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Efficacy and safety of PD-1/PD-L1 inhibitor monotherapy or combination therapy versus platinum-based chemotherapy as a first-line treatment of advanced urothelial cancer: A systematic review and meta-analysis

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Abstract

Background: Recent clinical trials have shown that inhibitors targeting programmed cell death protein 1 (PD-1) or its ligand (programmed cell death-ligand 1 [PD-L1]) provide significant efficacy and clinical benefit in the treatment of advanced or metastatic urothelial carcinoma (UC). This systematic review and meta-analysis aimed to compare the effectiveness and safety of PD-1/PD-L1 inhibitors in combination with chemotherapy or PD-1/PD-L1 inhibitor monotherapy versus platinum-based chemotherapy as a first-line treatment for advanced UC.

Materials and methods: From the beginning of the database construction to February 4, 2024, a combination of medical subject headings and free-text words was searched using the Population Intervention Comparison Outcome Study design framework. The PubMed, Cochrane Library, Embase, and Web of Science electronic databases were searched. Meta-analyses of progression-free survival, overall survival, objective response rate (ORR), complete remission rate, duration of remission, and grade ≥3 adverse events were performed.

Results: Four studies were included in the meta-analysis. The PD-1/PD-L1 inhibitors plus chemotherapy therapy is associated with significantly better ORR compared with chemotherapy. Unfortunately, there were no significant differences between PD-1/PD-L1 inhibitor monotherapy and chemotherapy in terms of ORR, duration of remission, or overall survival.

Conclusions: Our findings indicate that PD-1/PD-L1 inhibitors plus chemotherapy therapy provides more oncological advantages than standard chemotherapy and should be recommended as a first-line treatment for advanced or metastatic UC. Attention must also be paid to the adverse effects of the combination of PD-1/PD-L1 inhibitors and chemotherapy.

Keywords: Urothelial carcinoma; Immune-checkpoint inhibitor; Programmed cell death protein 1; Programmed death-ligand 1 inhibitor

1. Introduction

Urothelial carcinoma (UC) is one of the most common genitourinary cancers, and one of the most common and deadliest malignancies in the world.[1,2] Tumors can occur anywhere in the genitourinary system, including the urethra, bladder (the most common site in >90% of cases), ureters, and renal pelvis.[3] Most patients present with early and potentially curable disease at diagnosis, with 10%–15% experiencing disease progression to an invasive form.[4] For muscle-invasive urothelial cancer, the standard treatment includes surgical options such as radical cystectomy or nephroureterectomy combined with neoadjuvant chemotherapy. Cisplatin-based combination chemotherapy is the standard of care.[5,6] In 2020, approximately 573,278 patients worldwide were diagnosed with bladder cancer, resulting in 212,536 deaths.[7] The prognosis for patients with advanced UC remains poor, with more than 90% of these patients dying of metastatic disease within 5 years.

Prior to the advent of immunotherapy, follow-up options for patients with refractory UC were limited to single-agent chemotherapeutic agents such as vincristine and docetaxel or optimal supportive care, and overall survival (OS) remained poor.[8,9] Response rates ranged from 40% to 60%, thereby increasing the median OS of patients with metastatic urothelial carcinoma (mUC) to nearly 15 months, and the lasting clinical benefit remains suboptimal, with few patients living for >24 months.[10] Although cisplatin-based chemotherapy has improved the survival of patients with mUC, recurrence remains common.[11] Over the past 5 years, immune checkpoint blockade has emerged as a new option for patients with mUC, and five immune checkpoint inhibitors (ICIs) have been approved for metastatic UC, including the programmed cell death protein 1 (PD-1) inhibitors,

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pembrolizumab and nivolumab, and the programmed cell death-ligand 1 (PD-L1) inhibitors, atezolizumab, durvalumab, and avelumab.[3]

The advent of immunotherapy has enriched the therapeutic landscape for UC by overcoming the existing therapeutic limitations of chemotherapy. It has been found that UC with genomic instability, high expression of PD-L1, DNA damage-responsive mutations, and high tumor mutation burden is more responsive to treatment with ICIs.[12] Despite improved survival outcomes with immunotherapeutic agents, only 30% of the patients who qualify for treatment experience lasting clinical benefits, possibly reflecting heterogeneous disease biology.[13–15] To understand the best treatment decisions and guide recommendations, we conducted a systematic review of all clinical trials evaluating first-line ICI therapy as a monotherapy or combination therapy for mUC treatment.

2. Materials and methods

This meta-analysis was performed in accordance with the 2020 standards of the Preferred Reporting Project for Systematic Review and Meta-Analyses. This study was registered with PROSPERO (registration number, CRD42024510339).

2.1. Search strategy

A combination of medical subject headings and free-text words was searched using the Population Intervention Comparison Outcome Study design framework. The PubMed, Cochrane Library, Embase, and Web of Science electronic databases were searched. The following search terms were adopted: (bladder cancer OR urothelial carcinoma OR urothelial cancer) AND (metastatic OR advanced) AND randomized controlled trial. Supplementary Material presents the search records in detail (Supplementary Table 1, http://links.lww.com/CURRUROL/A62).

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) randomized trial of PD-1 or PD-L1 as a first-line agent in the treatment of advanced urothelial cancer; (2) immunotherapy versus chemotherapy; and (3) at least one of progression-free survival (PFS), OS, or adverse events (AEs) was reported.

Studies meeting the following criteria were excluded: (1) other types of articles, such as reviews, case reports, animal experimental studies, letters to the editor, conference abstracts, and comments; (2) single-arm experiments; and (3) duplicate cohorts of patients.

2.3. Data extraction

Data were independently extracted by 2 researchers. Baseline patient characteristics were extracted (study name, year of publication, ClinicalTrials.gov, drug, number of patients, age, sex, performance status, primary tumor site, disease status, PD-L1 status, cisplatin eligibility, follow-up treatment, duration of follow-up, and primary outcome). We also reconstructed the Kaplan-Meier curve. Discrepancies were resolved by consultation with a third investigator.

2.4. Risk of bias assessment

The risk of bias in the included trials was assessed by two independent reviewers using the Cochrane risk-of-bias tool according to the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Any discrepancies were resolved through group discussion. A quality evaluation of the literature is shown in Figure 1.

2.5. Statistical analysis

Duplicate removal was performed using EndNote (version 20, Clarivate Analytics, https://support.clarivate.com/Endnote/s/article/EndNote-20-Release-Notes?language=en_US). Review manager 5.3 (Cochrane Collaboration, Oxford, United Kingdom), Statistical software R (version 4.3.1, https://www.r-project.org/), and the R packages "netmeta" and "IPDformKM" were used for data analysis. We quantified the Kaplan-Meier curves PCR and OS using the GetData Graphic Digitizer software (http://getdata-graph-digitizer.com/download.php) and reconstructed individual data using the IPDformKM software package (https://cran.r-project.org/web/packages/IPDfromKM/index.html). Individual patient-level data were reconstructed using the method established by Liu et al.[16] After reconstruction of individual patient data, the patients were divided into groups. Patients receiving chemotherapy were assigned to the chemotherapy cohort; patients receiving durvalumab, atezolizumab, pembrolizumab, and nivolumab were assigned to the PD-(L)1 inhibitor alone cohort; patients treated with durvalumab plus tremelimumab were assigned to the PD-(L)1 inhibitor plus other ICIs cohorts; and patients treated with atezolizumab plus chemotherapy, pembrolizumab plus chemotherapy, and nivolumab plus chemotherapy were assigned to the PD-(L)1 inhibitors plus chemotherapy cohort. Subsequently, we reestablished the survival curves for the 4 cohorts to gain insight into long-term survival after treatment with the three different interventions. All results were analyzed using a random-effects model. Statistical significance was set at $p < 0.05$.

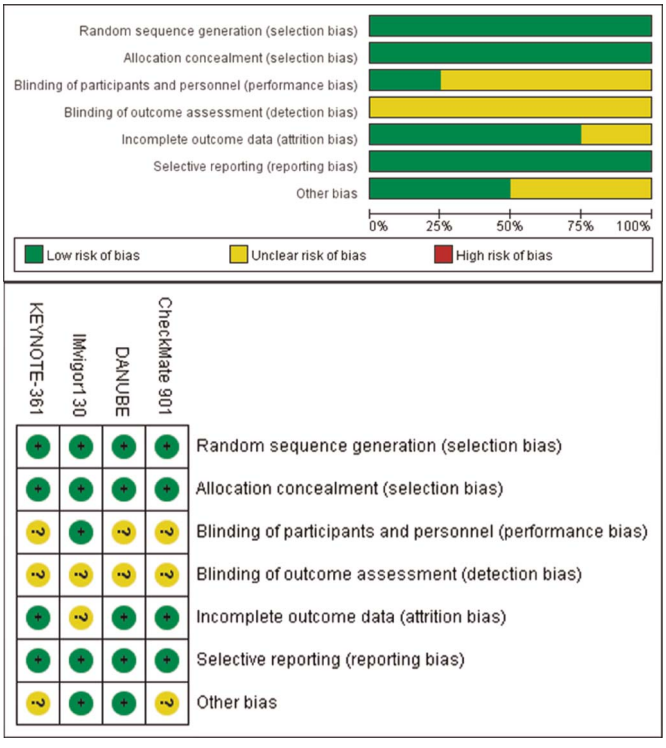

Figure 1. Risk of bias assessment diagram.

3. Results

3.1. Search results

After the initial search, 1196 publications were identified. However, after removing duplicate studies, 882 cases remained. Of these, 853 were eliminated from consideration after evaluating their titles and abstracts. Ultimately, 29 articles were accessible for comprehensive examination of their complete content. Following the application of the inclusion criteria, 4 trials were chosen for inclusion.[17–20] Three of the papers were 3-arm studies including chemotherapy alone, PD-(L)1 inhibitors alone, PD-(L)1 inhibitors plus other ICIs, or PD-(L)1 inhibitors plus chemotherapy, and the other paper was a 2-arm study looking at PD-(L)1 inhibitors plus chemotherapy compared to chemotherapy. The detail process of inclusion and exclusion of literature is shown in Figure 2.

3.2. Patient characteristics

This study included 3463 patients diagnosed with metastatic or advanced UC. Among them, 1400 patients were assigned to receive chemotherapy alone, 1319 patients were randomly assigned to receive PD-(L)1 inhibitors alone therapy, 802 patients were assigned to receive PD-(L)1 inhibitors plus chemotherapy, and 342 patients were assigned to receive PD-(L)1 inhibitors plus other ICI therapy. The baseline features of the patients, such as drug use, number of patients, age, sex, performance status, primary tumor site, disease status, PD-L1 status, cisplatin eligibility, follow-up treatment, and duration, were comparable. All the chemotherapy cohorts were administered a platinum-based combination treatment. Table 1 presents the characteristics of the included studies.

3.3. Meta-analysis

Overall survival Three cohorts reported PD-(L)1 inhibitors alone therapy, including DANUBE (durvalumab), IMvigor130 (atezolizumab), and KEYNOTE-361 (pembrolizumab). Three cohorts reported PD-(L)1 inhibitors plus chemotherapy therapy, which included IMvigor130 (atezolizumab plus chemotherapy), KEYNOTE-361 (pembrolizumab plus chemotherapy), and CheckMate 901 (nivolumab plus chemotherapy). One cohort, DANUBE (durvalumab plus tremelimumab), reported PD-(L)1 inhibitors plus other ICIs. The Kaplan-Meier curves were reconstructed (Fig. 3), showing that PD-(L)1 inhibitors plus chemotherapy had a comparatively superior long-term survival advantage over chemotherapy alone (hazard ratio [HR], 0.878; 95% confidence interval [CI], 0.786–0.982; p = 0.022), with a median survival time of 16.20 months (95% CI, 14.82–18.30 months). However, no statistically significant results were obtained for the analysis of the other 2 cohorts; PD-(L)1 inhibitors alone versus chemotherapy resulted in HR of 0.913 (95% CI, 0.831–1.004; p = 0.062) and a median survival time of 16.24 months (95% CI, 14.48–17.91 months), whereas PD-(L)1 inhibitors plus other ICIs resulted in HR of 0.913 (95% CI, 0.793–1.050; p = 0.203) and a median survival time of 15.24 months (95% CI, 13.18–18.34 months). We also analyzed the HR values of OS reported in the included literature, and the

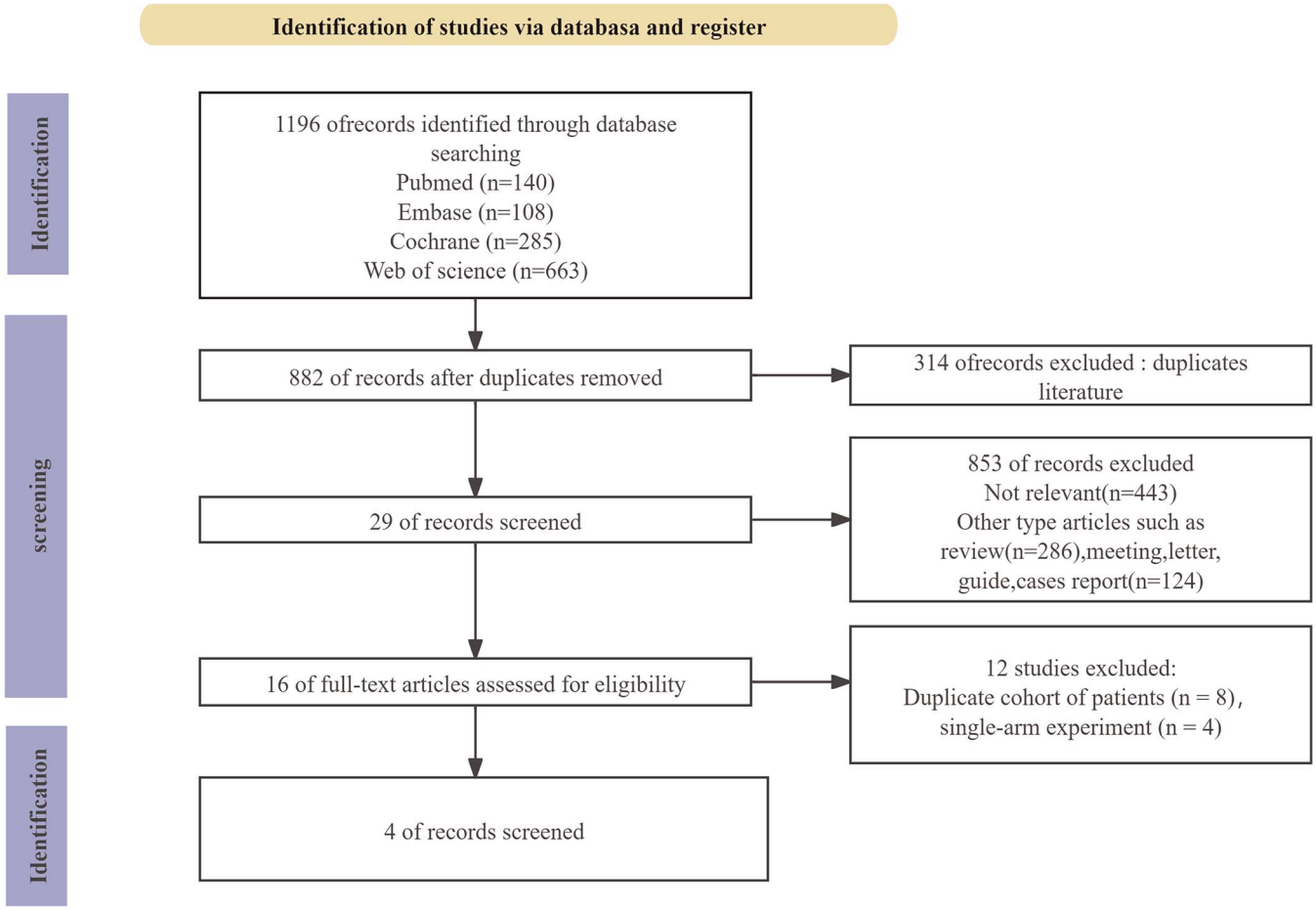

Figure 2. Flow chart of literature search strategies.

results obtained were consistent with the results of our individual data reconstruction. The forest plot (Fig. 4) revealed that PD-(L)1 inhibitors plus chemotherapy therapy is associated with significantly longer OS than chemotherapy alone (pooled HR, 0.83; 95% CI, 0.74–0.92; p = 0.0006; I^2, 0%) and that both PD-(L)1 inhibitors alone and PD-(L)1 inhibitors plus other ICI cohort analyses were not statistically significant, with the following results: pooled HR of 0.97 (95% CI, 0.87–1.08; p = 0.60; I^2, 0%) and pooled HR of 0.85 (95% CI, 0.71–1.02; p = 0.08), respectively; the 3 cohorts combined resulted in the following: pooled HR of 0.89 (95% CI, 0.83–0.96; p = 0.01; I^2, 0%).

Progression-free survival Only 3 cohorts in the included literature reported PFS with PD-(L)1 inhibitors plus chemotherapy, including CheckMate 901 (nivolumab plus chemotherapy), IMvigor130 (atezolizumab plus chemotherapy), and KEYNOTE-361 (pembrolizumab plus chemotherapy). We similarly reconstructed the data for PFS. The Kaplan-Meier curves (Fig. 5) revealed that PD-(L)1 inhibitors plus chemotherapy therapy is associated with significantly longer PFS than chemotherapy alone (HR, 0.757; 95% CI, 0.683–0.838; p < 0.001). Similarly, we analyzed the HR values for PFS reported in the literature, and the results of the forest plot (Fig. 6) were the same as those analyzed after we reconstructed the individual data; PD-(L)1 inhibitors plus chemotherapy had superior PFS (pooled HR, 0.78; 95% CI, 0.70–0.86; p < 0.001; I^2, 0%).

Objective response rate We analyzed the objective response rate (ORR) values, and the results of the forest plot (Fig. 7A) showed that the ORR of PD-(L)1 inhibitors plus chemotherapy was superior to that of chemotherapy (pooled odds ratio [OR], 1.44; 95% CI, 1.12–1.85; p = 0.005; I^2, 53%), but the results of the PD-(L)1 inhibitors alone therapy analysis (OR, 0.42; 95% CI, 0.33–0.53; p < 0.001; I^2, 42%) and PD-(L)1 inhibitors plus other ICIs analysis (pooled OR, 0.59; 95% CI, 0.43–0.80; p = 0.0007) showed that both the ORR was not as beneficial as chemotherapy, and the results of the 3 cohorts combined (pooled OR, 0.75; 95% CI, 0.46–1.21; p < 0.001; I^2, 96%) showed no difference in outcome.

Complete response rate The forest plot (Fig. 7B) revealed that chemotherapy is associated with significantly better complete remission rate than PD-(L)1 inhibitors plus chemotherapy (pooled OR, 1.72; 95% CI, 1.26–2.33; p = 0.0005; I^2, 27%). However, the results of the analysis of PD-(L)1 inhibitors alone (OR, 0.94; 95% CI, 0.69–1.28; p = 0.69; I^2, 0%) and the analysis of PD-(L)1 inhibitors plus other ICIs (OR, 1.25; 95% CI, 0.70–2.25) showed that the complete remission rate of both was not statistically significant, and the results of the 3 cohorts combined have no difference in outcome (OR, 1.30; 95% CI, 0.99–1.72; p = 0.03; I^2, 72.8%).

Duration of response The forest plot revealed that PD-(L)1 inhibitors plus other ICIs were associated with a significantly longer duration of response (DOR) than chemotherapy alone (pooled mean difference [MD], 7.30; 95% CI, 2.04–12.56; p = 0.006). The forest plot revealed that PD-(L)1 inhibitors plus chemotherapy therapy is associated with significantly longer DOR than chemotherapy alone (pooled MD, 1.33; 95% CI, 0.26–2.39; p = 0.01; I^2, 0%). However, the results of the analysis of PD-(L)1 inhibitors alone therapy (MD, 7.25; 95% CI, –0.01–14.51; p = 0.05) showed that the DOR was not statistically significant. The 3 cohorts combined have significantly longer DOR than chemotherapy alone (MD, 2.70; 95% CI, 0.68–4.73; p = 0.03; I^2, 71.8%) (Fig. 8A).

Grade ≥3 AEs The forest plot revealed that PD-(L)1 inhibitors alone (pooled OR, 0.22; 95% CI, 0.11–0.46; p < 0.001; I^2, 92%) and PD-(L)1 inhibitors plus other ICIs (pooled OR, 0.11; 95% CI, 0.07–0.16; p < 0.001) caused fewer grade ≥3 AEs than chemotherapy alone and were safe for patients. The forest plot revealed that PD-(L)1 inhibitors plus chemotherapy therapy causes more ≥3 AEs and are relatively less safe than chemotherapy

Table 1

Characteristics of included studies and patients.

Study	IMvigor130			DANUBE			KEYNOTE361			CheckMate 901	
Year	2020			2020			2021			2023	
ClinicalTrials.gov	NCT02807636			NCT02516241			NCT02853305			NCT03036098	
Drugs	Atezolizumab monotherapy vs. atezolizumab plus platinum-based chemotherapy vs. chemotherapy (gemcitabine plus cisplatin or gemcitabine plus carboplatin)			Durvalumab monotherapy vs. durvalumab plus tremelimumab vs. chemotherapy (gemcitabine plus cisplatin or gemcitabine plus carboplatin)			Pembrolizumab monotherapy vs. pembrolizumab plus platinum-based chemotherapy vs. chemotherapy (gemcitabine plus cisplatin or gemcitabine plus carboplatin)			Nivolumab-combination therapy vs. gemcitabine-cisplatin	
Compound	Atezo + Chemo	Atezo	Chemo	Durva + Treme	Durva	Chemo	Pembro + Chemo	Pembro	Chemo	Nivol	Chemo
Number, n	451	362	400	342	346	344	351	307	352	304	304
Age, yr	69 (62–75)	67 (62–74)	67 (61–73)	68 (60–73)	67 (60–73)	68 (60–73)	69 (41–91)	68 (29–89)	69 (36–90)	65 (32–86)	65 (35–85)
Male	75%	77%	75%	75%	72%	80%	78%	74%	74%	77.6%	77.0%
ECOG PS >1	13%	9%	10%	0%	0%	0%	7%	8%	6%	0.7%	0%
Primary tumor (lower tract)	71%	75%	75%	78%	82%	75%	82%	79%	77%	NA	NA
Disease status (metastatic)	89%	88%	92%	96%	97%	94%	NA	NA	NA	85.9%	88.5%
Lymph node only	18%	19%	17%	21%	18%	22%	23%	21%	27%	NA	NA
Visceral metastasis	57%	56%	60%	78%	82%	77%	74%	78%	72%	NA	NA
High PD-L1	24%	24%	23%	60%	60%	60%	45%	52%	45%	36.5%	36.2%
Chemotherapy (cisplatin)	30%	37%	34%	NR	NR	NR	46%	45%	46%	NA	NA
Subsequent therapy	26%	40%	41%	45%	47%	54%	35%	41%	61%	NA	NA
Subsequent ICI therapy	5%	2%	20%	3%	5%	32%	7%	5%	48%	NA	NA
Median follow-up (95% CI), mo	11.8 (6.1–17.2)			41.2 (37.9–43.2)			31.7 (27.7–36.0)			33.6 (7.4–62.4)	
Primary endpoint	PFS, OS			OS			PFS, OS			PFS, OS	

CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICI = immune checkpoint inhibitor; NA = not available; OS = overall survival; PD-L1 = programmed cell death-ligand 1; PFS = progression-free survival.

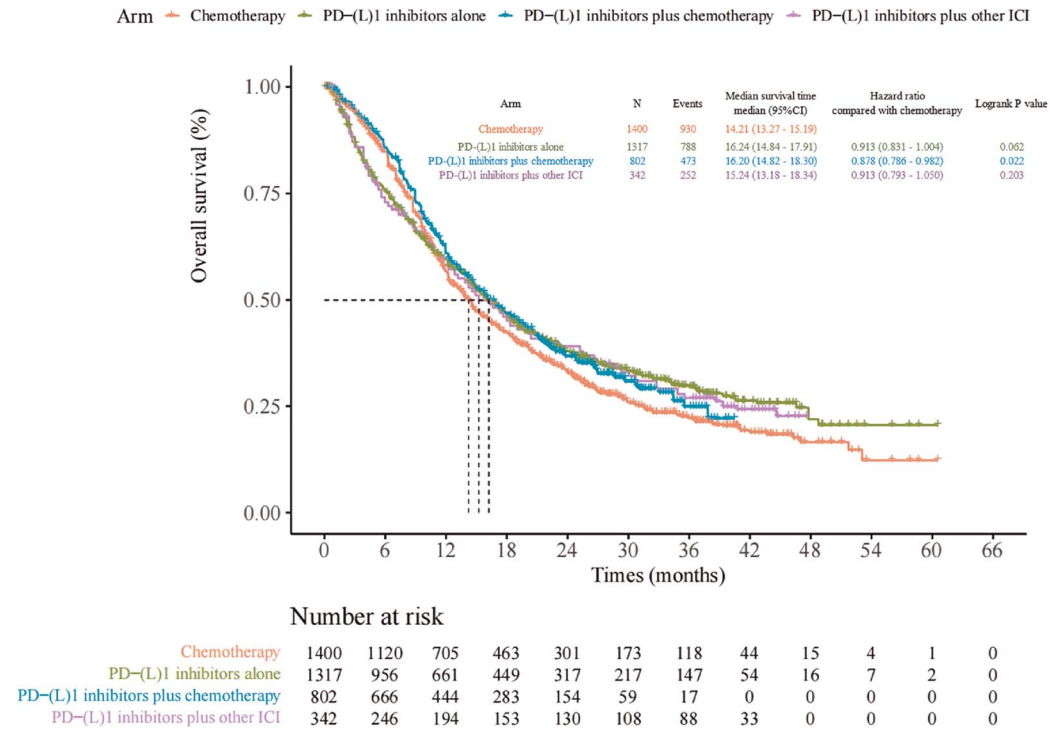

Figure 3. Kaplan-Meier curves for OS. ICI = immune checkpoint inhibitor; OS = overall survival; PD-L1 = programmed cell death-ligand 1.

alone (pooled OR, 1.44; 95% CI, 1.09–1.89; p = 0.01; I^2, 34%). The results of the 3 cohorts combined showed no statistical difference (OR, 0.44; 95% CI, 0.18–1.04; p = 0.06; I^2, 97%) (Fig. 8B).

The OS and PFS of patients with high PD-L1 expression levels The forest plot (Fig. 9A) revealed that PD-(L)1 inhibitors plus chemotherapy (pooled HR, 0.82; 95% CI, 0.68–0.99; p = 0.04; I^2, 0%) and PD-(L)1 inhibitors plus other ICIs (pooled HR, 0.82; 95% CI, 0.68 0.99; p = 0.04; I^2, 0%) therapy are associated with significantly longer OS than chemotherapy alone in patients with high PD-L1 status. The results of PD-(L)1 inhibitors alone therapy versus chemotherapy (pooled HR, 0.94; 95% CI, 0.79–1.11; p = 0.45; I^2, 0%) showed that the OS was not statistically significant. Reported PFS with high PD-L1 expression was only observed in the PD-(L)1 inhibitors plus chemotherapy cohort. The forest plot (Fig. 9B) revealed that PD-(L)1 inhibitors plus chemotherapy therapy was associated with significantly longer PFS than chemotherapy alone in patients with high PD-L1 status (pooled HR, 0.70; 95% CI, 0.58–0.84; p = 0.0002; I^2, 0%).

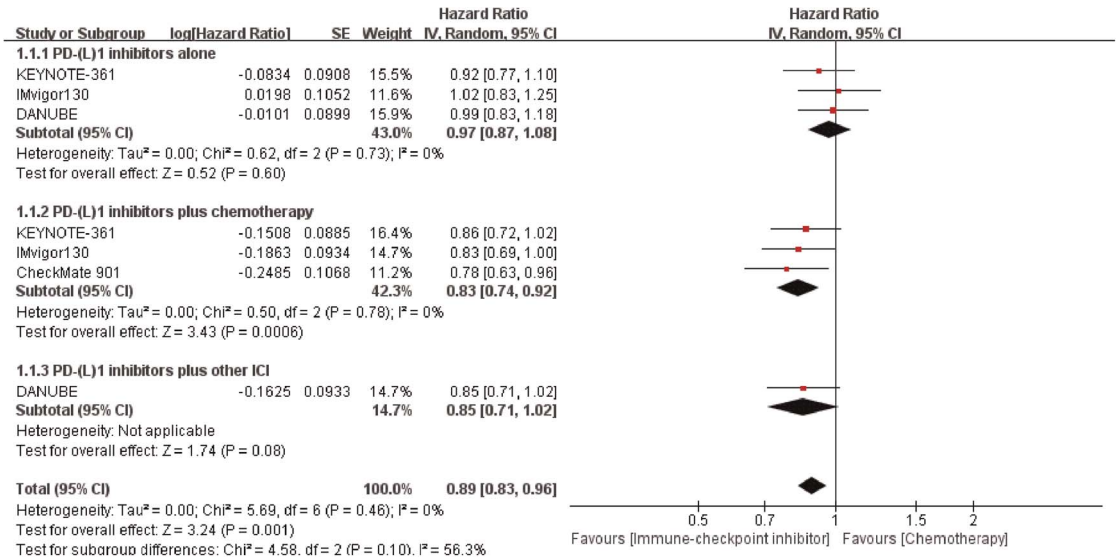

Figure 4. Forest plot of OS. CI = confidence interval; ICI = immune checkpoint inhibitor; OS = overall survival; PD-L1 = programmed cell death-ligand 1.

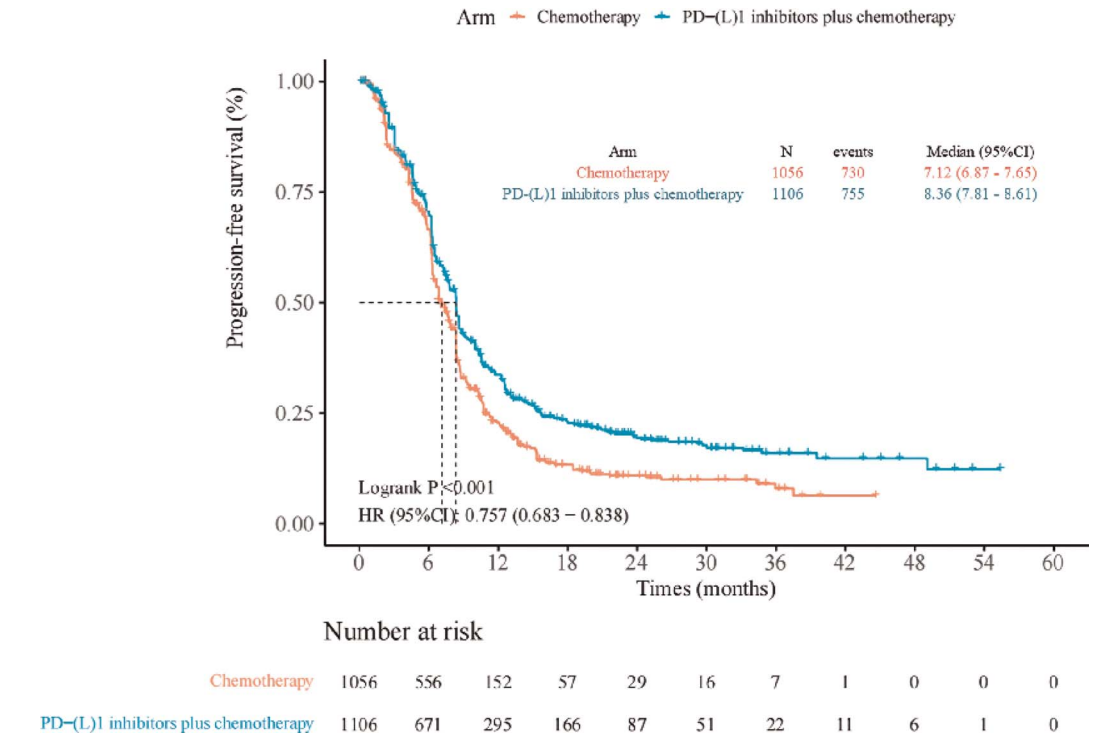

Figure 5. Kaplan-Meier curves for PFS. CI = confidence interval; HR = hazard ratio; PD-L1 = programmed cell death-ligand 1; PFS = progression-free survival.

Publication bias Publication bias of the OS was assessed using a funnel plot. No obvious evidence of publication bias was observed in the bilaterally symmetrical funnel plots of OS (Fig. 10).

4. Discussion

As PD-(L)1 inhibitors have shown significant clinical benefits in patients with advanced/metastatic UC, an increasing number of clinical trials have been conducted to evaluate the safety and efficacy of PD-(L)1 inhibitors in the treatment of patients with UC. In these clinical trials, PD-(L)1 inhibitors have been used alone, in combination with chemotherapy, or in combination with other ICIs. In this study, we conducted a systematic review and meta-analysis to assess the effect of first-line immunotherapy in patients with mUCs eligible for platinum-based chemotherapy, including cisplatin. This approach has led to several intriguing findings. From the analysis, we can see that treatment with PD-(L)1 inhibitors alone and PD-(L)1 inhibitors plus other ICIs did not significantly improve the survival prognosis of patients with UC, and the OS between and chemotherapy alone was still similar; however, they had a more severe ORR than chemotherapy alone, but both of these treatments had better safety outcomes. The PD-(L)1 inhibitors plus chemotherapy appeared to have a better survival prognosis than chemotherapy, as well as in patients with mUC in a high PD-L1 expression state, but the safety was the worst among these treatment options. This suggests that PD-L1 can be used to predict the pathological aspects of the response to PD-(L)1 inhibitors. Overall, there is a clear rationale for exploring ICIs as a first-line maintenance therapy for UC, given the immunogenic nature of UC, the antitumor activity, favorable safety profile of ICIs, and the cytotoxic and immunogenic effects of chemotherapy.

Chemotherapy directly causes cancer cell death and retards tumor growth through various mechanisms, including direct lysis of tumor cells, inhibition of cell cycle, DNA damage, inhibition of DNA replication, disruption of cellular metabolism, and

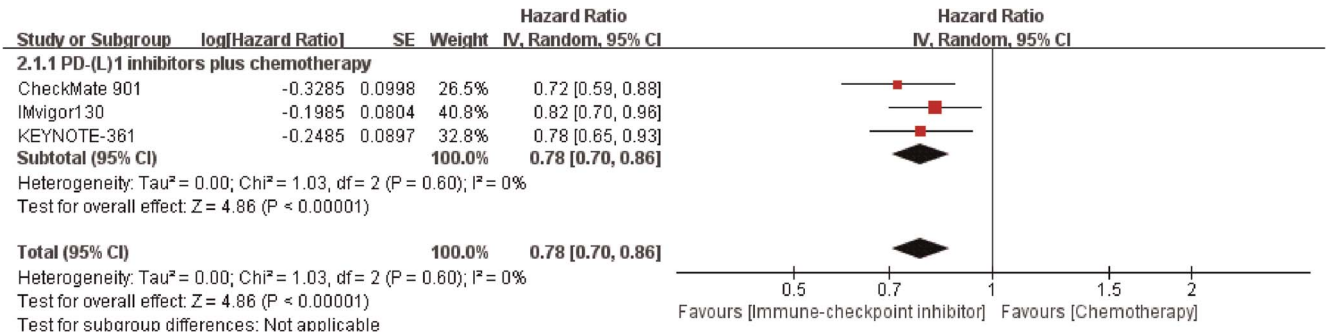

Figure 6. Forest plot of PFS. CI = confidence interval; PD-L1 = programmed cell death-ligand 1; PFS = progression-free survival.

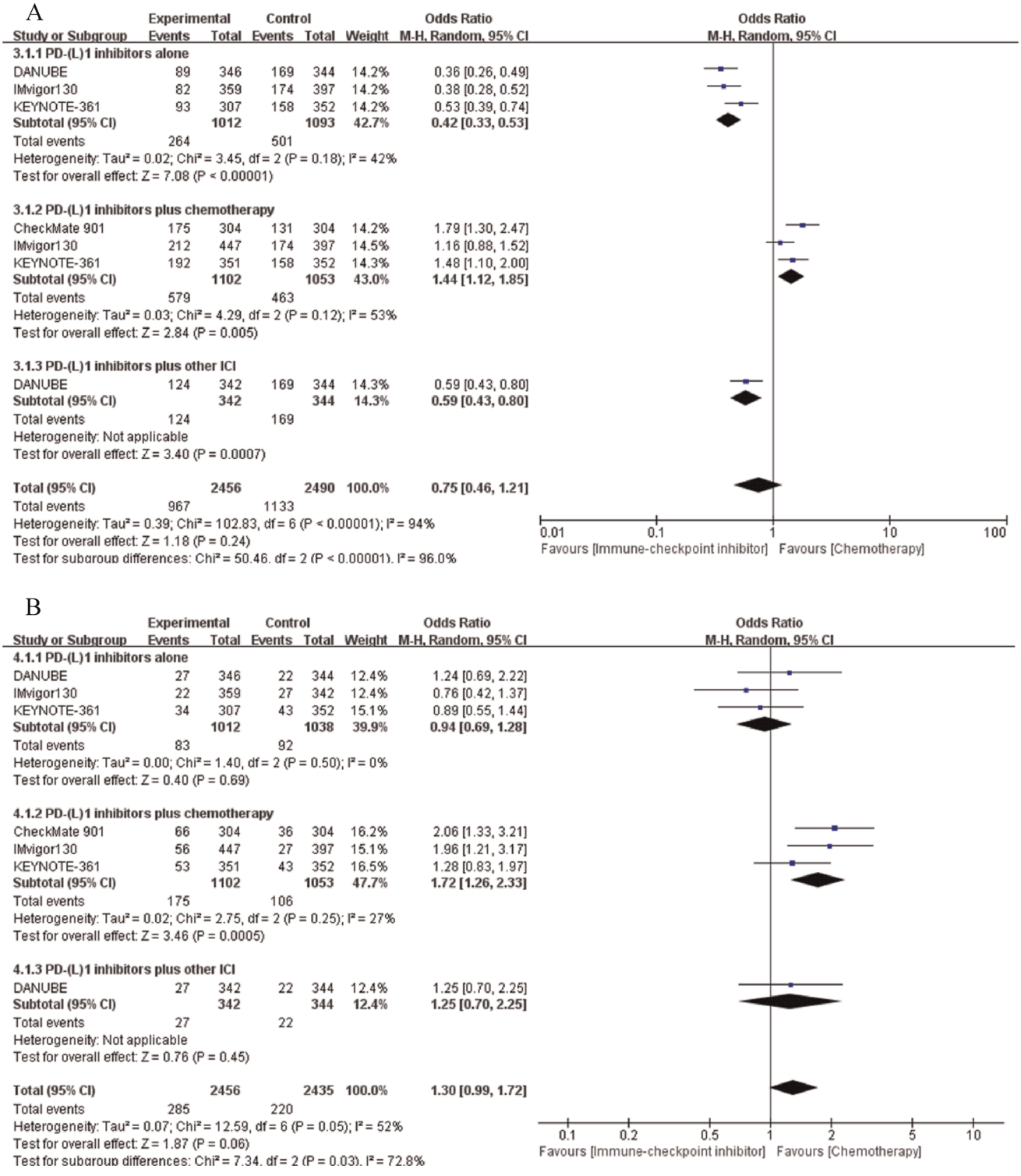

Figure 7. Forest plot of ORR and CRR. CI = confidence interval; CRR = complete response rate; ICI = immune checkpoint inhibitor; ORR = objective response rate; PD-L1 = programmed cell death-ligand 1.

inhibition of microtubule assembly.[21] Cisplatin-based combination chemotherapy has been the preferred treatment option for decades. Platinum-based combinations include gemcitabine plus cisplatin; methotrexate, vincristine, adriamycin, and cisplatin; dose-dense methotrexate, vincristine, adriamycin, and cisplatin; or paclitaxel, cisplatin, and gemcitabine. Immune checkpoint inhibitor can block the PD-1/PD-L1 signaling pathway to relieve the inhibition of T cells by tumor cells, thereby achieving tumor therapy. The programmed cell death protein 1 (PD-1) and its ligand PD-L1 signaling pathway can be targeted to release the inhibition of T-cells by tumor cells, thereby achieving the purpose of tumor treatment.[22,23] Chemotherapy has also been reported to promote antitumor immune responses by inducing the release and presentation of cancer antigens and by reducing regulatory

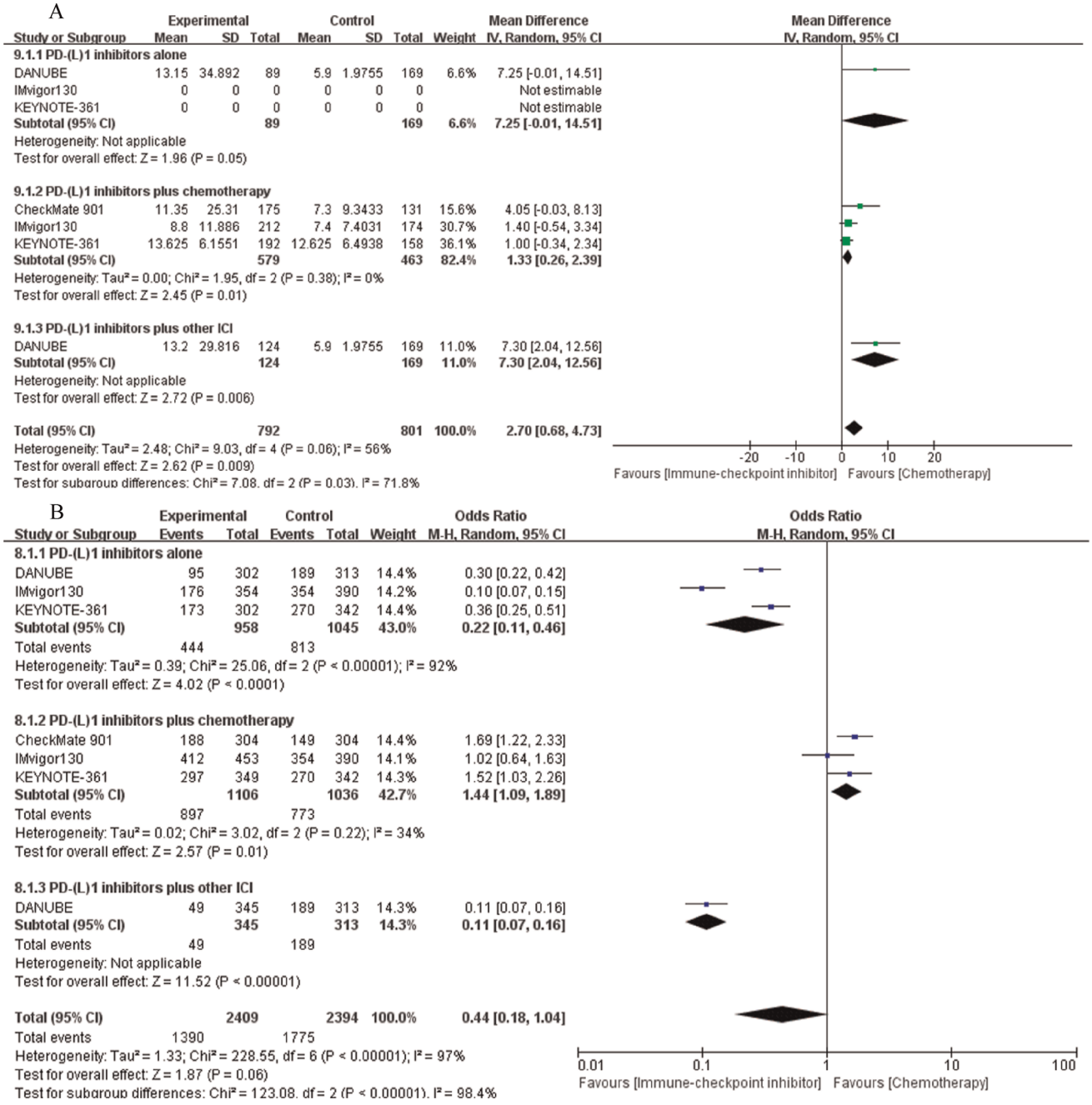

Figure 8. Forest plot of DOR and grade ≥3 AEs. AE = adverse events; CI = confidence interval; DOR = duration of response; ICI = immune checkpoint inhibitor; PD-L1 = programmed cell death-ligand 1; SD = standard deviation; .

immune cells.[24] Gemcitabine and cisplatin also reduced the proportion of regulatory immune cells in other cancer types.[25,26] These findings suggest that gemcitabine and/or cisplatin-containing regimens may reduce the proportion of myeloid-derived suppressor cells, suggesting poor prognosis, thereby promoting an antitumor immune response in UC.[27] The combination of PD-1/PD-L1 inhibitors and chemotherapy for advanced UC exploits this mechanism.

Chemotherapy for UC frequently results in severe toxicity and hematological and nonhematological side effects, even in the absence of cisplatin.[28–30] Another limitation of chemotherapy is that many patients are ineligible for cisplatin treatment based on the standard criteria for UC.[31,32] Platinum-based chemotherapy is the standard of care for locally advanced or mUC; however, there is still an unmet clinical need owing to its poor long-term efficacy. Therefore, there is a great need for more effective and less toxic treatments. Immunotherapy offers additional treatment options for these patients.

Unfortunately, first-line immunotherapy has been explored over the years, with repeated failures and no statistically significant improvement in long-term survival compared to chemotherapy alone in the DANUBE, IMvigor130, and KEYNOTE-361 clinical trials, with no statistically significant differences in outcomes.[18–20] However, PD-(L)1 inhibitors plus chemotherapy improved patients' PFS and ORR with more AEs, which suggests that the combination strategy did not yield optimal benefits. The optimal combination regimen is still undiscovered, and there is still a lot

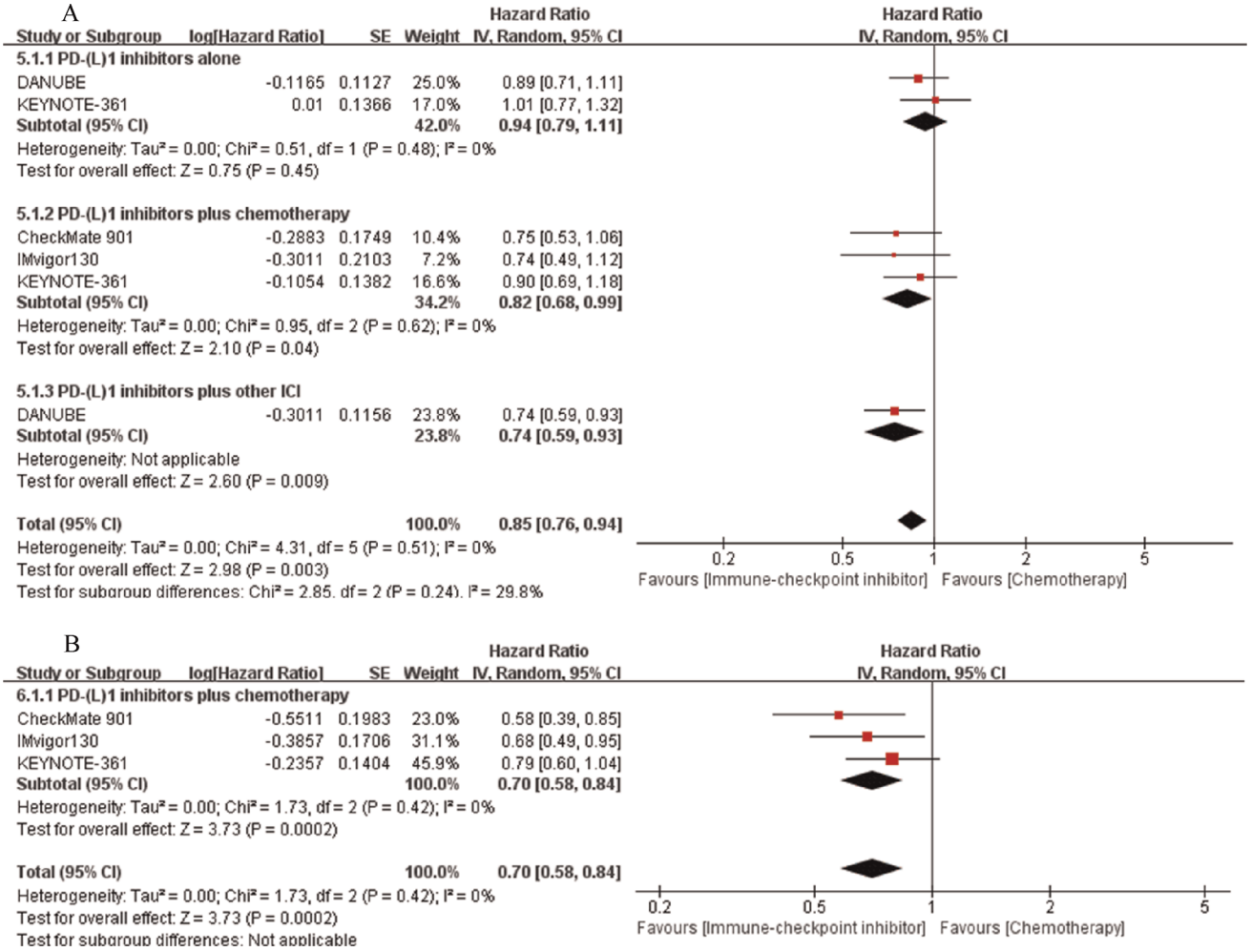

Figure 9. Forest plot of high PD-L1 status OS and PFS. CI = confidence interval; ICI = immune checkpoint inhibitor; PD-L1 = programmed cell death-ligand 1; PFS = progression-free survival; OS = overall survival.

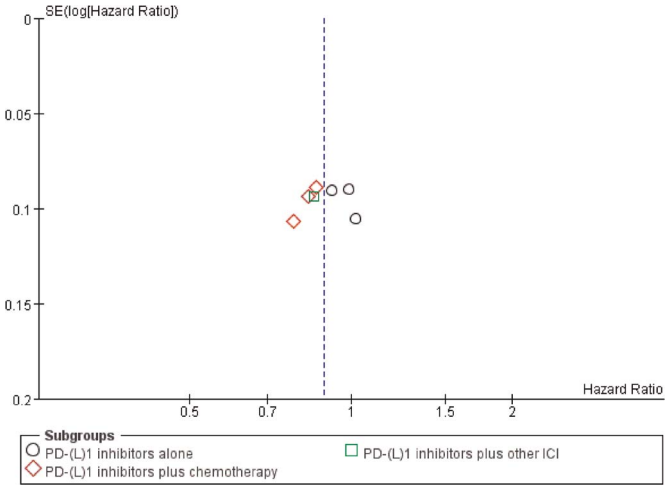

Figure 10. Funnel plot of the OS. OS = overall survival; PD-L1 = programmed cell death-ligand 1.

of potential for improvement in terms of drug dosage, order of the agents, choice of drugs, and timing of administration. The recent CheckMate-901 study evaluating nivolumab in combination with cisplatin-based chemotherapy as the first-line treatment of UC announced welcome news of a dual benefit in OS and PFS. Overall survival was longer with nivolumab combination therapy than with gemcitabine-cisplatin alone (HR for death, 0.78; 95% CI, 0.63–0.96; p = 0.02), and PFS was also longer with nivolumab combination therapy than with gemcitabine-cisplatin alone (HR for progression or death, 0.72; 95% CI, 0.59–0.88; p = 0.001). It marks the first PD-1 inhibitor to achieve full coverage of the efficacy benefits of nivolumab in adjuvant and advanced (first- and second-line) UCs.[17] The OS and PFS of nivolumab in combination with chemotherapy for the first-line treatment of UC have achieved statistical significance and far-reaching clinical significance across the board, breaking through the difficult barrier of long-term survival indices that previous immunotherapy studies have never been able to cross, and put together an important piece of the jigsaw puzzle for the comprehensive exploration of immunotherapy in the field of UC. Clinical studies combining immunosuppressive agents are also underway, but have not resulted in significant findings. A Phase III NCT02516241 clinical trial (DANUBE) evaluated the impact of mUC receiving durvalumab alone, durvalumab plus tremelimumab, and chemotherapy only on

overall patient survival. In the intention-to-treat population, the median OS was 15.1 months (13.1–18.0) in the durvalumab plus tremelimumab group versus 12.1 months (10.9–14.0) in the chemotherapy group (0.85; 95% CI, 0.72–1.02; $p = 0.075$). Immune checkpoint inhibitor alone or in combination as a first-line treatment for mUC requires further study and analysis. In addition, uncertainty remains regarding the optimal use of ICIs. For example, the optimal treatment duration for responders and the optimal duration of treatment interruption for progressors remain controversial.

Although PD-L1 predicts an improvement in the ORR to immune checkpoint blockade drugs, there are also responders in the PD-L1 low/deficient subgroup. Such responses have been reported for several immune checkpoint blockade drugs (pembrolizumab, atezolizumab, durvalumab, nivolumab, and avelumab monoclonal antibodies), highlighting the relative predictive value of PD-L1.[28–30] Overall, there is a clear rationale for exploring ICIs as a first-line maintenance therapy for UC, given the immunogenic nature of UC, antitumor activity, favorable safety profile of ICIs, and cytotoxic and immunogenic effects of chemotherapy.[33]

Antibody-drug conjugates are a class of highly effective biopharmaceutical drugs designed for treating many types of cancer. This innovative approach delivers cytotoxic molecules in a targeted manner to eliminate cancer cells while reducing off-target toxicity to healthy tissues. Two recent Food and Drug Administration–approved drugs for UCs mandate the use of vedolizumab and sacituzumab glucocorticosteroid, targeting Nectin-4 and trop-2, respectively.[34] Immune checkpoint inhibitor therapy has been widely used for the treatment of advanced UC; however, because of the complexity of the immune mechanism, it is difficult to achieve the expected effects with a single therapy. As research on tumor immunotherapy continues, an increasing number of optimal treatment protocols will be developed. With further research on genomics and related immune mechanisms and advances in immunoassay technology, the use of multiple ICI combination therapy is a developing trend. Simultaneously, the establishment of clinical prediction models and search for more accurate predictive biomarkers can more comprehensively predict ICI efficacy.

Despite the comprehensive nature of this systematic review, some limitations must be considered. First, despite the similarities in study design, line of treatment, and target disease, differences in patient characteristics at study entry between the DANUBE, IMvigor130, and KEYNOTE-361 trials should be considered. Second, we included data from studies using different ICIs at different doses, which means that we may have overlooked differences in OS and ORR outcomes between drugs. Lastly, the number of papers included in this meta-analysis was limited, some of the data from the included studies were immature, the four clinical trials used different ICIs, and different detection methods and definitions for PD-L1-positive expression may have affected the efficacy of immunotherapy. Nevertheless, this study has several strengths. First, few meta-analyses have assessed the efficacy and safety of PD-(L)1 inhibitors in the treatment of UC; this was addressed by our study. Second, Kaplan-Meier curves for OS and PFS were reconstructed using the IPDformKM software package, providing a visual impression of tumor prognosis. Specifically, we analyzed 3 regimens: PD-(L)1 inhibitor alone, PD-(L)1 inhibitor plus other ICIs, and PD-(L)1 inhibitor plus chemotherapy.

In conclusion, our analysis demonstrates the superiority of ICIs in combination with chemotherapy. However, the available data are still immature and further clinical trials are required to validate this conclusion.

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None.

Statement of ethics

This meta-analysis was performed in accordance with the 2020 standards of the Preferred Reporting Project for Systematic Review and Meta-Analyses. This study was registered with PROSPERO (registration number, CRD42024510339).

Conflict of interest statement

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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Author contributions

XH: Investigation, data curation, writing - original draft;
SH: Investigation, data curation, writing - original draft;
QJ: Conceptualization, methodology, linguistic polishing;
WL: Investigation, supervision;
CH: Writing - review and editing;
WH: Investigation, data curation.

Data availability statement

The generated/analyzed datasets used in this study can be found at figshare (https://doi.org/10.6084/m9.figshare.25283680).

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