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Efficacy and safety of CTLA-4 inhibitors combined with PD-1 inhibitors or chemotherapy in patients with advanced melanoma

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ABSTRACT

Background: Although immune checkpoint inhibitor monotherapy has demonstrated significant efficacy in advanced melanoma, no study has systematically evaluated the efficacy and safety of the combination regimens. In this study, we conduct a comprehensive meta-analysis to explore the efficacy and safety of CTLA-4 inhibitors combined with PD-1 inhibitors or chemotherapy in advanced melanoma.

Methods: We performed a systematic search of Medline, PubMed, Embase and Web of Science for relevant clinical trials. The primary objective was to explore the efficacy and safety of combination regimens compared to monotherapy. The secondary objective was to compare the difference in efficacy between CTLA-4 inhibitors plus PD-1 inhibitors and CTLA-4 inhibitors plus chemotherapy.

Results: A total of 12 trials involving 3308 patients were included for our meta-analysis. For combination regimens compared to monotherapy, the pooled HR for overall survival (OS) was 0.67 (95%CI 0.53–0.81) and for progression-free survival (PFS) was 0.56 (95%CI 0.41–0.71). For CTLA-4 inhibitors plus PD-1 inhibitors, the combined one-year OS rate (OSR_{1y}), six-month PFS rate ($PFSR_{6m}$) and disease control rate (DCR) were 64.0% (95%CI: 49.6%–78.4%), 56.4% (95%CI: 50.1%–62.7%) and 69.9% (95%CI: 65.1%–74.7%), respectively. For CTLA-4 inhibitors plus chemotherapy, the combined OSR_{1y}, $PFSR_{6m}$ and DCR were 35.2% (95%CI: 25.4%–45.0%), 54.6% (95%CI: 42.7%–66.60%) and 33.5% (95%CI: 28.0%–38.9%), respectively.

Conclusions: Combination regimens significantly improved OS and PFS of advanced melanoma patients compared to monotherapy. An acceptable safety profile was observed in both CTLA-4 inhibitors plus PD-1 inhibitors and CTLA-4 inhibitors plus chemotherapy. A comparison of these two combination regimens showed that patients who received CTLA-4 inhibitors plus PD-1 inhibitors had a better therapeutic effect compared to those receiving CTLA-4 inhibitors plus chemotherapy. Further randomized clinical trials are urgently required to validate our results.

1. Introduction

Malignant melanoma is a highly aggressive and lethal skin cancer, which originates from melanocytes. About 200,000 new cases of malignant melanomas occur each year worldwide, of which > 65,000 die from advanced melanoma according to WHO statistics [1–4]. Most patients with a local melanoma can be cured, while patients diagnosed with metastatic disease had a poor prognosis, with a median overall survival of 8 months and 5-year survival rate of 10% [5]. The current treatment strategy of advanced melanoma is mainly to up-regulate antitumor immunity by blocking two immunosuppressive molecules, cytotoxic T lymphocyte associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1). Ipilimumab, a fully human, IgG1 monoclonal antibody, enhances the T cell response by blocking CTLA-4 pathway [6]. Nivolumab, a fully human, IgG4 monoclonal antibody, augments T-cell activation and proliferation by specifically disrupting the interaction of PD-1 receptor with its ligands (PD-L1 and PD-L2). Ipilimumab monotherapy and nivolumab monotherapy in melanoma

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patients have showed a significant survival benefit compared with chemotherapy. The objective response rate in these two monotherapy was up to 15% and 30% respectively [7–10]. Preclinical data have demonstrated that dual blockade significantly improves antitumor immune response compared to single blockade. Meanwhile, preclinical models have showed that chemotherapy can induce tumor cells to express PD-L1 molecules, thereby enhancing the anti-tumor activity of immune cells [11–13]. The above information suggests that combination therapy for advanced melanoma could be a potential strategy to improve the efficacy of immune checkpoint inhibitors. However, few studies have systematically evaluated the efficacy and safety of CTLA-4 inhibitors combined with PD-1 inhibitors or chemotherapy in advanced melanoma. The optimal combination of CTLA-4 inhibitors, PD-1 inhibitors and chemotherapy for the treatment of advanced melanoma remains controversial. Therefore, we performed this meta-analysis to systematically explore the efficacy and safety of the combination of CTLA-4 inhibitors with PD-1 inhibitors or chemotherapy in advanced melanoma based on present clinical evidence.

2. Material and methods

We strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to perform this meta-analysis [14].

2.1. Search strategy and study selection

We conducted a comprehensive search of PubMed, Medline, Embase and Web of Science for relevant clinical trials published between Jan 2008 and Aug 2018. The following search terms were used: PD-1 inhibitors, CTLA-4 inhibitors, chemotherapy, nivolumab, pembrolizumab, ipilimumab, tremelimumab, efficacy, safety and combination immunotherapy. We then reviewed abstracts and presentations of European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) meeting for more clinical data. Additionally, we also manually identified the reference lists of the final included studies to extend our search.

Trials that fulfilled the following predetermined criteria were included in our meta-analysis: (1) randomized controlled or single-arm trials that assessed CTLA-4 inhibitors combined with PD-1 inhibitors or chemotherapy in advanced melanoma; (2) melanoma patients with treated or untreated brain metastases; (3) trials reported any of the following outcomes: overall survival (OS), progression-free survival (PFS), disease control rate (DCR), objective response rate (ORR) and adverse events (AEs); and (4) trials reported number and sample size for all-grade or high -grade adverse events.

The following predetermined exclusion criteria were used: (1) unpublished clinical trials, case reports, retrospective studies, letters to the editors and review articles; (2) studies without related data; and (3) duplicate publications. Three investigators (YLZ, RX and ZHW) reviewed the list of retrieved studies and selected the eligible studies independently according to inclusion and exclusion criteria. Any disagreement was discussed and resolved through consensus among all investigators.

2.2. Data extraction

Data extraction was performed by two independent investigators (BZ and RX) and any discrepancies between reviewers were resolved by the achievement of consensus. From all eligible studies, the following information was extracted: first author's name, year of publication, randomization, trial phase, treatment arms, number of patients for analysis and patients' mean age. The primary outcomes were OS, PFS, ORR and DCR (complete response rate + partial response rate + stable disease rate). The secondary outcomes were adverse events including vomiting, fatigue, pyrexia, appetite decreased, diarrhea, colitis, amylase increased, lipase increased, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, hypothyroidism, hyperthyroidism and pneumonitis. The severity of adverse events was reported according to version 3 or 4 of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). We also extracted six-month PFS rate ($PFSR_{6m}$) or one-year OS rate (OSR_{1y}) from the combination regimen groups.

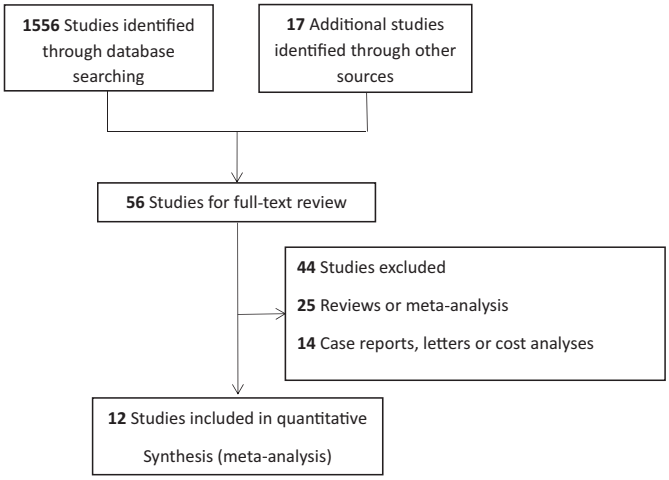

Fig. 1. The detailed process of study selection and reasons for exclusion.

2.3. Risk of bias assessment

The Cochrane risk of bias assessment was used to explore sources of bias among all included studies. The following criteria were assessed: (1) randomized Sequence Generation, (2) allocation concealment, (3) blinding of participants, personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective outcome reporting, and (7) other sources of bias. We described each item as low risk, high risk or unclear risk. Because single-arm trials had a natural high risk of bias, we did not assess their bias. Two authors independently perform the risk of bias assessment and any discrepancies were resolved by the achievement of consensus.

2.4. Statistical analysis

The primary objective of our study was to explore the efficacy and safety of combination regimens for advanced melanoma compared to monotherapy. The secondary objective was to compare the difference in efficacy between CTLA-4 inhibitors combined with PD-1 inhibitors and CTLA-4 inhibitors combined with chemotherapy according to $PFSR_{6m}$, OSR_{1y}, ORR and DCR. We used the Q test and I^2 statistic to evaluate the heterogeneity among included studies. I^2 value of $< 25\%$, 25–50% and $> 50\%$ was considered as low, moderate, or high heterogeneity, respectively. If there was significant heterogeneity between the individual studies ($I^2 > 50\%$), a random-effect model was used for meta-analysis. Otherwise, a fixed-effect model was used. Hazard ratios were used to calculate the pooled time-to event data and risk ratios (RR) was calculated for dichotomous data. The safety was assessed by calculating overall incidence of all-grade AEs. All 95% confidence intervals (CI) were two-sided. Sensitivity analysis was used to examine the stability of combined results by removing one study at a time. Subgroup analyses were conducted according to the therapeutic regimens. Publication bias was evaluated by the Begg's test and Egger's test [15,16]. Risk of bias was summarized by using Review Manager 5.3 software (Nordic Cochrane Center, Copenhagen, Denmark). All statistical analyses were performed by using StataSE12.0 software (StataCorp, College Station, Texas). $p \leq 0.05$ was considered statistically significant.

Table 1
Characteristic of the eligible studies in the meta-analysis.

Study	Year	Phase	Treatment arms	No. of patients	Whether randomized	Age (years) Median (range)	Overall survival HR (95% CI)	Progression-free survival HR (95% CI)
Hersh [17]	2011	2	Ipilimumab + dacarbazine	35	Randomized	60 (27–82)	0.83 (0.51–1.37)	Not given
			Ipilimumab	37		66 (25–82)		
Hodi [18]	2016	2	Nivolumab + ipilimumab	95	Randomized	64 (27–87)	0.74 (0.43–1.26)	0.36 (0.22–0.56)
			Ipilimumab	47		67 (31–80)		
Long [19]	2018	2	Nivolumab + ipilimumab	35	Randomized	59 (53–68)	A: 0.92 (0.41–2.07)	A: 0.43 (0.24–0.74)
			Nivolumab	26		63 (52–74)	B: 0.33 (0.14–0.78)	B: Not given
			Nivolumab	16		51 (48–56)		
Robert [8]	2011	3	Ipilimumab + dacarbazine	250	Randomized	57.5	0.72 (0.59–0.88)	0.86 (0.75–0.98)
			Dacarbazine	252		56.4		
Wolchok [20]	2017	3	Nivolumab + ipilimumab	314	Randomized	61 (18–88)	A: 0.85 (0.68–1.07)	A: 0.78 (0.64–0.96)
			Nivolumab	316		60 (25–90)	B: 0.55 (0.45–0.69)	B: 0.43 (0.35–0.52)
			Ipilimumab	315		62 (18–89)		
Larkin [21]	2015	3	Nivolumab + ipilimumab	314	Randomized	59 (18–88)	Not given	A: 0.74 (0.60–0.92)
			Nivolumab	316		59 (25–90)		B: 0.42 (0.31–0.57)
			Ipilimumab	315		61 (18–89)		
Postow [22]	2015	1	Nivolumab + ipilimumab	95	Randomized	64 (27–87)	Not given	0.40 (0.23–0.68)
			Ipilimumab	47		67 (31–80)		
Wolchok [23]	2013	1	Concurrent regimen	53	Randomized	58(22–79)	Not given	Not given
			Sequenced regimen	33		64(23–89)		
Giacomo [24]	2012	2	Ipilimumab + fotemustine	86	Non-randomized	54 (43–66)	Not applicable	Not applicable
Tawbi [25]	2018	2	Nivolumab + ipilimumab	94	Non-randomized	59 (22–81)	Not applicable	Not applicable
Patel [26]	2016	2	Ipilimumab + temozolomide	64	Non-randomized	62 (33–75)	Not applicable	Not applicable
Long [27]	2017	1b	Pembrolizumab + ipilimumab	153	Non-randomized	60 (53–70)	Not applicable	Not applicable

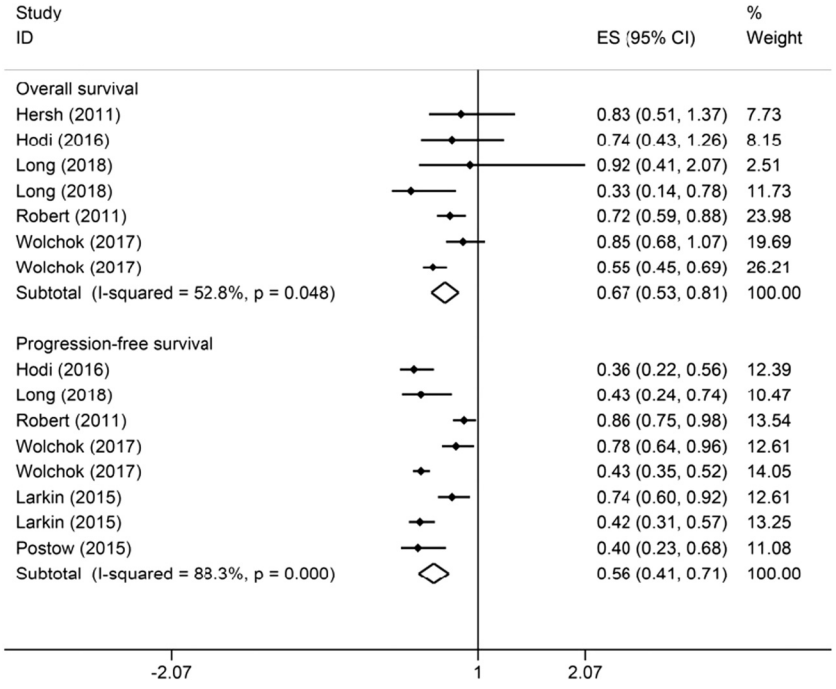

Fig. 2. Forest plot of the pooled overall survival and progression-free survival in advanced melanoma patients who received CTLA-4 inhibitors combined with PD-1 inhibitors or chemotherapy compared to monotherapy.

Table 2
Subgroup analysis of overall survival (OS), progression-free survival (PFS) overall response rate (ORR) of combination therapy compared with monotherapy.

Subgroup	Overall survival HR (95%CI)	Progression-free survival HR (95%CI)	Overall response rate HR (95%CI)
CTLA-4 inhibitors + PD-1 inhibitors	0.64 (0.44, 0.84)	0.51 (0.39, 0.64)	2.54 (1.62, 3.97)
CTLA-4 inhibitors + chemotherapy	0.73 (0.59, 0.87)	0.86 (0.75, 0.98)	2.64 (0.55, 12.75)
Overall	0.67 (0.53, 0.81)	0.56 (0.41, 0.71)	2.54 (1.65, 3.91)

Table 3
The pooled incidence of all-grade treatment-related AEs in advanced melanoma patients for included studies.

All-grade AEs	No. events	Statistical method	Incidence (95% CI)
CTLA-4 inhibitors plus PD-1 inhibitors			
Vomiting	137/1020	Fixed-effects model	0.12 (0.09, 0.15)
Pyrexia	162/867	Fixed-effects model	0.19 (0.16, 0.21)
Appetite decreased	150/867	Fixed-effects model	0.17 (0.15, 0.20)
Fatigue	432/1055	Random-effects model	0.42 (0.37, 0.47)
Colitis	139/1114	Random-effects model	0.12 (0.08, 0.15)
Diarrhea	432/1055	Random-effects model	0.38 (0.32, 0.45)
ALT increased	234/1114	Random-effects model	0.23 (0.17, 0.28)
AST increased	205/1114	Random-effects model	0.20 (0.15, 0.25)
Hypothyroidism	177/1055	Random-effects model	0.17 (0.11, 0.22)
Hyperthyroidism	69/707	Random-effects model	0.08 (0.05, 0.12)
Amylase increased	86/742	Fixed-effects model	0.11 (0.08, 0.13)
Lipase increased	90/589	Fixed-effects model	0.15 (0.12, 0.18)
Pneumonitis	65/742	Fixed-effects model	0.08 (0.06, 0.10)
CTLA-4 inhibitors plus chemotherapy			
Vomiting	119/397	Random-effects model	0.30 (0.09, 0.52)
Fatigue	125/346	Random-effects model	0.32 (0.06, 0.59)
Pyrexia	120/346	Fixed-effects model	0.34 (0.29, 0.39)
Appetite decreased	54/247	NA	0.22 (0.17, 0.27)
Diarrhea	135/346	Random-effects model	0.39 (0.25, 0.54)
Colitis	18/311	Random-effects model	0.07 (0.00, 0.13)
ALT increased	111/311	Random-effects model	0.38 (0.26, 0.49)
AST increased	99/311	Random-effects model	0.34 (0.22, 0.47)
CTLA-4 inhibitors monotherapy			
Vomiting	31/403	Fixed-effects model	0.07 (0.05,0.10)
Pyrexia	55/714	Fixed-effects model	0.08 (0.07,0.09)
Appetite decreased	89/714	Fixed-effects model	0.13 (0.10,0.15)
Fatigue	228/753	Random-effects model	0.32 (0.26,0.39)
Colitis	83/753	Fixed-effects model	0.11 (0.09,0.13)
Diarrhea	249/753	Fixed-effects model	0.33 (0.30,0.36)
ALT increased	18/403	Fixed-effects model	0.04 (0.02,0.06)
AST increased	17/403	Fixed-effects model	0.04 (0.02,0.06)
Hypothyroidism	40/714	Random-effects model	0.06 (0.03,0.09)
Hyperthyroidism	6/622	Fixed-effects model	0.01 (0.00,0.02)
Lipase increased	22/403	Fixed-effects model	0.05 (0.03,0.08)
Pneumonitis	50/714	Random-effects model	0.07 (−0.01,0.15)

3. Results

3.1. Search results and study characteristics

Using our search strategy, a total of 1573 potential relevant studies were identified. After initial title and abstract screening, 56 studies were eligible for full-text review. We finally included 12 studies according to our inclusion and exclusion criteria, 8 of which were randomized controlled trials, and 4 were single-arm trials. Fig. 1 showed the detailed process of study selection and reasons for exclusion. Among all 12 studies, there were three phase 1 trials, six phase 2 trials and three phase 3 trials. For combination regimens, eight studies evaluated CTLA-4 inhibitors combined with PD-1 inhibitors and four studies evaluated CTLA-4 inhibitors combined with chemotherapy. The number of patients involved in each trial ranged from 64 to 945. Of the total 3308 patients included in our meta-analysis, 1153 were enrolled in CTLA-4 inhibitors combined with PD-1 inhibitors trials, 435 were enrolled in CTLA-4 inhibitors combined with chemotherapy trials, 1720 were enrolled in monotherapy regimen. (See Table 1.)

3.2. Efficacy of combination therapy compared with monotherapy

A total of five randomized controlled trials involving 1738 advanced melanoma patients reported the overall survival HR for combination regimens compared with monotherapy. There was significant heterogeneity between the individual studies ($p = 0.048$, $I^2 = 52.8\%$). Based on the random-effect model, the pooled HR and its 95%CI for OS showed a significant difference between combination therapy and monotherapy (HR 0.67; 95%CI 0.53–0.81, Fig. 2). A combination of CTLA-4 inhibitors and PD-1 inhibitors or chemotherapy resulted in a significant improvement on OS compared to monotherapy. Six randomized trials including 2753 patients were incorporated in the PFS analysis. There was evidence of significant heterogeneity between the studies ($P = 0.00$, $I^2 = 88.3\%$). Using the random-effect model, the pooled HR of PFS was 0.56 (95%CI 0.41–0.71, Fig. 2). Advanced melanoma patients treated with combination therapy had a longer PFS compared with monotherapy. For ORR, patients who received CTLA-4 inhibitors combined with PD-1 inhibitors or chemotherapy had significantly higher ORR compared with monotherapy (RR 2.54; 95%CI 1.65, 3.91, Table 2). We also performed subgroup analyses according to types of combination regimens. Our meta-analysis indicated that whether CTLA-4 inhibitors combined with PD-1 inhibitors or CTLA-4 inhibitors combined with chemotherapy, combination therapy showed significant improvement on survival benefits compared to monotherapy, except for ORR in CTLA-4 inhibitors combined with chemotherapy (Table 2).

3.3. Toxicity and tolerability

We have demonstrated that combination immunotherapy increased the risk of developing adverse events in cancer patients compared to monotherapy [28]. In this study, we summarized data from single-arm studies to further present the differences on toxicity and tolerability between CTLA-4 inhibitors plus PD-1 inhibitors and CTLA-4 inhibitors plus chemotherapy. We pooled the incidence of selected adverse events with 95%CI. Table 3 showed the incidence of all-grade treatment-related AEs. In patients receiving CTLA-4 inhibitors plus PD-1 inhibitors, all-grade vomiting occurred in 137 of 1020 (12%), pyrexia in 162 of 867 (19%), fatigue in 432 of 1055 (42%), colitis in 139 of 1114 (12%), diarrhea in 432 of 1055 (38%), ALT elevation in 234 of 1114 (23%), AST elevation in 205 of 1114 (20%), hypothyroidism in 177 of 1055 (17%), hyperthyroidism in 69 of 707 (8%), amylase elevation in 86 of 742 (11%), lipase elevation in 90 of 589 (15%) and pneumonitis in 65 of 742 (8%). For patients treated with CTLA-4 inhibitors plus chemotherapy, all-grade vomiting occurred in 119 of 397 (30%), fatigue in 125 of 346 (32%), pyrexia in 120 of 346 (34%), appetite decreased in 54 of 247 (22%), diarrhea in 135 of 346 (39%), colitis in 18 of 311 (7%), ALT increased in 111 of 311 (38%) and AST increased in 99 of 311 (34%). We also pooled the incidence of all-grade adverse events in patients treated with CTLA-4 inhibitors monotherapy. The results showed that CTLA-4 inhibitors combined with PD-1 inhibitors or chemotherapy increased the risk of developing adverse events, except for colitis. (See Table 4.)

Table 4
The pooled $PFSR_{6m}$, OSR_{1y}, ORR and DCR with 95% CI in advanced melanoma patients for included studies.

Outcome analyses	Pooled $PFSR_{6m}$ (95%CI) Model	Pooled OSR_{1y} (95%CI) Model	Pooled ORR (95%CI) Model	Pooled DCR (95%CI) Model
CTLA-4 inhibitors + PD-1 inhibitors	0.56 (0.50, 0.63) Random	0.64 (0.50, 0.78) Random	0.58 (0.55, 0.61) Fixed	0.70 (0.65, 0.75) Random
CTLA-4 inhibitors + chemotherapy	0.35 (0.25, 0.45) Random	0.55 (0.43, 0.67) Random	0.14 (0.03, 0.25) Fixed	0.33 (0.28, 0.39) Fixed

3.4. CTLA-4 inhibitors plus PD-1 inhibitors versus CTLA-4 inhibitors plus chemotherapy

We established a comparison of efficacy between CTLA-4 inhibitors plus PD-1 inhibitors (CPP) and CTLA-4 inhibitors plus chemotherapy (CPC) by calculating the pooled $PFSR_{6m}$, OSR_{1y}, ORR and DCR. The combined $PFSR_{6m}$ was 56.4% (95%CI: 50.1%–62.7%) in CPP group and 35.2% (95%CI: 25.4%–45.0%) in CPC group. The combined OSR_{1y} was 64.0% (95%CI: 49.6%–78.4%) in CPP group and 54.6% (95%CI: 42.7%–66.60%) in CPC group. The combined ORR was 58.3% (95%CI: 55.3%–61.4%) in CPP group and 14.0% (95%CI: 2.5%–25.5%) in CPC group. The combined DCR was 69.9% (95%CI: 65.1%–74.7%) in CPP group and 33.5% (95%CI: 28.0%–38.9%) in CPC group.

4. Discussion

The efficacy and safety of CTLA-4 inhibitors alone and PD-1 inhibitors alone for treatment of advanced melanoma have been evaluated in many systematical review and meta-analyses. Although immune checkpoint inhibitor monotherapy significantly prolongs the overall survival of melanoma patients, the objective response rate to immune checkpoint inhibitors in patients remains relatively low. Ipilimumab alone was related to responses in 10% to 15% of patients and approximately 20% of previous treated patients achieved long-term survival [6,29,30]. And nivolumab alone was associated with 30 to 40% objective responses and most of the responses were durable [7]. Therefore, multiple combination regimens were underway, aiming to improve the response rate of patients to these antibodies, for long-term survival. A previous meta-analysis indicated that advanced lung cancer patients treated with PD-1/PD-L1 inhibitors combined with chemotherapy or CTLA-4 inhibitors had significant survival benefits, an acceptable safety profile and increased response rate, suggesting that combination therapy may be a potential strategy to address the problem of low response rates in patients [31]. Although several randomized and single-arm trials have investigated CTLA-4 inhibitors combined with PD-1 inhibitors or chemotherapy in advanced melanoma, no study has been conducted to systematically evaluate the efficacy and safety of these combination regimens and no comparison of efficacy among these combination regimens was established. Therefore, in this study, we summarized a large amount of clinical data to conduct a comprehensive analysis of combination therapy for advanced melanoma. More importantly, we established a comparison of efficacy between CTLA-4 inhibitors plus PD-1 inhibitors and CTLA-4 inhibitors plus chemotherapy based on $PFSR_{6m}$, OSR_{1y}, ORR and DCR.

To the best of our knowledge, this is the first meta-analysis on the efficacy and safety of CTLA-4 inhibitors combined with PD-1 inhibitors or chemotherapy in advanced melanoma. Meanwhile, this is the first study comparing efficacy and safety difference between CTLA-4 inhibitors plus PD-1 inhibitors and CTLA-4 inhibitors plus chemotherapy for treatment of melanoma.

In comparison with monotherapy, CTLA-4 inhibitors combined with PD-1 inhibitors or chemotherapy significantly improved OS and PFS in patients with advanced melanoma. Combination regimens were associated with significantly higher ORR of patients. In subgroup analyses, an improved survival was also observed in both CTLA-4 inhibitors plus PD-1 inhibitors group and CTLA-4 inhibitors plus chemotherapy group. Because of the small sample size, we could not make any conclusion about ORR of patients who received CTLA-4 inhibitors combined with chemotherapy. However, CTLA-4 inhibitors plus PD-1 inhibitors increased ORR by 33% compared with monotherapy. For safety and tolerability analysis, we have demonstrated that patients treated with combination therapy were at increased risk of immune-related adverse events [28]. In this study, we calculated the incidence of adverse events with 95%CI. The most commonly reported adverse events for CTLA-4 inhibitors combined with PD-1 inhibitors were vomiting, pyrexia, appetite decreased, fatigue, colitis, diarrhea, ALT increased, AST increased, hypothyroidism, hyperthyroidism, amylase increased, lipase increased and pneumonitis. The most commonly reported adverse events in the combination of CTLA-4 inhibitors and chemotherapy were vomiting, pyrexia, appetite decreased, fatigue, colitis, diarrhea, ALT increased and AST increased. We did not pool the incidence of high-grade adverse events because of their lower incidence. Notably, the incidence and risk of immune-related high-grade adverse events like colitis and ALT were relatively high, accounting for > 60% of all-grade immune-related adverse events. In addition, compared to CTLA-4 inhibitors plus chemotherapy, CTLA-4 inhibitors plus PD-1 inhibitors can induce more types of immune-related adverse events such as hypothyroidism, hyperthyroidism and pneumonitis. If not promptly recognized, pneumonitis and endocrine dysfunction can be life threatening [21,28]. For comparison of efficacy between these two combination regimens, CTLA-4 inhibitors plus PD-1 inhibitors significantly improved $PFSR_{6m}$ (56.4% vs 35.2%), OSR_{1y} (64.0% vs 54.6%), ORR (58.3% vs 14.0%) and DCR (69.9% vs 33.5%) than CTLA-4 inhibitors plus chemotherapy. Obviously, CTLA4 inhibitors combined with PD-1 inhibitors for the treatment of advanced melanoma was superior to CTLA-4 inhibitors plus chemotherapy.

Our study had several limitations. First, only one trial investigating pembrolizumab combined with ipilimumab was included in our meta-analysis, which limited us to further perform subgroup analysis. We cannot verify the conclusions drawn from indirect comparisons because no clinical trial has directly compare the difference in efficacy between CTLA-4 inhibitors plus PD-1 inhibitors and CTLA-4 inhibitors plus chemotherapy in advanced melanoma. Additionally, although only one trial investigated the efficacy of combination therapy in melanoma patients with untreated brain metastases [19], we found it did not affect the final conclusion after we conducted a sensitivity analysis.

4.1. Publication bias and sensitivity analysis

The Begg's and Egger's tests showed that there was no evidence of significant publication bias among the efficacy and safety analysis. Considering the significant heterogeneity between the individual studies, we conducted a sensitivity analysis to examine the stability of the combined results. The sensitivity analysis indicated that removing any single study did not significantly alter our results (data not shown).

5. Conclusions

Our meta-analysis showed that combination therapy with CTLA-4 inhibitors plus PD-1 inhibitors or chemotherapy had superior survival benefit and an acceptable safety profile over monotherapy in advanced melanoma. Patients who received CTLA-4 inhibitors plus PD-1 inhibitors had a better therapeutic effect compared to those receiving CTLA-4 inhibitors plus chemotherapy. Of note, the occurrence of fatal immune related adverse events in combination CTLA-4 inhibitors and PD-1 inhibitors needs to be given enough attention. Further prospective randomized clinical trials are urgently required to validate our findings.

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Conflicts of interests

None.

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