Lung Cancer 135 (2019) 196–204

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Efficacy and safety of first-line carboplatin-versus cisplatin-based chemotherapy for non-small cell lung cancer: A meta-analysis

Frank Griesinger[a], Ellen E. Korol[b], Sheena Kayaniyil[b,*], Nebibe Varol[c], Timo Ebner[d], Sarah M. Goring[b]

[a] Pius-Hospital, University Medicine Oldenburg, Department of Hematology and Oncology, University Department Internal Medicine-Oncology, 26121, Oldenburg, Germany
[b] ICON plc., Vancouver, V6B 1P1, Canada
[c] Bristol-Myers Squibb Pharmaceuticals Ltd., Uxbridge, UB8 1DH, UK
[d] Bristol-Myers Squibb GmbH&Co. KGaA, 80636, München, Germany

ARTICLE INFO

Keywords:
Non-small cell lung cancer
Platinum doublet
Cisplatin
Carboplatin
Meta-analysis

ABSTRACT

Objectives: Platinum-based chemotherapy is the mainstay of first-line (1L) therapy for advanced non-small cell cancer (NSCLC). The objective of this study was to evaluate the relative efficacy, safety, and health-related quality of life (HRQoL) of carboplatin- versus cisplatin-based chemotherapy in 1L NSCLC.

Materials and Methods: A meta-analysis by the Cochrane group (2013) was updated. Systematic searches of CENTRAL, Medline, Embase, Latin American and Caribbean Health Sciences database, clinicaltrials.gov and conference proceedings were conducted to include randomized controlled trials (RCTs) published between 2013-January 2018 which compared carboplatin and cisplatin combined with: gemcitabine, vinorelbine, docetaxel, paclitaxel, irinotecan, or pemetrexed. Endpoints included overall survival (OS), one-year OS, objective response rate (ORR), grade 3/4 drug-related toxicities, and HRQoL.

Results: Twelve RCTs (2,048 patients) were identified from 4,139 records for inclusion in the meta-analysis. There were no significant differences in OS (hazards ratio [HR]: 1.08, 95% confidence interval [CI]: 0.96, 1.21) and one-year OS (relative risk [RR]: 0.97, CI: 0.89, 1.07) between carboplatin- and cisplatin-based chemotherapy. A small effect on ORR favouring cisplatin was detected (RR = 0.88; CI: 0.78, 0.99). Differences in drug-related toxicities were observed between carboplatin- and cisplatin-based chemotherapy for thrombocytopenia, anaemia, neurotoxicity, and the risk of nausea/vomiting. Three RCTs comparing HRQoL between carboplatin- and cisplatin-based chemotherapy found no significant differences.

Conclusions: This updated evidence base corroborates findings of previous meta-analyses showing no difference in OS between carboplatin- and cisplatin-based chemotherapy, despite a slight benefit in ORR for cisplatin. Toxicity profiles should be considered alongside patients' comorbidities in the choice of therapy.

1. Introduction

Lung cancer is the leading cause of cancer death worldwide, and non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers [1]. For advanced disease (stage IIIB-IV), first-line treatment options have evolved in recent years; however, the mainstay consists of platinum-based chemotherapy doublets [2,3].

The two platinum analogues used in clinical practice are cisplatin and carboplatin. These agents have well established differences in toxicity profiles: cisplatin is associated with emesis, nephrotoxicity, and neurotoxicity, whereas the myelosuppressive effects of carboplatin lead to hematologic toxicities [4,5]. Differences in drug efficacy between the two agents are less clear, and prescribing preference of one platinum over the other has been the subject of debate. In the United States, less than 10% of physicians prescribing platinum-doublet-based regimens use cisplatin as the platinum agent [6], whereas until recently, European guidelines were explicit in preferring cisplatin for otherwise healthy patients, which is reflected in its more widespread use in many European countries [3,7,8].

Previous meta-analyses have been conducted to understand how clinical outcomes differ between cisplatin- and carboplatin-based chemotherapy doublets, across a wide range of cancers [4]. In advanced NSCLC, the most recent meta-analysis has indicated no difference in overall survival (OS), yet a potentially greater benefit with cisplatin on

* Corresponding author at: ICON plc., 450-688 W. Hastings St., Vancouver, BC V6B 1P1, Canada.
E-mail addresses: Griesinger@Pius-Hospital.de, frank.griesinger@uol.de (F. Griesinger), sheena.kayaniyil@iconplc.com (S. Kayaniyil), nebibe.varol@bms.com (N. Varol), timo.ebner@bms.com (T. Ebner).

https://doi.org/10.1016/j.lungcan.2019.07.010
Received 14 June 2019; Accepted 12 July 2019

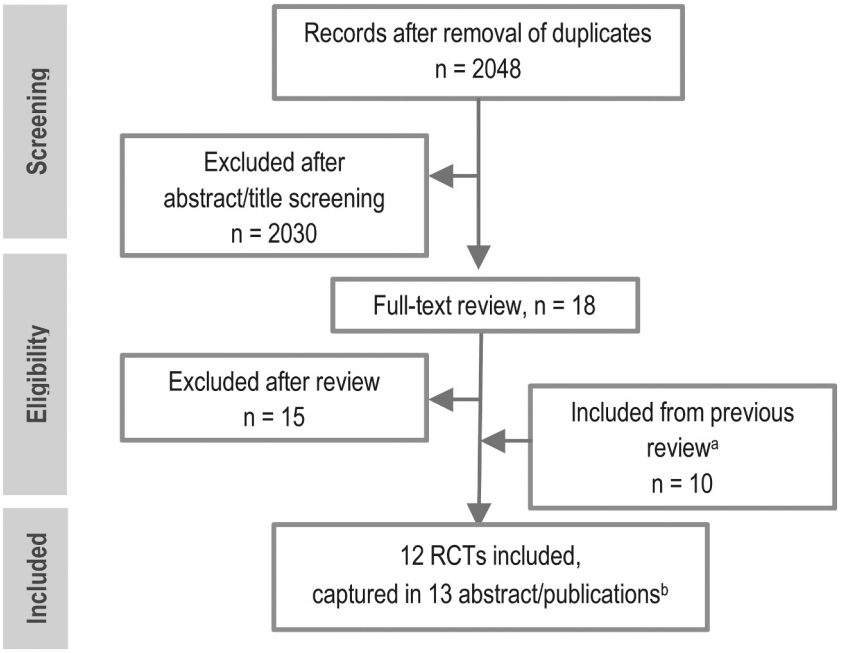


Fig. 1. PRISMA flow diagram.
[a]de Castria et al. (2013) [9].
[b]Two new RCTs were identified, as well as one RCT which was included in the review by de Castria et al. (2013) as a conference abstract (Ferry 2011), and whose full-text publication was included in the present study (Ferry 2017).

objective response rates (ORR) [9].

In light of the rapidly changing landscape of NSCLC therapy and corresponding expansion of trial data, it would be important to update these comparisons with such new evidence. Therefore, our objective was to compare the efficacy, safety, and health-related quality of life (HRQoL) of carboplatin- versus cisplatin-based combination chemotherapy used as the first-line treatment for patients with advanced NSCLC, incorporating up-to-date evidence in this setting.

2. Materials and methods

2.1. Systematic literature review

A systematic literature review (SLR) was conducted to identify randomized controlled trials (RCTs) conducted among treatment-naïve adult patients with advanced NSCLC who had received platinum doublet-based chemotherapy. RCTs were required to directly compare carboplatin-based with cisplatin-based therapy, in combination with the same chemotherapy agent: gemcitabine, docetaxel, paclitaxel, vinorelbine, irinotecan, or pemetrexed. RCTs were required to report OS, one-year survival rate, ORR, drug toxicities, or HRQoL.

Searches were run in January 2018 using the following electronic databases: The Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Embase and the Latin American and Caribbean Health Sciences (LILACS) database. In addition, the following sources were also searched: Proceedings of the American Society of Clinical Oncology Meetings (ASCO; 2013 to 2017), ClinicalTrials.gov (2016 to 2017), and reference lists of included RCTs. Search terms were based on a previous SLR conducted by the Cochrane group [9], and RCTs identified in that previous review were included. The timeframe for our database searches was between January 2013 and January 2018, as the period prior to 2013 was covered by the previous review. Additionally, new searches involving pemetrexed-based therapy (which was not included in the previous review) were run from database inception to 2018 [9].

All publications identified from the search underwent a two-stage selection process: a review of the titles and abstracts (screening), followed by a review of the full-text articles that passed the screening (eligibility). Two reviewers independently determined whether articles met inclusion criteria, with a third reviewer adjudicating discrepancies as needed. An experienced analyst extracted data (including study design, patient characteristics, details of interventions, and outcome measures) from each included RCT, and a senior reviewer checked all fields. All RCTs newly identified and eligible for inclusion were assessed by an experienced reviewer using the Cochrane Collaborations recommended risk of bias tool [10]. The risk of bias assessments for the remaining included studies were obtained from the previous review [9].

Missing data were informed using three approaches: 1) contacting study authors; 2) reviewing data presented in previous meta-analyses (hazard ratios [HR] from Ardizzoni et al. (2007) [11], who had access to individual patient-level data, and other estimates from the Cochrane meta-analysis); and 3) digitally reconstructing the Kaplan-Meier curves to estimate HRs [12].

2.2. Evidence synthesis

A meta-analysis was conducted for carboplatin-based regimens relative to cisplatin-based regimens on the following endpoints: OS using HR, one-year OS rate using relative risk (RR), drug toxicities (grade III or IV toxicity based on reported events by cycle and by participant) using RR, and ORR using RR. All comparisons were made for carboplatin- versus cisplatin-based therapy; a point estimate lower than one indicated a lower risk or probability associated with carboplatin for: death (OS HR); being alive at one year (OS RR); experiencing an adverse event (AE RR); or achieving an objective response (ORR RR). The main analysis was conducted using random-effects models. Heterogeneity was measured using the I^2 statistic, with values greater than 50% indicating substantial heterogeneity. All analyses were performed using R version 3.4.1 [13].

Due to limited reporting and heterogeneity in methods of reporting and scales used, HRQoL data were summarized in a tabular format.

Pre-specified subgroup analyses were performed on efficacy endpoints to examine findings according to the type of chemotherapy doublet, and according to pre-defined dose ranges of cisplatin: low

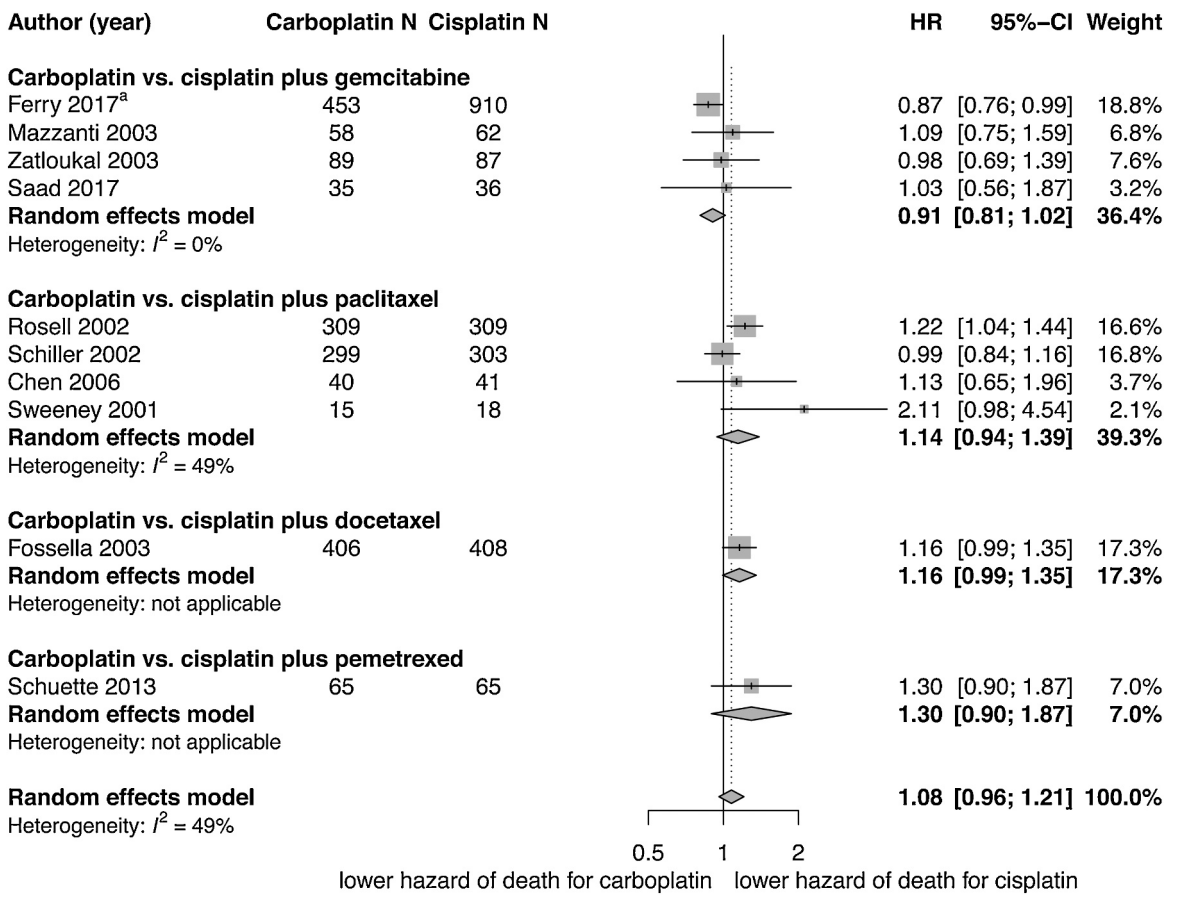


Fig. 2. Forest plot for overall survival.
CI: confidence interval; HR: Hazard Ratio.
[a]Both arms using cisplatin-based regimens were grouped in the same analysis. HRs less than 1 indicate a lower hazard of death (i.e. better outcomes) for carboplatin-containing regimens versus cisplatin-containing regimens.

(40–80 mg/m^2) and high (80–100 mg/m^2). Sensitivity analyses included using fixed effect models for efficacy endpoints, and removing studies where the concomitant chemotherapy dose differed in the carboplatin vs. cisplatin study arm, for all endpoints.

3. Results

The SLR search yielded a total of 2,048 records. Of these, 12 RCTs were included, which involved a total of 4,139 patients (Fig. 1) [14–25]. Relative to the previous Cochrane meta-analysis upon which the current review was based, two new RCTs were added, and updated results were captured from a third RCT [24–26]. Of the included RCTs, the platinum agents were combined with: gemcitabine (n = 5) [14,18,23,24,26], paclitaxel (n = 5) [15,19–22], docetaxel (n = 1) [17], or pemetrexed (n = 1) [25].

Overall, a large majority of patients in the included RCTs had stage IV NSCLC (**Appendix A, Table A.1**). The median age in all studies was at least 58 years, and most studies had a greater proportion of males than females. One RCT was conducted in an elderly population, with nearly half of patients having performance status (PS) 2 [15]. One RCT was restricted to squamous NSCLC patients [24]; other RCTs included patients with either squamous (17%–56% of patients) or non-squamous histology [20,21].

Cisplatin was typically administered on day 1 at 60–80 mg/m^2; one RCT included a dose of 100 mg/m^2 on day one [22], and two RCTs [14,24] used a dosing schedule of 30–40 mg/m^2 on days one and three (**Appendix A, Table A.2**). Additionally, Ferry et al. (2017) examined cisplatin dosing of 50 mg/m^2 against a dosing of 80 mg/m^2, both administered on day one [26]. Carboplatin was typically dosed using an area under the concentration curve (AUC) of 5–6 mg/mL/min on day one; one RCT allowed AUC 4–6 mg/mL/min [14], and one RCT used a dose of 350 mg/m^2 [22]. Two RCTs involved different paclitaxel dosing strategies between the cisplatin and carboplatin treatment arms [20,21].

3.1. Efficacy

Ten of the 12 RCTs expressed OS as a HR [15,17–21,23–26]. The overall pooled estimate for carboplatin relative to cisplatin suggested no significant difference in the risk of death (HR = 1.08; 95% confidence interval [CI]: 0.96,1.21; I^2 = 49%) (Fig. 2).

Eleven RCTs reported 1-year OS [15,17–26]; there was no significant difference in 1-year survival rate (RR = 0.97; 95% CI: 0.89, 1.07; I^2 = 14%) and no significant heterogeneity among the trials (Fig. 3).

ORR was evaluated in all 12 included RCTs [14,15,17–26]. The meta-analysis indicated that the probability of achieving a response was significantly lower for carboplatin compared to cisplatin (RR = 0.88; 95% CI: 0.78, 0.99) (Fig. 4). Relative to the combination partners of platinum, this effect was only statistically significant with docetaxel regimens (RR = 0.76; 95% CI: 0.60, 0.95), while it was not significant for all other platinum combination partners. There was no significant heterogeneity among the trials (I^2 = 15%).

Subgroup analyses and sensitivity analyses were consistent with the main results, although differences in ORR were non-significant when fewer RCTs were included in the meta-analysis (**Appendix A, Table A.3**).

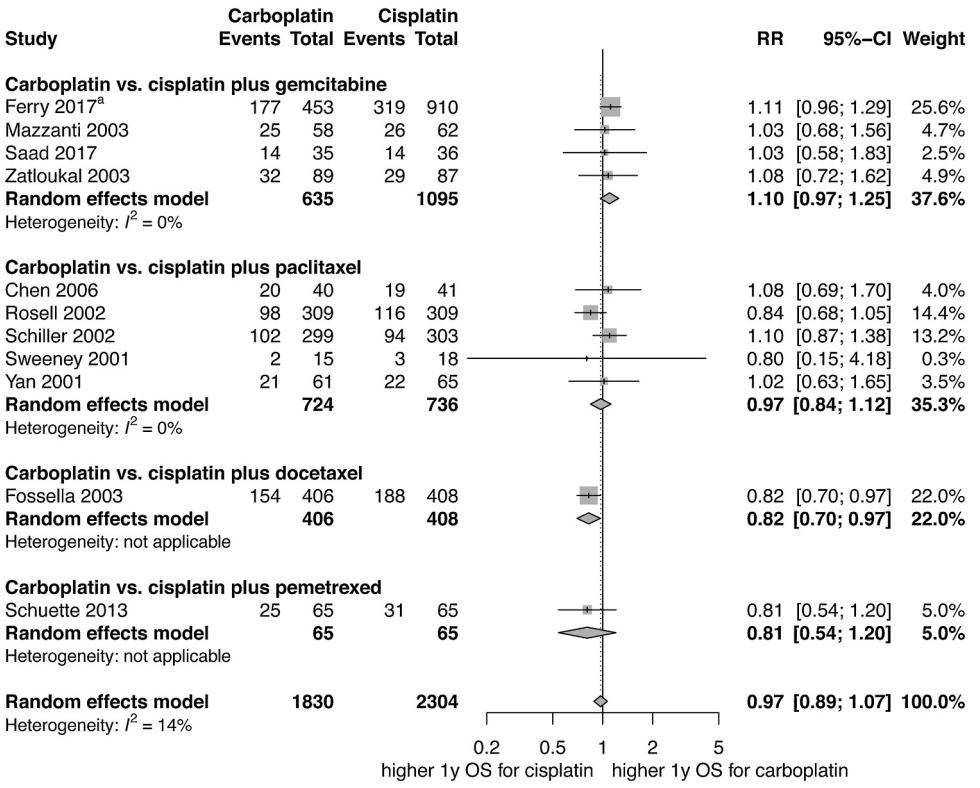


Fig. 3. Forest plot for overall survival rate at one year.
CI: confidence interval; RR: Relative Risk.
[a]Both arms using cisplatin-based regimens were grouped in the same analysis. RRs less than 1 indicate worse overall survival at 1y for carboplatin-containing regimens versus cisplatin-containing regimens.

3.2. Toxicity

Toxicity rates were reported as number of events per participant or events per cycle. Two RCTs provided summaries of grade 3/4 toxicity by cycle; both in combination with gemcitabine [18,26]. The risk of anemia was significantly higher with carboplatin than with cisplatin (RR = 3.94; 95% CI: 1.80, 8.65) (Fig. 5). No statistically significant differences were detected for other grade 3/4 adverse events assessed by cycle.

Eleven of the 12 RCTs reported grade 3/4 adverse events by participant (Fig. 6a and b) [14,15,17,19–26]. The risk of nausea/vomiting was 47% higher with cisplatin than with carboplatin (RR = 0.53; 95% CI: 0.38, 0.73). Thrombocytopenia occurred among 7%–25% of patients receiving a carboplatin-based regimen, which was significantly more frequent compared with cisplatin-based regimens (RR = 2.46; 95% CI: 1.49, 4.04).

Although the main analysis unexpectedly indicated a higher risk of neurotoxicity associated with carboplatin (RR = 1.55; 95% CI: 1.06, 2.27), the difference was non-significant (RR = 1.33; 95% CI: 0.79, 2.25) after removal of two RCTs that used higher paclitaxel doses for patients receiving carboplatin relative to those receiving cisplatin [20,21]. The sensitivity analysis estimates were otherwise consistent with the main findings (**Appendix A, Table A.3**).

3.3. HRQoL

Four RCTs assessed differences in HRQoL outcomes in carboplatin- and cisplatin-based regimens [17,19,24,26], although only three provided comparisons between carboplatin and cisplatin arms [19,24,26]. The RCTs involved different HRQoL measures, precluding any formal synthesis of HRQoL outcomes. The scales included: the EuroQol group standardized instrument, the EQ-5D [17,26]; the Functional Assessment of Cancer Therapy – Lung (FACT-L) (including the trial outcome index [TOI]) [17,24]; the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) and the EORTC QOL-LC13 (13-item quality of life lung cancer-specific questionnaire) [19,26]. None of the RCTs detected differences in the global scales between the cisplatin and carboplatin arms. However, Rosell et al. (2002) reported statistically significant differences in symptom sub-scales favouring cisplatin for haemoptysis and pain in the chest ($p < 0.05$), pain ($p < 0.10$) and pain medication consumption ($p < 0.10$), and favouring carboplatin for appetite loss ($p < 0.10$).

3.4. Risk of bias

The results of the risk of bias assessment is presented in **Appendix A, Figure A.1**. Allocation was adequately concealed in most studies, although no relevant information was provided by Saad et al. (2017). Eleven of the RCTs did not report complete information about the blinding process; the study by Schuette et al. (2013) was classified as high risk for selection bias given that it was an open-label study; additionally, this study was designed as a non-comparative trial. Overall, selective reporting was not identified as a main source of bias in the included studies; only Cai et al. (2002) and Rosell et al. (2002) did not report survival data. Phase II studies were identified as high risk for other bias. As explained by de Castria et al. (2013), the study conducted by Rosell et al. (2002) was classified as high risk for other bias due to the fact that 34% of subjects randomized to carboplatin required a dose reduction and that this may be associated with a lower effectiveness.

4. Discussion

This systematic review and meta-analysis captured up-to-date evidence, current to 2018, on the relative effects of carboplatin- versus

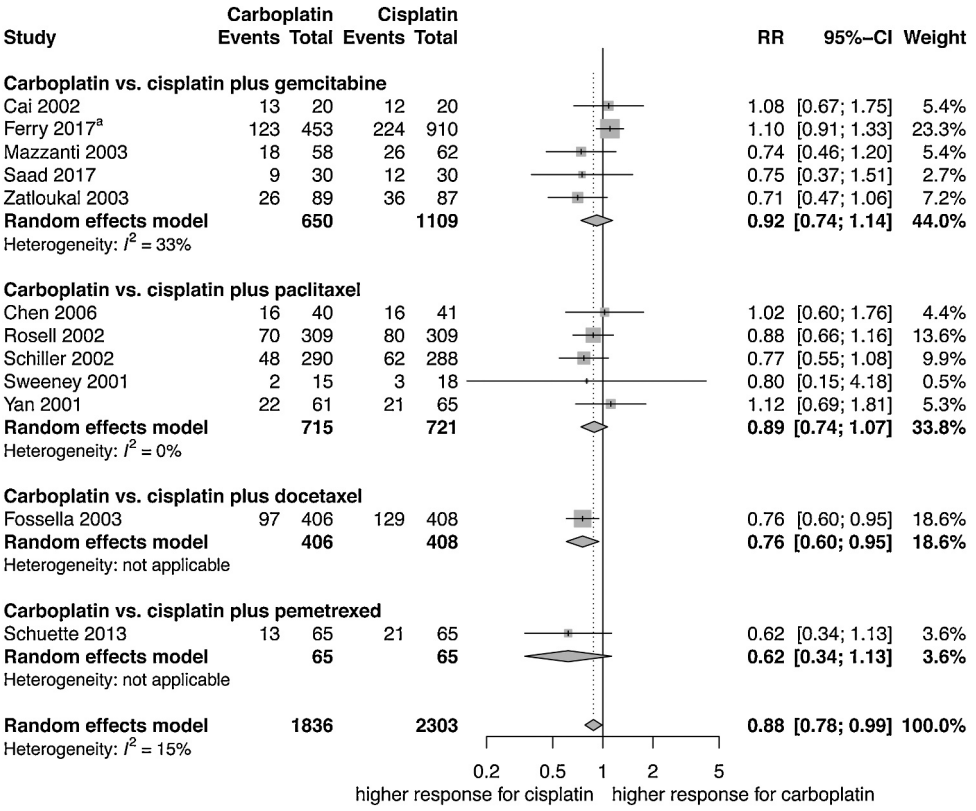


Fig. 4. Forest plot for objective response rate.
CI: confidence interval; RR: Relative Risk.
[a]Both arms using cisplatin-based regimens were grouped in the same analysis. RRs less than 1 indicate worse response rates for carboplatin-containing regimens versus cisplatin-containing regimens.

cisplatin-based chemotherapy doublets in advanced NSCLC.

The efficacy-related findings in our analysis are consistent with the previous research [9] upon which our study was based and revealed a small yet statistically significant benefit in response rates associated with cisplatin, yet no significant difference in OS. Earlier meta-analyses showed significantly better OS associated with cisplatin over carboplatin, when used in combination with third-generation chemotherapy agents, although no difference when used in combination with older chemotherapies [11,27]. These findings had been incorporated into earlier European guidelines, which explicitly recommended cisplatin over carboplatin among younger and relatively fit patients [28]. However, the effect size in early meta-analyses had been modest, and as newer RCTs were added to the evidence base, the overall pooled estimate became non-significant. The most recent European guidelines and the National Comprehensive Cancer Network (NCCN) guidance no longer state an explicit preference for cisplatin [3,29]. A major addition to the most recent evidence base was the full reporting of the Phase 3 RCT by the British Thoracic Oncology Group (the BTOG2 trial), by Ferry et al [26]. In this large RCT (n_{ITT} = 1363), the investigators sought to resolve the debate regarding carboplatin vs. cisplatin, taking into account both the choice of platinum as well as cisplatin dosing (to address differences in cisplatin dosing across Europe). Their findings for OS - carboplatin 6 AUC superior to cisplatin 50 mg/m^2, and non-inferior to cisplatin 80 mg/m^2 – contrast with those from a majority of studies in our analysis. Notably, in our pooled meta-analysis, this single study contributed nearly 20% of the weight to the overall pooled estimate for OS, and over 50% of the weight to the gemcitabine-specific subgroup estimate for OS. The authors (Ferry et al.) attributed the discrepancy between findings from their trial and those in previous research to differences of dosing, including changes in carboplatin dosing over the years (shifting from body surface area to Calvert formula, methods for estimating glomerular filtration rate, or the choice to use a lower dose of carboplatin). These considerations all apply to our current meta-analysis.

The pooled estimate for ORR showed a statistically significant benefit associated with cisplatin-based chemotherapy. This finding has been reported across several types of cancer, and may benefit patients who have severe symptoms by shrinking the tumour and relieving tumour-size-related symptoms [4,30]. Although the overall pooled effect was statistically significant, only one RCT, not designed to compare the platinum agents, had a statistically significant effect size on its own [17]. This three-arm trial was designed to compare vinorelbine plus cisplatin against docetaxel-based platinum doublets and therefore the finding of better ORR with cisplatin vs. carboplatin was not explicitly reported or explored by the study authors [17,25]. With the strongest evidence coming from trials that were not designed to address this study question, along with previously noted differences in dosing strategies across RCTs, this finding should be interpreted with caution.

Toxicity-related findings from our meta-analysis are consistent with the known profiles of carboplatin and cisplatin. Higher risk of nausea and vomiting has long been associated with cisplatin, which is typically administered alongside anti-emetic agents and intravenous hydration. These requirements are burdensome, decrease quality of life, and can deter physicians from prescribing cisplatin to certain patients. However, the prevalence of grade 3/4 nausea/vomiting in cisplatin arms was considerably lower in RCTs conducted in the last decade (up to 8%) than in older RCTs (up to 49%), which reflects considerable improvements in the efficacy of anti-emetic medications [31]. The nephrotoxic effects known to be associated with cisplatin were not statistically significant in our analysis, although we observed a non-significant trend toward a lower risk of renal toxicity associated with carboplatin. This non-significant finding may also reflect that the

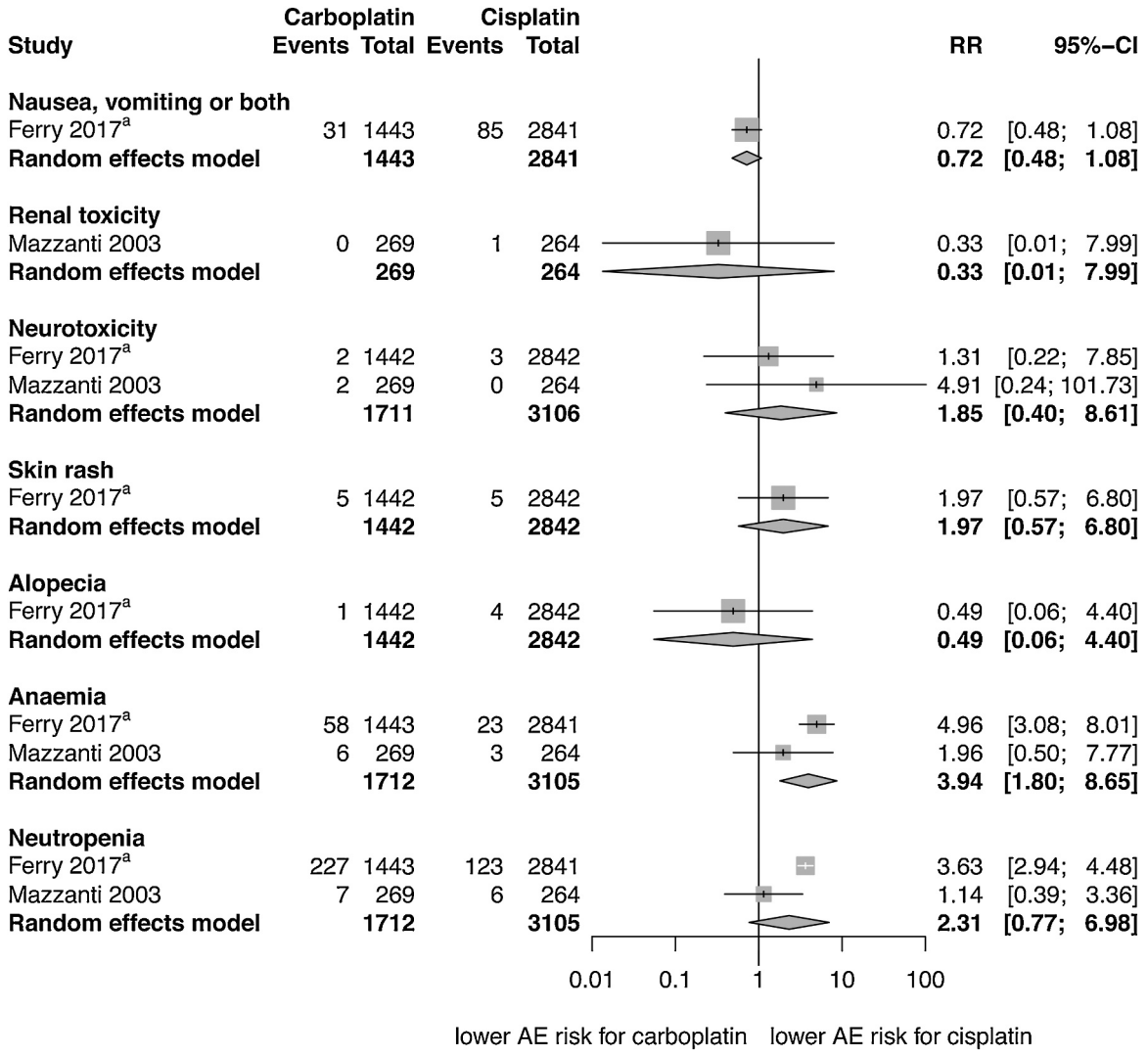


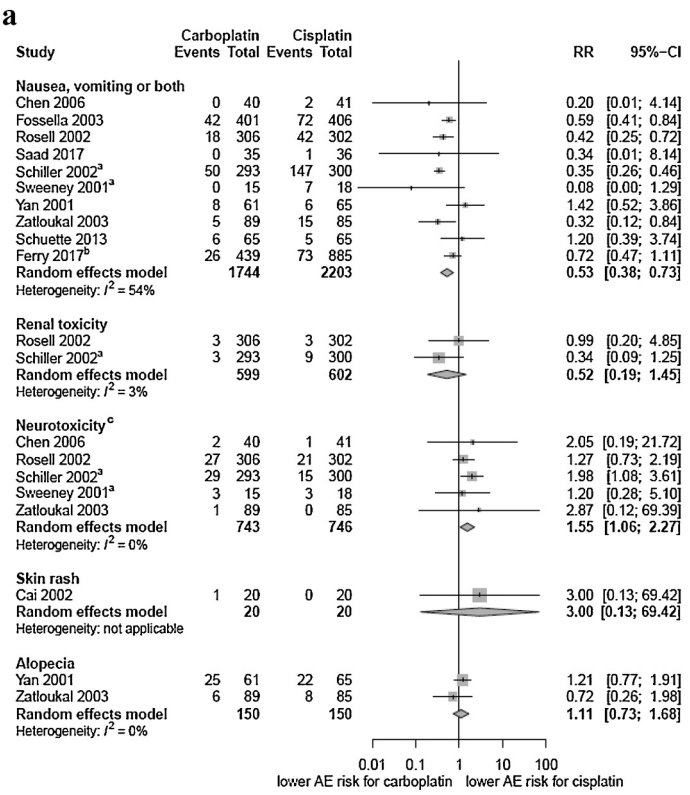
Fig. 5. Forest plot for grade 3/4 toxicity by cycle.
CI: confidence interval; RR: Relative Risk.
[a]Both arms using cisplatin-based regimens were grouped in the same analysis. I^2 not presented due to small number of RCTs. RRs less than 1 indicate lower risk of adverse events for carboplatin-containing regimens versus cisplatin-containing regimens.

eligibility criteria of included RCTs stipulated that patients have adequate renal function. The significantly increased risks of thrombocytopenia (by patient) and anaemia (by cycle) and trend toward increased risk of neutropenia associated with carboplatin are consistent with the known myelosuppressive effects of carboplatin. The finding of higher rates of neurotoxicity associated with carboplatin was non-significant in the sensitivity analysis that removed RCTs involving different dosing schedules of paclitaxel across study arms (with a 225 mg/m^2 3-h infusion used in the carboplatin arm, and a 135 mg/m^2 24-h infusion used in the cisplatin arm). This is consistent with other evidence suggesting that paclitaxel can cause neurotoxicity [32,33].

Although no statistical differences in global HRQoL scales were detected in any of the RCTs, some clinicians continue to strongly favour carboplatin over cisplatin based on the perceived impact of toxicities, such as nausea/vomiting and ototoxicity, on patients' quality of life. Physicians consider those toxicities more impactful on quality of life than carboplatin-related toxicities such as thrombocytopenia, which is largely asymptomatic [30,34]. Furthermore, the finding of no difference in HRQoL contrasts with studies conducted in other cancers, which have demonstrated better overall HRQoL associated with carboplatin-based regimens [35,36]. The detailed HRQoL findings from the BTOG2 RCT are forthcoming and may provide further insights [26].

Taken together, our findings provide an up-to-date synthesis of the efficacy, toxicity and HRQoL associated with cisplatin and carboplatin based on RCTs; however, our findings can be generalized only to clinical trial-eligible patients. A majority of patients enrolled into RCTs in our meta-analysis had PS 0–1 and no renal or hepatic impairment; several RCTs also excluded patients with brain metastases, pre-existing neuropathy, or other serious concomitant illnesses. A large European prospective real-world study (FRAME), demonstrated that patients receiving carboplatin tend to have significantly more comorbidities, more likely to have PS 2–3, and be significantly older; in fact, 47% of patients receiving carboplatin were older than 70 years compared with only 15% of those receiving cisplatin [7]. These practice patterns align with European guidelines, which advise against using cisplatin-based platinum doublets among patients with poor PS and selected older patients, e.g. those with poor organ function. Those populations were not fully explored in our current analysis, and findings should not be extrapolated to those groups [3].

Bevacizumab and new immunotherapies are currently licensed for use in combination with platinum doublets or are being tested in Phase 3 clinical trials [37–41], yet these combinations were not included in



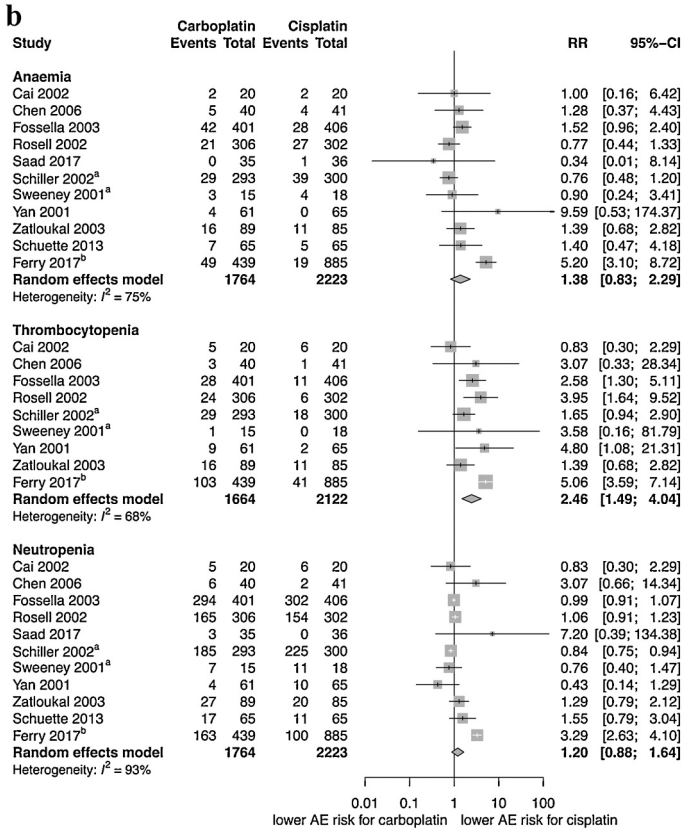


Fig. 6. a Forest plot for grade 3/4 non-hematologic toxicity by participant.
CI: confidence interval; RR: Relative Risk.
[a]Paclitaxel dosing differed between study arms.
[b]Both arms using cisplatin-based regimens were grouped in the same analysis. RRs less than 1 indicate lower risk of adverse events for carboplatin-containing regimens versus cisplatin-containing regimens.
[c]In a sensitivity analysis excluding RCTs where paclitaxel dosing differed between arms[a], the effect estimate was RR = 1.33; 95% CI: 0.79 to 2.25.
Fig. 6b Forest plot for grade 3/4 hematologic toxicity by participant.
CI: confidence interval; RR: Relative Risk.
[a]Paclitaxel dosing differed between study arms.
[b]Both arms using cisplatin-based regimens were grouped in the same analysis. RRs less than 1 indicate lower risk of adverse events for carboplatin-containing regimens versus cisplatin-containing regimens.

our current review. To our knowledge, there are no RCTs conducted among patients with advanced NSCLC that directly compare carboplatin against cisplatin in combination with either bevacizumab or an immunotherapy [42]. Some immunotherapy trial designs have permitted investigators to select either platinum agent; however, prognostic factors are likely to be imbalanced between those receiving carboplatin and cisplatin, as treatment assignment was not randomized. For example, in KeyNote 189, nearly three quarters of patients received

carboplatin, and these patients were older, had worse performance status and were more likely to have brain metastasis than those receiving cisplatin [43]. Thus, any forthcoming comparisons between platinum agents would need to adjust for these confounding factors and would have lower internal validity than RCT-based estimates.

Our study has certain limitations that should be taken into account. As with any systematic review and meta-analysis, our data rely on previously published research. Non-reporting was a challenge, in particular for HRs of OS. Relative to the previous meta-analysis [9], we updated the HRs using more recent methodology and previously published estimates based on individual patient-data. While the results remained broadly similar, our estimates remain subject to the limitations of these methodologies [11,12]. Our approach to identifying RCTs relied on adding to the evidence base collected by the Cochrane group through an incremental search, rather than conducting *de novo* searches of our own [9]. While the fact that we did not run the original searches may be a limitation of the current study, the rigour of Cochrane group's methodology combined with the fact that the set of RCTs included in the current review align with other systematic reviews on this topic suggests that this approach did not impact the study's comprehensiveness. As pointed out by Ferry et al. [26], meta-analyses are limited by the heterogeneity in dosing across the trials, as well as changes in treatment patterns over time. Although we conducted a dose-based subgroup analysis, the relatively small number of included RCTs prevented us from exploring additional differences in dosing strategies, or investigating trends over time. Histology-based subgroup data were not available in the majority of trials, as such the individual patient-level data analysis previously performed by Ardizzoni et al. could not be updated [11].

4.1. Conclusions

Collectively, this study provides updated estimates that show a lack of a difference in survival between the platinum-doublet regimens. The small relative benefit of cisplatin on ORR and the different toxicity profiles between carboplatin- and cisplatin-based chemotherapy should be considered based on patients' symptoms, preferences, and comorbidities in the selection of first-line NSCLC therapy.

Frank Griesinger has no conflicts of interest regarding the current manuscript. F.Griesinger has given scientific presentations for ASTRA, Boehringer, Bristol-Myers Squibb (BMS), Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Ariad, Abbvie, Siemens, has received funds for scientific research by ASTRA, Boehringer, BMS, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Siemens, has been on advisory boards for ASTRA, Boehringer, BMS, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Ariad, Abbvie, Siemens, and has received travel grants by ASTRA, Boehringer, BMS, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Ariad, Abbvie, Siemens. ICON plc. is a contract research organization commissioned by BMS to conduct the study reported in this manuscript. Ellen Korol was a salaried employee of ICON plc. at the time of study conduct. Sheena Kayaniyil is a salaried employee of ICON plc. Nebibe Varol and Timo Ebner are BMS employees, and report BMS stock ownership. Sarah Goring received payment from ICON plc. as an independent contractor.

Declaration of Competing Interest

Frank Griesinger has no conflicts of interest regarding the current manuscript. F.Griesinger has given scientific presentations for ASTRA, Boehringer, Bristol-Myers Squibb (BMS), Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Ariad, Abbvie, Siemens, has received funds for scientific research by ASTRA, Boehringer, BMS, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Siemens, has been on advisory boards for ASTRA, Boehringer, BMS, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Ariad, Abbvie, Siemens, and has received travel grants by ASTRA, Boehringer, BMS, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Ariad, Abbvie, Siemens. ICON plc. is a contract research organization commissioned by BMS to conduct the study reported in this manuscript. Ellen Korol was a salaried employee of ICON plc. at the time of study conduct. Sheena Kayaniyil is a salaried employee of ICON plc. Nebibe Varol and Timo Ebner are BMS employees, and report BMS stock ownership. Sarah Goring received payment from ICON plc. as an independent contractor.

Acknowledgements

This work was funded by Bristol-Myers Squibb (BMS).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.lungcan.2019.07.010.

References

[1] American Cancer Society, What Is Non-small Cell Lung Cancer? [cited 2018 September 10, 2018]; Available from: (2018) https://www.cancer.org/cancer/non-small-cell-lung-cancer/about/what-is-non-small-cell-lung-cancer.html.
[2] N. Hanna, et al., Systemic therapy for stage IV non-small-cell lung cancer: American society of clinical oncology clinical practice guideline update, J. Clin. Oncol. 35 (30) (2017) 3484–3515, https://doi.org/10.1200/JCO.2017.74.6065.
[3] D. Planchard, et al., Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 29 (Supplement 4) (2018) iv192–iv237, https://doi.org/10.1093/annonc/mdy275.
[4] G. Ho, N. Woodward, J. Coward, Cisplatin versus carboplatin: comparative review of therapeutic management in solid malignancies, Crit. Rev. Oncol. Hematol. 102 (2016) 37–46, https://doi.org/10.1016/j.critrevonc.2016.03.014.
[5] D. Trump, et al., Platinum analogue combination chemotherapy: cisplatin and carboplatin–a phase I trial with pharmacokinetic assessment of the effect of cisplatin administration on carboplatin excretion, J. Clin. Oncol. 5 (8) (1987) 1281–1289, https://doi.org/10.1200/JCO.1987.5.8.1281.
[6] A. Abernethy, et al., Real-world first-line treatment and overall survival in non-small cell lung cancer without known EGFR mutations or ALK rearrangements in US community oncology setting, PLoS One 12 (6) (2017) e0178420, https://doi.org/10.1371/journal.pone.0178420.
[7] E. Smit, et al., Cisplatin and carboplatin-based chemotherapy in the first-line treatment of non-small cell lung cancer: analysis from the European FRAME study, Lung Cancer 92 (2016) 35–40, https://doi.org/10.1016/j.lungcan.2015.11.022.
[8] J. de Castro, et al., Systemic therapy treatment patterns in patients with advanced non-small cell lung cancer (NSCLC): PIvOTAL study, Eur. J. Cancer Care (Engl) 26 (6) (2017), https://doi.org/10.1111/ecc.12734.
[9] T.B. de Castria, et al., Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer, Cochrane Database Syst. Rev. (8) (2013) CD009256, https://doi.org/10.1002/14651858.CD009256.pub2.
[10] The Cochrane Collaboration, J.P.T. Higgins, S. Green (Eds.), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011], The Cochrane Collaboration, 2011Available from www.handbook.cochrane.org.
[11] A. Ardizzoni, et al., Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis, J. Natl. Cancer Inst. 99 (11) (2007) 847–857, https://doi.org/10.1093/jnci/djk196.
[12] P. Guyot, et al., Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves, BMC Med. Res. Methodol. 12 (2012) 9, https://doi.org/10.1186/1471-2288-12-9.
[13] R Core Team, R: a language and environment for statistical computing, R Foundation for Statistical Computing, (2017) Available from: https://www.R-project.org/.
[14] X. Cai, et al., [Comparison of efficacy and toxicity between gemcitabine plus carboplatin and gemcitabine plus cisplatin in the treatment of advanced non-small cell lung cancer], Zhongguo Fei Ai Za Zhi 5 (6) (2002) 427–428, https://doi.org/10.3779/j.issn.1009-3419.2002.06.09.
[15] Y.M. Chen, et al., A Phase II randomized study of paclitaxel plus carboplatin or cisplatin against chemo-naive inoperable non-small cell lung cancer in the elderly, J. Thorac. Oncol. 1 (2) (2006) 141–145.
[16] D.B.L. Ferry, H. Jarrett, D. Dunlop, J. Thompson, M. Kumar, G. Skailes, M. Nicolson, R. Shah, P. Leonard, A. Chetiyawardana, P. Wells, C. Lewanski, P. Woll, B. Crosse, M. Hill, S. Pirrie, K. O'Byrne, British Thoracic Oncology Group Trial, BTOG2: randomised phase III clinical trial of gemcitabine (1250mg/m2) combined with cisplatin 50 mg/m2 (GC50) versus cisplatin 80 mg/m2 (GC80) versus carboplatin AUC6 (GCb6) in advanced NSCLC, Thorax 66 (Suppl. 4) (2011) S85, https://doi.org/10.1136/thoraxjnl-2011-201054b.85.
[17] F. Fossella, et al., Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group, J. Clin. Oncol. 21 (16) (2003) 3016–3024, https://doi.org/10.1200/JCO.2003.12.046.
[18] P. Mazzanti, et al., Randomized, multicenter, phase II study of gemcitabine plus

cisplatin versus gemcitabine plus carboplatin in patients with advanced non-small cell lung cancer, Lung Cancer 41 (1) (2003) 81–89.
[19] R. Rosell, et al., Phase III randomised trial comparing paclitaxel/carboplatin with paclitaxel/cisplatin in patients with advanced non-small-cell lung cancer: a co-operative multinational trial, Ann. Oncol. 13 (10) (2002) 1539–1549.
[20] J.H. Schiller, et al., Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer, N. Engl. J. Med. 346 (2) (2002) 92–98, https://doi.org/10.1056/NEJMoa011954.
[21] C.J. Sweeney, et al., Outcome of patients with a performance status of 2 in Eastern Cooperative Oncology Group Study E1594: a Phase II trial in patients with metastatic nonsmall cell lung carcinoma, Cancer 92 (10) (2001) 2639–2647.
[22] D. Yan, et al., [A randomized phase II trial of paclitaxel in combination chemotherapy with platinum in the treatment of non-small cell lung cancer], Zhongguo Fei Ai Za Zhi 4 (3) (2001) 188–190, https://doi.org/10.3779/j.issn.1009-3419.2001.03.08.
[23] P. Zatloukal, et al., Gemcitabine plus cisplatin vs. Gemcitabine plus carboplatin in stage IIIb and IV non-small cell lung cancer: a phase III randomized trial, Lung Cancer 41 (3) (2003) 321–331.
[24] A.S. Saad, R.R. Ghali, M.A. Shawki, A prospective randomized controlled study of cisplatin versus carboplatin-based regimen in advanced squamous nonsmall cell lung cancer, J. Cancer Res. Ther. 13 (2) (2017) 198–203, https://doi.org/10.4103/0973-1482.187287.
[25] W.H. Schuette, et al., A randomized phase II study of pemetrexed in combination with cisplatin or carboplatin as first-line therapy for patients with locally advanced or metastatic non-small-cell lung cancer, Clin. Lung Cancer 14 (3) (2013) 215–223, https://doi.org/10.1016/j.cllc.2012.10.001.
[26] D. Ferry, et al., Carboplatin versus two doses of cisplatin in combination with gemcitabine in the treatment of advanced non-small-cell lung cancer: results from a British Thoracic Oncology Group randomised phase III trial, Eur. J. Cancer 83 (2017) 302–312, https://doi.org/10.1016/j.ejca.2017.05.037.
[27] K. Hotta, et al., Meta-analysis of randomized clinical trials comparing cisplatin to carboplatin in patients with advanced non-small-cell lung cancer, J. Clin. Oncol. 22 (19) (2004) 3852–3859, https://doi.org/10.1200/JCO.2004.02.109.
[28] M. Reck, et al., Metastatic non-small cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 00 (2014) 1–13, https://doi.org/10.1093/annonc/mdu199.
[29] National Comprehensive Care Network (NCCN), Non-Small Cell Lung Cancer NCCN Clinical Practice Guidelines in Oncology, (2018).
[30] C. Azzoli, M. Kris, D. Pfister, Cisplatin versus carboplatin for patients with metastatic non-small-cell lung cancer–an old rivalry renewed, J. Natl. Cancer Inst. 99 (11) (2007) 828–829, https://doi.org/10.1093/jnci/djk222.
[31] P. Hesketh, K. Bohlke, M. Kris, Antiemetics: American society of clinical oncology clinical practice guideline update summary, J. Oncol. Pract. 13 (12) (2017) 825–830, https://doi.org/10.1200/JOP.2017.026351.
[32] E. Gornstein, T. Schwarz, The paradox of paclitaxel neurotoxicity: mechanisms and unanswered questions, Neuropharmacology 76 (2014) 175–183, https://doi.org/10.1016/j.neuropharm.2013.08.016 Pt A.
[33] C. Scripture, W. Figg, A. Sparreboom, Peripheral neuropathy induced by paclitaxel: recent insights and future perspectives, Curr. Neuropharmacol. 4 (2) (2006) 165–172.
[34] M. Snee, Quality of life comparing carboplatin with cisplatin in the treatment of non-small cell lung cancer, Eur. J. Cancer 91 (2018) 167, https://doi.org/10.1016/j.ejca.2017.11.019.
[35] E. Greimel, et al., Randomized study of the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer study Group comparing quality of life in patients with ovarian cancer treated with cisplatin/paclitaxel versus carboplatin/paclitaxel, J. Clin. Oncol. 24 (4) (2006) 576–586, https://doi.org/10.1200/JCO.2005.02.4067.
[36] C. Lakusta, et al., Quality of life in ovarian cancer patients receiving chemotherapy, Gynecol. Oncol. 81 (3) (2001) 490–495, https://doi.org/10.1006/gyno.2001.6199.
[37] F. Barlesi, et al., IMpower132: efficacy of atezolizumab (atezo) + carboplatin (carbo)/cisplatin (cis) + pemetrexed (pem) as 1L treatment in key subgroups with stage IV non-squamous non-small cell lung cancer (NSCLC), Ann. Oncol. 29 (Supplement 8) (2018) viii743–viii744.
[38] H. Borghaei, et al., Nivolumab + Ipilimumab, Nivolumab + chemotherapy, and chemotherapy in chemo-naive patients with advanced Non-small cell lung cancer and < 1% tumor PD-L1 expression: results from CheckMate 227, 2018 ASCO Annual Meeting, (2018).
[39] R. Jotte, et al., IMpower131: primary PFS and safety analysis of a randomized phase III study of Atezolizumab + Carboplatin + paclitaxel or nab-paclitaxel vs. Carboplatin + nab-paclitaxel as 1L therapy in advanced squamous NSCLC, 2018 ASCO Annual Meeting, (2018).
[40] M. Reck, et al., Nivolumab + Ipilimumab vs platinum-doublet chemotherapy as first-line treatment for advanced Non-small cell lung cancer: safety analysis and patient-reported outcomes for CheckMate 227, 2018 ASCO Annual Meeting, (2018).
[41] M.A. Socinski, et al., IMpower150: overall survival analysis of a randomized phase III study of atezolizumab + chemotherapy +- bevacizumab in 1L nonsquamous NSCLC, 2018 ASCO Annual Meeting, (2018).
[42] S. Zhao, et al., Bevacizumab in combination with different platinum-based doublets in the first-line treatment for advanced nonsquamous non-small-cell lung cancer: a network meta-analysis, Int. J. Cancer 142 (8) (2018) 1676–1688, https://doi.org/10.1002/ijc.31175.
[43] D. Abreu, et al., KEYNOTE-189 study of pembrolizumab (pembro) plus pemetrexed (pem) and platinum vs placebo plus pem and platinum for untreated, metastatic, nonsquamous NSCLC: Does choice of platinum affect outcomes? Ann. Oncol. 29 (Supplement 8) (2018) p. mdy292.086.