessment (detection bias) (other outcomes)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.10. Comparison 1: Platinum doublet versus non-platinum therapy, Outcome 10: Toxicity – asthenia (any grade)

Study or Subgroup	Platinum doublet Events	Total	Non-platinum therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Quoix 2011	28	61	21	62	59.9%	1.36 [0.87 , 2.11]
Schuette 2017	5	7	4	6	12.4%	1.07 [0.51 , 2.23]
Spigel 2018	12	55	10	59	27.7%	1.29 [0.61 , 2.74]
Total (95% CI)		**123**		**127**	**100.0%**	**1.30 [0.92 , 1.85]**
Total events:	45		35			

Heterogeneity: Chi² = 0.30, df = 2 (P = 0.86); I² = 0%
Test for overall effect: Z = 1.47 (P = 0.14)
Test for subgroup differences: Not applicable



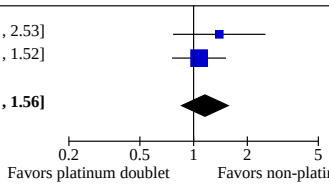


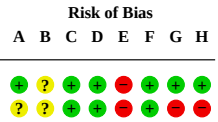
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias) (overall survival)
(E) Blinding of outcome assessment (detection bias) (other outcomes)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.11. Comparison 1: Platinum doublet versus non-platinum therapy, Outcome 11: Toxicity – fatigue (any grade)

Study or Subgroup	Platinum doublet Events	Total	Non-platinum therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Morabito 2013	15	28	10	26	26.4%	1.39 [0.77 , 2.53]
Spigel 2018	30	55	30	59	73.6%	1.07 [0.76 , 1.52]
Total (95% CI)		**83**		**85**	**100.0%**	**1.16 [0.86 , 1.56]**
Total events:	45		40			

Heterogeneity: Chi² = 0.55, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.95 (P = 0.34)
Test for subgroup differences: Not applicable





Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias) (overall survival)
(E) Blinding of outcome assessment (detection bias) (other outcomes)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.12. Comparison 1: Platinum doublet versus non-platinum therapy, Outcome 12: Toxicity – anemia grade 3–5

Study or Subgroup	Platinum doublet Events	Total	Non-platinum therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 Platinum doublet versus non-platinum monotherapy						
Kosmidis 2007	3	40	1	45	7.1%	3.38 [0.37 , 31.16]
Morabito 2013	5	28	0	26	4.8%	10.24 [0.59 , 176.56]
Quoix 2011	6	61	2	62	11.5%	3.05 [0.64 , 14.52]
Reynolds 2009	12	79	6	81	18.9%	2.05 [0.81 , 5.20]
Spigel 2018	6	55	2	59	11.6%	3.22 [0.68 , 15.28]
Zukin 2013	12	103	4	102	16.6%	2.97 [0.99 , 8.91]
Subtotal (95% CI)		**366**		**375**	**70.5%**	**2.78 [1.58 , 4.89]**
Total events:	44		15			

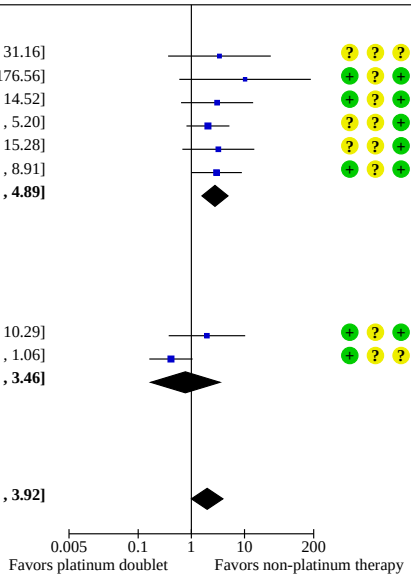
Heterogeneity: Tau² = 0.00; Chi² = 1.34, df = 5 (P = 0.93); I² = 0%
Test for overall effect: Z = 3.55 (P = 0.0004)

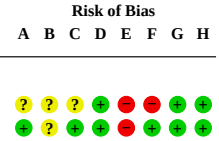
1.12.2 Platinum doublet versus non-platinum doublet						
Flotten 2012	4	56	2	55	10.7%	1.96 [0.37 , 10.29]
Saito 2012	5	40	13	43	18.8%	0.41 [0.16 , 1.06]
Subtotal (95% CI)		**96**		**98**	**29.5%**	**0.77 [0.17 , 3.46]**
Total events:	9		15			

Heterogeneity: Tau² = 0.75; Chi² = 2.59, df = 1 (P = 0.11); I² = 61%
Test for overall effect: Z = 0.34 (P = 0.73)

Total (95% CI)		**462**		**473**	**100.0%**	**1.98 [1.00 , 3.92]**
Total events:	53		30			

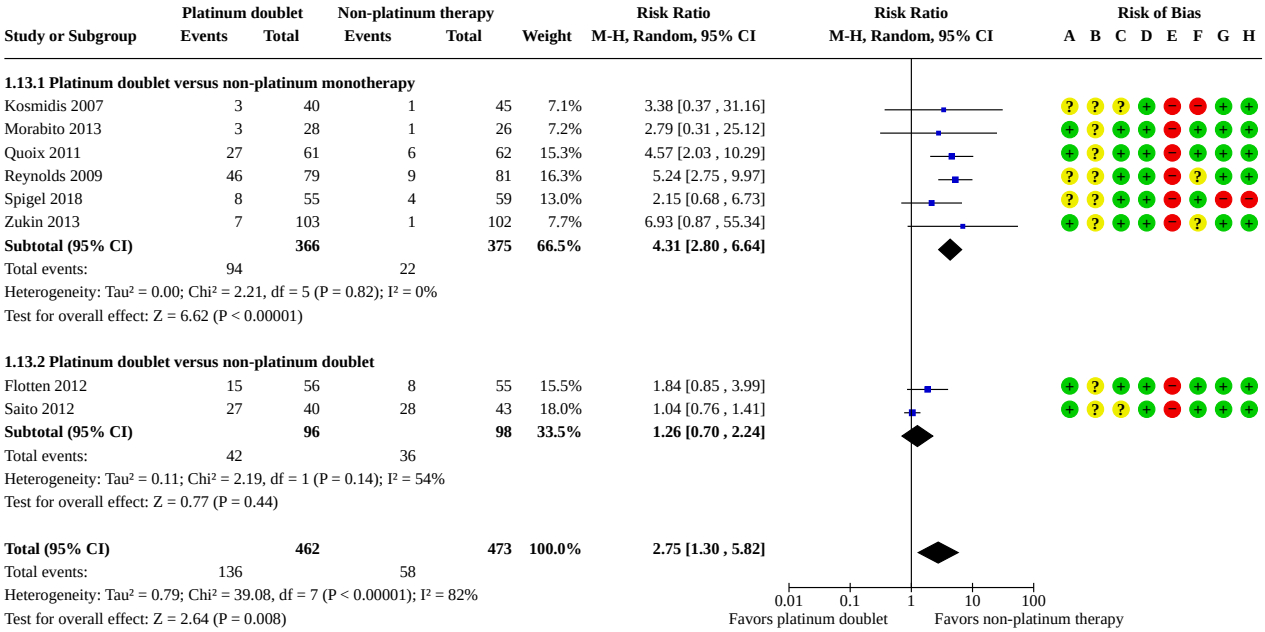
Heterogeneity: Tau² = 0.41; Chi² = 13.07, df = 7 (P = 0.07); I² = 46%
Test for overall effect: Z = 1.97 (P = 0.05)
Test for subgroup differences: Chi² = 2.46, df = 1 (P = 0.12), I² = 59.3%





Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias) (overall survival)
(E) Blinding of outcome assessment (detection bias) (other outcomes)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.13. Comparison 1: Platinum doublet versus non-platinum therapy, Outcome 13: Toxicity – neutropenia grade 3–5

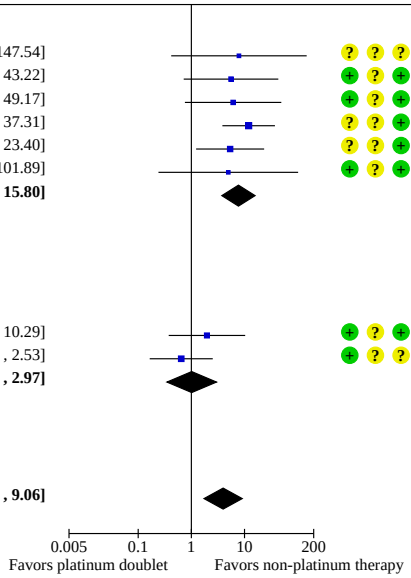


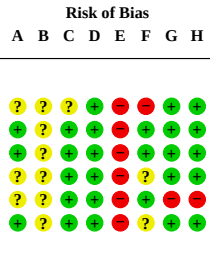
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias) (overall survival)
(E) Blinding of outcome assessment (detection bias) (other outcomes)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.14. Comparison 1: Platinum doublet versus non-platinum therapy, Outcome 14: Toxicity – thrombocytopenia grade 3–5

Study or Subgroup	Platinum doublet Events	Total	Non-platinum therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.14.1 Platinum doublet versus non-platinum monotherapy						
Kosmidis 2007	3	40	0	45	6.4%	7.85 [0.42 , 147.54]
Morabito 2013	6	28	1	26	10.7%	5.57 [0.72 , 43.22]
Quoix 2011	6	61	1	62	10.5%	6.10 [0.76 , 49.17]
Reynolds 2009	35	79	3	81	19.7%	11.96 [3.83 , 37.31]
Spigel 2018	10	55	2	59	15.8%	5.36 [1.23 , 23.40]
Zukin 2013	2	103	0	102	6.1%	4.95 [0.24 , 101.89]
Subtotal (95% CI)		**366**		**375**	**69.1%**	**7.69 [3.74 , 15.80]**
Total events:	62		7			
Heterogeneity: Tau² = 0.00; Chi² = 1.05, df = 5 (P = 0.96); I² = 0%						
Test for overall effect: Z = 5.55 (P < 0.00001)						
1.14.2 Platinum doublet versus non-platinum doublet						
Flotten 2012	4	56	2	55	13.9%	1.96 [0.37 , 10.29]
Saito 2012	3	40	5	43	17.0%	0.65 [0.16 , 2.53]
Subtotal (95% CI)		**96**		**98**	**30.9%**	**1.02 [0.35 , 2.97]**
Total events:	7		7			
Heterogeneity: Tau² = 0.02; Chi² = 1.04, df = 1 (P = 0.31); I² = 3%						
Test for overall effect: Z = 0.03 (P = 0.98)						
Total (95% CI)		**462**		**473**	**100.0%**	**3.96 [1.73 , 9.06]**
Total events:	69		14			
Heterogeneity: Tau² = 0.57; Chi² = 12.11, df = 7 (P = 0.10); I² = 42%						
Test for overall effect: Z = 3.26 (P = 0.001)						
Test for subgroup differences: Chi² = 9.42, df = 1 (P = 0.002), I² = 89.4%						

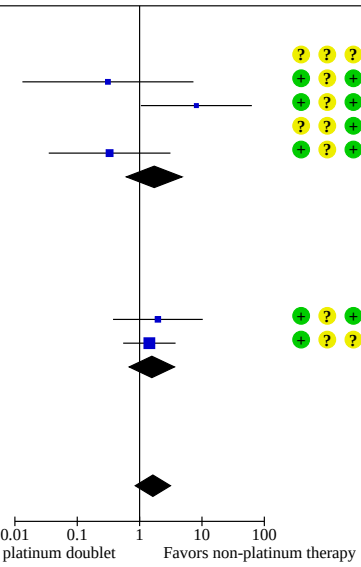


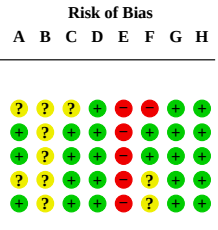


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias) (overall survival)
(E) Blinding of outcome assessment (detection bias) (other outcomes)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.15. Comparison 1: Platinum doublet versus non-platinum therapy, Outcome 15: Toxicity – febrile neutropenia

Study or Subgroup	Platinum doublet Events	Total	Non-platinum therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.15.1 Platinum doublet versus non-platinum monotherapy						
Kosmidis 2007	0	40	0	45		Not estimable
Morabito 2013	0	28	1	26	11.6%	0.31 [0.01 , 7.30]
Quoix 2011	8	61	1	62	7.4%	8.13 [1.05 , 63.07]
Reynolds 2009	0	79	0	81		Not estimable
Zukin 2013	1	103	3	102	22.6%	0.33 [0.03 , 3.12]
Subtotal (95% CI)		**311**		**316**	**41.6%**	**1.72 [0.61 , 4.80]**
Total events:	9		5			
Heterogeneity: Chi² = 5.41, df = 2 (P = 0.07); I² = 63%						
Test for overall effect: Z = 1.03 (P = 0.30)						
1.15.2 Platinum doublet versus non-platinum doublet						
Flotten 2012	4	56	2	55	15.1%	1.96 [0.37 , 10.29]
Saito 2012	8	40	6	43	43.3%	1.43 [0.54 , 3.77]
Subtotal (95% CI)		**96**		**98**	**58.4%**	**1.57 [0.68 , 3.62]**
Total events:	12		8			
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 1.06 (P = 0.29)						
Total (95% CI)		**407**		**414**	**100.0%**	**1.63 [0.85 , 3.12]**
Total events:	21		13			
Heterogeneity: Chi² = 5.48, df = 4 (P = 0.24); I² = 27%						
Test for overall effect: Z = 1.48 (P = 0.14)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.90), I² = 0%						



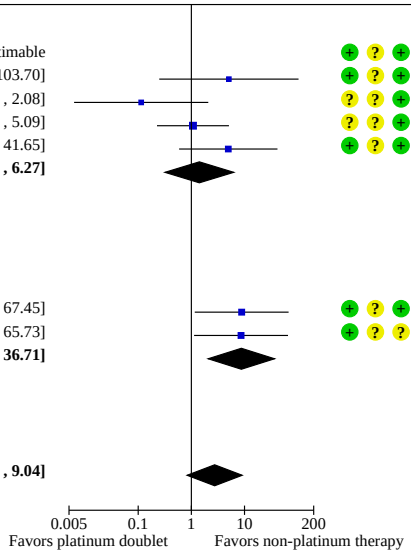


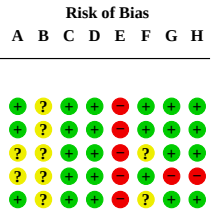
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias) (overall survival)
(E) Blinding of outcome assessment (detection bias) (other outcomes)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.16. Comparison 1: Platinum doublet versus non-platinum therapy, Outcome 16: Toxicity – nausea/vomiting grade 3–5

Study or Subgroup	Platinum doublet Events	Total	Non-platinum therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.16.1 Platinum doublet versus non-platinum monotherapy						
Morabito 2013	0	28	0	26		Not estimable
Quoix 2011	2	61	0	62	11.1%	5.08 [0.25 , 103.70]
Reynolds 2009	0	79	4	81	11.7%	0.11 [0.01 , 2.08]
Spigel 2018	3	55	3	59	23.3%	1.07 [0.23 , 5.09]
Zukin 2013	5	103	1	102	17.3%	4.95 [0.59 , 41.65]
Subtotal (95% CI)		**326**		**330**	**63.5%**	**1.41 [0.32 , 6.27]**
Total events:	10		8			
Heterogeneity: Tau² = 0.94; Chi² = 5.08, df = 3 (P = 0.17); I² = 41%						
Test for overall effect: Z = 0.45 (P = 0.65)						
1.16.2 Platinum doublet versus non-platinum monotherapy doublet						
Flotten 2012	9	56	1	55	18.2%	8.84 [1.16 , 67.45]
Saito 2012	8	40	1	43	18.2%	8.60 [1.13 , 65.73]
Subtotal (95% CI)		**96**		**98**	**36.5%**	**8.72 [2.07 , 36.71]**
Total events:	17		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 2.95 (P = 0.003)						
Total (95% CI)		**422**		**428**	**100.0%**	**2.74 [0.83 , 9.04]**
Total events:	27		10			
Heterogeneity: Tau² = 0.96; Chi² = 8.95, df = 5 (P = 0.11); I² = 44%						
Test for overall effect: Z = 1.66 (P = 0.10)						
Test for subgroup differences: Chi² = 2.97, df = 1 (P = 0.08), I² = 66.3%						



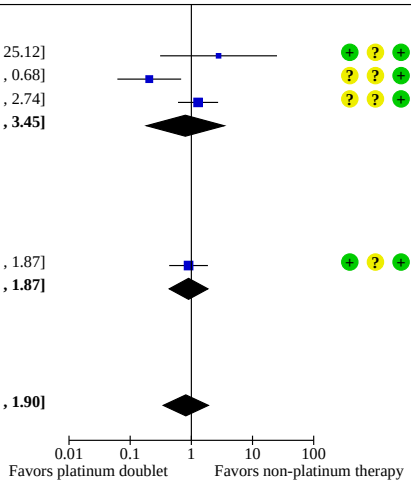


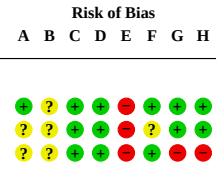
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias) (overall survival)
(E) Blinding of outcome assessment (detection bias) (other outcomes)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.17. Comparison 1: Platinum doublet versus non-platinum therapy, Outcome 17: Toxicity – fatigue grade 3–5

Study or Subgroup	Platinum doublet Events	Total	Non-platinum therapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.17.1 Platinum doublet versus non-platinum monotherapy						
Morabito 2013	3	28	1	26	11.1%	2.79 [0.31 , 25.12]
Reynolds 2009	3	79	15	81	23.3%	0.21 [0.06 , 0.68]
Spigel 2018	12	55	10	59	32.5%	1.29 [0.61 , 2.74]
Subtotal (95% CI)		**162**		**166**	**66.9%**	**0.80 [0.18 , 3.45]**
Total events:	18		26			
Heterogeneity: Tau² = 1.19; Chi² = 7.94, df = 2 (P = 0.02); I² = 75%						
Test for overall effect: Z = 0.30 (P = 0.76)						
1.17.2 Platinum doublet versus non-platinum doublet						
Flotten 2012	11	56	12	55	33.1%	0.90 [0.43 , 1.87]
Subtotal (95% CI)		**56**		**55**	**33.1%**	**0.90 [0.43 , 1.87]**
Total events:	11		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.28 (P = 0.78)						
Total (95% CI)		**218**		**221**	**100.0%**	**0.81 [0.35 , 1.90]**
Total events:	29		38			
Heterogeneity: Tau² = 0.43; Chi² = 7.90, df = 3 (P = 0.05); I² = 62%						
Test for overall effect: Z = 0.48 (P = 0.63)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%						

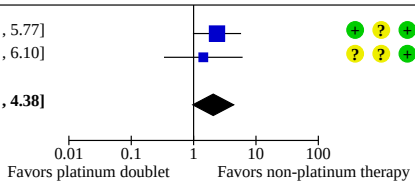


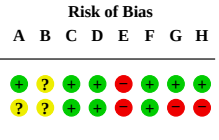


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias) (overall survival)
(E) Blinding of outcome assessment (detection bias) (other outcomes)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.18. Comparison 1: Platinum doublet versus non-platinum therapy, Outcome 18: Toxicity – asthenia grade 3–5

Study or Subgroup	Platinum doublet Events	Total	Non-platinum therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Quoix 2011	14	61	6	62	67.3%	2.37 [0.98 , 5.77]
Spigel 2018	4	55	3	59	32.7%	1.43 [0.34 , 6.10]
Total (95% CI)		**116**		**121**	**100.0%**	**2.06 [0.97 , 4.38]**
Total events:	18		9			
Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 1.89 (P = 0.06)						
Test for subgroup differences: Not applicable						





Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias) (overall survival)
(E) Blinding of outcome assessment (detection bias) (other outcomes)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

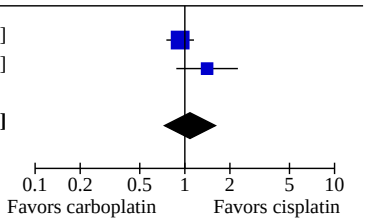
Comparison 2. Carboplatin versus cisplatin therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 12-month survival rates (direct comparison)	2	131	Risk Ratio (IV, Random, 95% CI)	1.08 [0.73, 1.60]
2.2 12-month survival rates (indirect analysis)	11	1567	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.87, 0.97]
2.2.1 Carboplatin versus non-platinum monotherapy versus	9	1344	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.86, 0.96]
2.2.2 Cisplatin versus non-platinum doublet	2	223	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.89, 1.09]
2.3 Tumor response rate (direct comparison)	2	131	Risk Ratio (IV, Fixed, 95% CI)	0.64 [0.31, 1.34]

Analysis 2.1. Comparison 2: Carboplatin versus cisplatin therapy, Outcome 1: 12-month survival rates (direct comparison)

Study or Subgroup	Carboplatin regimen Events	Total	Cisplatin regimen Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Langer 2007 (1)	40	54	39	49	63.6%	0.93 [0.75 , 1.15]
Sweeney 2001 (2)	13	15	8	13	36.4%	1.41 [0.88 , 2.26]
Total (95% CI)		**69**		**62**	**100.0%**	**1.08 [0.73 , 1.60]**
Total events:	53		47			

Heterogeneity: Tau² = 0.05; Chi² = 2.45, df = 1 (P = 0.12); I² = 59%
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable

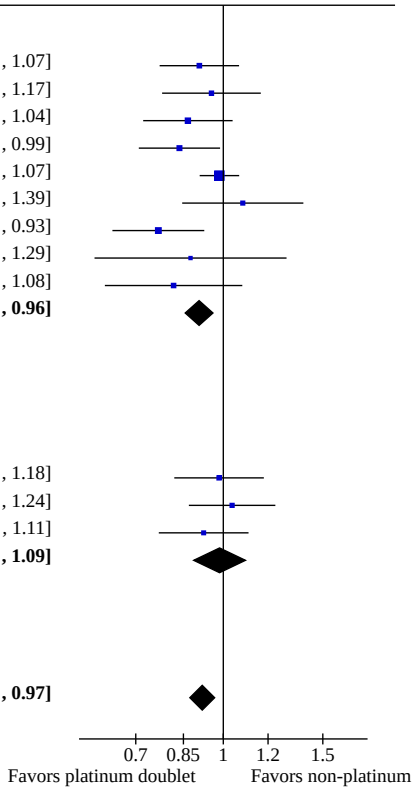


Footnotes

(1) Carboplatin + paclitaxel and cisplatin + gemcitabine.
(2) Carbo + paclitaxel vs cisplatin + gemcitabine. For comparison with Langer 2007, cis + pacl and cis + doc excluded from analysis.

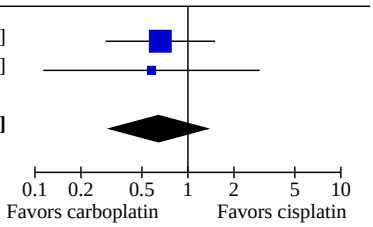
Analysis 2.2. Comparison 2: Carboplatin versus cisplatin therapy, Outcome 2: 12-month survival rates (indirect analysis)

Study or Subgroup	Platinum doublet Events	Total	Non-platinum therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Carboplatin versus non-platinum monotherapy versus						
Lilenbaum 2005	40	49	45	50	6.9%	0.91 [0.77 , 1.07]
Kosmidis 2007	34	43	39	47	5.8%	0.95 [0.78 , 1.17]
Reynolds 2009	58	85	67	85	10.4%	0.87 [0.72 , 1.04]
Quoix 2011	46	61	55	61	8.5%	0.84 [0.71 , 0.99]
Flotten 2012	186	222	183	215	28.8%	0.98 [0.91 , 1.07]
Saito 2012	32	41	31	43	4.7%	1.08 [0.85 , 1.39]
Zukin 2013	62	103	80	102	12.5%	0.77 [0.64 , 0.93]
Schuette 2017	6	7	6	6	1.1%	0.88 [0.59 , 1.29]
Spigel 2018	34	61	43	63	6.6%	0.82 [0.62 , 1.08]
Subtotal (95% CI)		**672**		**672**	**85.2%**	**0.91 [0.86 , 0.96]**
Total events:	498		549			
Heterogeneity: Chi² = 11.04, df = 8 (P = 0.20); I² = 28%						
Test for overall effect: Z = 3.42 (P = 0.0006)						
2.2.2 Cisplatin versus non-platinum doublet						
Le Chevalier 2001	35	42	39	46	5.8%	0.98 [0.82 , 1.18]
Le Chevalier 2001	29	33	39	46	5.0%	1.04 [0.87 , 1.24]
Morabito 2013	24	28	26	28	4.0%	0.92 [0.77 , 1.11]
Subtotal (95% CI)		**103**		**120**	**14.8%**	**0.98 [0.89 , 1.09]**
Total events:	88		104			
Heterogeneity: Chi² = 0.81, df = 2 (P = 0.67); I² = 0%						
Test for overall effect: Z = 0.28 (P = 0.78)						
Total (95% CI)		**775**		**792**	**100.0%**	**0.92 [0.87 , 0.97]**
Total events:	586		653			
Heterogeneity: Chi² = 13.00, df = 11 (P = 0.29); I² = 15%						
Test for overall effect: Z = 3.33 (P = 0.0009)						
Test for subgroup differences: Chi² = 1.87, df = 1 (P = 0.17), I² = 46.5%						



Analysis 2.3. Comparison 2: Carboplatin versus cisplatin therapy, Outcome 3: Tumor response rate (direct comparison)

Study or Subgroup	Carboplatin regimen Events	Total	Cisplatin regimen Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Langer 2007 (1)	8	54	11	49	79.6%	0.66 [0.29 , 1.51]
Sweeney 2001 (2)	2	15	3	13	20.4%	0.58 [0.11 , 2.94]
Total (95% CI)		**69**		**62**	**100.0%**	**0.64 [0.31 , 1.34]**
Total events:	10		14			
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%						
Test for overall effect: Z = 1.18 (P = 0.24)						
Test for subgroup differences: Not applicable						



Footnotes

(1) Carboplatin + paclitaxel and cisplatin + gemcitabine.

(2) Carbo + paclitaxel vs cisplatin + gemcitabine. For comparison with Langer 2007, cis + pacl and cis + doc excluded from analysis.

ADDITIONAL TABLES

Table 1. Non-platinum therapy versus platinum doublet: used regimens per study

Study	Number of people with PS 2	Cycle length (days)	Non-platinum regimen	Platinum regimen	Duration
Flotten 2012	55/56	21	1. Vinorelbine capsules 60 mg/m^2 2. Gemcitabine 1000 mg/m^2 on days 1 and 8	1. Vinorelbine capsules 60 mg/m^2 on day 1 and 8 2. Carboplatin AUC 5 on day 1	NR
Kosmidis 2007	47/43	28	Gemcitabine 1250 mg/m^2 on days 1 and 14	1. Gemcitabine 1250 mg/m^2 2. Carboplatin AUC 3 on day 1 and 14	Gemcitabine: 0.5 hours Carboplatin: 1 hours
Le Chevalier 2001	46/(42 or 33)	N/A	Vinorelbine 30 mg/m^2 weekly	1. Vinorelbine 30 mg/m^2 weekly 2. Cisplatin 120 mg/m^2 on days 1 and 29 and then every 6 weeks *or* 1. Vindesine 3 mg/m^2 weekly for 6 weeks and then every 6 weeks 2. Cisplatin 120 mg/m^2 on days 1 and 29 and then every 6 weeks	Vinorelbine: 20 minutes Vindesine: push Cisplatin: 1 hour
Lilenbaum 2005	50/49	21	Paclitaxel 225 mg/m^2 on day 1	1. Paclitaxel 225 mg/m^2 on day 1 2. Carboplatin AUC 6	Paclitaxel: 3 hours Carboplatin: 30 minutes
Morabito 2013	28/28	21	Gemcitabine 1200 mg/m^2 on days 1 and 8	1. Gemcitabine 1000 mg/m^2 on days 1 and 8 2. Cisplatin 60 mg/m^2 on day 1	Gemcitabine: 30 minutes Cisplatin: NR
Quoix 2011	62/61	21/28	Vinorelbine 25 mg/m^2 on days 1 and 8 *or* Gemcitabine 1150 mg/m^2 on days 1 and 8	1. Paclitaxel 90 mg/m^2 on days 1, 8, and 15 2. Carboplatin AUC 6 on day 1	NR
Reynolds 2009	85/85	21	Gemcitabine 1250 mg/m^2 on days 1 and 8	1. Gemcitabine 1000 mg/m^2 on days 1 and 8 2. Carboplatin AUC 5 on day 1	NR
Saito 2012	43/41	21	1. Vinorelbine 25 mg/m^2 on days 1 and 8 2. Gemcitabine 1000 mg/m^2 on days 1 and 8	1. Paclitaxel 200 mg/m^2 on day 1 2. Carboplatin AUC 6 on day 1	Paclitaxel: 3 hours Carboplatin: 1 hour

Table 1. Non-platinum therapy versus platinum doublet: used regimens per study *(Continued)*

					Vinorelbine: 6–10 minutes Gemcitabine: 30 minutes
Schuette 2017	6/7	21	1. Pemetrexed 500 mg/m^2 on day 1 2. Bevacizumab 7.5 mg/kg on day 1	1. Pemetrexed 500 mg/m^2 on day 1 2. Carboplatin AUC 5 on day 1 3. Bevacizumab 7.5 mg/kg on day 1	Pemetrexed: 10 minutes Carboplatin: 30–60 minutes Bevacizumab: 90–30[a]
Spigel 2018	63/61	21	1. Pemetrexed 500 mg/m^2 on day 1 2. Bevacizumab 15 mg/kg on day 1	1. Pemetrexed 500 mg/m^2 on day 1 2. Carboplatin AUC 5 on day 1 3. Bevacizumab 15 mg/kg on day 1	NR
Zukin 2013	102/103	21	Pemetrexed 500 mg/m^2 on day 1	1. Pemetrexed 500 mg/m^2 on day 1 2. Carboplatin AUC 5 on day 1	NR

AUC: area under the curve; PS: performance score, NR: not reported, N/A: not applicable.
[a]The first bevacizumab treatment was administered as an intravenous infusion over 90 minutes after chemotherapy. If the first infusion was well tolerated, the second infusion was given over 60 minutes and all subsequent infusions over 30 minutes.

Table 2. Treatment efficacy (response rate, overall survival, progression-free survival, 6-/12-month survival rates) of non-comparable therapies.

Study	Study regimens	Number of people with PS 2	Response rate (% [95% CI])	OS (median [95% CI])	PFS (median [95% CI])	6-month OS (%)	12-month OS (%)	HR (95% CI)
Gridelli 2007	1. Pemetrexed + gemcitabine	17	NR	3.9	1.9	NR	NR	—
	2. Pemetrexed	14		1.8	1.3			
Gronberg 2009	1. Carboplatin + pemetrexed	47	NR	4.3 (3.3 to 5.4)	NR	36.2	23.4	For OS: 1.02 (0.25 to 4.22)
	2. Carboplatin + gemcitabine	49		5.1 (3.3 to 7.0)		46.9	20.4	
Hainsworth 2007	1. Docetaxel	57	NR	2.9	NR	NR (graph)	NR (graph)	—
	2. Docetaxel + gemcitabine	65		3.8				
Karam-peazis 2011	1. Docetaxel	19	5.3	3.3 (0.2 to 20.6)	NR	NR	NR	—
	2. Vinorelbine	7	11.8	2.8 (0.9 to 40.6)				
Kosmidis 2012	1. Vinorelbine	36	5	3.1 (2.3 to 3.9)	2.1 (1.8 to 2.4)	NR	13.9	—
	2. Paclitaxel	38	13	5.1 (2.7 to 7.9)	2.6 (1.7 to 4.7)		21.0	
Langer 2007	1. Carboplatin + paclitaxel	54	14 (6.4 to 23.4)	6.2 (NR)	3.5 (2.6 to 6.0)	NR	25.5 (13.1 to 38.0)	
	2. Cisplatin + gemcitabine	49	23 (13.1 to 34.4)	6.9 (NR)	3.0 (1.7 to 4.8)		19.6 (8.7 to 30.5)	
Morere 2010	1. Docetaxel	42	7	6.6 (3.5 to 8.3)	2.2 (1.6 to 4.6)	51.8 (31.9 to 68.4)	19.9 (7.3 to 37.0)	OS: 0.89 (0.57 to 1.41)
	2. Gemcitabine	42	0	3.1 (2.0 to 6.4)	2.1 (1.3 to 3.1)	37.9 (20.9 to 54.9)	8.4 (1.5 to 23.3)	PFS: 0.66 (0.37 to 1.16)
Sweeney 2001	1. Cisplatin + paclitaxel	14	17 (3.4 to 39.6)	7.0 (range 0.5–29)	1.4 (range 0.2–11.7)	NR	19.0	—
	2. Cisplatin + gemcitabine	13	23 (5.5 to 57.2)	7.9 (range 0.4–16.2)	4.6 (range 0.4–14.6)		38.5	

Table 2. Treatment efficacy (response rate, overall survival, progression-free survival, 6-/12-month survival rates) of non-comparable therapies. *(Continued)*

	3. Cisplatin + docetaxel	18	6 (1.0 to 27.3)	2.3 (range 0.2–31)	1.4 (range 0.2–21.4)		10.5	
	4. Carboplatin + paclitaxel	15	13 (1.7 to 40.5)	4.6 (range 0.9–13.3)	1.5 (range 0.5–13.3)		13.3	
Yadav 2021	1. Carboplatin + pemetrexed	23	NR	9.03 (4.06 to 17.63)	3.27 (1.8 to 9.67)	59.1 (36.1 to 76.2)	45.5 (24.4 to 64.3)	OS: 1.11 (0.54 to 2.28) PFS: 1.21 (0.64 to 2.29)
	2. Carboplatin + paclitaxel	21	—	6.66 (2.93 to 20.46)	2.93 (1.6 to 6.4)	61.9 (38.1 to 78.8)	41.67 (20.5 to 61.7)	

CI: confidence interval; HR: hazard ratio; NR: not reported; OS: overall survival; PFS: progression-free survival; PS: Performance Status.

Table 3. Overall survival and 6-/12-month survival rates for non-platinum therapy versus platinum doublet

Study	Number of people with PS 2	Non-platinum therapy			Platinum doublet			HR (95% CI)	P value
		Median OS (months) (95% CI)	6-month OS (%) (95% CI)	12-month OS (%) (95% CI)	Median OS (months) (95% CI)	6-month OS (%) (95% CI)	12-month OS (%) (95% CI)		
Flotten 2012	55/56	4.0 (NR)	29 (NR)	15 (NR)	4.5 (NR)	43 (NR)	16 (NR)	0.86 (0.59 to 1.25)	0.418
Kosmidis 2007	47/43	4.8 (2.45 to 7.25)	NR	17.8 (NR)	6.7 (2.47 to 10.8)	NR	20 (NR)	0.85 (0.54 to 1.35)	0.49
Le Chevalier 2001	42/33/46	3.9 (NR)	NR	15 (NR)	CisVino: 4.1 (NR)	NR	17 (NR)	NR	NR
					CisVind: 4.1 (NR)	NR	13 (NR)	NR	NR
Lilenbaum 2005	50/49	2.4 (1.9 to 3.6)	NR	10 (4 to 23)	4.7 (3.1 to 6.9)	NR	18 (10 to 33)	0.60 (0.40 to 0.91)	0.016
Morabito 2013	28/28	3.0 (1.9 to 6.3)	21.4 (NR)	7.1 (NR)	5.9 (2.8 to 11.3)	46.4 (NR)	14.2 (NR)	0.52 (0.28 to 0.98)	0.039

Table 3. Overall survival and 6-/12-month survival rates for non-platinum therapy versus platinum doublet *(Continued)*

Quoix 2011	62/61	3.6 (2.3 to 4.3)	26.7 (16.3 to 38.2)	10.0 (4.1 to 19.1)	6.1 (4.2 to 8.3)	50.9 (37.3 to 62.9)	23.9 (13.7 to 35.6)	0.63 (0.43 to 0.91)	0.006
Reynolds 2009	85/85	5.1 (3.9 to 6.3)	NR	21.2 (NR)	6.7 (4.9 to 10.0)	NR	31.3 (NR)	NR	0.242
Saito 2012	43/41	5.9 (NR)	NR	22.0 (9.3 to 34.6)	6.0 (NR)	NR	27.9 (14.5 to 41.3)	NR	NR
Schuette 2017	6/7	7.0 (0.2 to 11.6)	66.6 (NR)	0 (NR)	3.8 (0.3 to 5.2)	14.3 (NR)	14.3 (NR)	1.48 (0.44 to 5.00)	0.325
Spigel 2018	63/61	Pem: 7.7 (3.0 to 11.2)	NR	30 (18 to 43)	8.7 (5.4 to 13.0)	NR	32 (21 to 45)	NR	NR
		PemBev: 8.6 (5.3 to 11.2)	NR	32 (21 to 45)					
Zukin 2013	102/103	5.3 (4.1 to 6.5)	44.9 (NR)	21.9 (NR)	9.3 (7.4 to 11.2)	66.8 (NR)	40.1 (NR)	0.62 (0.46 to 0.83)	0.001
Total	1244 participants								

CI: confidence interval; CisVind: cisplatin + vindesine; CisVino: cisplatin + vinorelbine; HR: hazard ratio; NR: not reported; OS: overall survival; pem: pemetrexed; PemBev: pemetrexed + bevacizumab.

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 via PubMed 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]"

(Continued)

#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]"

(Continued)

#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

(Continued)

#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

(Continued)

#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

HISTORY

Protocol first published: Issue 8, 2019

CONTRIBUTIONS OF AUTHORS

Drafting the protocol: all review authors.

Developing and running the search strategy: RG, WG, LCG Trial Search Co-ordinator.

Obtaining copies of studies: RG, WG, AW.

Selecting which studies to include: RG, WG.

Extracting data from studies: RG, WG.

Entering data into Review Manager 5: RG.

Conducting the analysis: RG, KJ, WG.

Interpreting the analysis: all review authors.

Drafting the final review: all review authors.

Updating the review: all review authors.

DECLARATIONS OF INTEREST

RG: none.

KJ: none.

BV: none.

FV: none.

AB declares institutional fees from Sanofi and Genzyme US Companies, from Teva Pharmaceutical Industries and AstraZeneca and from GlaxoSmithKline and unrestricted research grant: Grant/Contract from Teva Pharmaceutical Industries.

AW declares being Independent Contractor – Consultant for Eli Lilly and Company and having received grant/contract from Pfizer Pharma GMBH, Boehringer Ingelheim, AstraZeneca, F. Hoffmann-La Roche, and Takeda Oncology.

WG is Fiduciary Officer for the European Respiratory Society and for the NVALT (Dutch Society of Respiratory Physicians) and has no conflicts of interests.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are two differences in methodology between protocol and review (Gijtenbeek 2019). We did not perform any subgroup analyses due to a lack of data. We chose to present the sensitivity analysis in line in the results section instead of a predefined table.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Combined Chemotherapy Protocols [therapeutic use]; Carboplatin [therapeutic use]; *Carcinoma, Non-Small-Cell Lung [drug therapy] [genetics]; Cisplatin; *Lung Neoplasms [drug therapy] [genetics]; Mutation

MeSH check words

Humans