International Immunopharmacology 74 (2019) 105691

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

A large scale meta analysis identifies common adverse events with checkpoint inhibitors vs chemotherapy in melanoma patients

Ruyi Zhang[a], Xuehui Li[a], Zhiyu You[a], Li Jiang[a], Yaguang Weng[b], Qiong Shi[b], Lin Du[c], Shujuan Yan[d,*]

[a] Department of Clinical Laboratory, First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, Guiyang 550001, China
[b] Key Laboratory of Diagnostic Medicine Designated by the Chinese Ministry of Education, Chongqing Medical University, Chongqing 400016, China
[c] Department of Clinical Laboratory, The People's Hospital of Xingyi, Xingyi 562400, China
[d] Department of Clinical Laboratory, Guizhou Provincial People's Hospital, The Affiliated Hospital of Guizhou University, Guiyang, Guizhou Province 550000, China

ARTICLE INFO

Keywords:
Melanoma
Immunotherapy
Checkpoint inhibitor
Adverse effect

ABSTRACT

Background: A meta-analysis was performed to assess the risk of common adverse events in melanoma patients treated with checkpoint inhibitors.
Methods: Eligible studies were downloaded from PubMed, Embase, and Cochrane databases based on an established strategy. Review manager version 5.3 was used to analyze data.
Results: After exclusion of ineligible studies, six studies were finally included in the meta-analysis, which comprised of 2136 patients in intervention group and 1773 patients in control group. There was a difference in low grade risk of pruritus (OR 5.63, 95% CI 2.92–10.85, $P < 0.00001$), diarrhea/colitis (OR 1.51, 95% CI 1.09–2.09, $P = 0.01$), but not fatigue (low grade, OR 0.96, 95% CI 0.72–1.29, $P = 0.80$; high grade, OR 0.72, 95% CI 0.23–2.24, $P = 0.57$) and some high grade risk between the intervention group and control group. Subgroups analysis revealed that low grade risk of pruritus (OR 8.17, 95% CI 4.29–15.55, $P < 0.00001$) and high grade risk of pruritus (OR 7.08, 95% CI 1.25–40.09, $P = 0.03$) were significantly different between patients treated with chemotherapy and those treated with checkpoint inhibitors. But fatigue and diarrhea/colitis were not different between the two groups.
Conclusion: Checkpoint inhibitors are associated with a higher risk in some side effects than chemotherapy in melanoma patients. Therefore, strategies that reduce the risk of adverse events in patients taking checkpoint inhibitors should be developed.

1. Introduction

Malignant melanoma is a skin disease that originates from melanocytes [1]. The most common type is cutaneous malignant melanoma. Recent decades have witnessed an increase in the incidence of malignant melanoma cases, with an estimated 232,100 (1.7%) new cases diagnosed annually globally, with about 55,500 (0.7%) cases of deaths [2]. The data collected by the Surveillance Epidemiology and End Results from the National Cancer Institute indicated that the incidence of malignant melanoma is steadily increasing among white people, as reflected by a 60% increase in the last 3 decades [3]. Therefore, malignant melanoma has become one of the major public health issues and an important topic in cancer research [4].

There are many therapeutic approaches for melanoma. Classic systemic treatments of metastasized malignant melanoma include alkylating drugs, such as DTIC (dacarbazine), TMZ (temozolomide) as monotherapy or combination with platinum compounds, like cisplatin, carboplatin or other alkylating agents, like fotemustine, melphalan [5,6]. Clinical use of monotherapy, has been particularly successful in improving patient conditions [7]. However, the response rates (RRs) and median overall survival rate (OS) for melanoma patients are 5–12% and < 1–8 months, respectively [8,9]. And therapeutic regimen where chemotherapy and interferon (IFN) are combined have been developed, but the effect is not satisfactory. In the past decade, mutation-based drugs have been designed, BRAF inhibitor (vemurafenib, dabrafenib, encorafenib) and MEK inhibitor (trametinib, cobimetinib, binimetinib) have been approved to treat melanoma [10,11]. The main limitation of these inhibitors is their relatively short median response time, because most patients will develop drug resistance within 6 months.

In 2013, “Cancer immunotherapy” was ranked among the top ten

* Corresponding author at: No.83 Zhongshan East Road, Nanming District, Guiyang 550001, China.
E-mail address: shujyan@aliyun.com (S. Yan).

https://doi.org/10.1016/j.intimp.2019.105691
Received 2 January 2019; Received in revised form 2 June 2019; Accepted 6 June 2019
Available online 25 June 2019
1567-5769/ © 2019 Elsevier B.V. All rights reserved.

breakthroughs in *Science*. In 2014, Food and Drug Administration (FDA) approved two checkpoint (or immunotherapy) drugs, pembrolizumab (keytruda, Merck & Co. Inc.) and nivolumab (opdivo, Bristol-Myers Squibb company) to treat melanoma [12,13]. Since then, melanoma therapy has undergone enormous changes. Another checkpoint drug, ipilimumab (yervoy, Bristol-Myers Squibb company) was also approved by FDA [14]. These drugs sensitizes the immune system to recognize and remember melanoma cells. Clinical studies have shown that the response of patients to immunotherapy treatment is durable, and is sustained even after completion of treatment [15].

In China, it is believed that a drug has one-third poison. This implies that each drug, is associated with some level of toxicity or side effects. When the melanoma patients treated with drugs, they had to face the risk of adverse drug reaction. The major side effects of chemotherapy are fatigue, hair loss, easy bruising and bleeding, nausea and vomiting. The common adverse effects of DTIC are nausea and vomiting, bone marrow suppression with a nadir of platelets and leukocytes within 3–4 weeks [16]. Apart from the common side effects, like fatigue, nausea and vomiting or itching, checkpoint drugs are also associated with unique inflammatory adverse effects (AEs) knows as immune related adverse events (irAEs) [17,18]. Indeed, checkpoint drugs have drawn much attention in the last few years. It is therefore important to analyze the adverse effects of checkpoint drugs to understand their risks and benefits. In this study, common adverse effects associated with checkpoint drugs and chemotherapy drugs were investigated through a systematic review and meta-analysis.

2. Materials and methods

This systematic review and meta-analysis conformed to the guidelines of the Cochrane handbook for systematic reviews of interventions and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).

2.1. Data sources and search strategy

Three electronic databases, PubMed (Medline), Embase and Cochrane Central Register of Controlled Trials were searched (up to October 31, 2018) using vocabulary and text words with synonymous meaning. Titles and abstracts were used to formulate the search strategies. Independent concepts in the search terms were linked with “AND” logical term, immunotherapy drugs, melanoma or clinical trials. A complete search strategy is shown in the Supplementary materials. The search results were compiled using EndNote software. Automatic checks were performed to eliminate duplicates.

Two investigators (L.J and X.H.L) reviewed the title and abstract of the initial studies retrieved. The full text of each study which matched the inclusion criteria was read by three people (Q.S, Y.G.W and S.J.Y) to further assess eligibility. Disagreements were resolved through discussions and consensus.

2.2. Selection criteria

Studies that met the following criteria were included: (1) Random assignment of participants for treatment with single agent PD-1 (programmed cell death-1)/CTLA-4 (cytotoxic T lymphocyte associated antigen 4) inhibitors or placebo/chemotherapy; (2) phases II-III clinical trials for patients with melanoma; (3) Reporting of sample size and event rate or events for any grade adverse effects. Common adverse effects and other clinically relevant symptoms that assess drug safety in clinical trial, as recommended by the National Cancer Institute's Symptom Management and Health Related Quality of Life Steering Committee were reported. Papers were excluded if they were retrospective studies or not written in English. If data from the same clinical trial was reported in different publications, only the most recent or most comprehensive report was included.

2.3. Data extraction

Two investigators (L.D and R.Y.Z) independently performed data extraction. This included: (1) Basic study characteristics; title of manuscript, primary author's name, year of publication, phase of clinical trial, masking, ClinicalTrials.gov number. (2) Patient characteristics; occurrence of any grade (grades 1–5), low grade (1–2), and high grade (3–5) side effects. (fatigue, pruritus, diarrhea, colitis, nausea, rash, vomiting, decrease appetite, hypothyroidism, constipation, neutropenia). Adverse effects were recorded according to the CTCAE (common terminology criteria for adverse events). (3) Study design; treatment arms, and name, class and dose of drug, and schedule. Differences were resolved by consensus.

The quality of studies was evaluated using the Cochrane evaluation handbook of randomized controlled trials bias tool. Six dimensionality parameters, random sequence generation (selection bias), allocation concealment (selection bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective report (reporting bias), and other bias were assessed. Each parameter was categorized as: low risk of bias (+), high-risk of bias (−), or unclear (±).

2.4. Data analysis

Review manager version 5.3 (Copenhagen, Denmark) and EXCEL was used for statistical analysis. Two investigators independently assessed the quality of included studies. Intervention group represent patients who were treated with checkpoint inhibitors, control group represent patients who were treated with chemotherapy or placebo. Overall event rates were calculated by dividing the number of patients across trials with a definite adverse event by the total number of patients at risk. The total number of adverse events were calculated to determine whether a meta-analysis was feasible. The 95% confidence intervals and the odds ratio (OR) were calculated for adverse event rates (low grade or high grade) in the intervention group and compared with control group on account of the reported number of events and sample size. The Cochran Q test and I^2 statistics were used to measure heterogeneity across trials for each outcome. If I^2 values are $< 30\%$, 30%–59%, 60%–75%, and $> 75\%$, they were considered to be low, moderate, substantial, and significant heterogeneity, respectively. If significant heterogeneity was not observed, a fixed effects model was performed to calculate OR and 95% confidence interval. When significant heterogeneity was observed, OR and 95% confidence interval were calculated using the random effects model. Intervention arms were separately compared to the control arm if there were more than one intervention arms in a study. If necessary, subgroup analysis was conducted by segregating control group (divided into chemotherapy group or placebo group).

3. Results

The search strategy yielded a total of 6893 records from PubMed, Embase and Cochrane databases, among which 6 articles which met our inclusion criteria were included in the meta-analysis, Fig. 1.

3.1. Study characteristics

The effectiveness and adverse effects were evaluated in the intervention group (population ranging from 178 to 509) and control group (population ranging from 179 to 505), Table 1. Of six studies, five studies were phase III clinical trials, whereas one was a phase II clinical trial. Two types of checkpoint inhibitors (PD-1/CLTA-4) were tested in the clinical trials. Four studies used PD-1 inhibitors (Nivolumab, Perbrolizumab, Nivolumab) and two studies used CLTA-4 inhibitors (Ipilimumab, Tremelimumab) as the interventions (total 2136 patients). Four studies and two studies used chemotherapy and placebo as the

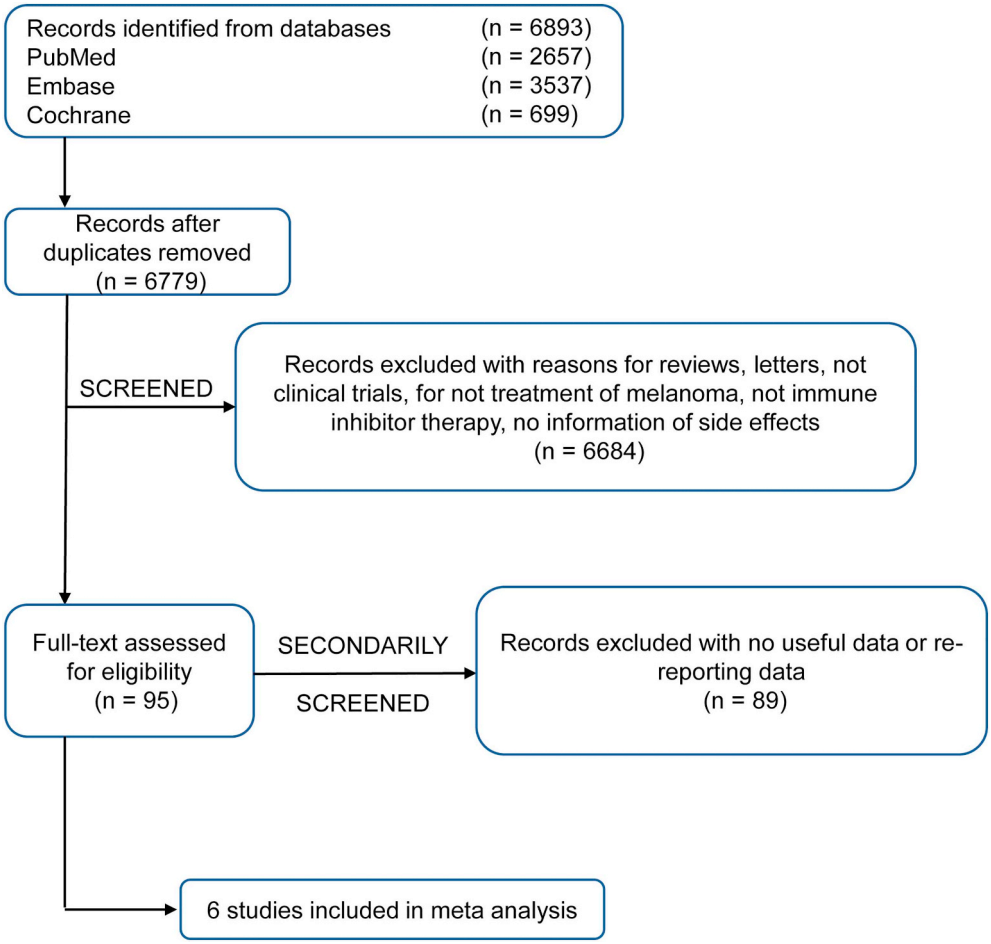

Fig. 1. Study flow diagram.

control groups (total 1944 patients), respectively. There were two arms in one study by Ribas, the first arm was 2 mg/kg Perbrolizumab, the second arm was 10 mg/kg Perbrolizumab. Three studies reported unresectable melanoma patients, two studies required that melanoma patients be in stage III, and two studies recruited patients with unresectable or metastatic melanoma who had failed treatment with BRAF/MEK inhibitor. To detect differences within the group, subgroups were set up for the adverse effects of fatigue, pruritus and diarrhea/colitis. The risk of bias is shown in the Supplementary materials (Sup Fig. 1).

3.2. The risk of fatigue

There was no significant difference between intervention group and control group in the risk of grades 1–2 fatigue (OR 0.96, 95% CI 0.72–1.29, $P = 0.80$) and grades 3–5 (OR 0.72, 95% CI 0.23–2.24, $P = 0.57$). Similarly, when the chemotherapy subgroup was set up, no significant difference was observed between the intervention group and chemotherapy group in grades 1–2 grades or 3–5 fatigue (Fig. 2).

3.3. The risk of pruritus

Fig. 3 shows that patients treated with checkpoint inhibitors had

Table 1
Characteristics of all included studies.

First Author (year)	Clinical Trial Information	Phase	PD-1/PD-L1/CTLA-4	Study Arms	NO. of Patients	Population
Eggermont (2015)	NCT00636168	III	CLTA-4	Ipilimumab	475	Stage III cutaneous melanoma
				Placebo	476	
Weber (2015)	NCT01721746	III	PD-1	Nivolumab	272	Unresectable or metastatic melanoma, and progressed after ipilimumab or BRAF inhibitor
				Chemotherapy	133	
Ribas (2015)	NCT01704287	II	PD-1	Perbrolizumab 2 mg/kg	180	Unresectable or metastatic melanoma, and progressed after ipilimumab or BRAF/MEK inhibitor
				Perbrolizumab 10 mg/kg	181	
				Chemotherapy	179	
Ribas (2013)	NCT00257205	III	CLTA-4	Tremelimumab	328	Unresectable stage IIIc or IV melanoma
				Chemotherapy	327	
Robert (2014)	NCT01721772	III	PD-1	Nivolumab	210	Previously untreated patients who had metastatic melanoma without a BRAF mutation
				Dacarbazine	208	
Eggermont (2018)	NCT02362594	III	PD-1	Perbrolizumab	514	Resected Stage III Melanoma
				Placebo	505	

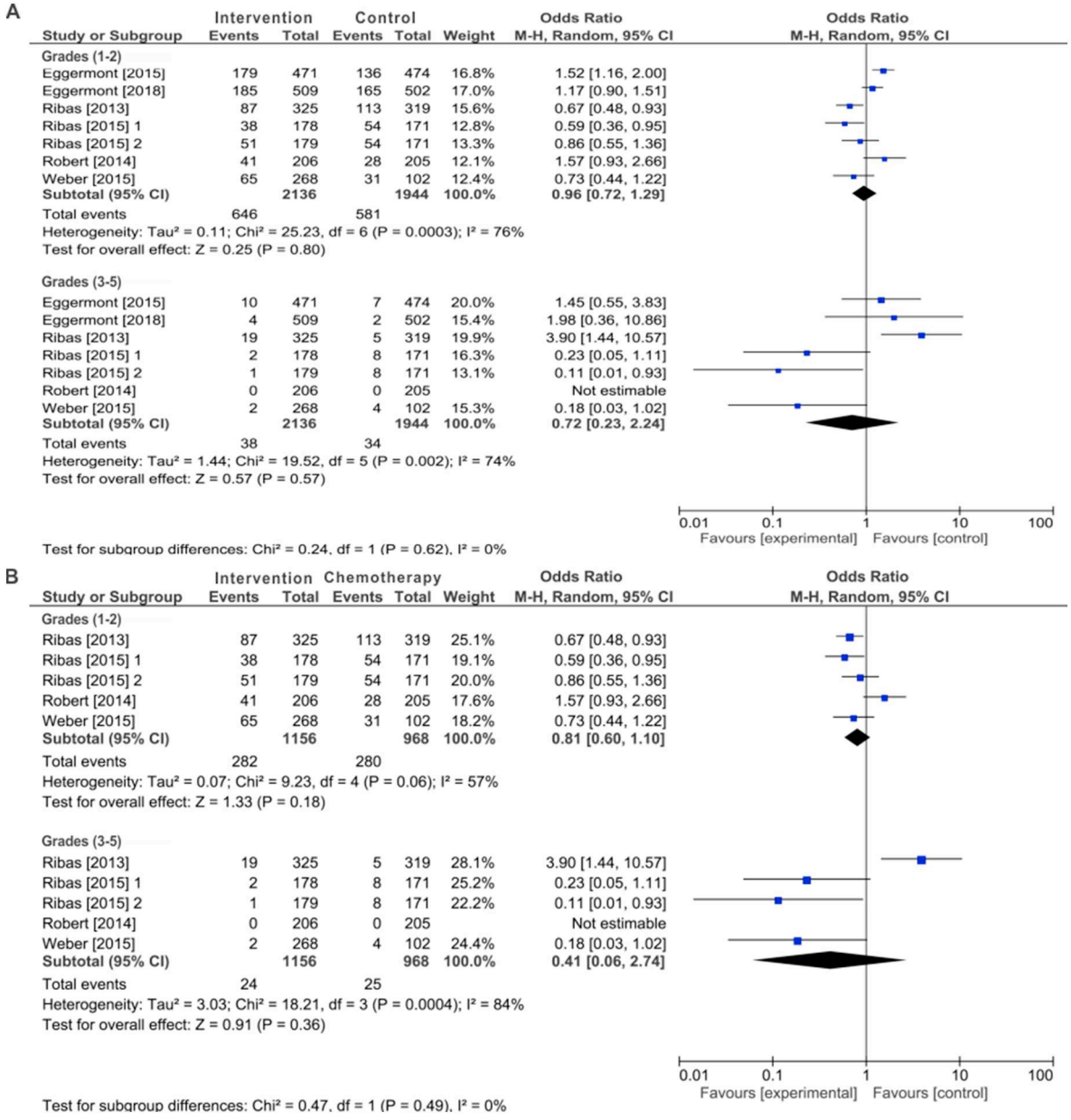

Fig. 2. Forest plot of meta-analysis for fatigue. (A) Checkpoint group vs control group. (B) Checkpoint group vs chemotherapy group.

significantly different levels of pruritus when compared with control group in low grade (OR 5.63, 95% CI 2.92–10.85, $P < 0.00001$). But there was no significant difference between patients treated with checkpoint inhibitors and control group patients in high grade pruritus (OR 2.72, 95% CI 0.74–9.95, $P = 0.13$). Further subgroup analysis for chemotherapy revealed that the I^2 value of low grades (89% vs 66%) and high grades (34% vs 0) was decreased than before subdivision. This implies that the level of heterogeneity was reduced after subgroup analysis. Pruritus displayed obvious differences between intervention group and chemotherapy group with regard to low grades (OR 8.17, 95% CI 4.29–15.55, $P < 0.00001$) and high grades (OR 7.08, 95% CI 1.25–40.09, $P = 0.03$).

3.4. The risk of diarrhea/colitis

The intervention group had higher risk of grades (1–2) diarrhea/colitis compared to the control group (OR 1.51, 95% CI 1.09–2.09, $P = 0.01$). As for grades (3–5), diarrhea, and colitis, there was no significant difference between intervention group and control group (OR 2.28, 95% CI 0.74–7.06, $P = 0.15$). In the subgroup analysis for chemotherapy, the difference in low grade (OR 1.39, 95% CI 0.86–2.27, $P = 0.19$) and high grade (OR 1.03, 95% CI 0.13–8.02, $P = 0.98$) and diarrhea/colitis between intervention group and chemotherapy group disappeared (Fig. 4).

3.5. Summary of adverse effects

The 6 studies reported a total of 2136 patients in intervention group among whom 1428 patients (66.85%) had adverse effects, whereas 1431 patients (73.611%) had adverse effects among 1944 patients in the control group. There was no significant difference between intervention group and control group in terms of total adverse effects of either low grade (OR 0.89, 95% CI 0.56–1.42, $P = 0.62$) or high grade (OR 0.97, 95% CI 0.46–2.04, $P = 0.93$). As individual adverse effects, patients had high risk suffer from low grade adverse effect of rash (OR 3.26, 95% CI 1.93–5.52, $P < 0.00001$), hypothyroidism (OR 7.14, 95% CI 4.42–11.55, $P < 0.00001$) in the intervention group. However, patients had high risk suffered from low grade adverse effect of nausea

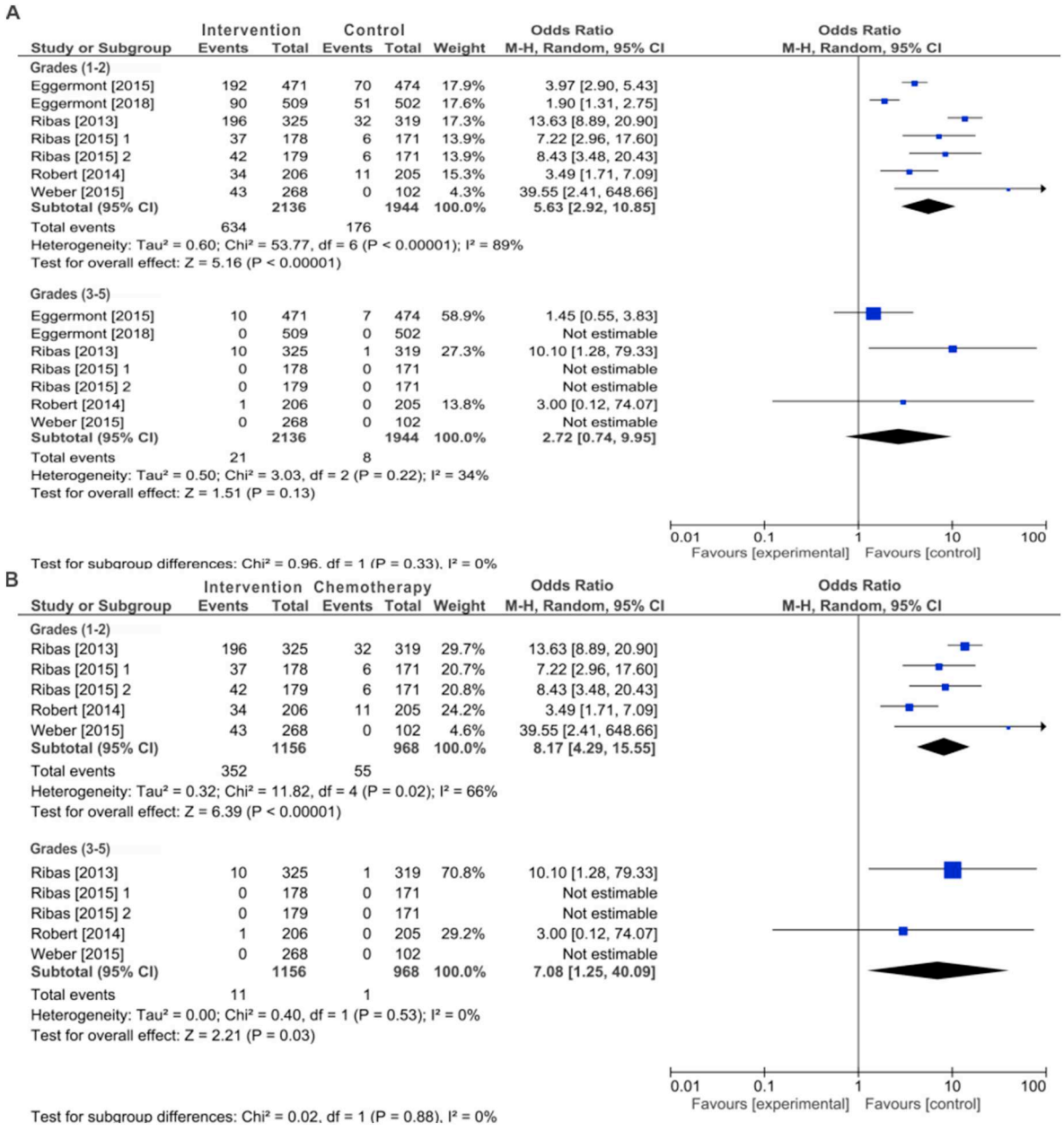

Fig. 3. Forest plot of meta-analysis for pruritus. (A) Checkpoint group vs control group. (B) Checkpoint group vs chemotherapy group.

(OR 0.45, 95% CI 0.21–0.95, $P = 0.04$), vomiting (OR 0.37, 95% CI 0.15–0.91, $P = 0.03$), constipation (OR 0.42, 95% CI 0.25–0.71, $P = 0.001$), and neutropenia (OR 0.08, 95% CI 0.03–0.23, $P < 0.00001$) in the control group (Table 2).

There was no statistical difference between intervention group and control group in high grade adverse effects, except decrease appetite (OR 7.00, 95% CI 1.86–26.37, $P = 0.004$), hypothyroidism (OR 13.52, 95% CI 3.22–56.80, $P = 0.0004$) and neutropenia (OR 0.03, 95% CI 0.01–0.10, $P < 0.00001$) had statistically significant difference.

4. Discussion

Malignance melanoma is associated with poor prognosis [19]. This is due to the lack of efficient therapeutic options. In the past decades, several novel pharmacological agents such as BRAF/MEK inhibitors and checkpoint inhibitors have been approved by FDA [20].

In particular, the development of checkpoint inhibitors has revolutionized the treatment of advanced melanoma. The three main checkpoint inhibitors approved by FDA are: ipilimumab (Yervoy®, CTLA-4 inhibitor) [21], pembrolizumab (Keytruda®, PD-1 inhibitor) [22] and nivolumab (Opdivo®, PD-1 inhibitor) [13,23]. The clinical trials of tremelimumab, a CTLA-4 inhibitor, are in progress, and it is expected to be clinically applied as an anti-tumor drug. Previously, it was reported that tremelimumab failed to treat melanoma in phase III clinical trial based on preliminary analysis [24]. However, within a year, it was noted that the survival curves of intervention group and control group were different. Researchers have raised doubts as to whether the conventional response evaluation criteria for solid tumors (RECIST) is effective for evaluating the effect of immunotherapy. This led to the utilization of the immune related response criteria (irRC) in subsequent immunotherapy trials (ipilimumab) [25]. Based on the findings that there was no severe side effect in the subsequent clinical trials of tremelimumab, this drug was included in this meta-analysis.

To improve their efficacy, several attempts have been made to develop new treatment strategy, some drugs were attempted or applied to combined with checkpoint drugs [26–28]. As a result, the risk and

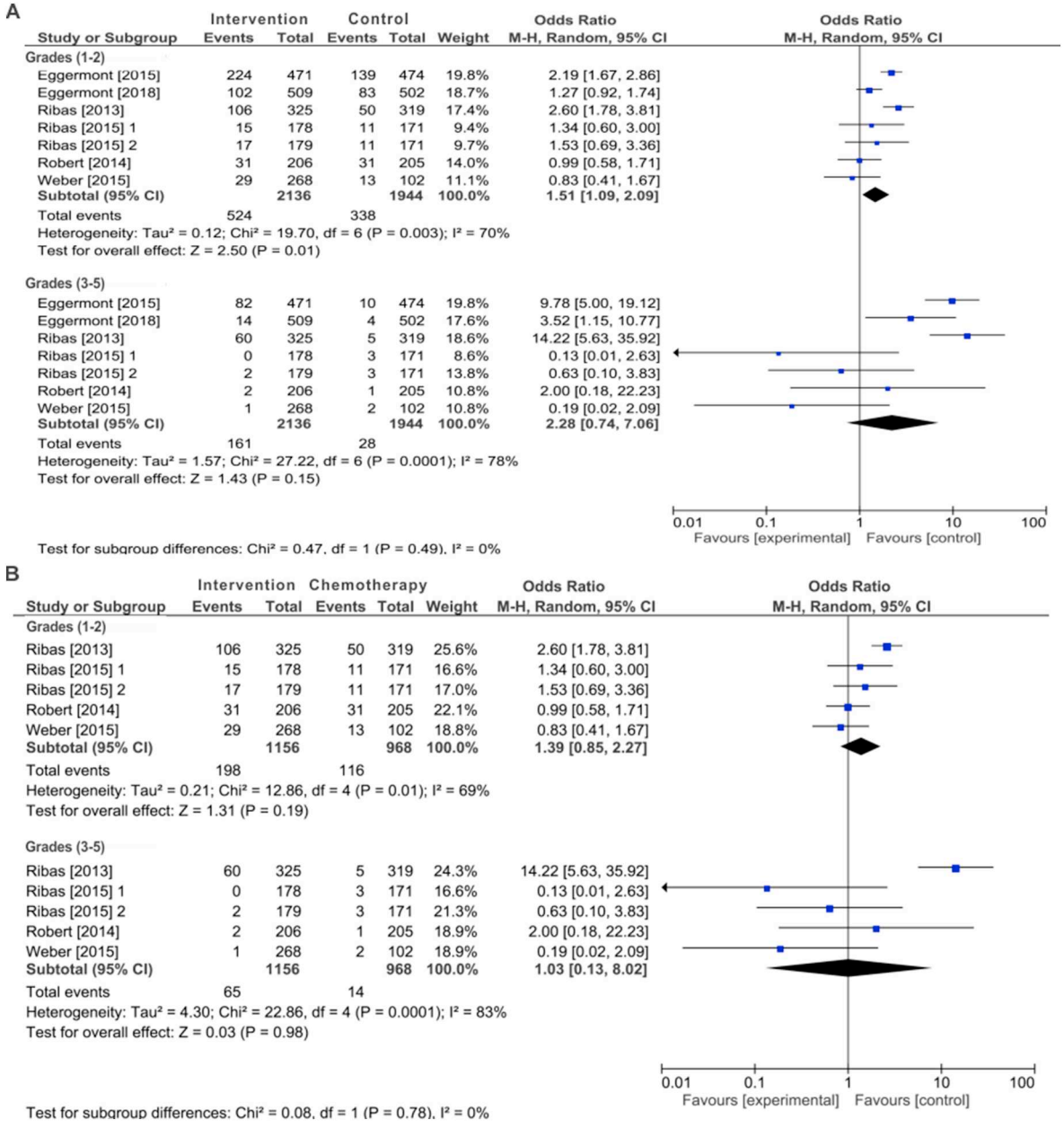

Fig. 4. Forest plot of meta-analysis for diarrhea/colitis. (A) Checkpoint group vs control group. (B) Checkpoint group vs chemotherapy group.

frequency of side effect events increased. One of study by Robert showed that a raised in liver function values is an important adverse effect was observed more frequently than expected with the combination therapy. Yet, some drugs used in combination with checkpoint inhibitor have similar side effects of checkpoint inhibitor. Therefore, it is necessary to explore unique adverse effects produced by checkpoint inhibitors or identify which drug is causing the adverse effect in combination therapy. In this study, we investigated adverse effects to monotherapy, hoped that provided some reference for analyzing the side effects of combination therapy. The results showed that the total side effects produced by the use of checkpoint inhibitors or (chemotherapy/placebo) in melanoma patients did not differ significantly between these treatments. This implies that the safety profile of checkpoint inhibitors is equivalent to that of chemotherapy. Three of most important common adverse effects (fatigue, pruritus, diarrhea/colitis) were investigated in detail by establishing subgroup analyses.

The most common therapy-related side events of any grade reported in the pivotal clinical trials is fatigue. Our analysis revealed that there was no difference in fatigue (low grade or high grade) between checkpoint inhibitors group and control group. A previous study which compared adverse effects between aiti-PD-1 and anti-PD-L1 obtained a similar result [29]. To alleviate the symptom, it's should be optimized from sleep disfunction, comorbidities and nutritional deficiency, and physical exercise, pharmacotherapy and psychotherapy may be helpful. However, if grade IV fatigue happened, treatment with checkpoint inhibitors should be suspended.

Pruritus is one of the commonly diagnosed dermatological adverse effect, bothering 15–33% melanoma patients [30]. Compared with control group, melanoma patients treated with checkpoint inhibitors had a higher risk that suffered from low grade pruritus (OR 5.63, 95% CI 2.92–10.85, $P < 0.00001$). However, when chemotherapy subgroup analysis was performed, a significant difference was observed between intervention group and chemotherapy group in low grade (OR 8.17, 95% CI 4.29–15.55, $P < 0.00001$) and high grade (OR 7.08, 95% CI 1.25–40.09, $P = 0.03$) pruritus. These data implied that occurrence of low grade and high grade pruritus should be monitored in melanoma

Table 2
Incidence of adverse events.

Adverse effects	Quantity of studies	Intervention (events/total)	Control (events/total)	*P* value	OR (95% Cl)
Low grade					
Any events	7	1428/2136	1431/1944	0.62	0.89 (0.56, 1.42)
Fatigue	7	648/2136	581/1944	0.80	0.96 (0.72, 1.29)
Fatigue (subgroup)	5	282/1156	280/968	0.18	0.81 (0.60, 1.10)
Puritus	7	634/2136	176/1944	< 0.00001	5.63 (2.92, 10.85)
Puritus (subgroup)	5	352/1156	55/968	< 0.00001	8.17 (4.29, 15.55)
Diarrhea/colitis	7	524/2136	338/1944	0.01	1.51 (1.09, 2.09)
Diarrhea/colitis (subgroup)	5	198/1156	116/968	0.19	1.39 (0.86, 2.27)
Nausea	6	325/1868	463/1842	0.04	0.45 (0.21, 0.95)
Rash	6	427/1868	172/1842	< 0.0001	3.26 (1.93, 5.52)
Vomiting	6	148/1627	215/1442	0.03	0.37 (0.15, 0.91)
Decrease appetite	5	154/1421	122/1237	0.30	1.14 (0.89, 1.46)
Hypothyroidism	5	129/1662	20/1637	< 0.00001	7.14 (4.42, 11.55)
Constipation	5	88/1156	166/968	0.001	0.42 (0.25, 0.71)
Neutropenia	5	3/1156	37/968	< 0.00001	0.08 (0.03, 0.23)
High grade					
Any events	7	680/2136	465/1944	0.93	0.97 (0.46, 2.04)
Fatigue	7	38/2136	34/1944	0.57	0.72 (0.23, 2.24)
Fatigue (subgroup)	5	24/1156	25/968	0.36	0.41 (0.06, 2.74)
Puritus	7	21/2136	8/1944	0.13	2.72 (0.74, 9.95)
Puritus (subgroup)	5	11/1156	1/968	0.03	7.08 (1.25, 40.09)
Diarrhea/colitis	7	161/2136	28/1944	0.15	2.28 (0.74, 7.06)
Diarrhea/colitis (subgroup)	5	65/1156	14/968	0.98	1.03 (0.13, 8.02)
Nausea	6	325/1868	18/1842	0.59	0.69 (0.18, 2.64)
Rash	6	9/1868	1/1842	NA	NA
Vomiting	6	20/1627	21/1442	0.50	0.74 (0.31, 1.79)
Decrease appetite	5	17/1421	2/1237	0.004	7.00 (1.86, 26.37)
Hypothyroidism	5	25/1662	0/1637	0.0004	13.52(3.22, 56.80)
Constipation	5	2/1156	3/968	0.50	0.53 (0.08, 3.36)
Neutropenia	5	1/1156	69/968	< 0.00001	0.03 (0.01, 0.10)

NA = not applicable.

patients taking checkpoint inhibitors. However, therapy-related pruritus can be especially annoying, but it is generally amenable to treatment, usually do not require dosage reduction or even suspended of treatment. All observed patients had suffered from low or moderate grade pruritus are successfully managed with topical steroids such as mometasone furoate cream and anti-histamines.

Diarrhea/colitis was found to be one of the irAEs [31]. In a previous study [32], it was found that the use of PD-1/PD-L1 inhibitors and chemotherapy for advanced solid cancer produced diarrhea/colitis to the same extent. Another study showed that the use of pembrolizumab increased the risk of all-grade colitis in non-small-cell lung cancer patients, but not in melanoma patients. In this study, patients treated with checkpoint inhibitors were more likely to suffer from low grade diarrhea/colitis (OR 1.51, 95% CI 1.09–2.09, $P = 0.01$), but not high grade diarrhea/colitis compared with control group. In line with published reports, this meta-analysis reveals that the risk of diarrhea/colitis in patients treated with chemotherapy and those receiving checkpoint inhibitors is generally similar but patients taking certain checkpoint inhibitors medications should be monitored. Low grade diarrhea/colitis can initially be treated solely on the basis of symptoms, for instance with electrolyte and loperamide replacement. If persistence or progression of diarrhea/colitis, discriminating other cause like alimentary infection should be ruled out by fecal examination. When the high grade diarrhea/colitis occurred, the treatment should be stop and high-dose corticosteroid therapy initiated. Base on the regimen, symptoms were usually notable improvement after seven to ten days. In order to ensure complete healing, it is advised that slowly taper the corticosteroid dose over a period of at least one month.

Nevertheless, this study has the following limitations. As was showed in the Results section, there was high heterogeneity among the studies included in this meta-analyses. Attempts were made to reduce heterogeneity by setting up subgroup analyses. Although this reduced heterogeneity to some extent, in some cases, the level of heterogeneity was increased. Thus, further research is required to re-examine the adverse effects which had high heterogeneity. In addition, we included tremelimumab in this study although it is not approved by FDA. This might have introduced bias in the results. Thirdly, diarrhea and colitis were combined in the meta-analysis, because one of the studies included coalesced diarrhea and colitis data and the data from that study could not be ignored. Finally, the population were pooled from studies that patients previously treated with different therapeutic regimen or at different disease stage, it may lead to miss differences in adverse event rates. Given the variation in therapeutic regimen and disease stage, subgroup analyses to investigate these factors were not easy to perform. However, when sufficient data are available, subgroup analysis should be performed for the above factors.

In summary, this study identified some high risk adverse events in melanoma patients taking checkpoint inhibitors. Therefore, strategies that reduce the risk of adverse events in patients taking checkpoint inhibitors should be developed.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2019.105691.

Funding

This study was supported by the Guizhou high-level innovative talents project, QKPT[2017]5724-6 and Guizhou department and platform talents, [2017]5735-31.

Declaration of Competing Interest

All authors have no competing interests.

References

[1] M.H. Law, D.T. Bishop, J.E. Lee, M. Brossard, N.G. Martin, E.K. Moses, F. Song, J.H. Barrett, R. Kumar, D.F. Easton, Genome-wide meta-analysis identifies five new susceptibility loci for cutaneous malignant melanoma, Nat. Genet. 47 (9) (2015) 987–995.

[2] V. Annese, L. Beaugerie, L. Egan, L. Biancone, C. Bolling, C. Brandts, D. Dierickx, R. Dummer, G. Fiorino, J.M. Gornet, European evidence-based consensus: inflammatory bowel disease and malignancies, J. Crohns Colitis 9 (11) (2015) 945–965.
[3] M. Rastrelli, S. Tropea, C.R. Rossi, M. Alaibac, Melanoma: epidemiology, risk factors, pathogenesis, diagnosis and classification, In Vivo 28 (6) (2014) 1005–1011.
[4] H. Wen, T. Guo, C. Feng, Body-mass index and metastatic melanoma outcomes, Lancet Oncol. 19 (5) (2018) e223.
[5] K. Kawaguchi, K. Igarashi, T. Murakami, B. Chmielowski, T. Kiyuna, M. Zhao, Y. Zhang, A. Singh, M. Unno, S.D. Nelson, Tumor-targeting Salmonella typhimurium A1-R combined with temozolomide regresses malignant melanoma with a BRAF-V600E mutation in a patient-derived orthotopic xenograft (PDOX) model, Oncotarget 7 (52) (2016) 85929–85936.
[6] J.J. Luke, J.B. Allred, L.E. Horvath, B.R. Bastos, C. Erlichman, G.K. Schwartz, Randomized phase II study comparing the MET inhibitor cabozantinib to temozolomide (TMZ) or dacarbazine (DTIC) in ocular melanoma: A091201, Proc. Am. Soc. Clin. Oncol. 33 (15_suppl) (2015) TPS9087-TPS9087.
[7] G. Moriceau, W. Hugo, A. Hong, H. Shi, X. Kong, C.Y. Clarissa, R.C. Koya, A.A. Samatar, N. Khanlou, J. Braun, Tunable-combinatorial mechanisms of acquired resistance limit the efficacy of BRAF/MEK cotargeting but result in melanoma drug addiction, Cancer Cell 27 (2) (2015) 240–256.
[8] A.V. Balar, M.D. Galsky, J.E. Rosenberg, T. Powles, D.P. Petrylak, J. Bellmunt, Y. Loriot, A. Necchi, J. Hoffman-Censits, J.L. Perez-Gracia, Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial, Lancet 389 (10064) (2017) 67–76.
[9] G.V. Long, D. Stroyakovskiy, H. Gogas, E. Levchenko, F. De Braud, J. Larkin, C. Garbe, T. Jouary, A. Hauschild, J.J. Grob, Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial, Lancet 386 (9992) (2015) 444–451.
[10] H. Shi, W. Hugo, X. Kong, A. Hong, R.C. Koya, G. Moriceau, T. Chodon, R. Guo, D.B. Johnson, K.B. Dahlman, Acquired resistance and clonal evolution in melanoma during BRAF inhibitor therapy, Cancer Discov. 4 (1) (2014) 80–93.
[11] G.V. Long, D. Stroyakovskiy, H. Gogas, E. Levchenko, F. de Braud, J. Larkin, C. Garbe, T. Jouary, A. Hauschild, J.J. Grob, Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma, N. Engl. J. Med. 371 (20) (2014) 1877–1888.
[12] C. Robert, J. Schachter, G.V. Long, A. Arance, J.J. Grob, L. Mortier, A. Daud, M.S. Carlino, C. McNeil, M. Lotem, Pembrolizumab versus ipilimumab in advanced melanoma, N. Engl. J. Med. 372 (26) (2015) 2521–2532.
[13] C. Robert, G.V. Long, B. Brady, C. Dutriaux, M. Maio, L. Mortier, J.C. Hassel, P. Rutkowski, C. McNeil, E.K. Warzocha, Nivolumab in previously untreated melanoma without BRAF mutation, N. Engl. J. Med. 372 (4) (2015) 320–330.
[14] J. Larkin, B. Chmielowski, C.D. Lao, F.S. Hodi, W. Sharfman, J. Weber, K.P. Suijkerbuijk, S. Azevedo, H. Li, D. Reshef, Neurologic serious adverse events associated with nivolumab plus ipilimumab or nivolumab alone in advanced melanoma, including a case series of encephalitis, Oncologist 22 (6) (2017) 709–718.
[15] D. Paggio, C. Joseph, Immunotherapy: cancer immunotherapy and the value of cure, Nat. Rev. Clin. Oncol. 15 (5) (2018) 268–270.
[16] C. Ma, A.W. Armstrong, Severe adverse events from the treatment of advanced melanoma: a systematic review of severe side effects associated with ipilimumab, vemurafenib, interferon alfa-2b, dacarbazine and interleukin-2, J. Dermatol. Treat. 25 (5) (2014) 401–408.
[17] S. Baxi, A. Yang, R.L. Gennarelli, N. Khan, Z. Wang, L. Boyce, D. Korenstein, Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis, Bmj (2018), https://doi.org/10.1136/bmj.k793.
[18] J. Huo, X.L. Du, D.R. Lairson, W. Chan, M.J. Jiang, T.A. Buchholz, B.A. Guadagnolo, Utilization of surgery, chemotherapy, radiation therapy, and hospice at the end of life for patients diagnosed with metastatic melanoma, Am. J. Clin. Oncol. 38 (3) (2015) 235–241.
[19] D. Massi, D. Brusa, B. Merelli, C. Falcone, G. Xue, A. Carobbio, R. Nassini, G. Baroni, E. Tamborini, L.J.A. Cattaneo, The status of PD-L1 and tumor-infiltrating immune cells predict resistance and poor prognosis in BRAFi-treated melanoma patients harboring mutant BRAFV600, Ann. Oncol. 26 (9) (2015) 1980–1987.
[20] D.T. Frederick, A. Piris, A.P. Cogdill, Z.A. Cooper, C. Lezcano, C.R. Ferrone, D. Mitra, A. Boni, L.P. Newton, C. Liu, BRAF inhibition is associated with enhanced melanoma antigen expression and a more favorable tumor microenvironment in patients with metastatic melanoma, Clin. Cancer Res. 19 (5) (2013) 1225–1231.
[21] A.M. Eggermont, V. Chiarion-Sileni, J.-J. Grob, R. Dummer, J.D. Wolchok, H. Schmidt, O. Hamid, C. Robert, P.A. Ascierto, J.M. Richards, Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial, Lancet Oncol. 16 (5) (2015) 522–530.
[22] A. Ribas, I. Puzanov, R. Dummer, D. Schadendorf, O. Hamid, C. Robert, F.S. Hodi, J. Schachter, A.C. Pavlick, K.D. Lewis, Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial, Lancet Oncol. 16 (8) (2015) 908–918.
[23] J.S. Weber, S.P. D'Angelo, D. Minor, F.S. Hodi, R. Gutzmer, B. Neyns, C. Hoeller, N.I. Khushalani, W.H. Miller Jr., C.D. Lao, Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial, Lancet Oncol. 16 (4) (2015) 375–384.
[24] A. Ribas, R. Kefford, M.A. Marshall, C.J. Punt, J.B. Haanen, M. Marmol, C. Garbe, H. Gogas, J. Schachter, G. Linette, Phase III randomized clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma, J. Clin. Oncol. 31 (5) (2013) 616–622.
[25] F.S. Hodi, W.-J. Hwu, R. Kefford, J.S. Weber, A. Daud, O. Hamid, A. Patnaik, A. Ribas, C. Robert, T.C. Gangadhar, Evaluation of immune-related response criteria and RECIST v1. 1 in patients with advanced melanoma treated with pembrolizumab, J. Clin. Oncol. 34 (13) (2016) 1510–1517.
[26] J. Cui, L. Li, C. Wang, H. Jin, C. Yao, Y. Wang, D. Li, H. Tian, C. Niu, G. Wang, Combined cellular immunotherapy and chemotherapy improves clinical outcome in patients with gastric carcinoma, Cytotherapy 17 (7) (2015) 979–988.
[27] A.M. Mahtab, M. Bazinet, A. Vaillant, Safety and efficacy of nucleic acid polymers in monotherapy and combined with immunotherapy in treatment-naive Bangladeshi patients with HBeAg+ chronic hepatitis B infection, PLoS One 11 (6) (2016) e0156667.
[28] A.B. Warner, M.A. Postow, Combination controversies: checkpoint inhibition alone or in combination for the treatment of melanoma, Oncology 32 (5) (2018) 228–234.
[29] W. You, M. Liu, J.D. Miao, Y.Q. Liao, Y.B. Song, D.K. Cai, Y. Gao, H. Peng, A network meta-analysis comparing the efficacy and safety of anti-PD-1 with anti-PD-L1 in non-small cell lung cancer, J. Cancer 9 (7) (2018) 1200–1206.
[30] V. Sibaud, Dermatologic reactions to immune checkpoint inhibitors, Am. J. Clin. Dermatol. 19 (3) (2018) 345–361.
[31] J.R. Kuo, A.D. Davis, E.A. Rodriguez, M.F. Vela, R.I. Heigh, M.A. Salomao, S.R. Gurudu, Severe Diarrhea in the Setting of Immune Checkpoint Inhibitors, Case Rep. Gastroenterol. 12 (3) (2018) 704–708.
[32] T.F. Nishijima, S.S. Shachar, K.A. Nyrop, H.B. Muss, Safety and tolerability of PD-1/PD-L1 inhibitors compared with chemotherapy in patients with advanced cancer: a meta-analysis, Oncologist 22 (4) (2017) 470–479.