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Efficacy of immune-checkpoint inhibitors in PD-L1 selected or unselected patients vs. control group in patients with advanced or metastatic urothelial carcinoma

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ABSTRACT

Most patients with advanced or metastatic urothelial carcinoma do not benefit significantly from Immune checkpoint inhibitors (ICIs) use. A systematic review and meta-analysis of randomized controlled trials to assess the efficacy and activity of ICIs, in terms of Overall Survival (OS), Progression-free survival (PFS), and Objective Response Rate (ORR). We systematically searched for articles from PubMed, Cochrane Library, Embase, and Web of science from their inception to December 1, 2020 with no language restrictions. The search was performed to identify all clinical trials (phase I, phase II, phase III) of ICIs for treating urothelial carcinoma. The endpoints of the meta-analysis were OS, PFS, and ORR, compared unselected patients and in the subgroup of patients characterized by high expression of PD-L1 (PD-L1 selected patients). Sixteen studies comprising 5559 patients were identified, of which data for OS comparison were available from 4 RCTs (2342 patients), two studies for PFS (649 patients), and four RCTs were eligible for ORR analysis (2921 patients). Both pembrolizumab and atezolizumab have showed to improve OS compared to chemotherapy in unselected patients (HR 0.86, 95% CI 0.80–0.93, $P = .0001$, $I^2 = 60\%$), while the difference was not significant in PD-L1 selected patients (HR 0.91, 95% CI 0.77–1.07, $P = .23$, $I^2 = 0\%$). PFS difference was not observed in neither unselected population nor PD-L1 selected patients, the pooled HR of PFS for immunotherapy compared to control treatment was 1.05 (95% CI 0.74–1.49, $P = .79$, $I^2 = 85\%$) and 0.84 (95% CI 0.68–1.03, $P = .09$, $I^2 = 0\%$, respectively. Similar result was observed in ORR, the pooled HR of ORR for immunotherapy compared to control treatment was 1.45 (95% CI 0.53–3.98, $P = .47$, $I^2 = 95\%$) and 2.19 (95% CI 0.79–6.08, $P = .13$, $I^2 = 83\%$), respectively. Immunotherapy could significantly improve survival advantage in unselected patients but not in PD-L1 selected population, indicating that PD-L1 expression may not be a reliable marker in previously platinum-treated patients.

Introduction

Urothelial carcinoma (UC), also named transitional cell carcinoma, which accounts for 2% of all cancer-related deaths, is the third most prevalent malignancy in adults.[1] Advanced UC including locally advanced or metastatic tumors has a poor prognosis, with few patients surviving more than 5 years after diagnosis.[2,3] The treatment for advanced urothelial carcinoma is one of the difficulties in oncotherapy and an open challenge for clinicians and researchers.

Systemic cisplatin-based combinations, including dose-dense regimens, remain the standard of care for untreated patients with metastatic or inoperable UC and are associated with an OS of about 14 months and around 40% of the patients achieving an objective response.[4,5] Unfortunately, a not negligible percentage of patients (up to 30%) with metastatic UC are unfit to receive standard cisplatin-based therapy due to renal impairment, poor performance status or/and other comorbidities, leading to a further deterioration of the prognosis.[4,5] Recently, vinflunine has been approved as second-line treatment in Europe, and patients with the recurrent or resistant disease may be allowed to receive single-agent chemotherapy (pemetrexed, gemcitabine, paclitaxel, docetaxel) and combination chemotherapy in America.[6,7] However, median overall survival with second-line chemotherapy only ranges from 5 to 7 months, and with less than 10% of the patients achieving an OS.[6–9] Above mentioned results suggesting that alternative treatment options are urgently needed for patients who have failed in standard platinum-based regimens.

Antibodies targeting programmed death receptor 1 (PD-1), programmed death receptor ligand-1 (PD-L1), or cytotoxic T-lymphocyte associated protein 4 (CTLA- 4) can boost T-cell-mediated anti-tumor immunity by blocking inhibitory signals trigged by immune checkpoint proteins.[10–12] In the past few years, ICIs, a new class of drugs, have changed the treatment of metastatic UC with an interesting results.[11–14] Both anti-PD-L1 and anti-PD-1 antibodies have been approved by FDA and are associated with anti-tumor responses in patients with metastatic

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UC, exhibiting the therapeutic potential of ICIs.[13,14] Recently, Bellmunt *et al.* reported that pembrolizumab was associated with a significant improvement of median overall survival as compared with chemotherapy group in both total population and PD-L1 positive group, with a pooled hazard ratio (HR) equal to 0.73 (95% confidence interval (CI), 0.59 to 0.91; $P = .002$) and 0.57 (95% CI, 0.37 to 0.88; $P = .005$), respectively.[12] While the trial testing for Atezolizumab was formally negative.[11] Moreover, all ICIs tested have evaluated companion diagnostics focusing on PD-L1 expression, whether PD-L1 can be used as a predictive and reliable biomarker is still controversial.

Despite these conflicting outcomes, immunotherapy represents a new promising approach for the treatment of patients with advanced or metastatic UC. Within this scenario, a systematic review and meta-analysis were conducted to systematically assess the efficacy of ICIs in PD-L1 selected or unselected population vs control group in patients with metastatic UC. Besides, whether the PD-L1 molecule can be used as a reliable biomarker were also evaluated. Hope this analysis could improve our understanding of ICIs treatment, and thus providing evidence-based support to help the oncologists with their clinical decisions.

Methods

Search strategy

We systematically searched for articles from PubMed, Cochrane Library, Embase, and Web of science from their inception to December 1, 2020, with no language restrictions. References of the retrieved articles were also searched for additional studies. The search was performed to identify all clinical trials (phase I, phase II, phase III) of ICIs for treating urothelial carcinoma. The search terms '(Urothelial carcinoma OR Urothelial cancer OR transitional cell carcinoma OR bladder cancer) AND (PD-1 inhibitor OR PD-L1 inhibitor OR Atezolizumab OR Avelumab OR Durvalumab OR Nivolumab OR Pembrolizumab)' were used to find relevant studies.

Study eligibility

Inclusion criteria: (1) a PD-1 or PD-L1 checkpoint inhibitor was administered for patients with urothelial carcinomas. (2) reported PD-L1 expression status, (3) all studies were clinical trials, including single-arm or randomized control trials (RCTs), (4) the studies should report the OS, PFS or ORR data, and (5) published in English. Exclusion criteria were studies reporting insufficient data. When more than one publication reporting on the same study population, the studies with the most updated and/or comprehensive data were included.

Data extraction

The information extraction and assessment were performed independently by two different investigators and the disagreements were solved through consensus or by a discussion with a third author. The following information was extracted for each study: (a) first author and publication year; (b) study phase, treatment strategies, a number of patients received treatment, age of patients, and follow-up duration; (c) PD-L1 assay and PD-L1 cutoff used to define positive status; (d) OS, PFS and ORR outcomes, in the intention-to-treat population and in the subgroup of cases selected for high PD-L1 expression.

Quality assessment

Two independent reviewers evaluated methodological quality. A third review author resolved disagreement through discussion and consensus. RCTs were appraised for methodological quality using the criteria developed by the Cochrane risk of bias tool, which includes random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other bias.[15]

Statistical analysis

The endpoints of the meta-analysis were OS, PFS, and ORR. To assess randomized trials comparing an immune-checkpoint inhibitor vs. control in patients with advanced urothelial carcinoma in terms of OS, PFS, and ORR, a meta-analysis of randomized trials was analyzed using Review Manager for Windows (RevMan5.3). The summary measure was hazard ratio with 95% confidence interval for OS and PFS, and odds ratio, with 95% confidence interval for ORR. All statistical tests were two sided, and P values $\leq$ 0.05 were considered significant. Statistical heterogeneity was assessed using the Q statistic and the I^2 method. Mantel-Haenszel fixed effects model was used when there was no significant heterogeneity between studies; otherwise, a random effects model was chosen.

To evaluate the influence of single-agent immune-checkpoint inhibitors in terms of ORR in both randomized and nonrandomized trials, the rate and the 95% confidence interval were calculated for the overall case series.[16]

Evidence synthesis

Study selection and trial characteristics

The whole literature search process was summarized in Figure 1. Overall, a total of 5559 patients from 16 studies were included in the meta-analysis.[11–14,17–28] Follow-up duration ranged from 4.3 to 37.8 months. Eleven out of 15 studies were single-arm trials, and five studies were randomized trials with the standard of the care control arm. The characteristics of the included studies are presented in Table 1. The outcomes, PD-L1 assays, and PD-L1 cutoff of the included studies are presented in Table 2.

Study quality assessment

The risk of bias of the included RCTs was evaluated and was summarized in Appendix 1. Generally, a low risk of bias was identified, meeting the general requirement for meta-analysis.
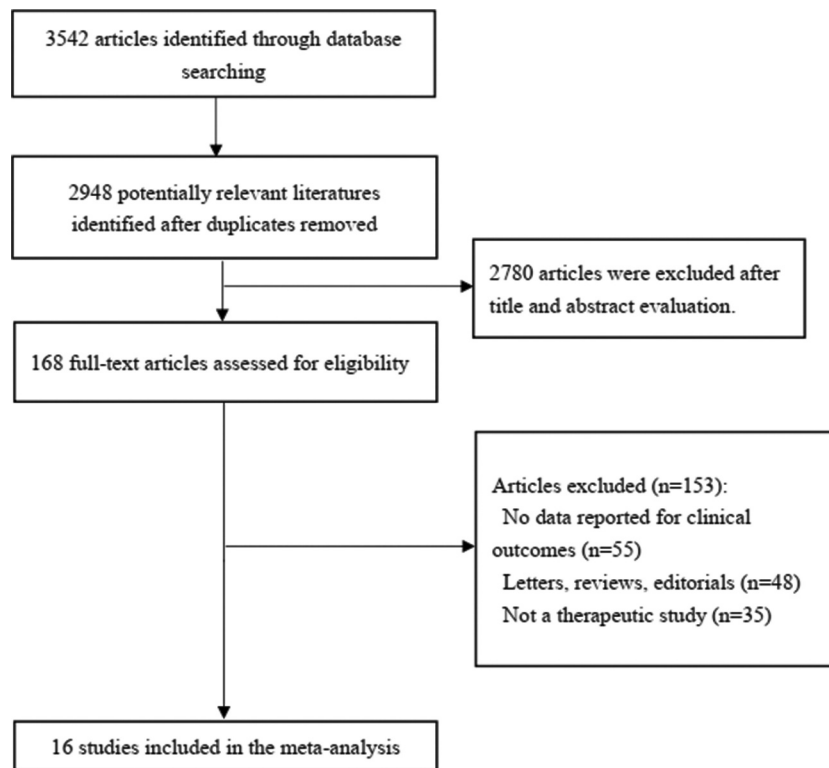
Figure 1. The search startegy of the meta-analysis.

Overall survival

Data for OS comparison were available from four RCTs, for a total of 2342 randomized patients. The outcome occurred in 1154 patients (49.27%) in the ICIs group and 1188 patients (50.73%) in the control group. In the intention-to-treat patients, without any selection for PD-L1 status (unselected), both drugs were associated with a significant improvement of OS, with a pooled hazard ratio equal to 0.86 (95% confidence interval 0.80 to 0.93, $P = .0001$, $I^2 = 60\%$; Figure 2).

On the contrary, in the "selected" subgroup of patients characterized by high expression of PD-L1 (10% cutoff with pembrolizumab and IC2/3 with atezolizumab), the pooled result was not statistically significant (HR 0.91, 95%, CI 0.77 to 1.07, $P = .23$, $I^2 = 0\%$; Figure 3). In summary, the two drugs produced similar results in the "supposed" selected patients, but different results in the whole population: pembrolizumab produced a statistically significant result (HR 0.77, 95% CI 0.68 to 0.87, $p < .0001$, $I^2 = 0\%$), while atezolizumab was associated with a non-significant result (HR 0.92, 95% CI 0.83 to 1.01, $P = .09$, $I^2 = 42\%$).

Progression-free survival

Data for PFS comparison were available from 2 RCTs, for a total of 649 randomized patients. In the intention-to-treat population, the pooled hazard ratio of PFS for immunotherapy compared to control treatment was 1.05 (95% CI 0.74 to 1.49, $P = .79$, $I^2 = 85\%$; Figure 4).

Even in the "selected" subgroup of patients characterized by high expression of PD-L1, the pooled result was not statistically

significant (HR 0.84, 95% CI 0.68 to 1.03, $P = .09$, $I^2 = 0\%$; Figure 5).

Objective response rate

Data for ORR comparison were available from four RCTs (2921 patients). In the intention-to-treat patients, the pooled odds ratio of ORR for immunotherapy compared to control treatment was 1.45 (95% CI 0.53–3.98, $P = .47$, $I^2 = 95\%$; Figure 6). Pembrolizumab and avelumab were associated with a statistically significant higher in ORR compared to control (odds ratio (OR) 2.08, 95% CI 1.29 to 3.34, $P = .002$ and OR 7.42, 95% CI 2.87 to 19.22, $P < .0001$), while atezolizumab was not (OR 0.61, 95% CI 0.24 to 1.58, $P = .31$).

Even in the "selected" subgroup of patients characterized by high expression of PD-L1, the pooled result was not statistically significant (OR 2.19, 95% CI 0.79 to 6.08, $P = .13$, $I^2 = 83\%$; Figure 7). Pembrolizumab and avelumab were associated with a statistically significant improvement in ORR compared to control (OR 3.86, 95% CI 1.43 to 10.46, $P = .008$ and OR 13.32, 95% CI 3.11 to 57.03, $P = .0005$), while atezolizumab was not (OR 0.93, 95% CI 0.60 to 1.44, $P = .74$).

Considering both randomized and non-randomized trials, information about ORR was available from 16 trials (3324 patients) (Table 2). In this group, patients obtaining partial or complete response were 591, with a pooled probability of ORR equal to 19.64% (95% CI 0.18 to 0.21). In the subgroup of 1009 patients selected, within each trial, for the highest expression of PD-L1 (with different definition and cutoff in each trial), patients obtaining partial or complete response were 273, with a pooled probability of ORR equal to 30.12% (95% CI 0.27 to 0.33).

Table 1. Main characteristics of the included studies.

Author, year, reference	Study phase	NCT number	Study design	Line of therapy	PD-1/PD-L1 inhibitor	Dose/duration	Patients received treatment (N)	Age (years)[median (range)]	Male, %	Follow-up period (months) (median)
Massard, 2016	Phase I/II	NCT01693562	Expansion cohort study	First-line	Durvalumab	10 mg/kg every 2 weeks	61	66 (34–81)	42, 68.9%	4.3
Powles, 2017	Phase I/II	NCT01693562	Basket trial	Previously treated	Durvalumab	10 mg/kg every 2 weeks	191	67 (34–88)	136, 71.2%	5.78
Powles, 2018	Phase III	NCT02302807	Randomized control trial	Previously treated	Atezolizumab	1200 mg every 3 weeks	931 (467 Atezolizumab)	67 (33–88)	718, 77.1%	17.3
Patel, 2018	Phase I	NCT01772004	Pooled analysis of two expansion cohorts	Previously treated	Avelumab	10 mg/kg every 2 weeks	249	68 (63–76)	178, 72%	9.9
Sharma, 2017	Phase II	NCT02387996	Single-arm trial	Previously treated	Nivolumab	3 mg/kg every 2 weeks	270	66 (38–90)	211, 78%	7
Plimack, 2017	Phase Ib	NCT01848834	Basket trial	First-line	Pembrolizumab	10 mg/kg every 2 weeks	33	70 (44–85)	23, 70%	13
Bellmunt, 2017	Phase III	NCT02256436	Randomized control trial	Previously treated	Pembrolizumab	200 mg every 3 weeks	542 (270 Pembrolizumab)	67 (29–88)	402, 74.2%	13.1
Balar, 2017	Phase II	NCT02335424	Single-arm trial	First-line	Pembrolizumab	200 mg every 3 weeks	370	74 (34–94)	286, 77%	5
Balar, 2017	Phase II	NCT02108652	Single-arm trial	First-line	Atezolizumab	1200 mg every 3 weeks	119	73 (51–92)	96, 81%	17.2
Apolo, 2017	Phase Ib	NCT01772004	Expansion cohort study	Previously treated	Avelumab	10 mg/kg every 2 weeks	44	68 (63–73)	30, 68.2%	16.5
Sharma, 2016	Phase I/II	NCT01928394	Multi-arm trial	Previously treated	Nivolumab	3 mg/kg every 2 weeks	78	66 (31–85)	54, 69%	15.2
Rosenberg, 2016	Phase II	NCT02108652	Single-arm trial	Previously treated	Atezolizumab	1200 mg every 3 weeks	310	66 (32–91)	241, 78%	11.7
Petrylak, 2018	Phase I	NCT01375842	Single-arm trial	Previously treated	Atezolizumab	15 mg/kg or 1200 mg every 3 weeks	95	66 (36–89)	72, 76%	37.8
Galsky, 2020	Phase III	NCT02807636	Randomized control trial	First-line	Atezolizumab	1200 mg every 3 weeks	762 (362 Atezolizumab)	67 (61–74)	578, 75.9%	11.8
Galsky, 2019	Phase II	NCT02500121	Randomized control trial	Previously treated	Pembrolizumab	200 mg every 3 weeks	107 (55 Pembrolizumab)	67 (41–87)	81, 75.7%	12.9

Table 2. Study outcomes, PD-L1 assays and PD-L1 cutoff.

Author, year, reference	Unselected patients			Patients selected for highest PD-L1 expression			Evaluation of PD-L1	PD-L1 cutoff
	Objective response rate (ORR) [n/N, %]	Progression-free survival (PFS) [month (95%CI)]	Overall survival (OS) [month (95%CI)]	Objective response rate (ORR) [n/N, %]	Progression-free survival (PFS) [month (95%CI)]	Overall survival (OS) [month (95%CI)]		
Massard, 2016	13/42, 31%	NR	NR	13/28, 46.4%	NR	NR	Ventana SP263assay	Positive (TC or IC > 25%), Negative (both TC and IC < 25%)
Powles, 2017	34/191, 17.8%	1.5 (1.4–1.9)	18.2 (8.1-NR)	27/98, 27.6%	2.1 (1.4–2.8)	20.0 (11.6-NR)	Ventana SP263assay	High (≥ 25% TC or IC), Low (< 25% of both TC and IC)
Powles, 2018	62/462, 13.4% [control: 62/461, 13.4%]	2.1 (2.1–2.2)[control: 4.0 (3.4–4.2)]	8.6 (7.8–9.6)[control: 8.0 (7.2–8.6)]	26/113, 23%[control: 25/116, 21.6%]	2.4 (2.1–4.2)[control: 4.2 (3.7–5.0)]	11.1 (8.6–15.5) [control: 10.6 (8.4–12.2)]	Ventana SP142assay	IC0 (< 1%), IC1 (≥1% to < 5%), IC2/3 (≥5%)
Patel, 2017	27/161, 17.0%	6.3 (6.0–10.1)	6.5 (4.8–9.5)	15/63, 24.0%	11.9 (6.1–18.0)	8.2 (5.7–13.7)	PD-L1 IHC 73–10 pharmDx assay	Positive (TC ≥5%), Negative (TC < 5%)
Sharma, 2017	52/265, 19.6%	2.00 (1.87–2.63)	8.74 (6.05-NR)	23/81, 28.4%	NR	11.30 (8.74-NR)	Dako PD-L1 IHC28–8 pharmDx kit	Positive (TC ≥1% or 5%), Negative (TC < 1% or 5%)
Plimack, 2017	7/27, 26%	2 (2–4)	13 (5–12)	2/14, 14%	NR	NR	PD-L1 IHC 22C3pharmDx assay	Positive (≥1%), Negative (< 1%)
Bellmunt, 2017	57/270, 21.1% [control: 31/272, 11.4%]	2.1 (2.0–2.2) [control: 3.3 (2.3–3.5)]	10.3 (8.0–11.8)[control: 7.4 (6.1–8.3)]	16/74, 21.6%[control: 6/90, 6.7%]	NR	8.0 (5.0–12.3)[control: 5.2 (4.0–7.4)]	PD-L1 IHC 22C3pharmDx assay	Positive: CPS≥ 10%
Balar, 2017	89/370, 24%	2 (2–3)	NR	31/80, 39%	NR	NR	PD-L1 IHC 22C3pharmDx assay	Positive: CPS≥10%
Balar, 2017	27/119, 23%	2.7 (2.1–4.2)	15.9 (10.4-NE)	9/32, 28%	4.1 (2.3–11.8)	12.3 (6.0-NE)	Ventana SP142assay	IC0 (< 1%), IC1 (≥1% to < 5%), IC2/3 (≥5%)
Apolo, 2017	8/44, 18.2%	11.6 weeks (6.1–17.4)	13.7 (8.5-NE)	7/13, 53.8%	48.1 weeks (11.1-NE)	NE (8.5-NE)	PD-L1 IHC 73–10pharmDx assay	Positive (TC ≥5%), Negative (TC < 5%)
Sharma, 2016	19/78, 24.4%	2.8 (1.5–5.9)	9.7 (7.3–16.2)	6/25, 24.0%	5.5 (1.4–11.2)	16.2 (7.6-NE)	Dako PD-L1 IHC28–8 pharmDx kit	Positive (TC ≥1% or 5%), Negative (TC < 1% or 5%)
Rosenberg, 2016	45/310, 15%	2.1 (2.1–2.1)	7.9 (6.6–9.3)	26/100, 26%	2.1 (2.1–4.1)	11.4 (9.0-NE)	Ventana SP142assay	IC0 (< 1%), IC1 (≥1% to < 5%), IC2/3 (≥5%)
Petrylak, 2018	25/95, 26%	2.7 (1.4–4.3)	10.1 (7.3–17.0)	20/50, 40%	5.5 (2.7–10.8)	14.6 (9.0-NE)	Ventana SP142assay	IC0 (< 1%), IC1 (≥1% to < 5%), IC2/3 (≥5%)
Galsky, 2020	82/359, 23%[control: 174/397, 44%]	NR	15.7 (13.1–17.8) [control: 13.1 (11.7–15.1)]	34/88, 39%[control: 37/84, 44%]	NR	NE (17.7-NE)[control: 17.8 (10.0-NE)]	Ventana SP142assay	IC0 (< 1%), IC1 (≥1% to < 5%), IC2/3 (≥5%)
Galsky, 2019	10/43, 23%[control: 4/42, 10%]	5.4 (3.1–7.3)[control: 3.0 (2.7–5.5)]	22 (12.9-NR) [control:18.7 (11.4-NR)]	NR	NR	NR	PD-L1 IHC 22C3pharmDx assay	High: CPS≥ 10%
Powles, 2020	34/350, 9.7% [control: 5/350, 1.4%]	3.7 (3.5–5.5) [control: 2 (1.9–2.7)]	21.4 (18.9–26.1)[control:14.3 (12.9–17.9)]	26/189, 13.8% [control: 2/169, 1.2%]	5.7 (3.7–7.4) [control: 2.1 (1.9–3.5)]	NE (20.3-NE) [control: 17.1 (13.5–23.7)]	Ventana SP263assay	Positive (TC or IC > 25%), Negative (both TC and IC < 25%)

Abbreviations: ORR: objective response rate; PFS: progression-free survival; CI: confidence interval; OS: overall survival; NR: not reported; NE: not estimable; TC: tumor cell; IC: immune cell; CPS: combined positive score.
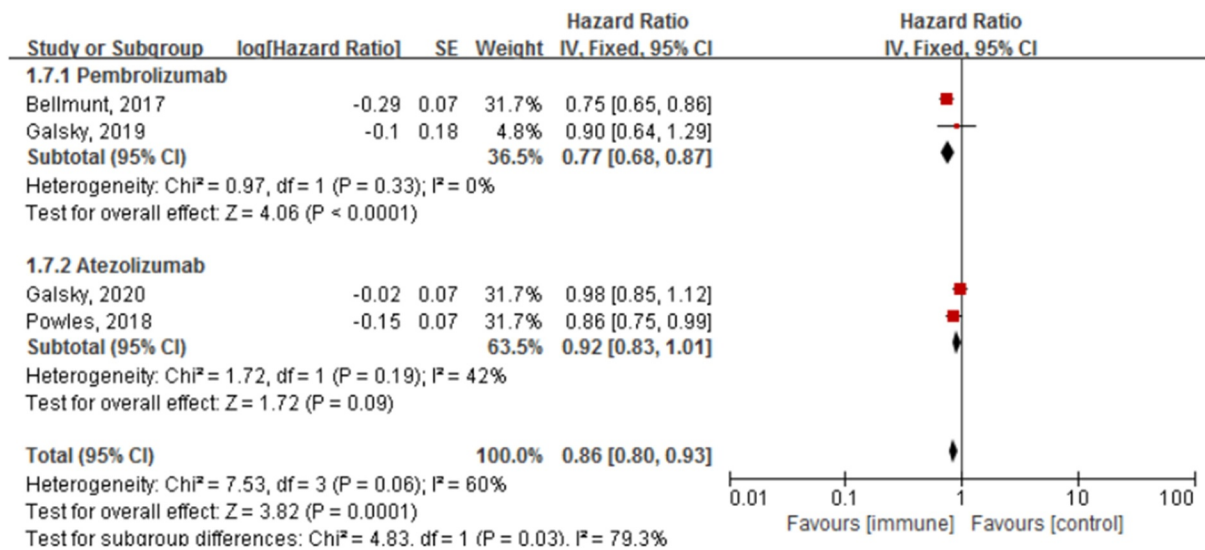
Figure 2. Forest plots of overall survival in intention-to-treat population in randomized clinical trials comparing immune checkpoint inhibitors vs. chemotherapy.
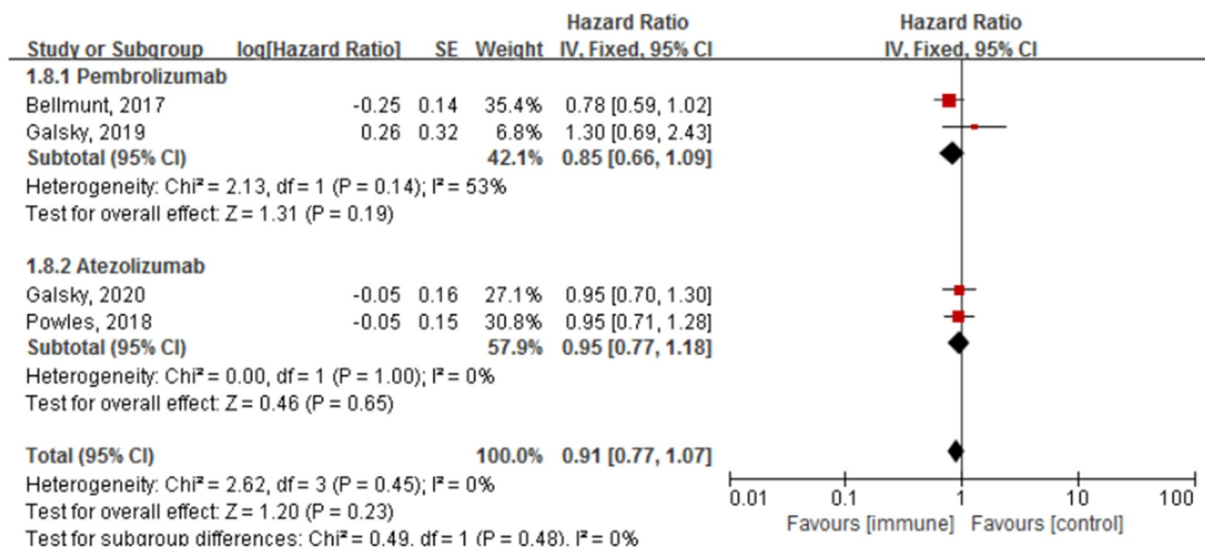

Figure 3. Forest plots of overall survival in highly PD-L1 selected population in randomized clinical trials comparing immune checkpoint inhibitors vs. chemotherapy.
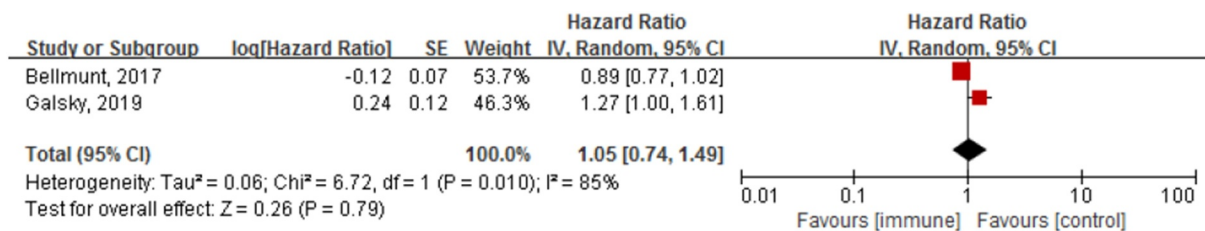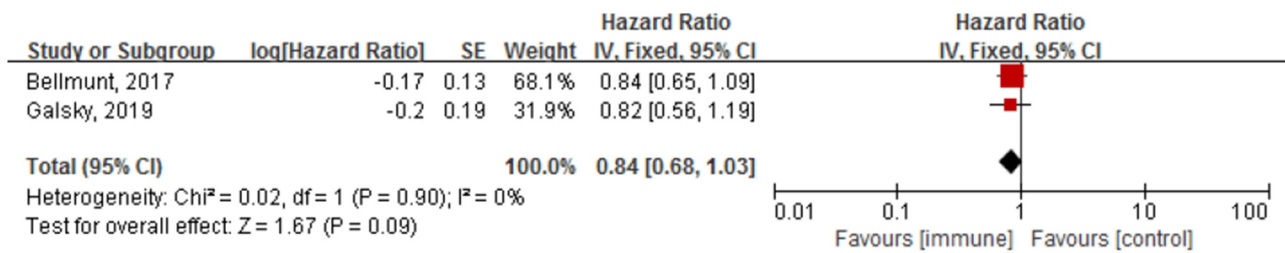

Figure 4. Forest plots of progression free survival in intention-to-treat population in randomized clinical trials comparing immune checkpoint inhibitors vs. chemotherapy.

Discussion

Patients with advanced or metastatic UC have few treatment choices and low survival rates, particularly after standard platinum-based regimens. ICIs provided an immense breakthrough for the treatment of metastatic UC. In this meta-analysis, the outcomes of 4859 patients with advanced or metastatic UC from 15 well-organized phase I/II/III clinical trials were identified to explore the efficacy of ICIs in PD-L1 selected or unselected population vs control group on OS, ORR, and PFS.

The study for the first time demonstrated that pembrolizumab and atezolizumab improve OS compared to control group

Figure 5. Forest plots of progression free survival in highly PD-L1 selected population in randomized clinical trials comparing immune checkpoint inhibitors vs. chemotherapy.
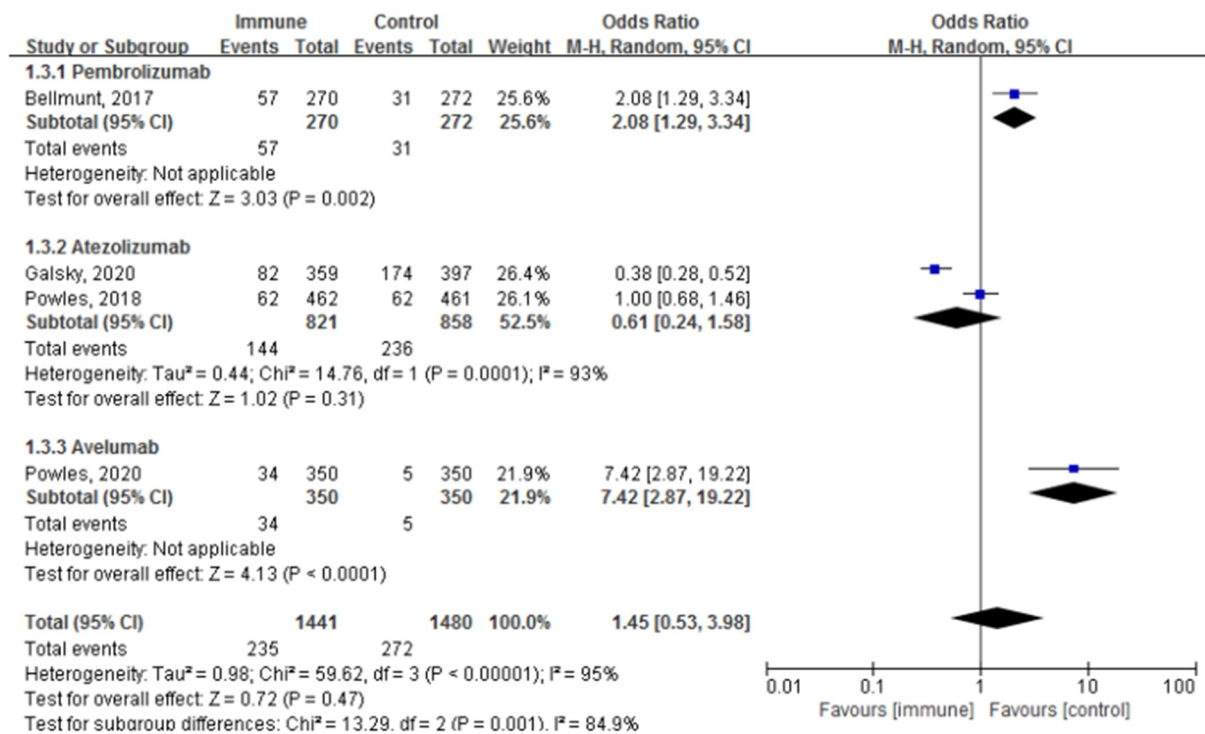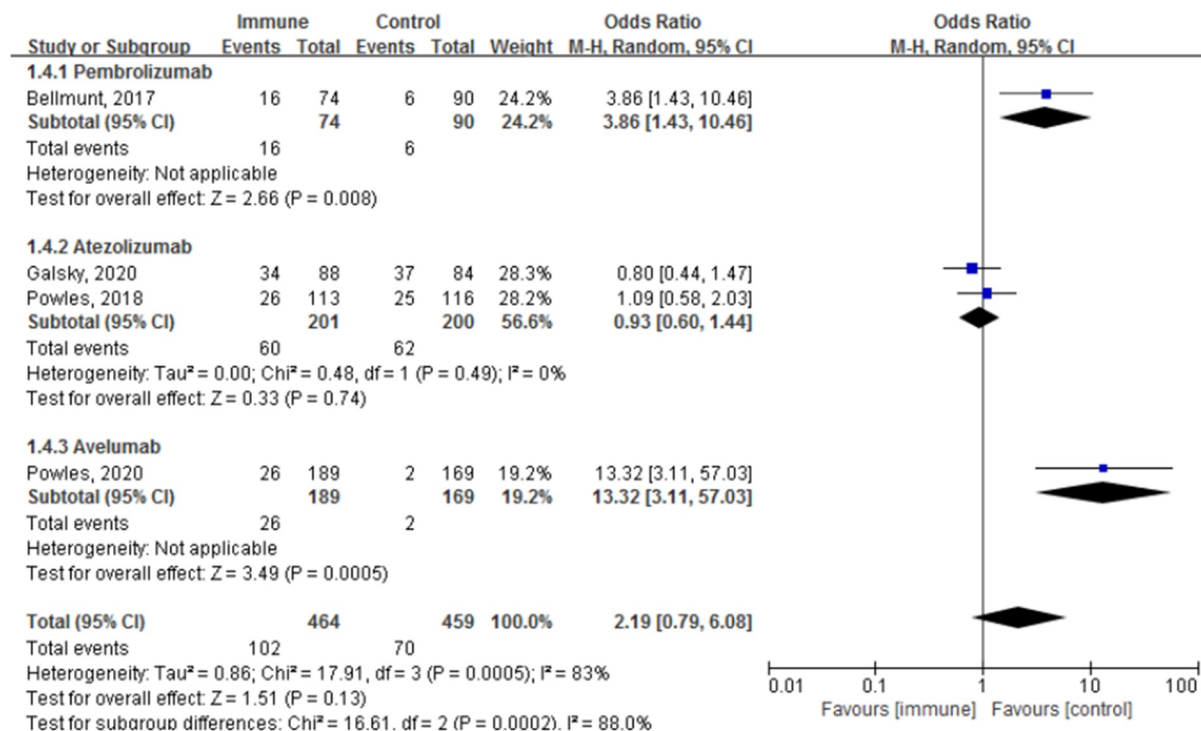

Figure 6. Forest plots of objective responsive rate in intention-to-treat population in randomized clinical trials comparing immune checkpoint inhibitors vs. chemotherapy.

in unselected population ($P = .0001$), while the difference was not observed in selected group ($P = .23$); Notably, PFS and ORR differences were not observed in neither unselected group ($P = .79$ and $P = .85$) nor PD-L1 highly expressed group ($P = .09$ and $P = .44$) for immunotherapy compared to control group. Above mentioned results suggest that ICIs could significantly improve OS compared to control treatment, but not PFS and ORR, in unselected patients, while the positive result was not observed in PD-L1 selected patients, suggesting that PD-L1 expression may not be a reliable marker for OS, ORR, and PFS in metastatic UC immunotherapy.

Regarding to the OS comparison, four RCTs including 2342 randomized patients were enrolled. Both pembrolizumab and atezolizumab could significantly improve OS compared to control group in unselected patient (HR 0.86, 95% CI 0.80––0.93, $P = .0001$). This finding seems to confirm that immunotherapy represents an active treatment in patients with metastatic UC, resulting in an OS improvement over the control group. Of note, only pembrolizumab, not atezolizumab, was associated to OS improvement when analyzed separately,

with a pooled HR equal to 0.77 ($p < .0001$ and 0.92 ($P = .09$), respectively. However, in PD-L1 highly expressed group (10% cutoff with pembrolizumab and IC2/3 with atezolizumab), OS did not differ significantly between patients in the immunotherapy group and those in the chemotherapy group, with a pooled HR equal to 0.91 ($P = .23$, I2 = 0%; Figure 3), indicating that PD-L1 expression may not be a reliable marker to predict OS. Similarly, a systematic review conducted by Nunno et al (2 RCTs, 1473 randomized patients) concluded that both drugs were associated with a non-significant result in the PD-L1 highly expressed group ($p = .12$).[29] It is noteworthy that in selected patients when analyzed separately, pembrolizumab produced a statistically significant result (HR 0.57, 95% CI 0.37–0.88),[29] However, this phenomenon was not observed in our study.

In our study, two RCTs involved 649 randomized patients were enrolled for PFS comparison. There was no significant between-group difference (immunotherapy compared to chemotherapy or placebo) in the duration of PFS in the total population ($P = .79$) or among patients who had a tumor PD-

Figure 7. Forest plots of objective responsive rate in highly PD-L1 selected population in randomized clinical trials comparing immune checkpoint inhibitors vs. chemotherapy.

L1 combined positive score of 10% or more (P = .09). Indeed, an open-label, international, phase 3 trial conducted by KEYNOTE-045 Investigators demonstrated that there was no significant difference in the duration of PSF between the pembrolizumab group and the chemotherapy group in neither unselected nor selected group.[12]

About the ORR comparison, performed on three available RCTs, for a total of 2221 patients. ORR was not observed in neither unselected group nor the highly PD-L1 expression group, the pooled HR of ORR for immunotherapy compared to control treatment was 1.05 (P = .79) and HR 0.84 (P = .09), respectively. In subgroup analysis, pembrolizumab was associated with a statistically significant improvement in ORR compared to the control group, while atezolizumab was not in neither unselected (P = .002 for pembrolizumab and P = .31 for atezolizumab) nor selected group (P = .008 for pembrolizumab and P = .74 for atezolizumab), suggesting that pembrolizumab led to better clinical outcomes of ORR over control group as compared to other ICIs. Based on our pooled results in ORR analysis, PD-L1 expression does not seem an optimal predictive marker for ORR.

PD-L1 staining assays were summarized in Table 2. Among them, five distinct assays for PD-L1 IHC scoring were applied, including Ventana SP263 assay, Ventana SP142 assay, Dako PD-L1 IHC 73–10 kit, Dako PD-L1 IHC 28–8 pharmDx kit, and PD-L1 IHC 22C3 pharm Dx assay. The clinical trials conducted by different groups tended to use different approaches for PD-L1 staining assay. Based on different PD-L1 staining assays, the definitions of PD-L1 positivity cutoffs are varied, clinical trials with pembrolizumab used PD-L1 tumor and infiltrating immune cells expression (Positive: score≥ 10%),[12] atezolizumab evaluated PD-L1 expression on infiltrating immune cells (Positive score≥

5%),[11] while CheckMate 275 trials with nivolumab apply only Tumor cell PD-L1 membrane expression (Positive: score ≥ 5%).[20] Different PD-L1 staining assays and definitions of PD-L1 positivity cutoffs maybe the limitations and difficulties to use PD-L1 as a predictive marker for OS, ORR, and PFS in metastatic UC. Considering the dynamic nature of the immune system, there will be a challenge to the development of predictive biomarkers over and together with PD-L1 assessment. In addition, PD-L1 status especially between primary tumors and visceral/liver metastases differed greatly, [30] and the analyzed clinical trials mostly used archival FFPE samples of often years old tumors for PD-L1 assessment instead of freshly obtained tumor biopsies. The reasons mentioned above may partially explain why PD-L1 might not be sufficient for predicting response to therapy.

Critically, several limitations exist in our meta-analysis. First, since the enrolled trials had various definitions of PD-L1 expression level on the basis of different assays and PD-L1 immunohistochemistry scoring with diverse staining cutoffs, which might influence the inclusion of patient populations and limit the interpretation of pooled estimation (Table 2). Second, we pooled data from studies that used different ICIs at variable doses so we may have missed differences in OS and ORR outcomes across drugs or based on dosage differences. Given the wide variation in drug and dose across studies, we performed subgroup analyses to examine these factors. Third, although several included studies were different treatment strategies and inconsistent lengths of follow up, all RCTs were confirmed to be a low risk of bias after the quality assessment. Therefore, the pooled results of the meta-analysis should be reliable. Despite several above-mentioned shortcomings, our analysis still proposed a credible suggestion that immunotherapy was associated with a significant improvement of OS in unselected patients,

whereas not in patients selected for PD-L1 highly expression, suggesting that PD-L1 expression may not be a reliable marker for ICIs therapy in metastatic urothelial carcinoma.

Conclusions

Here, a systematic review and meta-analysis were performed to explore the efficacy of immunotherapy in patients with advanced/metastatic UC based on PD-L1 unselected or selected group. Our results demonstrated both PD-1 and PD-L1 targeting ICIs could significantly improve OS compared to the control group in an unselected population. Based on the poor predictive value of PD-L1 expression in enrolled clinical trials, further efforts should be spent on the research of other reliable markers. A better biomarker for patient selection is essential before biomarkers can be used to stratify candidates for immunotherapy.

Disclosure statement

No potential conflicts of interest were disclosed.

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Appendix 1. The risk of bias of the included randomized control trials.