A Comparison of nivolumab and pembrolizumab for advanced NSCLC in the second-line treatment: A Systematic Review and Network Meta-analysis

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Research

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Abstract

Objectives : As reported, nivolumab and pembrolizumab have shown to be superior to docetaxel in advanced NSCLC. Therefore, we performed a systematic review and network meta-analysis to compare the efficacy and safety of nivolumab and pembrolizumab.

Materials and Methods : Randomized controlled trials (RCTs) assessing the effect and safety of nivolumab or pembrolizumab versus docetaxel for patients with advanced NSCLC in the second-line treatment were included. Two investigators independently searched articles, extracted data, and assessed the quality of included studies. After that, we performed pairwise direct meta-analyses (nivolumab vs. docetaxel and pembrolizumab vs. docetaxel) and indirect comparison (nivolumab vs. pembrolizumab) using network meta-analyses methods.

Results : Four RCTs involving 2391 patients were included in the meta-analysis. In analyses of overall survival (OS), progression-free survival (PFS) and overall response rate (ORR) in the direct meta-analysis, nivolumab and pembrolizumab both showed survival benefits when compared with docetaxel. For the indirect comparison, nivolumab show no signifcant difference in OS, PFS and ORR when compared with pembrolizumab (OS: HR 1.03; 95% CI 0.84–1.26; PFS: HR 0.95; 95% CI 0.80–1.14; ORR: HR 1.08; 95% CI 0.67–1.73). For the safety analysis, nivolumab and pembrolizumab both have less toxicity than docetaxel. In indirect comparison, nivolumab showed less all-grade toxicity (OR 0.71; 95% CI 0.49–1.04) and grade 3–5 toxicity (OR 0.32; 95% CI 0.21–0.49) when compared with pembrolizumab.

Conclusion : Our meta-analysis suggests that nivolumab and pembrolizumab demonstrated similar clinical benefit for patients with advanced NSCLC in the second-line treatment. It seems that nivolumab has less toxicity when compared with pembrolizumab.

Introduction

Lung cancer remains the leading cause of cancer incidence and mortality in global, accounting for an estimated 2.1 million new Lung cancer cases and 1.8 million deaths in 2018 [1, 2]. Lung cancer roughly divided into two categories: non-small-cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC accounts for approximately 85% of lung cancer cases and has high mortality worldwide [3]. The mutations of targeted driver EGFR, BRAF, HER2 and the rearrangements of ALK or ROS1 only exist in part of lung adenocarcinoma, for the other NSCLCs without targeted molecular abnormalities, conventional platinum-based doublet therapy was the only therapeutic option with a response rate ranging between 15% and 30%. In addtion, the majority of the NSCLC patients have incurable, metastatic or locally advanced disease at the time of diagnosis, most of NSCLC patients will develop disease recurrence or progression in the course of the disease, little therapeutic progress has been made since the approval of docetaxel for second-line treatment in 1999 [4–7].

The recent introduction of immune checkpoint inhibitors (ICI) targeting the programmed cell death-1 (PD-1)/programmed death-ligand 1 (PD-L1) axis has revolutionized the approach to treating NSCLC in second-line even first-line treatments. The PD-1 molecule is mianly expressed in T/B cells. Its main function is to limit the activity of T cells in peripheral tissues, where the effector phase takes place. Inflammatory signals in tissues induce the expression of PD-L1 and PD-L2, which downregulate the activity of T cells, limiting collateral tissue damage and maintaining the self-tolerance [8]. Lots of tumor cells express high PD-L1 levels, including NSCLC, suggesting that PD-1/PD-L1 pathway activation is a common mechanism used by tumors to avoid immune surveillance [9, 10]. Blockade of PD-1 signaling can restore CD8 + T-cell functions and cytotoxic capabilities from the exhausted tumor-infiltrating lymphocytes (TILs) and enhance antitumor immunity [11, 12].

Anti-PD-1 monoclonal antibodies, nivolumab and pembrolizumab both showed improvement in overall survival (OS) compared with chemotherapy in the second-line and later-lines treatment of advanced NSCLC, offering better survival outcome than docetaxel[13–16]. Nivolumab (Opdivo®, Bristol Mayer Squibb) is a genetically engineered, fully human immunoglobulin G4 (IgG4) monoclonal antibody specific for human PD-1 [17]. Nivolumab binds PD-1 with high affinity and blocks its interactions with both PD-L1 and PD-L2 [18]. In phase I and II clinical trials, for the patients with advanced NSCLC who received previously treated, nivolumab have approximately 15% and 17% response rates, with a median overall survival of 8.2 to 9.2 months and survival rates of 41% at 1 year and 19% at 3 years [19–21]. Nivolumab showed promising anti-tumor activity and tolerable toxicities. In the phase III study, CheckMate 017 and CheckMate 057 were studies focused on squamous NSCLC and Nonsquamous NSCLC stage III B or IV patients that have failed to a first-line platinum-based doublet respectively. Nivolumab showed improved overall survival and quality of life, and a favorable safety profile compared with docetaxel in patients with previously treated advanced NSCLC [14, 15]. Futhermore, CheckMate 078, a phase III study which focused on predominantly Chinese population of patients with advanced or metastatic NSCLC, also showed improved overall survival and quality of

life. Due to the benefit in overall survival, nivolumab was approved by FDA as a second-line treatment for NSCLC that have failed to a first line of chemotherapy cisplatin-base doublet in 2015.

Pembrolizumab (MK-3475, Keytruda®, Merck Sharp & Dohme), a highly selective IgG4 kappa isotype monoclonal antibody against PD-1, highly binds PD-1 selectively and blocks the PD-1, PD-L1/PD-L2 axis, thereby overcoming the major immune checkpoint inhibitor [22]. In the phase I KEYNOTE 001 clinical trial, the overall response rate was 19.4% and overall median progression-free survival (PFS) and overall survival was 3.7 months and 12 months [23]. In the phase II/III KEYNOTE 010 clinical trial, pembrolizumab also demonstrated improved overall survival and quality of life when compared with docetaxel in patients with previously treated advanced NSCLC whose tumors express a PD-L1 tumor proportion score (TPS) ≥ 50%. Based on these results, pembrolizumab was approved by FDA for metastatic NSCLC patients who present PD-L1 expression and failed to first line of chemotherapy in 2015.

However, to date, no clinical comparison of nivolumab and pembrolizumab for advanced NSCLC in the second-line treatment has been reported, we performed a systematic review and network meta-analysis to assess the efficacy and safety of nivolumab versus pembrolizumab (Fig. 1).

Ethics Approval

All analyses were based on previous published studies,thus no ethical approval and patient consent are required.

Materials And Methods

Literature Search Strategy

This Systematic Reviews and Meta-analysis were conducted according to PRISMA guideline [24]. A systematic review was conducted using the PubMed, Embase and Cochrane databases to identify phase III clinical trials comparing nivolumab or pembrolizumab with docetaxel in advanced NSCLC who had progression during or after first-line chemotherapy from the date of their inception until August 2019. The search strings were based on MeSH terms, including: “non-small-cell lung cancer”, “nivolumab”, and “pembrolizumab”. These terms were used in different combinations, there was no limitation on publication status or language. We also searched to identify additional eligible studies missed by the search strategies by the reference lists of retrieved studies and relevant reviews.

Study Selection Criteria

The study Selection criteria were determined on the basis of “PICOS” principle: P, population: advanced NSCLC; I, intervention: nivolumab or pembrolizumab; C, comparison: docetaxel; O, outcomes: efficacy and safety; S, study: randomized, controlled trial. The outcomes should include overall survival (OS, defined as time from randomisation to death from any cause), progression free survival (PFS, defined as time from randomisation to first radiological or clinical finding of disease progression or death from any cause), ORR (objective tumour response rate, defined as proportion of patients with complete or partial response) all-grade toxicity and grade 3–5 toxicity. If multiple publications were available for the same trial, only the most recent publication was selected for inclusion. We excluded the studies lacking data integrity, nonhuman studies, systematic reviews, case–control studies.

Data Extraction

Two investigators independently extracted data from the included articles, including publication time, characteristics of enrolled patients, study design, sample size, the regimens of therapy, the primary end point, the secondary endpoints and outcomes of the various subgroups. The primary endpoint of interest was overall survival. Secondary endpoints were progression-free survival, overall response rate and safety (combination of any adverse event in any all-grade toxicities and any grade 3–5 toxicity).

Statistical analysis

RevMan software version 5.3 (Cochrane Collaboration, Oxford, UK) and R software (version 3.3.2, R Foundation for Statistical Computing) were used in our meta-analysis. Probability values were two-sided, and $P < 0.05$ was considered of statistical significance. The 95% confidence interval (CI) and hazard ratio (HR) of all results were extracted from the included trial results, the relevant variance estimates were calculated from the CIs. The odds ratio (OR) with 95% CIs for dichotomous outcomes (overall response rate, all-grade toxicity and grade 3 to 5 toxicity) were also calculated and used to estimate the pooled effects. All meta analyses were performed using random-effects models by HRs or ORs with 95% CIs. We carried out traditional pairwise meta-analysis of studies that directly compared different treatment modalities (nivolumab vs. docetaxel and pembrolizumab vs. docetaxel), after that, we performed network meta-

analysis indirectly compared nivolumab with pembrolizumab through R package [25, 26]. Because of the small number of included trials, examine publication bias was not carried out.

Assessment For Risk Of Bias

We performed the bias risk assessment with the Cochrane Hand book for Systematic Reviews of interventions [27]. The assessment has seven domains of quality assessment for randomized controlled studies, including, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective bias and other biases. Each study was evaluated and rated three categories of biases: low risk of bias (when the risk of bias was low in all key domains); unclear risk of bias (when the risk of bias was low or unclear in all key domains); and high risk of bias (when the risk of bias was high in one or more key domains). Two investigators independently searched articles, extracted data, and assessed the quality of included studies. Any discrepancy was solved by consensus.

Results

Literature Review Results

Through all databases searches, 317 articles were identifified (Fig. 2). In the first round analysis, 102 abstracts repeated in different databases were excluded. All remaining abstracts were reviewed, and 4 randomized, controlled trials involving 2391 patients (CheckMate 017, CheckMate 057, CheckMate 078 and KEYNOTE-010 trials) fulfilled eligibility criteria and study quality requirements. These trials were randomized and followed intention-to-treat analysis for the primary endpoint (overall survival) and secondary endpoints (progression-free survival, overall response rate). All trials were centrally randomized.

Study Design Of Included Trials

All four trials involved adult patients with advanced NSCLC who had progression during or after first-line chemotherapy (platinum-based doublet chemotherapy mainly). In addtion, the CheckMate 017 trial only involved advanced Squamous NSCLC, the CheckMate 057 trial only involved advanced nonsquamous NSCLC, the CheckMate 078 trial involved Chinese population of patients predominantly, and the KEYNOTE-010 trial involved advanced NSCLC with PD-L1 expression on at least 1% of tumour cells. All selected trials were superiority trials comparing treatment with nivolumab or pembrolizumab versus docetaxel (Table 1). In the CheckMate 017, CheckMate 057 and CheckMate 078 trials, patients received nivolumab at 3 mg/kg every 2 weeks or docetaxel at 75 mg/m^2 every 3 weeks. In the KEYNOTE-010 trial, patients received pembrolizumab at 2 mg/kg or 10 mg/kg every 3 weeks or docetaxel at 75 mg/m^2 every 3 weeks. Among 2391 patients, 765 received nivolumab, 690 patients received pembrolizumab, and 936 patients were treated with docetaxel. The treatment continued until disease progression, intolerable toxic effects, physician decision, patient withdrawal, or other reasons.

Table 1
Main characteristics of the four studies included in the meta-analysis

	CheckMate 017	CheckMate 057	CheckMate 078	KEYNOTE-010
Year of publication	2015	2015	2019	2016
Object of study	Nivolumab vs. Docetaxel	Nivolumab vs. Docetaxel	Nivolumab vs. Docetaxel	Pembrolizumab vs. Docetaxel
Type of study	Prospective phase III randomized tria	Prospective phase III randomized tria	Prospective phase III randomized tria	Prospective phase II/III randomized tria
Primary endpoint	Overall survival	Overall survival	Overall survival	Overall survival
Patients enrolled	Advanced Squamous NSCLC who had progression during or after first-line chemotherapy	Advanced Nonsquamous NSCLC who had progression during or within platinum-based doublet chemotherapy	Advanced NSCLC who had progression during or after platinum-based doublet chemotherapy	Advanced NSCLC who had progression after platinum-based chemotherapy, with PD-L1 expression on at least 1% of tumour cells
Number of patients	272	582	504	1033
Treatment arm	3 mg/kg every 2 weeks	3 mg/kg every 2 weeks	3 mg/kg every 2 weeks	2 mg/kg or 10 mg/kg every 3 weeks
Control arm (Docetaxel)	75 mg/m^2 every 3 weeks	75 mg/m^2 every 3 weeks	75 mg/m^2 every 3 weeks	75 mg/m^2 every 3 weeks

Assessment Of Risk Of Bias

Risk of bias analysis (Fig. 3) showed that two studies had high risk of blinding of participants and personnel bias, the other two trials were rated with low risk of bias.

Patients

Most demographic and baseline characteristics were similar between the trials (Table 2). The CheckMate 078 trial mostly involved Asian patients, whereas the other three trials involved White, Asian and Black patients. The majority of patients in the four trials were Eastern Cooperative Oncology Group (ECOG) performance status (PS) 1. In the treatment arm, the CheckMate 078 trial excluded all the patients with EGFR or ALK mutations, however, the proportion of EGFR and ALK mutation were unkonwn in CheckMate 017 trial, 15% and 4% in CheckMate 057 trial, 9% and 1% in KEYNOTE-010 trial. All the patients had at least 1 line of prior treatment.

Table 2

Baseline Caracteristics of the studies included

	CheckMate 017		CheckMate 057		CheckMate 078		KEYNOTE-010	
	Nivolumab (n = 135)	Docetaxel (n = 137)	Nivolumab (n = 292)	Docetaxel (n = 290)	Nivolumab (n = 338)	Docetaxel (n = 166)	Pembrolizumab (n = 690)	Docetaxel (n = 343)
Average age (year)	62	64	61	64	60	60	63	62
Range	39–85	42–84	37–84	21–85	27–78	38–78	56–69	56–69
Sex								
Man	111(82%)	97(71%)	151(52%)	168(58%)	263(78%)	134(81%)	426(62%)	209(61%)
Woman	24(18%)	40(29%)	141(48%)	122(42%)	75(22%)	32(19%)	264(38%)	134(39%)
ECOG PS								
0	27(20%)	37(27%)	84(29%)	95(33%)	47(14%)	21(13%)	232(34%)	116(34%)
1	106(79%)	100(73%)	208(71%)	194(67%)	291(86%)	144(87%)	454(66%)	224(65%)
Race								
White	122(90%)	130(95%)	267(91%)	266(92%)	30(9%)	15(9%)	496(72%)	251 (73%)
Asian	4(3%)	2(1%)	9(3%)	8(3%)	308(91%)	151(91%)	145(21%)	72 (21%)
Black	1(1%)	2(1%)	7(2%)	9(3%)	0(0%)	0(0%)	21(3%)	7 (2%)
Nonspecifiied	2(1%)	1(1%)	9(3%)	7(2%)	0(0%)	0(0%)	10(1%)	2 (1%)
Disease stage								
IIIB	29(21%)	24(18%)	20(7%)	24(8%)	NA	NA	NA	NA
IV	105(78%)	112(82%)	272(93%)	266(92%)	NA	NA	NA	NA
Smoking status								
Former or current	121(90%)	129(94%)	231(79%)	227(78%)	236(70%)	118(71%)	564(82%)	269 (78%)
Never	10(7%)	7(5%)	58(20%)	60(21%)	102(30%)	48(29%)	123(18%)	67 (20%)
Unknown	4(3%)	1(1%)	3(1%)	3(1%)	0(0%)	0(0%)	3(□1%)	7 (2%)
Tumor histology								
Squamous	135(100%)	137(100%)	0(0%)	0(0%)	133(39%)	67(40%)	156(23%)	66 (19%)
Non-squamous	0(0%)	0(0%)	292(100%)	290(100%)	205(61%)	99(60%)	484(70%)	240 (70%)
Other	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	15(2%)	10 (3%)
EGFR status								
Wild-type	NA	NA	168 (58%)	172 (59%)	338(100%)	166(100%)	581(84%)	294 (86%)
Mutant	NA	NA	44 (15%)	38 (13%)	0(0%)	0(0%)	60(9%)	26 (8%)
Unknown	NA	NA	80 (27%)	80 (28%)	0(0%)	0(0%)	49(7%)	23 (7%)
ALK translocation								
No	NA	NA	113 (39%)	130 (45%)	338(100%)	166(100%)	612(89%)	310 (90%)
Yes	NA	NA	13 (4%)	8 (3%)	0(0%)	0(0%)	6(1%)	2 (1%)

	CheckMate 017		CheckMate 057		CheckMate 078		KEYNOTE-010	
Unkown	NA	NA	166 (57%)	152 (52%)	0(0%)	0(0%)	72(10%)	31 (9%)

Efficacy

1 patient (1/135), 4 patients (4/292) and 1 patient (1/338) in the CheckMate 017, CheckMate 057 and CheckMate 078 trials had complete response respectively. There was no report of complete response in the KEYNOTE-010 trial.

Firstly, we performed a traditional pairwise meta-analysis of studies that directly compared diferent treatment modalities. In an analysis of overall survival in the direct meta-analysis, nivolumab and pembrolizumab both showed survival benefits compared to docetaxel (nivolumab: HR 0.68; 95% CI 0.59–0.78; pembrolizumab HR 0.66; 95% CI 0.57–0.76) (Fig. 4). In the direct pairwise meta-analysis for progression-free survival, nivolumab showed survival benefit compared to docetaxel (HR 0.78; 95% CI 0.63–0.96), pembrolizumab also showed benefit when compared with docetaxel (HR 0.84; 95% CI 0.7–0.95) (Fig. 5). In the direct pairwise meta-analysis for overall response rate, nivolumab and pembrolizumab also showed efficacy compared to docetaxel (nivolumab: OR 2.5; 95% CI 1.41–4.46; pembrolizumab OR 2.17; 95% CI 1.57–3.00) (Fig. 6).

Subsequently, we performed a network meta-analysis of studies that indirectly compared nivolumab and pembrolizumab. Nivolumab showed no signifcant difference in overall survival, progression-free survival and overall response rate when compared to pembrolizumab (OS: HR 1.03; 95% CI 0.84–1.26; PFS: HR 0.95; 95% CI 0.80–1.14; ORR: HR 1.08; 95% CI 0.67–1.73). (Fig. 7).

Safety

For the safety analysis, 2299 patients were included. In the CheckMate 017, CheckMate 057, CheckMate 078 and KEYNOTE-010 trials, the toxicity profile of 12 patients, 22 patients, 11 patients, and 42 patients respectively were missing from the results. The most common treatment-related adverse events (AEs) were fatigue, decreased appetite, rash, asthenia, diarrhea and nausea. We also performed a traditional pairwise meta-analysis of studies that directly compared the toxicity. Indirect comparison showed nivolumab and pembrolizumab both have less all-grade toxicity (except the toxicity of rash) when compared with docetaxel (for any event toxicity, nivolumab: OR 0.30; 95% CI 0.22–0.39; pembrolizumab OR 0.42; 95% CI 0.33–0.55) (Fig. 8). For the grade 3–5 toxicity, nivolumab and pembrolizumab also demonstrated less toxicity (except the toxicity of rash) when compared with docetaxel (for any event at grade 3–5 toxicity, nivolumab: OR 0.10; 95% CI 0.07–0.13; pembrolizumab: OR 0.31; 95% CI 0.24–0.40) (Fig. 9).

In indirect comparison, nivolumab showed less all-grade toxicity when compared with pembrolizumab, especially in subgroup of nausea (OR 0.57; 95% CI 0.34–0.95) (Fig. 10), however, there was no significant difference (for any event toxicity, OR 0.71; 95% CI 0.49–1.04). For the grade 3–5 toxicity, nivolumab showed signifcant difference when compared to pembrolizumab (for any event at grade 3–5 toxicity, OR 0.32; 95% CI 0.21–0.49) (Fig. 11). In general, it seems that nivolumab is safer than pembrolizumab.

Discussion

Non-small cell lung cancer (NSCLC) is the leading cause of cancer death worldwide. Unfortunately, the majority of the patients have incurable, metastatic or locally advanced disease at the time of diagnosis [28, 29]. Previously treated advanced NSCLC without genetic mutation represents an area of unmet need, with little progress made since the approval of docetaxel in the past 20 years [4, 5]. A retrospective review showed that the survival of advanced NSCLC receiving second-line treatment remains poor, with a median overall survival of 6.4 months and survival rates of 22% at 1 year and 5% at 2 years [30]. Nivolumab and pembrolizumab have been approved as second-line treatment for patients with advanced NSCLC that progressed after first-line chemotherapies. However, to date, no clinical comparison of nivolumab and pembrolizumab in second-line treatment has been reported. The aim of this study was to compare the efficacy and safety of nivolumab and pembrolizumab for patients with advanced NSCLC in second-line therapy.

This meta-analysis showed that the baseline characteristics of the four trials were some different. The CheckMate 017 trail only included squamous NSCLS, the CheckMate 057 trial only included nonsquamous NSCLS, the CheckMate 078 and KEYNOTE 010 trials both included squamous and nonsquamous NSCLS. The proportion of patients with former or current smoking in the CheckMate 017 trail was much higher than the other trials. For the race population, CheckMate 078 were Chinese population of patients predominantly. In addtion, the patients with EGFR or ALK mutation were excluded in the CheckMate 078 trial. Most important of all, all the CheckMate trials included people regardless of the expression of PD L-1, the KEYNOTE 010 trial only enroll patients with PD-L1-positive.

The global phase III CheckMate 017 and 057 trials established the efficacy and safety of nivolumab in patients with squamous and nonsquamous advances NSCLC respectively, after that, the phase III CheckMate 078 trial established the role of nivolumab in population mainly in Chinese patients. Consistent with CheckMate 017 and CheckMate 057 trials, HRs for overall survival in CheckMate 078 favored nivolumab in patients with squamous (HR: 0.61) and nonsquamous (HR: 0.76) histology, compared with 0.59 in CheckMate 017 and 0.73 in CheckMate 057. In addtion, ORs for overall response rate in CheckMate 078 (OR:4.4) favored nivolumab in patients was better than that in CheckMate 017 (OR:2.6) and CheckMate 057 (OR:1.7). The global phase III KEYNOTE 010 also established the efficacy and safety of pembrolizumab in patients with advanced NSCLC with PD-L1-positive. HRs for overall survival in KEYNOTE 010 favored pembrolizumab in patients with 2 mg/kg pembrolizumab (HR: 0.71) and 10 mg/kg pembrolizumab (HR: 0.61), ORs for overall response rate favored pembrolizumab in patients was 2.17. It is noteworthy that, in these trials, the patients with EGFR or ALK mutation did not have benefit form nivolumab or pembrolizumab. In the CheckMate 057 trial, there were no significant difference in overall survival between nivolumab and docetaxel among women, patients aged ≥ 75 years and patients who never smoked. Futhermore, in the KEYNOTE 010 trial, there were no significant difference in overall survival between pembrolizumab and docetaxel among squamous NSCSL and patients aged ≥ 65 years, but the data also suggest a clinical benefit in these subgroup. Therefore, nivolumab and pembrolizumab both showed efficacy in patients with advances NSCLC who have received one or more previous treatment regimen. However, nivolumab and pembrolizumab have not been compared in a head-to-head study, our data showed that nivolumab and pembrolizumab both showed overall survival, progression-free survival and overall response rate benefit when compared with docetaxel. However, the progression-free survival with nivolumab in the CheckMate 057 and pembrolizumab in KEYNOTE 010 trial were not superior to that of docetaxel in patients, overall survival with nivolumab and pembrolizumab were both superior to that of docetaxel in the total population and most of subgroup population, suggesting that progression-free survival might not appropriately reflected the true benefit of nivolumab or pembrolizumab. In the indirect comparison, nivolumab showed no significant difference in overall survival, progression-free survival and overall response rate when compared with pembrolizumab.

Quality of life is crucial to patients with advanced NSCLC in second-line and later-line treatments, therefore, the prevention and management of Adverse Events (AEs) are crucial to best practice for management of this patient population. Fortunately, nivolumab and pembrolizumab both led to less adverse events in the four trails. The most common nivolumab-related AEs observed were fatigue, decreased appetite, nausea, asthenia and diarrhea in the CheckMate 017 and CheckMate 057 trials and rash, fatigue, decreased appetite, anemia and leukopenia in the CheckMate 078 trial. The most common pembrolizumab-related AEs observed in the KEYNOTE 010 trial were fatigue, decreased appetite, rash, nausea and diarrhea. The grade ≥ 3 toxicity among the four trials were scarce. However, PD-1 have unique toxic effects which are referred to as immune-related adverse events (IRAEs) [31, 32]. Pneumonitis, defined as inflammation of the lung parenchyma and appears to occur more commonly in patients with lung cancer receiving anti-PD-1/PD-L1 therapy in particular [33], has emerged as a uncommon but serious and potentially life-threatening IRAE resulting in pneumonitis-related deaths in these four trials. Pneumonitis was also the most cause for discontinued treatment in the four trials. Our data showed that nivolumab and pembrolizumab both have less toxicity (except the toxicity of rash) when compared with docetaxel. In indirect comparison, nivolumab showed less all-grade toxicity when compared with pembrolizumab (OR 0.32; 95% CI 0.21–0.49), however, there was no significant difference. Nivolumab also has much less toxic in the grade 3–5 toxicity when compared with pembrolizumab (OR 0.71; 95% CI 0.49–1.04). In general, it seems that nivolumab is safer than pembrolizumab.

Based on the following three reasons: Firstly, nivolumab have more clinical researches, including phase III clinical trial mainly in Chinese population. Secondly, nivolumab and pembrolizumab showed survival benefit for the patients regardless of the expression of PD L-1 and the patients with PD-L1-positive respectively (the patients with PD-L1-negative were not included in KEYNOTE 010 trial). Thirdly, nivolumab have less all-grade toxicity and grade 3–5 toxicity when compared with pembrolizumab. We considered that nivolumab may be superior to pembrolizumab for advanced NSCLC in the second-line treatment. Further direct well-designed, head-to-head, prospective studies are needed to confirm these findings. Limitation of this meta-analysis should be taken into account. Firstly, because of the strict design, only four RCTs were included, it was insufficient to do sensitivity analysis and Begg tests. Secondly, moderate heterogeneity was observed in our meta-analysis, this heterogeneity mainly might be attributed to sample size and baseline characteristics of patients. Finally, because of lack of information, we were unable to compare the cost-effectiveness of both drugs.

Conclusions

Based on efficacy and safety, our meta-analysis suggests that nivolumab and pembrolizumab demonstrated similar clinical benefit for patients with advanced NSCLC in the second-line treatment. It seems that nivolumab has less toxic in all-grade toxicity and grade 3–5 toxicity when compared with pembrolizumab. We considered that nivolumab may be superior to pembrolizumab for advanced NSCLC in the second-line treatment. Further direct well-designed, head-to-head, prospective studies are needed to confirm these findings.

Declarations

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Authors' contributions

Jie Zhang and Jing Zhu conceived and designed this study. Jie Zhang and Rui Zhou performed the literature search. Jie Zhang, Rui Zhou and Jing Zhu performed the data analysis. Rui Zhou and Jing Zhu wrote the paper. All authors read and approved the final manuscript.

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Conflicts of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Availability of data and materials

All the data used in this study can be obtained from the original articles.

Ethics approval and consent to participate

All analyses were based on previous published studies; thus, ethical approval and patient consent are not required.

Consent for publication

All analyses were based on previous published studies; thus, no consent for publication is required.

Competing interests

The authors declare that they have no competing interests.

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Figures

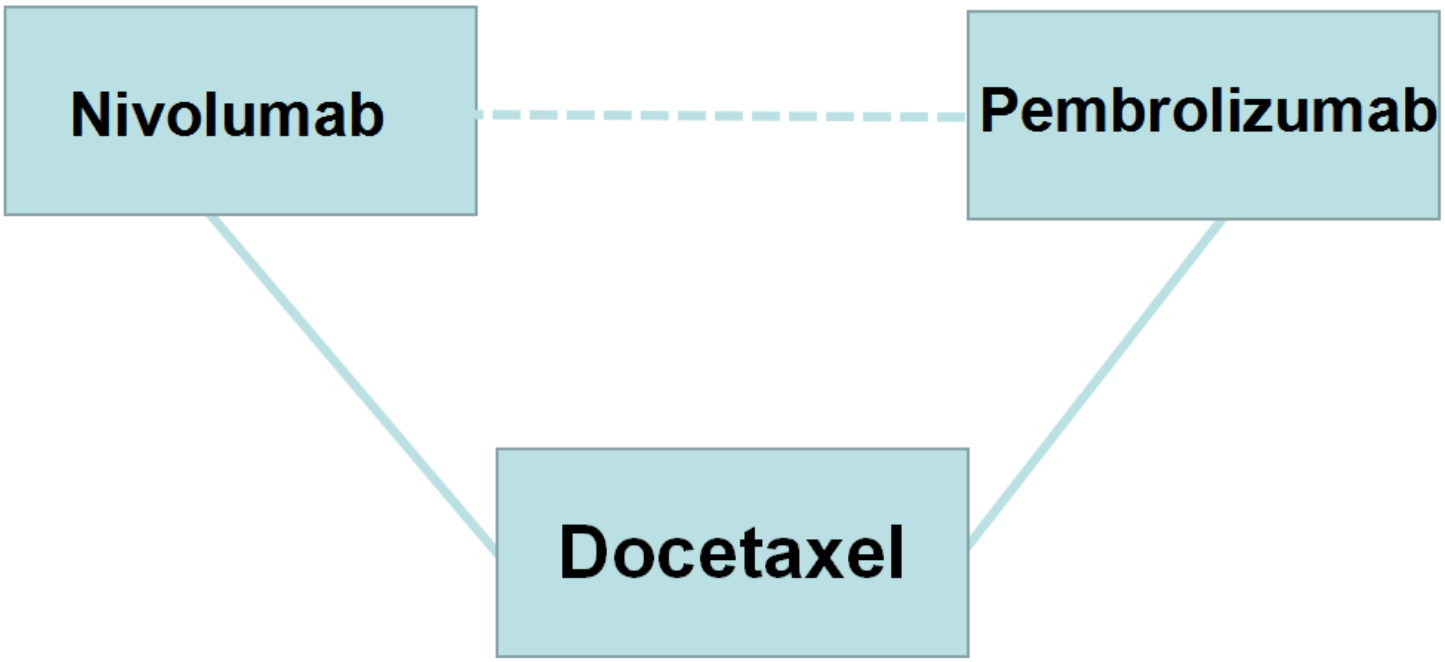

Figure 1

Network of Treatment Comparison.

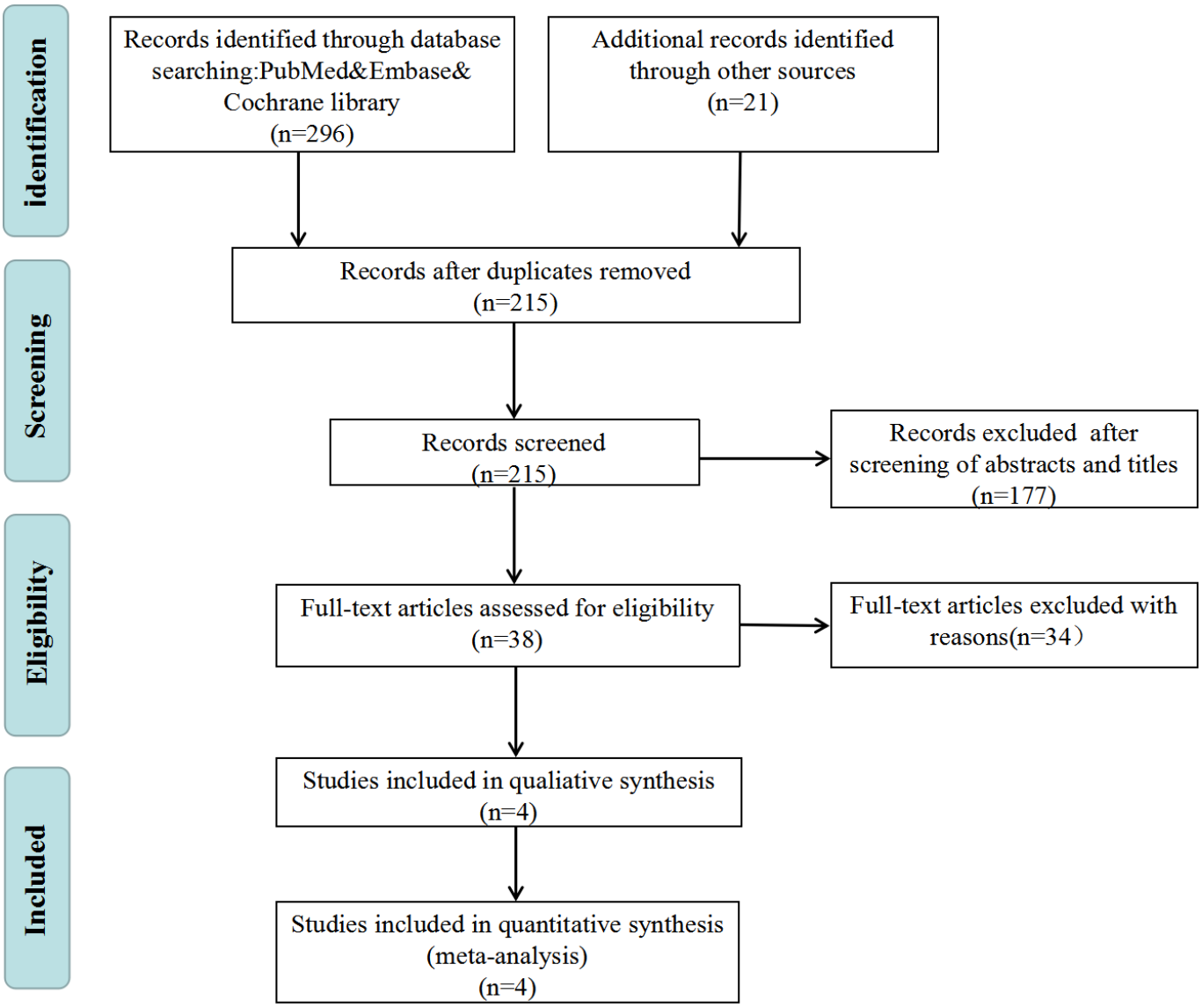

Figure 2

Study Selection.

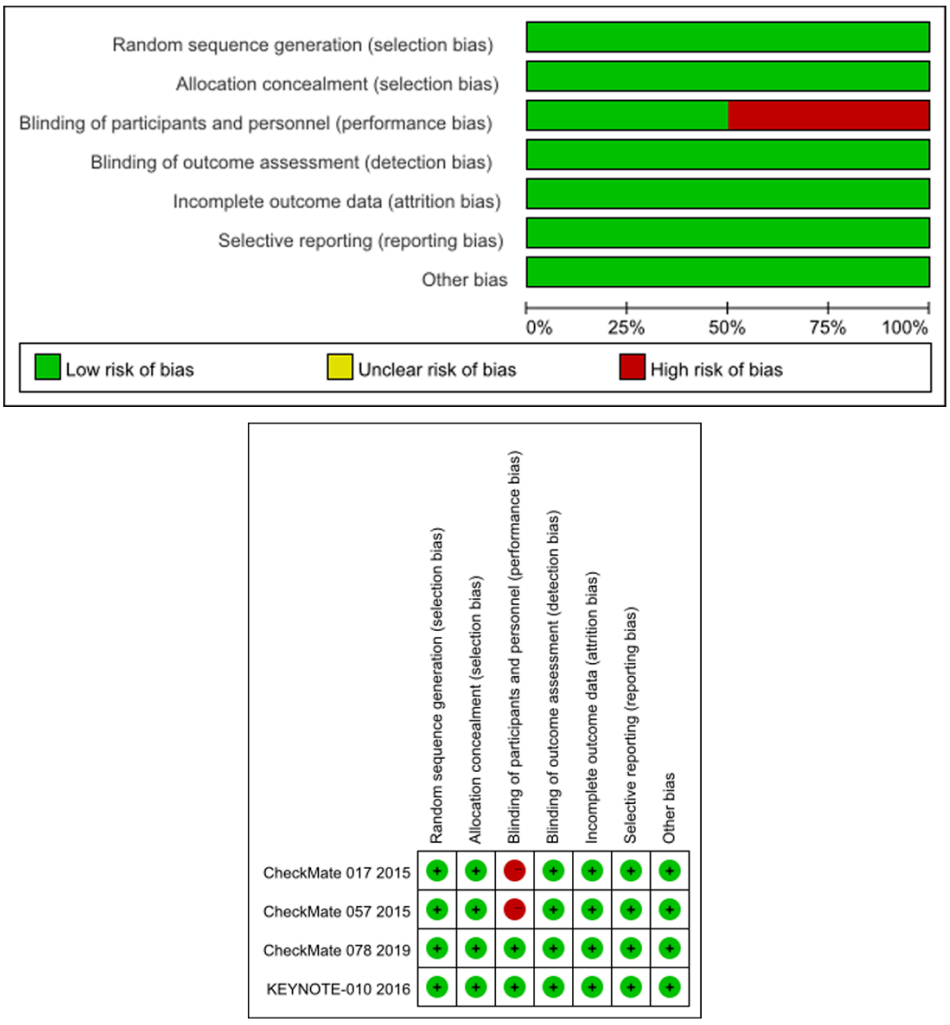

Figure 3

Risk of bias graph and Risk of bias summary.

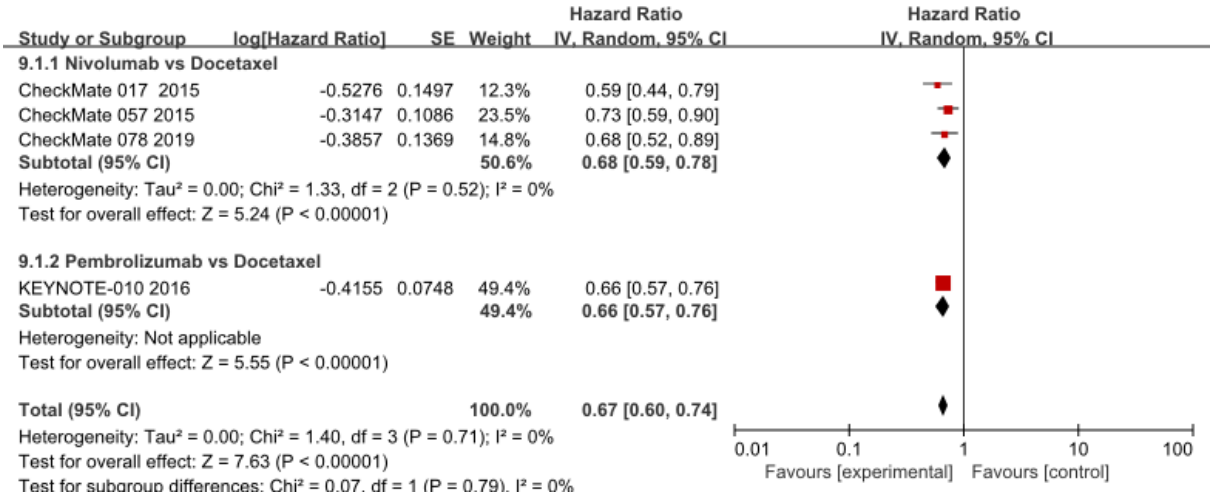

Figure 4

Overall Survival. Direct Analysis.

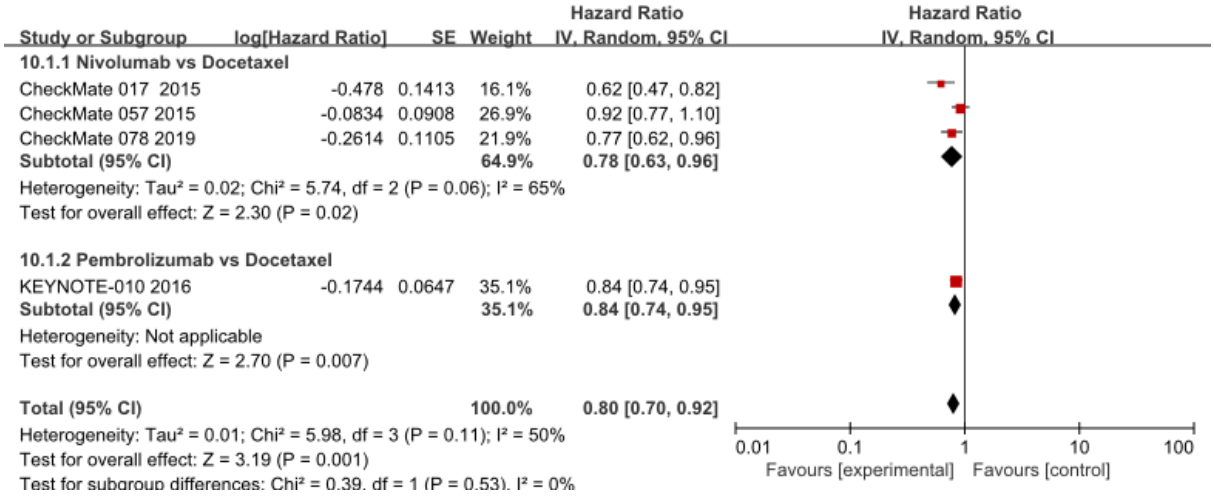

Figure 5

Progression-free Survival. Direct Analysis.

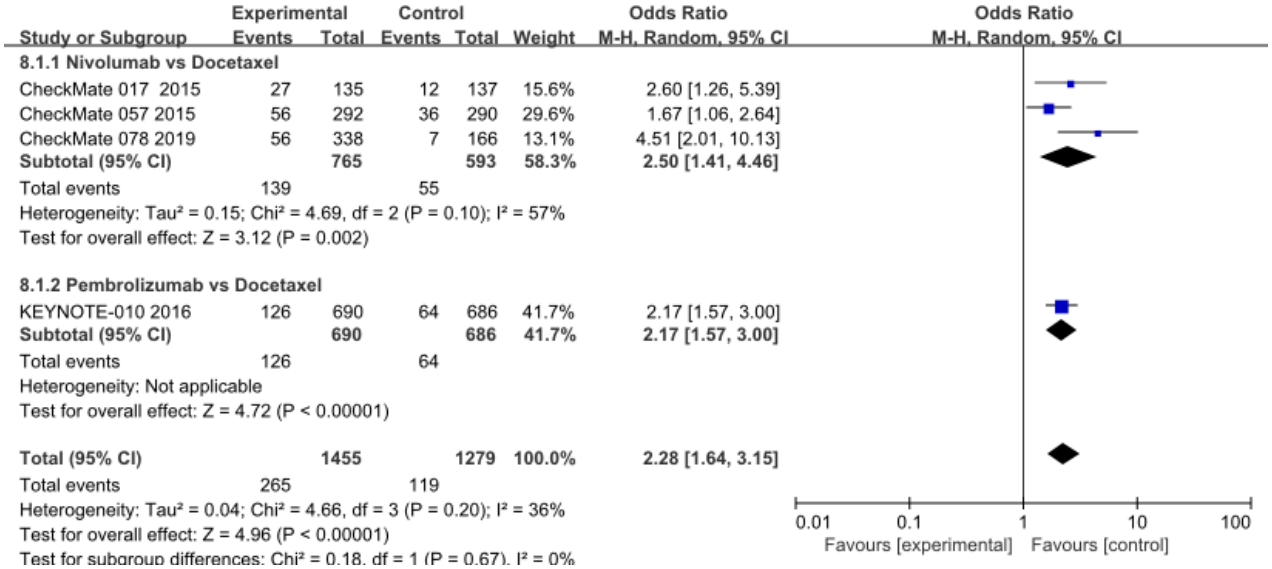

Figure 6

Overall Response Rates. Direct Analysis.

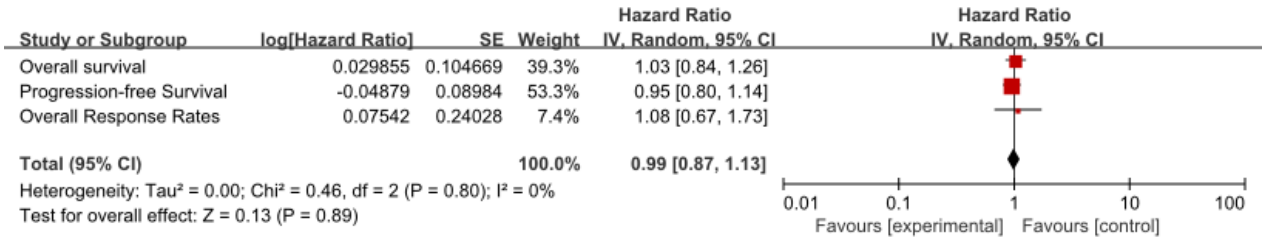

Figure 7

ORR,PFS,OS.indirect analysis.

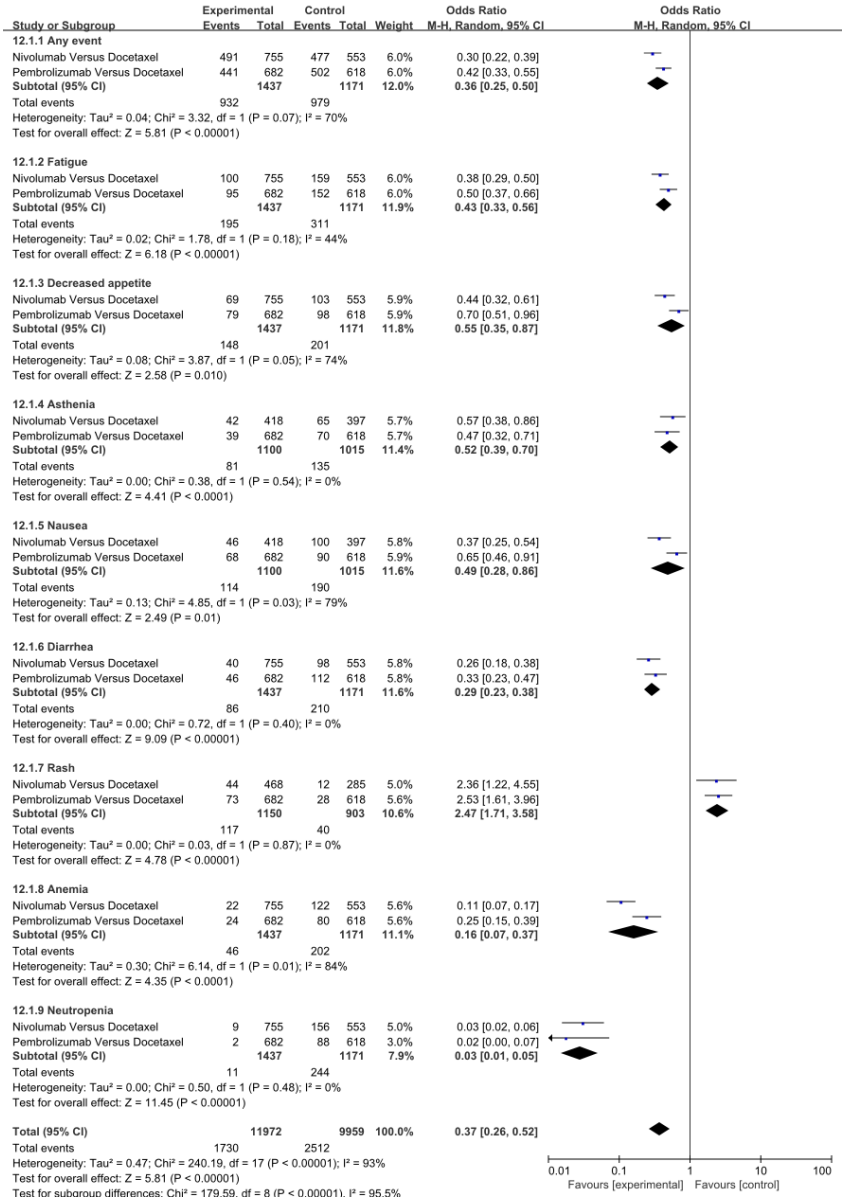

Figure 8

Safety. Direct Analysis of All-grade Toxicities.

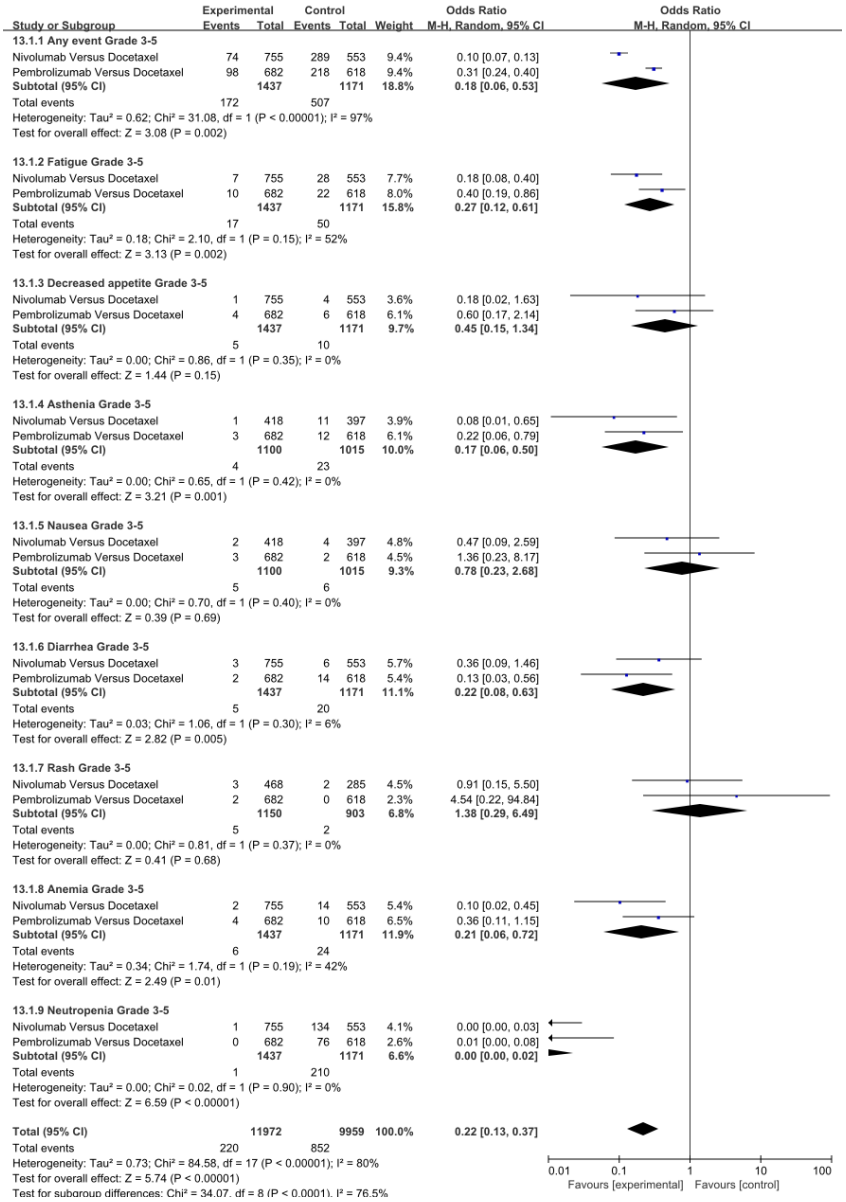

Figure 9

Safety. Direct Analysis of Grade 3 to 5 Toxicities.

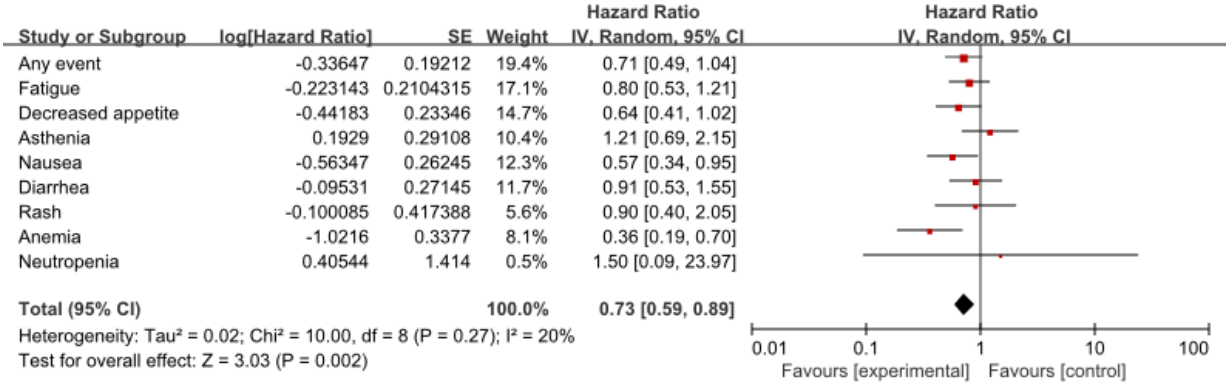

Figure 10

Safety. Indirect Analysis of All-grade Toxicities.

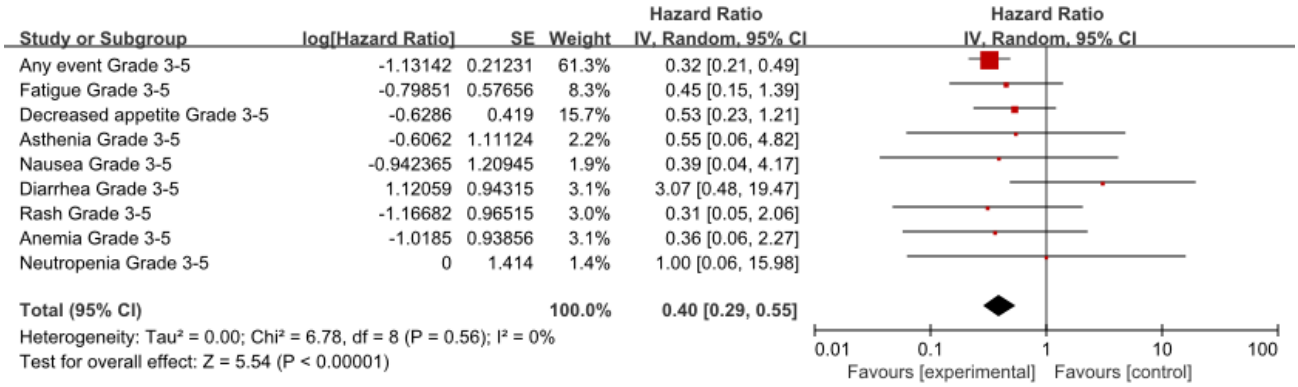

Figure 11

Safety. Indirect Analysis of Grade 3 to 5