Medicine®

OPEN

Risk of gastrointestinal toxicities with PD-1 inhibitors in cancer patients
A meta-analysis of randomized clinical trials

Wei Wei, MD[a], Zhibin Luo, PhD[b,*]

Abstract

Background: Anti-programmed cell death protein 1 (PD-1) antibodies have demonstrated significant clinical activity in many cancer entities. Gastrointestinal toxicities are one of its major side effects, but the overall risks have not been systematically evaluated. Thus, the purpose of this study was to evaluate the incidence and risk of gastrointestinal toxicities with PD-1 inhibitors in cancer patients through a meta-analysis.

Methods: Eligible studies were searched for in PubMed, Embase, and the Cochrane Library. We included randomized controlled trials with cancer patients treated with PD-1 inhibitors with adequate data on gastrointestinal adverse events.

Results: A total of 14 randomized controlled trials involving 7508 patients met eligibility criteria for this meta-analysis. The relative risk of all-grade diarrhea and colitis was 0.66 (95% confidence interval (CI): [0.50, 0.87]; $P = .003$) and 3.36 (95% CI: [1.25, 9.04]; $P = .02$), respectively. The relative risk of high-grade diarrhea and colitis was 0.58 (95% CI: [0.30, 1.11]; $P = .10$) and 4.31 (95% CI: [1.11, 16.79]; $P = .04$), respectively. Compared with ipilimumab alone, the nivolumab/ipilimumab combination was associated with a higher risk of developing all-grade diarrhea. Additionally, PD-1 inhibitor monotherapy resulted in a lower risk of developing gastrointestinal adverse events compared with ipilimumab alone.

Conclusions: Our meta-analysis has demonstrated that the use of PD-1 inhibitors is associated with an increased risk of colitis compared with chemotherapy or everolimus.

Abbreviations: CIs = confidence intervals, HNSCC = squamous-cell carcinoma of the head and neck, ICC= either dacarbazine 1000 mg/m^2 every 3 weeks, or carboplatin area under the curve 6 plus paclitaxel 175 mg/m^2 every 3 weeks, irAEs = immune-related adverse events, NSCLC = non-small-cell lung cancer, PD-1 = anti-programmed cell death protein 1, RCC, renal cell carcinoma. RR = relative risk, SE = Standard error.

Keywords: cancer, gastrointestinal toxicities, meta-analysis, PD-1 inhibitors

1. Introduction

The programmed cell death protein 1 (PD-1) is an inhibitory receptor that limits autoimmunity by preventing overactivation of T cells. Blocking the PD-1 pathway with antibodies can increase tumor-specific CD4+ T cell activity and restore antitumor immunity.[1–3] In recent years, PD-1 inhibitor monotherapy has shown remarkable therapeutic efficacy in the clinic, leading to FDA approval of these agents for cancer therapy. Nivolumab is a fully human monoclonal immunoglobulin G4 anti-PD-1 antibody that has been approved for the treatment of patients with unresectable or metastatic melanoma, metastatic squamous non-small-cell lung cancer (NSCLC), advanced renal cell carcinoma and classical the Hodgkin lymphoma.[4–6] Pembrolizumab is another human PD-1-blocking antibody that has been approved for the treatment of patients with melanoma, NSCLC and squamous-cell carcinoma of the head and neck (HNSCC).[7–10] Furthermore, the combination of anti-PD-1 antibodies and other drugs also showed significant effects in many refractory cancers.[11,12]

Although anti-PD-1 immune checkpoint monoclonal antibodies have demonstrated antitumor activity against a variety of malignancies, they also cause a series of immune-related adverse events (irAEs), which are different from those caused by traditional therapies. Many clinical trials have shown that these adverse reactions involve the skin, liver, and gastrointestinal, endocrine, and other organ systems. Gastrointestinal AEs mainly include diarrhea and colitis, which are very common and may be fatal.[13] Although a previously published meta-analysis showed that the use of immune checkpoint inhibitors (CTLA-4 and PD-1 inhibitors) was associated with an increased risk of all-grade and high-grade colitis,[14] 7 out of 10 randomized clinical trials (RCTs) included in the analysis used anti-CTLA-4 monoclonal antibodies and only 3 RCTs used an anti-PD-1 antibody (nivolumab). Therefore, the contribution of anti-PD-1 treatment to gastrointestinal AEs remains unclear. Thus, in this report, we conducted a meta-analysis to investigate the incidence and relative risk (RR) of gastrointestinal AEs associated with the use of PD-1 inhibitors in cancer patients.

2. Materials and methods

2.1. Search strategy

We searched PubMed, Embase, and the Cochrane Library for relevant clinical trials. The most recent search date was July 4, 2016. We searched both Medical Subject Headings and free text words to identify relevant studies. The search terms included: "pembrolizumab," "lambrolizumab," "keytruda," "MK-3475," "SCH900475," "nivolumab," "opdivo," "BMS-936558," "MDX-1106," "ONO-4538," "randomized controlled trials" or "clinical trials." The search was limited to RCTs published in English. Additionally, in cases of duplicate publications, only the most complete, recent, and updated report of the clinical trial was included. This meta-analysis was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analyses Statement.[15]

2.2. Study selection

Clinical trials that fulfilled the following criteria were included: (1) Randomized phase II and III trials; (2) patients allocated to treatment with PD-1 inhibitors or control (chemotherapy, everolimus or ipilimumab); (3) events or event rates available for gastrointestinal AEs. Independent reviewers first screened reports by their titles and abstracts. Full texts of the relevant articles were then retrieved to assess eligibility. The references of relevant reports were also reviewed.

2.3. Data extraction and quality assessment

Data extraction was conducted independently by 2 authors, and any discrepancies were resolved by consensus. The data extraction tables were used to collect relevant data for each clinical trial. The following information was extracted from each study: first author's name, year of publication, trial phase, cancer type, type of PD-1 inhibitors used, treatment arms, number of patients included, number of events with all-grade (grades 1–5) and high-grade (grades 3–5) gastrointestinal AEs. Diarrhea and colitis were the gastrointestinal AEs included (Table 1).

Data on gastrointestinal AEs were extracted from each clinical trial. AEs of all-grades and high-grades were defined according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute. The quality of each trial was assessed according to the Jadad Scale, including randomization, blinding, and withdrawals.[16] The Cochrane Risk of Bias Assessment was used to explore sources of bias in the included randomized trials. The following criteria were evaluated: (1) randomized sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective outcome reporting, and (7) other sources of bias. Risk of bias was labeled as high, low or unclear (Fig. 1).

2.4. Statistical analysis

Safety data from the clinical trials were used to extract information on incidence of gastrointestinal AEs and treatment with PD-1 inhibitors in patients. The principal measurements were RR and the corresponding 95% confidence intervals (CIs) of all-grade (grade 1–5) gastrointestinal AEs. For trials with a control arm, we calculated RRs and 95% CIs. To calculate 95% CIs, the variance of a log-transformed study-specific RR was derived using the delta method. Statistical heterogeneity of results between the studies included in the meta-analysis was assessed with the Cochran Q statistic, and the inconsistency was quantified

with the I^2 statistic, which estimates the percentage of total variation across studies due to heterogeneity rather than chance. If the P-values were < 0.10, the heterogeneity was considered statistically significant and a random-effects model was used. Otherwise, a fixed-effects model was used instead. To fully understand the relationship between PD-1 inhibitors and gastrointestinal AEs, the following subgroup analyses were conducted: (1) PD-1 inhibitor monotherapy (nivolumab or pembrolizumab) versus control (chemotherapy or everolimus), (2) nivolumab combined with ipilimumab versus ipilimumab monotherapy control (anti-CTLA-4 monoclonal antibody), and (3) PD-1 inhibitor monotherapy (nivolumab or pembrolizumab) versus ipilimumab monotherapy control. To find the source of heterogeneity, we performed subgroup analyses based on tumor type, drug class, and exposure time. Publication bias was assessed with funnel plots. A P-value $<.05$ was considered significant. All statistical analyses were performed with Review Manager 5.3 (Copenhagen, Denmark).

2.5. Ethics

All the analyses were based on previous published studies; therefore ethical approval is not necessary for systematic review and meta-analysis.

3. Results

3.1. Search results and study characteristics

Based on our search strategy, a total of 781 potentially relevant clinical trials with PD-1 inhibitors were identified. Exclusion criteria are shown in Figure 2. Fourteen full-text articles were included in our analysis, including 12 phase III trials and 2 phase II trials.[9,11,12,17–27] Six studies evaluated nivolumab monotherapy versus chemotherapy controls,[18–23] one study evaluated nivolumab monotherapy versus everolimus,[25] 4 studies evaluated pembrolizumab monotherapy versus chemotherapy control,[17,24,26,27] 2 studies evaluated nivolumab/ipilimumab combinations versus ipilimumab monotherapy,[11,12] and 2 studies evaluated pembrolizumab monotherapy or nivolumab monotherapy versus ipilimumab control.[9,12] Six studies evaluated melanoma, one study evaluated renal cell carcinoma, 5 studies evaluated advanced NSCLC, one study evaluated recurrent HNSCC, and one study evaluated urothelial carcinoma. Per the inclusion criteria of most the trials, patients with active brain metastases, autoimmune disease or impaired renal, hepatic, or bone marrow function were excluded. The majority of patients had an Eastern Cooperative Oncology Group performance status between 0, 1, and 2. The baseline characteristics and the number of all-grade events in each trial are presented in Table 1.

3.2. Overall incidence of all-grade and high-grade gastrointestinal AEs

For the gastrointestinal AE incidence analysis, only clinical trials with arms receiving one of the PD-1 inhibitor monotherapies were included. Thus, a total of 3815 patients from 12 studies were included for the calculation of the incidence of all-grade gastrointestinal AEs. All-grade diarrhea was reported in all 12 studies with a frequency between 6.8% and 16.9%. All-grade colitis was reported in 6 out of the 12 studies and the frequency was between 0.6% and 3.6%. Data for high-grade gastrointestinal AEs were collected from a total of 3401 patients from 11 studies. High-grade diarrhea was reported in 10 out of 11 studies with a frequency ranging from 0.4% to 3.9%. High-grade colitis was reported in 6 out of the 11 studies with a frequency ranging

Table 1

Baseline characteristics of included studies.

Study	Phase	Cancer type	Number of patients	Dose of the PD-1 inhibitors	Gastrointestinal adverse events	Jadad score
Robert et al[9]	III	Melanoma	Arm A: Nivolumab (206pts) Arm B: Dacarbazine (205pts)	Nivolumab 3 mg/kg every 2 weeks	Diarrhea: All-grade: 33 vs 32 High-grade: 2 vs 1 Colitis: All-grade: 2 vs 0 High-grade: 1 vs 0	5
Ribas et al[24]	II	Melanoma	Arm A: Pembrolizumab (178pts) Arm B: Pembrolizumab (179pts) Arm C: Chemotherapy (171pts)	Pembrolizumab 2 mg/kg or Pembrolizumab 10 mg/kg every 3 weeks	Diarrhea: All-grade: 15 vs 19 vs 14 High-grade: 0 vs 2 vs 3	3
Herbst et al[17]	II/III	NSCLC	Arm A: Pembrolizumab (339pts) Arm B: Pembrolizumab (343pts) Arm C: Docetaxel (309pts)	Arm A: Pembrolizumab 2 mg/kg Arm B: Pembrolizumab 10 mg/kg	Diarrhea: All-grade: 24 vs 22 vs 56 High-grade: 2 vs 0 vs 7 Colitis: All-grade: 4 vs 2 vs 0 High-grade: 3 vs 1 vs 0	3
Reck et al[26]	III	NSCLC	Arm A: Pembrolizumab (154pts) Arm B: Chemotherapy (150pts)	Pembrolizumab 200 mg every 3 weeks	Diarrhea: All-grade: 22 vs 20 High-grade: 6 vs 2 Colitis: All-grade: 3 vs 0 High-grade: 2 vs 0	3
Bellmunt et al[27]	III	Urothelial carcinoma	Arm A: Pembrolizumab (266pts) Arm B: Chemotherapy (255pts)	Pembrolizumab 200 mg every 3 weeks	Diarrhea: All-grade: 24 vs 33 High-grade: 3 vs 2 Colitis: All-grade: 6 vs 1 High-grade: 3 vs 0	3
Robert et al[22]	III	Melanoma	Arm A: Pembrolizumab (278pts) Arm B: Pembrolizumab (277pts) Arm C: Ipilimumab (256pts)	Arm A: Pembrolizumab 10 mg/kg every 2 weeks Arm B: Pembrolizumab 10 mg/kg every 3 weeks	Diarrhea: All-grade: 47 vs 40 vs 58 High-grade: 7 vs 3 vs 8 Colitis: All-grade: 5 vs 10 vs 21 High-grade: 4 vs 7 vs 18	3
Brahmer et al[20]	III	NSCLC	Arm A: Nivolumab (131pts) Arm B: Docetaxel (129pts)	Nivolumab 3 mg/kg every 2 weeks	Diarrhea: All-grade: 10 vs 26 High-grade: 0 vs 3 Colitis: All-grade: 1 vs 0 High-grade: 1 vs 0	3
Postow et al[37]	II	Melanoma	Arm A: Nivolumab plus Ipilimumab (94pts) Arm B: Ipilimumab (46pts)	Ipilimumab combined with nivolumab (1 mg/kg)	Diarrhea: All-grade: 42 vs 17 High-grade: 10 vs 5 Colitis: All-grade: 22 vs 6 High grade: 16 vs 3	5
Weber et al[36]	III	Melanoma	Arm A: Nivolumab (268pts) Arm B: ICC (102pts)	Nivolumab 3 mg/kg every 2 weeks	Diarrhea: All-grade: 30 vs 15 High-grade: 1 vs 2	3
Motzer et al[25]	III	RCC	Arm A: Nivolumab (406pts) Arm B: Everolimus (397pts)	Nivolumab 3 mg/kg every 2 weeks	Diarrhea: All-grade: 50 vs 84 High-grade: 5 vs 5	3
Borghaei et al[19]	III	NSCLC	Arm A: Nivolumab (287pts) Arm B: Docetaxe (268pts)	Nivolumab 3 mg/kg every 2 weeks	Diarrhea: All-grade: 22 vs 62 High-grade: 2 vs 3	3
Carbone et al[21]	III	NSCLC	Arm A: Nivolumab (267pts) Arm B: platinum-based chemotherapy (263pts)	Nivolumab 3 mg/kg every 2 weeks	Diarrhea: All-grade: 37 vs 34 High-grade: 3 vs 5	3
Larkin et al[10]	III	Melanoma	Arm A: Nivolumab plus placebo (313pts) Arm B: Nivolumab plus Ipilimumab (313pts) Arm C: Ipilimumab (311pts)	Nivolumab 3 mg/kg combined with placebo Ipilimumab combined with nivolumab (1 mg/kg)	Diarrhea: All-grade: 60 vs 138 vs 103 High-grade: 7 vs 29 vs 19 Colitis: All-grade: 4 vs 37 vs 36 High-grade: 2 vs 24 vs 27	5
Ferris et al[23]	III	HNSCC	Arm A: Nivolumab (236pts) Arm B: methotrexate, docetaxel, or cetuximab (111pts)	Nivolumab 3 mg/kg every 2 weeks	Diarrhea: All-grade: 16 vs 15 High-grade: 0 vs 2 Colitis: All-grade: 0 vs 1 High-grade: 0 vs 0	3

HNSCC = squamous-cell carcinoma of the head and neck, ICC = either dacarbazine 1000 mg/m^2 every 3 weeks, or carboplatin area under the curve 6 plus paclitaxel 175 mg/m^2 every 3 weeks, NSCLC = non-small-cell lung cancer, RCC = renal cell carcinoma.
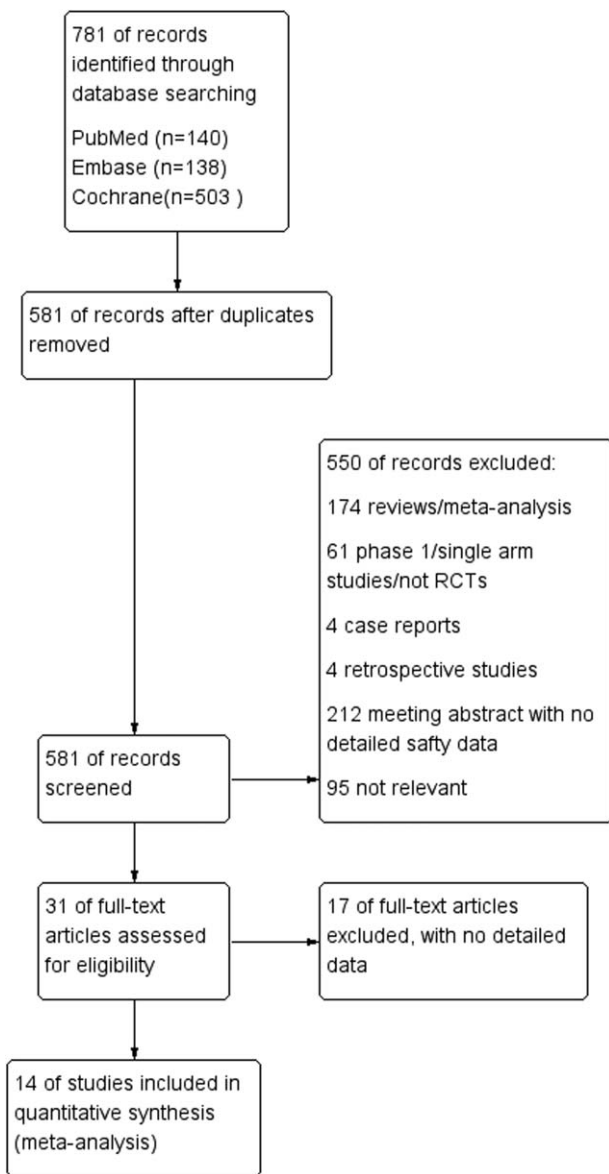
Figure 1. Flowchart of study selection procedure.

from 0.3% to 2.5%. In addition, 9 studies used the same dose of PD-1 inhibitors in patients, and 2 studies assessed the impact of different doses of pembrolizumab on patients. One study showed that the incidence of all-grade diarrhea caused by low-dose and high-dose pembrolizumab was 8.4% and 10.6%, respectively. However, the other study showed that the incidence of all-grade diarrhea caused by low-dose and high-dose pembrolizumab was 7.1% and 6.4%. Furthermore, one study showed that the frequency of high-grade diarrhea in high-dose pembrolizumab was lower than that in low-dose group (0 vs 0.6%). Thus, there was no significant correlation between the different doses of PD-1 inhibitors and the incidence of gastrointestinal AEs. But this conclusion still requires more trials to be further verified.

3.3. RR of gastrointestinal AEs in patients treated with PD-1 inhibitor monotherapy versus chemotherapy or everolimus control

The RR of gastrointestinal AEs was calculated by comparing the development of AEs from PD-1 inhibitor monotherapy to those from the control arm in the same trial to determine the specific contribution of PD-1 inhibitors to the development of gastrointestinal AEs. A total of 5620 patients from 11 studies were included for the calculation of the RR of all-grade gastrointestinal AEs. The RR of all-grade diarrhea and colitis was 0.66 (95% CI: [0.50, 0.87]; $P=.003$) and 3.36 (95% CI: [1.25, 9.04]; $P=.02$), respectively (Figs. 3 and 4A). Thus, the use of PD-1 inhibitor monotherapy is associated with a significantly increased risk of developing all-grade colitis. The RR of high-grade diarrhea and colitis was 0.58 (95% CI: [0.30, 1.11]; $P=.10$) and 4.31 (95% CI: [1.11, 16.79]; $P=.04$), respectively (Figs. 3B and 4B). The combined results demonstrated that the use of PD-1 inhibitor monotherapy is associated with a significantly increased risk of developing high-grade colitis. A fixed-effects model was used for analyzing the RR of developing all-grade and high-grade colitis, while a random-effects model was used for calculating the RR of developing all-grade and high-grade diarrhea with PD-1 inhibitor monotherapy treatment.

3.4. RR of gastrointestinal AEs in patients treated with a nivolumab/ipilimumab combination versus ipilimumab monotherapy control

To determine whether nivolumab/ipilimumab combinations result in an increased risk of gastrointestinal toxicities compared
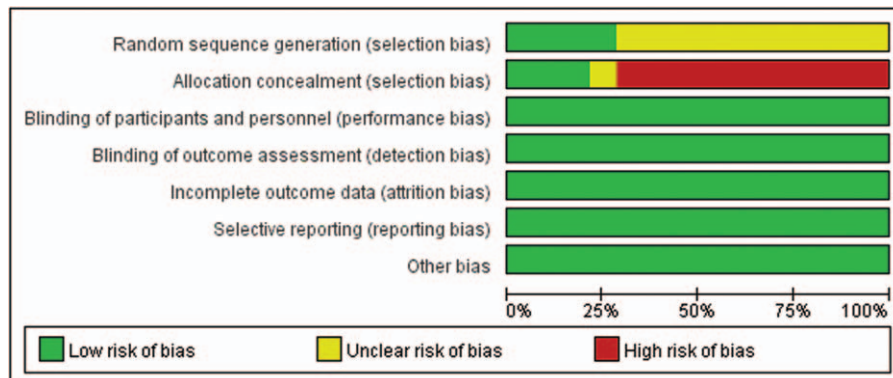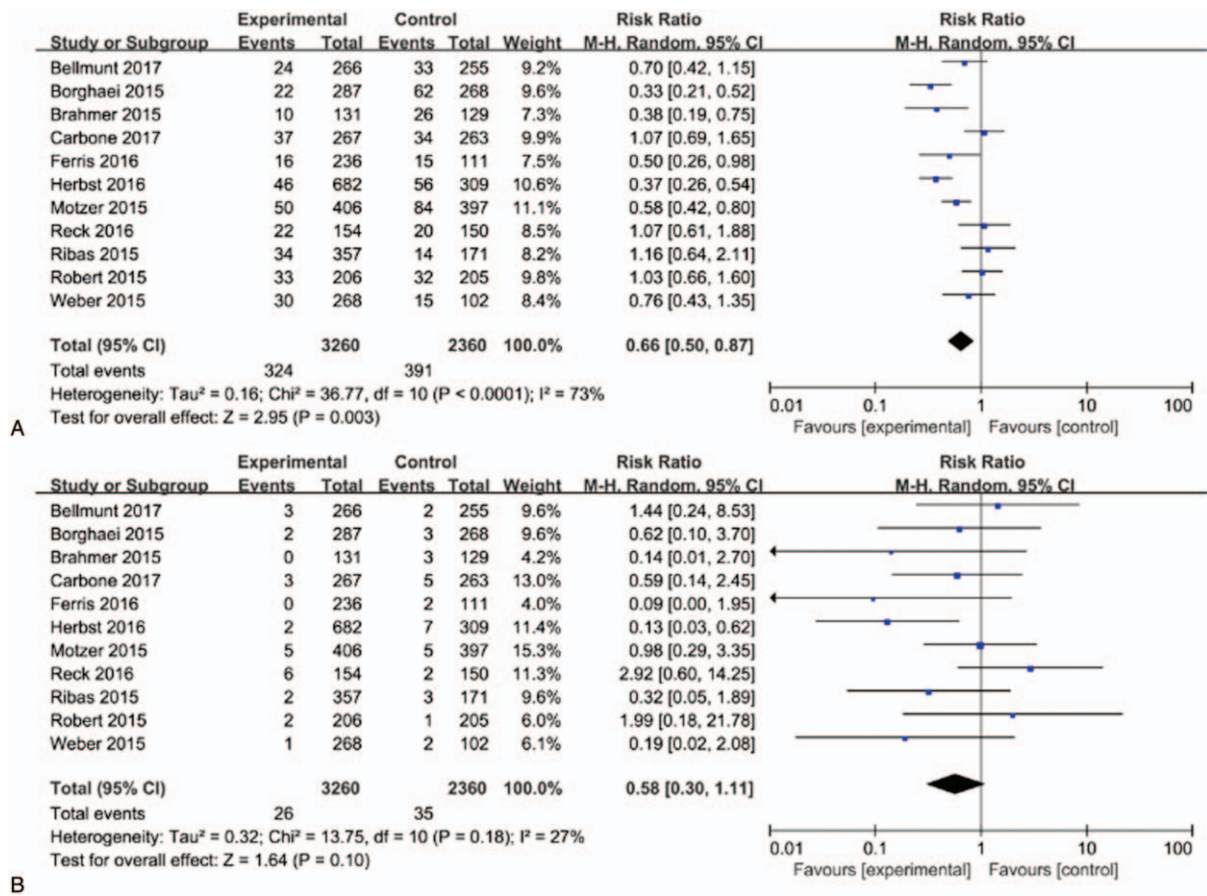

Figure 2. Risk of bias summary.

Figure 3. Forest plots of relative risk of all-grade (A) and high-grade (B) diarrhea associated with PD-1 inhibitors versus chemotherapy or everolimus control.
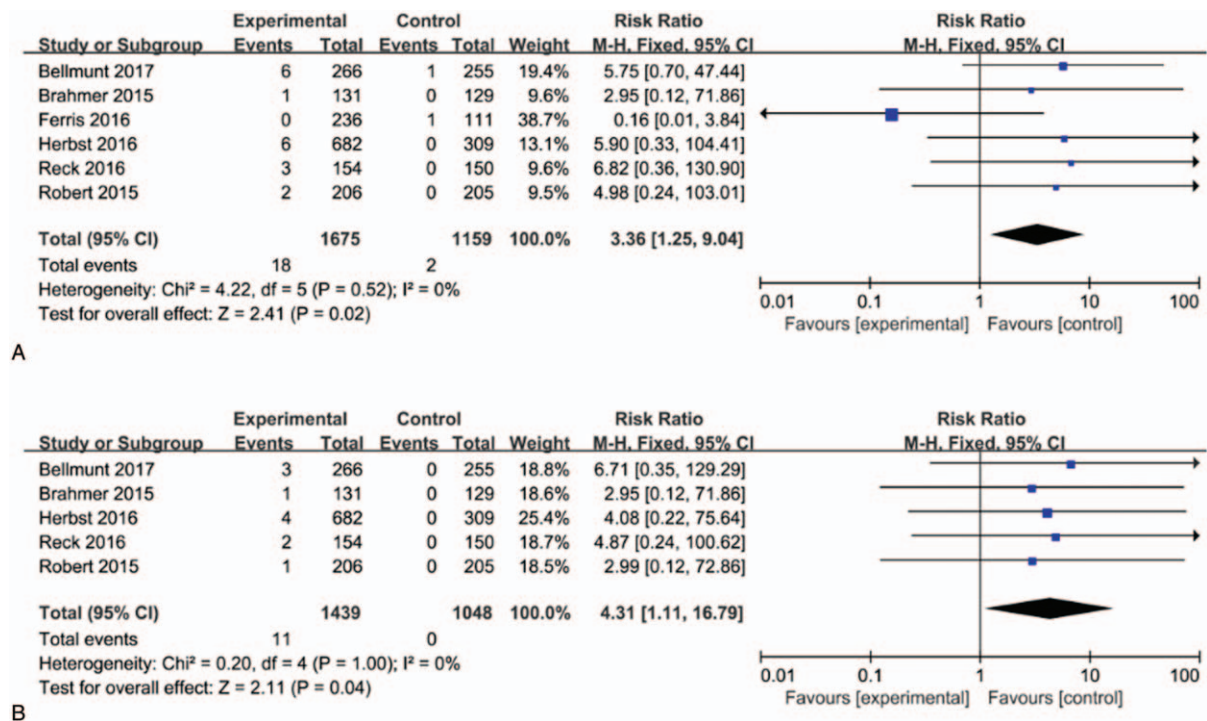

Figure 4. Forest plots of relative risk of all-grade (A) and high-grade (B) colitis associated with PD-1 inhibitors versus chemotherapy or everolimus control.
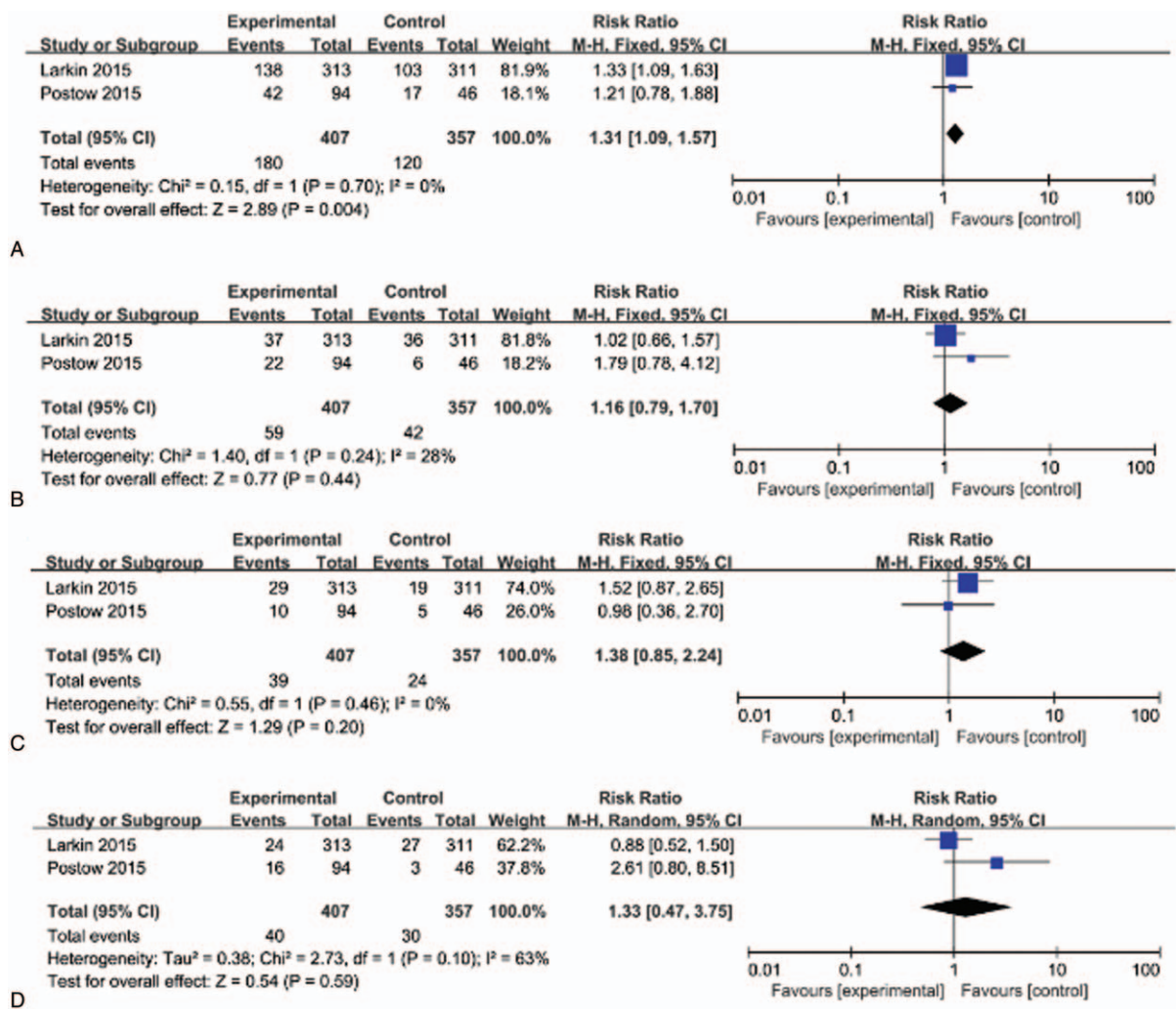
Figure 5. Forest plots of relative risk of all-grade diarrhea (A), all-grade colitis (B), high-grade diarrhea (C) and high-grade colitis (D) associated with a nivolumab/ipilimumab combination versus ipilimumab monotherapy control.

to ipilimumab monotherapy, we calculated the RR of gastrointestinal AEs by comparing the nivolumab/ipilimumab combination to the ipilimumab monotherapy control. The RR of all-grade diarrhea and colitis was 1.31 (95% CI: [1.09, 1.57]; $P = .004$) and 1.16 (95% CI: [0.79, 1.70]; $P = .44$), respectively (Fig. 5A and B). The RR of high-grade diarrhea and colitis was 1.38 (95% CI: [0.85, 2.24]; $P = .20$) and 1.33 (95% CI: [0.47, 3.75]; $P = .59$), respectively (Fig. 5C and D). These results indicate that a nivolumab/ipilimumab combination is associated with a higher risk of developing all-grade diarrhea.

3.5. RR of gastrointestinal AEs in patients treated with nivolumab or pembrolizumab monotherapy versus ipilimumab monotherapy control

To compare the risk of gastrointestinal toxicities with PD-1 inhibitor monotherapy (nivolumab or pembrolizumab) versus ipilimumab, we conducted an analysis comparing nivolumab or pembrolizumab monotherapy versus ipilimumab monotherapy. The RR of all-grade diarrhea and colitis was 0.63 (95% CI: [0.51, 0.77]; $P < .00001$) and 0.20 (95% CI: [0.07, 0.62]; $P = .005$),

respectively (Fig. 6A and B). Moreover, there was a statistically significant decreased risk of high-grade gastrointestinal AEs with a RR of 0.44 (95% CI: [0.24, 0.83]; $P = .01$) for diarrhea and 0.16 (95% CI: [0.04, 0.65]; $P = .01$) for colitis (Fig. 6C and D). Hence, compared with ipilimumab, PD-1 inhibitor monotherapy (nivolumab or pembrolizumab) results in a lower risk of developing gastrointestinal AEs.

3.6. Subgroup analyses

Subgroup analyses grouped by the different drugs (nivolumab versus pembrolizumab) showed no evidence of subgroup differences in regard to the risk of diarrhea (Fig. 7). Additionally, there were no obvious subgroup differences based on cancer type (melanoma, NSCLC, renal cell carcinoma, HNSCC, and urothelial carcinoma) (Fig. 8).

3.7. Publication bias

The funnel plot (Fig. 9) demonstrated that no significant publication bias existed in this meta-analysis.
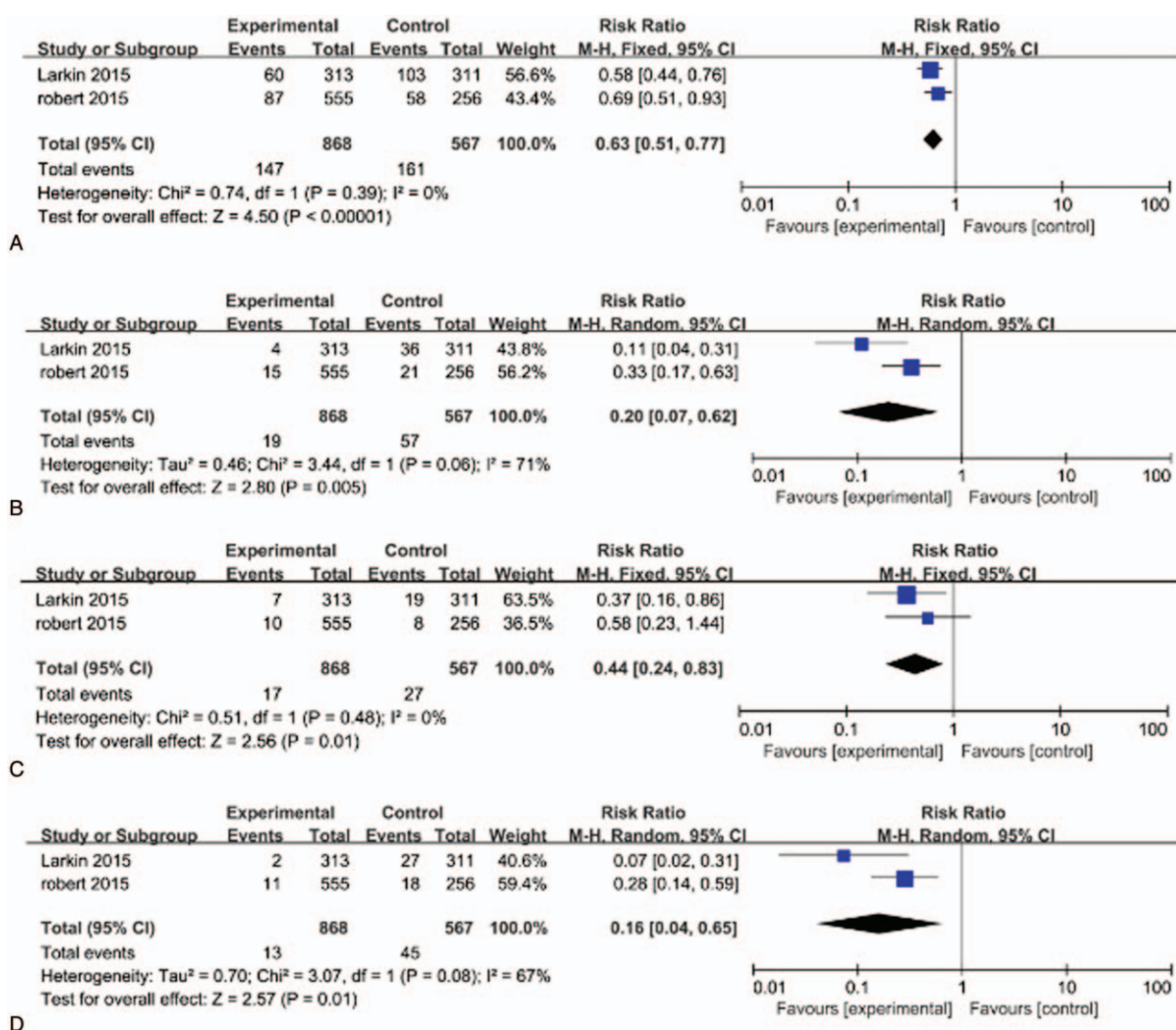
Figure 6. Forest plots of relative risk of all-grade diarrhea (A), all-grade colitis (B), high-grade diarrhea (C) and high-grade colitis (D) associated with nivolumab or pembrolizumab monotherapy versus ipilimumab monotherapy control.

4. Discussion

To date, the incidence and relative risks of development of gastrointestinal AEs from PD-1 inhibitor treatment have not been adequately assessed. Here, we report the results of a meta-analysis including data from 14 clinical trials and 7508 cancer patients, focused on PD-1 inhibitor-associated gastrointestinal AEs. Our results demonstrated that compared to chemotherapy or everolimus control arms, the use of PD-1 inhibitor mono-therapy was associated with a significantly increased risk of developing all-grade and high-grade colitis. A nivolumab/ ipilimumab combination was associated with a higher risk of developing all-grade diarrhea when compared to ipilimumab monotherapy. Our analysis also revealed that compared to ipilimumab monotherapy, the PD-1 inhibitor monotherapy (nivolumab or pembrolizumab) resulted in a significantly lower risk of developing gastrointestinal AEs.

Our analysis showed that the RR of all-grade diarrhea and colitis was 0.66 (95% CI: [0.50, 0.87]; $P = .003$) and 3.36 (95% CI: [1.25, 9.04]; $P = .02$), and the RR of high-grade diarrhea and colitis was 0.58 (95% CI: [0.30, 1.11]; $P = .10$) and 4.31 (95% CI: [1.11, 16.79]; $P = .04$), respectively. However, a previously published study by Abdel-Rahman et al[14] reported different RR values. In their analysis, the RR of all-grade diarrhea and colitis was 1.64 (95% CI: [1.19,2.26]; $P = .002$) and 10.35 (95% CI: [5.78,18.53]; $P < .00001$), respectively. The RR of high-grade diarrhea and colitis was 4.46 (95% CI: [1.46, 13.57]; $P = .008$) and 15.81 (95% CI: [6.34, 39.42]; $P < .00001$), respectively. Abdel-Rahman et al concluded that patients treated with PD-1 and CTLA-4 inhibitors have an increased risk of all-grade and high-grade diarrhea and colitis. The discrepancy in RR of gastrointestinal AEs in checkpoint blockade-treated patients calculated between the study published by Abdel-Rahman et al and our study may be due to the different treatment agents. All the trials included in our analysis used PD-1 inhibitors. However, only 3 of the 10 trials Abdel-Rahman et al included evaluated PD-1 inhibitors while the other 7 evaluated CTLA-4 inhibitors (6 trials evaluated ipilimumab and one trial evaluated tremelimu-mab). Moreover, in our comparison of the nivolumab/ipilimu-mab combination and ipilimumab monotherapy groups, the RR of all-grade diarrhea in our analysis indicated that the combination of anti-CTLA-4 and anti-PD-1 inhibitors was likely associated with a higher risk of developing all-grade diarrhea. In addition, the incidence of gastrointestinal AEs was significantly increased when nivolumab and ipilimumab were combined (the
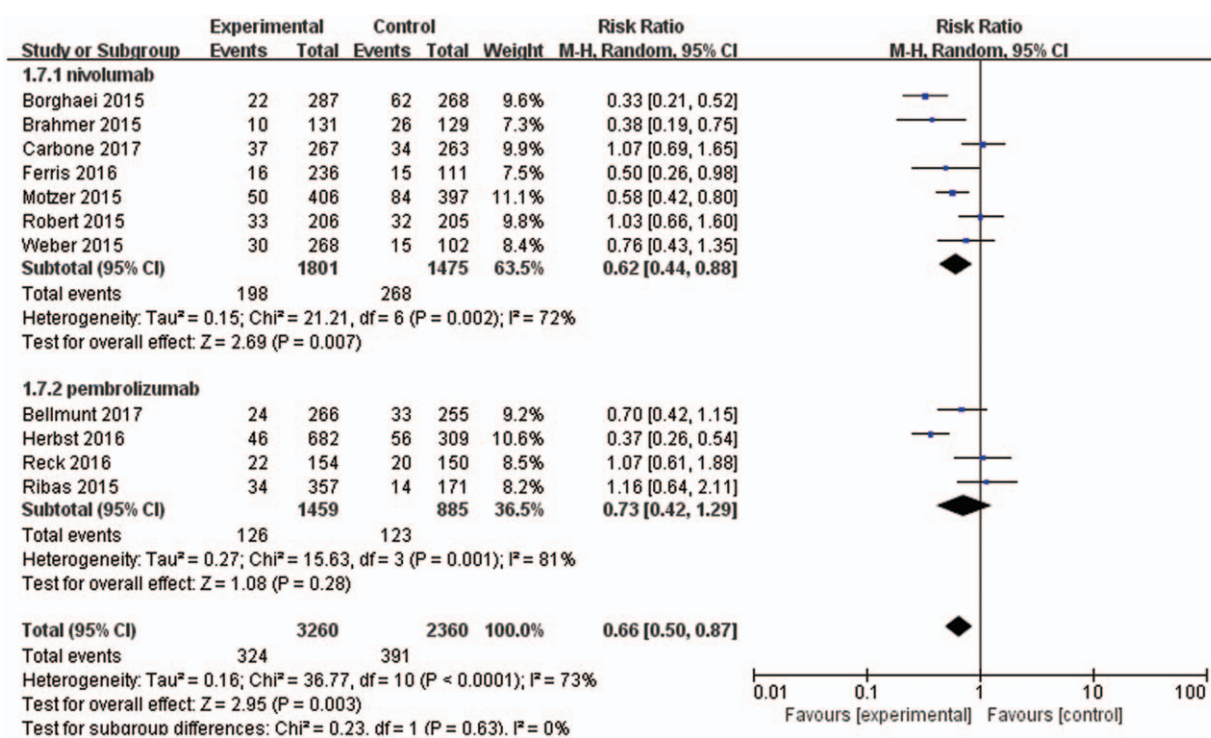
Figure 7. Subgroup analysis according to treatment type (nivolumab vs pembrolizumab).

frequency of all-grade diarrhea and colitis was 44.7% and 23%, respectively). In conclusion, the above data reminds us that the combination of 2 or more immune checkpoint inhibitors warrants special attention when determining the treatment regimen.

Previous studies have shown that the frequency of ipilimumab-induced diarrhea and colitis is 32.8%, whereas the frequency of anti-PD-1 antibody-induced gastrointestinal AEs ranges from 6.0% to 16.0%.[22,28–30] To compare the risk of gastrointestinal toxicity with PD-1 and CTLA-4 inhibitor monotherapy, we conducted an analysis comparing nivolumab or pembrolizumab monotherapy versus ipilimumab monotherapy. We found that when considering the RR of all-grade diarrhea and colitis, the PD-1 inhibitor monotherapy (nivolumab or pembrolizumab) resulted in a lower risk of developing gastrointestinal AEs compared with ipilimumab monotherapy. However, this result is inconsistent with that from a previously reported study by Abdel-Rahman et al.[14] In their analysis, they did not find a significant difference in RR of colitis between ipilimumab and nivolumab treatment. This discrepancy may be due to differences in analyses. We analyzed 2 trials[9,12] that directly involved PD-1 inhibitor monotherapy (nivolumab or pembrolizumab), with ipilimumab treatment being used as the control group. On the contrary, Abdel-Rahman et al compared treatment with nivolumab and ipilimumab through subgroup analysis, with chemotherapy being the control group. Therefore, their indirect comparison method may be less accurate and reliable. It should be noted that our calculations suggested the presence of heterogeneity in the 2 trials we analyzed. This heterogeneity may be due to inconsistent treatment times between the 2 pembrolizumab-treated groups, where one group received pembrolizumab at a dose of 10 mg/kg of body weight every 2 weeks and the other group received pembrolizumab at a dose of 10 mg/kg of body weight every 3

weeks. Although the RR calculation only accounts for 2 RCTs, these results should also be kept in mind. Additional trials to help further assess the safety profile of anti-PD-1 antibodies are therefore welcomed in the field.

Gastrointestinal AEs are the most common irAEs associated with immune checkpoint inhibitor treatment, often resulting in diarrhea and colitis. It has been reported that diarrhea is observed in 17% of melanoma patients treated with nivolumab, and only 1.2% of treated patients experience high-grade toxicities. Colitis is observed in up to 2.8% of cancer patients treated with pembrolizumab. The median time to irAEs from pembrolizumab treatment is much longer compared to nivolumab.[31] In our analysis, high-grade diarrhea was observed in up to 3.9% of NSCLC patients and colitis was observed in up to 3.6% of melanoma patients treated with pembrolizumab.[9,26] Moreover, intestinal perforation from anti-PD-1 treatment was reported.[32]

The gastrointestinal tract is not only an important portal of entry for pathogens into the body, but it also plays a highly active role in the immune system. The resident microbial population comprises trillions of bacteria, in addition to various viral and fungal species. The gastrointestinal tract regulates various immune functions through a complex innate and adaptive immune cell network, where T cells are the largest and most relevant class of immune cells in the body.[33] PD-1 inhibitor-related colitis is the result of the interaction between genes, the environment, the immune system and microbes. Many biomarkers have been proposed to predict gastrointestinal complications and are being studied. One study has shown that the *Helicobacter pylori* HP0175(peptidyl prolyl cis, trans-isomerase of *H pylori*) protein elicits a peculiar Th17(interleukin-17) inflammation which, if long lasting and unabated, may represent an immunopathological condition that link the infection and gastric cancer, suggesting that the Th17 pathway and HP0175 may
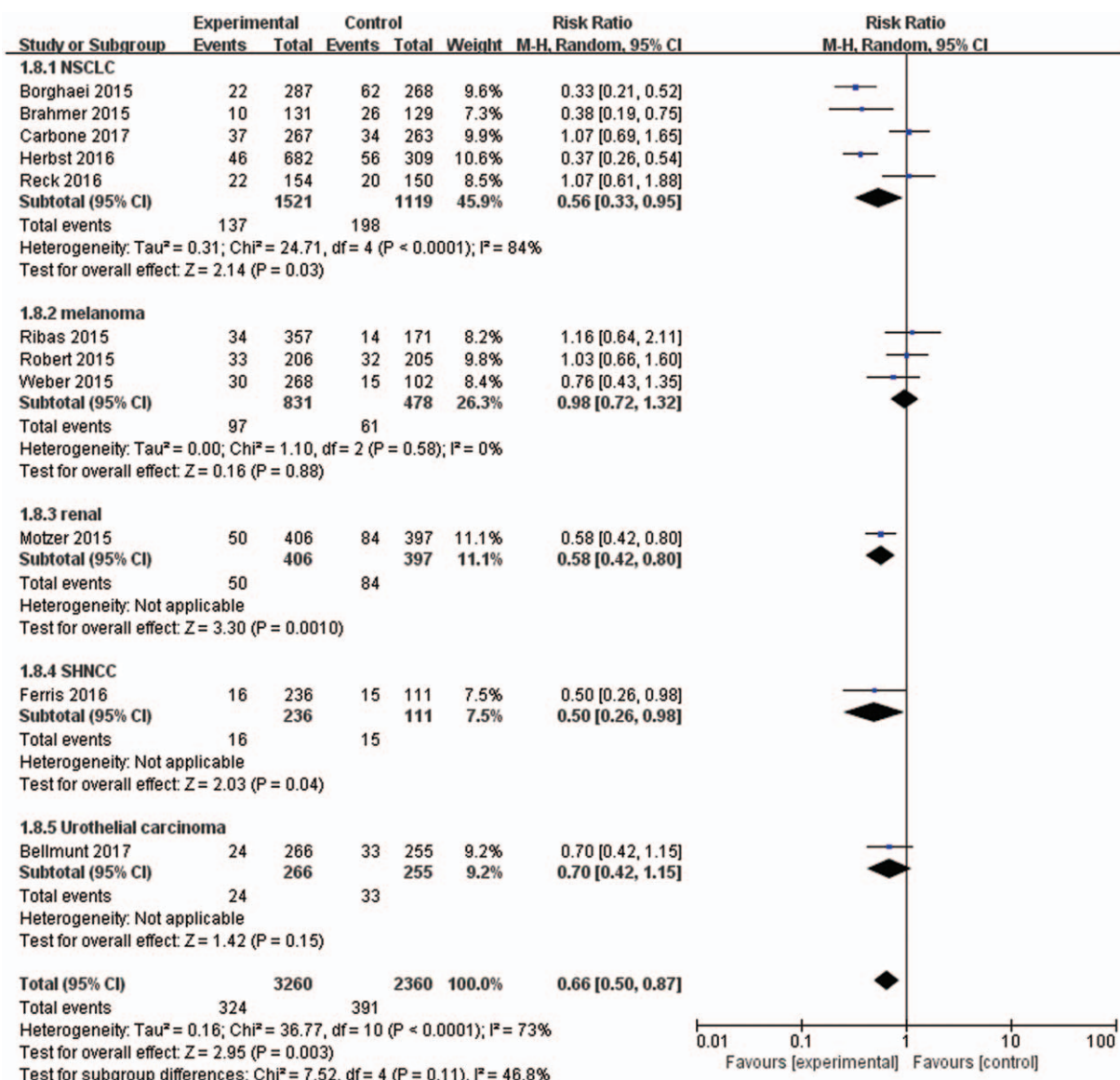
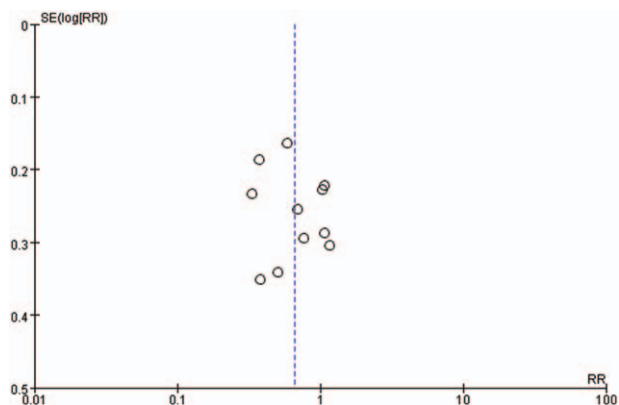**Figure 8.** Subgroup analysis according to tumor type.

Figure 9. Funnel plot. RR = Relative risk, SE = Standard error.

represent novel therapeutic targets for the prevention and treatment of the disease.[34] In addition, genetic predisposition and the role of the microbiota is also the focus of a recent study.[35]

Considering the broad application of anti-PD-1 agents in solid tumors and hematologic malignancies such as melanoma, lung cancer, and classical Hodgkin's lymphoma, the management of gastrointestinal AEs is an important factor that cannot be ignored, especially considering that these PD-1 inhibitors are associated with a high incidence of treatment-related grades 3 and 4 AEs. Medical staff and patients should be fully aware of the gastrointestinal AEs associated with PD-1 inhibitors and report any symptoms in a timely and accurate manner, especially since irAEs usually begin with minimal symptoms. Close monitoring and prompt treatment of early symptoms can effectively reduce the risk of life-threatening complications such as intestinal perforation. If the diagnosis is unclear or if the patient has chronic

grade 2 AEs, a colonoscopy along with a biopsy should be considered. Systemic corticosteroids are an effective treatment for gastrointestinal AEs in most patients. Loperamide has also been shown to be helpful in relieving diarrhea. If symptoms worsen, patients should report these changes in a timely manner. In the case of grades 3/4 AEs, systemic corticosteroids are required. In addition, if grade 2 AEs persist, the application of systemic corticosteroids should be strongly considered. Oral steroids such as prednisone at a dose of 1 to 2 mg/kg per day can help alleviate AEs. However, for patients who require hospitalization, regardless of the presence of an important complication, intravenous methylprednisolone for 1 to 2 days should first be tried, followed by an oral taper of prednisone. If steroid treatment improves symptoms, steroids should be used continuously until grade 0 or 1 toxicity is reached and for at least 30 days to achieve full tapering. In the case of steroid resistance, infliximab (5 mg/kg once every 2 weeks) can be used after 72 hours, but should not be used in patients with intestinal perforation or sepsis.[31,36] Treatment with infliximab can significantly improve gastrointestinal AEs, sometimes within 24 hours.[37] However, if the AEs are too severe and are not responding to symptom-alleviating medication, it is necessary to stop PD-1 inhibitor treatment.

Our meta-analysis has some limitations. First, the number of published clinical trials of PD-1 inhibitors is not sufficient to fully assess the incidence and risk of gastrointestinal AEs. Second, different doses and frequencies of PD-1 inhibitor administration were used in the clinical trials. The baseline characteristics of the patients were also different, which may increase the clinical heterogeneity of the trial and make interpretation of the meta-analysis more difficult. We have tried to overcome this heterogeneity by using subgroup analyses. However, the heterogeneity of pooled RR was not significant for all-grade diarrhea. Finally, our analysis was performed at the study level rather than the level of the individual patient, meaning that the potential variables at the patient level were not included in the analysis.

5. Conclusion

Our meta-analysis has demonstrated that PD-1 inhibitors dramatically increase the risk of colitis in cancer patients compared with chemotherapy or everolimus treatment. The risk of all-grade diarrhea is higher in patients treated with a nivolumab/ipilimumab combination compared with ipilimumab monotherapy. Moreover, compared with ipilimumab, PD-1 inhibitor treatment results in a significantly lower risk of gastrointestinal AEs. These data can help clinicians more effectively assess gastrointestinal toxicity of PD-1 inhibitors and make data-driven decisions.

References

[1] Hirano F, Kaneko K, Tamura H, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res 2005;65:1089–96.

[2] Topalian SL, Drake CG, Pardoll DM. Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity. Curr Opin Immunol 2012;24:207–12.

[3] Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature 2014;515:568–71.

[4] Wolchok JD. PD-1 Blockers. Cell 2015;162:937.

[5] Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer 2016;54:139–48.

[6] Younes A, Santoro A, Shipp M, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. Lancet Oncol 2016;17:1283–94.

[7] Barbee MS, Ogunniyi A, Horvat TZ, et al. Current status and future directions of the immune checkpoint inhibitors ipilimumab, pembrolizumab, and nivolumab in oncology. Ann Pharmacother 2015;49:907–37.

[8] Muller M, Schouten RD, De Gooijer CJ, et al. Pembrolizumab for the treatment of non-small cell lung cancer. Expert Rev Anticancer Ther 2017;17:399–409.

[9] Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015;372:2521–32.

[10] Larkins E, Blumenthal GM, Yuan W, et al. FDA approval summary: pembrolizumab for the treatment of recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy. Oncologist 2017;22:873–8.

[11] Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015;372:2006–17.

[12] Larkin J, Hodi FS, Wolchok JD. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:1270–1.

[13] Postow MA. Managing immune checkpoint-blocking antibody side effects. Am Soc Clin Oncol Educ Book 2015;76–83.

[14] Abdel-Rahman O, ElHalawani H, Fouad M. Risk of gastrointestinal complications in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. Immunotherapy 2015;7:1213–27.

[15] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8:336–41.

[16] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–2.

[17] Herbst RS, Baas P, Kim DW, 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.

[18] Weber JS, D'Angelo SP, 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.

[19] Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015;373:1627–39.

[20] Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015;373:123–35.

[21] Carbone DP, Reck M, Paz-Ares L, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med 2017;376:2415–26.

[22] Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015;372:320–30.

[23] Ferris RL, Blumenschein GJr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 2016;375:1856–67.

[24] 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.

[25] Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1803–13.

[26] Reck M, Rodriguez-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.

[27] Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017;376:1015–26.

[28] Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.

[29] Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443–54.

[30] Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018–28.

[31] Eigentler TK, Hassel JC, Berking C, et al. Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. Cancer Treat Rev 2016;45:7–18.

[32] Hofmann L, Forschner A, Loquai C, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. Eur J Cancer 2016;60:190–209.

[33] Shale M, Schiering C, Powrie F. CD4(+) T-cell subsets in intestinal inflammation. Immunol Rev 2013;252:164–82.

[34] Amedei A, Munari F, Bella CD, et al. Helicobacter pylori secreted peptidyl prolyl cis, trans-isomerase drives Th17 inflammation in gastric adenocarcinoma. Int Emerg Med 2014;9:303–9.

[35] Cramer P, Bresalier RS. Gastrointestinal and hepatic complications of immune checkpoint inhibitors. Curr Gastroenterol Rep 2017;19:3.

[36] Weber JS, Postow M, Lao CD, et al. Management of adverse events following treatment with anti-programmed death-1 agents. Oncologist 2016;21:1230–40.

[37] Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. J Clin Oncol 2015;33:1974–82.