The efficacy and safety of combined immune checkpoint inhibitors (nivolumab plus ipilimumab): a systematic review and meta-analysis

Lihu Gu

Ningbo No 2 Hospital

Shengnan Li

Zhejiang Chinese Medical University

Nannan Du

Zhejiang Chinese Medical University

Qigu Yao

Zhejiang University First Affiliated Hospital State Key Laboratory for Diagnosis and Treatment of Infectious Diseases

Xiaojun Fu

Ningbo No 2 Hospital

Yuanmei Lou

Zhejiang Chinese Medical University

Mengru Wang

Kaifeng University

Feiyan Mao

Ningbo No 2 Hospital

Danyi Mao

Zhejiang Chinese Medical University

Parikshit Asutosh Khadaroo

Monash University Faculty of Medicine Nursing and Health Sciences

Yingying Tang (✉ ningbohwamei@163.com)

Ningbo No 2 Hospital

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Abstract

Background: Currently, nivolumab and ipilimumab are the most widely used immune checkpoint inhibitors. We performed a meta-analysis to evaluate the efficacy and treatment-related adverse events (TRAEs) of nivolumab-ipilimumab combination therapy in cancer treatment.

Methods: We examined data from PubMed, Web of science, EBSCO and Cochrane library. Eleven articles fulfilled our criteria, which we divided into 3 groups; nivolumab and ipilimumab versus ipilimumab, nivolumab and ipilimumab versus ipilimumab and nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (N1I3) versus nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (N3I1). We measured the complete response (CR), partial response (PR), objective response rate (ORR) and TRAEs in any grade and grade 3 or higher.

Results: Compared with ipilimumab alone, the combined immunotherapy had better CR (RR: 4.89, $p < 0.001$), PR (RR: 2.75, $p < 0.001$), and ORR (RR: 3.31, $p < 0.001$). The overall effect estimate favored the combined immunotherapy group in terms of the ORR (RR: 1.40, $p < 0.001$) and PR (RR: 1.50, $p < 0.001$) than nivolumab alone. Finally, N1I3 showed better PR (RR: 1.35, $p = 0.006$) and ORR (RR: 1.21, $p = 0.03$) than N3I1. The incidence of any TRAEs was similar between the both groups (RR: 1.05, $p = 0.06$). However, the incidence of serious adverse events (grade 3 or higher) were lower in group N3I1 than group N1I3 (RR: 1.51, $p < 0.001$).

Conclusion: This meta-analysis showed that the curative effect of nivolumab plus ipilimumab was better than that of ipilimumab or nivolumab monotherapy. In the combination group, N1I3 combination was more effective than N3I1. Although the side effects were slightly increased in group N1I3, the overall safety was acceptable.

Background

Cytotoxic T lymphocyte associated protein 4 (CTLA-4) is a receptor on the surface of activated T cells[1]. It mainly acts by binding B7 ligands on antigen presenting cells (APCs). The protein compete with the cluster of differentiation 28 (CD28) receptor for B7 ligands. During T cell activation, CD28 receptors on T-cells bind to B7 ligands on antigen presenting cells (APCs) and provide the essential second activation signal for T-cells[2–4]. Programmed cell death protein 1 (PD-1) is a cell-surface receptor commonly found in T cells, B cells and NK cells[5]. By inhibiting the phosphatidylinositol 3-kinase (PI3K) pathway, PD-1 signaling inhibits the activation of the cell survival factor Bcl-xL and the expression of transcription factors such as GATA-3, T-bet and Eomes[6], that regulate T cell functions. The CTLA-4 and PD-1, two common immuno-checkpoint inhibitors (ICIs) on activated T cells, are the most reliable targets for cancer treatment. To date, seven drugs targeting CTLA-4/PD-1 have been approved for treatment of different types of cancer, including melanomas[7], lung [8], breast [9], cervical [10] and liver cancer[11].

In clinical studies, CTLA-4 and PD-1 monotherapy inhibitors have shown impressive, lasting effects, that have significantly prolong the survival of responsive patients[12, 13]. For example, colorectal cancer (CRC) is the third most common cancer in the United States. Despite advances in chemotherapy, survival

rates in patients with metastatic CRC remains low. However, CRC patients treated with immuncheckpoint inhibitors showed better response[14]. Hepatectomy is an important method to treat liver cancer, but up to 70% of patients may have a recurrence of liver diseases within 5 years, even after receiving treatment for hepatocellular carcinoma (HCC) at early stage. However, Immunotherapy has recently been shown to be effective against HCC, marking a milestone in the history of this intractable disease[15]. Unfortunately though, the efficacy of immune-monotherapy is limited by low response rates, with only a small proportion of patients responding to treatment[13]. For example, more than 50% of patients with metastatic melanoma did not respond to monotherapy[16]. Fortunately, a combination therapy (nivolumab with ipilimumab) has demonstrated numerically higher response rates and improved long-term clinical benefit relative to anti-PD-1/PD-L1 or anti-CTLA-4 monotherapy [14]. Combinations of immunotherapies is one of the most promising new methods. Presently, nivolumab and ipilimumab are the most widely used immune checkpoint inhibitors against cancer [17]. This meta-analysis aimed at investigating the role of nivolumab-ipilimumab combination therapy in cancer treatment.

Materials And Methods

Search and Selection

We did a meta-analysis of relevant articles, published before by June 2019. We searched through four electronic databases; PubMed, Web of science, EBSCO and Cochrane library for data with relevant clinical trials, based on these key words; (nivolumab OR PD-1 OR programmed death 1) and (ipilimumab or CTLA-4 or cytotoxic T-lymphocyte-associated protein 4).

Selection Criteria

Studies in the selected articles were to meet four criteria; (1) Participants: solid tumor patients receiving combined ICIs (nivolumab and ipilimumab); (2) Intervention: combined ICIs including nivolumab and ipilimumab simultaneously; (3) Comparisons: nivolumab or ipilimumab alone; (4) Outcomes: objective response rate (ORR), partial response rate (PR), complete response (CR), and treatment-related adverse events (TRAEs), otherwise they were excluded.

Data Extraction

We focused on trial phases, tumor types, the number and characteristics of participants, the anti-tumour agents, dosage and frequency of drug administration with a keen interest on the prognoses, specifically the ORR, CR, and PR. The curative effects were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST). Incidence of TRAEs, including any grade and grade 3 or higher was also evaluated, based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE).

Quality Assessment

We evaluated the quality of data in the relevant articles using the Cochrane Collaboration tool based on the following domains; allocation concealment, masking of outcome assessors, blinding of participants, incomplete follow-up, and selective outcome reporting.

Statistical analysis

Statistical analyses were done by Review Manager software (RevMan5.3), at 95% confidence intervals (CI). Subgroup analyses were done based on the intervention; nivolumab plus ipilimumab versus ipilimumab alone, nivolumab plus ipilimumab versus nivolumab alone, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (N1I3) versus nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (N3I1). All analyses (ORR, CR, PR, and all-grade and serious grade (grade 3–5) TRAEs) were performed based on the fixed/random-effect. For meta-analysis, we used risk ratios (RR) to compare dichotomous variables. Heterogeneity in the meta-analysis results was done using the I-square (I^2) test. Statistically significant was measured at P values of 0.05.

Results

Literature search

We identified 4361 studies in the literature search. We removed 2133 duplicates and further 2228 after careful evaluation. Although 56 articles met the inclusion criteria, 45 were removed besides qualifying for meta-analysis for a number of reasons. Some did not include the combination of nivolumab plus ipilimumab or non-prospective clinical trials while others did not include treatments, single arm study or did not have relevant outcome. In the end, 11 articles[18–28] qualified for the meta-analysis (Supplementary Fig. 1).

Study Characteristics

The characteristics of each study are shown in Supplementary Table 1. The 11 clinical trials included 2484 patients. Of these 879 received nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (N1I3), 560 received nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (N3I1), 688 received nivolumab alone, while 357 were put on ipilimumab alone. The selected studies had varied cases, from melanoma, metastatic urothelial carcinoma, small cell lung cancer (SCLC), esophagogastric cancer (EGC), malignant pleural mesothelioma (MPM), renal cell carcinoma (RCC), sarcoma, glioblastoma. There were two phase I clinical trials, two phase I-II clinical trials, four phase II clinical trials, two phase III clinical trials and one phase III-IV clinical trials.

Nivolumab Plus Ipilimumab Versus Ipilimumab Alone

Compared with ipilimumab alone, nivolumab-ipilimumab synergy caused a greater effect under CR (RR: 4.89, 95% CI: 2.91–8.23, $p < 0.001$), PR (RR: 2.75, 95% CI: 2.05–3.69, $p < 0.001$) and ORR (RR: 3.31, 95% CI: 2.60–4.20, $p < 0.001$) as shown in Fig. 1. Although incidence of any TRAEs was similar between the two groups (RR: 1.05, $p = 0.44$), ipilimumab monotherapy resulted in less serious cases, (grade 3 or higher) than nivolumab-nivolumab combination group (RR: 2.16, 95% CI: 1.78–2.61, $p < 0.001$) as shown in Fig. 2.

Nivolumab Plus Ipilimumab Versus Nivolumab Alone

Overall, nivolumab-ipilimumab combination showed better ORR (RR: 1.40, 95% CI: 1.22–1.61, $p < 0.001$) and PR (RR: 1.50, 95% CI: 1.23–1.83, $p < 0.001$) than nivolumab alone, however, there was no statistically significant difference in the CR (RR: 1.13, $p = 0.39$) between the two as shown in Fig. 3.

In terms of adverse effects, incidence of any TRAEs and serious TRAEs were elevated in nivolumab monotherapy than in nivolumab- ipilimumab combination (RR: 1.10, 95% CI: 1.00–1.21, $p = 0.04$; RR: 2.10, 95% CI: 1.57–2.81, $p < 0.001$, respectively) as shown in Fig. 4.

N1I3 Versus N3I1

Since the combined therapeutic effect was better than that of monotherapies, subgroup analysis of the combination therapy was further investigated. The N1I3 group showed better PR (RR: 1.35, 95% CI: 1.09–1.68, $p = 0.006$) and ORR (RR: 1.21, 95% CI: 1.02–1.44, $p = 0.03$), while there was no significant difference in CR (RR: 0.83, $p = 0.40$) between the two subgroups as shown in Fig. 5. There was no difference in TRAEs between the two groups as well (RR: 1.05, $p = 0.06$), however, N1I3 produced more serious adverse events (grade 3 or higher) than group N3I1 (RR: 1.51, 95% CI: 1.27–1.78, $p < 0.001$) as shown in Fig. 6).

Specific adverse treatment events by subgroup were also analyzed. Incidences of any grade adverse events were more elevated in group N1I3. These include increased alanine aminotransferase (ALT) (RR: 1.48, $p = 0.02$), increased aspartate aminotransferase (AST) (RR: 1.68, $p = 0.004$), diarrhea (RR: 1.47, $p = 0.005$), hypothyroidism (RR: 1.40, $p = 0.04$) and vomiting (RR: 1.77, $p = 0.02$). As shown in Table 1, Adverse reactions, such as high ALT (RR: 2.25, $p = 0.006$) and diarrhea ((RR: 2.90, $p < 0.001$), of grade 3 or above, were also high in group N1I3 than in group N3I1.

Table 1
Subgroup analysis of the treatment-related adverse events (TRAEs)

NIVO1 + IPI3 vs. NIVO3 + IPI1	No. of studies	RR	95%CI	p	Effect model	Heterogeneity	
						(I ²)	p
Any grade increased ALT	6	1.48	1.06–2.06	0.02	Fixed	33%	0.19
Any grade increased AST	6	1.68	1.18–2.39	0.004	Fixed	41%	0.13
Any grade in pruritus	6	1.09	0.87–1.37	0.46	Fixed	0%	0.53
Any grade in diarrhoea	6	1.47	1.18–1.83	0.005	Fixed	23%	0.26
Any grade in fatigue	6	1.06	0.88–1.29	0.53	Fixed	19%	0.29
Any grade in nausea	5	1.34	0.99–1.81	0.06	Fixed	0%	0.63
Any grade in hypothyroidism	5	1.40	1.01–1.94	0.04	Fixed	0%	0.78
Any grade in decreased appetite	5	1.16	0.81–1.64	0.42	Fixed	11%	0.35
Any grade in vomiting	4	1.77	1.11–2.84	0.02	Fixed	27%	0.25
Any grade in rash	6	1.29	0.98–1.70	0.07	Fixed	19%	0.29
Grade 3 or higher increased ALT	6	2.25	1.26–4.00	0.006	Fixed	0%	0.45
Grade 3 or higher increased AST	6	1.89	0.91–3.91	0.09	Fixed	12%	0.34
Grade 3 or higher in pruritus	6	0.82	0.22–3.10	0.77	Fixed	0%	0.53
Grade 3 or higher in diarrhoea	6	2.90	1.63–5.15	< 0.001	Fixed	0%	0.85
Grade 3 or higher in fatigue	6	1.37	0.53–3.54	0.51	Fixed	19%	0.29
NIVO1 + IPI3, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, every 3 weeks for 4 doses (induction phase), followed by nivolumab 3 mg/kg, every 2 weeks until disease progression or unacceptable toxicity incidence of TRAEs (maintenance phase); NIVO3 + IPI1, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg, every 3 weeks for 4 doses (induction phase), followed by nivolumab 3 mg/kg, every 2 weeks until disease progression or unacceptable toxicity incidence of TRAEs (maintenance phase).							

NIVO1 + IPI3 vs. NIVO3 + IPI1	No. of studies	RR	95%CI	p	Effect model	Heterogeneity	
						(I ²)	p
Grade 3 or higher in nausea	5	2.45	0.71–8.51	0.16	Fixed	0%	0.41
Grade 3 or higher in vomiting	4	1.63	0.39–6.79	0.50	Fixed	0%	0.51
Grade 3 or higher in rash	6	1.69	0.39–7.26	0.48	Fixed	0%	0.51
NIVO1 + IPI3, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, every 3 weeks for 4 doses (induction phase), followed by nivolumab 3 mg/kg, every 2 weeks until disease progression or unacceptable toxicity incidence of TRAEs (maintenance phase); NIVO3 + IPI1, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg, every 3 weeks for 4 doses (induction phase), followed by nivolumab 3 mg/kg, every 2 weeks until disease progression or unacceptable toxicity incidence of TRAEs (maintenance phase).							

Discussion

Immunotherapy plays an important role in controlling tumors. Combined immunotherapy is based on the use of more than one immunotherapy. It can intervene and regulate multiple processes of immune response through [29], chemoradiotherapy [30–32] and targeted therapy [33, 34] by promoting anti-tumor immune response reduce the risk of drug resistance. The combination of immunotherapies is one of the most promising approaches being studied [35]. In particular, the combination of anti-PD-1 (nivolumab) and anti-CTLA-4 (ipilimumab) has shown positive results in tumor treatment and significant enhancement in patients with metastatic melanoma [36], advanced RCC [37], and metastatic CRC [16, 38]. Cope et al. reported that recurrent SCLC showed better response to nivolumab-ipilimumab compared to the current chemotherapy, interpreted as long-term survival benefits [39]. Ready et al. reported that a combination of nivolumab and low-dose ipilimumab was effective and tolerable as a first-line treatment of advanced/metastatic non-small cell lung cancer (NSCLC) [40]. Based on conditional survival analysis of first-line treatment, Shao [41] showed that patients with advanced RCC put on nivolumab plus ipilimumab therapy had high survival rate compared with sunitinib.

Recently, the combination therapy of ipilimumab and anti-PD-1 antibody showed promising clinical benefit in some malignant tumors [42], advanced melanoma [43], RCC and other tumors [44]. Combination therapy and ipilimumab or nivolumab monotherapy showed improved ORR, CR and PR [37, 41, 45, 46]. The present systematic review showed that the combination of nivolumab and ipilimumab had significantly high CR, PR and ORR compared with ipilimumab monotherapy. Complete response with nivolumab-ipilimumab therapy was 4.89 times higher than ipilimumab monotherapy, while the PR and ORR were 2.75 and 3.31 times than ipilimumab monotherapy, respectively. These findings show that the combination therapy was more effective than ipilimumab monotherapy. Elsewhere, Postow et al [26] reported that nivolumab-ipilimumab combination therapy had a higher ORR and progression-free survival rate compared with ipilimumab monotherapy, in treatment-naïve patients with advanced melanoma.

Increased response rate and improved progression-free survival was reported in ipilimumab-nivolumab combination when compared with ipilimumab alone in a randomized phase III trial in treatment-naïve patients with metastatic melanoma[47].

Nivolumab is a class of ICIs that PD-1 receptors that activate downstream signaling pathways by inducing FoxP3 expression[48] and promoting Treg (iTreg) cell differentiation[16]. The incidence of CR and PR and ORR in individuals on nivolumab-ipilimumab combination therapy was 1.13, 1.50 and 1.40 times respectively, as high than those on nivolumab monotherapy. These findings emphasize the effectiveness of the combination therapy. Antonia et al.[18] reported that nivolumab-ipilimumab combination therapy had a higher prolonged anti-tumour activity in previously treated patients than nivolumab monotherapy. Preliminary data on metastatic RCC, suggests that combination therapy had a higher ORR than nivolumab monotherapy in a different trials[20, 49]. Morse [14] reported that a combination therapy (nivolumab with low-dose ipilimumab) had numerically higher response rates and improved long-term clinical benefit relative to anti-programmed death-1 monotherapy. Principally CTLA-4 binds B7 ligands (B7-1/CD80 and B7-2/CD86) on antigen presenting cells that compete with the CD28 receptor[16]. The CTLA-4 protein and its B7 ligand are mainly expressed on immune cells, suggesting that CTLA-4 pathway plays a major role in lymph nodes. PD-L1, the PD-1 ligand, is widely expressed, mainly on regulatory peripheral T cells [50]. Although CTLA-4 and PD-1 antibodies are both checkpoint inhibitors, their action mechanisms are neither the same nor complementary[51]. Therefore, higher anti-tumor activity was seen with a combination therapy than ipilimumab or nivolumab[52].

Based on our analysis, we can conclude that the combination of nivolumab and ipilimumab is more effective than nivolumab alone, consistent with previous findings [18, 19]. In contrast, Kreft [53] showed that there was no difference in action and outcome between nivolumab monotherapy and ipilimumab-nivolumab combination therapy in patients with melanoma. Elsewhere, checkpoint monotherapy inhibitors targeting PD-1 and PD-L1 were not effective in metastatic colorectal cancer patients with microsatellite stable tumors[54].

Many combination immunotherapies have been developed, nivolumab-ipilimumab being the most common[55]. There are two dosages of this combination; nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (N1I3) and nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (N3I1), however no studies have been done to determine their differential effectiveness, if any. This possibility should be evaluated.. Although there was no significant difference between N1I3 and N3I1 in CR, N1I3 yielded better results in PR and ORR than N3I1, suggesting that the efficacy of N1I3 may be better than that of N3I1. Sharma et al. [28] reported that with longer follow-up, N1I3 showed sustained antitumor activity than N3I1. Glutsch on his part investigated the presence and extend of side effects in advanced melanoma cases on ipilimumab-nivolumab combined immunotherapy. Here, renal toxicity was tolerable, and three doses of nivolumab (1 mg/kg) in combination with ipilimumab (3 mg/kg) showed deep partial relief on chest and abdominal CT scans[56]. This result not only support our findings on N1I3, but emphasized on the potential benefit of combination immunotherapies in tumor.

We also analyzed all common adverse reactions of every grade. Adverse reactions of grade 3 or higher in group combination were elevated than those in monotherapies. Nivolumab-ipilimumab increased response rate with more side effects than ipilimumab monotherapy. Kreft [53] reported that combined ipilimumab and nivolumab was associated with a higher TRAEs compared with the monotherapy, but N1I3 induced elevated grade 3 or higher TRAEs than N3I1, consistent with Antonia et al.[18]. When comparing treatment groups, common grade 3 or 4 TRAEs in the nivolumab-ipilimumab group arose early but resolved within the first 4–6 months of treatment [46]. In contrast, both early and chronic toxicity were apparent in the sunitinib group, despite dose adjustments. Most selected treatment-related adverse events occurring within 30 days of the last dose in the nivolumab-ipilimumab group were low-grade, and the majority resolved and were manageable using established algorithms[57]. Health-related quality life was maintained or significantly improved from baseline analysis of patients under nivolumab-ipilimumab compared those on sunitinib alone, further supporting the preference of the combination therapy.

The main TRAEs associated with nivolumab use include increased ALT and AST, pruritus, diarrhoea, fatigue, nausea, hypothyroidism, decreased appetite, vomiting, and rash. After extensive systematic review, Bajwa et al. found that the most common adverse effects encountered were colitis (14/139), hepatitis (11/139), adrenocorticotrophic hormone insufficiency (12/139), hypothyroidism (7/139), type 1 diabetes (22/139), acute kidney injury (16/139) and myocarditis (10/139). The most common treatment approach was the cessation of the immune checkpoint inhibitor, initiation of steroids and supportive therapy[58, 59]. Motzer et al.[46] reported that among all patients treated, the most common TRAEs in the grade 3–4 nivolumab and ipilimumab groups were elevated lipase (57 of 547 [10%]), elevated amylase (31 [6%]) and elevated ALT (28 [5%])[35]. Reporting of corticosteroid use for ICIs has been effective among various studies.

There is an increasing number of immunotherapy and molecular targeting agents being evaluated in monotherapies as well as in various combinations, but the choice of right therapy, sequence and dosage of candidate agents and immunotherapies and treatment for patients that progress on immune checkpoint inhibitors remains a challenge

Limitation

This meta-analysis only included four phase I clinical trials, which may reduce the credibility of the findings. In addition, this paper contains multiple tumor types, which may make the results of the study untargeted. It is necessary to point out that this paper was not able to extract hazard ratio (HR) as the effect size was insufficient, but this is the first meta-analysis to compare nivolumab plus ipilimumab with ipilimumab or nivolumab monotherapy.

Conclusions

This paper showed that the curative effect of nivolumab-ipilimumab combination therapy is better than ipilimumab or nivolumab monotherapy. In the combination group, N1I3 is more effective than N3I1.

Although side effects were slightly increased in group N1I3, the overall safety was reliable.

Abbreviations

8-OHdG: 8-hydroxy-2'-deoxyguanosine; 95% CI: 95% confidence interval; CSS: Cancer-specific survival; DFS: Disease-free survival;

Declarations

Ethics approval and consent to participate

No animal or human participant was involved in this study.

Consent for publication

Not applicable.

Availability of data and materials

All data are available within the article.

Competing interests

There were no conflicting interests.

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Authors' contributions

Conceptualization: Yingying Tang; Data curation: Lihu Gu, Shengnan Li, and Nannan Du; Formal analysis: Lihu Gu, Qigu Yao; Investigation: Shengnan Li, Xiaojun Fu, and Yuanmei Lou; Writing original draft: Mengru Wang, Feiyan Mao, and Danyi Mao, Parikshit Asutosh Khadaroo.

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- Melanoma; Rapid Eradication of a Bulky Melanoma Mass with One Dose of Immunotherapy; Genetic Basis for Clinical Response to CTLA-4 Blockade; Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma; Nivolumab plus Ipilimumab in Advanced Melanoma; Safety and Tumor Responses with Lmbrolizumab (Anti-PD-1) in Melanoma; Hepatotoxicity with Combination of Vemurafenib and Ipilimumab. *The New England journal of medicine* 2018, 379(22):2185.
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Supplementary Figure & Table Captions

Supplementary Table. 1 Characteristics of included clinical trials in the meta-analysis.

Supplementary Figure 1. Flow chart of study selection.

Figures

Figure 1

Forest plot of the overall effect between nivolumab combined with ipilimumab and ipilimumab alone. (A) complete response (CR), (B) partial response (PR), (C) objective response rate (ORR).

Figure 2

Forest plot of the adverse events between nivolumab combined with ipilimumab and ipilimumab alone. (A) Any grade TRAEs, (B) grade 3 or higher TRAEs.

Figure 3

Forest plot of the overall effect between nivolumab-ipilimumab combined therapy and nivolumab monotherapy. (A) complete response (CR), (B) partial response (PR), (C) objective response rate (ORR).

Figure 4

Forest plot of the adverse events between nivolumab combined with ipilimumab and nivolumab alone.
(A) any grade TRAEs, (B) grade 3 or higher TRAEs.

Figure 5

Forest plot of the overall effect of the nivolumab-ipilimumab group therapy (N1I3 versus N3I1). (A) complete response (CR), (B) partial response (PR), (C) objective response rate (ORR).

Supplementary Files

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