

Original

Comparing the Adverse Event Profiles of Nivolumab and Docetaxel in Previously-treated or Refractory Advanced Non-small Cell Lung Cancer : A Meta-analysis of Two Phase 3 Trials

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Abstract : Nivolumab has recently been approved as a second-line treatment for squamous and non-squamous advanced non-small cell lung cancers (NSCLC). However, no studies have statistically evaluated the adverse event profiles for nivolumab and conventional second-line agents, such as docetaxel. Thus, there is unmet medical need for statistical analysis comparing the adverse effects of nivolumab and docetaxel in patients with advanced NSCLC. This meta-analysis evaluated the non-inferiority and superiority of the adverse event profiles for nivolumab and docetaxel in patients with previously-treated or refractory advanced NSCLC. The meta-analysis examined two phase 3 trials and compared the incidences of drug-induced adverse events for the nivolumab-treated and docetaxel-treated patient groups. The primary outcomes were the odds ratios (ORs) and 95% confidence intervals (CIs) for any adverse event, fatigue, nausea, decreased appetite, diarrhea, myalgia, anemia, alopecia, neutropenia, febrile neutropenia, and leukopenia. Compared to docetaxel, the adverse event profile for nivolumab was non-inferior and superior for any adverse event (OR, 0.27; 95% CI, 0.19–0.39), fatigue (OR, 0.44; 95% CI, 0.31–0.62), nausea (OR, 0.37; 95% CI, 0.25–0.54), decreased appetite (OR, 0.58; 95% CI, 0.39–0.87), diarrhea (OR, 0.29; 95% CI, 0.19–0.45), myalgia (OR, 0.18; 95% CI, 0.09–0.38), anemia (OR, 0.08; 95% CI, 0.04–0.16), alopecia (OR, 0.01; 95% CI, 0.00–0.06), neutropenia (OR, 0.01; 95% CI, 0.00–0.04), febrile neutropenia (OR, 0.02; 95% CI, 0.00–0.16), and leukopenia (OR, 0.04; 95% CI, 0.01–0.19). These results suggest that, compared to docetaxel, nivolumab may be better tolerated for managing advanced NSCLC.

Key words : nivolumab, docetaxel, adverse events, non-small cell lung cancer

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Introduction

During the past decade, there have been remarkable developments in the treatment strategies for recurrent or previously-treated non-small cell lung cancer (NSCLC)^{1, 2)}. For example, epidermal growth factor receptor (EGFR) tyrosine inhibitors (e.g., gefitinib, erlotinib, and afatinib) are now available and considered as the best treatment options for patients with NSCLC harboring *EGFR* mutations^{1, 3)}. However, the treatment options remain limited and do not provide the desired therapeutic outcomes for all patients with NSCLC³⁾.

Several reports have demonstrated that docetaxel provides prolonged survival, compared to best supportive care⁴⁾. Thus, docetaxel was approved as a second-line chemotherapy for previously-treated or refractory advanced NSCLC. Furthermore, pemetrexed has been confirmed to provide a non-inferior median survival, compared to docetaxel, in randomized controlled trials (RCTs), which supported the approval of pemetrexed as a second-line chemotherapy⁵⁾.

Two phase 3 RCTs have compared nivolumab and docetaxel for previously-treated or refractory advanced NSCLC^{6, 7)}. These studies revealed that nivolumab provided better overall survival, response rates, and progression-free survival than docetaxel. Moreover, the incidence of treatment-related grade 3–4 adverse events was lower in the nivolumab groups, than in the docetaxel groups. However, specific adverse events were not statistically evaluated in these studies, and relevant statistical data are needed to confirm the safety of nivolumab. Therefore, this meta-analysis aimed to compare the incidence of treatment-related adverse events for nivolumab and docetaxel, using data from the previous phase 3 trials.

Methods

Literature search

The MEDLINE (PubMed), Scopus, and Cochrane Library databases were searched for publications up to June 2016, using the following query: nivolumab [Title / Abstract] AND docetaxel [Title / Abstract] AND Randomized Controlled Trial [ptyp]. We considered publications in all languages, and studies were considered eligible if they were phase 3 RCTs that compared the clinical efficacies of nivolumab and docetaxel in patients with NSCLC. The main search involved the PubMed database, which is an open access database that is suitable for comprehensive literature searches. The Scopus database was used to ensure that all eligible articles had been detected in the PubMed database. We also searched the Cochrane Library database for additional references. The reference lists of the identified studies were also searched for other relevant publications.

Risk of bias assessment

The Cochrane methodology was used to examine each included study for random sequence generation, allocation concealment, blinding of the participants and personnel, blinding of the outcome assessment, incomplete outcome data, selective reporting, and other forms of potential bias⁸⁾.

Quality assessment

The methodological quality of the included trials was evaluated using the Jadad score, which grades studies based on their randomization, blinding, and dropout results⁹⁾. Statistical heterogeneity among the trials was assessed using the I^2 statistic, which measures the degree of heterogeneity in outcome measures by calculating the percentage of the total variation among the included studies^{10, 11)}. Random effects¹¹⁾ and fixed effects¹²⁾ models were planned for instances with and without statistical heterogeneity, respectively. The primary outcomes were defined as the risks of any adverse event, fatigue, nausea, decreased appetite, diarrhea, myalgia, anemia, alopecia, neutropenia, febrile neutropenia, and leukopenia, because they were commonly included as outcome measures of past RCTs comparing nivolumab and docetaxel in patients with NSCLC.

Statistical analysis

Differences in the incidences of drug-induced adverse events between the nivolumab and docetaxel groups were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Differences between the two groups were considered statistically significant at a P -value of < 0.05 . Based on previous reports, we defined non-inferiority for the outcome measures as being an upper 95% CI ≤ 1.3 ^{13, 14)}. All analyses were performed using RevMan software (version 5.3; Cochrane Corporation, Oxford, UK) and STATA (version 14.0; Stata Corp., College Station, TX).

Evaluation of publication bias

Publication bias occurs if the results of published studies differ systematically from those of unpublished studies. We evaluated the possibility of publication bias using a funnel plot, in which the standard error of the log [OR] for each study was plotted against its OR¹⁵⁾. A funnel plot is a scatter plot of the intervention effect, which is estimated from individual studies against a measure of each study's size^{15, 16)}. Similar to forest plots, it is most common to plot the effect estimate on the horizontal axis and the study's size measure on the vertical axis. In contrast, conventional graphical displays for scatter plots show the outcome on the vertical axis and the covariate on the horizontal axis. Therefore, effects estimated from small studies will have broader scattering at the bottom of the graph, with narrower spreading in larger studies. In the absence of bias, the plot should approximately resemble a symmetrical funnel. In cases of bias (e.g., smaller studies without significant effects remaining unpublished), an asymmetrical funnel appears with a gap in a bottom corner of the graph^{15, 16)}. We evaluated the funnel plot's asymmetry using Begg's test¹⁵⁾.

Results

Study selection, Jadad scores, and study characteristics

The study selection process is shown in Fig. 1. Three relevant citations were retrieved from the databases, although in one study, the incidences of adverse events were not compared for nivolumab and docetaxel and thus that study was excluded. Two RCTs were ultimately included

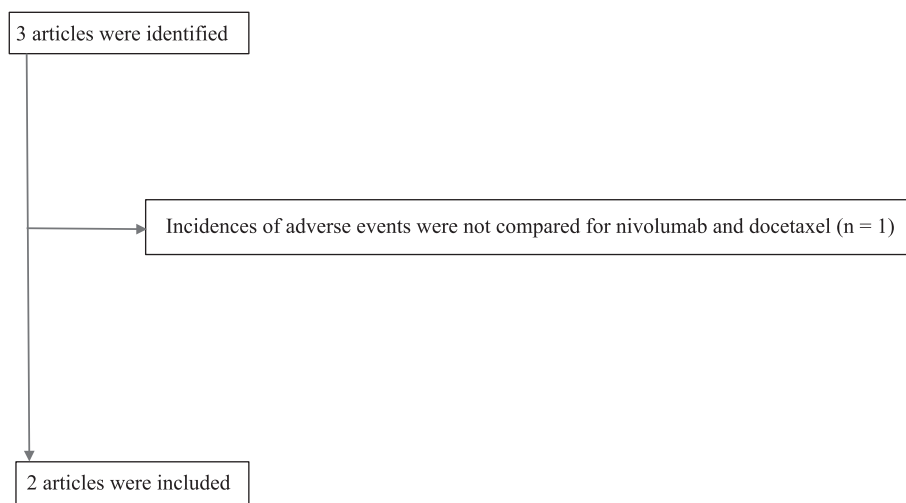


Fig. 1. The study selection process

Table 1. Jadad quality scores for the randomized controlled trials that were included in the meta-analysis

Study	Factors and Jadad score			Total Jadad score
	Randomization	Blinding	Withdrawal or dropout	
Borghaei <i>et al</i> ⁷⁾	2	2	1	5
Brahmer <i>et al</i> ⁶⁾	2	2	1	5

Table 2. Characteristics of the studies that were included in the meta-analysis

Study	Year of publication	Type of study	No. of patients	Criteria	Drugs and dosages	Primary endpoint
Borghaei <i>et al</i> ⁷⁾	2015	RCT	582	Previously-treated advanced non-squamous NSCLC	Nivolumab at 3 mg / kg every 2 weeks or docetaxel at 75 mg / m ² every 3 weeks	OS
Brahmer <i>et al</i> ⁶⁾	2015	RCT	272	Previously-treated advanced squamous-cell NSCLC	Nivolumab at 3 mg / kg every 2 weeks or docetaxel at 75 mg / m ² every 3 weeks	OS

RCT, randomized controlled trial; NSCLC, non-small cell lung cancer; OS, overall survival.

in the present meta-analysis^{6, 7)}, and both studies had Jadad scores of 5 (Table 1), which confirmed that they were of high quality. The characteristics of the two studies are listed in Table 2.

Risk of bias

The risk of bias in the studies was evaluated based on their random sequence generation, allocation concealment, blinding of the participants and personnel, blinding of the outcome

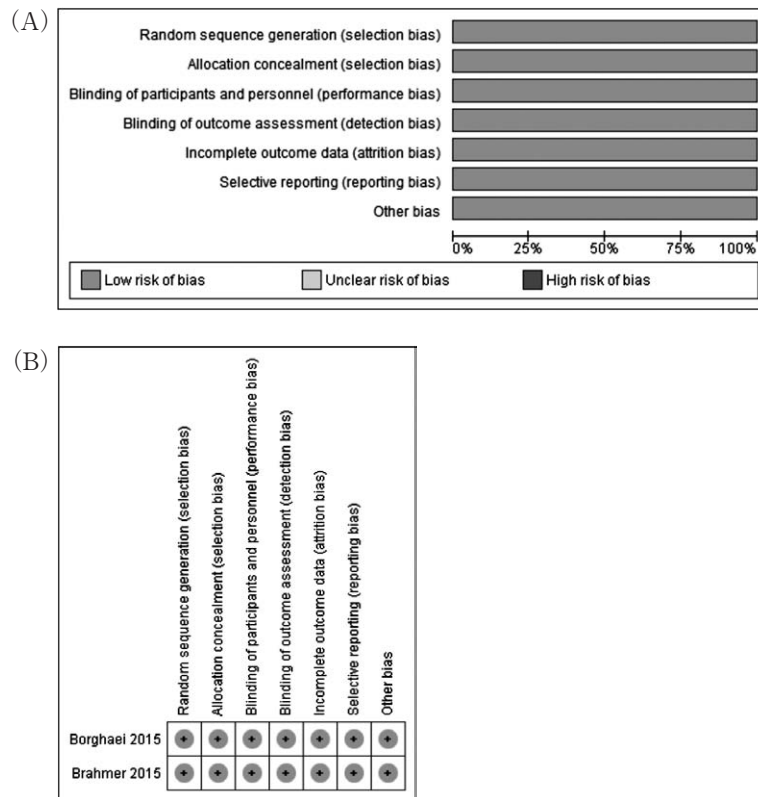


Fig. 2. Risk of bias

The risk of bias graph shows the authors' judgments regarding the risk of bias items, presented as percentages, in both of the included studies (A). The risk of bias summary shows the authors' judgments regarding the risk of bias items for each included study (B).

assessment, incomplete outcome data, selective reporting, and other forms of potential bias. Both studies were considered to have a low risk of bias for all factors, and the authors' judgements regarding these assessments are shown in Fig. 2.

Adverse events

There was no inter-study heterogeneity, as measured using the I^2 statistic, and the analyses were performed using the fixed-effect model (Fig. 3). These analyses revealed that nivolumab was both non-inferior and superior to docetaxel (Table 3) for any adverse event, fatigue (all grades and grades 3-4), nausea, decreased appetite, diarrhea, myalgia, anemia (all grades and grades 3-4), alopecia, neutropenia (all grades and grades 3-4), febrile neutropenia (all grades and grades 3-4), and leukopenia (all grades and grades 3-4).

Bias assessment

A funnel plot (Fig. 4) revealed that the two samples were distributed symmetrically, and Begg's test did not reveal significant asymmetry ($P = 1.00$). This result suggested that there

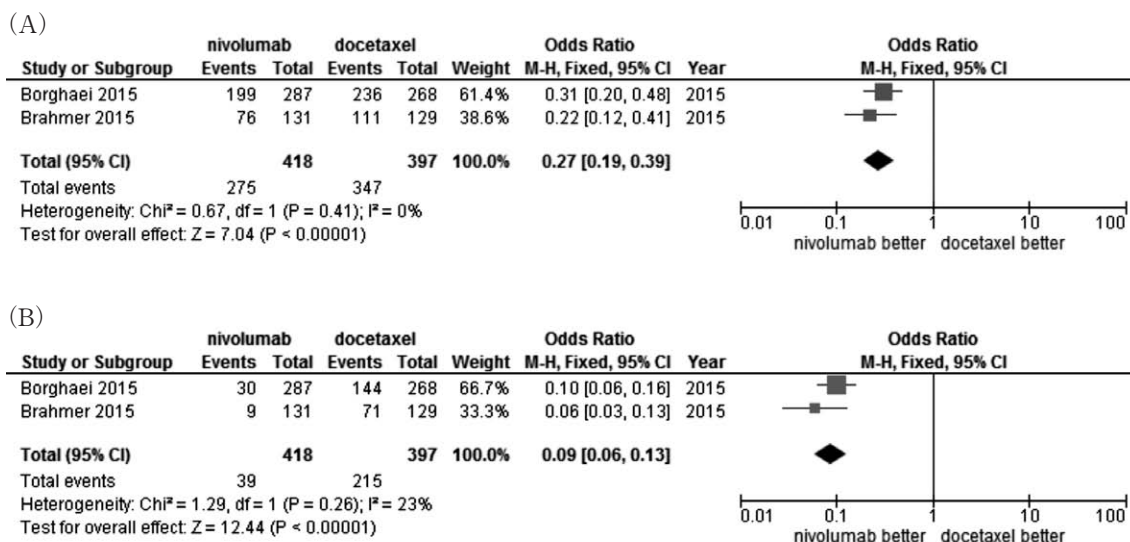


Fig. 3. Forest plots for (A) any adverse event (any grade) and (B) grade 3-4 adverse events in the two included studies by Borghaei *et al*⁷⁾ and Brahmer *et al*⁶⁾. M-H, Mantel-Haenszel; CI, confidence interval.

Table 3. Results from the non-inferiority and superiority tests

Outcome	OR (95% CI)	Non-inferiority	Superiority	P-value
Fatigue	0.44 (0.31-0.62)	Accepted	Accepted	<0.001
Fatigue (grade 3-4)	0.16 (0.05-0.46)	Accepted	Accepted	<0.001
Nausea	0.37 (0.25-0.54)	Accepted	Accepted	<0.001
Nausea (grade 3-4)	0.53 (0.11-2.49)	NS	NS	0.42
Decreased appetite	0.58 (0.39-0.87)	Accepted	Accepted	0.009
Decreased appetite (grade 3-4)	0.32 (0.05-2.01)	NS	NS	0.22
Diarrhea	0.29 (0.19-0.45)	Accepted	Accepted	<0.001
Diarrhea (grade 3-4)	0.36 (0.08-1.57)	NS	NS	0.18
Myalgia	0.18 (0.09-0.38)	Accepted	Accepted	<0.001
Myalgia (grade 3-4)	2.81 (0.11-69.31)	NS	NS	0.53
Anemia	0.08 (0.04-0.16)	Accepted	Accepted	<0.001
Anemia (grade 3-4)	0.12 (0.02-0.67)	Accepted	Accepted	0.015
Alopecia	0.01 (0.00-0.06)	Accepted	Accepted	<0.001
Alopecia (grade 3-4)	0.11 (0.01-8.07)	NS	NS	0.49
Neutropenia	0.01 (0.00-0.04)	Accepted	Accepted	<0.001
Neutropenia (grade 3-4)	0.01 (0.00-0.04)	Accepted	Accepted	<0.001
Febrile neutropenia	0.02 (0.00-0.15)	Accepted	Accepted	<0.001
Febrile neutropenia (grade 3-4)	0.02 (0.00-0.16)	Accepted	Accepted	<0.001
Leukopenia	0.04 (0.01-0.19)	Accepted	Accepted	<0.001
Leukopenia (grade 3-4)	0.05 (0.01-0.25)	Accepted	Accepted	<0.001

OR, odds ratio; CI, confidence interval; NS, not significant; Accepted, non-inferiority or superiority of nivolumab to docetaxel.

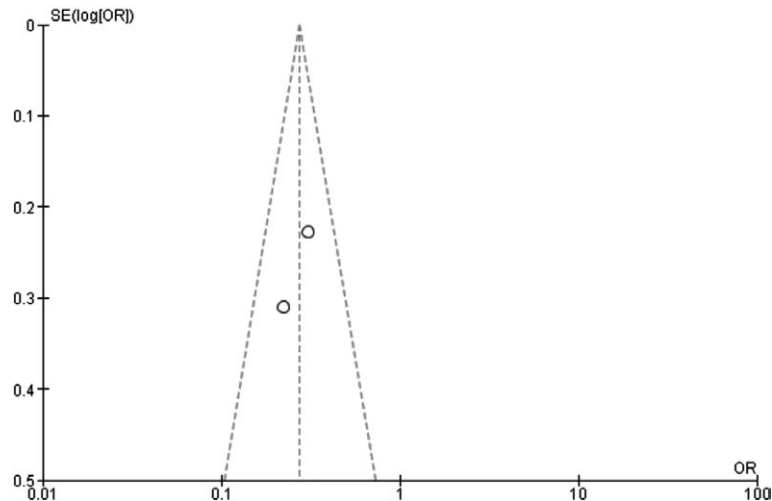


Fig. 4. Bias assessment plot
 Funnel plot showing the symmetrical distribution of the two samples.
 SE, standard error ; OR, odds ratio.

was no significant publication bias, and that any publication bias did not substantially affect the conclusions. Therefore, the results of the meta-analysis were considered valid.

Discussion

The present meta-analysis revealed that nivolumab was non-inferior and superior, compared to docetaxel, in terms of any adverse event, fatigue (all grades and grades 3–4), nausea, decreased appetite, diarrhea (all grades and grades 3–4), myalgia, anemia (all grades and grades 3–4), alopecia, neutropenia (all grades and grades 3–4), febrile neutropenia (all grades and grades 3–4), and leukopenia (all grades and grades 3–4). Although there were no significant differences in grade 3–4 nausea, grade 3–4 decreased appetite, grade 3–4 myalgia, and grade 3–4 alopecia, it is possible that these adverse events may be less common among patients who received nivolumab (vs. docetaxel).

Previous studies have revealed that nivolumab provides better survival improvement and acceptable adverse events, compared to chemotherapy, in patients with advanced NSCLC^(6, 7). Based on these findings, nivolumab was recently approved in the US, Europe, and in some Asian countries as a second-line treatment for both squamous and non-squamous advanced NSCLC⁽¹⁷⁾. However, no studies have statistically compared the adverse event profiles of nivolumab and docetaxel. Therefore, ours is the first meta-analysis to confirm that nivolumab has an adverse event profile that is non-inferior and superior to that of docetaxel in patients with advanced NSCLC, which suggests that nivolumab is significantly more tolerable in this patient population.

These results are biologically plausible, as docetaxel interferes with the cell cycle and is cytotoxic to all dividing cells^(18, 19), which can interfere with the division of both tumor cells and normal tissues, such as epidermal cells, bone marrow cells, and other germ cells^(18–20). Therefore, hematological and non-hematological adverse events are relatively common during docetaxel

treatment, and these adverse effects can become permanent. In contrast, nivolumab interferes with the function of a negative regulator of T-cell activation and its downstream signaling, which allows immune cells to attack the tumor²¹⁾. This mechanistic difference may help partially explain the fact that nivolumab is more tolerable and is associated with a significantly lower risk of severe treatment-related adverse events, compared to docetaxel. However, nivolumab is not entirely safe, as previous studies have revealed associations with increased risks of thyroid dysfunction, fulminant type 1 diabetes mellitus, and vitiligo^{17, 22, 23)}. Therefore, additional detailed clinical information and biomarkers are needed to predict these treatment-related adverse events in patients who receive nivolumab¹⁷⁾.

The present study has several limitations that should be acknowledged. First, we only considered published studies and it is possible that publication bias may be present, although this was not apparent in the funnel plot. Second, a meta-analysis is a form of retrospective research that is subject to the methodological limitations of all retrospective studies. For example, both of the studies included in the present meta-analysis were supported by pharmaceutical companies, and the authors reported receiving personal fees and grant support. Therefore, the source of funding may make a difference. Moreover, outcome selection bias might be present. Third, we only considered a small sample of studies (two reports) in our analyses. Meta-analysis of two studies is not uncommon, as in orphan disease. However, meta-analysis of only two studies may be considered an unsolved problem in the presence of heterogeneity, although heterogeneity was not observed in this meta-analysis.

Conclusion

Nivolumab was non-inferior and superior for treating advanced NSCLC, compared to docetaxel, in terms of any adverse event, fatigue (all grades and grades 3-4), nausea, decreased appetite, diarrhea, myalgia, anemia (all grades and grades 3-4), alopecia, neutropenia (all grades and grades 3-4), febrile neutropenia (all grades and grades 3-4), and leukopenia (all grades and grades 3-4). These results suggest that nivolumab may be more tolerable for managing advanced NSCLC, compared to docetaxel. However, given the limitations of the present meta-analysis, further research is needed to confirm the safety of nivolumab treatment for advanced NSCLC.

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Conflicts of interest disclosure

None of the authors have any conflicts of interest to declare.

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