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Programmed Death 1 and Programmed Death Ligand 1 Inhibitors in Advanced and Recurrent Urothelial Carcinoma: Meta-analysis of Single-Agent Studies

Alessandro Tafuri[1,4], **David D. Smith**[5], **Giovanni E. Cacciamani**[1], **Sarah Cole**[2], **Aliasger Shakir**[1], **Sarmad Sadeghi**[2], **Nicholas J. Vogelzang**[6], **David Quinn**[2], **Parkash S. Gill**[3], **Inderbir S. Gill**[1]

[1]USC Institute of Urology and Catherine & Joseph Aresty Department of Urology

[2]Department of Medicine, Division of Oncology

[3]Department of Medicine, Pathology and Urology, University of Southern California, Keck School of Medicine, Los Angeles, CA

[4]Department of Urology, University of Verona, Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy

[5]Biostatistics Division, Mercy Lab Foundation, Irvine, CA

[6]US Oncology Comprehensive Cancer Centers of Nevada, Las Vegas, NV

Abstract

We performed a systematic review and meta-analysis on the response rates of patients with treatment-refractory urothelial carcinoma treated with programmed cell death 1 (PD-1) and programmed death ligand 1 (PD-L1) inhibitors. We reviewed the literature for prospective studies evaluating PD-1/PD-L1 inhibitors in refractory urothelial carcinoma patients, which formed the basis for US Food and Drug Administration approval of 5 different antagonistic antibodies targeting PD-1 or PD-L1 (atezolizumab, durvalumab, avelumab, nivolumab, and pembrolizumab). We considered studies examining PD-1/PD-L1etreated patients, which we identified using the following key terms in the Pubmed, Scopus, Web of Science, ClinicalTrial.gov, and Cochrane Library databases. Eligible studies had ≥ 20 patients each and reported response rates, duration of response, and overall survival (OS). We performed fixed and random-effects meta-analyses to model the point estimates for objective response rate and complete response. The median progression-free survival (PFS) and OS for studies reporting these statistics were evaluated. We found 10 eligible studies that met our inclusion criteria, providing extractable numerators and denominators for response rates, PFS, and OS for 1934 patients with metastatic urothelial

Address for correspondence: Inderbir S. Gill, MD, USC Institute of Urology, 1441 Eastlake Ave, Suite 7416, Los Angeles, CA 90089 , igill@med.usc.edu.

A.T. and D.D.S. contributed equally to this article.

Supplemental Data

Supplemental tables and figure accompanying this article can be found in the online version at https://doi.org/10.1016/j.clgc.2020.01.004.

Disclosure

The authors have stated that they have no conflict of interest.

carcinoma. The objective response rate was 18% (95% confidence interval, 15–22) for second-line or later therapies. The random-effects estimate for complete response was 4% (95% confidence interval, 3–5), including all disease locations and all PD-1 and PD-L1 inhibitors. Median OS and PFS were < 13 months and 3 months, respectively, across all studies, irrespective of PD-L1 expression. We found that the estimated response rates of agents included in this meta-analysis seem to be more favorable than other salvage therapies.

Keywords

Advanced urothelial cancer; Atezolizumab; Avelumab; Durvalumab; Metastatic urothelial cancer; Nivolumab; PD-1/PD-L1 inhibitors; Pembrolizumab; Second-line treatment

Introduction

Urothelial carcinoma is among the 10 most common cancers[1] and occurs in an older population with a median age of 62 years in men and 67 in women.[2] More than 150,000 patients die each year worldwide.[1] Systemic platinum-based combination chemotherapy is highly active, with response rates near 50%; however, the response is short-lived, with a median progression-free survival (PFS) of approximately 8 months.[3] Almost 50% of patients are ineligible to receive platinum-based chemotherapy as a result of various risk factors, including renal insufficiency, neuropathy, and hearing defects.[4] Patients who experience relapse after first-line chemotherapy have no standardized chemotherapy regimen. Several agents, including gemcitabine, vinflunine, paclitaxel, docetaxel, oxaliplatin, ifosfamide/topotecan, lapatinib, and gefitinib, have been studied with low overall response rates ranging 0% and 28% and have a short duration of response.[5–7] Notably, the overall response rate to vinflunine is 8.6%, median PFS is 3 months, and overall survival (OS) is 6.9 months.[8] Second-line or later single-agent and doublet chemotherapy regimens do not extend OS beyond 1 year.[6]

Recent advances in immune checkpoint inhibitor (ICI) therapy have shifted clinical investigations toward immunotherapy in urothelial cancer. This breakthrough in immunotherapy has come from the basic understanding that tumor microenvironment renders immune cells inactive. Exhausted immune cells allow tumors to escape host immune response. Programmed cell death 1 (PD-1) expression on T cells when stimulated by their cognate ligands (programmed death ligand [PD-L] 1/2) inhibit T-cell activation.[9] PD-L1 and PD-L2 are induced on tumor cells and tumor-infiltrating monocyte/macrophages.[9] Cytotoxic T-lymphocyte antigen 4 (CTLA-4) is another checkpoint inhibitor of T-cell function. CTLA-4 competes with CD28 in binding CD80 and CD86 on T cells and blocks the activation signal.[9] Inhibitory antibodies to PD-1/PD-L1 or CTLA-4 reactivate and expand T cells within the tumor.[10,11]

A number of prospective phase 2 and 3 trials have been conducted after chemotherapy failure. Results show consistent and durable responses to all 5 agents (atezolizumab, durvalumab, avelumab, nivolumab, and pembrolizumab).[12–16] All 5 PD-1 and PD-L1 antagonistic antibodies have received regulatory approval in the setting of prior chemotherapy failure. A summary of single agents is reported in Box 1. There are numerous

other studies in progress combining other agents—not only in patients with relapsed or refractory disease but also first-line patients, as well as patients being treated in the adjuvant and neoadjuvant settings[19] (Supplemental Table 1 in the online version). While the level of expression of PD-L1 has been associated with higher response rates in some of the studies, responses are seen in both PD-L1epositive and PD-L1enegative cases, thus highlighting the need for better predictive markers of response.

Tumor mutation burden predicts the generation of neoantigens and thus the immune response, especially after immune checkpoint blockade therapy. Tumor mutation burden is thus another potential marker for response.[20] The number of resident immune cells within the tumor in addition to tumor stroma also predicts the response to checkpoint-targeted therapy consistent with the ICI therapy—activating immune cells. Thus, tumors lacking immune cells (cold tumors) are less likely to respond. Quantitative measurement of immune cells within different compartments of the tumor requires further improvement and increased rigor in current assays.[21]

Our objective was to summarize the current state of ICI therapy in the setting of failure to first-line therapy in locally advanced or metastatic urothelial cancer; and to evaluate the response rates among the reported clinical trials.

Methods

Search Strategy

For this systematic review, we followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement[22] and rated the level of evidence using the scheme recommended by the methods and guide for effectiveness and comparative effectiveness review of the Agency for Healthcare Research and Quality.[23] PubMed, Scopus, Web of Science, ClinicalTrial.gov, and Cochrane Library databases were searched systematically for all full-text English-language articles on US Food and Drug Administration—approved PD-1 and PD-L1 inhibitors (atezolizumab, durvalumab, avelumab, nivolumab, and pembrolizumab) for the second-line treatment of advanced urothelial cancer published up to July 31, 2018. A complete update of the searches was done in January 1, 2019. References were manually reviewed to identify supplementary studies of interest. This study was registered with PROSPERO under registration code CRD42019131282.

Selection of Eligible Studies and Data Extraction

Two paired investigators (A.T. and G.E.C.) independently screened all articles gathered from literature review (Figure 1). The key terms used were as follows: ((((((PD-1) AND Urothelial carcinoma)) OR ((PD-L1) AND Urothelial carcinoma)) OR ((CTLA-4) AND Urothelial carcinoma))) OR (((((PD-1) AND Bladder Cancer)) OR ((PD-L1) AND Bladder Cancer)) OR ((CTLA-4) AND Bladder Cancer)). The terms “PD-1” and “PD-L1” were used interchangeably. Any disagreements about eligibility were resolved by discussion between the all investigators until a consensus was reached. We included only prospective trials reporting the outcomes of interest. Eligible studies were defined as those with ≥ 20 patients

that reported response rates, ideally with frequency counts. Studies on recurrent advanced and progressive urothelial carcinoma were included; studies that included other cancers were not considered. In the case of multiple publications on the same group of patients, only the most recent publication with the largest cohort was included in the analysis. For quantitative analysis, only multi-institutional studies that reported data not previously published in single-center studies were included. When an institution published multiple articles with overlapping series but describing a different follow-up, we considered only the most recently published paper.

All data retrieved from the systematically reviewed studies were recorded in an electronic database. The PICOTS (Population, Intervention, Comparators, Outcomes, Timing and Setting) format scrupulously summarized our research and analysis strategy for evaluating the operative, perioperative, functional, oncologic, and survival outcomes (Supplemental Table 2 in the online version). All articles were categorized according to the Oxford Level of Evidence Working Group 2011 levels of evidence for therapy studies[24] and accordingly to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system[25] (Supplemental Table 3 in the online version).

Data Quality Assessment

Two paired investigators (A.T. and A.S.) independently assessed the risk of bias for all studies using Cochrane tools.[26] Risk of bias assessments were generated (Supplemental Figure 1 in the online version).

Statistical Analysis

After data extraction, we tabulated the frequency of partial response (PR) and complete response (CR) as well as study parameters. Tables 1 and 2 show the median PFS and OS for studies reporting these statistics. We additionally performed a fixed-effects meta-analysis that adjusted for median age across the entire patient cohort. We used fixed and random-effects meta-analyses to estimate the PR + CR rates and 95% confidence intervals. All analyses were performed by R 3.5.1 software with the meta and metafor software packages.[31,32] $P < .05$ was considered statistically significant.

Results

After removing articles that were subsequently updated (n = 4) and articles with incomplete data (n = 1), we found 13 articles that matched our selection criteria. Among these, 2 studies evaluated PD-1 and PD-L1 inhibitors as first-line treatment; these were excluded.[17,33] Another paper published in 2018, which was an update of a study initially published in 2014, was excluded because a high percentage of patients in the updated study received ICI therapy as first-line treatment,[34] and we decided to consider only the initial series of this study to minimize bias.[27] Overall, we considered 10 studies reporting data on PD-1 and PD-L1 inhibitors as second-line or later treatment[12–16,18,27–30] (Figure 1).

Table 1 shows the list of single-agent second-line trials that we considered for our meta-analysis. Many studies reported data in a 4-tier PD-L1 staining scoring system in tumor cells. These corresponded to: 0 (no staining), 1 (any tumor cell staining, < 5% of tumor

cells), 2 (5%−50% of tumor cells), or 3 (> 50% of tumor cells).[35] For table entries that show, for example, “2–3,” that study reported combined results for categories 2 and 3 combined. Specifically, “2–3” in Table 1 reports the response rates of patients with PD-L1 expression > 5%.

A total of 1934 patients were represented in this analysis. They had a median (interquartile range) age of 67 (57–75) years.

Table 2 shows the PFS and OS (in months) for the studies included in the meta-analysis with extractable data. Median PFS was between 2.1 and 2.75 months depending on PD-L1 expression for atezolizumab, and between 2.0 and 5.5 months for nivolumab. Pembrolizumab showed a PFS between 2 and 2.1 months. Across all 7 studies that reported second-line and later with all PD-L1 staining groups combined,[12,14–16,18,29,30] all had median PFS < 3 months. Depending on PD-L1 expression, median OS was between 6.5 and 17.8 months for atezolizumab, and between 5.95 and 16.2 months for nivolumab. Pembrolizumab showed an OS between 10 and 13 months. Median OS was < 13 months and PFS was < 3 months across all studies reporting extractable data, irrespective of PD-L1 immunohistochemistry (IHC) expression. In arms with samples sizes of > 60, median OS was < 12 months across all studies, irrespective of PD-L1 IHC expression.

The estimate and standard error for age in the model were −0.0077 and 0.0152, respectively ($P = .61$). This was likely because there was little variability among the studies’ age medians.

Table 3 shows the summary objective response rate (ORR) across all immunotherapy arms for second-line and later interventions. As shown in Figure 2, we also calculated the ORR among all studies combined. Our estimated ORR was 18% (95% confidence interval [CI], 15–22). We also calculated the ORR according to PD-L1 expression. The estimated ORR was 16% (95% CI, 10–25) for IHC 0 in 311 patients (Figure 3) and 22% (95% CI, 18–27) for IHC 1–2–3 in 421 patients (Figure 4). The tau-square variable was statistically significant in the combined PD-L1 staining groups’ meta-analysis, indicating that the random-effects meta-analysis was more appropriate than the fixed-effects estimates (Figures 2–4). We also measured the CR rate, which is the ultimate goal in cancer therapy. Figure 5 shows the estimated CR rate in 1664 patients from 9 studies reporting extractable data. The random-effects estimate for CR was 4% (95% CI, 3–5) including all disease locations and all PD-1 and PD-L1 inhibitors.

Discussion

In the present meta-analysis, we evaluated 10 studies that investigated the use of PD-1/PD-L1 inhibitors in the treatment of advanced urothelial carcinoma after prior chemotherapy treatment. A total of 1934 patients were represented in this analysis. The pooled meta-analysis revealed an overall response rate of 18% (95% CI, 15–22).Median OS was <13 months and PFS was <3 months across all studies reporting extractable data, irrespective of IHC expression.

There have been a number of meta-analyses published studying the efficacy of PD-1/PD-L1 inhibitors in the post—first-line setting for urothelial cancer. Rassy et al[36] studied the survival outcomes of pembrolizumab, vinflunine, and atezolizumab across 3 comparative trials. Two studies included in this meta-analysis were derived from abstracts presented at conferences. One compared atezolizumab and chemotherapy, and the other compared vinfluine versus supportive care (and were not included in our study). Another study that evaluated pembrolizumab versus chemotherapy was included in our meta-analysis.[16] This study reported that in 1125 patients with metastatic urothelial cancer, pembrolizumab was the only treatment with a positive effect on OS compared to best supportive care.

A meta-analysis by Raggi et al[6] analyzed the results of 46 arms of single and doublet treatment arms in the post—first-line therapy setting in 1910 cases with metastatic urothelial cancer. They reported a response rate of 14.2% (95% CI, 11.1–17.9) and 31.9% (95% CI, 27.3–36.9) for single-agent and doublet cytotoxic chemotherapy. ORR with double chemotherapy was slightly better than ICI therapy. Notably, PFS was 2.69 and 4.05 months for single and doublet therapy, respectively, which was not dissimilar to ICI therapy. However, OS was 6.98 and 8.50 months, respectively. Combination therapy, although superior to single agent chemotherapy, was not superior to immune checkpoint therapy. The authors evaluated studies published between 1990 and 2014, and they included a large portion of partial data presented during international conferences. Further, data stratified according to PD-L1 expression were not reported.

Liu et al[37] presented a meta-analysis of anti—PD-1/PD-L1 antibodies in urothelial carcinoma patients. They selected studies that included first-line and subsequent therapy. The 6 studies of 828 subjects that were included in that study overlap with our search. They divided patients into 3 groups according to PD-L1 expression using < 1%, and between 1% and 5 % and ≥ 5%, and found that patients with PD-L1 expression ≥ 5% had disease that responded significantly better than other groups (ORR 45%, 95% CI 29–71 vs. 43%, 95% CI 25–73). As a result of potential differences in various biologic variables in first-line and subsequent therapy, we only considered subjects with refractory disease in our analysis, and using 1% of PD-L1 expression as cutoff, we found an ORR of 16% (95% CI, 10–25) in patients with low expression and 22% (95% CI, 18–27) in patients with high expression.

Di Nunno et al[38] performed a meta-analysis that included 9 prospective single-arm and which 2 randomized studies, with the latter comparing single-agent immune checkpoint inhibitors versus single-agent chemotherapy in platinum-resistant advanced urothelial carcinoma. Their results demonstrated that ICIs improve OS compared to chemotherapy in unselected patients (hazard ratio 0.80, 95% CI 0.69–0.93, $P = .003$), but the difference was not significant for PD-L1 expression selected patients (hazard ratio 0.72, 95% CI 0.48–1.09, $P = .12$). There was an overlap between our eligible studies and those presented by Di Nunno et al because they considered OS and ORR to be efficacy outcomes. Their meta-analysis methods were comparable with ours, although our analyses were constrained to ORR of immune checkpoint inhibitors using frequency data. Pooled ORR in the Di Nunno data set was 17.7% (95% CI, 16–20), and the ORR in patients with high PD-L1 expression was 27% (95% CI, 25–32). We did not perform any meta-analyses on hazard ratios, opting instead to tabulate PFS and OS in our eligible studies for completeness.

In another meta-analysis, Fan et al[39] found that in patients with advanced or metastatic urothelial carcinoma treated with PD-1/PD-L1 inhibitors, ORR was 21% (95% CI 18–24; $P = .07$), and the 1-year OS and 1-year PFS rates were 48% (95% CI, 42–54; $P = .0013$) and 21% (95% CI, 0.16–0.26; $P = .04$), respectively. They included 14 clinical trials that evaluated immune checkpoint inhibitors as a first-line and/or later treatment that have been reported in 14 abstracts or original articles.

To our knowledge, ours is the first meta-analyses to integrate both raw response frequencies and expression levels of PD-L1 in second-line or later treatment of urothelial carcinoma treated with ICIs. This analysis was possible because the articles we included provided detailed results and tabulations. Our summary tables of their results may be useful for future meta-analyses as new data emerge with these agents in this unique patient population. In particular, we were unable to perform formal analysis in a high-risk patient population like patients with pathologic disease variants (squamous cell, small cell, sarcomatoid), upper urinary tract disease, low hemoglobin (≤ 10 g/dL) levels, low performance status, visceral disease, and liver metastasis. There was sufficient heterogeneity between studies to warrant hierarchical models for our meta-analyses, and future meta-analyses should consider similar approaches. Importantly, we found an estimated ORR of 22% (95% CI, 18–27) in patients with IHC ≥ 1, which is higher than those with IHC < 1 (ORR 16%, 95% CI 10–25). PD-L1 expression predicts higher response rates with PD-1— and PD-L1—directed therapy. Studies investigating additional combination therapies can increase response rates in both groups. Studies involving agents that induce PD-L1 expression are ongoing and may increase the likelihood of response to ICI therapy.[21] Additionally, there are patients expressing low or no target expression who have some level of response. This highlights the need for other biomarkers as well as a for a universal PD-L1 marker, which is not likely to happen anytime soon. The response rates are numerically lower with PD-L2 antibodies. It is not possible to determine if the differences only reflect the patient populations or whether they represent a biologic difference in blocking PD-L1 and PD-L2 with PD-1 antibodies.[21] Furthermore, evidence suggests that first-line ICI therapy has resulted in higher responses and even greater durability in many other cancers.[40,41] Mature data are pending for urothelial cancer.

Interestingly, in the Keynote-052 study, pembrolizumab was studied as a first-line treatment in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer.[17] ORR was observed in 89 (24%) of 370 of patients, with response ongoing in 74 (83%) of 80 of cases at a median follow-up of 5 months. Furthermore, there was a positive correlation between PD-L1 expression (≥ 10%) and response.[17]

Another multicenter single-arm phase 2 trial of atezolizumab was conducted as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma.[33] At a median follow up of 17.2 months, the ORR was 23% and the CR was 9%. However, 8 of 27 of those with response to therapy had disease that had progressed by the data cutoff. Median PFS was 2.7 months (95% CI, 2.1–4.2). Median OS was 15.9 months (95% CI, 10.4-not estimable).[33] There are several ongoing studies in first-line therapy combining checkpoint inhibitor and chemotherapy.

Durable response with checkpoint inhibitor antibody therapy in relapsed and refractory urothelial cancer and first-line therapy has led to their investigation in the neoadjuvant and adjuvant settings. Two trials have been reported, and many others are in progress. Specifically, in the PURE-01 study, Necchi et al[42] reported the results of a phase 2 trial in muscle-invasive bladder cancer (T2-T4a N0 M0) in 50 patients. Pembrolizumab was provided at 200 mg every 3 weeks for 3 doses. Radical cystectomy was then performed to assess response. Pathologic CR was observed in 42% of the cases. Another similar trial (Abacus) studied 74 patients with muscle-invasive bladder cancer (T2-T4a). Patients received 2 doses of atezolizumab at 1200 mg 3 weeks apart. Pathologic CR was seen in 29% of the cases. In both trials, the pathologic CR was numerically higher in PD-L1—high cases.[43] Pathologic CR predicts better survival and low relapse rates. These and other studies are paving the way toward a regimen that allows organ preservation. Similarly, ICI is being studied in the adjuvant setting. Checkpoint inhibitor therapy is also under investigation in non—muscle-invasive bladder cancer,[19] combined with bacillus Calmette-Guérin[44] and after bacillus Calmette-Guérin failure.

In the present study, we did not present pooled estimates of time-to-event data (eg, OS and PFS) because there are many biases implicit in pooling standard estimates of summary statistics.[45,46] This is not necessarily the case when hazard ratios are reported because linear models and inverse-weighted techniques have generally shown consistent results.[47,48] Individual patient data are generally required for less unbiased estimates for time-to-event end points outside of hazard ratios. We did not have individual patient data, so we opted to present the point estimates of each arm.

We performed a risk of bias evaluation of the included studies. We found an intermediate to high risk of bias related to the nature of the studies (Supplemental Figure 1 in the online version). Many publication bias analyses require reporting of *P* values and odds or hazard ratios in comparative trials. However, many of our included studies were single-arm studies or in early clinical phases. The mechanism of correlation of publication to reporting clinical experience is difficult to quantify and hence to estimate. Our analyses are thus not free of publication bias.

Conclusion

We performed a systematic review and meta-analysis of the clinical trials investigating second-line therapy for recurrent urothelial carcinoma. Response rates varied from 16% to 22%. CR rate is underwhelming and occurs in < 5% of cases. PFS for the whole cohort is short, but responses are durable. Biomarkers for response in these studies have been limited to PD-L1 expression. Although there is a numerical increase in response rates among the patients with higher PD-L1 expression, the results are not statistically significant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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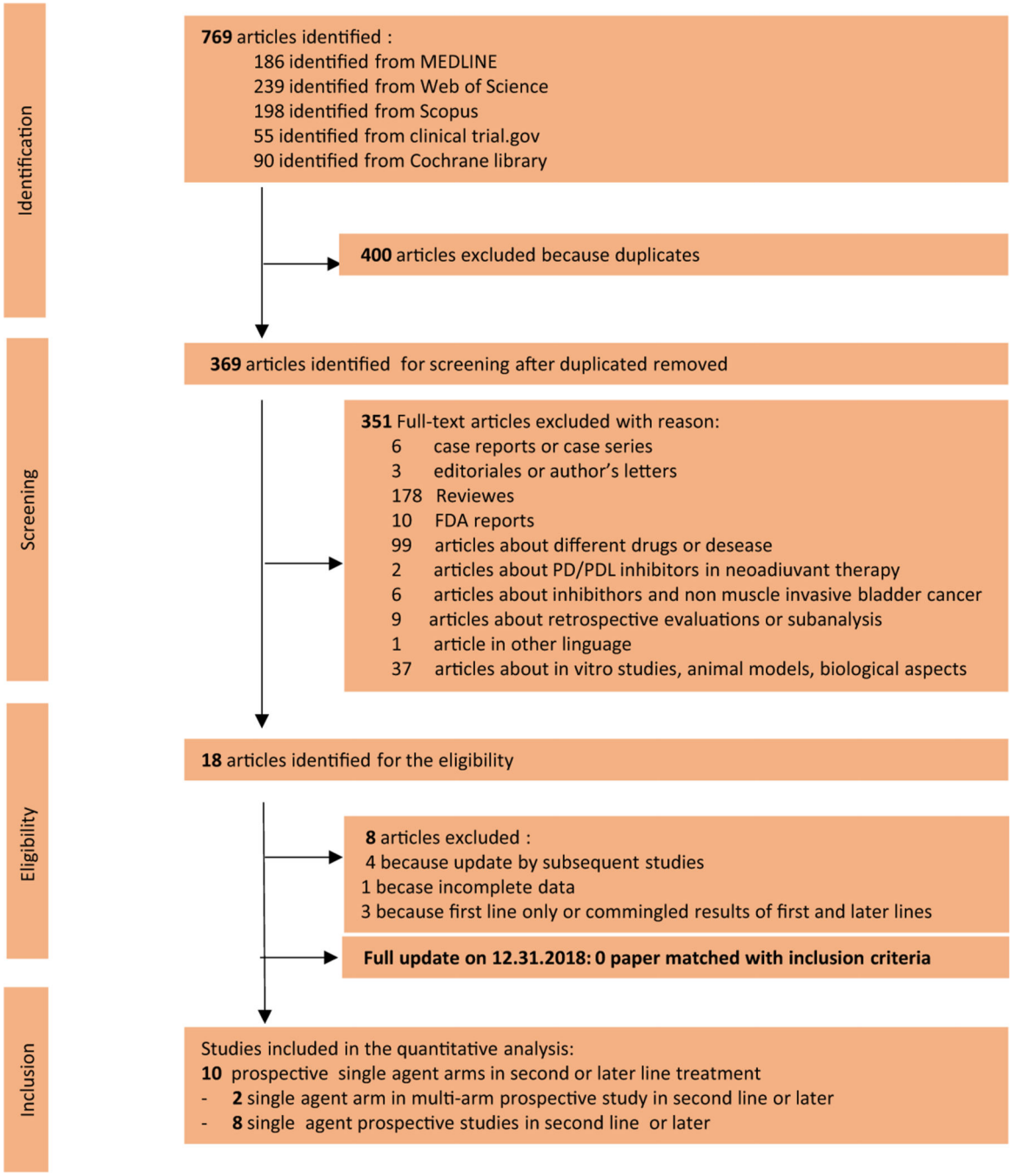

Figure 1.
Schema for Study Identification and Selection

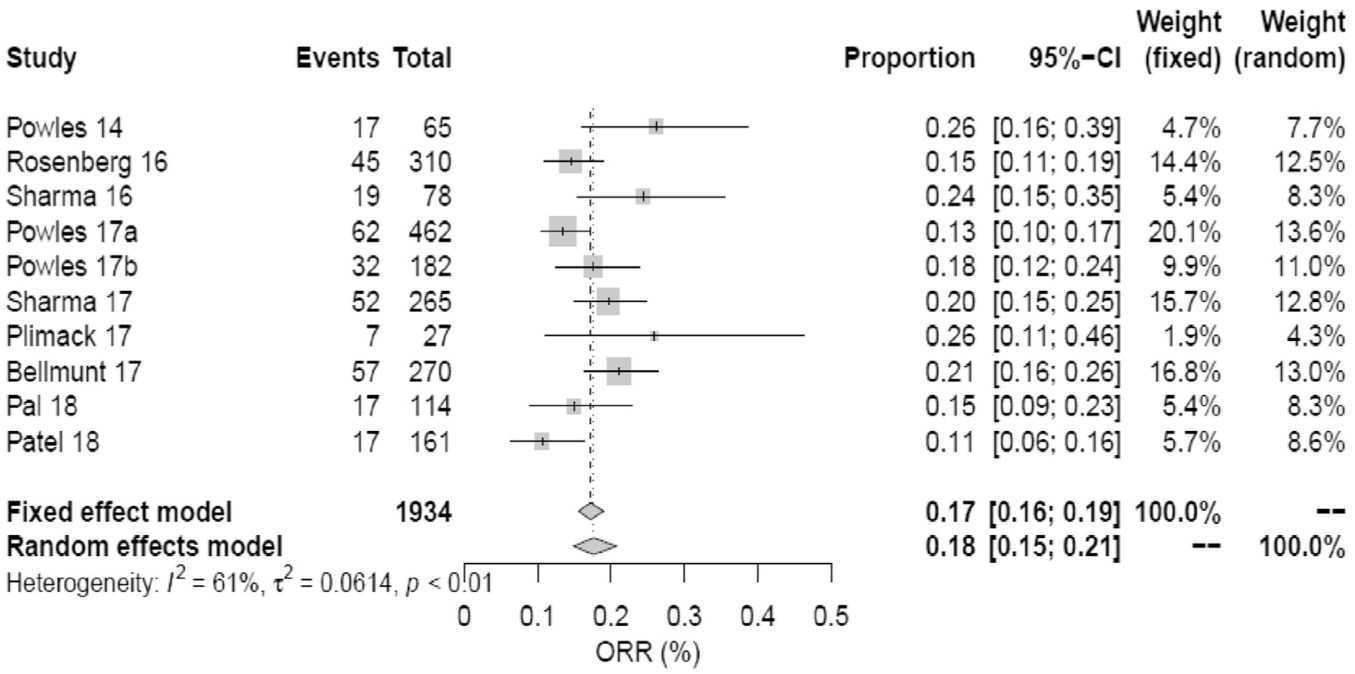

Figure 2.

Meta-analysis for ORR for All Patients in Second-Line and Later Studies

Abbreviation: ORR = objective response rate.

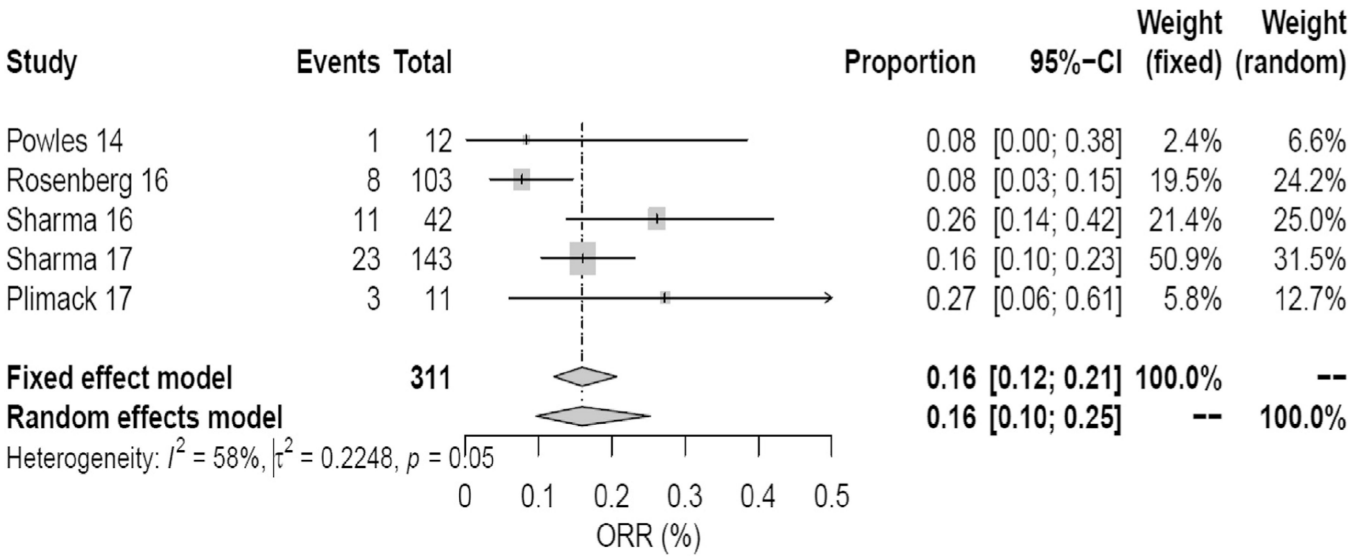

Figure 3.

Meta-analysis for ORR for PD-L1 immunohistochemistry (IHC) 0 (Expression < 1%) Patients in Second-Line and Later Studies

Abbreviation: ORR = objective response rate.

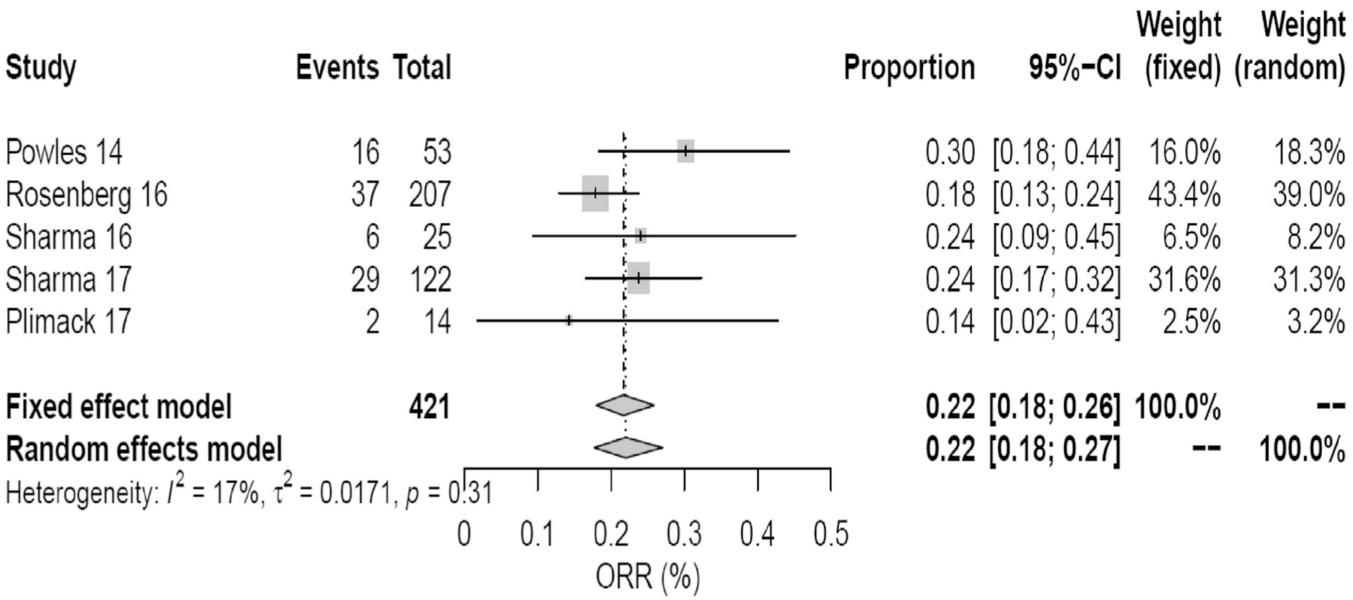

Figure 4.

Meta-analysis for ORR for IHC 1–2–3 (Expression ≥ 1%) Patients in Second-Line and Later Studies

Abbreviations: IHC = immunohistochemistry; ORR = objective response rate.

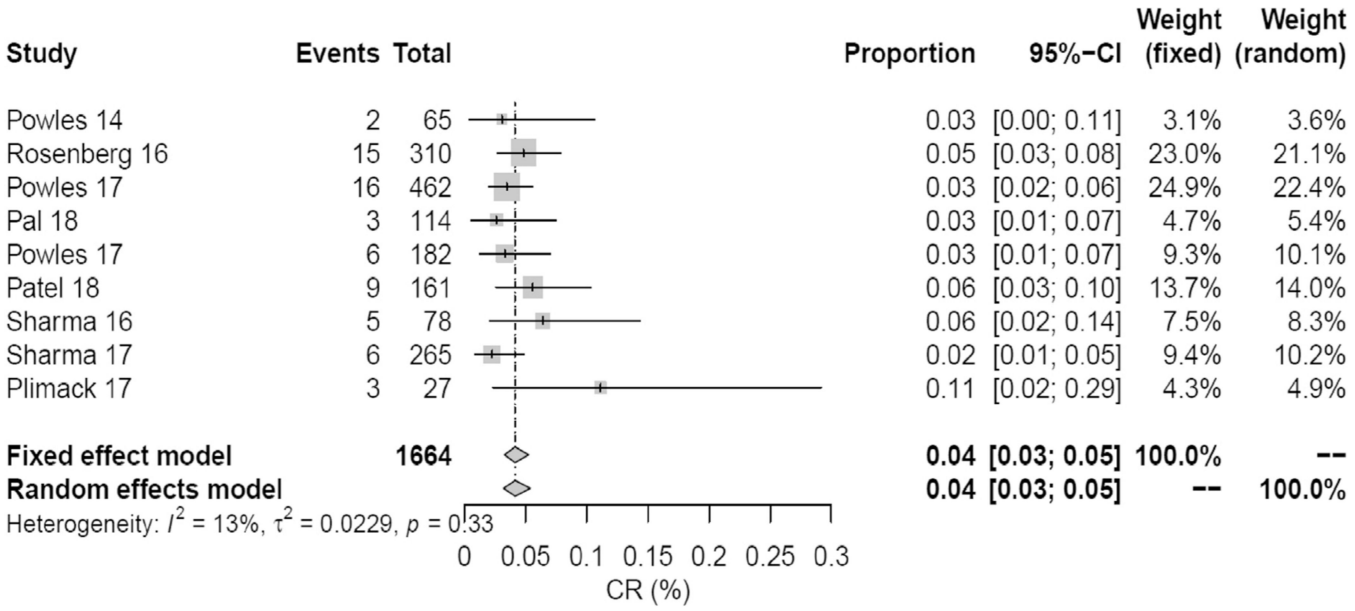

Figure 5.

Meta-analysis for CR for Included Studies

Abbreviations: CR = complete response.

Table 1

Response Rates for Single-Agent Trials Included in Meta-analysis

Study	Year	NCT	Phase	Drug	PD-L1	Freq PR + CR	Freq CR	N
Powles[27]	2014	NCT01375842	1	Atezolizumab	All	17	2	65
					0	1		12
					1–2–3	16		53
					0–1	4	0	35
					2–3	13	2	30
Rosenberg[12]	2016	NCT02108652	2	Atezolizumab	All	45	15	310
					0	8	2	103
					1–2–3	37	13	207
					1	11	2	107
					2–3	26	11	100
Pal[28]	2018	NCT02589717	2	Atezolizumab	All	17	3	114
Powles[29]	2017a	NCT02302807	3	Atezolizumab	All	62	16	462
					2–3	26	8	113
Powles[13]	2017b	NCT01693562	1/2	Durvalumab	All	32	6	182
Patel[14]	2018	NCT01772004	1	Avelumab	All	17	9	161
					0–1	10	2	76
					2–3	15	6	63
Sharma[15]	2016	NCT01928394	1/2	Nivolumab	All	19	5	78
					0	11	1	42
					1–2–3	6	6	25
Sharma[18]	2017	NCT02387996	2	Nivolumab	All	52	6	265
					0	23		143
					1–2–3	29		122
					2–3	23		81
Plimack[30]	2017	NCT01848834	1b	Pembrolizumab	All	7	3	27
					0	3		11
					1–2–3	2		14
Bellmut[16]	2017	NCT02256436	3	Pembrolizumab	All	57		270

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All treatments are second line or later.

Abbreviations: CR = complete response; Freq = frequency; NCT = ClinicalTrial.gov identifier; PD-L = programmed death ligand; PR = partial response.

Table 2

PFS and OS (Months) for Studies Included in Meta-analysis

Study	Year	NCT	Phase	Drug	PD-L1	Med PFS	Med PFS CI LL	Med PFS CI UL	Med OS	Med OS CI LL	Med OS CI UL
Rosenberg[12]	2016	NCT02108652	2	Atezolizumab	All	2.1	2.1	2.1	11.4	9.0	
					0				6.5	4.4	8.3
					1				6.7	5.1	8.8
					2–3	2.1	2.1	4.1	11.4	9.0	
Powles[29]	2017a	NCT02302807	3	Atezolizumab	All	2.1	2.1	2.2	11.1	8.6	15.5
					2–3	2.4	2.1	4.2	17.8	9.7	
					2–3	2.75	1.41	4.15	8.2	5.7	13.7
Sharma[15]	2016	NCT01928394	1–2	Nivolumab	All	2.8	1.5	5.9	9.7	7.3	16.2
					0	2.8	1.4	6.5	16.2	7.6	
					1–2–3	5.5	1.4	11.2	9.9	7	
Sharma[18]	2017	NCT02387996	2	Nivolumab	All	2	1.87	2.63	8.74	6.05	
					0				5.95	4.3	8.08
					1–2–3				11.3	8.74	
Plimack[30]	2017	NCT01848834	1b	Pembrolizumab	All	2	2	4	13	5	20
Bellmut[16]	2017	NCT02256436	3	Pembrolizumab	All	2.1	2	2.2	10.3	9	11.8
Patel[14]	2018	NCT01772004	1	Avelumab	All	1.45	1.38	2.33	6.5	4.8	9.5
					0–1	1.41	1.36	1.85	6.2	4.3	14
					2–3	2.75	1.41	4.15	8.2	5.7	13.7

All treatments are second line or later.

Abbreviations: CI = confidence interval; CR = complete response; LL = lower limit; Med = median; NCT = ClinicalTrial.gov identifier; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival; PR = partial response; UL = upper limit.

Table 3

Summary of Random-Effects Meta-Analyses for ORR Across Different Levels of PD-L1 IHC Expression

PD-L1 IHC Expression	ORR (%)	Lower CI	Upper CI	No. of Studies Reporting	Cumulative No.
All	18	15	22	10	1934
0	16	10	25	5	311
1–2–3	22	18	27	5	421
0–1	13	8	20	2	111
2–3	27	22	33	5	387

Abbreviations: CI = confidence interval; IHC = immunohistochemistry; ORR = overall response rate; PD-L1 = programmed death ligand 1.

Box 1

Summary of Single-Agent Immune checkpoint inhibitors as Second-Line Treatment

Pembrolizumab	Pembrolizumab, a PD-1 humanized antibody with subnanomolar affinity for the target, has been studied in urothelial cancer after failure of a systemic platinum-containing regimen for relapsed or refractory locally advanced or metastatic disease, or patients with disease that failed to respond after 12 months of neoadjuvant/adjuvant chemotherapy for muscle-invasive bladder cancer. Pembrolizumab prevents binding of both PD-L1 and PD-L2 and thus prevents T-cell inactivation from either ligand. Pembrolizumab was found to be superior to systemic chemotherapy, with a response rate of 21.1%, 11.4% for chemotherapy. Responses in general are durable with pembrolizumab compared to chemotherapy. Poor-risk patients are those with liver involvement, hemoglobin < 10 g/dL, and low ECOG performance status. These data were not provided for patients previously treated with cis-platinum. However, response among patients ineligible for platinum when treated with pembrolizumab had lower response (17% vs. 30% in patients with vs. without liver involvement, respectively[17]). Liver involvement remains a challenging subset. Median PFS remains low in the whole group, at 2.1 and 3.3 months for pembrolizumab and chemotherapy, respectively. Overall median survival was superior at 10.3 vs. 7.4 months for pembrolizumab compared to chemotherapy, indicating that patients whose disease does not respond may also benefit from pembrolizumab therapy.
Nivolumab	Nivolumab, a fully human PD-1 inhibitory antibody, blocks the binding of both PD-L1 and PD-L2 to the PD-1 receptor. Nivolumab is approved for therapy in the second line and beyond for metastatic bladder cancer. In a large study of 265 eligible patients whose disease had failed to respond to prior systemic therapy for locally advanced or metastatic urothelial cancer, 19.6% experienced a response; median PFS and OS were 2 and 8.7 months, respectively.[18] PD-L1 expression of ≥ 1% or greater vs. < 1% showed response rates of 23.8% and 16.1%, respectively. Response among patients with low or no expression indicate the need for improvement in biomarkers for response.[18]
Atezolizumab	Atezolizumab, a PD-L1 inhibitory antibody, blocks binding of PD-L1 but not PD-L2 to the PD-1 receptor. In a large clinical trial, 310 patients with relapsed or refractory disease that did not respond to systemic chemotherapy were treated with single-agent atezolizumab. PD-L1 expression was divided into 3 groups: < 1%, ≥ 1% but < 5%, and ≥ 5%. ORR was 15%. Patients with the highest PD-L1 expression had an ORR of 27%. Of the high-risk patients with liver involvement, responses were seen in 5% of the cases, compared to 19% without liver involvement.[12]
Avelumab	Avelumab, a PD-L1 inhibitory antibody, blocks the binding of PD-L1 to PD-1. A total of 249 patients received the study drug, with an ORR of 17% and a median OS of 6.5 months.[14]
Durvalumab	Durvalumab is a PD-L1 high-affinity inhibitory IgG1 monoclonal antibody studied as second-line therapy in 2017.[13] A total of 191 patients experienced an ORR of 17.8% (with complete remission in 3.7%), 27.6% of the patients with high PD-L1 expression (≥ 25% of tumor cells or tumor-infiltrating immune cells), and 5.1% of the patients with low or negative PD-L1 expression experienced response. For patients with liver metastases, the response rate was 7.3% (95% confidence interval, 2.7–15.2). Median PFS was 1.5 months.[13]

Abbreviations: ECOG = Eastern Cooperative Oncology Group; Ig = immunoglobulin; ORR = overall response rate; OS = overall survival; PD-1 = programmed cell death 1; PD-L1/2 = programmed death ligand 1/2; PFS = progression-free survival.