

Nivolumab Monotherapy or Combination Therapy with Ipilimumab for Lung Cancer: A meta-analysis of Randomized Controlled Trials

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Abstract

Background: The high incidence and mortality of lung cancer have seriously affected human life and health. Nivolumab is a monoclonal antibody that can inhibit programmed death 1 (PD-1) and Ipilimumab is a monoclonal antibody against CTLA-4 (cytotoxic T lymphocyte-associated antigen 4), both of which can prevent the immune escape of tumor cells. Our goal was to synthesize evidence from published randomized controlled trials involving the safety and efficacy of either Nivolumab alone or in combination for the treatment of unresectable lung cancer.

Methods: We searched the following electronic databases: PubMed, Embase, and Cochrane libraries, and screened the retrieved records for eligibility. We used the Stata16 software for the analyses. The results of the analysis are expressed as hazard ratios (HRs) or risk ratios (RRs) and their corresponding 95% confidence intervals (CI).

Results: The final analysis included nine trials involving 4754 patients. Among patients with advanced lung cancer, patients using immunosuppressive therapy had better overall survival (OS), progression-free survival (PFS), and an objective response rate (ORR) than patients receiving chemotherapy. The HR of Nivolumab monotherapy or combination therapy with OS was compared with that of chemotherapy (HR: 0.73, 95% CI: 0.64–0.83; HR: 0.75, 95% CI: 0.60–0.93), and the HR of PFS was (HR: 0.81, 95% CI: 0.69–0.94; HR: 0.86, 95% CI: 0.76–0.98).

Conclusions: Immunotherapy has been shown to have more clinically meaningful survival benefits for patients with lung cancer, whether monotherapy or combination immunotherapy.

Systematic review registration PROSPERO CRD42020213440.

Background

Lung cancer is the most common malignant tumor and the most common cause of cancer-related death worldwide^[1]. In 2017, there were 2.2 million cases of trachea, bronchus, and lung cancer in the world, with 1.9 million deaths, accounting for approximately 19% of all cancer-related deaths^[2]. The high mortality^[3] rate and low 5-year survival rate^[4] of lung cancer have led to effective cancer treatments, which have directed lung cancer research. Systemic cytotoxic chemotherapy has been the main treatment for advanced non-small cell lung cancer (NSCLC), but the benefits of chemotherapy have reached a stable stage and new forms of treatment are required. Although there have been increasingly more research on alternative treatments for gene mutations, their success is still limited^[5,6]. Thus, we have again turned our attention to immunotherapy. Tumors can escape immune surveillance in the body because of changes within themselves or the tumor microenvironment, or through immune regulatory mechanisms, that is, the internal regulatory mechanism by which tumors induce or suppress immune responses^[7]. Immunotherapy mainly regulates the interaction between T cells and antigen-presenting cells (APC) or tumor cells to help release suppressed immune responses^[8]. At present, immunotherapy has become an important treatment method^[9].

Nivolumab (BMS-936558) was the first PD-1 inhibitor approved for advanced NSCLC^[10]. Nivolumab has a high affinity for activated T cells, B cells, natural killer cells, and PD-1 on the surface of monocytes. Previous studies have found that the pharmacokinetics of Nivolumab is linear in the dose range of 0.1 to 20 mg/kg. Additionally, after drug withdrawal, receptor saturation can be maintained for several months^[11,12]. In a multicenter phase one dose-escalation cohort expansion trial^[13], 129 patients with advanced NSCLC were evaluated and Nivolumab was divided into three dose groups: 1 mg/kg, 3 mg/kg, and 10 mg/kg. The 5-year results showed that the objective response rate (ORR) and median overall survival (OS) of patients treated with Nivolumab was 17.1% and 9.9 months, respectively. The 3 mg/kg dose group had the best effect wherein the median OS reached 14.9 months. This 5-year follow-up study showed that the 5-year OS rate for all patients was 16%, and the 5-year OS rate for squamous cell carcinoma (16%) and non-squamous cell carcinoma (15%) was similar.

In 2015, Nivolumab was approved (FDA) for the treatment of advanced metastatic squamous and non-squamous NSCLC after platinum chemotherapy [13].

Ipilimumab is a monoclonal antibody against human CTLA-4. It was approved by the FDA in 2011 for the treatment of unresectable or metastatic melanoma [14]. In a multicenter phase II study of small-cell lung cancer, the effects on patients were compared for those receiving chemotherapy alone or in combination with Ipilimumab. Compared with the control group, the Ipilimumab group had obvious advantages in immune-related progression-free survival (irPFS) and OS [14]. Larkin found that for patients with previously untreated metastatic melanoma, the survival rate of patients receiving Nivolumab plus Ipilimumab was significantly improved when compared with those receiving Ipilimumab alone [15].

In this meta-analysis, our goal was to synthesize the evidence of published randomized controlled trials (RCTs) to study the safety and effectiveness of Nivolumab monotherapy and that of Nivolumab combined with Ipilimumab.

Materials And Methods

This meta-analysis was based on PRISMA guidelines. The studies included in this meta-analysis have been published, and, as such, ethical approval and informed consent were not required.

Inclusion and exclusion criteria

We included RCTs that met the following criteria: (i) population: patients with advanced stage III or IV lung cancer; (ii) intervention: Nivolumab alone or in combination with Ipilimumab; (iii) control: Nivolumab monoclonal antibody or any other effective chemotherapy; (iv) Results: objective response rate, complete response rate, partial response rate, PFS rate, and safety results. We excluded tests that met the following conditions: (i) non-English publications and (ii) conference papers. In multiple reports, we used the data from the latest report.

Search strategy

We searched electronic databases for documents published as of December 2020. The databases included Embase, Cochrane Library, and PubMed. We used an advanced search for all databases. Search criteria used (Opdivo [title/abstract]), (Nivolumab [title/abstract]), (Ipilimumab [title/abstract]), and (non-small cell lung cancer [Title/Abstract]), (NSCLC [Title/Abstract]), (lung cancer [Title/Abstract]), or (small cell lung cancer [title/abstract]).

Data extraction

Two reviewers extracted data from qualified studies and differences were resolved with a discussion. The name of the first author and the year of publication were used to identify the study. For each study, the following information was extracted: first author name, annual publications, experimental stage, number of subjects, interventions, prognosis (OS, PFS, adverse effects [AEs], ORR). The characteristics of the included studies are shown in Figure 1.

Quality assessment

The Cochrane Collaboration tool was used to assess the risk of RCT bias, considering the following aspects: whether the method of allocation was truly random, whether proper concealment of allocation existed, whether equality occurred between the two groups at baseline in terms of prognostic features, whether the eligibility criteria were described, whether blinding of the outcome assessors was performed, whether the report was complete, and whether the report was selective (Table 1). A funnel plot and Egger's test were used to assess publication bias.

Statistical analysis

All analyses were performed using Stata 16.0 and ICT (Indirect Treatment Comparisons, Canadian Agency for Drugs and Technologies in Health). The results of the meta-analysis were expressed as hazard ratios (HR) or risk ratios (RRs) and their corresponding 95% CI. PFS and OS were expressed with HRs and corresponding 95% CI. The RR and corresponding 95% CI were the comprehensive measure of the risk of ORR and AEs. We first tested heterogeneity among studies using I^2 statistics and $I^2 < 50\%$ was considered a low level of heterogeneity, whereas $I^2 \geq 50\%$ indicated a high level of heterogeneity. Based on the statistical significance of the heterogeneity test, we used a random effects model ($I^2 \geq 50\%$) or a fixed effects model ($I^2 < 50\%$) to calculate the combined results. Metaninf and meta-regression were used to explore the sources of heterogeneity.

Results

1. Articles included

The initial search resulted in 1792 records from the Cochrane Library, Embase, and PubMed. Among them, 687 studies were deleted as duplicate records, and 65 potential studies were identified as full-text reviews. Among them, the single-arm test was excluded because of the lack of a control group. Nine RCTs involving 4754 patients met the inclusion criteria and were included in this meta-analysis. Figure 2 details the selection process. Publication bias detection was performed for OS analysis. The funnel plot showed there may be incomplete symmetry; therefore, we conducted the Egger's test (Figure 3(a)). The Egger's test ($|P| = 0.656 > 0.05$) showed no publication bias.

Effectiveness

OS of Nivolumab plus Ipilimumab or Nivolumab alone

Compared with chemotherapy, Nivolumab monotherapy benefited OS (Figure 4(a), HR: 0.78, 95% CI: 0.65–0.94, $I^2=71.4\%$, $P=0.007$), and the combination of Nivolumab and Ipilimumab also had a beneficial effect compared with that of Nivolumab monotherapy (Figure 4(a), HR: 0.96, 95% CI: 0.85–1.08, $I^2=0.0\%$, $P=0.726$). A direct comparison using ICT showed the OS of Nivolumab and Ipilimumab combination therapy compared with that of chemotherapy (HR: 0.75, 95% CI: 0.60–0.93). Heterogeneity of the Nivolumab monotherapy group was $I^2 > 50\%$. Sensitivity analysis was performed, which suggested that Carbone's (2019) study may be the source of heterogeneity (Figure 3(b-OS)). Acceptable heterogeneity was obtained when Carbone's (2019) study was excluded (Figure 4(b), HR: 0.73, 95% CI: 0.64–0.83, $I^2=31.4\%$, $P=0.224$). A direct comparison using ICT showed the OS of Nivolumab and Ipilimumab combination therapy compared with that of chemotherapy (HR: 0.70, 95% CI: 0.60–0.84).

PFS of Nivolumab plus Ipilimumab and Nivolumab alone

Compared with chemotherapy, Nivolumab monotherapy benefited PFS (Figure 5(a), HR: 0.87, 95% CI: 0.72–1.05, $I^2=73.0\%$, $P=0.005$), and the combination of Nivolumab and Ipilimumab also was beneficial compared with that of Nivolumab monotherapy (Figure 5(a), HR: 0.86, 95% CI: 0.76–0.98, $I^2=21.3\%$, $P=0.282$). A direct comparison using ICT showed the PFS of Nivolumab and Ipilimumab combination therapy compared with that of chemotherapy (HR: 0.75, 95% CI: 0.60–0.93). The heterogeneity of the Nivolumab monotherapy groups was $I^2 > 50\%$. Sensitivity analysis was performed, suggesting that Carbone's (2019) study may be the source of heterogeneity (Figure 3(b-PFS)). Acceptable heterogeneity was obtained when Carbone's (2019) study was excluded (Figure 5(b), HR: 0.81, 95% CI: 0.69–0.94, $I^2=46.6\%$, $P=0.131$). A direct comparison using ICT showed the PFS of Nivolumab and Ipilimumab combination therapy compared with that of chemotherapy (HR: 0.70, 95% CI: 0.57–0.85).

ORR of Nivolumab plus Ipilimumab or Nivolumab alone

The Nivolumab monotherapy group had a higher ORR than the chemotherapy group (Figure 6, RR:1.43, 95% CI: 0.91–2.25, $I^2=85.4\%$, $P=0.000$), and the ORR of Nivolumab combined with Ipilimumab was higher than that of Nivolumab monotherapy (Figure 6, RR: 1.38, 95% CI: 1.12–1.70, $I^2=12.2\%$, $P=0.332$). A direct comparison using ICT showed the ORR of Nivolumab and Ipilimumab combination therapy compared with that of chemotherapy (RR: 1.97, 95% CI: 1.20–3.25). The heterogeneity of the Nivolumab monotherapy groups was $I^2>50\%$. We failed to find the source of heterogeneity by sensitivity analysis (Figure 3(c-ORR)). Meta-regression was conducted to detect the source of heterogeneity, which may be related to the PS score of patients in the study. Meta-regression results showed the more people with a high PS score in a given study, the better the ORR.

Subgroup Meta-analysis

The HRs in this analysis of OS favored immunotherapy across most prespecified subpopulations; the exception was the small cell lung cancer subpopulations (Figure 7). Similar results were shown in the PFS analysis (Figure 7).

3. Safety analysis

Compared with chemotherapy grade, Nivolumab exhibited statistical significance in all grades of AEs, high-grade AEs (Table 2), and compared with Nivolumab, Nivolumab combined with Ipilimumab exhibited statistical significance in all grades of AEs and high-grade AEs (Table 3). The overall results showed that the Nivolumab plus Ipilimumab group had a higher risk of adverse events and the Nivolumab group had a lower risk.

Discussion

This study reports the results of a meta-analysis. Compared with chemotherapy, Nivolumab monotherapy or combination therapy with Ipilimumab has better efficacy. Additionally, compared with Nivolumab monotherapy, combination therapy had better efficacy. Nivolumab resulted in a significantly longer OS and a higher response rate. Furthermore, the Nivolumab group showed acceptable safety compared with the Ipilimumab combination group or the chemotherapy group.

In recent years, research on immune checkpoint inhibitors of PD-1, PDL1, and CTLA-4 have become a hot topic in the field of cancer because of their remarkable efficacy in prolongation of the survival of patients with non-small cell lung cancer, melanoma, and renal cell carcinoma^[16,17]. In the PD-1/PD-L1 pathway, PD-1 can be expressed on T cells, B lymphocytes, and natural killer (NK) cells, among others^[9,18]. They combine with PD-L1 and PD-L2, resulting in T cell response in the tumor microenvironment^[19]. A variety of tumor cells can express PDL1, and PD-1 binds to PDL1 to inhibit CD8 cytotoxic immune response and anti-tumor immune response, resulting in tumor immune tolerance^[20]. Previous studies have found that PD-1 inhibitors are meaningful and safe for the survival of lung cancer patients^[21]. The expression of PD-L1 is a predictive biomarker of ORR for advanced NSCLC using PD-1/PD-L1 inhibitors^[22]. The CD28/CTLA-4 immunomodulatory system exists when CTLA-4 combines with B7 molecule antigen-presenting cells (APC), which can reduce T cell activity and prevent T cell activation channels from exerting immunosuppressive effects in tumors^[23].

Nivolumab and Ipilimumab were the first combination of PD-1/CTLA-4, which has shown safety and superior efficacy in metastatic melanoma^[15]. Long-term follow-up results from CheckMate 067^[24] showed that Nivolumab monotherapy or combination therapy with Ipilimumab improved patients' ORR, PFS, and OS. The 3-year and 4-year survival rates in the Nivolumab + Ipilimumab group were 58% and 53%, respectively. In Amr Menshaw's study^[25], Nivolumab alone or in combination with Ipilimumab was more effective than Ipilimumab alone or chemotherapy in melanoma patients. Nivolumab resulted in a significantly longer PFS and a higher response rate. The Nivolumab group showed acceptable safety compared with the Ipilimumab and chemotherapy groups. In 2016, Nivolumab and Ipilimumab were approved in the United States and the European Union for the treatment of non-primary melanoma. Clinical trials of combined immunotherapy in melanoma, lung cancer, and kidney cancer are still ongoing.

The MYSTIC [26] trial is a phase III trial of patients with lung cancer that uses the same strategy but different drugs, such as Durvalumab (anti-PD-L1) and Tremelimumab (anti-CTLA-4) as first-line therapy. This experiment included 1118 patients, and the median OS was 11.9 months (95% CI, 9.0–17.7) with Durvalumab plus Tremelimumab (HR vs. chemotherapy, 0.85; 98.77% CI, 0.61–1.17; P=0.20). Median PFS was 3.9 months (95% CI, 2.8–5.0) with Durvalumab plus Tremelimumab vs 5.4 months (95% CI, 4.6–5.8) with chemotherapy (HR, 1.05; 99.5% CI, 0.72–1.53; P=0.71). ARCTIC [27] is another clinical trial evaluating the combination of Durvalumab and Tremelimumab compared to SOC chemotherapy. The results of the two studies suggested that Durvalumab alone or in combination with Tremelimumab had clinically significant improvement in OS and PFS compared with SOC. Safety was similar to that of previous studies.

Combination therapy seems to be the best strategy. However, we should also endeavor to find biomarkers, such as absolute lymphocyte count and tumor-infiltrating T cells to predict treatment response, which will not only contribute to the development of immunotherapy but may also achieve personalization of treatment.

CheckMate 568 (NCT02659059) [28] is a large single-arm phase 2 study of first-line Nivolumab plus Ipilimumab in the treatment of NSCLC. The primary endpoint was the objective mitigation rate (ORR) reviewed independently, and the secondary endpoint was the ORR analysis of TMB. The results showed that $TMB \geq 10$ mut/Mb was related to the enhancement of the Nivolumab plus Ipilimumab treatment response regardless of the expression level of PD-L1, having an ORR > 40% [28]. Although TMB was measured in three experiments in this study, the defining point of TMB could not be unified; therefore, this study did not conduct a summary analysis of TMB.

Some of the results of our study were heterogeneous. In studies on OS and PFS, we found that the results were homogeneous after the elimination of the Carbone (2019) [31] study. Heterogeneity may be mainly derived from clinical heterogeneity. Compared with other studies (Brahmer (2015) [30], Borghaei (2015) [29], Wu (2019) [34], Hellmann (2019) [32]), docetaxel was not used in the control group in the Carbone (2019) study. The baseline characteristics of the patients were also different. In the Carbone (2019) study, 78.2% of people had PD1 expression $\geq 5\%$, which was higher than that in other studies (Brahmer, 2015; Borghaei, 2015; Wu, 2019; Hellmann, 2019). Additionally, fewer people in the study had an ECOG PS ≥ 1 . Similar to other meta-analyses, our study had some limitations. The data were extracted from the summary data, not from individual patients in each trial. Therefore, the results of this analysis need to be treated with caution.

Conclusion

Nivolumab was beneficial to patients with lung cancer, whether in monotherapy or combination therapy.

Abbreviations

PD-1: programmed cell death-1; CTLA-4: cytotoxic T lymphocyte-associated antigen 4; RR: Relative risk; OR: Odd ratio; HR: Hazard ratio; CI: Confidence intervals.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

All data generated or analysed during this study are included in this published article.

Competing Interests

The authors declare no competing financial interests.

Funding

Not applicable.

Author contributions

Ran Wang and Sijing Zhou designed and supervised the study. Huihui Jiang, Aiqun Xu and Wanli Xia drafted the manuscript, carried out the literature search, and extracted the data from the eligible studies. Xingyuan Xia, Pulin Li, Binbin Zhang, Ke Zhu contributed to the quality control of study inclusion and discussion. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Tables

Table 1. Quality assessment by the Cochrane Collaboration's tool							
Reference	Random Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Borghaei, H(2015)	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk
Brahmer, J. (2015)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Carbone, D. P. (2017)	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk
Hellmann,M.D(2019)	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk
Ready, N. E.(2020)	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk
Wu, Y. L.(2019)	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Hellmann,M.D(2017)	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Bazhenova, L(2019)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Owonikoko, T(2019)	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk

Table2. Pooled relative risk of all grade and high grade irAEs for nivolumab vs chemotherapy									
All grade irAEs	No. of trials	Pooled RR (95% CI)	Pooled RR	p Value	High grade irAEs	No. of trials	Pooled RR (95% CI)	Pooled RR	p Value
Total incidence	4	0.728-0.805	0.765	0.000	Total incidence	4	0.149-0.324	0.220	0.000
Discontinuation	1	0.454-1.180	0.732	0.200	Discontinuation	1	0.657-2.254	1.217	0.533
Fatigue	4	0.440-0.627	0.525	0.000	Fatigue	4	0.103-0.418	0.208	0.000
Rash	3	0.647-4.516	1.71	0.279	Rash	3	0.248-5.904	1.210	0.814
Nausea	3	0.221-0.534	0.344	0.000	Nausea	3	0.107-1.447	0.394	0.160
Vomiting	1	0.144-0.422	0.246	0.000	Vomiting	1	0.005-1.611	0.090	0.102
Decreased appetite	4	0.345-0.643	0.471	0.000	Decreased appetite	4	0.071-1.387	0.315	0.127
Constipation	1	0.148-0.633	0.306	0.001	Constipation	1	0	0	0
Diarrhea	3	0.231-1.172	0.52	0.115	Diarrhea	3	0.178-1.424	0.504	0.196
Pneumonia	1	0.729-224.957	12.803	0.081	Pneumonia	1	0	0	0
Arthralgia	1	0.294-1.995	0.766	0.585	Arthralgia	1	0	0	0
Neutrophil count decreased	2	0.018-0.111	0.045	0.000	Neutrophil count decreased	2	0.004-0.149	0.025	0.000
Neutropenia	4	0.005-0.144	0.028	0.000	Neutropenia	4	0.005-0.066	0.019	0.000
Anemia	4	0.075-0.161	0.11	0.000	Anemia	4	0.024-0.228	0.075	0.000
Leukopenia	3	0.028-0.435	0.11	0.002	Leukopenia	3	0.012-0.225	0.053	0.000
WBC count decreased	1	0.059-0.225	0.116	0.000	WBC count decreased	1	0.113-0.253	0.169	0.000

Table3. Pooled relative risk of all grade and high grade irAEs for combination vs nivolumab.									
All grade irAEs	No. of trials	Pooled RR (95% CI)	Pooled RR	p Value	High grade irAEs	No. of trials	Pooled RR (95% CI)	Pooled RR	p Value
Total incidence	3	1.088-1.265	1.173	0.000	Total incidence	3	1.389-2.836	1.984	0.000
Discontinuation	3	0.880-3.699	1.804	0.107	Discontinuation	2	1.025-5.220	2.313	0.043
Fatigue	3	0.737-1.651	1.103	0.634	Fatigue	3	0.735-8.608	2.515	0.142
Pruritis	3	1.354-2.568	1.865	0.000	Pruritis	3	0.245-91.337	4.731	0.304
Rash	3	0.708-1.935	1.171	0.539	Rash	3	0.533-3.968	1.454	0.465
Hyperthyroidism	1	0.947-13.480	3.573	0.060	Hyperthyroidism	1	0.188-111.215	4.577	0.350
Hypothyroidism	2	1.243-2.795	1.864	0.003	Hypothyroidism	2	0.124-14.921	1.358	0.803
Elevated lipase	1	0.862-5.550	2.188	0.099	Elevated lipase	1	0.758-19.335	3.828	0.104
Nausea	3	1.164-2.514	1.711	0.006	Nausea	3	0.862-9.813	2.908	0.085
Vomiting	3	0.968-4.509	2.089	0.061	Vomiting	3	0.232-10.670	1.573	0.643
Decreased appetite	2	1.388-3.077	2.067	0.000	Decreased appetite	2	0.187-15.222	1.687	0.641
Elevated AST	1	0.862-5.550	2.188	0.099	Elevated AST	1	0.758-19.335	3.828	0.104
Constipation	1	1.069-6.332	2.602	0.035	Constipation	1	0	0	0
Diarrhea	3	1.067-4.345	2.153	0.032	Diarrhea	3	0.578-10.444	2.456	0.224
Pneumonitis	2	0.673-4.696	1.778	0.245	Pneumonitis	2	0.463-6.106	1.681	0.430
Arthralgia	1	0.364-2.694	0.99	0.984	Arthralgia	1	0	0	0

Figures

Summary of the studies included

Author	Year	Study Name/ID	Design	Arms (n)	Histological Type	mPFS	mOS
Borghaei ^[29]	2015	CheckMate057, NCT01673867	Randomized, open-label, phase III study	Nivo3 q2wks (292) vs Doc 75 mg/m ² q3wks (290)	nsNSCLC	2.3 (2.2–3.3) 4.2 (3.5–4.9)	12.2 (9.7–15.0) 9.4 (8.1–10.7)
Brahmer ^[30]	2015	CheckMate017, NCT01642004	Randomized, open-label, phase III study	Nivo3 q2wks (135) vs Doc 75 mg/m ² q3wks (137)	SqNSCLC	3.5 (2.1–4.9) 2.8 (2.1–3.5)	9.2 (7.3–13.3) 6.0 (5.1–7.3)
Carbone ^[31]	2017	CheckMate026, NCT02041533	Randomized, open-label, phase III study	Nivo3 q2wks (271) vs Chem q3wks for 4-6 cycles (270)	NSCLC	4.2(3.1-5.5) 5.8(5.4-6.9)	13.7(11.8-15.4) 13.8(11.0-17.0)
Hellmann ^[32]	2019	CheckMate227, NCT02477826	Randomized, open-label, phase III study	Nivo3 q2wks+ipi1 q6wks (576) vs Nivo 240mg q2wks (391) vs Chem (570)	NSCLC	5.1(4.1-6.3) 4.2(3.0-5.6) 5.6(4.6-5.8)	17.1(15.0-20.1) 15.7(13.3-18.1) 14.9(12.7-16.7)
Ready ^[33]	2020	CheckMate032, NCT01928394	Randomized, open-label, phase I/II study	Nivo1 + ipi3 q3ws for four cycles vs nivo3 mg/kg every q2ws	SCLC	1.5 (1.4-2.2) 1.4 (1.3–1.4)	4.7 (3.1-8.3) 5.7 (3.8–7.6)
Wu, ^[34]	2019	CheckMate078, NCT02613507	Randomized, open-label, phase III study	Nivo3 q2wks (338) vs Doc75 mg/m ² q3wks (166)	NSCLC	2.8 (2.4–3.4) 2.8 (1.6–2.9)	12.0 (10.4–14.0) 9.6 (7.6–11.2)
Hellmann ^[35]	2017	CheckMate012, NCT01454102	Randomized, open-label, phase I study	Nivo3 q2ws + ipi1 q12ws (38) vs nivo3 q2ws + ipi1 q6ws (39) vs nivo3 q2ws (52)	NSCLC	8.1 (5.6-13.6) 3.9 (2.6-13.2) 3.6 (0.1+ to 28.0+)	9.4 (3.6-12.8) 3.9 (2.6-13.2) 19.4 (0.2 to 35.8+)
Bazhenova ^[36]	2019	Lung-MAP S1400I, NCT02785952	Randomized, open-label, phase III study	Nivo3 q2ws + ipi1 q6ws (125) vs nivo3 q2ws (127)	SqNSCLC	3.8 (2.3-4.2) 2.9 (1.8-3.9)	10.0 (8.0-12.8) 11.0 (8.2-13.5)
Owonikoko ^[37]	2019	CheckMate 451, NCT02538666	Randomized, open-label, phase III study	Nivo1 q3ws + ipi3 q3ws (279) Vs nivo240mg q2ws (280) vs placebo :(275)	ED-SCLC	- - -	- - -

Plus symbol (+) indicates a censored value; nsNSCLC: Nonsquamous Non-Small-Cell Lung Cancer; SqNSCLC: Squamous-Cell Non-Small-Cell Lung Cancer; NSCLC: Non-Small-Cell Lung Cancer; SCLC: small cell lung cancer ; ED-SCLC: extensive disease small cell lung cancer; ipi1: ipilimumab 1mg/kg, ipi3: ipilimumab 3mg/kg, nivo1: nivolumab 1mg/kg, nivo3: nivolumab 3mg/kg;

Figure 1

Studies included in this article.



PRISMA 2009 Flow Diagram

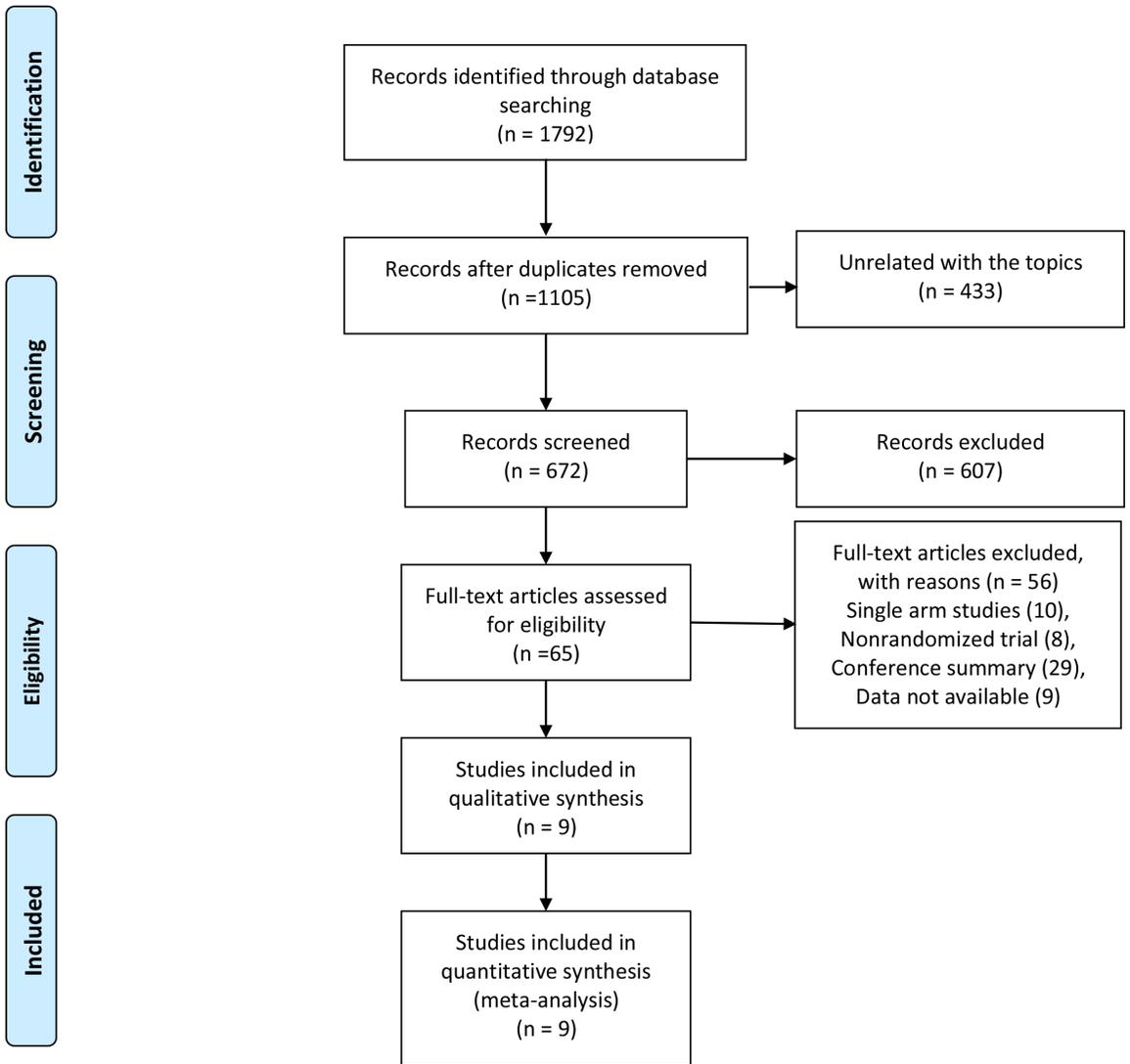


Figure 2

Flow diagram of the literature search and trial selection process.

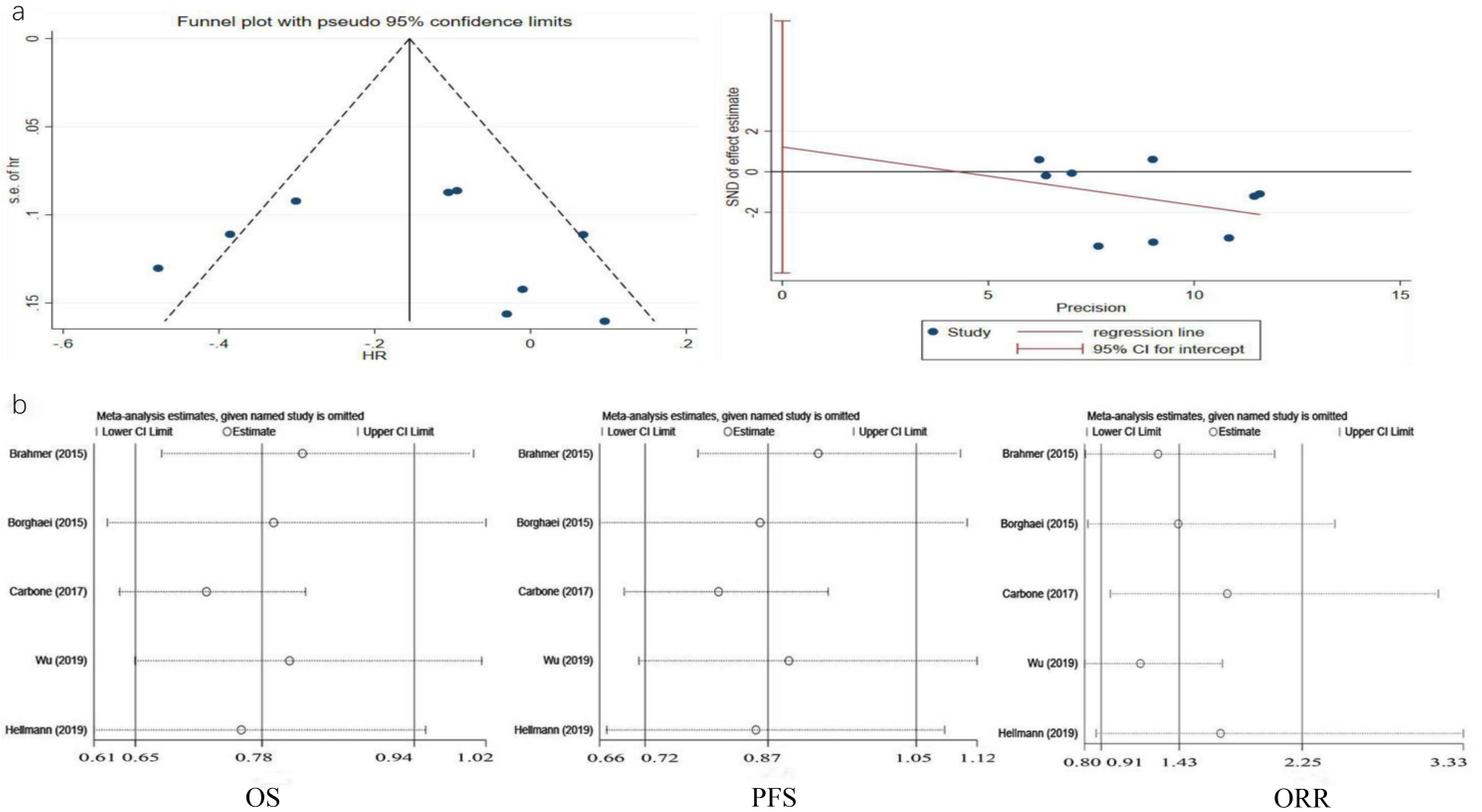
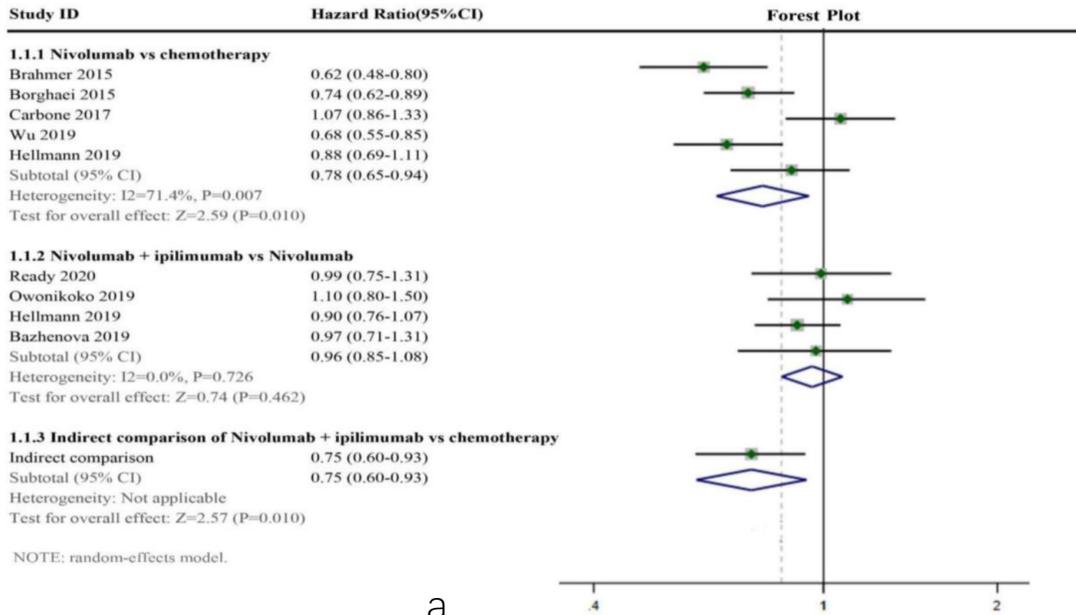
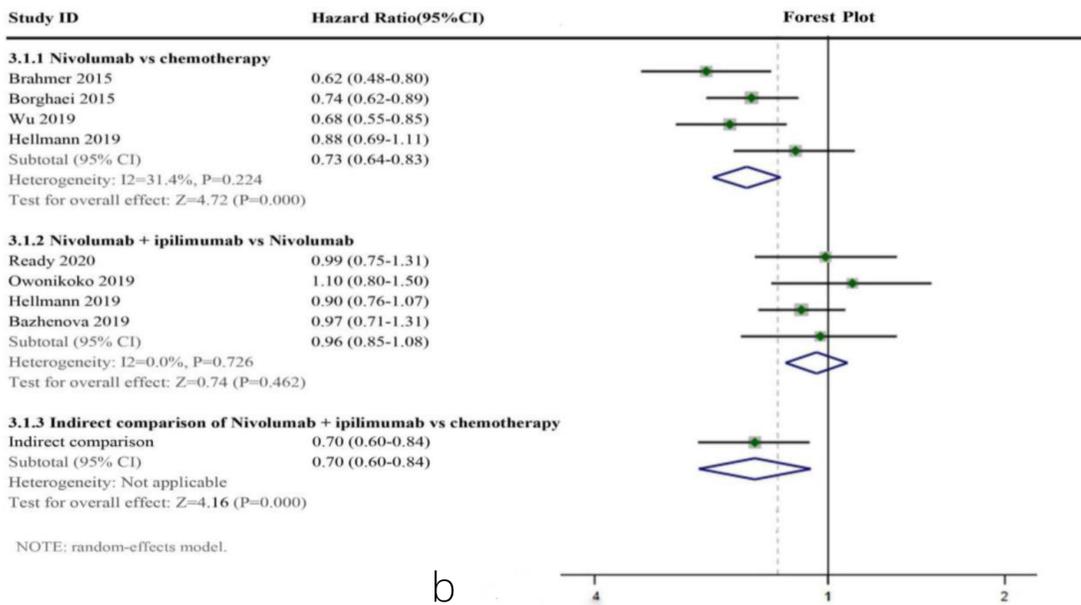


Figure 3

Publication bias and sensitivity analysis. (A) Detection of publication bias; (a) funnel plot; (b) Egger's test; (B) sensitivity analysis of overall survival, progression-free survival, and objective response rate. (a) Nivolumab monotherapy versus chemotherapy in OS; (b) Nivolumab monotherapy versus chemotherapy in PFS; (c) Nivolumab monotherapy versus chemotherapy in ORR.



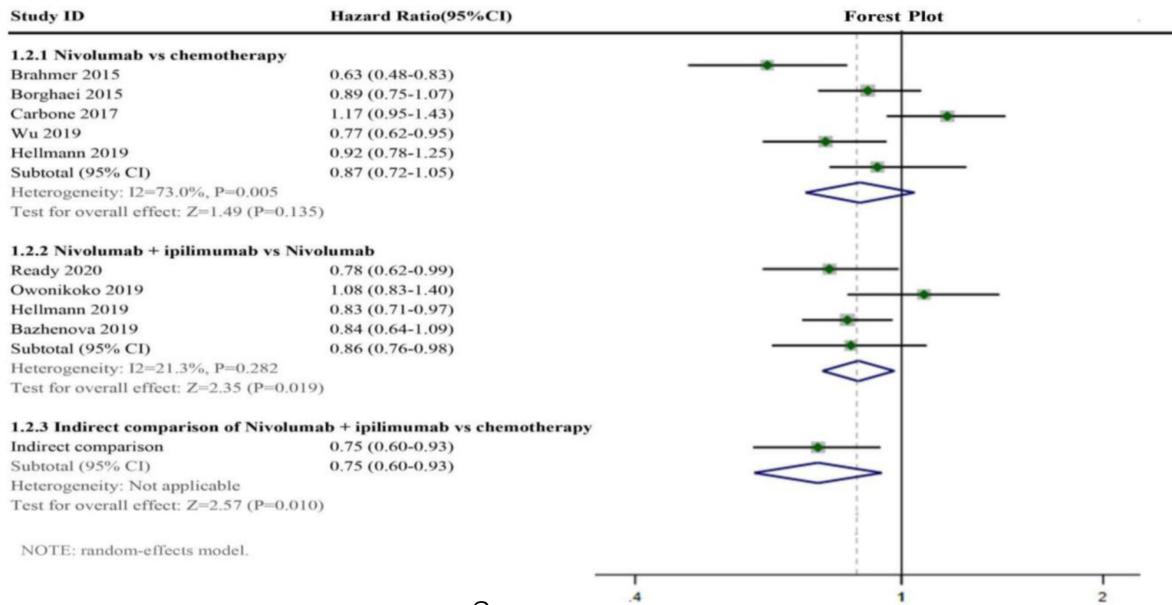
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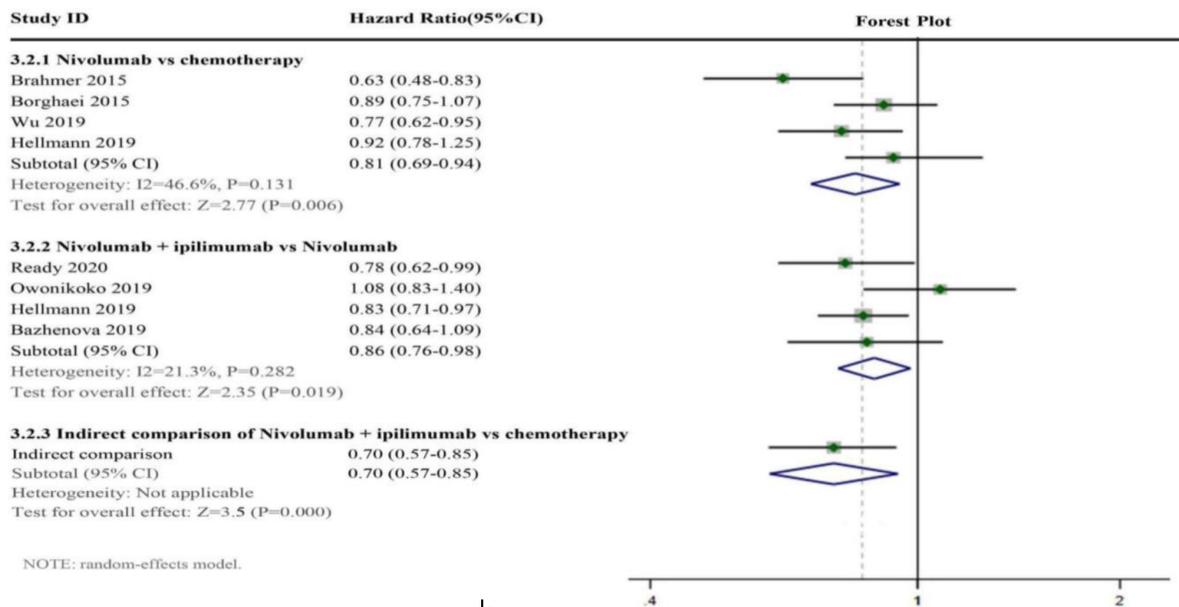
b

Figure 4

Forest plots of overall survival (OS). (A) Forest plots of overall survival (OS) for Nivolumab alone or in combination with Ipilimumab; CI, confidence interval; (B) Forest plots of OS for Nivolumab alone or in combination with Ipilimumab after removing one study; CI, confidence interval.



a



b

Figure 5

Forest plots of progressive-free survival (PFS). (A) Forest plots of PFS for Nivolumab alone or in combination with Ipilimumab; CI, confidence interval; (B) Forest plots of PFS for Nivolumab alone or in combination with Ipilimumab after removing one study; CI, confidence interval.

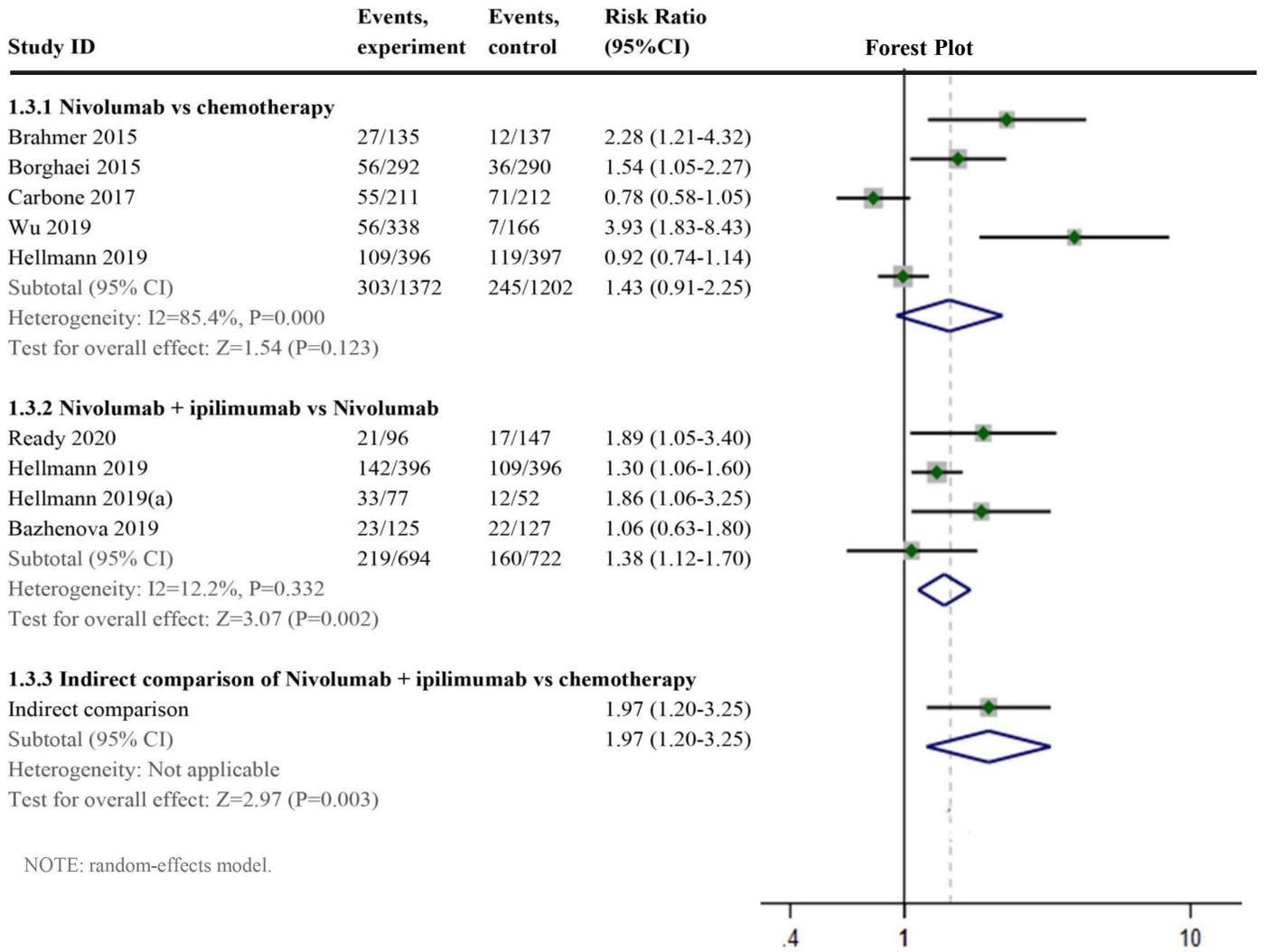


Figure 6

Forest plots of objective response rate (ORR). Forest plots of ORR for Nivolumab alone or in combination with Ipilimumab; CI, confidence interval.

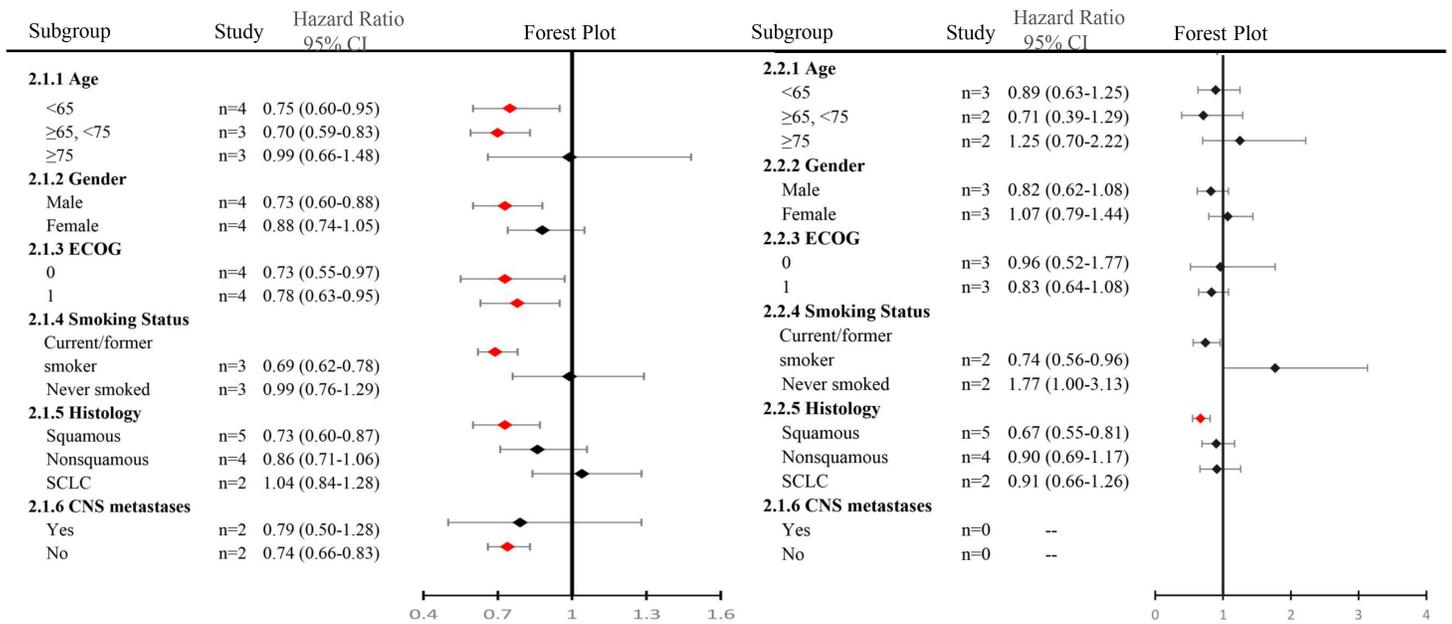


Figure 7

Subgroup meta-analysis of progression-free survival (PFS) and overall survival (OS). (2.1) Nivolumab alone or in combination with Ipilimumab versus chemotherapy in PFS; (2.2) Nivolumab alone or in combination with Ipilimumab versus chemotherapy in OS. CI: 95 % confidence interval.