Systematic Review and Meta-Analysis

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Durvalumab and tremelimumab combination therapy versus durvalumab or tremelimumab monotherapy for patients with solid tumors

A systematic review and meta-analysis

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Abstract

Background: The combination of durvalumab and tremelimumab results in clinical benefit, with a tolerable safety profile in patients with solid tumors.

Objective: To evaluate the efficacy and safety of durvalumab in combination with tremelimumab compared with either drug alone.

Methods: The online databases (PubMed, Web of Science, EMBASE, and Cochrane Library) were searched for potential clinical studies up to Nov 26, 2019. Eligible studies were prospective and registered clinical trials. Pooled odds ratios for objective response rate and disease control rate and pooled risk ratios for treatment-related adverse events were meta-analyzed. A random-effect model was used due to the synthesis of different cancer types.

Results: Overall, 5 studies were eligible for systematic review, 3 of which were further meta-analyzed. Durvalumab plus tremelimumab was superior to tremelimumab monotherapy in improving disease control rate in head and neck squamous cell carcinoma. However, there were no significant differences between dual immunotherapy and mono-immunotherapy in pancreatic ductal adenocarcinoma and gastric and gastroesophageal junction adenocarcinoma. Additionally, pooled analyses illustrated that no significant differences in treatment-related adverse events were displayed between the 2 groups.

Conclusion: Durvalumab and tremelimumab combination therapy had a good safety profile and resulted in clinical benefit in head and neck squamous cell carcinoma. Future explorations are needed to further confirm the application of durvalumab plus tremelimumab.

Abbreviations: 95% CI = 95% confidence interval, APC = antigen-presenting cell, CTLA-4 = cytotoxic T-lymphocyte antigen 4, DCR = disease control rate, GGA = gastric and gastroesophageal junction adenocarcinoma, HNSCC = head and neck squamous cell carcinoma, NSCLC = non–small cell lung cancer, OR = odds ratio, ORR = objective response rate, PD-1 = programmed cell death-1, PDA = pancreatic ductal adenocarcinoma, PD-L1 = programmed cell death ligand-1, PFS = progression-free survival = OS = overall survival, RR = risk ratio.

Keywords: durvalumab, immunotherapy, meta-analysis, solid tumor, tremelimumab

1. Introduction

Inhibitors of programmed cell death-1 (PD-1) and its ligand (PD-L1) have shown improved survival compared to chemotherapy on the treatment of advanced solid tumors.[1,2] However, survival outcomes still need to be improved in patients with recurrent or metastatic solid tumors.

During recent years, dual immune checkpoint inhibition has been a new treatment strategy for advanced patients.[3,4] PD-1

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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inhibitors and cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors are immune checkpoint antibodies with distinct but complementary mechanisms of action. Owing to the synergistic roles of the PD-1 or PD-L1 and CTLA-4 in T-cell activation, the combination of inhibitors targeting PD-1/PD-L1 and CTLA-4 signaling pathways warrants investigation.[5] The combination of nivolumab, a fully human anti–PD-1 inhibitor, and ipilimumab, a fully human anti–CTLA-4 inhibitor, has shown encouraging clinical benefit characterized by antitumor effects and tolerable safety profiles.[6–11]

Durvalumab plus tremelimumab is another combination regimen. Durvalumab is a highly selective human IgG1 monoclonal inhibitor that blocks interaction with PD-1 and CD80 to overcome blockage of primary human T-cell activation.[12] Remarkable clinical activity and manageable safety of durvalumab were reported in various solid tumors, including melanoma, lung cancer, head and neck cancer, breast cancer, and urothelial carcinoma.[13–19] Further, adding tremelimumab, a high affinity human IgG2 monoclonal antibody of CTLA-4,[20] to durvalumab therapy has also been under detection in different cancers.[21–26] Although combining durvalumab and tremelimumab results in clinical benefit, whether combination therapy is superior to durvalumab or tremelimumab monotherapy remains uncertain.

Accordingly, we conducted this systematic review and meta-analysis to assess the efficacy and safety of durvalumab plus tremelimumab combination therapy versus durvalumab or tremelimumab monotherapy in solid tumors.

2. Methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guideline.[27] The data used in the analysis were not original raw data but were based on the published clinical studies with ethical approvals. Therefore, ethical approval was not necessary.

2.1. Search strategy

The electronic databases PubMed, Web of Science, EMBASE and Cochrane Library were systemically searched for all relevant records until Nov 26, 2019. Search terms were "tremelimumab", "durvalumab," and "trial or clinical trial or clinical study." Reference lists of relevant published studies and review articles were manually searched for more eligible trials.

2.2. Inclusion criteria and study selection

Eligible studies should meet all of the following criteria:

(1) patients in the studies were diagnosed with solid tumors,
(2) patients did not previously receive immunotherapy,
(3) patients in 1 arm were treated with tremelimumab and durvalumab combination therapy,
(4) studies were prospective and registered clinical trials,
(5) the combination group did not include chemotherapy, target therapy, radiotherapy, or others,
(6) efficacy and safety data were available.

We have no restrictions on language. Conference abstracts were excluded, due to the absence of raw data and the increase of heterogeneity. B-CW and P-CL independently conducted the selection process. Any discrepancies were resolved by discussion.

2.3. Data extraction

Detailed reviews of full-text articles regarding basic characteristics, outcomes and toxicities were performed by B-CW and P-CL independently. The first author, year of publication, register number, study design, county, cancer type, number of patients, mean age, lines of prior therapy, dosing schedule, objective response rate (ORR), disease control rate (DCR), overall survival (OS), progression-free survival (PFS), and treatment-related adverse events data reporting in the articles and supplementary materials were collected from each eligible study.

2.4. Statistical analysis

Data from randomized studies (ORR and DCR) was assessed by odds ratio (OR) and 95% confidence interval (CI). The treatment-related analyses were assessed by risk ratio (RR) and 95% CI. RevMan version 5.3 software (Cochrane Collaboration's Information Management System) was used to meta-analyzed the above-mentioned data. Heterogeneity among the studies was tested by I^2 statistic percentages and the Cochran Q Chi-squared test. A random-effects model was applied in the analyses owing to the small size of enrolled studies.

2.5. Risk of bias assessment

For pooled analyses of the ORR and DCR in randomized studies, the Cochrane Risk of Bias Tool was applied to evaluate the risk of bias.

3. Results

3.1. Search results

Figure 1 displays the selection process. Four hundred eighty-seven potential records were included for the initial assessment. One hundred sixty-four duplicates were excluded. Further, 150 records were excluded after review of the titles and abstracts. One hundred seventy-three records underwent full-text assessment. We excluded 168 records because they were reviews/comments/ letters/ news (n = 55), conference abstracts (n = 109), case reports (n = 3), or unregistered studies (n = 1). Finally, 5 clinical studies were found to meet the inclusion criteria.[28–32] All the selected studies were included in the systematic review, and 3 of 5 were included in the meta-analysis.[28–30]

3.2. Characteristics

The basic characteristics of the 5 eligible studies are list in Table 1. One study was phase 1b clinical trial, 1 was phase 1b/2 clinical trial, and three were phase 2 clinical trials. There were 5 caner types including non-small cell lung cancer (NSCLC), mesothelioma, pancreatic ductal adenocarcinoma (PDA), head and neck squamous cell carcinoma (HNSCC), and gastric and gastro-esophageal junction adenocarcinoma (GGA). All patients enrolled in the studies were diagnosed with advanced solid tumors. Most patients had received 1 line of prior systemic therapy. Three studies comprised durvalumab monotherapy and 2 studies contained tremelimumab monotherapy.

Table 2 showed the median PFS and OS in the studies. Mesothelioma patients treated with durvalumab plus tremelimumab had the longest median survival time (median PFS: 5.7 months, 95% confidence interval [CI] 1.7–9.7; median OS: 16.6

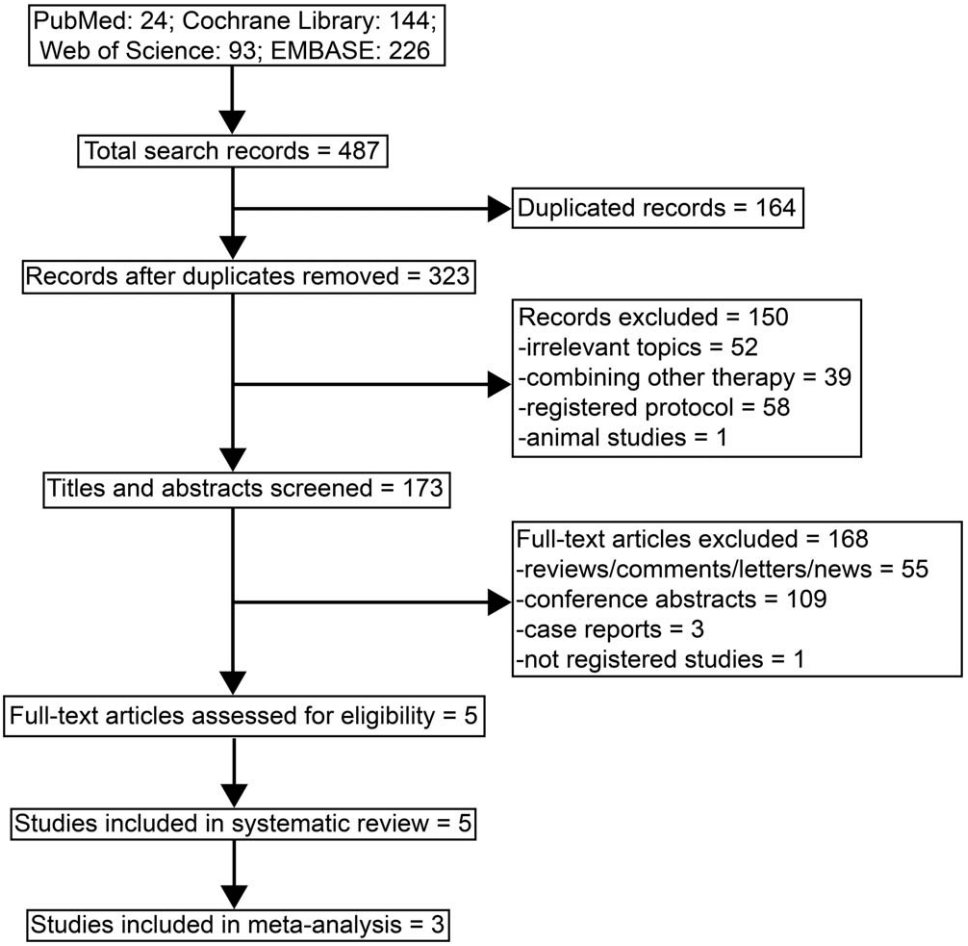

Figure 1. Flow chart of the selection process.

months, 95% CI 13.1–20.1). Although the median OS of patients with PDA, HNSCC, and GGA ranged from 3.1 to 10.6 months, the median PFS time was no more than 2 months.

3.3. Responses

The forest plots of odds ratios for ORR and DCR are shown in Figures 2 and 3. Pooled results showed that combining durvalumab and tremelimumab did not significantly improve the ORR compared with durvalumab (OR 1.12, 95% CI 0.43–2.90, $P = .81$) or tremelimumab (OR 2.40, 95% CI 0.47–12.32, $P = .29$) (Fig. 2). In addition, no statistically significant differences were observed in DCR when comparing combination therapy against monotherapy (durvalumab and tremelimumab versus durvalumab: OR 1.09, 95% CI 0.39–3.02, $P = .87$; durvalumab and tremelimumab versus tremelimumab: OR 2.76, 95% CI 0.28–27.24, $P = .38$) (Fig. 3).

In subgroup analyses, durvalumab plus tremelimumab was shown to have a higher rate of disease control in HNSCC compared to tremelimumab alone (OR 9.41, 95% CI 1.22–72.41, $P = .03$). In PDA and GGA, durvalumab plus tremelimumab was not superior to durvalumab or tremelimumab monotherapy.

3.4. Treatment-related adverse events

The forest plots of risk ratios for any grade and grade ≥ 3 treatment-related adverse events are shown in Figures 4 and 5. Durvalumab plus tremelimumab showed similar risks of any grade treatment-related adverse events with durvalumab monotherapy (RR 1.01, 95% CI 0.69–1.49, $P = .95$) and tremelimumab monotherapy (RR 1.02, 95% CI 0.79–1.32, $P = .87$) (Fig. 4). In subgroup analysis, P value did not indicate statistical significance. However, compared with durvalumab, combination therapy exhibited higher risks of any grade treatment-related adverse events in PDA (RR 1.10) and GGA (RR 4.06). However, a lower risk of any grade treatment-related adverse events was seen in HNSCC (RR 0.92). While compared with tremelimumab monotherapy, combination therapy showed a higher risk of any grade treatment-related adverse events in HNSCC (RR 1.05) but a lower risk in GGA (RR 0.68).

In comparison with patients in monotherapy groups, patients in the durvalumab and tremelimumab combination therapy group showed no significant increases in grade ≥ 3 treatment-related adverse events (durvalumab and tremelimumab versus durvalumab: RR 1.64, 95% CI 0.86–3.13, $P = .14$; durvalumab and tremelimumab versus tremelimumab: RR 0.87, 95% CI 0.46–1.65, $P = .67$) (Fig. 5). Although we failed to find the

Table 1

Basic characteristics of the selected prospective and registered clinical trials.

Study	Year	Register number*	Design	Country	Cancer type	No. patients	Mean age (yr)	Lines of prior therapy	Dosage
Scott Antonia	2016	NCT02000947	A multicenter, non-randomized, open-label, phase 1b trial	The United States	Non-small cell lung cancer	102	67.0	≥ 0	Durvalumab (3 mg/kg, 10 mg/kg, 15 mg/kg, or 20 mg/kg every 4 wk, or 10 mg/kg) every 2 wk plus tremelimumab (1 mg/kg, 3 mg/kg, or 10 mg/kg) every 4 wk for 6 doses then every 12 wk for 3 doses.
Luana Calabrò	2018	NCT02588131	A non-randomized, open-label, single-center, phase 2 trial	Italy	Mesothelioma	40	64.0	≤ 1	Tremelimumab (1 mg/kg) plus durvalumab (20 mg/kg) every 4 wk for 4 doses, followed by maintenance durvalumab at the same dose and schedule for 9 doses.
Eileen M. O'Reilly	2019	NCT02558894	A multicenter, randomized, open-label, phase 2 trial	Canada, Germany, the Netherlands, South Korea, Spain, and the United States	Pancreatic ductal adenocarcinoma	65	61.0	1	Durvalumab (1500 mg every 4 wk) plus tremelimumab (75 mg every 4 wk) for 4 cycles followed by durvalumab therapy (1500 mg every 4 wk); OR durvalumab monotherapy (1500 mg every 4 wk) for up to 12 mo or until the onset of progressive disease or unacceptable toxic effects.
Lillian L. Siu	2019	NCT02319044	A randomized, open-label, multicenter, global phase 2 study	15 countries in North America, Europe, and Asia Pacific	Head and neck squamous cell carcinoma	267	61.0	1	Durvalumab (20 mg/kg every 4 wk) plus tremelimumab (1 mg/kg every 4 wk) for 4 cycles, followed by durvalumab (10 mg/kg every 2 wk); OR durvalumab (10 mg/kg every 2 wk) monotherapy; OR tremelimumab (10 mg/kg every 4 wk for 7 doses then every 12 wk for 2 doses) monotherapy.
Ronan J. Kelly	2019	NCT02340975	A randomized, multicenter, open-label, phase 1b/2 study	Canada, Japan, Korea, Singapore, Taiwan/China, and the United States	Gastric and gastroesophageal junction adenocarcinoma	113	54.0-64.0	≤ 2	Durvalumab 20 mg/kg plus tremelimumab 1 mg/kg every 4 wk for 4 cycles, followed by durvalumab 10 mg/kg every 2 wk for up to 12 mo; OR durvalumab monotherapy (10 mg/kg) every 2 wk; OR tremelimumab monotherapy (10 mg/kg) every 4 wk for 7 doses and then every 12 wk for 2 doses (for a total of up to 9 doses)

* ClinicalTrials.gov identifier.

Table 2

Median progression-free survival and overall survival in the eligible studies.

Study	Groups	mPFS	mOS
Scott Antonia 2016	D + T	NR	NR
Luana Calabrò 2018	D + T	5.7 mo (95% CI 1.7–9.7)	16.6 mo (95% CI 13.1–20.1)
Eileen M. O'Reilly 2019	D + T; D	1.5 mo (95% CI 1.2-1.5) 1.3–1.5 mo	3.1 mo (95%CI 2.2–6.1) 3.6 mo (95% CI 2.7–6.1)
Lillian L. Siu 2019	D + T; D; T	2.0 mo (95% CI 1.9–2.1) 1.9 mo (95% CI 1.8–2.8) 1.9 mo (95% CI 1.8–2.0)	7.6 mo (95% CI 4.9–10.6) 6.0 mo (95% CI 4.0–11.3) 5.5 mo (95% CI 3.9–7.0)
Ronan J. Kelly 2019	D + T; D; T	1.8 mo 1.6 mo (95% CI 1.0–1.8) 1.7 mo (95% CI 0.8–5.3)	7.0–10.6 mo 3.4 mo (95% CI 1.7–4.4) 7.7 mo (95% CI 2.1–13.7)

CI = confidence interval, D = durvalumab, mOS = median overall survival, mPFS = median progression-free survival, NR = not reported, T = tremelimumab.

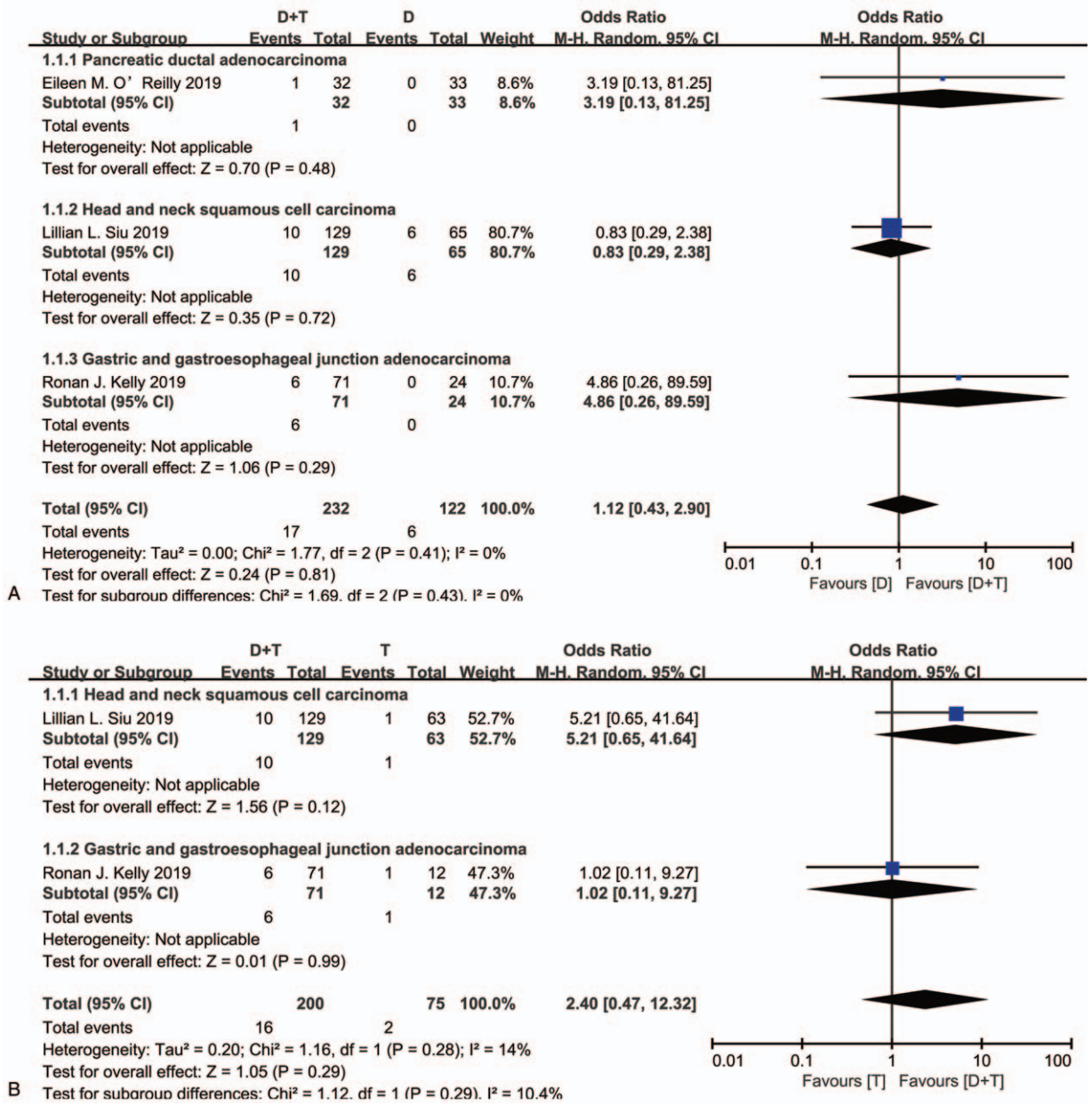

Figure 2. Forest plots of odds ratios for objective response in advanced solid tumors. (A) Durvalumab plus tremelimumab (D+T) versus durvalumab (D); (B) Durvalumab plus tremelimumab (D+T) versus tremelimumab (T).

statistical differences, subgroup analyses showed that combination therapy exerted higher risks of grade ≥ 3 treatment-related adverse events in 3 cancer types (PDA: RR 3.5; HNSCC: RR 1.28; GGA: RR 1.74) against durvalumab monotherapy. Nevertheless, durvalumab plus tremelimumab displayed lower risks of grade ≥ 3 treatment-related adverse events against tremelimumab monotherapy (HNSCC: RR 0.93; GGA: RR 0.34).

3.5. Bias assessment

All studies were open-label clinical trials, with 2 non-randomized and 3 randomized trials. The randomized clinical studies had reported all their pre-defined results. Accordingly, the meta-analyses of ORR and DCR were at moderate risk of reporting bias (Fig. 6).

4. Discussion

In this study, the combination therapeutic regimen showed no significant increase in treatment-related adverse events. However, higher effects were not observed in the combination therapy group. In the eligible studies, for advanced gastric and gastroesophageal junction adenocarcinoma, the combining durvalumab and tremelimumab displayed a numerically higher ORR than durvalumab monotherapy.[30] Nevertheless, durvalumab plus tremelimumab showed similar efficacy to durvalumab monotherapy in recurrent or metastatic head and neck

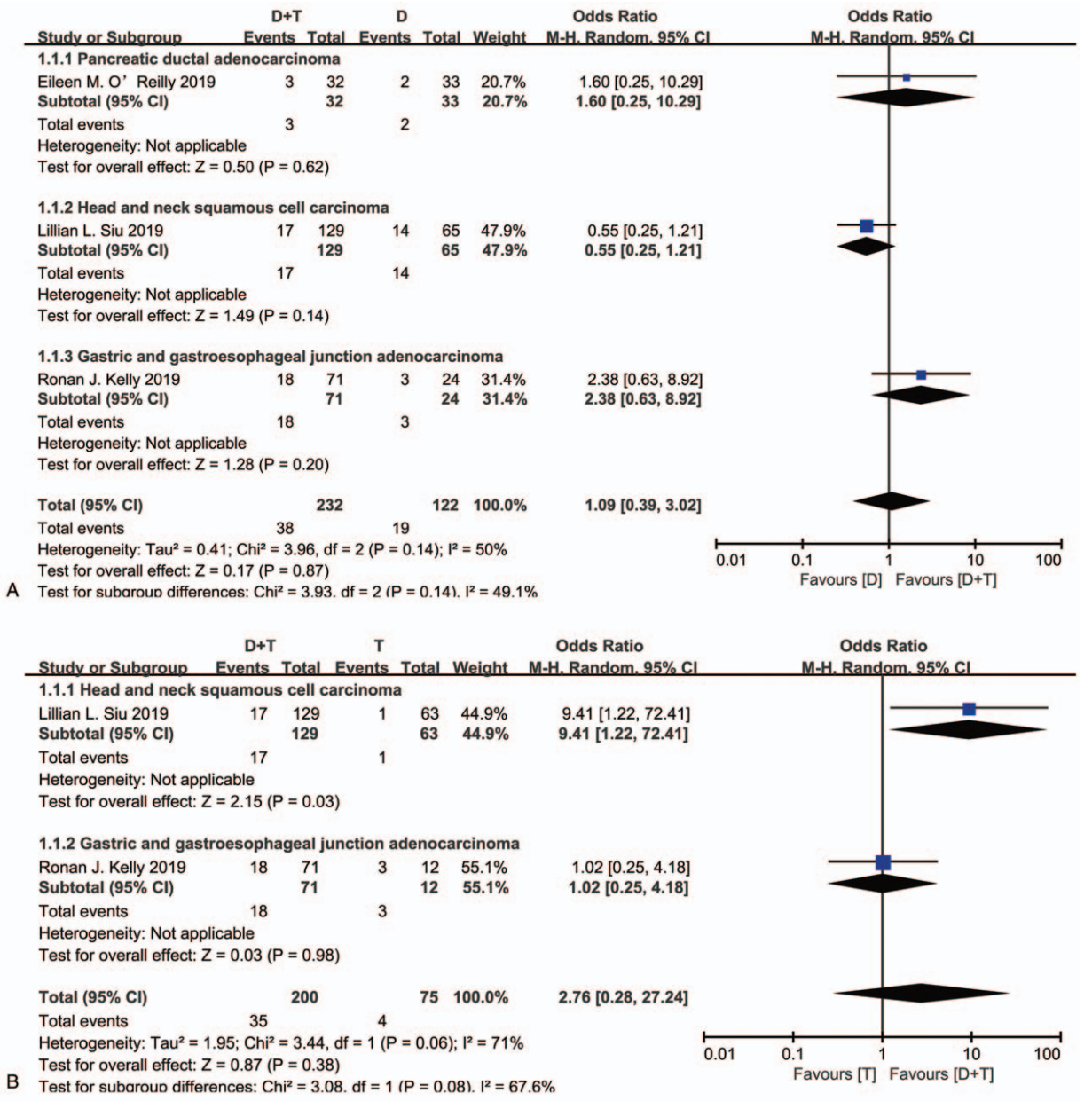

Figure 3. Forest plots of odds ratios for disease control in advanced solid tumors. (A) Durvalumab plus tremelimumab (D+T) versus durvalumab (D); (B) Durvalumab plus tremelimumab (D+T) versus tremelimumab (T).

squamous cell carcinoma and pancreatic ductal adenocarcinoma.[28,29] It is important to assess what factors might have contributed to the failure of combinatorial therapy.

Tumor cells elude recognition and destruction by the immune system via activating the immune checkpoint signaling pathway.[33–35] Nowadays, immune checkpoint inhibitors have revolutionized the treatment of patients with solid tumors.[36,37] Both CTLA-4 and PD-1 are able to regulate the activation of T-cell, however, the mechanisms of action were distinct.

The action mechanism of CTLA-4 remains less clear. To our minds, CTLA-4 was used by regulatory T (Treg) cells to elicit suppression; however, CTLA-4 also operates to trigger inhibitory signals in conventional T cells. T cell motility is increased by CTLA-4 via limiting contact time between T cells and antigen-presenting cells (APCs). In this condition, CTLA-4 ligation transmits "arrest" signals between T cells and APC.[38] Another study has demonstrated that anti-CTLA-4 treatment increases the action of Treg and CD4 T cells but decreases the action of CD8 T cells.[39] Accordingly, blockage of CTLA-4 might overcome immune resistance in the host peripheral immune system.

PD-1 is frequently expressed on tumor-infiltrating lymphocytes (especially CD4+ T cells).[40–42] In the peripheral tissues, PD-1 limits the activation of T-cell through suppressing the induction of cytokines and the expression of anti-apoptotic proteins. PD-1 is also over-expressed on intra-tumoral Treg cells and might enhance the immunosuppressive capability.[43–46] PD-L1 is

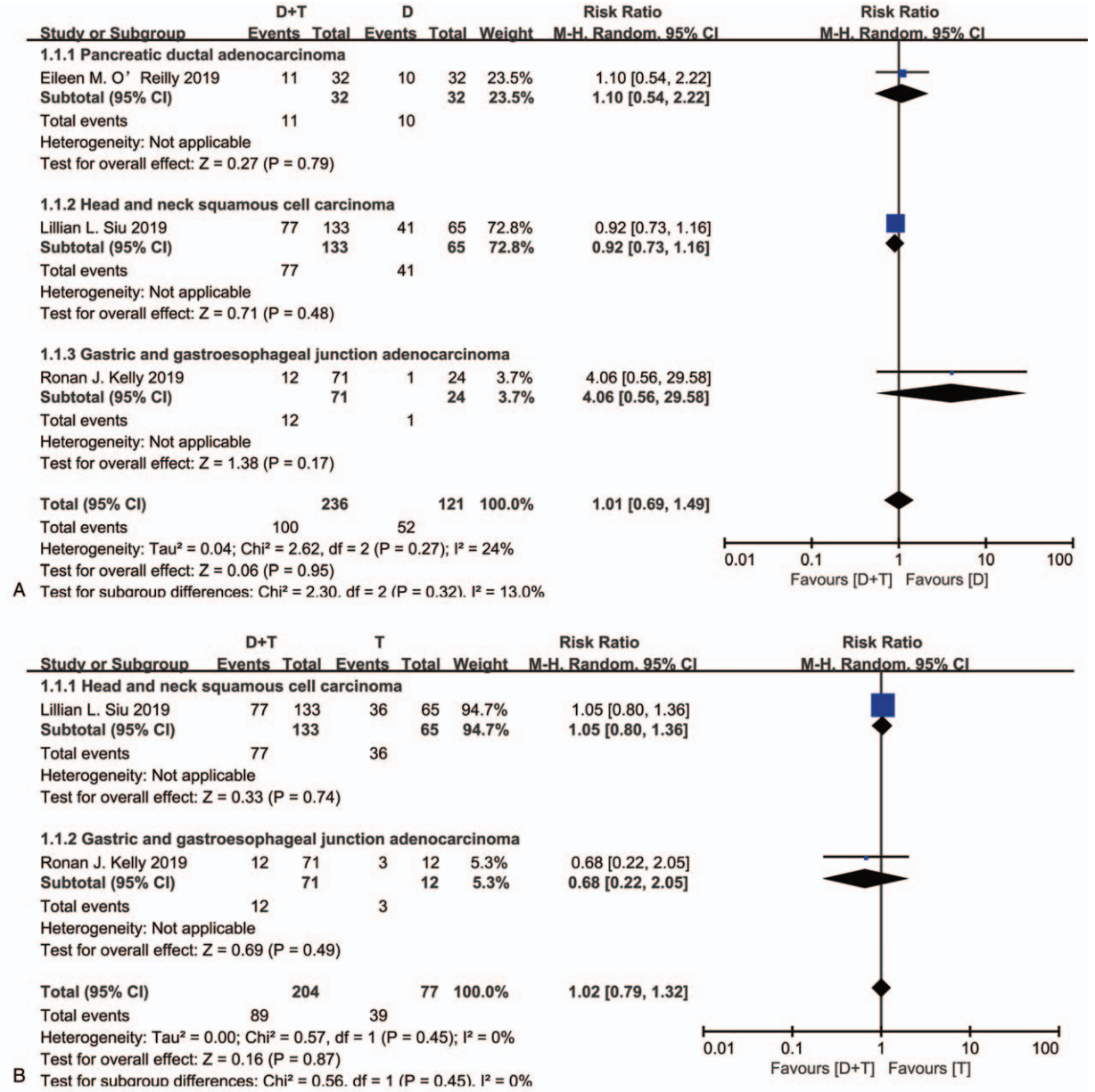

Figure 4. Forest plots of risk ratios for any grade treatment-related adverse events in advanced solid tumors. (A) Durvalumab plus tremelimumab (D+T) versus durvalumab (D); (B) Durvalumab plus tremelimumab (D+T) versus tremelimumab (T).

mainly upregulated on the surface of cancer cells. In addition, PD-L1 is expressed in tumor-infiltrating immune cells. These basic characteristics suggest that anti-PD-1/PD-L1 therapeutics could reverse immune resistance in the tumor microenvironment.[47]

Consequently, dual inhibition of CTLA-4 and PD-1/PD-L1 might be a reasonable and potentially synergistic therapeutic modality advanced cancer patient. In a randomized, double-blind, phase II study, the response rates of melanoma patients were significantly higher in nivolumab plus ipilimumab group (61%) than in ipilimumab group (11%) ($P < .001$).[48] A phase III clinical study, Checkmate-067, showed a median PFS of 11.5 months in patients treated with nivolumab and ipilimumab combination therapy, compared with 2.9 and 6.9 months in patients treated with ipilimumab or nivolumab monotherapy, respectively.[13] Another open-label, phase III trial displayed that nivolumab plus ipilimumab prolong median OS compared to chemotherapy in advanced NSCLC patients regardless of the status of PD-L1 (17.1 versus 13.9 months), and suggested combining nivolumab and ipilimumab as a first-line treatment for advanced NSCLC.[6]

The blockage of CTLA-4 and PD-1 exerts critical anti-tumor effects.[49] However, such benefits were not observed when solid tumor patients were treated with durvalumab and tremelimumab in our study.

Even nivolumab and durvalumab are working to block the PD-1/PD-L1 signaling pathway, the combining sites are different. Nivolumab is a PD-1 inhibitor, whereas durvalumab is a PD-L1 inhibitor. There are now lacking the head-to-head clinical studies

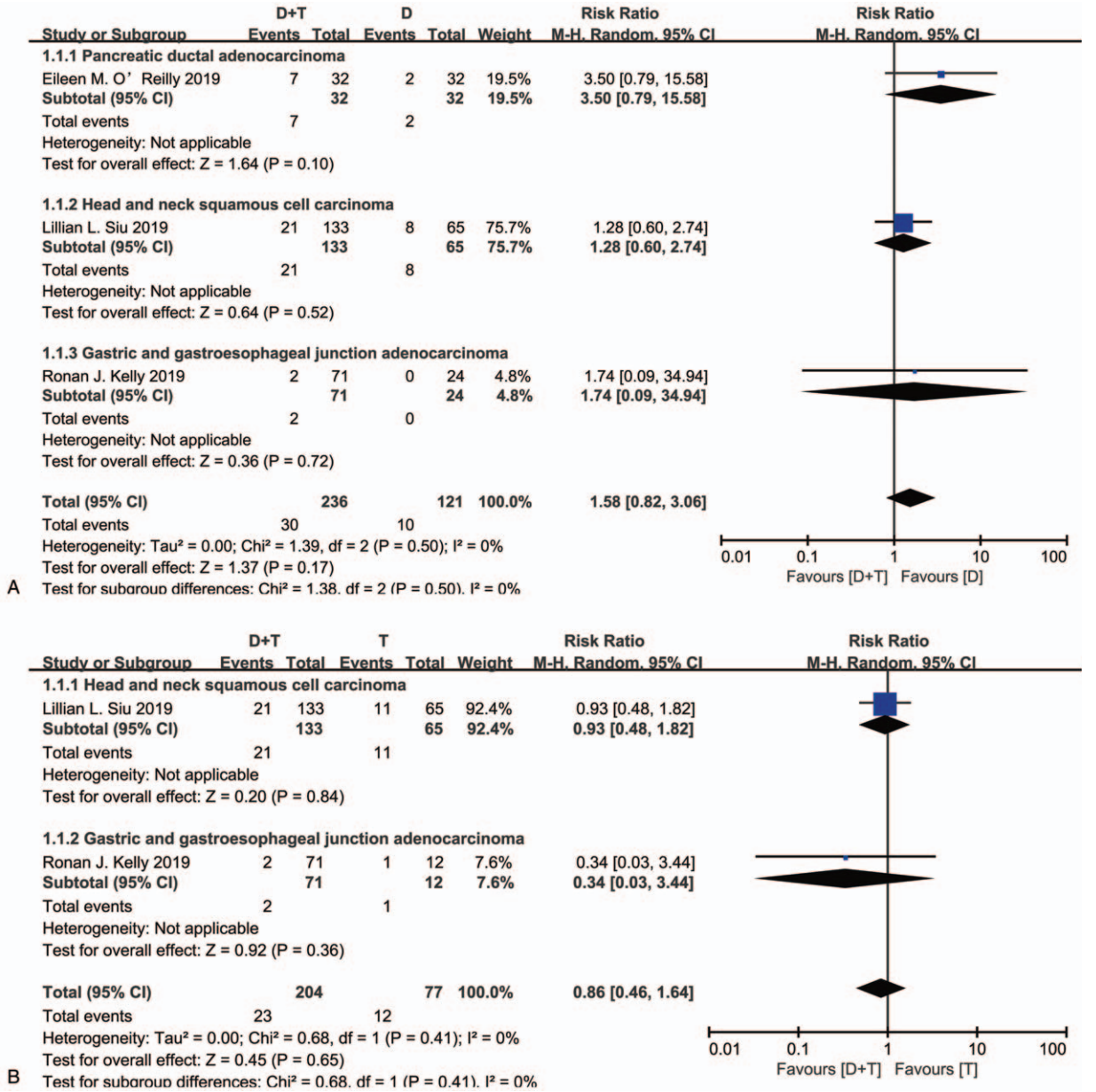

Figure 5. Forest plots of risk ratios for grade ≥3 treatment-related adverse events in advanced solid tumors. (A) Durvalumab plus tremelimumab (D+T) versus durvalumab (D); (B) Durvalumab plus tremelimumab (D+T) versus tremelimumab (T).

comparing the efficacy between anti-PD-1 therapy and anti-PD-L1 therapy. According to previously published studies, PD-1 antibodies and PD-L1 antibodies showed unequal treatment effects.[50–52]

The lack of efficacy of adding tremelimumab to durvalumab may be attributed to the mechanism of action, as tremelimumab is an IgG2 monoclonal antibody that does not cause lysis of regulatory T cells through the way of antibody-dependent cell-mediated cytotoxicity, which is observed with ipilimumab.[53]

For patients treated previously systematic chemotherapeutics in the eligible studies, the immune microenvironment might have been changed. Tumor-infiltrating lymphocytes are associated with the response to immunotherapy.[54–56] However, T cell exhaustion could drive a decline in the ability of T cells to kill tumor cells. A recent study indicated that T cells were stored in dense antigen-presenting-cell niches within the tumor microenvironment, but tumors that failed to form these immune niches were not extensively infiltrated by T cells. Patients with advanced or recurrent disease lack these niches, suggesting that niche breakdown in tumor tissues may be a key factor of immune resistance or escape.[57]

Several limitations exist in this analysis. All enrolled studies are phase I or II clinical trials, whereas data from randomized controlled phase III studies are lacking. In addition, open-label studies might increase publication bias even the trials were conducted in various centers. The analysis of ORR and DCR

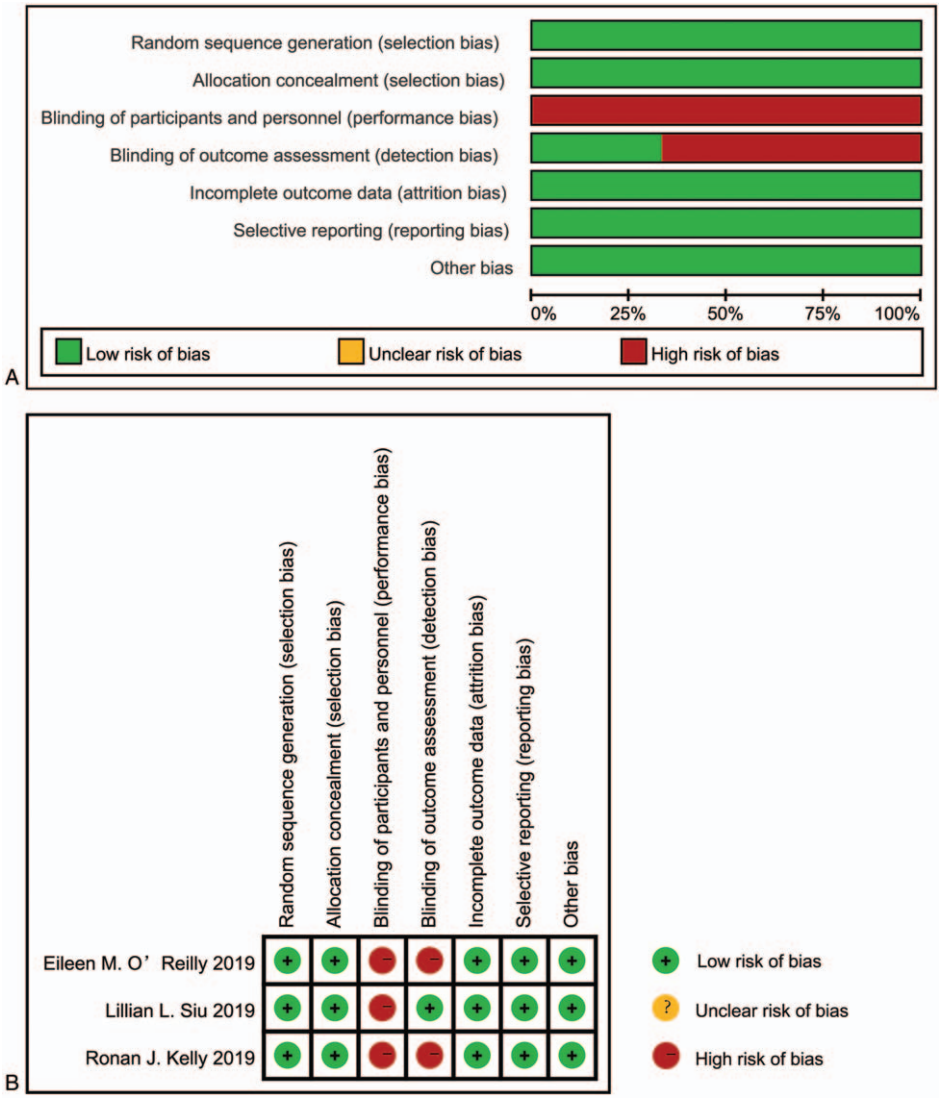

Figure 6. Risk of bias. (A) Each risk of bias item presented as percentages across all included randomized clinical studies; (B) Each risk of bias item for each included randomized clinical study. 'green+': low risk, 'red -': high risk, 'yellow?': unclear risk of bias.

comprised 3 types of cancers that might not fully represent the efficacy of combination therapy in solid tumors. The type of tumors was complex and different cancer types had different inflamed and tumor mutation burden backgrounds, which could directly diminish the interpretability of the meta-analysis.

5. Conclusion

Durvalumab and tremelimumab combination therapy appeared active for the treatment of HNSCC. However, future studies are also needed to identify the patients that most possibly benefit from dual immune checkpoint inhibitors.

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Author contributions

Study design, data extraction, and data analysis: BW, GL, and PL; manuscript writing and edition: BW, JF and QL.
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Visualization: Bi-Cheng Wang.
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Writing – review & editing: Bi-Cheng Wang, Ji-Quan Fan, Quentin Liu.

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