


# PD-1 and CTLA-4 inhibitors in combination vs. alone for the treatment of advanced melanoma

## A systematic review and meta-analysis

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### Abstract

**Background:** Metastatic melanoma treatment has drastically changed during the past decade with the advent of immunotherapy. We conducted a meta-analysis, to assess PD-1 and CTLA-4 inhibitors in combination vs. alone for the treatment of advanced melanoma.

**Methods:** The EMBASE, Medline via PubMed, Scopus, Cochrane Central, and Web of Science databases were searched. The records retrieved were screened for eligibility. Odds ratio (OR) was applied to compare dichotomous variables. All the results were reported with 95% confidence intervals (CI). Mantel–Haenszel method was used to estimate pooled OR and 95% confidence intervals for dichotomous data.

**Results:** We retrieved 3092 citations of which we included 3 randomized controlled trials and 2 retrospective, cohort studies. The pooled OR was 2.144 (95% CI: 1.650–2.786,  $I^2 = 80.38\%$   $P = .000$ ) for overall response and 2.117 (95% CI: 1.578–2.841,  $I^2 = 70.17\%$   $P = .000$ ) for the complete response (CR). Subgroup analysis in nivolumab category showed that the pooled OR was 1.766 (95% CI: 1.324–2.355,  $I^2 = 0.0\%$   $P = .000$ ) for the overall response and was 1.284 (95% CI: 0.889–1.855,  $I^2 = 0.0\%$   $P = .182$ ) for the CR and in the ipilimumab category the pooled OR was 5.440 (95% CI: 2.896–10.220,  $I^2 = 70.89\%$   $P = .001$ ) for the overall response and was 5.169 (95% CI: 3.163–8.446,  $I^2 = 0.0\%$   $P = .000$ ) for the CR. The incidence of any treatment-related adverse events was significantly higher in the combination group than that of the nivolumab monotherapy 4.044 (95% CI: 1.740–9.403,  $I^2 = 91.64\%$   $P = .001$ ) or the ipilimumab monotherapy 2.465 (95% CI: 0.839–7.236,  $I^2 = 93.02\%$   $P = .101$ ).

**Conclusion:** Combination therapy with ipilimumab plus nivolumab is a promising strategy in the treatment of patients with advanced melanoma with superior overall and complete responses over either monotherapies.

**Abbreviations:** CIs = confidence intervals, CMA = comprehensive meta-analysis software, CR = complete response, HR = hazard ratio, ICB = immune checkpoint blockade, IrAEs = immune-related adverse events, OR = odds ratio, ORR = objective response ratio, OS = overall survival, PFS = progression-free survival, PRISMA = preferred reporting items for systematic reviews and meta-analyses, ROB = risk of bias.

**Keywords:** immunotherapy, ipilimumab, melanoma, meta-analysis, nivolumab, systematic review

## 1. Introduction

Metastatic melanoma treatment has drastically changed during the past decade with the advent of immunotherapy and then molecular targeted therapy. Today, 5-year survival is achievable in almost 50% of the patients with metastatic melanoma when treated with combination immunotherapy.<sup>[1]</sup> This is in contrast to

10 years ago when metastatic melanoma was considered unvaryingly lethal with an overall survival rate of less than 5%.<sup>[2]</sup>

The last decade has observed a significant change in the treatment of metastatic or unresectable melanoma patients, with the advent of immune checkpoint blockade proteins including ipilimumab, nivolumab, pembrolizumab, and combination ipilimumab-nivolumab. These antibodies are coinhibitory protein

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The data adopted in this meta-analysis are available from the corresponding author on reasonable request.

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receptors (PD-1 and CTLA-4 coinhibitory receptors) which are located on the surface of the lymphocytes.<sup>[3]</sup> Their ligands (e.g., PD-L1/PD-L2 and B7, respectively), on the other hand, are expressed on the tumor cells and restrain T-cells function rendering them unable to mount a response against cancer cells and causing resistance of malignant melanoma in many patients to conventional anticancer therapy.<sup>[4]</sup>

In 2010, Hodi et al, showed, for the first time, that overall survival in patients with metastatic melanoma improved with the treatment via the anti-CTLA-4 antibody (ipilimumab).<sup>[5]</sup> Also, data on 1861 patients across 12 trials treated with ipilimumab revealed a 3-year survival rate of approximately 20% (plateaued afterward, supporting the durability of response to CTLA-4 blockade).<sup>[6]</sup> Accordingly, monoclonal antibodies targeting PD-1 were developed which demonstrated clinical activity in melanoma<sup>[7]</sup> with an even higher overall response rate (30%–40% at 5 years) compared to CTLA-4 blockade and ongoing durable responses in 70%–80% of responding patients.<sup>[8]</sup> Subsequently, dual immune checkpoint blockade (ICB) with ipilimumab-nivolumab was introduced and demonstrated considerable enhancements in response rate (58%) compared with ipilimumab or nivolumab alone in patients with advanced melanoma. Besides, both nivolumab-containing arms demonstrated superior overall survival (OS) compared with ipilimumab alone.<sup>[9]</sup> More data emerging from five-year follow-up verified a substantial OS where more than half of patients (52%) in the ICB group were still alive at the time of assessment. The median treatment-free interval was also demonstrably high reaching 18.1 months, highlighting the durability of these responses.<sup>[1]</sup> Nevertheless, this was accompanied by significant toxicity from dual ICB resulting in treatment interruption or discontinuation in more than 50% of the patients.<sup>[10]</sup> Nivolumab plus ipilimumab showed a high survival rate and safety outcomes in other studies, further backing up the application of this combination for advanced melanoma in multiple subgroups.<sup>[11]</sup>

A meta-analysis of two studies showed that nivolumab-plus ipilimumab combination therapy had an obvious significant advantage over the ipilimumab monotherapy in patients with advanced melanoma.<sup>[12]</sup> Considering the increase in the number of studies performed in the field, we conducted a meta-analysis, to assess PD-1 and CTLA-4 inhibitors in combination Vs. alone for the treatment of advanced melanoma.

## 2. Materials and Methods

This review was conducted according to a predetermined protocol based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.<sup>[13]</sup>

### 2.1. Literature search

The EMBASE, Medline via PubMed, Scopus, Cochrane Central, and Web of Science databases were electronically searched using the following terms “anti-PD-1” “nivolumab,” “pembrolizumab,” “anti-CTLA-4,” “ipilimumab,” and “melanoma” and the following search strategy ((((((PD-1[Title/Abstract]) OR (pembrolizumab [Title/Abstract])) OR (nivolumab [Title/Abstract])) AND (ctla-4[Title/Abstract])) OR (ipilimumab [Title/Abstract])) AND (melanoma [Title/Abstract])). Two independent reviewers screened the titles and abstracts of retrieved citations. Accordingly, the full texts of the retrieved papers were screened and included only when they fulfilled our criteria. The electronic search was accompanied by manual searches for references to the included studies and related citations. Discrepancies were resolved by discussion between reviewers or by a third senior author. Only original research studies in English were considered. The search had no time restriction.

### 2.2. Inclusion and exclusion criteria

English full-text randomized controlled trials (RCTs) that fulfilled the following criteria were included in this meta-analysis: patients with advanced stage III or stage IV melanoma, in whom nivolumab or ipilimumab was administered alone (control) or in combination (intervention), and assessed progression-free survival (PFS) rate, overall survival (OS; the time from the initiation of treatment until death), complete response rate, partial response rate, objective response rate (ORR), stable disease rate, and safety measures as their outcomes. On the other hand, non-English articles, nonoriginal articles, thesis or conference papers that were never subsequently published, and studies on animals (in vivo) and cell lines (in vitro) were excluded from this study.

### 2.3. Data extraction

Data extraction was independently conducted by two reviewers using a standardized approach. Disagreements were resolved by discussion with a third senior reviewer. Data on authors' names, year of publication, journal name, study phase, the sample size in each arm, immunotherapy regimen used, the mean age of patients, and information regarding study design (randomization, allocation concealment, description of withdrawals per arm, and blinding) for the trials included in the study.

### 2.4. Quality assessment

Cochrane Collaboration's tool for risk of bias (ROB) assessment was used to assess the quality of the included studies. The items of this tool were as follows; allocation concealment, selective outcome reporting, blinding of participants, masking of outcome assessors, generation of allocation sequence, incomplete follow-up, and other potential sources of bias. A senior author judged any disagreements between the 2 reviewers who performed the assessment. For each element, the risk of bias was considered as low, unclear, or high. If the reviewer could find information on all the parameters mentioned in the tool or no information at all, then the study was allocated to one of the low bias or high bias categories, respectively. If the information retrieved by the reviewer was partial or unclear, the risk of bias was considered to be unclear.<sup>[14]</sup>

### 2.5. Statistics

The Comprehensive Meta-Analysis Software (CMA) software version 2.0 was used to analyze the data. Odds ratio (OR) was applied to compare dichotomous variables. All the results were reported with 95% confidence intervals (CI). Mantel-Haenszel method was used to estimate pooled OR and 95% confidence intervals for dichotomous data. Heterogeneity of the data was assessed using *I*-square (*I*<sup>2</sup>) test and considered high if *I*<sup>2</sup>>50%. In this case, the random effect model was chosen; otherwise, the fixed effect model was used. Subgroup analyses were conducted based on the intervention of the study design: anti-PD-1 plus anti-CTLA-4 versus anti-PD-1 (nivolumab), and anti-PD-1 plus anti-CTLA-4 versus anti-CTLA-4 (ipilimumab). Funnel plotting, Egger's regression, and trim and fill were not used for the assessment of publication bias in this literature as the number of studies was less than 10. *P* < .05 is considered statistically significant.

## 3. Results

### 3.1. General characteristics of the included studies

We retrieved 3092 citations, including 3088 publications by electronic search of databases, and 4 studies by a manual search of websites and checking reference lists of the included studies. After the removal of duplicate records, a total of 2839

titles were screened, during which 2779 articles were excluded. Accordingly, and after abstract and full-text screening, 3 randomized controlled trials and 2 retrospective, cohort studies were included in this meta-analysis. The detailed information regarding the number of identified studies, and the stages of evaluation and exclusion is presented in Figure 1 (see PRISMA flow diagram).

The characteristics of the included studies are presented in Table 1. Of the included RCTs, one publication was from phase III and two citations were from phase II. A total of 1605 patients were included in this meta-analysis of which 675 were in the combination therapy group, 359 in the nivolumab monotherapy group, and 571 in the ipilimumab monotherapy group. PFS was the main endpoint in 4 of the included citations and OS was the primary outcome in 4 of the included papers. In all of the included studies, PFS and OS were higher in the combination therapy group (nivolumab plus ipilimumab) than those of the monotherapy groups (nivolumab or ipilimumab).

### 3.2. Efficacy

The main endpoints of the included studies were ORR, PFS, and OS for efficacy. However, not all of the included studies reported all of these endpoints. For example, ORR was reported only by one of the included studies. Subgroup analyses were conducted based on the intervention of the study design. The heterogeneity of the included studies was found to be high thus random effect model was used for the analyses. The PFS and/or OS of these trials are presented in Table 1. Overall analysis showed that the pooled OR was 2.144 (95% CI: 1.650–2.786,  $I^2 = 80.38\%$   $P = .000$ ; Fig. 2) for overall response and 2.117 (95% CI: 1.578–2.841,  $I^2 = 70.17\%$   $P = .000$ ; Fig. 3) for the complete response (CR).

### 3.3. Nivolumab plus ipilimumab vs. nivolumab

Subgroup analysis in this category showed that the pooled OR was 1.766 (95% CI: 1.324–2.355,  $I^2 = 0.0\%$   $P = .000$ ; Fig. 2) for the overall response and was 1.284 (95% CI: 0.889–1.855,

$I^2 = 0.0\%$   $P = .182$ ; Fig. 3) for the CR. These findings indicated a significantly higher overall response but not CR and thus beneficial for the patients in the combination therapy group compared with the nivolumab group in the included population. Also, in the combination therapy group, significantly longer OS and PFS were observed in each of the included studies. However, analysis was not possible for these variables (Table 1).

### 3.4. Nivolumab plus ipilimumab vs. ipilimumab

Subgroup analysis in this category revealed that the pooled OR was 5.440 (95% CI: 2.896–10.220,  $I^2 = 70.89\%$   $P = .001$ ; Fig. 2) for the overall response and was 5.169 (95% CI: 3.163–8.446,  $I^2 = 0.0\%$   $P = .000$ ; Fig. 3) for the complete response (CR). These findings indicated a significantly higher overall response, CR, and thus beneficial for the patients in the combination therapy group compared with the ipilimumab group in the included population. Also, in the combination therapy group, significantly longer OS and PFS were observed in each of the included studies. However, analysis was not possible for these variables (Table 1).

### 3.5. Safety analysis

Larkin et al showed that 59%, 23%, and 28% of patients in the nivolumab-plus-ipilimumab, nivolumab, and ipilimumab groups, respectively, had grade 3 or 4 treatment-related side effects.<sup>[1]</sup> Hodi et al showed that at the time of the most recent data lock, the rates of treatment-related adverse events of any grade were 92% (86 of 94 patients) and 94 percent (43 of 46 patients), respectively. The most common adverse reactions to therapy were diarrhea, rash, fatigue, and pruritus in both groups. Consistent with Larkin et al, study, Hodi et al, showed that the frequency of grade 3–4 adverse events was higher in the combination therapy group.<sup>[15]</sup> However, da Silva et al, found that the rate of grade 3–4 adverse events was similar between the groups. Diarrhea or colitis was the most frequent grade 3–5 treatment-related adverse event, followed by a rise in alanine aminotransferase or aspartate aminotransferase in this study.<sup>[16]</sup>

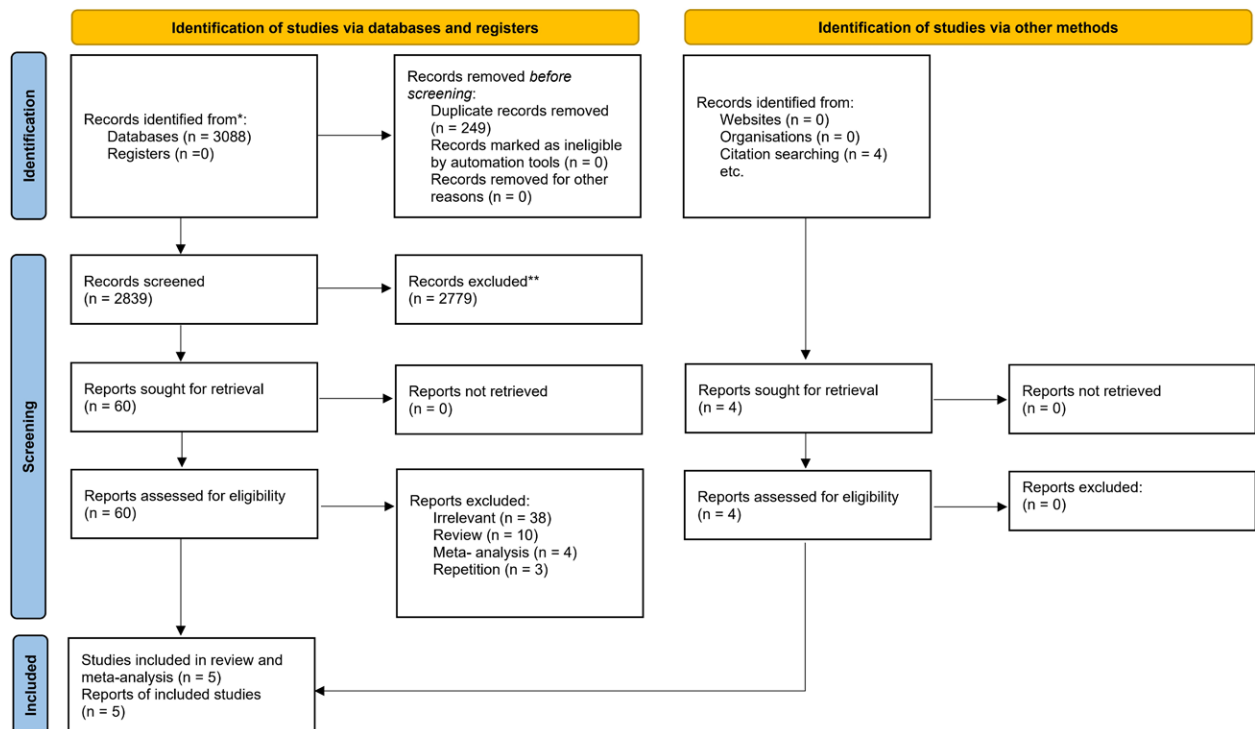
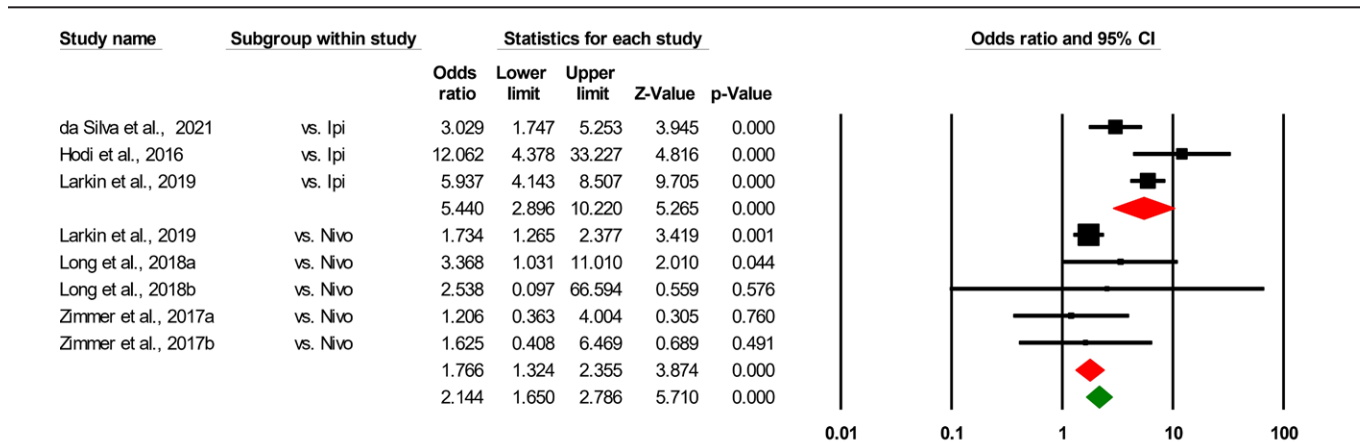


Figure 1. PRISMA flowchart of the included studies in the systematic review and meta-analysis.

**Table 1**  
**Characteristics of included studies in the meta-analysis.**

Study	Phase	No. of patients	Age	Primary end points	Progression-free survival (PFS; months)	Overall survival (OS; months)
Larkin et al., 2019	III	945 underwent randomization (314 to the nivolumab-plus-ipilimumab group, 316 to the nivolumab group, and 315 to the ipilimumab group)	?	PFS and OS	Five-year progression-free survival was 36%, 29%, and 8% in the nivolumab-plus-ipilimumab, nivolumab, and ipilimumab groups, respectively	Among patients with tumors with BRAF mutations and those with tumors without BRAF mutations, overall survival at 5 years was 60% and 48%, respectively, in the nivolumab-plus-ipilimumab group; 46% and 43% in the nivolumab group; and 30% and 25% in the ipilimumab group
Hodi et al., 2016	II	95 patients in nivolumab plus ipilimumab and 47 in ipilimumab	?	OS	-	Overall survival rates in all randomized patients were 63.8% (95% CI: 53.3–72.6) for nivolumab plus ipilimumab vs 53.6% (95% CI: 38.1–66.8) for ipilimumab alone
Zimmer et al., 2017	Retrospective cohort	47 patients were treated with ipilimumab and 37 patients with ipilimumab and nivolumab	65 (29–80) for the ipi and 56 (27–81) for the combination	PFS and OS	Median PFS for the ipi-group and the combination-group was 3 months (95% CI: 2.8–3.8 months) and 2 months (95% CI: 1.9–3 months), respectively.	One-year overall survival rates for the ipi- and the combination-group were 54% and 55%, respectively
Da Silva et al., 2021	Retrospective cohort	162 patients in ipilimumab monotherapy and 193 patients in ipilimumab plus anti-PD-1	61.0 (51.5–70.0) for the ipi and 67.0 (58.0–74.0) for the combination	ORR, PFS, and OS	Progression-free survival was also longer with ipilimumab plus anti-PD-1 (median 3.0 months [95% CI: 2.6–3.6]) than with ipilimumab (2.6 months [2.4–2.9])	Overall survival was longer in the ipilimumab plus anti-PD-1 group (median overall survival 20.4 months [95% CI: 12.7–34.8]) than with ipilimumab monotherapy (8.8 months [6.1–11.3])
Long et al., 2018	II	36 in cohort A (Combination), 27 in cohort B, and 16 in cohort C (nivolumab)	59 (53–68) for the combination and 63 (52–74) and 51 (48–56) for the nivolumab	Intracranial response from week 12 and PFS	53% for the combination vs. 20% and 13% for the nivolumab	-

ipi = ipilimumab, ORR = objective response rate, OS = overall survival, PFS = progression-free survival.



**Figure 2.** Forest plot of standardized mean difference (SMD) for overall response for combination therapy vs. both ipilimumab and nivolumab therapy in patients with advanced melanoma. The green square shows the overall pooled effect. Red squares show pooled effect in each subgroup. Black squares indicate the SMD in each study. Horizontal lines represent a 95% confidence interval (CI).

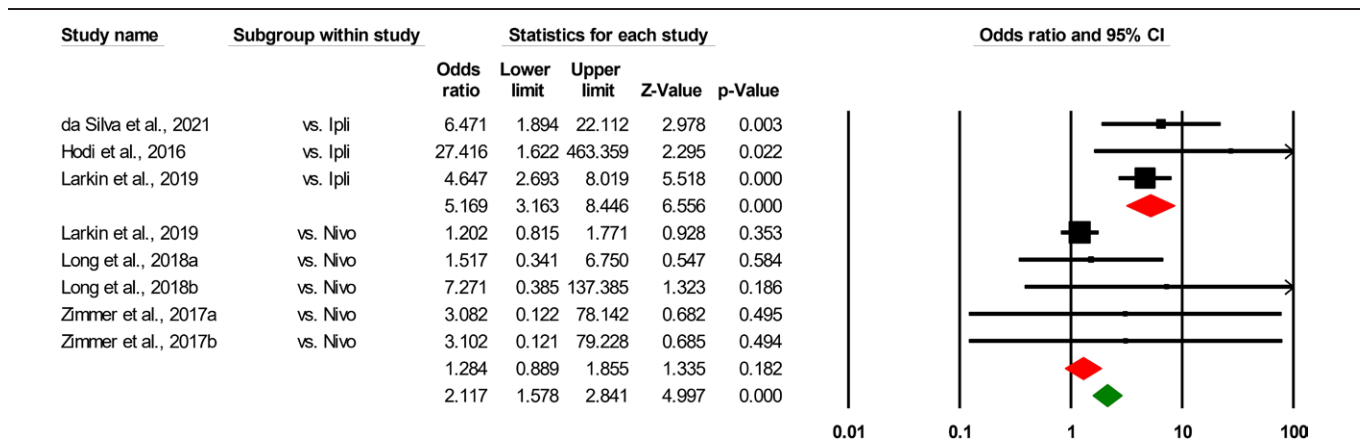
Our analysis revealed that the incidence of any treatment-related adverse events was significantly higher in the combination group than that of the nivolumab monotherapy 4.044 (95% CI: 1.740–9.403,  $I^2 = 91.64\%$   $P = .001$ ; Fig. 4). However, the heterogeneity of the included studies was high. Also, the incidence of any treatment-related adverse events was higher in the combination group than that of the ipilimumab monotherapy 2.465 (95% CI: 0.839–7.236,  $I^2 = 93.02\%$   $P = .101$ ; Fig. 5). However, this did not reach a

statistical significance and the heterogeneity of the included studies was modest.

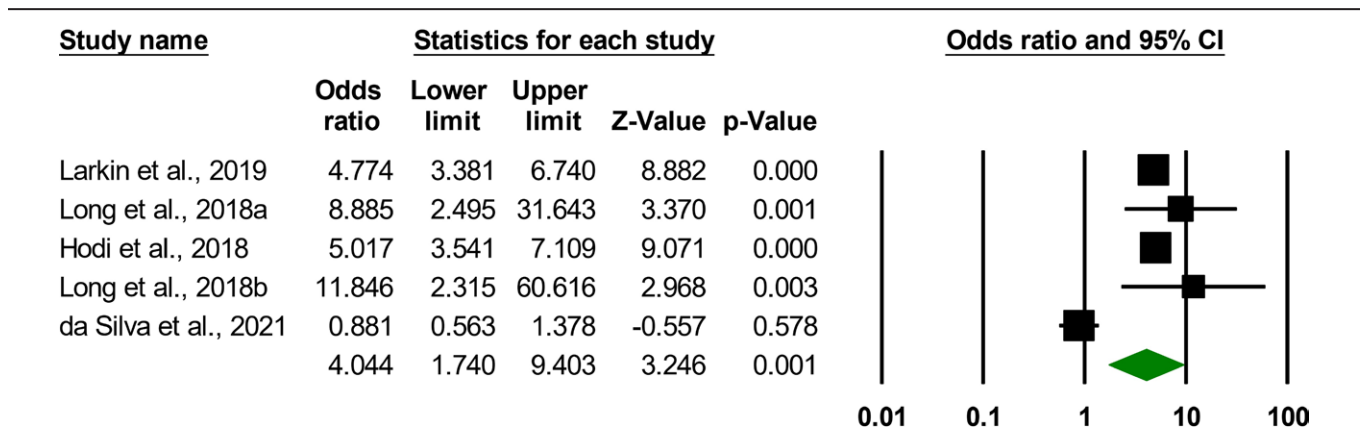
**3.6. Publication bias assessment**

The quality of included studies was evaluated based on the standards of RCT quality assessment of the Cochrane Reviewer handbook.<sup>[14]</sup> There was no attrition bias and reporting bias in the included studies. However, detection, performance, and selection

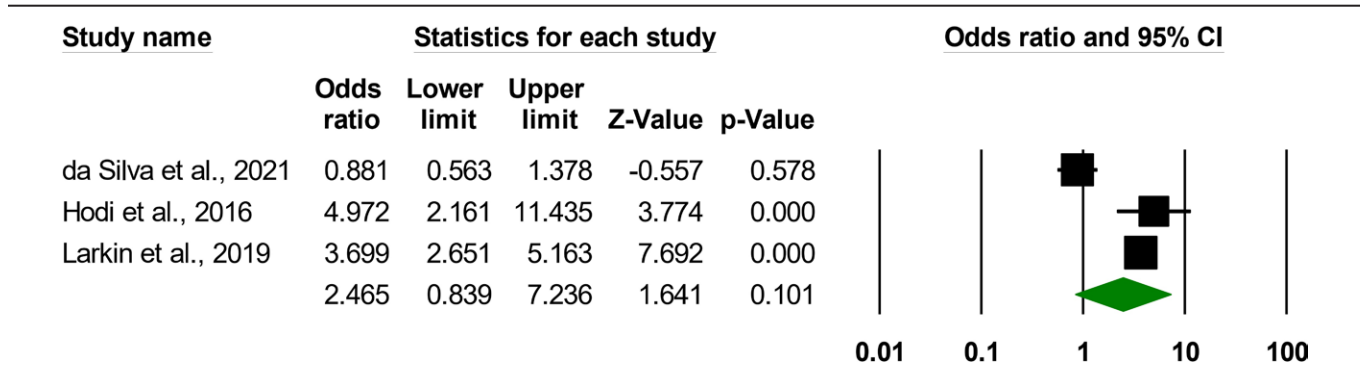




**Figure 3.** Forest plot of standardized mean difference (SMD) for complete response for combination therapy vs. both ipilimumab and nivolumab therapy in patients with advanced melanoma. Green square shows overall pooled effect. Red squares show pooled effect in each subgroup. Black squares indicate the SMD in each study. Horizontal lines represent a 95% confidence interval (CI).



**Figure 4.** Forest plot of standardized mean difference (SMD) for treatment related-adverse event for combination therapy vs. nivolumab therapy in patients with advanced melanoma. The green square shows the overall pooled effect. Black squares indicate the SMD in each study. Horizontal lines represent a 95% confidence interval (CI).



**Figure 5.** Forest plot of standardized mean difference (SMD) for treatment related-adverse event for combination therapy vs. ipilimumab therapy in patients with advanced melanoma. The green square shows the overall pooled effect. Black squares indicate the SMD in each study. Horizontal lines represent a 95% confidence interval (CI).

(allocation concealment) biases were found in three of the included citations.<sup>[16-18]</sup> Also, random sequence generation was not implemented in two of the included publications<sup>[16,18]</sup> (Fig. 6).

**4. Discussions**

The results emerging from this systematic review and meta-analysis showed that combination therapy with nivolumab plus ipilimumab was more effective than nivolumab or ipilimumab alone in the treatment of advanced metastatic melanoma (treated or

untreated). This was suggested by higher overall response and CR of the combination therapy compared with either of the monotherapies. However, this was accompanied by a higher incidence of grade 3/4/5 adverse events in the combination therapy than in either of the monotherapies.

**4.1. A closer look at individual studies**

Our pooled analysis was in total agreement with the results of individual trials included in this study. In that light, Larkin

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
da Silva et al., 2021	-	-	-	-	+	+	
Hodi et al., 2016	+	+	+	+	+	+	
Larkin et al., 2019	+	+	+	+	+	+	
Long et al., 2018	+	-	-	-	+	+	
Zimmer et al., 2017	-	-	-	-	+	+	

Figure 6. Different levels of risk of bias for each item in included studies. The Cochrane risk of bias tool was used for the detection of publication bias.

et al, showed (CheckMate 067) that the median OS was over 60.0 months in the combination therapy group as opposed to 36.9 and 19.9 months in the nivolumab and ipilimumab groups, respectively. Also, the hazard ratio (HR) for death was found to be lower in the combination therapy group than in ipilimumab alone (nivolumab plus ipilimumab vs. ipilimumab, 0.52; HR for death with nivolumab vs. ipilimumab, 0.63). Five-year follow-up of the patients showed a 52% OS in the combination therapy group as compared with nivolumab or ipilimumab alone (44% and 26%, respectively). The authors reported no new late toxic effects nor sustained deterioration of health-related quality of life in the combination group compared with the monotherapies.<sup>[1]</sup> Similarly, in another study by

Hodi et al, (CheckMate 069) it was found that OS rates in all randomized patients were 63.8% (95% CI: 53.3–72.6) for the combination therapy group vs 53.6% (95% CI: 38.1–66.8) for ipilimumab alone at a median follow-up of 24 months. However, grade 3–4 adverse events associated with combination therapy were observed in 51 [54%] of 94 patients vs 9 [20%] of 46 patients linked to ipilimumab alone. The results of this study indicated that the combination of nivolumab plus ipilimumab may result in a higher OS rate vs ipilimumab in patients with advanced melanoma.<sup>[19]</sup> In line with previous studies, in a multicenter retrospective cohort study Zimmer et al, found that OS rates for the monotherapy and the combination groups were 16% and 21%, respectively. The disease

control rate was 42% for the monotherapy and 33% for the combination groups. One-year OS rates for the monotherapy and the combination groups were 54% and 55%, respectively. The authors, however, stated that the combination therapy with nivolumab and ipilimumab was significantly less effective in patients with advanced melanoma with previous anti-PD failure compared with treatment-naïve melanoma patients.<sup>[18]</sup> This was, in contrast, to da Silva et al findings, which showed that in advanced melanoma patients who were resistant to anti-PD-1 monotherapy, combination therapy had higher efficacy than monotherapy with a higher ORR (60 [31%] of 193 patients vs 21 [13%] of 162 patients;  $P < .0001$ ), longer PFS (median 3.0 months [95% CI: 2.6–3.6] vs 2.6 months [2.4–2.9]; HR, 0.69, 95% CI: 0.55–0.87;  $P = .0019$ ), and longer OS (median overall survival 20.4 months [95% CI: 12.7–34.8] vs 8.8 months [6.1–11.3]; HR, 0.50, 95% CI: 0.38–0.66;  $P < .0001$ ), with a similar rate of grade 3–5 toxicity. The results of this study suggested combination therapy with ipilimumab and nivolumab as a superior option over ipilimumab monotherapy in advanced melanoma patients.<sup>[16]</sup> Long et al found that combination therapy with nivolumab plus ipilimumab results in higher an intracranial response than ipilimumab monotherapy (16 (46%; 95% CI: 29–63) of 35 patients, 5 (20%; 7–41) of 25, and 1 (6%; 0–30) of 16, respectively) in patients with metastatic melanoma to the brain.<sup>[17]</sup>

A meta-analysis by Menshawy et al<sup>[20]</sup> performed on 1910 patients (nivolumab group,  $n = 1207$  and control group,  $n = 703$ ) showed that combination therapy with nivolumab plus ipilimumab had higher ORR [RR: 3.58, 95% CI: 2.08–6.14], complete response rate (RR: 5.93, 95% CI: 2.45–14.37), partial response rate (RR: 2.80, 95% CI: 2.16–3.64), stable disease rate (RR: 0.56, 95% CI: 0.41–0.76), and PFS (hazard ratio: 0.67, 95% CI: 0.60–0.74) compared with ipilimumab monotherapy. However, this meta-analysis is rather old and did not include the 5-year update from the CheckMate 067 study by Larkin et al,<sup>[11]</sup> and also recent studies by da Silva et al<sup>[16]</sup> and Long et al.<sup>[17]</sup> On the other hand, this study included a study by Postow et al,<sup>[21]</sup> which is an earlier version of the CheckMate 069 study by Hodi et al<sup>[19]</sup> and should not be included in the meta-analysis as a separate entity. Another meta-analysis by Hao et al performed on two studies showed that combination therapy with nivolumab plus ipilimumab had a visible significant advantage over the ipilimumab monotherapy.<sup>[12]</sup> But the number of studies was too low to decide on anything.

#### 4.2. Safety

One of the main concerns with immune checkpoint inhibitors is the risk of immune-related adverse events (IrAEs). Nivolumab was shown to be well tolerated by patients with advanced melanoma. On the one hand, it is speculated that combination therapy with immunotherapies elevates the incidence of potential IrAEs. In a systematic review and meta-analysis by Almutairi et al., it was found that the incidences of potential IrAEs in combination therapies vs. monotherapies were higher for most types of IrAEs. This caused hyperglycemia, thyroid, hepatic, and musculoskeletal disorders in the patients receiving these medications.<sup>[22]</sup> On the other hand, it was argued that the emergence of both early and late IrAEs could be regarded as a favorable prognostic parameter in patients receiving immunotherapy and immunoradiotherapy for solid tumors especially if these events are delayed; as they are accompanied by increased overall response rate and improved OS and PFS in these patients.<sup>[23,24]</sup> In any case, the oncologist should take into consideration the occurrence of IrAEs in patients with advanced melanoma especially those with a history of autoimmune disease, poor kidney function of grade 3 or greater, and use of CTLA-4 inhibitors.<sup>[25]</sup>

#### 4.3. Limitations

Our study had several shortcomings that should be taken into consideration when interpreting the results. We based our analysis on unadjusted data. This means that confounders such as age, BRAF mutation status, prior systemic therapy, PD-L1 status, and gender were not considered in this meta-analysis. This might be the result of the low number of studies existing in the field and included in this meta-analysis. An increase in the number of studies published in this field and also adjustments for confounders mentioned above might result in more accurate outcomes. Besides, this study was limited to English full-text original papers. This results in missing data emerging from conferences and also other languages. Further, the existence of an open-labeled clinical trial, and also pharmaceutical companies-funded studies increased the ROB in our study.

#### 5. Conclusions

Data emerging from this study showed that combination therapy with ipilimumab plus nivolumab meaningfully increased the overall response rate, including the CR, compared with monotherapy with ipilimumab or nivolumab in patients with advanced melanoma regardless of the patients untreated or after anti-CTLA-4 treatment. This was accompanied by higher incidences of potential IrAEs in combination therapy. In this light, combination therapy with ipilimumab plus nivolumab could be a promising strategy in the treatment of patients with advanced melanoma.

#### Author contributions

RZH, XLZ, JML, YJZ, XCZ, and FC performed the statistical analysis and wrote the manuscript. RZH, XLZ, JML, and YJZ conceived the study design and participated in the manuscript writing. XCZ and FC revised and edited the manuscript. All authors read the final manuscript.

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