Systematic Review and Meta-Analysis

Medicine®

OPEN

Risk of dermatologic and mucosal adverse events associated with PD-1/PD-L1 inhibitors in cancer patients

A meta-analysis of randomized controlled trials

Wenwei Yang, BSc[a,*], Shuquan Li, BSc[a], Qingrui Yang, MD[b]

Abstract

Background: Programmed death 1 protein (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors are promising cancer immunotherapy. Their dermatologic safety profiles are still poorly understood. The purpose of this article is to evaluate the incidence of selected dermatologic and mucosal adverse effects (AEs) and determine the risk of developing these adverse events associated with PD-1/PD-L1 inhibitors, compared with chemotherapy or ipilimumab.

Methods: PubMed was searched for eligible studies (up to February 21, 2019). Only phase II and phase III randomized controlled trials (RCTs) compared with chemotherapy or ipilimumab monotherapy were included in this meta-analysis.

Results: A total 11,465 patients from 18 clinical trials were included in this meta-analysis. Rash and pruritus were the most frequently reported dermatologic AE, with incidence 11.8% and 12.2% respectively. Compared with patients receiving chemotherapy, PD-1/PD-L1 inhibitor treated patients had higher risk of developing rash (RR = 1.84), pruritus (RR = 3.74) and vitiligo (RR = 9.54), and also lower risk in developing mucosal inflammation (RR = 0.26), stomatitis (RR = 0.26), and alopecia (RR = 0.03). Additionally, anti-PD1/PD-L1 drugs had similar risk of developing rash and lower risk of inducing pruritus compared to ipilimumab. In the subgroup analysis, PD-L1 inhibitor demonstrated better safety than PD-1 inhibitor in developing rash, with RR = 1.38 and RR = 2.11, respectively.

Conclusion: Our meta-analysis concluded that anti PD-1/PD-L1 drugs have different dermatological and mucosal safety profile compared to conventional therapy, and differences of dermatological toxicity between PD-1 and PD-L1 inhibitor warrant further investigation.

Abbreviations: 95% CI = 95% confidence interval, AE = adverse event, CTLA 4 = cytotoxic T-lymphocyte-associated protein 4, FDA = Food and Drug Administration, irAEs = immune-related adverse events, NSCLC = non-small cell lung cancer, PD-1 = programmed cell death protein 1, PD-L1 = programmed cell death protein ligand 1, PD-L2 = programmed cell death protein ligand 2, RCTs = randomized controlled trials, RR = relative risk, T_{REG} = regulatory T cell.

Keywords: alopecia, cancer, immune-related adverse events, meta-analysis, mucosal inflammation, PD-1 inhibitors, PD-L1 inhibitors, pruritus, rash, stomatitis, vitiligo

1. Introduction

How to detect and cure cancer has been a hot topic in the medical field. With the progress of cancer research, many effective therapies have been developed (e.g., surgery, chemotherapy, radiation therapy, targeted therapy). Recently, discovery of the immune checkpoint inhibitors, represented by CTLA-4 and PD-1/PD-L1 inhibitors, has brought revolutionary progress in the tumor treatment and ignited great enthusiasm for the tumor immunotherapy research. PD-1 is an inhibitory receptor with the negative immune regulatory effects. When PD-1 binds with its ligands PD-L1/PD-L2, the immune response of T lymphocyte is inhibited, which is called immune checkpoint.[1,2] Some tumor cells can evade immune elimination by over expressing PD-1 ligand.[3] By aiming at the negative immune regulatory factors, researchers developed the immune checkpoint blockade which could prevent PD-1 from combining with PD-L1. Subsequently, the negative immune regulatory effects are blocked, which significantly improves the immunologic functions of T lymphocytes.[4,5] Anti-PD-1/PD-L1 drugs have demonstrated the remarkable therapeutic efficacy in clinic, and 6 anti-PD-1/PD-L1

Editor: Giandomenico Roviello.

WY and SL have contributed equally to this work.

This study received no support in the form of equipment, drugs, grants, or funding. Authors declare that there are no conflicts of interest with regard to this study.

Supplemental Digital Content is available for this article.

[a] Department of Clinical Medicine, Queen Mary College of Nanchang University, Nanchang, Jiangxi, [b] Department of Rheumatology and Immunology, Shandong University Affiliated Provincial Hospital, Jinan, Shandong, China.

[*] Correspondence: Wenwei Yang, Department of Clinical Medicine, Queen Mary College of Nanchang University, Nanchang, Jiangxi 330031, China (e-mail: yww0619@163.com).

Medicine (2019) 98:20(e15731)

Received: 24 March 2019 / Received in final form: 24 April 2019 / Accepted: 25 April 2019

http://dx.doi.org/10.1097/MD.0000000000015731

drugs have been approved by the US drug regulatory authorities since 2014[6]: Merck's pembrolizumab (Keytruda, an anti-PD-1), BMS's nivolumab (Opdivo, an anti-PD-1), Roche's atezolizumab (Tecentriq an anti-PD-L1 antibody approved in 2016), Pfizer and Merck's avelumab (Bavencio an anti-PD-L1 antibody approved in 2017), Aspen Likang's durvalumab (Imfinzi an anti-PD-L1 antibody approved in 2017), and Regenerator and Sanofi's cemiplimab (Libtayo an anti-PD-1 antibody approved in 2018). With the support of a large number of clinical trials, these drugs have been approved to treat melanoma, non-small-cell lung cancer, renal cell carcinoma, bladder cancer, head and neck cancer, and other cancers. Since 2017, anti-PD-1/PD-L1 drugs have also been expanded to treat liver cancer, gastric cancer, lymphoma, Merkel cell carcinoma, cutaneous squamous cell carcinoma, and other diseases.[7–12]

Although the anti-tumor effects of PD-1/PD-L1 inhibitors have been proved clinically, various adverse effects (AEs) would also be noticed,[13] including fatigue, pyrexia, chills, and infusion reactions.[14] Several adverse events caused by the immune checkpoint inhibitors are known as immune-related adverse events (irAEs), which is considered to be different in mechanism and incidence from the adverse events induced by chemotherapy and targeted therapy.[15] Those irAEs are understood to be the manifestation of the autoimmunity. In other words, the hyperfunction of immune system affects the normal tissues and organs in bodies, due to the fact that the immune checkpoint inhibitors could boost the activity of immune system.[16,17] These irAEs are usually organ-specific, such as pneumonitis, colitis, hepatitis, hypothyroidism, and hyperthyroidism.[18,19] Skin is one of the main organs affected by autoimmune with several common dermatologic AEs induced. Serious dermatologic AEs might impair people's quality of life.

In this meta-analysis, we focused on 6 most common dermatological and mucosal adverse events, including rash, pruritus, mucosal inflammation, stomatitis, alopecia, and vitiligo, which are reported in many studies with high incidence.[16] There are a lot of data available from various clinical trials for PD-1/PD-L1 inhibitors recently, which could be used for our study. We chose chemotherapy and ipilimumab as control to explore the safety of different therapies. Ipilimumab is the first immune checkpoint blockade for CTLA-4 approved in 2011. As ipilimumab was widely used in clinic, we intended to explore the differences of dermatologic safety between ipilimumab and PD-1/PD-L1 inhibitors. By understanding the frequency and characteristics of dermatologic irAEs, the study could provide more options for physician to prescribe PD-1 inhibitors to treat patients appropriately.

A meta-analysis was conducted to compute the incidence and relative risk (RR) of all-grade and high-grade dermatological and mucosal adverse events in patients treated with PD-1/PD-L1 inhibitor monotherapy versus other monotherapy (chemotherapy and ipilimumab). All of the data used in this meta-analysis were collected from published literature and clinicaltrials.gov.

2. Methods

A meta-analysis is conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. There is no ethical approval needed since all of previously published data were used for this work.

2.1. Data source and search strategy

A systematic literature search was conducted to collect the information of dermatologic and mucosal adverse events in the clinical trials of PD-1/PD-L1 inhibitors. Medline (via PubMed) (up to February 21, 2019) and clinicaltrials.gov were searched for relevant data of clinical trials. Only the phases II/III randomized controlled trials (RCTs) were included in our analysis. Following generic names, brand names, and synonyms were used for the detailed search: pembrolizumab (MK-3475, SCH900475, Keytruda, lambrolizumab), nivolumab (BMS-936558, MDX-1106, ONO-4538, Opdivo), atezolizumab (MPDL-3280A, RG-7446, R05541267, Tecentriq), avelumab (MSB-0010718C), durvalumab (MEDI-4736), and cemiplimab (REGN2810, Libtayo). "Clinical trial" tag was used to limit search result, and additional studies from other sources were also added.

2.2. Study selection

Based on our criteria of selection, studies with following characteristics were included in our meta-analysis:

1. randomized controlled phase II and III trials;
2. patients in intervention arms were treated with PD-1/PD-L1 inhibitor monotherapy, and patients in control arm were also treated with monotherapy (chemotherapy or ipilimumab);
3. similar methodology used for all of selected studies;
4. significant skin AEs were clearly reported in the selected articles;
5. the studies were published in English.

Studies with the following characteristics should be excluded:

1. the duplicated study with insufficient data;
2. the study with control group treated with combination therapy and target therapy;
3. the study that is not a therapeutic research.

Both authors (W.W.Y. and S.Q.L.) completed the literature search independently and then discussed which articles should be included in our analysis. Disagreements were solved by consensus. For the cases of duplication, only the most completed and recent publications were chosen. Hence, each article included in this meta-analysis represents a unique study.

2.3. Data extraction

Data extraction was conducted by two authors (W.W.Y. and S. Q.L.) independently from all of available clinical studies that are relevant to this meta-analysis. The criteria of selection were strictly controlled whether a study is appropriate for our analysis, such as the study design, intervention, comparison, and patients. The variables extracted were: last name of first author, year of publication, title, name of journal, NCT number, phase of clinical study, tumor type, clinical study design, number of patients in the intervention groups, number of patients in the control groups, name and dose of PD-1/PD-L1 inhibitors, number of patients developing all-grade (grade 1–5) and high-grade (grade 3–5) AEs. Disagreements were resolved through discussion. All clinical studies included in the analysis used the Common Terminology Criteria for Adverse Events (CTCAE). If available, statistical results were extracted from all studies reporting all-grade (grade 1-5) or high-grade (grade 3-5) rash, pruritus, mucosal inflammation, alopecia, and vitiligo. Detailed clinical data were extracted from the publications, and some missing data were filled from

clinicaltrials.gov (serious adverse events on clinicaltrials.gov were considered as high-grade AEs).

2.4. Statistical analysis

In this meta-analysis, the incidence (with 95% confidence interval [CI]) of AEs in intervention arm was calculated by Open Meta-Analyst (Open MetaAnalyst for Windows 8 64bit, Brown University, 2013), using natural logarithm transformed proportion method and pooled using fixed or random effect model. Mentel-Haensszel method (Review Manager, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to perform the statistical analyses. The Risk Ratio (RR) was used to compare the risk of developing all-grade and high-grade AEs in the intervention arms with control arms. The RR above 1 and the lower limit of 95% RR CI larger than 1 suggest higher risk of developing skin disorders in patients treated with PD-1/PD-L1 inhibitor than those treated with other control monotherapy. Furthermore, the I^2 index and P-value were used to assess the heterogeneity of the clinical trials used. For $P < .1$, the homogeneity were assumed invalid and the random-effect model was used to compute the overall RR and 95% CI, and for $P \geq 0.1$, the fixed-effect model would be used. Subgroup difference test $P < .05$ was considered as the threshold for statistical significance. To understand how PD-1/PD-L1 drugs contribute to developing the skin AEs, several comparisons were:

1. PD-1/PD-L1 inhibitor monotherapy versus chemotherapy control (also monotherapy) in different dermatologic and mucosal AEs;
2. PD-1/PD-L1 inhibitor monotherapy versus ipilimumab control in different dermatologic AEs.

To identify the sources of heterogeneity, we conducted subgroup analyses based on drug class and tumor type in different AEs.

2.5. Quality assessment

The quality of 18 studies was assessed by two authors independently, using the Cochrane Risk of Bias Assessment. Risk of bias assessments and evaluation criteria are summarized in Fig. 1. All open-label trials are considered as high risk in blinding aspects and following outcome bias are also considered as high risk, since clinicians assessed adverse events for all studies. Patient stratification before randomization and interactive voice-response system randomization were regarded as low risk in allocation concealment. Discrepancy in assessment was resolved by consensus.

3. Results

3.1. Search results

There are 244 potentially relevant clinical studies identified, based on our search strategy. Two hundred twenty-six studies were excluded, and the exclusion criteria are shown in Fig. 2. Among 32 studies selected for further analysis, 11 studies were combination therapy or controlled with other targeted therapy, 3 studies were monotherapy compared with placebo. In this analysis, we focused on 18 chemotherapy or ipilimumab controlled studies, and only nivolumab, pembrolizumab, atezolizumab, and avelumab were included (conventional therapy-controlled studies for other 2 drugs could not be found).

3.2. Study characteristics

There were 18 full-text articles included in our analysis, including 15 phase III trials and 3 phase II trials. All 18 studies were multi-center clinical trials funded by the pharmaceutical industry. A total of 11,465 patients involved in these studies: 6226 patients allocated in intervention arms, and 5239 patients in control arm, respectively. Among these studies, 9 were carried out in patients with non-small cell lung cancer, 6 in melanoma, 2 in urothelial carcinoma, and 1 study evaluated gastric or gastro-esophageal junction cancer. Subjects in the intervention groups received pembrolizumab in 6 studies, nivolumab in 8 studies, atezolizumab in 3 studies, and avelumab in 1 study. All the intervention arms were the patients treated with PD-1/PD-L1 inhibitors monotherapy, and the control arms were patients receiving chemotherapy (15 studies) or ipilimumab (3 studies). All studies included in this meta-analysis were registered on ClinicalTrials.gov and the adverse events were reported in detail with accurate data. Table 1 shows the characteristics of included studies.

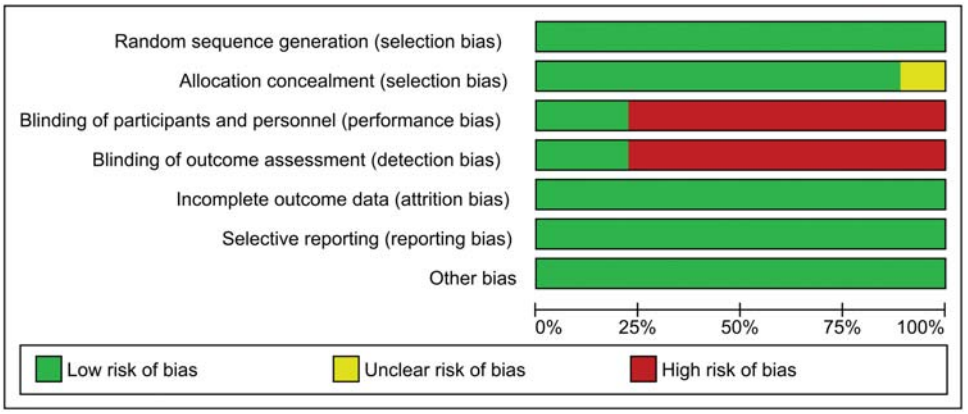

Figure 1. Risk of bias summary. Risk of bias was labeled as high (red), low (green) or unclear (yellow).

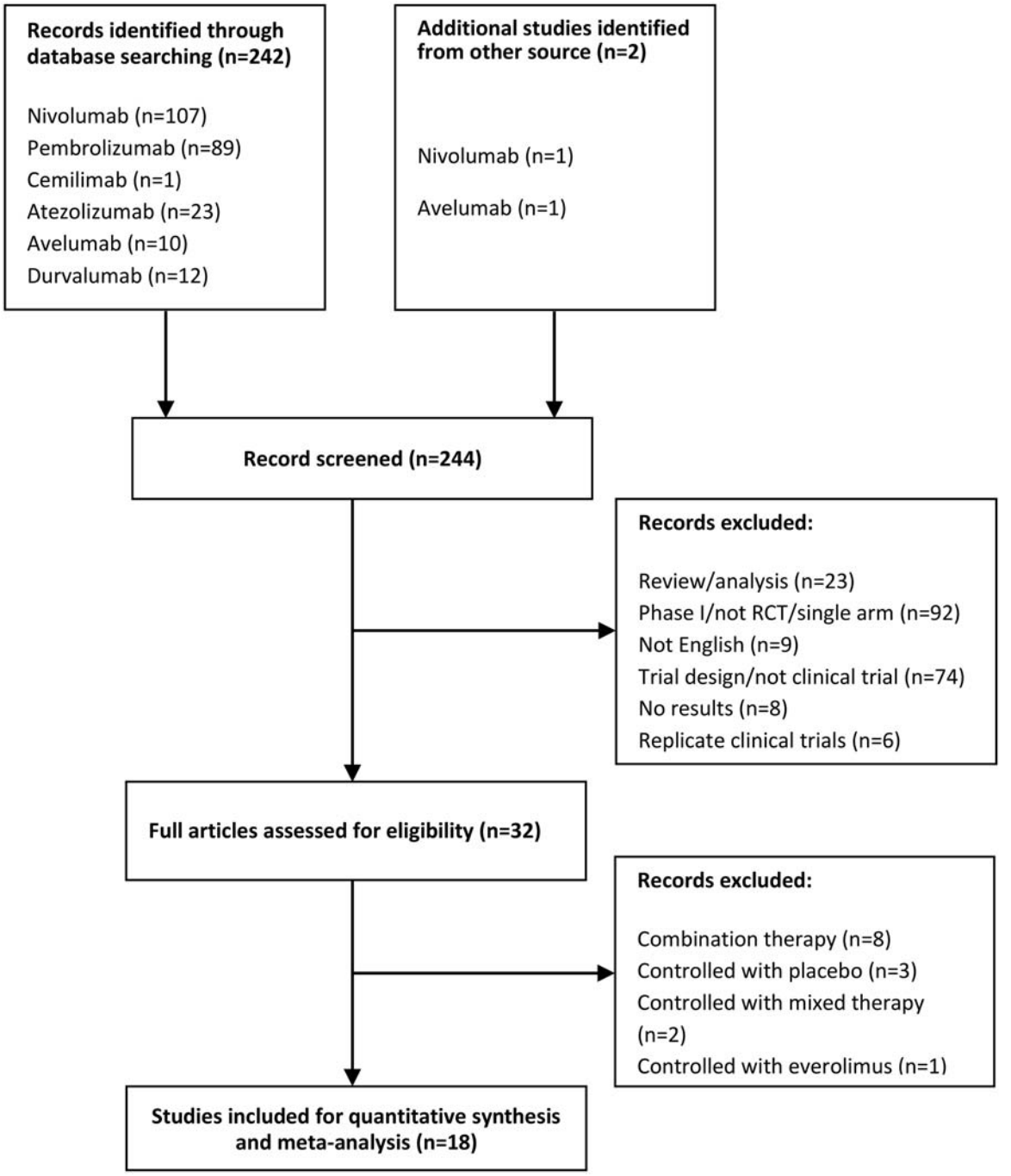

Figure 2. Flow diagram of the study selection procedure.

3.3. Incidence of all-grade and high-grade (≥3) dermatologic and mucosal adverse events

In this dermatologic and mucosal AE incidence analysis, only clinical trials with intervention groups receiving one of the PD-1/PD-L1 inhibitor monotherapies (pembrolizumab, nivolumab, atezolizumab, and avelumab) were included. We analyzed the incidence of rash, pruritus, mucosal inflammation, stomatitis, alopecia, and vitiligo developed by each PD-1/PD-L1 inhibitors with 95% CI (Table 2). Both all-grade and high-grade AEs were computed in this analysis. A total of 6226 patients from 18 studies were included for the calculation of the incidence. All-grade rash and pruritus data were extracted from all 18 studies with a relatively high incidence (11.8% with 95% CI: 9.8–14.1%, and 12.2% with 95% CI: 9.8–15.1%, respectively). The incidence of high-grade rash was higher than that of other high-grade AEs (0.6% with 95% CI: 0.4–0.9%).

3.4. Comparison between the risk of all-grade rash in patients treated with PD-1/PD-L1 inhibitor monotherapy versus chemotherapy and ipilimumab control

The relative risk of all-grade rash was computed by comparing the development of rash in patients treated with PD-1 or PD-L1

Table 1

Studies included in the meta-analysis.

Study	Year	Phase	Drug	Cancer type	Number of patients	Dose of PD-1/PD-L1 inhibitors
Shitara et al [20] NCT02370498	2018	III	Pembrolizumab	Gastric or gastro-esophageal junction cancer	Arm A: Pembrolizumab (294 pts) Arm B: Paclitaxel (276 pts)	Pembrolizumab 200 mg every 3 weeks
Schachter et al [21] NCT01866319	2017	III	Pembrolizumab	Melanoma	Arm A: Pembrolizumab (278 pts) Arm B: Pembrolizumab (277 pts) Arm C: Ipilimumab (256 pts)	Arm A: Pembrolizumab 10 mg/kg every 2 weeks Arm B: Pembrolizumab 10 mg/kg every 3 weeks
Bellmunt et al [22] NCT02256436	2017	III	Pembrolizumab	Urothelial carcinoma	Arm A: Pembrolizumab (266 pts) Arm B: Chemotherapy (255 pts)	Pembrolizumab 200mg every 3 weeks
Reck et al [23] NCT02142738	2016	III	Pembrolizumab	NSCLC	Arm A: Pembrolizumab (154pts) Arm B: Chemotherapy (151 pts)	Pembrolizumab 200 mg every 3 weeks
Herbst et al [24] NCT01905657	2015	II/III	Pembrolizumab	NSCLC	Arm A: Pembrolizumab (339 pts) Arm B: Pembrolizumab (343 pts) Arm C: Docetaxel (309 pts)	Arm A: Pembrolizumab 2 mg/kg Arm B: Pembrolizumab 10 mg/kg
Ribas et al [25] NCT01704287	2015	II	Pembrolizumab	Melanoma	Arm A: Pembrolizumab (178 pts) Arm B: Pembrolizumab (179 pts) Arm C: Chemotherapy (171 pts)	Arm A: Pembrolizumab 2 mg/kg every 3 weeks Arm B: Pembrolizumab 10 mg/kg every 3 weeks
Hellmann et al [26] NCT02477826	2018	III	Nivolumab	NSCLC	1. PD-L1 expression of ≥1% (1189 pts):Arm A: Nivolumab plus Ipilimumab (396 pts) Arm B: Chemotherapy (397 pts) Arm C: Nivolumab (396 pts) 2. PD-L1 expression of ≤1% (550 pts):Arm A: Nivolumab plus Ipilimumab (187 pts) Arm B: Chemotherapy (186 pts) Arm C: Nivolumab plus Chemotherapy (177 pts)	1. PD-L1 expression of ≥1% (1189 pts):Arm A: Nivolumab (3 mg/kg every 2 week) plus Ipilimumab (1 mg/kg every 6 week) Arm B: nivolumab (240 mg every 6 week) 2. PD-L1 expression of ≤1% (550 pts):Arm A: Nivolumab (3 mg/kg every 2 week) plus Ipilimumab (1 mg/kg every 6 week) Arm B: nivolumab (360 mg every 3 week) plus chemotherapy
Weber et al [27] NCT02388906	2017	III	Nivolumab	Melanoma	Arm A: Nivolumab (452 pts) Arm B: Ipilimumab (453 pts)	Nivolumab 3 mg/kg every 2 weeks
Wolchok et al [28] NCT01844505	2017	III	Nivolumab	Melanoma	Arm A: Nivolumab (313 pts) Arm B: Nivolumab plus Ipilimumab (313 pts) Arm C: Ipilimumab (311 pts)	A: Nivolumab 3 mg/kg every 2 weeks B: Nivolumab (1 mg/kg) every 3 weeks plus ipilimumab (3 mg/kg) every 3 weeks, followed by nivolumab (3 mg/kg) every 2 weeks
Carbone et al [29] NCT02041533	2017	III	Nivolumab	NSCLC	Arm A: Nivolumab (267 pts) Arm B: Platinum-based chemotherapy (263 pts)	Nivolumab 3 mg/kg every 2 weeks
Borghaei et al [30] NCT01673867	2015	III	Nivolumab	NSCLC	Arm A: Nivolumab (287 pts) Arm B: Docetaxel (268 pts)	Nivolumab 3 mg/kg every 2 weeks
Brahmer et al [31] NCT01642004	2015	III	Nivolumab	NSCLC	Arm A: Nivolumab (131 pts) Arm B: Docetaxel (129 pts)	Nivolumab 3 mg/kg every 2 weeks
Weber et al [32] NCT01721746	2015	III	Nivolumab	Melanoma	Arm A: Nivolumab (268 pts) Arm B: ICC (102 pts)	Nivolumab 3 mg/kg every 2 weeks
Robert et al [33] NCT01721772	2015	III	Nivolumab	Melanoma	Arm A: Nivolumab (206 pts) Arm B: Dacarbazine (205 pts)	Nivolumab 3 mg/kg every 2 weeks
Powles et al [34] NCT02302807	2017	III	Atezolizumab	Urothelial carcinoma	Arm A: Atezolizumab (459 pts) Arm B: Chemotherapy (443 pts)	Atezolizumab 1200 mg every 3 weeks
Rittmeyer et al [35] NCT02008227	2016	III	Atezolizumab	NSCLC	Arm A: Atezolizumab (609 pts) Arm B: Docetaxel (578 pts)	Atezolizumab 1200 mg every 3 weeks
Fehrenbacher et al [36] NCT01903993	2016	II	Atezolizumab	NSCLC	Arm A: Atezolizumab (142 pts) Arm B: Docetaxel (135 pts)	Atezolizumab 1200 mg every 3 weeks
Barlesi et al [37] NCT02395172	2018	III	Avelumab	NSCLC	Arm A: Avelumab (393 pts) Arm B: Docetaxel (365 pts)	Avelumab 10 mg/kg every 2 weeks

NSCLC = non-small cell lung cancer.

Table 2

Incidence of several skin immune-related adverse events by PD-1/PD-L1 inhibitors (values are in percentages of 95% confidence intervals).

Adverse effect	Grade	Pembrolizumab n = 2308	Nivolumab n = 2315	Atezolizumab n = 1210	Avelumab n = 393	Total n = 6226
Rash	All	12.8 (10.4–15.8)	12.7 (9.5–17.0)	10.6 (9.0–12.5)	3.3 (1.9–5.6)	11.8 (9.8–14.1)
	High	0.3 (0.1–0.7)	0.7 (0.4–1.2)	0.5 (0.1–4.4)	–	0.6 (0.4–0.9)
Pruritus	All	15.0 (10.9–20.7)	12.8 (9.2–17.8)	10.7 (6.9–16.5)	1.3 (0.5–3.0)	12.2 (9.8–15.1)
	High	0.1 (0.0–0.5)	0.2 (0.1–0.6)	0.2 (0.0–1.0)	–	0.2 (0.1–0.4)
Mucosal inflammation	All	0.8 (0.4–1.7)	1.9 (1.1–3.3)	2.9 (0.8–9.8)	0.5 (0.1–2.0)	1.4 (0.8–2.5)
	High	0.2 (0.0–0.7)	0.3 (0.1–1.2)	0.1 (0.0–0.7)	0.1 (0.0–2.0)	0.2 (0.1–0.4)
Stomatitis	All	3.2 (2.2–4.7)	2.0 (1.1–3.6)	2.9 (2.1–4.0)	0.8 (0.2–2.4)	2.7 (2.0–3.5)
	High	0.4 (0.1–1.8)	0.3 (0.1–1.4)	0.2 (0.0–1.2)	0.1 (0.0–2.0)	0.2 (0.1–0.6)
Alopecia	All	1.0 (0.6–1.5)	1.0 (0.5–2.0)	0.7 (0.2–2.8)	0.1 (0.0–2.0)	0.9 (0.6–1.3)
	High	0.1 (0.0–0.4)	0.2 (0.1–0.9)	0.2 (0.0–1.2)	0.1 (0.0–2.0)	0.2 (0.1–0.4)
Vitiligo	All	7.5 (4.0–14.1)	8.3 (5.7–12.1)	–	–	8.1 (6.1–10.7)
	High	0.1 (0.0–0.8)	0.3 (0.1–1.0)	–	–	0.2 (0.1–0.6)

inhibitor to those treated with the chemotherapy control arm (Fig. 3A) and ipilimumab control arm (Fig. 3B), respectively. The index was used to determine the contribution of PD-1/PD-L1 immune checkpoint inhibitors to the development of rash. The data, extracted from 15 studies with a total of 9125 subjects, were included for the calculation of the RR in the grades 1–5 rash. Compared with chemotherapy, the RR of all-grade rash developed by PD-1/PD-L1 inhibitors was 1.84 (95% CI: [1.47, 2.30]; $P < .001$), which suggests that the risk was higher with anti-PD-1 or anti-PD-L1 drugs. However, the RR of all-grade rash developed by anti-PD-1/PD-L1 drugs compared with ipilimumab (the other immune checkpoint inhibitor for CTLA-4) was 0.90 (95% CI: [0.65, 1.23]; $P = .50$). Thus, this analysis shows no evidence of the use of PD-1/PD-L1 inhibitor monotherapy associated with an obviously increased risk of developing all-grade rash compared with ipilimumab monotherapy. A random-effect model was used to analyze the RR of developing all-grade rash caused by PD-1/PD-L1 inhibitor monotherapy treatment.

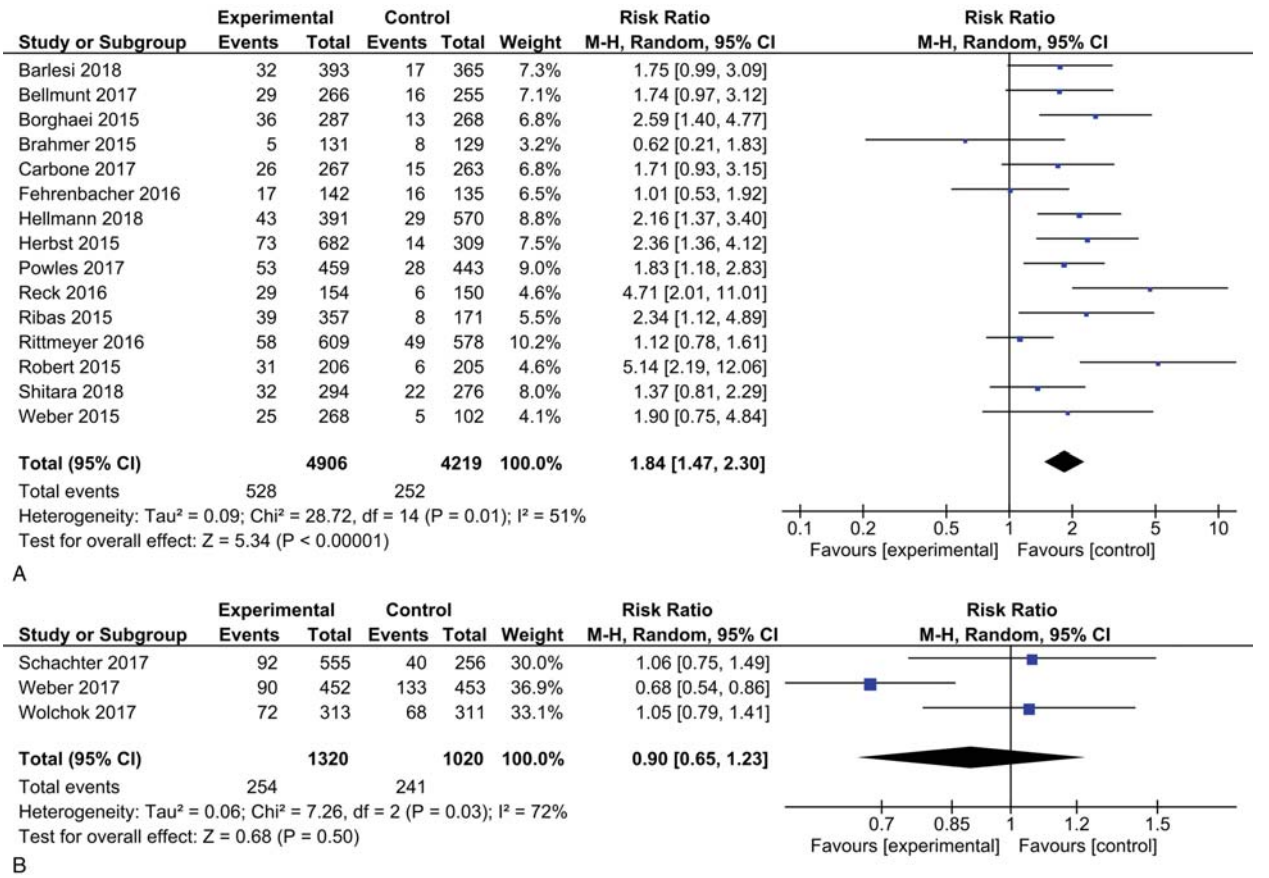

Figure 3. Forest plots of relative risk of all-grade rash in comparison of PD-1/PD-L1 inhibitors with chemotherapy control (A) and ipilimumab control (B).

3.5. Comparison between the risk of all-grade pruritus in patients treated with PD-1/PD-L1 inhibitor monotherapy versus chemotherapy and ipilimumab control

The risks of all-grade pruritus were analyzed, to compare the anti-PD-1/PD-L1 drugs monotherapy (pembrolizumab, nivolumab, atezolizumab, or avelumab) versus chemotherapy (Fig. 4A) and ipilimumab monotherapy (Fig. 4B), respectively. A total of 9125 patients from 15 studies were included for the RR calculation of all-grade pruritus compared with chemotherapy group. The RR of all-grade pruritus was 3.74 (95% CI: [2.79, 5.01]; $P < .001$) in the chemotherapy control studies and 0.68 (95% CI: [0.59, 0.78]; $P < .001$) in the ipilimumab control studies, respectively. The results indicate that, compared with chemotherapy, PD-1/PD-L1 inhibitor monotherapy results in a relatively higher risk of developing pruritus. By contrast, there was a significantly decreased risk of developing pruritus in patients treated with PD-1/PD-L1 inhibitors versus ipilimumab monotherapy. A random model was used to analyze the RR of developing all-grade pruritus in these studies.

3.6. Comparison between the risk of all-grade mucosal inflammation in patients treated with PD-1/PD-L1 inhibitor monotherapy versus chemotherapy control

Compared with chemotherapy, anti-PD-1/PD-L1 drugs showed notably decreased risk of developing grades 1–5 mucosal inflammation with the RR lower than 1 (0.26, 95% CI: [0.20, 0.35]; $P < .001$) (Fig. 5). A fixed-effects model was used to analyze the relative risk of developing all-grade mucosal inflammation in these studies, and the number of subjects included was 6274 from 9 studies.

3.7. Comparison between the risk of all-grade stomatitis in patients treated with PD-1/PD-L1 inhibitor monotherapy versus chemotherapy control

There were 10 studies reporting rates of stomatitis, where 6595 patients involved. From the forest plot (Fig. 6), the RR of developing all-grade stomatitis during the treatment with PD-1/PD-L1 inhibitors as compared to the chemotherapy monotherapy was 0.26 (95% CI: [0.21, 0.33]; $P < .001$). Thus, the patients treated with anti-PD-1 drugs or anti-PD-L1 drugs were less likely to experience stomatitis.

3.8. Comparison between the risk of all-grade alopecia in patients treated with PD-1/PD-L1 inhibitor monotherapy versus chemotherapy control

All-grade alopecia was reported in 13 studies, involving in total 7753 patients. RR of developing alopecia comparing PD-1/PD-L1 inhibitor monotherapy to chemotherapy was 0.03 (95% CI: [0.02, 0.06]; $P < .001$) (Fig. 7). PD-1/PD-L1 showed significantly lower risk of inducing alopecia comparing to chemotherapy. RR was calculated by the random-effects model.

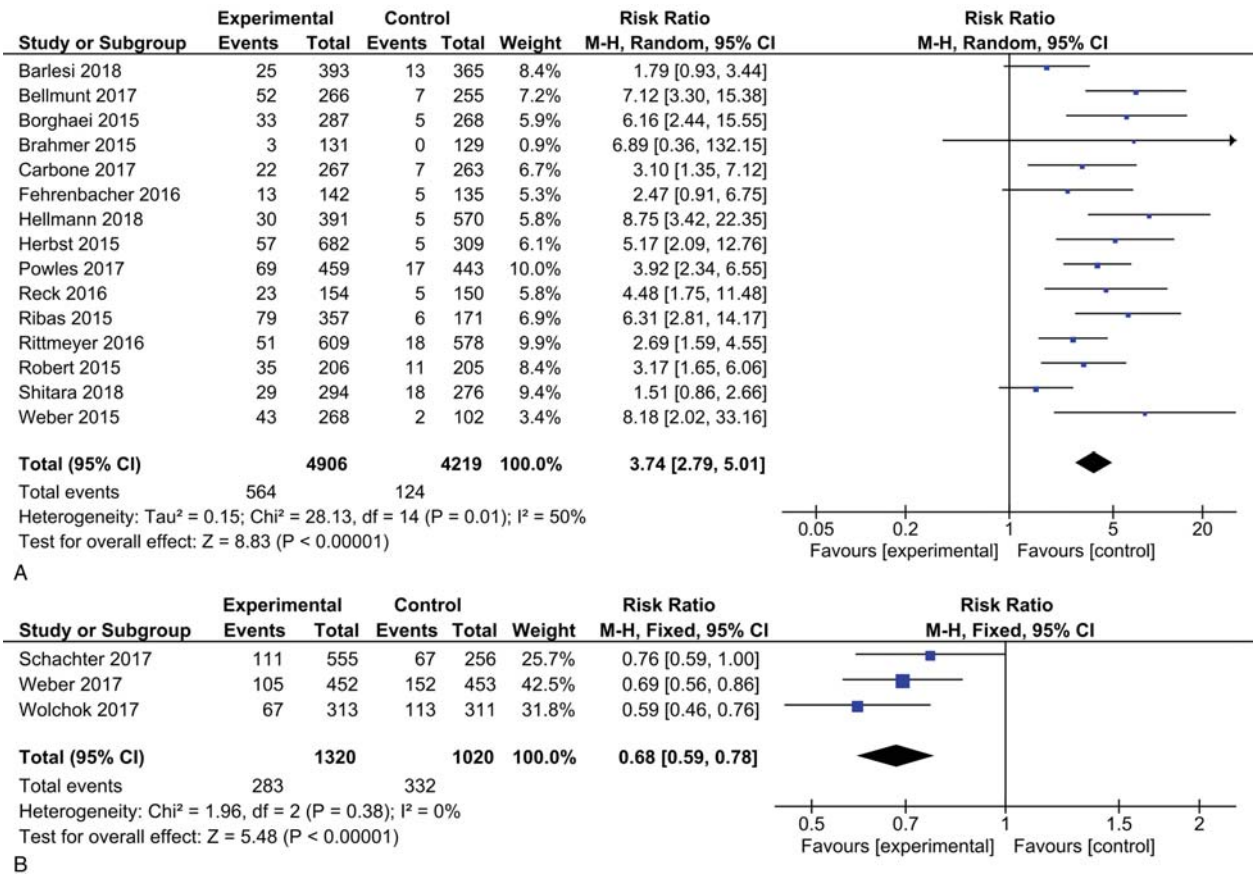

Figure 4. Forest plots of relative risk of all-grade pruritus in comparison of PD-1/PD-L1 inhibitors with chemotherapy control (A) and ipilimumab control (B).

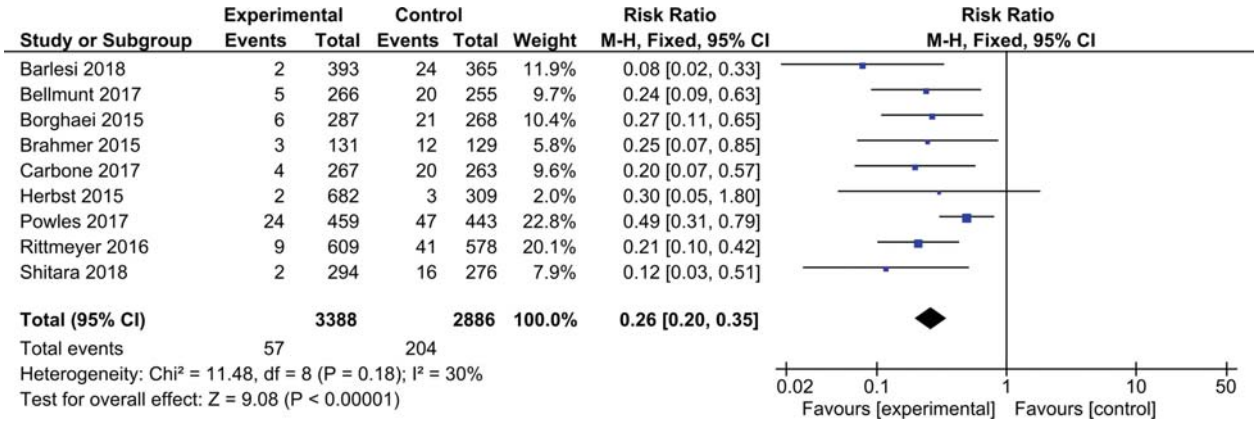

Figure 5. Forest plots of relative risk of all-grade mucosal inflammation in comparison of PD-1/PD-L1 inhibitors with chemotherapy control.

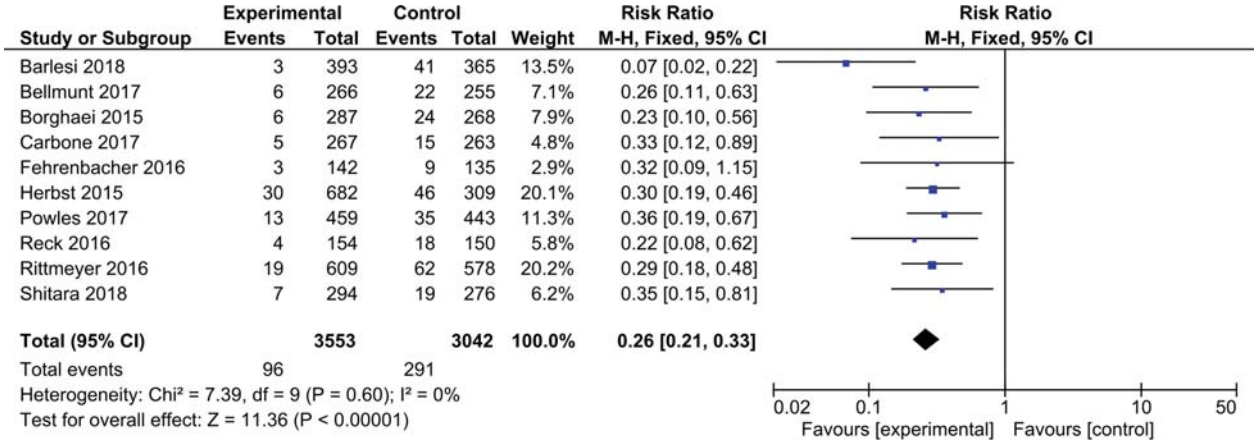

Figure 6. Forest plots of relative risk of all-grade stomatitis in comparison of PD-1/PD-L1 inhibitors with chemotherapy control.

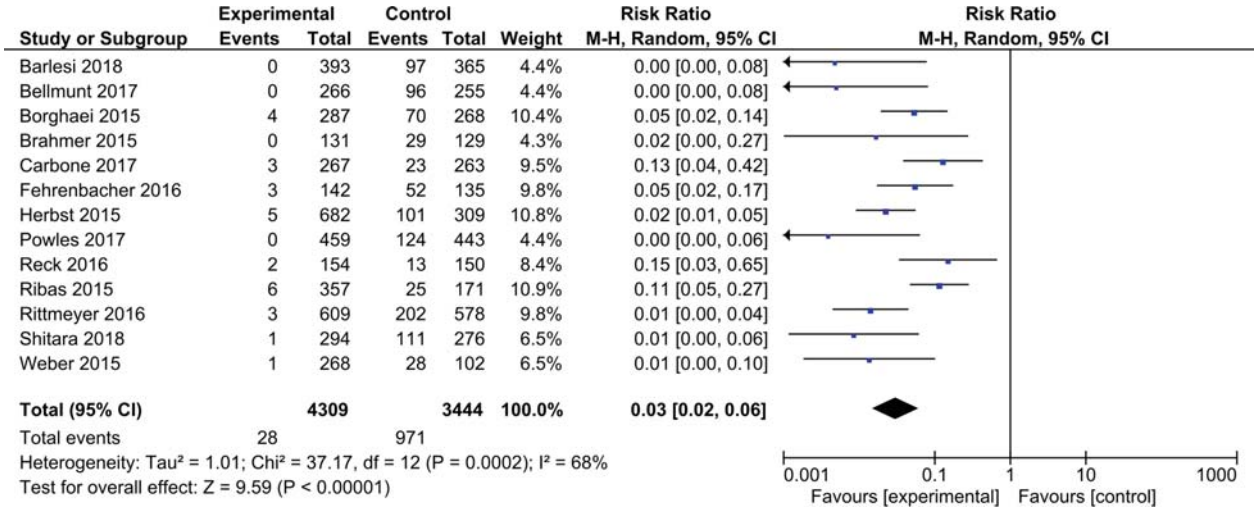

Figure 7. Forest plots of relative risk of all-grade alopecia in comparison of PD-1/PD-L1 inhibitors with chemotherapy control.

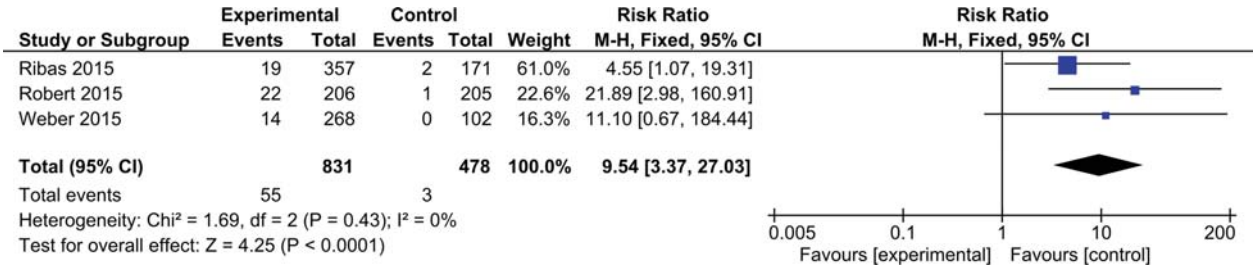

Figure 8. Forest plots of relative risk of all-grade vitiligo in comparison of PD-1/PD-L1 inhibitors with chemotherapy control.

3.9. Comparison between the risk of all-grade vitiligo in patients treated with PD-1/PD-L1 inhibitor monotherapy versus chemotherapy control

Patients developing vitiligo during PD-1/PD-L1 inhibitor treatment were reported in 3 studies, affecting 55 in 831 PD-1/PD-L1 inhibitor treated patients. RR of all grade vitiligo was 9.54 (95% CI: [3.37, 27.03]; $P < .001$) (Fig. 8), which was conducted by the fixed-effect model. Compared with chemotherapy, PD-1/PD-L1 inhibitor increased the risk of inducing vitiligo.

3.10. Subgroup analysis

To explain the heterogeneity generated in meta-analysis, subgroup analysis was conducted to further investigate the origin of differences among studies. The trials controlled with chemotherapy were analyzed. The AEs were selected only with relatively high heterogeneity, rash ($I^2 = 51\%$), pruritus ($I^2 = 50\%$) and alopecia ($I^2 = 68\%$), and the studies were stratified by cancer type, targeting location (PD-1 or PD-L1) or drug used.

For rash with the patients treated with PD-1/PD-L1 inhibitor monotherapy versus chemotherapy, PD-1 inhibitor (nivolumab and pembrolizumab) has significantly higher risk of inducing rash than PD-L1 inhibitor (atezolizumab and avelumab), and the RR for PD-1 inhibitor and PD-L1 inhibitor are 2.11 (95% CI: [1.63–2.74]; $P < .001$) and 1.38 (95% CI: [1.03–1.85]; $P = .03$), respectively (Fig. 9). PD-1 inhibitor was further stratified to investigate the differences between two drugs (pembrolizumab and nivolumab), but no significant differences were found in developing rush (Supplementary Figure S1, http://links.lww.com/MD/C990). Additionally, the rash subgroup stratified by cancer type was analyzed, and no statistical significance was found (Supplementary Figure S2, http://links.lww.com/MD/C990). For

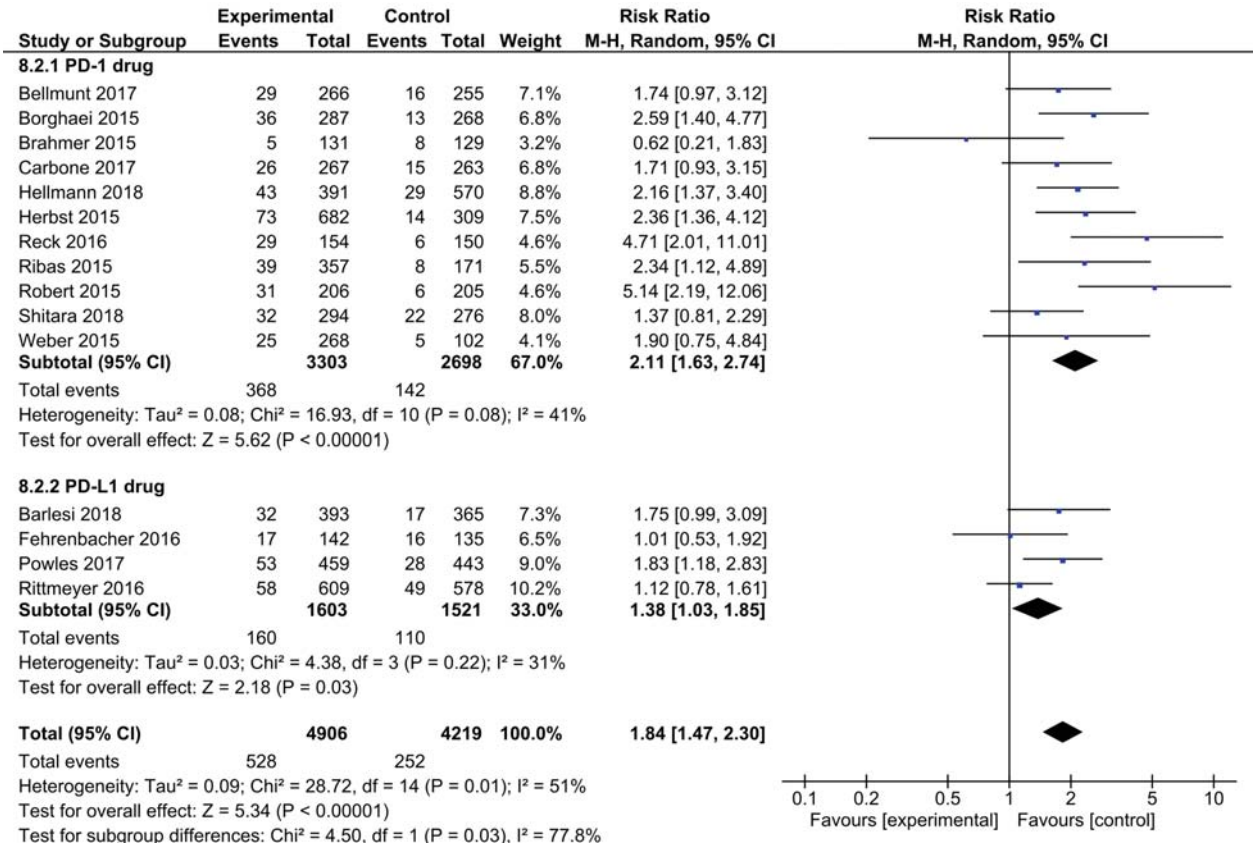

Figure 9. Rash subgroup analysis according to target location. Test for subgroup difference $P = .03$.

Pruritus, the RR for PD-1 inhibitor and PD-L1 inhibitor are 4.49 (95% CI: [3.04–6.65]; $P < .001$) and 2.76 (95% CI: [1.97–3.87]; $P < .001$), respectively. Subgroup difference test for PD-1 inhibitor and PD-L1 inhibitor was at the boundary of statistical significance ($P = .06$), which suggests PD-1 inhibitor might have higher risk of developing pruritus compared with PD-L1 inhibitor (Fig. 10). Cancer type stratification demonstrated gastric cancer has lower risk to induce pruritus (RR = 1.51, 95% CI: [0.86–2.66]; $P = .15$), compared to all cancer types (RR = 3.77, 95% CI: [3.11–4.58]; $P < .001$) (Fig. 11). Pembrolizumab and nivolumab did not have significant difference in developing pruritus (Supplementary Figure S3, http://links.lww.com/MD/C990). For alopecia, subgroup analysis was also performed as mentioned above, however, there was no significant difference between subgroups in alopecia (Supplementary Figures S4–S6, http://links.lww.com/MD/C990). All supplementary figures are attached in Supplemental Digital Content.

4. Discussion

PD-1/PD-L1 inhibitors are promising in treating multiple cancer type, and their AEs need to be fully investigated and understood. In this study, we analyzed 18 phase II/III RCTs of PD-1/PD-L1 inhibitors involving 11,465 patients and focused on common dermatological and mucosal AEs. In comparison to previous studies, mostly relying on phase I/II trials, our study mainly focused on the differences between PD-1/PD-L1 inhibitors and traditional therapies, and the incidence and RR were calculated with better accuracy based on the data from phase II/III trials.

The irAEs of PD-1/PD-L1 inhibitors are notable and should be studied thoroughly, even though the overall safety profile is good. Rash is the most common irAE induced by PD-1/PD-L1 inhibitors, and it usually happens after first few cycles of treatment.[38] Total risk of any grade rash is 11.8% (95% CI: 9.8–14.1%), and high-grade rash incidence is 0.6% (95% CI: 0.4–0.9%). Our results demonstrated that PD-1/PD-L1 inhibitors are more likely to induce rash comparing to chemotherapy (RR = 1.84), and it has similar risk to develop rash (RR = 0.90) comparing to ipilimumab. In a retrospective study, rash was found associated with favorable response rate, PFS and OS,[39] since rash is related to the robust immune reaction. Some case report also mentioned that lichenoid is related to T cell infiltration.[40] Although the relationship between rash and better clinical outcome is still vague, pathogenesis of rash warrants further investigation, and rash could be an indicator for drug response. Pruritus is also commonly seen in PD-1/PD-L1 inhibitors treated patients, with incidence of all grade and high grade 12.2% (95% CI: 9.8–15.1%) and 0.2% (95% CI: 0.1–0.4%), respectively. Compared to chemotherapy, PD-1/PD-L1 inhibitors increase the risk of developing pruritus with RR = 3.74, while previous meta-analysis conducted by Belum et al reported different pruritus RR against chemotherapy (pembrolizumab RR:34.5, nivolumab RR:49.9).[41] The discrepancy in RR of pruritus may be due to different clinical data included in our studies. All of clinical data analyzed in our study are latest data

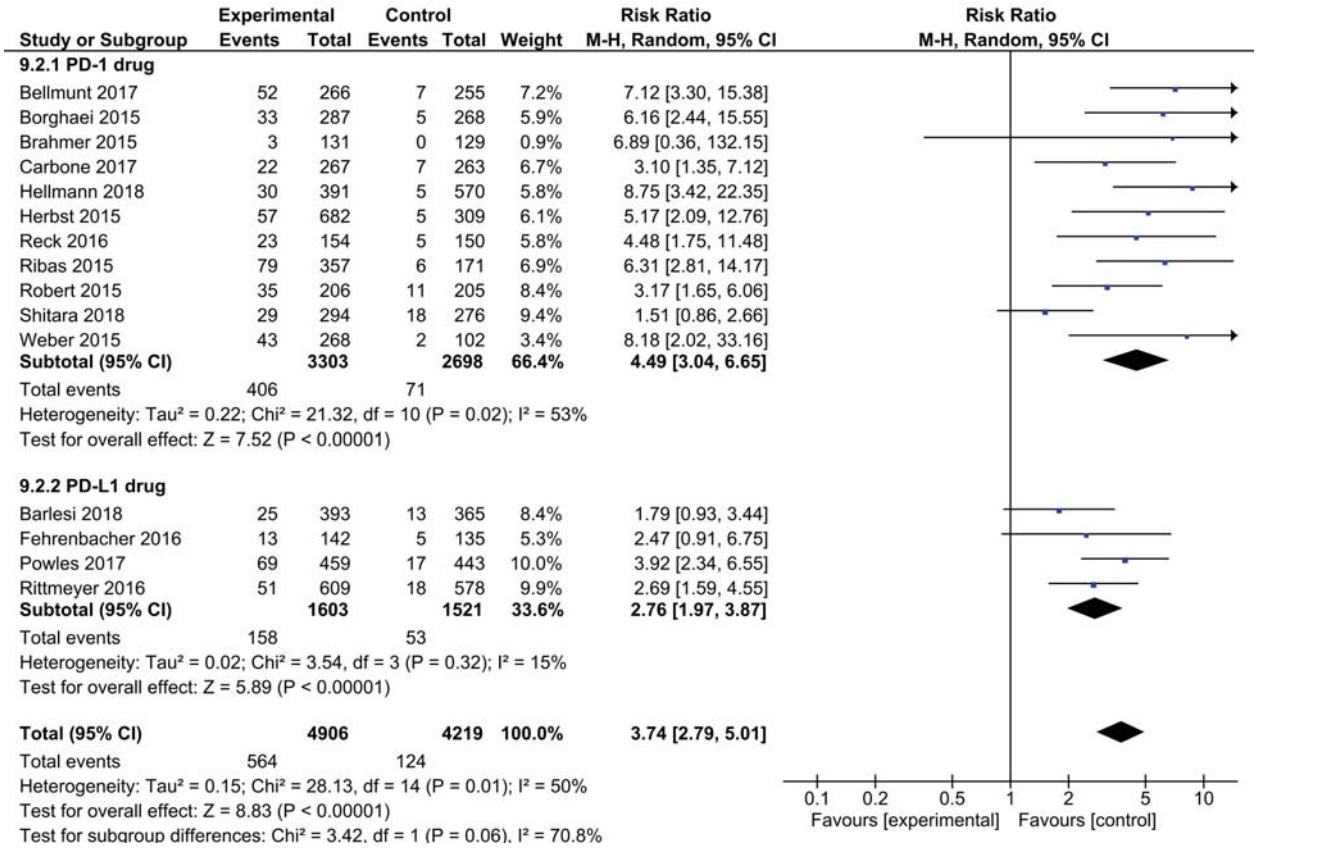

Figure 10. Pruritus subgroup analysis according to target location. Test for subgroup difference $P = .06$.

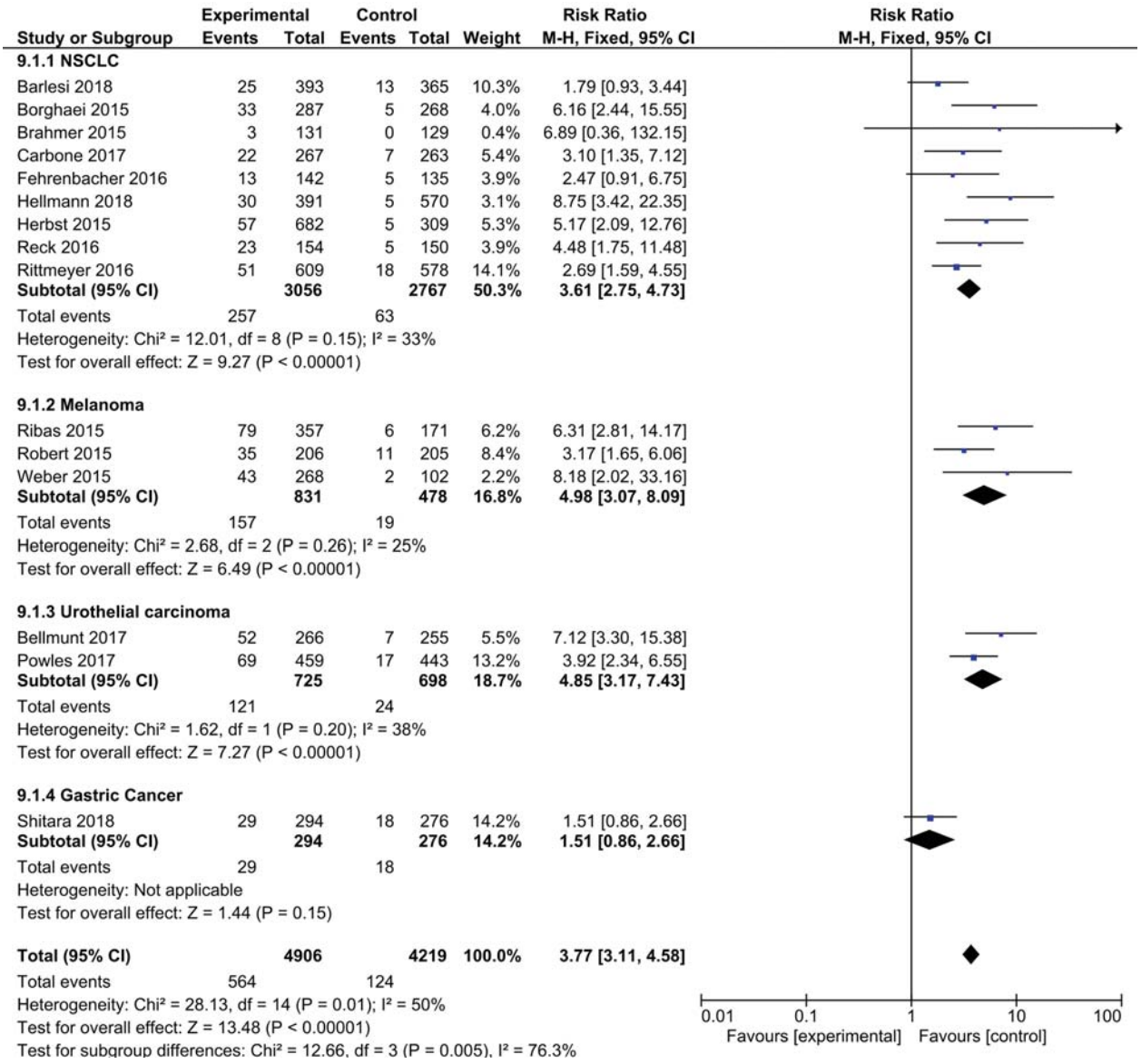

Figure 11. Pruritus subgroup analysis according to cancer type. Test for subgroup difference $P = .005$.

available from phase II/III trials. Compared to ipilimumab, PD-1/PD-L1 inhibitor shows better safety profile in pruritus (RR = 0.68). Pruritus is usually mild and low grade, while in some cases pruritus can interfere normal sleeping[42] and decrease the quality of life score. Pruritus was also reported to be harbinger of bullous pemphigoid,[43] which is a severe immunotherapy induced dermatological AE. Vitiligo is a common and unique characteristic of checkpoint immune-induced irAEs observed in the clinic[44] and RR of developing vitiligo compared against chemotherapy is 9.54. Vitiligo also implicates with enhanced auto-immunity and some studies also reported developing vitiligo related to positive drug efficacy.[45]

Apart from the shortage of PD-1/PD-L1 inhibitors mentioned above, we also noticed some positive safety profiles compared to traditional chemotherapy. Since PD-1/PD-L1 inhibitors do not interfere cell replication as conventional chemotherapy does, typical drawback in chemotherapy is reduced in the PD-1/PD-L1 inhibitor treatment. Risk of developing alopecia is significantly lower compared to chemotherapy (RR = 0.03) due to less cytotoxicity of PD-1/PD-L1 inhibitors. Although alopecia incidence 0.9% (95% CI: 0.6–1.3%) remains low in PD-1/PD-L1 inhibitors treated patients, some case reports suggest that PD-1/PD-L1 inhibitor induced alopecia has T-cell infiltrated hair follicle,[46] which suggests PD-1/PD-L1 inhibitor induced alopecia could be an irAE. As mucosa is also a fast-proliferating tissue, stomatitis and mucosal inflammation are less likely to develop during PD-1/PD-L1 inhibitors treatment.

Safety of PD-1/PD-L1 inhibitor was found better compared to ipilimumab, which is consistent with the results published in literatures.[47] According to a review by Boutros, CTLA-4 is an immune checkpoint receptor expressed on T cells, and its activation could inhibit early stage immune response of T cells.[47] Moreover, CTLA-4 is also expressed on regulatory T cells (T_{REG}), which are a group of cells inhibiting immune response in tumor microenvironment. Different from CTLA-4, PD-1 is mainly expressed in peripheral tissues and tumor

environment. PD-1 inhibitor could target T cells with more specificity. Therefore, blocking the combination of CTLA-4 and B7 ligand could lead to a more extensive activation of immune effect, and the activation of immune system explains why CTLA-4 inhibitor could trigger so many adverse reactions.[47] Some new findings suggest that CTLA-4 inhibitor exerts its antitumor effect by killing T_{REG}, but not blocking the CTLA-4 on T cells, which may also implicate in worse safety profile.[48,49]

In our subgroup analysis, for the first time we found PD-L1 inhibitor has better safety profile than PD-1 inhibitor in developing dermatological irAEs. Why PD-1 inhibitor has higher risk of rash and pruritus remains unknown. PD-1 and PD-L1 are two major parts in the same pathway, and they are expressed on different group of cells. PD-1 is an immunosuppressive molecule expressed on immune cells, while PD-L1 is a transmembrane protein expressed on tumor cells. Although sharing same immune checkpoint pathway, PD-1 inhibitor targets PD-1 receptor on T cell while PD-L1 molecule is expressed on multiple cell types. The expression quantities and locations of PD-1 and PD-L1 are different, which might affect the efficacy and consequential irAEs of their inhibitors. Currently many clinical trials are still ongoing, and more clinical data for PD-1/PD-L1 inhibitors are needed to verify this conclusion. Furthermore, PD-1 inhibitor subgroup analysis suggested pembrolizumab and nivolumab have similar dermatological toxicity, which may be due to acting on the same target. In cancer type subgroup analysis, we noticed that patients with gastric or gastro-esophageal junction cancer have better tolerability towards PD-1/PD-L1 inhibitor. Since only 1 RCT of this cancer was found, more evidences are needed to validate this observation and find its root cause (e.g., ethnicity).

Our meta-analysis has some limitations. First, the analysis was conducted at the group levels of clinical studies rather than individual patient level. Some important variables like age, prior therapy, or ethnicity were not included in this analysis. Most of these studies are open-label designed trials, which could result in the ascertainment bias. Second, different dose and frequency of drug administration in both intervention and control group could be the origin of heterogeneity. Some studies used clinician selected chemotherapy, which also implicated in inducing heterogeneity. Third, rash reported in different studies may have various definition based on investigators' objective diagnosis, and the details of rash were poorly described in their studies. Forth, although we searched and screened all studies based on clinical trial tag, we still lack specific studies for certain cancer types and studies controlled with ipilimumab.

This analysis provides physician useful information of PD-1/PD-L1 inhibitor dermatological and mucosal AEs. Patients susceptible to mucosal inflammation or with vulnerable mucosa might benefit from PD-1/PD-L1 inhibitor. Additionally, PD-L1 inhibitor might have better safety profile comparing to PD-1 inhibitor. Dermatological irAEs are common in PD-1/PD-L1 inhibitor treated patients. Since some irAEs are implicated with better clinical outcome, low-grade dermatological irAEs normally should not cause the discontinuation of the drug. However, some commonly seen irAEs might result in serious condition, which needs to be noticed. This meta-analysis also provides new ideas for researchers to explore the mechanism of drugs acting on different targets. With the progress of extensive in-depth studies, the safety profiles of PD-1/PD-L1 inhibitors will be fully understood to guide better clinical applications for the cancer patients.

5. Conclusion

Our meta-analysis demonstrated PD-1/PD-L1 inhibitors increase the risk of rash, pruritus, and vitiligo compared to the conventional chemotherapy, although they have better safety profile in alopecia, mucosal inflammation, and stomatitis. Additionally, anti-PD1 drugs have similar risk of developing rash and lower risk of inducing pruritus, compared with ipilimumab. Subgroup analysis suggests that PD-L1 inhibitor may have better safety profile than PD-1 inhibitor in developing dermatological irAEs. Dermatological and mucosal AEs of PD-1/PD-L1 inhibitors are the most prevalent and obvious AEs, which should be further systematically studied.

Author contributions

Data curation: Wenwei Yang, Shuquan Li.
Formal analysis: Qingrui Yang.
Investigation: Wenwei Yang, Shuquan Li.
Methodology: Shuquan Li.
Resources: Qingrui Yang.
Software: Wenwei Yang, Shuquan Li.
Supervision: Qingrui Yang.
Validation: Qingrui Yang.
Visualization: Wenwei Yang, Shuquan Li, Qingrui Yang.
Writing – original draft: Wenwei Yang, Shuquan Li.
Writing – review & editing: Wenwei Yang, Shuquan Li, Qingrui Yang.

Wenwei Yang orcid: 0000-0002-7292-5980.

References

[1] Mahoney KM, Rennert PD, Freeman GJ. Combination cancer immunotherapy and new immunomodulatory targets. Nat Rev Drug Discov 2015;14:561–84.
[2] Ni L, Dong C. New checkpoints in cancer immunotherapy 2017;276: 52–65.
[3] Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252–64.
[4] Sharpe AH. Introduction to checkpoint inhibitors and cancer immunotherapy. Immunol Rev 2017;doi:10.1111/imr.12531.
[5] Marin-Acevedo JA, Dholaria B, Soyano AE, et al. Next generation of immune checkpoint therapy in cancer: new developments and challenges. J Hematol Oncol 2018;11:39.
[6] USFDA. NDA and BLA Approvals. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/default.htm. Accessed February 21, 2019.
[7] USFDA. PRESCRIBING INFORMATION FOR OPDIVO. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125554s072lbl.pdf. Accessed February 21, 2019.
[8] USFDA. PRESCRIBING INFORMATION FOR TECENTRIQ. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761034s009lbl.pdf. Accessed February 21, 2019.
[9] USFDA. PRESCRIBING INFORMATION FOR BAVENCIO. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761049s003lbl.pdf. Accessed February 21, 2019.
[10] USFDA. PRESCRIBING INFORMATION FOR IMFINZI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761069s002lbl.pdf. Accessed February 21, 2019.
[11] USFDA. PRESCRIBING INFORMATION FOR KEYTRUDA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125514s040lbl.pdf. Accessed February 21, 2019.
[12] USFDA. PRESCRIBING INFORMATION FOR LIBTAYO. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761097s002lbl.pdf. Accessed February 21, 2019.
[13] Johnson DB, Sullivan RJ, Menzies AM. Immune checkpoint inhibitors in challenging populations. Cancer 2017;123:1904–11.

[14] Naidoo J, Page DB, Li BT, et al. Toxicitiesoftheanti-PD-1andanti-PD-L1 immune checkpoint antibodies. Ann Oncol 2015;26:2375–91.
[15] Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. J Clin Oncol 2015;33: doi:10.1200/JCO.2014.59.4358.
[16] Belum VR, Benhuri B, Postow MA, et al. Characterization and management of dermatologic adverse events to agents targeting the PD-1 receptor. Eur J Cancer 2017;60:12–25. doi:10.1016/j.ejca.2016.02.010.Characterization.
[17] Baxi S, Yang A, Gennarelli RL, et al. Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis. BMJ 2–8. doi:10.1136/bmj.k793.
[18] Omar Abdel-Rahman HEMF. Risk of elevated transaminases in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. Expert Opin Drug Saf 2015;14:1507–18.
[19] Abdel-rahman O, Fouad M. Risk of pneumonitis in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. Ther Adv Respir Dis 2016;10:183–93.
[20] Shitara K, Özgüroğlu M, Bang Y, et al. Articles Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. Lancet 2018;392:123–33.
[21] Schachter J, Ribas A, Long GV, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet 2017;390:1853–62.
[22] Bellmunt J, Wit R de, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017;376:1015–26.
[23] Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. N Engl J Med 2016;375:1823–33.
[24] Herbst RS, Baas P, Kim D, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387:1540–50.
[25] Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol 2015;16:908–18.
[26] Hellmann MD, Ciuleanu T-E, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med 2018;378:2093–104.
[27] Weber J, Mandala M, Vecchio MD, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med 2017;377:1824–35.
[28] Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2018;377:1345–56.
[29] Carbone DP, Reck M, Creelan B, et al. First-Line Nivolumab in Stage IV or Recurrent Non–Small-Cell Lung Cancer. N Engl J Med 2017; doi:10.1056/NEJMoa1613493.
[30] Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced non-squamous non-small cell lung cancer. N Engl J Med 2017;373:1627–39.
[31] Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2016;373:123–35.
[32] Weber JS, Angelo SPD, Minor D, et al. 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 2015;16:375–84.
[33] Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015;372:320–30.
[34] Powles T, Durán I, Heijden MS Van Der, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2017;391: doi:10.1016/S0140-6736(17)33297-X.
[35] Rittmeyer A, Barlesi F, Waterkamp D, et al. Articles atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:255–65.
[36] Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837–46.
[37] Barlesi F, Vansteenkiste J, Spigel D, et al. Avelumab versus docetaxel in patients with platinum-treated advanced non-small-cell lung cancer (JAVELIN Lung 200): an open-label, randomised, phase 3 study. Lancet Oncol 2018;19:1468–79.
[38] Sibaud V. Dermatologic reactions to immune checkpoint inhibitors. Am J Clin Dermatol 2017;19:345–61.
[39] Chang ALS, Min Lee CK, Tran DC, et al. Characterization of dermatitis after PD-1/PD-L1 inhibitor therapy and association with multiple oncologic outcomes: a retrospective case-control study. J Am Acad Dermatol 2018;79:1047–52.
[40] Schaberg KB, Novoa RA, Wakelee HA, et al. Immunohistochemical analysis of lichenoid reactions in patients treated with anti-PD-L1 and anti-PD-1 therapy. J Cutan Pathol 2016;43:339–46.
[41] Belum VR, Benhuri B, Postow MA, et al. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. Eur J Cancer 2016;60:12–25.
[42] Ito J, Fujimoto D, Nakamura A, et al. Aprepitant for refractory nivolumab-induced pruritus. Lung Cancer 2017;109:58–61.
[43] Lopez AT, Khanna T, Antonov N, et al. A review of bullous pemphigoid associated with PD-1 and PD-L1 inhibitors. Int J Dermatol 2018;57:664–9.
[44] Young A, Quandt Z, Bluestone JA. The balancing act between cancer immunity and autoimmunity in response to immunotherapy. Cancer Immunol Res 2018;6:1445–53.
[45] Hua C, Boussemart L, Mateus C, et al. Association of vitiligo with tumor response in patients with metastatic melanoma treated with pembrolizumab. JAMA Dermatol 2016;152:45.
[46] Zarbo A, Belum VR, Sibaud V, et al. Immune-related alopecia (areata and universalis) in cancer patients receiving immune checkpoint inhibitors. Br J Dermatol 2017;176:1649–52.
[47] Boutros C, Tarhini A, Routier E, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. Nat Rev Clin Oncol 2016;13:473–86.
[48] Du X, Liu M, Su J, et al. Uncoupling therapeutic from immunotherapy-related adverse effects for safer and effective anti-CTLA-4 antibodies in CTLA4 humanized mice. Cell Res 2018;28:1–5.
[49] Du X, Tang F, Liu M, et al. A reappraisal of CTLA-4 checkpoint blockade in cancer immunotherapy. Cell Res 2018;28:1–7.