

# Safety and efficacy of nivolumab compared with other regimens in patients with melanoma

## A network meta-analysis

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### Abstract

**Background:** Melanoma is a cancerous tumor that develops from melanocytes in the epidermal basal layer of the skin. It is a fatal skin cancer and the third most common kind of cutaneous tumor. We aim to evaluate the effect of nivolumab in melanoma patients compared with other regimens

**Methods:** This meta-analysis included only clinical trials, both randomized and nonrandomized. The main outcomes of interest were the response to treatment, overall survival (OS), progression-free survival, and adverse events.

**Results:** The overall effect estimates favored nivolumab group over the combination of nivolumab plus ipilimumab (HR 3.06, 95% CI 1.70-5.49) and chemotherapy group (HR 3.58, 95% CI 1.63-7.84) after 1 year. Compared to chemotherapy, nivolumab had lower rates of adverse events.

**Conclusion:** Nivolumab monotherapy yields high progression-free survival rates and has the same efficacy when combined with ipilimumab in a 1-year OS. However, after 2 and 3 years of follow-up, the combined regimen has more OS rates.

**Abbreviations:** AES = adverse events, CR = complete response, HR = hazard ratio, ICB = immune checkpoint blockers, OS = overall survival, PD = progressive disease, PD-1 = antiprogrammed death 1, PFS = progression-free survival, PR = partial response, RR = risk ratios, SD = stable disease.

**Key Words:** ipilimumab, melanoma, nivolumab

## 1. Introduction

Melanoma is a malignant tumor that originates from skin melanocytes, found mainly in the epidermal basal layer.<sup>[1]</sup> It is ranked first as the most fatal cancer affecting the skin, and the third leading type of cutaneous tumors. Death rates have reached approximately 78% of all deaths among different cancers of the skin.<sup>[2]</sup> Statistics have shown increased recurrence rates for surgically removed melanomas in earlier stages.<sup>[3]</sup> However, early discovery and excision yield good long-term prognosis and increases 5-year survival rates.<sup>[4]</sup>

Melanomas have been associated with genetic mutations that affect intracellular signaling pathways.<sup>[5]</sup> Numerous mutations, including BRAF, NRAS, NF1, and MITF mutations, have been described. However, the mutation in the BRAF gene is most commonly observed in approximately 40% to 60% of cases; about 90% of these cases involve V600E mutation.<sup>[6,7]</sup> The mutations in the mitogen-activated protein kinase pathway lead to an increase in abnormal proliferation of melanocytes and their capacity to invade other organs,<sup>[8]</sup> which worsens the prognosis of the disease.<sup>[6]</sup>

Patients with stage III melanoma have long been suffering low clinical outcomes.<sup>[9]</sup> Recently, immune checkpoint blockers drugs have shown high efficacy and increased survival rates.<sup>[9]</sup> Ongoing articles nowadays are concerned mainly with ipilimumab: a monoclonal antibody anticytotoxic T-lymphocyte targeting CTLA-4; nivolumab: An IgG4 monoclonal antibody blocking antiprogrammed death 1 (PD-1) agents and a combined regimen of nivolumab and ipilimumab for melanoma. Checkpoint inhibitors showed greater efficacy compared with standard chemotherapy clinically in overall survival rate and progression-free survival (PFS) rate in the treatment of solid tumors.<sup>[10]</sup> In 2017, nivolumab was approved by the Food and Drug Administration as a safe and effective treatment for melanoma.<sup>[11]</sup> Many studies compared nivolumab with ipilimumab regarding efficacy and safety endpoints.

In terms of PFS, both BRAFi plus MEKi combined therapies have shown the highest efficacy for patients with BRAF-mutant melanoma. On the other hand, anti-PD-1 plus anti-CTLA-4 and both anti-PD-1 monotherapies have shown significant increased overall survival rates, irrespective

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Not necessary as the network meta-analysis study is exempt from ethics approval as I collected and synthesized the data from previous clinical trials.

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of BRAF mutation. From the available evidence and current clinical guidelines, more research should be done to investigate the effectiveness of different sequences of these novel treatments.

In the past, ipilimumab played a significant role in improving overall survival (OS) rates in patients with melanoma. The drug was the first novel medication to achieve significant efficacy (10.1 mo OS) compared with patients receiving glycoprotein 100 peptide vaccine (6.4 mo OS).<sup>[12]</sup> The results caused a revolution in the therapeutic options of melanoma and combined treatments became available. Despite the superior efficacy of the novel drugs and combinations, few studies compared different immune checkpoint inhibitors and mitogen-activated protein kinase pathway inhibitors.

As a result, little evidence could be obtained regarding the efficacy and safety of each novel treatment using direct comparisons from clinical trials. It is, however, possible to indirectly compare data of available clinical trials using network meta-analysis (NMA). NMAs are useful to combine direct and indirect comparisons of included treatments that are not directly compared in an RCT, in a rank-order system from the highest efficacy to the lowest.<sup>[13–15]</sup>

Some systematic reviews were published before addressing this topic. However, most of them were performed before the introduction of immunotherapies.<sup>[16–18]</sup>

The study aims to cover all clinical trials on nivolumab compared with either ipilimumab alone, nivolumab in combination with ipilimumab, or standard chemotherapy. Therefore, we performed a systematic review and NMA of clinical trials to investigate the efficacy (primarily, overall survival and PFS) and safety (regarding mainly any adverse effects [AEs], or any treatment-related AEs) of nivolumab compared with other treatment regimens for melanoma.

## 2. Methods

This systematic review and NMA was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement of network meta-analyses.<sup>[19]</sup>

### 2.1. Eligibility criteria

All clinical trials, randomized and nonrandomized, were included in this study. The inclusion criteria were as follows: (a) clinical trials (phase I, phase II, and phase III) on patients with melanoma with its available long-term follow-up studies; (b) the intervention, nivolumab monotherapy, ipilimumab monotherapy, combined nivolumab and ipilimumab, and chemotherapy; (c) primary outcomes were the OS defined as the duration of survival from beginning of therapy initiation till death due to any reason, the PFS defined as the time elapsed since initiation of treatment till documented progression of the disease or mortality of any cause, and the treatment response; including complete response (CR) rate, partial response (PR) rate, stable disease (SD) rate, and progressive disease (PD) rate. Secondary outcomes were adverse events, and treatment-related adverse events. Studies with a small sample size (<20 patients), duplicates, conference publications, letters, incomplete, or unclear data even after contacting the authors, or narrative reviews, were excluded.

### 2.2. Data source

The following databases were searched: PubMed, Cochrane Library, Web of Science, and EMBASE for relevant English articles limited to humans, with no restriction to time. We developed our search strategy using a combination of these keywords: “melanoma” and “Nivolumab.” All studies were retrieved until

December 2019. We imported the results of our search into Microsoft Excel software.

Eligibility screening was conducted in 2 steps, each by 2 independent reviewers (M.A. and M.A.) to ensure not missing any included studies by (a) title and abstract screening for matching the inclusion criteria, and (b) full-text screening for eligibility to meta-analysis. Disagreements were resolved upon the opinion of a third reviewer (HA). Additionally, after the screening step, the references were searched for included trials of any study that might meet the inclusion criteria.

### 2.3. Data extraction

Data extraction was performed by 2 reviewers independently. The data extracted included the following from each study: baseline characteristics of patients such as age, sex, the sample size of each arm, the number of patients with BRAF mutations, and the design of each trial. Additionally, we extracted outcome endpoints such as OS, PFS, response rates, and AEs. This step was performed using Microsoft excel.

### 2.4. Risk of bias assessment

The 2 independent reviewers assessed risk of bias for both randomized and nonrandomized clinical trials that were included. For randomized trials, the Cochrane risk of bias tool<sup>[20]</sup> was utilized. This tool assesses the risk of bias through the following domains: (1) proper randomization of patients, (2) the blinding of allocation of patients into the intended treatment arms (allocation concealment), (3) blinding of patients only (termed single blinding), or blinding of both personnel and participants (double-blinding), (4) attrition bias, (5) whether the outcomes mentioned in the protocol are all reported or not (selection bias), (6) blinding of outcome assessors to prevent over- or under-estimation of outcome values, and (7) other bias. For nonrandomized trials, the ROBINS-1 tool<sup>[21]</sup> was utilized, the tool includes 3 main groups with risk of bias domains inside each group. (1) the preintervention group, which includes the following domains: Bias due to confounding and Bias in selection of participants into the study. (2) The intervention group contains only 1 domain: bias in classification of interventions. (3) The postintervention group which assesses the following domains: bias originating from deviations from intended interventions, missing data, measurement of outcomes bias, and bias in selection of the reported result.

### 2.5. Statistical analysis

The prominent strength of NMA is to provide a significant ranking for multiple treatments even without direct comparisons. Network meta-analyses derive indirect information from pairwise results, through providing hierarchical rankings of all evaluable regimens. This key feature is reflecting the 2 fundamental assumptions of NMA, known as transitivity and consistency.<sup>[22]</sup>

When the head-to-head results of Drug A versus Drug B and Drug B versus Drug C were provided respectively, then the hypothesis of transitivity also validates a statistical comparison between A and C. When all included studies are randomized controlled trials without significant methodological heterogeneity, their baseline parameters are the important factors to determine the clinical heterogeneity and therefore transitivity.<sup>[23]</sup>

Overall survival (OS) and PFS were measured using hazard ratio (HR) with its 95% confidence interval (95% CI). Risk ratios (RR) and 95% CIs were applied as the effect size for treatment response rates (CR, PR, SD, and PD); and AEs. If survival data or its CI was not directly provided, we estimated the values from the Kaplan-Meier curves by methods described by Tierney and colleagues.<sup>[24]</sup>

The random-effect model was conducted for all outcomes. Concerning the same comparison, the results were regarded as consistent if the 95% CI of both pairwise and NMA significantly overlapped. Consistencies between treatment effect estimates obtained from direct and indirect evidence are one of the key assumptions underpinning NMA. For treatments that belong to a closed loop in the network of evidence (i.e., there exists both direct and indirect information), the difference between the direct and indirect estimates is calculated together with its 95% confidence interval. In OS and PFS outcomes, we could not measure the inconsistency due to the lack of a closed-loop comparison. We used “network sidesplit” function to check whether there is any evidence in the indirect studies. If there are no multiarm studies, then this is equivalent to checking whether the side-splitting model is identified. However, if there are multiarm studies, then the 2 checks are not equivalent; that is, there may be no evidence in the indirect studies and yet the side-splitting model may be fully identified.

All statistical tests were 2-sided with  $\alpha$  of 0.05. We used STATA software 14.2 with the help of MetaInsight<sup>[25]</sup> powered by R-shiny using netmeta: Network Meta-Analysis using Frequentist Methods, R package version 0.9-8.

### 3. Results

#### 3.1. Results of the literature search

Databases searches retrieved 670 unique citations. After duplicate removal, 423 studies remained for screening. Title and abstract screening yielded 78 studies for full-text screening. After obtaining full-text papers, a total of 22 studies were finally included in our analysis. Figure 1 shows a PRISMA flow chart for online search and results from each database.

#### 3.2. Characteristics of the included studies

We included 13 original studies and 7 follow-up studies for the original trials. Three trials<sup>[26–28]</sup> compared nivolumab with chemotherapy. Two studies<sup>[29,30]</sup> compared combined nivolumab and ipilimumab versus ipilimumab, and 1 study<sup>[31]</sup> included 3 arms, nivolumab, combined nivolumab plus ipilimumab, and

ipilimumab. Other trials included only 1 treatment option either nivolumab, ipilimumab, or a combination of both drugs. Eleven studies<sup>[26,29,32–40]</sup> reported the overall survival rate, while 13 studies<sup>[26,27,29,30,32–34,36–41]</sup> reported the PFS. Twenty studies<sup>[26–34,36,38–46]</sup> reported the CR rate, and 17 studies<sup>[26–30,32–39,41,43,44,46]</sup> reported the PR rate. The SD and PD was reported by 20 studies.<sup>[26–34,36,38–46]</sup> A detailed description of the baseline characteristics of included participants is mentioned in Table 1.

#### 3.3. Summary of intervention groups

A total of 4421 patients were included in analysis, with a mean age of 58.6 years. A total of 2634 males (59.6%) and 1787 females (40.4%) were enrolled. Nivolumab was given for 17 groups (1987 patients), ipilimumab was administered in 862 patients (4 arms), chemotherapy was given to 682 patients (4 groups), and combined nivolumab and ipilimumab was given for 890 patients (16 groups).

#### 3.4. Risk of bias among studies

An overall low risk of bias was found among included non-randomized clinical trials. All studies were at low risk for all domains of the ROBINS-1 tool. As for randomized clinical trials, all studies adequately reported randomization of patients and proper allocation concealment. Considering the blinding of participants and personnel, 3 studies were open-labeled and not blinded. Therefore, they considered with a high risk of bias. Selection bias was low in all studies except 3 studies,<sup>[29,30,44]</sup> in which no sufficient data were found for a judgment. A detailed risk of bias assessment in each study is illustrated in Table S1 (Supplemental Digital Content, <http://links.lww.com/MD/G896>).

#### 3.5. Efficacy endpoints

**3.5.1. Response to treatment.** The rate of CR after treatment was reported in 11 studies.<sup>[26–31,33,36,41,43,45]</sup> The network of eligible comparisons for CR is shown in Figure S1A (Supplemental Digital Content, <http://links.lww.com/MD/G896>). Compared with chemotherapy, the CR was achieved significantly in nivolumab plus ipilimumab group (RR 11.41, 95% CI 5.06–25.71), nivolumab group (RR 9.56, 95% CI 4.32–21.16), and ipilimumab group (RR 2.71, 95% CI 1.17–6.30) (Figure 2A).

Evidence on PR was available from 11 studies.<sup>[26–31,33,36,41,43,45]</sup> The network of eligible comparisons for PR is shown in Figure 1B (Supplemental Digital Content, <http://links.lww.com/MD/G896>). Compared with chemotherapy, the PR was achieved significantly in nivolumab group (RR 2.23, 95% CI 1.71–2.91) and nivolumab plus ipilimumab group (RR 3.54, 95% CI 2.54–4.68), but not significant in ipilimumab alone group (RR 1.11, 95% CI 0.81–1.53) (Figure 2B).

Evidence on the rate of SD was available from 11 studies.<sup>[26–31,33,36,41,43,45]</sup> The network of eligible comparisons for the SD is shown in Figure 1C (Supplemental Digital Content, <http://links.lww.com/MD/G896>). Compared with the chemotherapy group, the rate of SD was significantly lower in the nivolumab group (RR 0.71, 95% CI 0.57–0.87), while significantly higher in the ipilimumab group (RR 1.57, 95% CI 1.81–2.08). The overall RR did not favor the nivolumab plus ipilimumab group over chemotherapy (Figure 2C).

The rate of disease progression after treatment was reported from ten studies.<sup>[26–31,33,36,41,45]</sup> The network of eligible comparisons for the rate of disease progression is shown in Figure 1D (Supplemental Digital Content, <http://links.lww.com/MD/G896>). Compared with the chemotherapy group, the rate of disease progression did not differ significantly from the ipilimumab group (RR 1.17, 95% CI 0.90–1.51). In the nivolumab group,

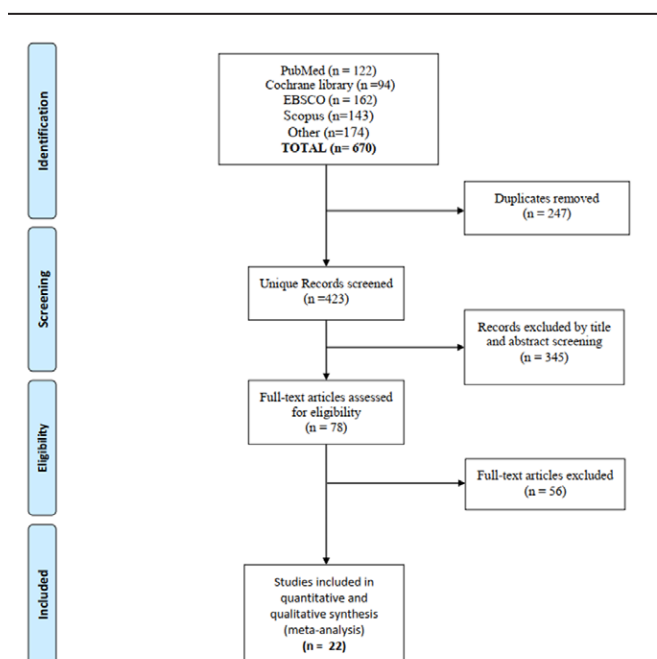


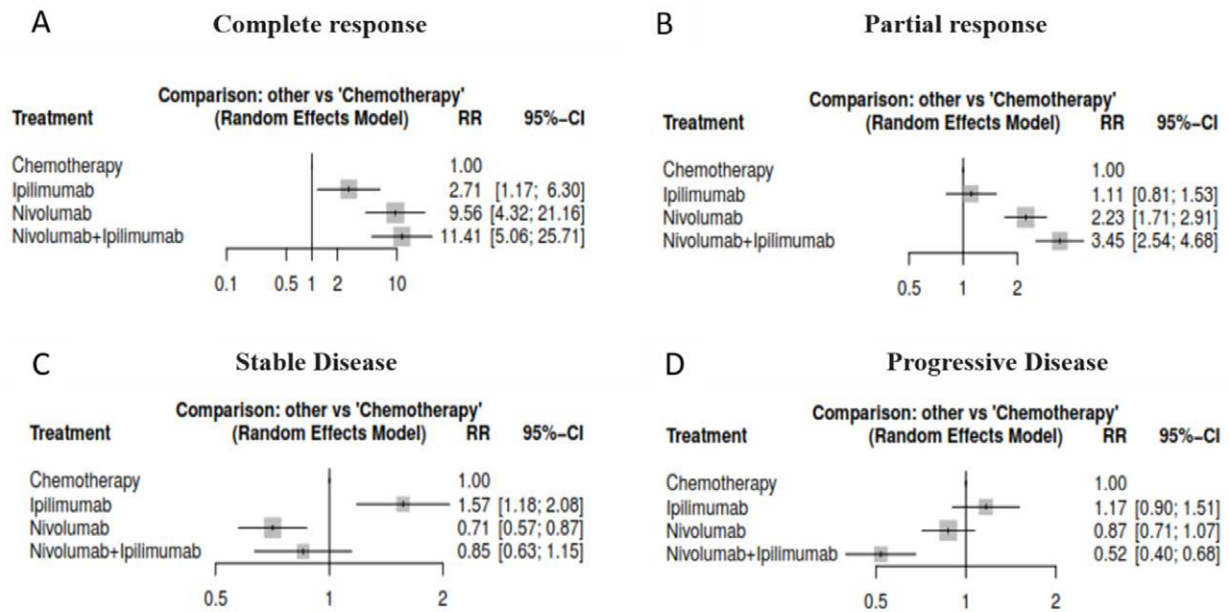
Figure 1. A PRISMA flow chart for our literature search.

**Table 1**  
Summary of baseline characteristics of included patients

Study ID	Design	Follow-up period, yrs	Interventions	Dose, mg/kg	Sample size	Men/women	Age, yrs	PD-L1 positive, n (%)	BRAF mutation, n (%)	MTC stage, n (%)	LDH > ULN, n (%)
Ascierto 2018	Follow of Robert 2015	3	Nivolumab	3	210	121/89	64.5 (13.4)	59 (28.1)	0 (0)	128 (61)	79 (37.6)
Callahan 2018	Follow of Wolchok 2013	3	Chemotherapy	1000 mg/m <sup>2</sup>	208	125/83	66.3 (15.2)	61 (29.3)	0 (0)	127 (61.1)	74 (35.6)
			Nivolumab + ipilimumab	0.3+3	14	51/44	58 (16.3)	58 (61.7)	24 (25.5)	52 (54%)	36 (38.8)
			Nivolumab + ipilimumab	1+3	17						
Gibney 2016	Non-RCT	3	Nivolumab + ipilimumab	3+3	16						
			Nivolumab + ipilimumab	3+3	6						
			Nivolumab	1	12	5/7	55 (11.2)	NR	NR	9 (75)	NR
Hodi 2016	RCT	2	Nivolumab	3	10	6/4	43 (12.5)	NR	NR	2 (20)	NR
			Nivolumab + ipilimumab	10	11	7/4	52 (13.7)	NR	NR	6 (67)	NR
Hodi 2018	Follow Larkin 2015	2	Nivolumab + ipilimumab	1+3	95	NR	NR	NR	NR	NR	NR
			Ipilimumab + placebo	3	47	NR	NR	NR	NR	NR	NR
Larkin 2015	RCT	2	Nivolumab	3	316	202/114	59 (15.66)	80 (25.3)	100 (31.6)	184 (58.2)	112 (35.4)
			Nivolumab + ipilimumab	1+3	314	206/108	59 (13.24)	68 (21.7)	101 (32.2)	181 (57.6)	114 (36.6)
			Ipilimumab	3	315	202/113	61 (19.9)	75 (23.8)	97 (30.8)	183 (58.1)	115 (36.5)
Larkin 2018	Follow of Weber 2015	3	Nivolumab	3	272	176/96	59 (14.5)	NR	60 (22)	203 (75)	140 (52)
			Chemotherapy	1000 mg/m <sup>2</sup>	133	85/48	62 (18.4)	NR	29 (22)	102 (77)	51 (38)
Larkin 2019	Follow Larkin 2015	1.5	Nivolumab + ipilimumab	1+3	35	29/6	59 (9.92)	NR	19 (54)	NR	18 (51)
			Nivolumab	3	25	19/6	63 (11.23)	NR	14 (56)	NR	14 (56)
Namikawa 2018	non-RCT	2.5	Nivolumab	3	16	11/5	51 (9.8)	NR	13 (81)	NR	3 (19)
			Nivolumab + ipilimumab	1+3	30	14/16	58.5 (20.1)	20 (83.3)	2 (6.7)	NR	9 (30)
Postow 2015	RCT	1.5	Nivolumab + ipilimumab	1+3	95	63/32	64 (19.8)	NR	23 (24)	44 (46)	24 (25)
			Ipilimumab	3	47	32/15	67 (18.9)	NR	10 (21)	21 (45)	11 (23)
Robert 2015	RCT	1	Nivolumab	3	210	121/89	64.5 (13.4)	74 (35.2)	0 (0)	128 (61)	79 (37.6)
Rozeaman 2019	RCT	1	Chemotherapy	1000 mg/m <sup>2</sup>	208	125/83	66.3 (15.2)	64 (35.6)	0 (0)	127 (61.1)	74 (35.6)
			Nivolumab + ipilimumab	1+3	30	19/11	64 (13.2)	NR	NR	NR	NR
Tawabi 2018	Non-RCT	2	Nivolumab + ipilimumab	3+1	30	14/16	54 (12.22)	NR	NR	NR	NR
			Nivolumab + ipilimumab	3+3	26	16/10	59 (15.44)	NR	NR	NR	NR
Weber 2013	Non-RCT	2	Nivolumab + ipilimumab	1+3	94	65/29	59 (18.33)	34 (36)	NR	NR	39 (41)
			Nivolumab	1	10	5/5	66.2 (13.4)	NR	NR	4 (40)	NR
Weber 2015	RCT	4	Nivolumab	3	13	6/7	61.5 (12.6)	NR	NR	13 (100)	NR
			Nivolumab + ipilimumab	10	11	7/4	58.5 (11.7)	NR	NR	6 (64)	NR
weber2017a	RCT	2	Nivolumab + ipilimumab	3+3	10	7/3	57.8 (15.6)	NR	NR	10 (100)	NR
			Nivolumab + ipilimumab	3+4	5	4/1	67.4 (17.6)	NR	NR	2 (40)	NR
weber2017b	RCT	2	Nivolumab + ipilimumab	3+5	41	29/12	62.1 (11.5)	NR	NR	30 (73)	NR
			Chemotherapy	3	272	176/96	59 (14.5)	NR	60 (22)	203 (75)	140 (52)
Wolchok 2013	Non-RCT	2	Nivolumab	1000 mg/m <sup>2</sup>	133	85/48	62 (18.4)	NR	29 (22)	102 (77)	51 (38)
			Ipilimumab	3	453	258/195	56 (17.8)	152 (33.6)	187 (41.3)	20/82 (24.4)	NR
Yamazaki 2017	Non-RCT	2	Nivolumab	10	453	269/184	54 (20)	154 (34)	194 (42.8)	21/87 (24.1)	NR
			Combined Nivolumab and ipilimumab	3	92	60/32	NR	NR	20 (21.7)	73 (80)	NR
Yamazaki 2019	Follow of Yamazaki 2017	3	Nivolumab	NR	53	NR	NR	NR	NR	NR	NR
			Nivolumab	3	24	14/10	63 (15.6)	NR	6 (25)	NR	NR

Data are mean (SD) unless otherwise specified. NR = not reported, PD = progressive disease.





**Figure 2.** Network meta-analysis of different treatments versus chemotherapy for (A) complete responses, (B) partial response, (C) stable disease, and (D) progressive diseases.

the rate of disease progression with lower than the chemotherapy group (RR 1.17, 95% CI 0.90-1.51, not significant); while, in the nivolumab plus ipilimumab group, the rate of disease progression was significantly lower than chemotherapy group (RR 0.52, 95% CI 0.40-0.68) (Figure 2D). Our analysis showed no source of inconsistency in any of the included comparisons.

The league tables for the pairwise comparison of each response to treatment were presented in Figure S2 (Supplemental Digital Content, <http://links.lww.com/MD/G896>).

**3.5.2. Overall survival rate.** Evidence on OS was available from 4 studies.<sup>[26,33,36,40]</sup> Direct comparison between the nivolumab and the combination of nivolumab plus ipilimumab showed no significant difference in 1-year OS (HR 1.31, 95% CI 0.88-1.96), while after 2 years and 3 years, the OS was significantly higher in nivolumab plus ipilimumab group (HR 1.41, 95% CI 1.09-1.8; HR 2.14, 95% CI 1.40-3.26, respectively). Compared with chemotherapy, the direct comparison showed that nivolumab (HR 1.54, 95% CI 0.85-2.78) and the combination of nivolumab plus ipilimumab (HR 1.17, 95% CI 0.76-1.81) after 1 year. While a significant higher 2 years and 3 years OS in the nivolumab group compared with chemotherapy (HR 1.52, 95% CI 1.07-2.18; HR 2.26, 95% CI 1.28-3.98) (Fig. 2). All the evidence about these contrasts came from the trials which directly compare this outcome. Therefore, we could not measure the inconsistency due to the lack of a closed-loop comparison.

**3.5.3. Progression-free survival rate.** Evidence on PFS was available from 6 studies.<sup>[26,29,30,33,36,40]</sup> Compared with nivolumab, the direct comparison showed that ipilimumab (HR 1.28; 95% CI 0.45-3.66), not significant. Although, the overall effect estimate favored the nivolumab group than the combination of nivolumab plus ipilimumab (HR 3.06, 95% CI 1.70-5.49) and chemotherapy group (HR 3.58, 95% CI 1.63-7.84) after 1 year. Ipilimumab alone showed a significantly higher PFS compared to the chemotherapy group (HR 2.79, 95% CI 1.38-5.66) (Fig. 3). Evidence for the aforementioned contrasts came from trials which directly compared this outcome. Therefore, we could not measure inconsistency due to the lack of a closed-loop comparison.

Regarding PFS after 2 and 3 years, NMA was not possible due to the lack of the minimum required number of studies. After 2

years of follow-up, 1 study<sup>[33]</sup> reported the PFS rate of nivolumab (37%) versus chemotherapy (7%), and another study<sup>[41]</sup> compared the combined regimen (38%) versus nivolumab (38%). The comparison between the combined regimen (51%) and ipilimumab (21%) was also reported by 1 study.<sup>[29]</sup> After 3 years of follow-up, only 1 study reported PFS rates of combined nivolumab and ipilimumab (39%), nivolumab (43%), and ipilimumab (10%). Evidence for the aforementioned contrasts came from trials which directly compared this outcome. Therefore, we could not measure inconsistency due to the lack of a closed-loop comparison.

**3.6. Safety endpoints**

The network of eligible comparisons for each AE is shown in Figure S3 (Supplemental Digital Content, <http://links.lww.com/MD/G896>). Compared to chemotherapy, the rates of any AE or treatment-related AE did not favor any of the other comparisons. Regarding arthralgia, the nivolumab group and ipilimumab group were associated with lower events when compared to chemotherapy (RR 0.55, 95% CI 0.35-0.89; RR 0.43, 95% CI 0.25-0.74, respectively). Nivolumab group was associated with significant lower events of nausea (RR 0.32, 95% CI 0.18-0.59), but no difference was seen in the ipilimumab group or nivolumab plus ipilimumab group when compared with chemotherapy. Furthermore, there was no significant difference between the nivolumab when compared to chemotherapy in term of diarrhea, while the ipilimumab group or nivolumab plus ipilimumab group were associated with significantly higher events of diarrhea when compared with chemotherapy (RR 1.61, 95% CI 1.08-2.39; RR 2.03, 95% CI 1.36-3.02, respectively) (Fig. 4).

The network of eligible comparisons showed that the nivolumab group, ipilimumab group, or nivolumab plus ipilimumab group was associated with significant lower events of vomiting when compared with chemotherapy (RR 0.24, 95% CI 0.15-0.39; RR 0.27, 95% CI 0.15-0.48; RR 0.52, 95% CI 0.30-0.90, respectively).

The same significant lower events of fatigue were observed. The network of eligible comparisons showed that the nivolumab

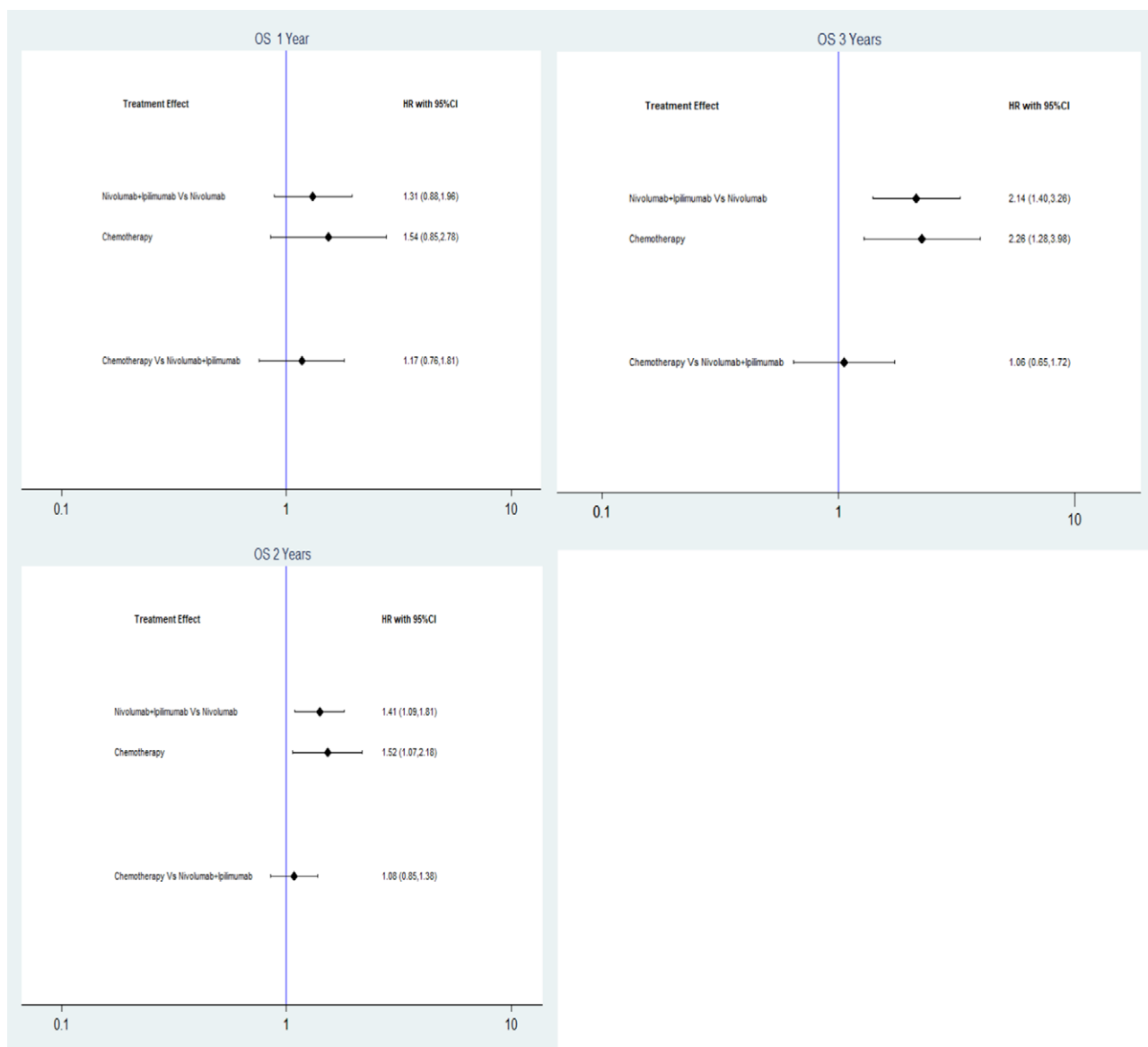


Figure 3. Direct meta-analysis of different treatments versus placebo in the overall survival.

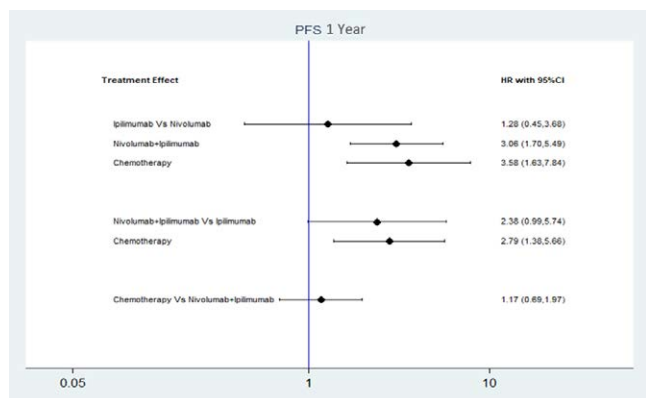


Figure 4. Direct meta-analysis of different treatments versus placebo in the progression-free survival.

group, ipilimumab group, or nivolumab plus ipilimumab group was associated with significant lower events of fatigue when compared to chemotherapy (RR 0.53, 95% CI 0.37-0.75;

RR 0.47, 95% CI 0.30-0.76; RR 0.53, 95% CI 0.33-0.84, respectively).

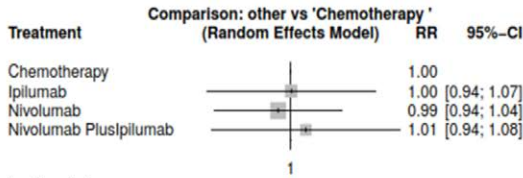
Pruritis, rash, and vitiligo events were significantly lower in nivolumab, ipilimumab, or nivolumab plus ipilimumab groups when compared with chemotherapy. Summary of the NMA of different treatments versus chemotherapy was presented in Figure 5.

#### 4. Discussion

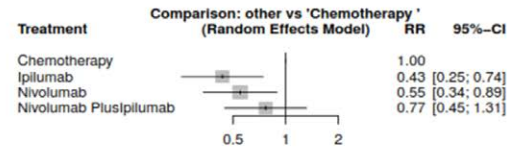
This study demonstrates that combined nivolumab plus ipilimumab provided a significant high CR rate, while nivolumab administration was associated with a high PR rate compared with the chemotherapy group. The rate of SD was significantly lower in the nivolumab group, but higher in the ipilimumab group. No significant difference was observed for the rate of disease progression in the nivolumab group when compared with chemotherapy. As for the AEs, nivolumab monotherapy is associated with the least side effects.

Our results are consistent with the previous NMA in the literature. A recent study reported that nivolumab and combined nivolumab plus ipilimumab were more effective in the

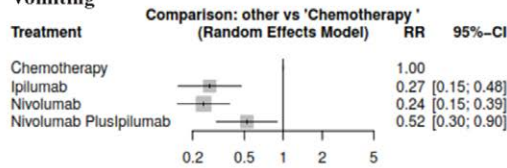
Any Adverse event



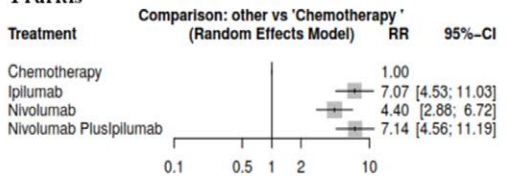
Arthralgia



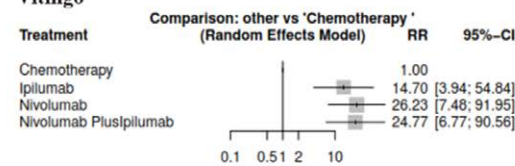
Vomiting



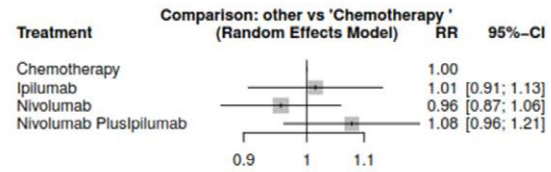
Pruritis



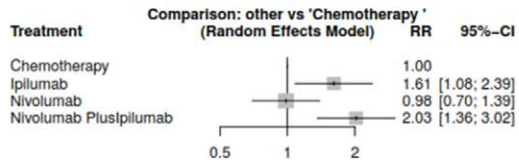
Vitiligo



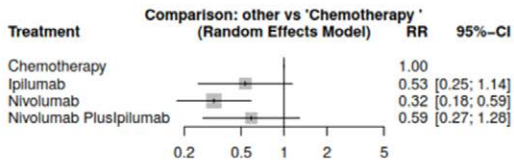
Treatment related Adverse event



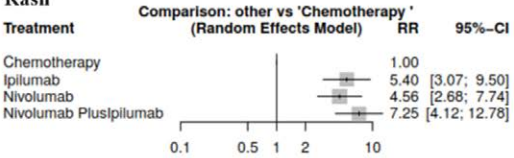
Diarrhea



Nausea



Rash



Fatigue

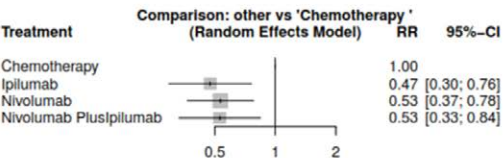


Figure 5. Network meta-analysis of different treatments versus chemotherapy.

treatment of melanoma compared with chemotherapy. In addition, nivolumab is associated with the lowest side effects. Another study<sup>[47]</sup> compared overall survival rates of nivolumab and combined nivolumab plus ipilimumab with dabrafenib plus trametinib and vemurafenib plus cobimetinib and the results showed that both nivolumab plus ipilimumab and nivolumab monotherapy associated with more OS rates than dabrafenib plus trametinib and vemurafenib plus cobimetinib. This study also found that nivolumab is significantly safer than chemotherapy in most safety aspects.

Contrary to the previous results,<sup>[47]</sup> Garzón-Orjuela et al<sup>[48]</sup> found that Dabrafenib/trametinib therapy is associated with higher OS rates when compared with ipilimumab, and more PFS rates when compared with both ipilimumab and nivolumab. However, as a limitation, the NMA stated that the quality of their evidence might be low. The same NMA also found that ipilimumab and combined ipilimumab plus nivolumab were associated with a higher incidence of AEs.

Another study<sup>[49]</sup> found that nivolumab is the best therapeutic drug for preventing the recurrence of melanoma. Nivolumab was associated with the greatest recurrence-free survival rates when compared with dabrafenib-trametinib and pembrolizumab. The study also reported that the incidence of any AE is best observed in the nivolumab-treated group.

A study of combined nivolumab plus ipilimumab and nivolumab monotherapy showed that both result in greater PFS rates than ipilimumab.<sup>[31]</sup> Combination therapy and nivolumab

monotherapy are both effective in treating melanoma, with the combination regimen more effective.<sup>[41]</sup> A further study found that nivolumab monotherapy or the combined regimen yields more PFS rates and objective response rates than ipilimumab.<sup>[30]</sup>

Although the included trials revealed that combined nivolumab plus ipilimumab is more effective than either agent alone, this study's analysis of a larger sample size showed that nivolumab monotherapy is associated with more PR rates.

Regarding AEs, chemotherapy has been reported to be associated with more AEs than nivolumab.<sup>[31,33]</sup> These findings give nivolumab a high safety ranking over other drugs. In this study analysis, nivolumab is associated with lower side effects than other regimens. However, immunological-related side effects tend to be higher in the nivolumab arm, such as pneumonia, vitiligo, and rash. Although the results were nonsignificant, analysis of a larger sample size in future studies might reveal more insights into the safety of the drug.

There has been a lack of critical specific judgment on the efficacy and safety of nivolumab for the treatment of melanoma. Therefore, we performed this NMA and a systematic review of all available clinical trials with all available follow-up studies to assess the efficacy and safety of nivolumab wither alone or in combination with ipilimumab compared chemotherapy at those studies for treating patients with melanoma and melanoma metastases, seeking for proper assessment of nivolumab for melanoma in terms of safety and efficacy among other checkpoint inhibitor (ipilimumab alone or in combination with

nivolumab) and chemotherapy. Previous meta-analyses reported the immune-related AEs of chemotherapy in the treatment of simple solid tumors.<sup>[50–55]</sup>

One study considered including stage III/IV melanoma, although they did not assess different terms of considering BRAF-V600 mutation to be positive. They reported that nivolumab combined with ipilimumab has better short-term effects compared with chemotherapy.<sup>[56]</sup> In a study by da Silveira et al<sup>[57]</sup> as well, they compared between immunotherapy and targeted therapy and chemotherapy for treatment of patients with advanced melanoma. They concluded that a combination of BRAFi and MEKi had better results in improving OS than that of chemotherapy and also better than BRAFi alone. Nevertheless, these combined 2 drugs showed a higher PFS and response rate response than BRAFi alone, chemotherapy, and anti-PD-1 immunotherapy. Another study has made a comparison between these drugs in terms of pharmacological class in the treatment of advanced melanoma and BRAF mutation, and results showed no significant difference in OS between combined targeted therapies (BRAF plus MEK) and immunotherapies (nivolumab and pembrolizumab).<sup>[58]</sup> Meanwhile, a higher efficacy in PFS has been reported favoring combined BRAF-MEK therapy to other groups (PD-1/CTLA-4 and BRAFi).

A study of survival in patients with advanced metastatic melanoma reported trials of patients with metastatic or unresectable melanoma and made a comparison between their Kaplan-Meier survival curves, and found promising survival outcomes at the beginning of targeted therapies with progressive worsening after 1 year of treatment. In contrast, immunotherapies have shown increased survival outcomes over time.<sup>[59]</sup> Therefore, results should be interpreted with caution as follow-up times differ along with methods of comparison curves (weighted average), and reported data is of the mixed population. Unfortunately, most of the trials have reported their results (especially OS) with relatively short follow-up time. Moreover, some patients had more than 1 line of treatment with more than 1 drug in a way that made an impact on the outcomes. In our study, trials with all available follow-up publications were included.

#### 4.1. Strengths and limitations

This study included the latest data up to December 2019, we included all clinical trials reporting safety and efficacy nivolumab for the treatment of melanoma. This NMA reported survival rates and treatment response rates of nivolumab, responses to treatment, AEs, and reported comparison of the different drugs on these parameters. Only clinical trials were included. The main strength of our study lies in the large sample size of included patients (4221 participants). This study also compared the most clinically used regimens in a NMA model and provided a direct and indirect comparison of regimens with each other. Another strength point is encompassing a follow-up period of 3 years for patients in different studies.

The main limitation is the exclusion of certain drugs as durvalumab and avelumab because they were only included in 1 trial. Another limitation is that the analysis of the AEs does not necessarily indicate a safety profile. A recently published study<sup>[60]</sup> has shown that cancer patients receiving these therapies usually have mild to moderate AEs, and are easily reversible with reduction of the dose or gradual withdrawal of treatment. This indicates that the incidence of AEs is largely predictable, and proper follow-up and monitoring may reduce the incidence of unnecessary discontinuation of drugs.<sup>[61]</sup>

#### 5. Conclusion

We conclude that combined ipilimumab and nivolumab provides the greatest CR rates as well as higher overall survival rates after 2 and 3 years. Nivolumab provides the best PR rates

and the least side effects when compared to chemotherapy. Regarding PFS, ipilimumab leads to higher PFS rates than chemotherapy. The results reveal that the efficacy of nivolumab versus the combined regimen is nearly equal. Comparing efficacy and safety and in order to avoid immunological-related side effects, we suggest nivolumab monotherapy as first-line therapy for patients with melanoma.

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