Original Article

# Efficacy and safety of programmed cell death-1/programmed cell death ligand-1 inhibitors in advanced urothelial malignancy: A systematic review and meta-analysis

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## ABSTRACT

**Introduction:** Programmed cell death-1/programmed cell death ligand-1 (PD-1/PDL-1) inhibitors are the newest class of approved drugs for advanced urothelial cancer (AdUC). This review aims to collate the evidence for their efficacy and safety in various treatment settings.

**Methods:** Extensive search of databases was performed (updated May 2018) and the protocol was registered on PROSPERO (CRD42017081568). The review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis statement. STATA (*v*12) and Revman 5.3.5 were used for data analysis.

**Results:** Ten nonrandomized, open-label clinical trials were included in this review. PD-1/PD-L1 inhibitors were used as second-line, stand-alone in eight trials and as first-line in cisplatin-ineligible in two trials. Heterogeneity was observed for study design, PDL-1 testing methods, cutoff criterias used and translational markers evaluated. The pooled objective response rate (ORR) was 18.2% (95% confidence interval [CI] 15.1–21.2, *n* = 1785) with PD-1/PDL-1 inhibitors in second-line settings as compared to 12.6% (95% CI 10.3–14.9, *n* = 736) with second-line chemotherapy and 23.7% (95% CI 19.9–27.4, *n* = 489) with PD-1/PDL-1 inhibitors as first-line therapy in cisplatin-ineligible patients. The median progression-free survival and overall survival was similar with PD-1/PD-L1 inhibitors in both second- and first-line treatment settings (1.5–2.9 vs. 2.0–2.7 months and 7.9–18.2 vs. 15.9 months) and second-line chemotherapy (3.3–4.0 months and 7.4–8 months). Odds of achieving ORR was 0.10 (95% CI 0.03–0.31, *n* = 229) in the second-line, stand-alone setting with a combined positive score (CPS) cutoff of 25% and was 0.34 (95% CI 0.19–0.62, *n* = 265) with a CPS cut-off of 10% in first-line setting in the cisplatin-ineligible.

**Conclusions:** PD-1/PDL-1 inhibitors appear to be promising in the treatment of AdUC and CPS may be a potentially reliable biomarker for predicting response but needs validation. Caution needs to be exercised until more data are available on imAEs and further studies are required to prove their worth as the standard of care.

## INTRODUCTION

Urothelial cancer (UC) is the ninth-most common malignancy reported worldwide.[1,2] Advanced UC is highly lethal. The current standard of care, platinum-based combination chemotherapy, was approved three decades ago.[3,4] The median overall survival (OS) with cisplatin-based therapy is 12-15 months and is about 9 months for carboplatin-based treatment.[5] Patients who do not respond to the first-line treatment have a median OS of only 5–7 months with the available

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second-line treatment options.[6] The commonly used second-line chemotherapy, paclitaxel or docetaxel are effective in about 10% of the patients, and the response is often partial and short-lived.[7-10] Therefore, there has been an unmet need to develop new therapies for these patients.

With years of research, it was found that the malignant cells might escape immune detection by exploiting the immune checkpoint, programmed cell death-1/programmed cell death ligand-1 (PD-1/PDL-1) pathway that suppresses T-cell responses. Therefore, it was conceptualized that blocking PD-1/PDL-1 pathway may cause prolonged T-cell activation and tumor rejection.[11-13] Monoclonal antibodies against PD-1 and PDL-1 are the newest class of drugs available for the treatment of advanced urothelial malignancy (AdUC). The first drug in this class, Atezolizumab, was approved by the US-Food and Drug Administration (FDA) in May 2016. Subsequently, four others, namely nivolumab, durvalumab, avelumab, and pembrolizumab have been approved. All of them have been labeled as second-line agents to be used if disease progresses with platinum-based regimens. Only atezolizumab and pembrolizumab are indicated for use as first-line agents when cisplatin use is contraindicated.[14] These drugs are expected to change the treatment landscape of AdUC. Therefore, it is essential to critically examine the extent of therapeutic benefit and the predictive markers of response as well as the adverse treatment outcomes with this class of agents. The objective of this systematic review is to synthesize the existing evidence assessing the overall efficacy and safety of the currently approved PD-1/PDL-1 inhibitors in AdUC.

## METHODS

The protocol was registered on PROSPERO (International Prospective Register of Systematic Reviews, CRD42017081568) and is available on the University of York website. Identified reports were reviewed according to the Consolidated Standards of Reporting Trials. The Preferred Reporting Items for Systematic Reviews and Meta-analysis were adopted for conducting the review.

### *Literature search*

Three authors SD, RR, and NJ independently performed the electronic database searches starting from January 1, 1980 to December 31, 2017 and were updated through May 2018. The databases included the Cochrane Central Register of Controlled Trials (CENTRAL; Wiley Cochrane Library), MEDLINE (Ovid®), EMBASE® (Elsevier), and Science Citation Index Expanded through Web of Science™. The clinical trial registries, namely ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform (http://apps.who.int/trialsearch) were also searched. The search terms included both text and medical subject heading (MeSH terms) [Supplementary Table]. Hand searching of the cross-references of the important studies was conducted to ensure that all relevant studies were identified. Google scholar and the conference proceedings were searched for additional information. The studies obtained by searching the literature were collated using the reference manager (EndNote X8), and duplicates were removed.

### *Selection criteria*

We included studies meeting the following criteria: (1) adult patients with metastatic or locally advanced UC with Eastern Cooperative Oncology Group performance status ≤2; (2) intervention trials evaluating the efficacy and safety of PD-1 or PDL-1 inhibitors used alone but not in combination with other treatments; (3) noncomparative or comparative clinical studies; (4) i – At least one of the outcomes was assessed: objective response rate (ORR), median progression-free survival (PFS) and OS,[15] ii – Additional efficacy outcomes such as median time to response, median doses of the drug required for response, median duration of response, disease control rate, PFS rate, and OS rate have been assessed, iii – Adverse events (AE) especially immune-mediated AEs (imAE) have been assessed for evaluating the safety of PD-1/PDL-1 inhibitors; and (5) the median follow-up duration was 5 months or more.

### *Subgroups*

The subgroup analyses were conducted for outcomes as per the PDL-1 expression status on the tumor cells or immune cells or both.

### *Data extraction*

Two authors SD and RR independently reviewed the manuscripts and abstracted the data against the predefined inclusion criteria. Data abstraction from the eligible studies was performed using a pilot-tested standardized data abstraction form. The extracted information included study identification, authors, phase of clinical trial, location, duration, design, participant characteristics, clinical setting, details of the intervention, sample size, duration of follow-up, outcome measures for both safety and efficacy, diagnostic tests employed to assess PDL-1 positivity status, translational biomarkers investigated and the sub-group analyses. All the information was compiled in standardized tables and disagreements were resolved by consensus. The analysis was finalized after thorough discussion among the review authors (SP, RM, AKM, and SKS).

### *Assessment of risk of bias*

We searched for an appropriate tool to assess the risk of bias for the nonrandomized, noncomparative, single-arm studies.[16] We also reviewed the studies based on the published data, nature of the outcomes assessed and the method of assessment. The heterogeneity in participant characteristics, interventions, and the PDL-1 diagnostic tests used were also noted. The Cochrane risk of bias tool (RoB 2) was used to evaluate the quality of randomized controlled trials (RCT).[17]

### *Data synthesis and analysis*

The Cochrane Handbook was consulted for data extraction.[18] STATA (v12; StataCorp, USA) and Revman 5.3.5 (The Nordic Cochrane Centre, Copenhagen, Denmark)[19] were used to analyze the data. The observed treatment effect was reported as pooled mean with 95% confidence interval (CI). $I^2$ statistics was used to assess for heterogeneity amongst the included studies and a value ≥ 50% was considered significant for using random effect model. However, we used random effect model for all pooled analysis considering the clinical heterogeneity between the studies. The reported means for the treatment arms were pooled in STATA to calculate the median effect size with 95% CI. Categorical outcomes were analyzed using Cochrane Mantel–Haenszel method in Revman. The observed probability of achieving treatment response was reported as odds ratios (OR) with 95% CI. The data were presented in a descriptive manner when the computation of a pooled effect size was not feasible. The subgroup analysis was performed for only ORR but not others due to nonavailability of adequate data. Egger's plot was used to assess publication bias and Galbraith plot to investigate for heterogeneity.

## RESULTS

### *Quantity of evidence identified*

One thousand two hundred and eighty-four relevant studies were identified by systematic search of the databases, and the full texts of 115 studies were examined for eligibility. A total of 10 clinical trials including 3010 participants, conducted in 11 countries in North America and Europe were included in this systematic review. The systematic process of study selection is described in Figure 1.

### *Characteristics of the included studies*

Two treatment categories were recognized (1) PD-1/PDL-1 inhibitors as second-line standalone treatment after disease progression with platinum-based chemotherapy: eight studies[20-28] (2) PD-1/PDL-1 inhibitors as first-line treatment in cisplatin-ineligible: two studies,[29,30]. Studies were excluded if combination therapies were evaluated[31] or the outcomes of interest were not reported, or the data for urothelial malignancy could not be retrieved from a basket type of trial design.[32] Adaptive and pragmatic trials with shorter follow-up were also excluded.[33] The summary information for the included studies is presented in Table 1.

Majority (8/10) of the included studies were non-randomized, open-label, single-arm, early phase clinical trials (I/II).[20-26,29,30] Two of the studies were phase-III open label randomized controlled trials (RCT) for pembrolizumab[27] and atezolizumab,[28] comparing them with second-line chemotherapy. The trials included participants with lymph node, viscera, and liver metastases but excluded the participants with brain metastasis. The major criterion for cisplatin ineligibility was poor renal function (>70% of the participants); others were hearing loss and peripheral neuropathy. The median duration of treatment reported in five out of ten included studies was 2.8–3.6 months (minimum of 0 to a maximum of 35.1 months). The median follow-up period for the trials evaluating these therapies ranged from 5.8 to 17.3 months. Response Evaluation

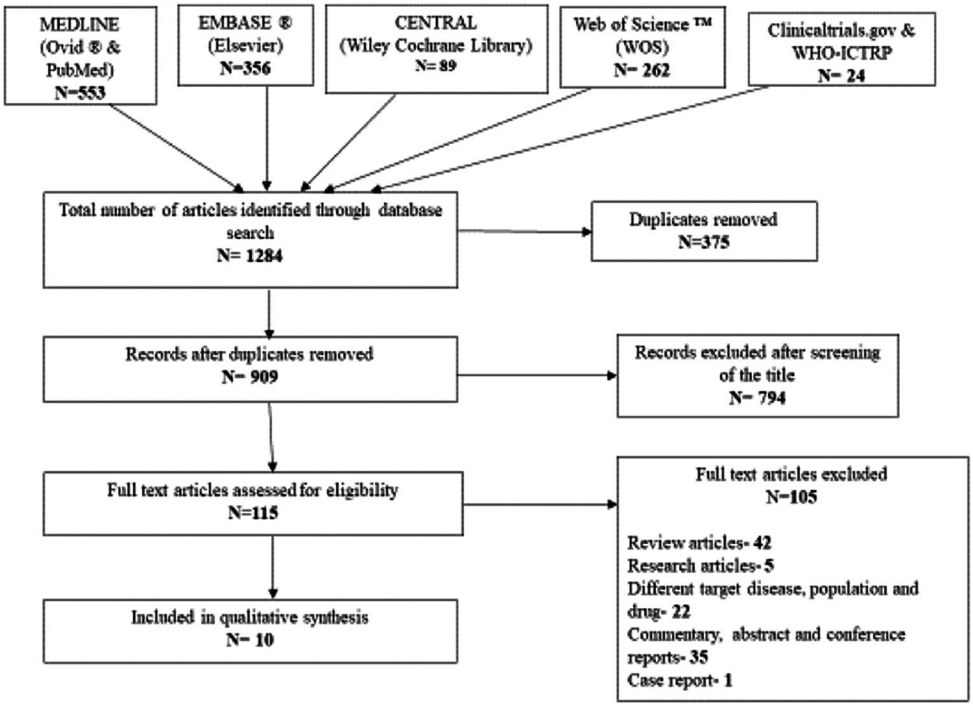


**Figure 1:** Study flow diagram programmed cell death-1/programmed cell death ligand-1 in advanced urothelial cancer

**Table 1: Study characteristics**

| Drug | Study ID location and duration | Study design | Sample size | Participant characteristics | Study interventions | Median Follow-up duration | Main outcome measure |
|---|---|---|---|---|---|---|---|
| **PD-1 inhibitors as second-line standalone agent** | | | | | | | |
| Nivolumab | Sharma *et al*., 2016[20]<br>Trial ID: NCT01928394 (CheckMate032)<br>Study Location: 16 sites in 5 countries<br>Study Duration: June 5, 2014–April 24, 2015 | Multicenter, randomized (unclear), allocation by interactive voice response system, open-label, phase 1/2 study, 2-stage, multi-arm (for the purpose of this review the data has been used from a single arm) | 78 | Age: 18 years or older<br>Disease: Histologically or cytologically confirmed carcinoma of the renal pelvis, ureter, bladder, or urethra | Nivolumab monotherapy<br>3 mg/kg IV infusion every 2 weeks<br>Additional arm<br>: Nivolumab + ipilimumab | 9 months | Primary Outcome: Confirmed investigator-assessed OR<br>Secondary outcome: Safety |
| Nivolumab | Sharma *et al*., 2017[21]<br>Trial ID: NCT02387996. (CheckMate 275)<br>Study Location: 63 sites in 11 countries<br>Study Duration: March 9, 2015-October 16, 2015 | Multicenter, nonrandomized, open-label, Phase-2, single arm | 270 | Age: 18 years or older<br>Disease: Histological evidence of metastatic or surgically unresectable locally advanced urothelial carcinoma | Nivolumab<br>3 mg/kg by 1-h IV infusion every 2 weeks | 6 months | Primary Outcome: OR in all treated patients<br>Secondary Outcomes : PFS and OS and investigator-assessed OR |
| Pembrolizumab | Bellmunt *et al*., 2017[27]<br>Trial ID: NCT02256436<br>Study Location: 120 sites in 29 countries<br>Study Duration: November 5, 2014-November 13, 2015 | Multicenter, randomized, open-label, phase 3, two arm study (KEYNOTE 045) | Total - 542<br>Pembrolizumab Group - 270,<br>Chemotherapy Group - 272 | Age: 18 years or older<br>Disease: Histologically or cytologically confirmed urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra | Intervention arm:<br>Pembrolizumab 200 mg IV every 3 weeks<br>Control arm:<br>Paclitaxel: 175 mg/m$^2$ of body-surface area, IV every 3 weeks<br>Docetaxel: 75 mg/m$^2$<br>Vinflunine: 320 mg/m$^2$<br>Randomized treatment allocation | 14.1 months | Primary Outcome: OS and PFS<br>Secondary Outcome: ORR, duration of confirmed response and Safety in the total population |
| **PDL-1 inhibitors as second-line standalone agent** | | | | | | | |
| Atezolizumab | Rosenberg *et al*., 2016[22]<br>Trial ID: NCT02108652<br>Study Location: 77 sites from North America and Europe<br>Study Duration: May 13, 2014-November 19, 2014 | Multicenter, nonrandomized, phase 2, global, single-arm, two cohort trial | Cohort 1: Cisplatin-ineligible patients<br>Cohort 2: Recurrent disease after platinum-based chemotherapy ($n$=310, included in the review) | Age: 18 years or older<br>Disease: Histologically or cytologically documented locally advanced or urothelial carcinoma (including renal pelvis, ureter, urinary bladder, or urethra) | Atezolizumab<br>Fixed dose of 1200 mg IV administered on day 1 of each 21-day cycle | 11.7 months | Primary outcome: ORR<br>Secondary outcome: Duration of response, PFS, and safety |

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**Table 1: Contd...**

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|---|---|---|---|---|---|---|---|
| **PD-1 inhibitors as second-line standalone agent** | | | | | | | |
| Atezolizumab | Powles *et al.*, 2018[28]<br>Trial ID: NCT02302807<br>Study location: 217 academic medical centers and community oncology practices mainly in Europe, North America, and the Asia-Pacific region<br>Study duration: January 13, 2015-February 15, 2016 | Multicenter, randomized controlled, open-label, phase 3, two-arm trial (IMvigor211) | TOTAL 931<br>Atezolizumab Group - 467<br>Chemotherapy Group - 464 | Age: 18 years or older<br>Disease: Metastatic urothelial carcinoma who had progressed after platinum-based chemotherapy | Atezolizumab 1200 mg IV administered every 3 weeks<br>Vinflunine 320 mg/$m^2$ IV or Paclitaxel 175: mg/$m^2$ IV or docetaxel 75 mg/$m^2$ IV (Every 3 weeks) | 17.3 months | Primary outcome: OS<br>Secondary outcome: Investigator-assessed ORR PFS, duration of response, safety and patient reported outcomes |
| Avelumab | Apolo *et al.*, 2017[25]<br>Trial ID: NCT01772004<br>Study location- 24 sites in the USA and Europe<br>Study duration: Ongoing. Start Date - January 31, 2013 | Multicenter, nonrandomized, open-label, phase 1b, multiple ascending-dose trial | 44 | Age: 18 years or older<br>Disease: Eligible participants had metastatic urothelial carcinoma of the renal pelvis, ureter, urinary bladder, or urethra, as confirmed by histology or cytology | Avelumab 10 mg/kg dose by 1-h IV infusion once every 2 weeks | 16.5 months (As of March 19, 2016) | Primary outcome: Safety and tolerability<br>Secondary outcome: Best OR, duration of response, PFS, OS, and evaluation of PD-L1 expression |
| Durvalumab | Massard *et al.*, 2016[24]<br>Trial ID: NCT01693562<br>Study location: 70 centers worldwide<br>Study duration: August 28, 2014-November 10, 2015 | Multicenter, nonrandomized, open-label, single-arm, phase-1/2, dose-escalation and dose-expansion study | 61 (40 PD-L1+ve and 21 PD-L1 -ve | Age: 18 years or older<br>Disease: Histologically or cytologically confirmed inoperable or metastatic transitional-cell urothelial carcinoma | Durvalumab 10 mg/kg every 2 weeks through IV infusion | 4.3 months | Primary outcome: Safety on the basis of assessment of adverse effects and serious adverse effects<br>Secondary outcome: ORR |
| Durvalumab | Powles *et al.*, 2017[23]<br>Trial ID: NCT01693562<br>Study location: 60 sites in 9 countries<br>Study duration: Ongoing. Start date- August 29, 2012 | Multicenter, nonrandomized, open-label, single-arm, Phase 1/2 study | 191 | Age: 18 years or older<br>Disease: Histologically and/or cytologically confirmed urothelial carcinoma were eligible for inclusion | Durvalumab 10 mg/kg (Q2W), IV infusion, every 2 weeks for up to 12 months | 5.78 Months (as of October 24, 2016 | Primary outcome: ORR<br>Secondary outcome: Duration of response, time to response, change in target lesion size, disease control rate (confirmed complete response or partial response or stable disease for ≥6 weeks), PFS and OS |
| **PD-1 inhibitors as first-line agent in cisplatin-ineligible** | | | | | | | |
| Pembrolizumb | Balar *et al.*, 2017 (a)[29]<br>Trial ID: NCT02335424<br>Study location: 91 academic medical centers in 20 countries<br>Study duration: February 24, 2015-August 8, 2016 | Multicenter, nonrandomized, single-arm, phase 2 study (KEYNOTE-052 | 370 | Disease: Age group - 18 years or older, cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer of the renal pelvis, ureter, bladder, or urethra | Pembrolizumab 200 mg IV every 3 weeks | 5 months | Primary Outcome: OR in patients with PD-L1-expressing tumors<br>Secondary Outcome: OS, PFS |

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**Table 1: Contd...**

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|---|---|---|---|---|---|---|---|
| **PD-1 inhibitors as second-line standalone agent** | | | | | | | |
| **PDL-1 inhibitors as first-line agent in cisplatin-ineligible** | | | | | | | |
| Atezolizumab | Balar *et al.*, 2017 (b)[30]<br>Trial ID: NCT02108652<br>Study location: 47 centers across 7 countries in North America and Europe<br>Study duration: June 9, 2014-March 30, 2015 | Multicenter, nonrandomized, single-arm, phase 2 trial (IMvigor210) | 119 | Disease: Participants aged 18 years or older with previously untreated locally advanced or metastatic urothelial cancer who were cisplatin ineligible | Atezolizumab 1200 mg IV dose every 21 days | 17.2 months | Primary outcome: Independently confirmed ORR<br>Secondary outcomes: Investigator-assessed ORR; duration of response, PFS, and OS |

OR=Objective response, PFS=Progression-free survival, OS=Overall survival, ORR=Objective response rate, IV=Intravenous. PD-1=Programmed cell death-1, PDL-1=Programmed cell death ligand-1

Criteria in Solid Tumors (RECIST) criteria version 1.1 was used to assess efficacy in all the studies. In majority of the trials, the treatment assessment was performed by a set of evaluators masked to the treatment allocation. Whenever these assessments were made by the principal investigator themselves, they were assisted by an Independent Central Review Committee. All trials coded the AE as per the Medical Dictionary for Regulatory Activities terminology. The severity of AE was classified according to the National Cancer Institute Common criteria for AEs version 4.0. PD-1/PDL-1 expression status in the tumor tissue was assessed by immunohistochemistry in all the included studies. However, it was not a mandatory requirement for inclusion. The staining antibodies, diagnostic testing methods, criterion for evaluation and the cutoff criteria for PDL-1 positivity varied across the studies. Exploratory translational biomarker and mutation analysis was reported only in four out of the ten clinical trials.[20,22,28,30]

### *Assessment of risk of bias*

We were unable to assess the risk of bias for the eight nonrandomized, noncomparative, single-arm intervention trials due to lack of a predefined tool for bias assessment.[20-26,29,30] However, the risk of bias in these studies was judged as moderate, based on the objective nature of the outcomes and the blinded review committee assisted assessment of the ORR in most of the studies. The RCTs[27,28] were judged to have mild-to-moderate risk of bias due to the open-label administration of the intervention and unmasked status of the outcome assessors [Supplementary Figure 1].

### *Efficacy outcomes*

#### *Objective response rate*

PD-1/PDL-1 inhibitors as second-line standalone: All the eight studies[20-28] reported the ORR. The pooled ORR was 18.2% (95% CI 15.1–21.2, $n$ = 1785) [Figure 2]. Two of the included studies were RCTs and included a second-line chemotherapy (vinflunine/paclitaxel/docetaxel) group as the control arm. The pooled ORR achieved with second-line chemotherapy was 12.6% (95% CI 10.3–14.9, $n$ = 736).

ORR with atezolizumab was found to be no better than second-line chemotherapy (13.4% [95% CI 10.5–16.9] vs. 13.4% [95% CI 10.5–16.9]),[28] whereas pembrolizumab was found to be significantly better than chemotherapy (21.1 [95% CI 16.4–26.5] vs. 11.4% [95% CI 7.9–15.8])[27] in the settings of a RCT.

PD-1/PDL-1 inhibitors as first-line treatment in cisplatin ineligible: There were two studies in this group.[29,30] The estimated pooled ORR was 23.7% (95% CI 19.9–27.4, $n$ = 489) [Figure 2].

### *Progression-free survival*

PD-1/PDL-1 inhibitors as second-line standalone treatment: Seven out of eight studies in this group[20-23,25-28] ($n$ = 1612)

reported the median PFS, which ranged from 1.5 to 2.9 months [Table 2]. The reported median PFS with second-line chemotherapy in two RCTs ranged from 3.3 to 4 months ($n$ = 736).[27,28]

Neither atezolizumab (2.1 months [95% CI 2.1–2.2] vs. 4.0 months [95% CI 3.4–4.2])[28] nor pembrolizumab (2.1 months [95% CI 2.0–2.,2] vs. 3.3 months [95% CI 2.3–3.5])[27] demonstrated advantage over the second-line chemotherapy for PFS in the RCT settings.

PD-1/PDL-1 inhibitors as first-line treatment in cisplatin ineligible: The reported median PFS in the two clinical trials[29,30] ranged from 2.0 to 2.7 months ($n$ = 310) [Table 2].

### *Overall survival*

PD-1/PDL-1 inhibitors as second-line standalone treatment: Six out of the eight studies ($n$ = 1612) reported median OS.[20-23,25,27] The upper limit of survival was not reached till the completion of the study in three trials,[20,23,25] hence was not estimable (NE). The median OS reported in the studies ranged from 7.9 to 18.2 months, and the quality of evidence was low [Table 2]. The median OS reported with second-line chemotherapy in both the RCTs was 7.4 to 8 months ($n$ = 736).[27,28]

OS did not significantly differ between atezolizumab and second-line chemotherapy (11.1 months [95% CI 8.6–15.5] vs. 10.6 months [95% CI 8.4–12.2]) in RCT settings[28] whereas pembrolizumab was reported to have a better median OS than second-line chemotherapy (10.3 months [95% CI 8.0–11.8] vs. 7.4 months [95% CI 6.1–8.3]).[27]

PD-1/PDL-1 inhibitors as first-line in cisplatin ineligible: OS was reported only for atezolizumab ($n$ = 119) but not for pembrolizumab.[30] The reported median OS was 15.9 months (95% CI 10.4 to NE) [Table 2].

### *Other measures related to efficacy*

The median time to response was reported in six out of eight trials in the second-line setting, and it ranged from 1.4 to 3.2 months.[21,23-25,30] Similarly, it was reported in both the trials in the first-line setting and ranged from 2 to 2.1 months.[29,30] None of the trials reported the median doses required to achieve the response. The median duration of response was not reached in eight out of ten trials, thereby meaning, an ongoing response in a subset of participants at trial closure.

Disease control rate data could be retrieved from seven out of eight trials in the second-line treatment setting.[20-25,28] The average disease control rate at 12 weeks was 42.1% ±8.8%. Out of the two RCTs, one[28] reported the disease control rate with second-line chemotherapy as 48% at 12 weeks. In the first-line treatment setting, atezolizumab[30] was reported to have the disease control rate of 46.7% at 12 weeks, but for pembrolizumab, this data was unavailable.[29]

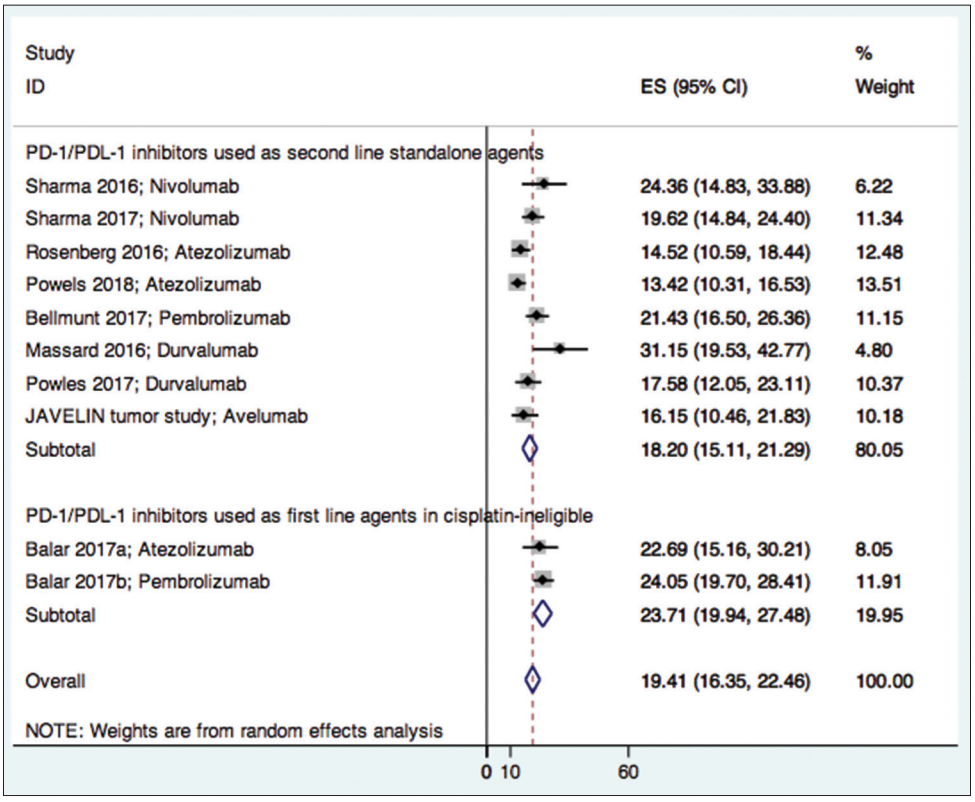


**Figure 2:** Summary of forest plot for the objective response rate achieved with programmed cell death-1/programmed cell death ligand-1 treatment in advanced urothelial cancer

The PFS and OS rates were not reported uniformly across the clinical trials. In the second-line setting, PFS rate was 21% (nivolumab),[21] 16% (durvalumab),[23] and 19.1% (avelumab)[25] at 12 months. The OS rate at 12 months was 46%, 55%, 54.3%, 46.2%, and 41.2% with nivolumab, durvalumab, avelumab, atezolizumab, and second-line chemotherapy, respectively. None of the trials in the first line treatment setting reported PFS outcomes.

### *Subgroup analysis as per the programmed cell death-1/programmed cell death ligand-1 positivity status in the tumor tissue*

Three out of ten studies assessed the expression of PDL-1 on tumor cells only,[20,21,25] three on tumor-infiltrating immune cells only,[22,28,30] and the rest on both types of cells and macrophages and expressed it as the combined positive score (CPS).[23,24,27,29] Studies used different cutoff criteria for PDL-1 positivity.

### *Programmed cell death ligand-1 expression on tumor cells*

*Cutoff as 1%*

Nivolumab, evaluated in second-line setting, with PDL-1 expression cut-off of 1%.[20,21] The ORR was achieved in 25.7% (95% CI 20.2–31.7) of the participants with PDL-1 expression of >1% as compared to 16.9% (95% CI 11.3–22.6) with <1% expression [Figure 3]. However, the odds of achieving objective response were similar (OR = 0.65, 95% CI 0.35–1.53, *n* = 413) in both the groups [Figure 4]. The median PFS was 5.5 months in >1% group as compared to 2.8 months in <1% group.[21] The median OS was 11.3 to 16.2 months in >1% group but 5.9 to 9.9 months in <1% group.[21,22] No differences were observed in the outcomes when assessing atezolizumab in first-line setting with PDL-1 expression cut-off of 1% (23% vs. 21% in >1% PDL-1 expression group and <1% expression group, respectively).[30]

*Cutoff as 5%*

Avelumab evaluated in second-line standalone setting with PDL-1 expression of 5% as cutoff.[25] ORR was achieved in 53.8% (95% CI 26.4–81.1) participants with >5% expression as compared to 4.2% (95% CI 0.8–7.6) in <5% expression [Figure 3]. The odds of achieving ORR were found to be marginally higher with higher PDL-1 expression (OR = 0.04, 95% CI 0.0–0.36, *n* = 37) [Figure 4]. The median PFS (12.1 months, 95% CI 2.8-NE vs. 1.7 months, 95% CI 1.5–3.0) and OS (NE, 95% CI 8.5-NE vs. 12.1 months, 95% CI 2.7-NE) were higher in participants with PDL-1 expression >5% as compared to <5%.[25] However, no differences in ORR (28% vs. 23%), median OS (12.3 vs. 19.1 months) and OS rate at 12 months (52% vs. 59%) were observed for atezolizumab in the first line setting in >5% compared to <5% expression group.[30]

### *Programmed cell death ligand-1 expression on tumor-infiltrating immune cells*

*Cutoff 1%*

Atezolizumab evaluated in the second-line[22] and first-line treatment setting[30] using 1% expression as cutoff. The ORR was achieved in 17.9% (95% CI 13–24) participants with >1% expression as compared to 8% (95% CI 3–15) with <1% expression in the second-line setting whereas the corresponding numbers were 23.7% (95% CI 15–35) and 20.5% (95% CI 9–36) in the first-line setting. The odds of achieving ORR with >1% PDL-1 expression was found to be better (OR = 0.39, 95% CI 0.17–0.86, *n* = 310) in second-line but not in the first-line setting (OR = 0.44, 95% CI 0.16–1.22) [Figure 4]. The PFS and OS data were not available for this sub-group.

*Cutoff 5%*

Data were available for atezolizumab evaluated in the second-line standalone setting[22,28] as well as first-line

**Table 2: Median progression-free survival and overall survival with programmed cell death-1/programmed cell death ligand-1 inhibitor use in Advanced Urothelial Cancers**

| Study ID | Study drug | Number of participants | Median PFS (months) | 95% CI | Median OS (months) | 95% CI |
|---|---|---|---|---|---|---|
| **PD-1 inhibitors as second-line standalone agent** | | | | | | |
| Sharma *et al*., 2016[20] | Nivolumab | 78 | 2.8 | 1.9-2.6 | 11.3 | 8.7-NE |
| Sharma *et al*., 2017[21] | Nivolumab | 270 | 2.0 | 1.5-5.9 | 9.7 | 7.3-16.2 |
| Bellmunt *et al*., 2017[27] | Pembrolizumab | 270 | 2.1 | 2-2.2 | 10.3 | 8-11.8 |
| **PDL-1 inhibitors as second-line standalone agent** | | | | | | |
| Rosenberg *et al*., 2016[22] | Atezolizumab | 310 | 2.1 | 2.1-4.1 | 7.9 | 6.6-9.3 |
| Powles *et al*., 2018[28] | Atezolizumab | 467 | 2.1 | 2.1-2.2 | 11.1 | 8.6-15.5 |
| Apolo *et al*., 2017[25] | Avelumab | 44 | 2.9 | 1.5-4.4 | 13.7 | 8.5-NE |
| Massard *et al*., 2016[24] | Durvalumab | 61 | NR | - | NR | - |
| Powles *et al*., 2017[23] | Durvalumab | 191 | 1.5 | 1.4-1.9 | 18.2 | 8.1-NE |
| **PD-1 inhibitors as first-line agent in cisplatin-ineligible** | | | | | | |
| Balar *et al*., 2017 (a)[29] | Pembrolizumab | 370 | 2.0 | 2.0-3.0 | NR | - |
| **PDL-1 inhibitors as first-line agent in cisplatin-ineligible** | | | | | | |
| Balar *et al*., 2017 (b)[30] | Atezolizumab | 119 | 2.7 | 2.1-4.2 | 15.9 | 10.4-NE |

NE=Not estimable, thereby meaning that the endpoint was not reached for some of the patients who were surviving at the closure of the study, NR=Not reported, PFS=Progression-free survival, CI=Confidence interval, NE=Not estimable, PD-1=Programmed cell death-1, PDL-1=Programmed cell death ligand-1, OS=Overall survival

setting using 5% PDL-1 expression as the cutoff.[30] In the second-line setting, ORR was achieved in 24.3% (95% CI 18.5–30.1) participants with >5% expression as compared to 9.8% (95% CI 7.3–12.2) in <5% expression group [Figure 3] and the odds of achieving ORR was 0.34 (95% CI 0.22–0.52, *n* = 772) [Figure 4]. However, in the first-line treatment setting, the ORR (28% vs. 21%) and the odds of response were similar (OR = 0.67, 95% CI 0.26–1.69, *n* = 71).[30] The median PFS and OS were reported only by *Rosenberg et al.*[22] There was no difference in PFS between the groups. However, the median OS appeared to be longer with PDL-1 expression >5% (11.4 months, 95% CI 9-NE) as compared to <5% (6.6 months, 95% CI 4.4–8.8).

### *Combined positive score*

#### *Cutoff 10%*

This data wasobtained from the study by *Balar et al.*[29] The ORR achieved with pembrolizumab, in the first-line setting, was 39% versus 20% and the odds of attaining ORR was also marginally higher in the group with CPS >10% compared to <10% (OR = 0.34, 95% CI 0.19–0.62, *n* = 265) [Figure 4]. The PFS and OS data were not available for this subgroup.

#### *Cutoff 25%*

Two trials evaluating durvalumab[23,24] used this cutoff criterion. The pooled ORR in the second-line treatment setting was 28.8% (95% CI 21.1–36.4) with CPS >25% compared to 4.4% (95% CI-0.4–8.6) in <25% group [Figure 3]. The odds of achieving ORR was somewhat higher in participants with high CPS (OR = 0.10, 95% CI 0.03–0.31, *n* = 229)[23,24] [Figure 4]. Only *Powles et al.*[23] reported median PFS and OS. The median PFS was 2.1 months (95% CI 1.4–2.8) versus 1.4 months (95% CI 1.3–1.5) and the median OS was 20 months (95% CI 11.6 to NE) versus 8.1 months (CI 3.1 to NE) in CPS expression >25% as compared to <25%.

### *Safety outcomes*

The safety analysis included all the 2268 participants from 10 studies. None of the studies reported the safety outcomes by PDL-1 expression status but only for the total cohort of participants treated. A mean of 69.1% ±7.9% participants experienced treatment-related AE, out of which 14.0% ± 5.8% were serious (Grade 3/4/5) in nature. Three studies reported no treatment-related deaths[22,24,25] and the average number of death was 0.8% ± 0.8%. The mean rate of treatment discontinuation was 4.6% ±2.5%, and the most common reason was AEs due to the study drug. Dose disruption or delay in treatment administration was reported to be as high as 34%.[29] The most common treatment-related AE was fatigue (21.5% ± 7.7%). The other common AEs were pruritus (12% ±7.5%), skin rash (7.1% ± 5.1%),

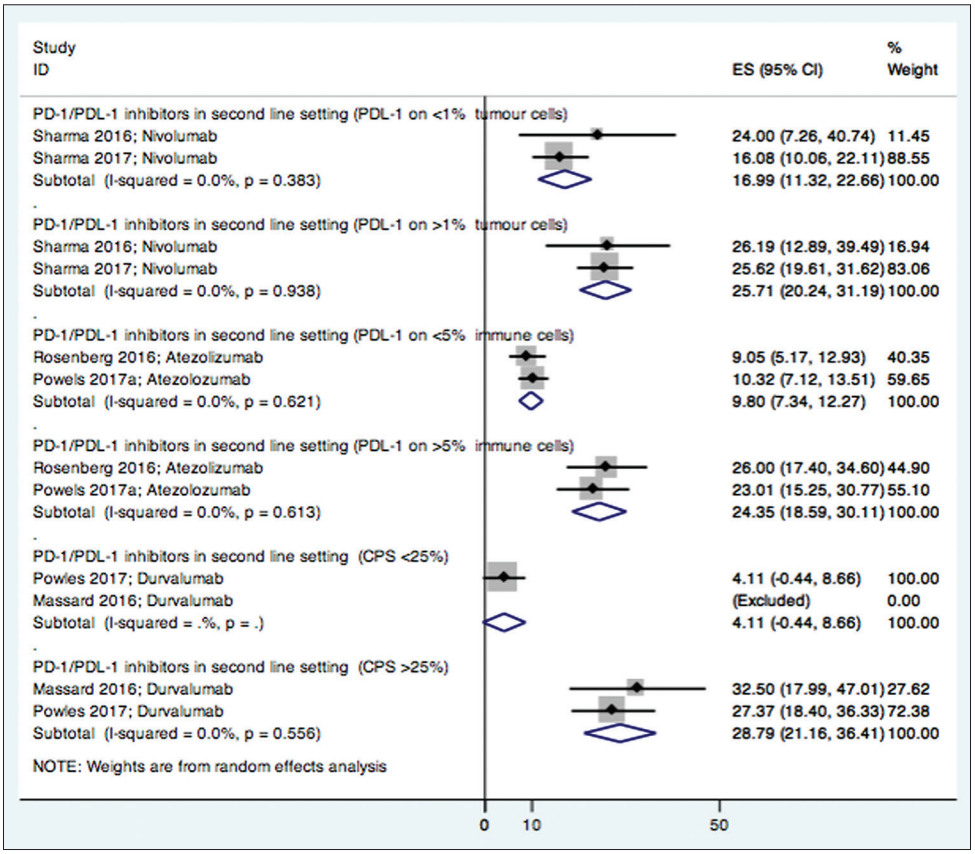


**Figure 3:** Summary of forest plot for the objective response rate achieved with programmed cell death-1/programmed cell death ligand-1 treatment in advanced urothelial cancer by programmed cell death ligand-1expression status

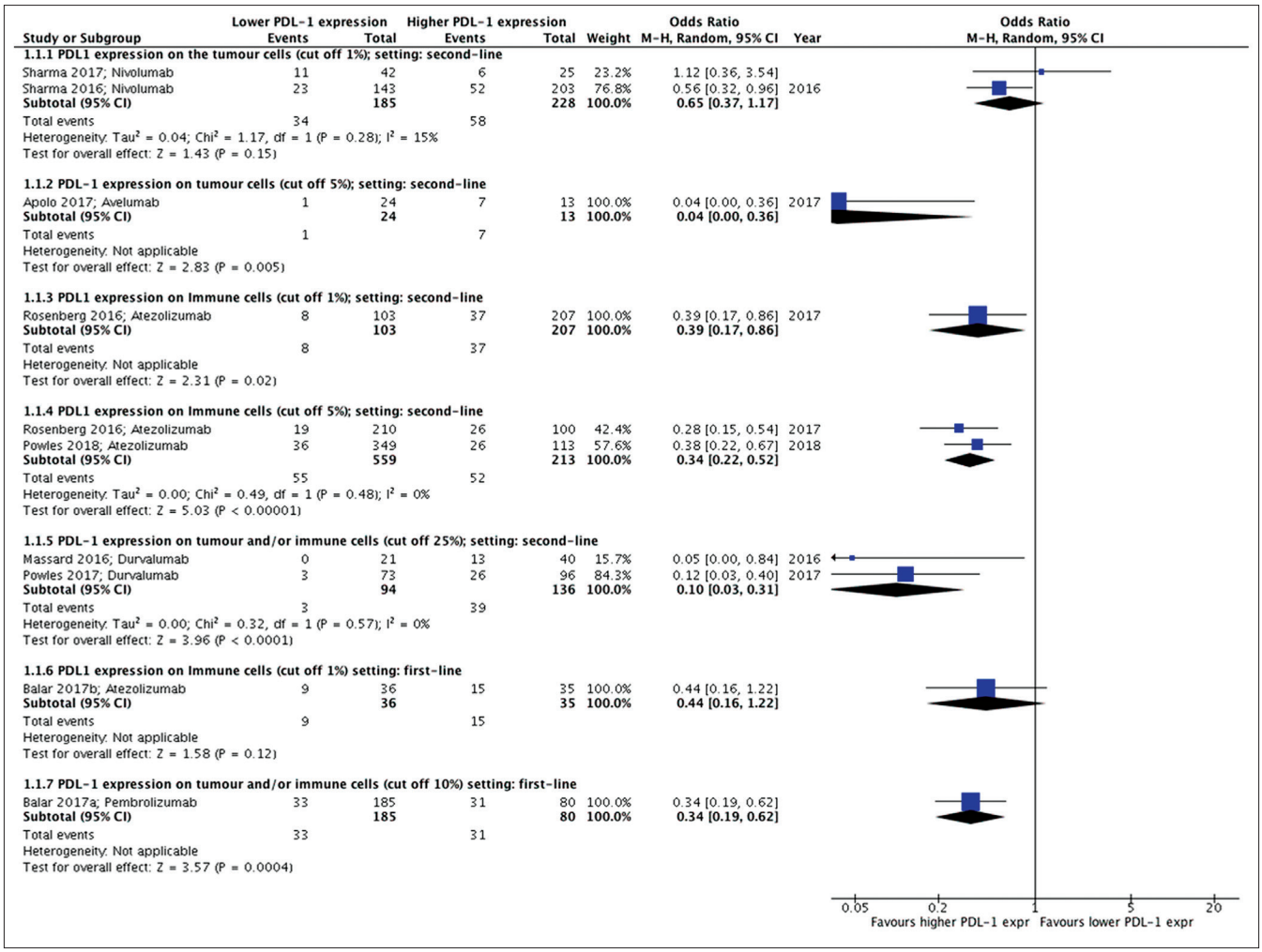


**Figure 4:** Forest plot for the odds of achieving objective response with programmed cell death-1/programmed cell death ligand-1 inhibitors in advanced urothelial cancer by programmed cell death ligand-1 expression status

diarrhea (8.6% ±3.3%), nausea (9.3% ± 3.1%), decreased appetite (8.2% ± 3.7%), arthralgia (3.9% ± 4.2%), and asthenia (5.1% ± 4.6%). No infusion-related AEs were reported for nivolumab, atezolizumab. These were 0.8% for pembrolizumab; 1%–3.2% for durvalumab and highest with avelumab (20.4%) [Table 3].

All the trials specifically looked for immune-related AE (imAE) induced by the PD-1/PDL-1 inhibitors. The onset of such imAE was reported to range from within a few weeks from the start of the treatment to several months after the end of the treatment. Skin and skin related AEs were the most common imAE [Table 4] and first ones to appear as reported in these trials. The other common imAE were hepatitis (4%–21.6%; 7/10 trials), pneumonitis (2.3%–12%; 9/10 trials), arthralgia (2.2%–12%; 6/10 trials), and thyroiditis or parathyroiditis (0.54%–8%; 5/10 trials). An immune-mediated inflammatory change in the central nervous system was reported with nivolumab (2%), atezolizumab (4%), and pembrolizumab (1.2%–1.8%). Uveitis was reported with avelumab (2.3%) and pembrolizumab (0.3%). The other imAE were infections, myalgia and hypersensitivity, and multi-organ dysfunctions [Table 4].

We tried to analyze the dose-response relationship between the drugs and the AE. The individual PD-1/PDL-1 inhibitor drugs were used as per the doses and intervals recommended by the manufacturers irrespective of second-line or first-line setting. The dosing schedule of nivolumab (3 mg/kg 1-h intravenous [IV] infusion every 2 weeks), pembrolizumab (200 mg IV every 3 weeks), atezolizumab (1200 mg IV administered every 3 weeks), avelumab (10 mg/kg 1-h IV infusion every 2 weeks), and durvalumab (10 mg/kg 1-h IV infusion every 2 weeks) varied significantly. As reported in majority of the clinical trials, the dose discontinuation, reductions and the change in the intervals were at the discretion of the treating physician. These are not described in sufficient detail so as to understand the type of AE leading to alteration in dosing. Therefore, the available evidence is insufficient to provide any meaningful insight in this regard.

### *Programmed cell death ligand-1 testing methods*

The diagnostic tests used for evaluating PDL-1 positivity status in the tumor tissue were (i) PDL-1 IHC 28-8 PharmDx detecting PDL-1 on tumor cells (Dako), (ii) SP-142 detecting PDL-1 on immune cells (Ventana), (iii) PDL-1 IHC 22C3 PharmDx (Dako) (iv) SP-263 (Ventana) detecting on tumor cells, macrophages, and immune cells. They were developed and validated alongside the development of nivolumab, atezolizumab, pembrolizumab, and durvalumab-avelumab, respectively. Two of the tests use rabbit monoclonal antibodies (SP-142 and SP-263) and the other two use mouse antibodies (22C3 and 28-8 pharmDx) All the tests require 4–5 mm thick fresh frozen paraffin-embedded tissue sections. The individual tests used specific cutoff criteria, namely IHC 28-8 PharmDx used 1% (tumor cells); SP-263 used 5% (tumor cells); SP-142 used 1, 1–5 and 5% (immune cells); and PDL-1 IHC 22C3 PharmDx used CPS score 10% or 25%.

### *Translational biomarker analysis*

Exploratory translational biomarker and mutation analyses were reported in four of the ten clinical trials evaluating nivolumab[20] and atezolizumab.[22,28,30] These included histological subtypes, mutation load and high-quality gene expression profiling for relevant helper as well as effector T-cells, their chemokines and cell surface markers. The TCGA histologic types that were likely to have a response to PD-1/PDL-1 inhibitors were (i) basal subtype-1 for nivolumab[20] and (ii) luminal cluster-II subtype for atezolizumab.[22,30] The basal subtype-1 patients, who responded to nivolumab had higher interferon-□, CXCL9/CXCL10, and CD8 expression.[22] The response to atezolizumab also correlated with increased trafficking of CD8+ cells and higher CXCL9/CXCL10 expression.[22] Higher median tumor mutation load was associated with a higher rate of response and increased median OS with atezolizumab.[22,28,30]

### *Publication bias and assessment of heterogeneity*

Egger's plot did not reveal significant publication bias [Supplementary Figure 2]. However, Galbraith plot demonstrated significant heterogeneity [Supplementary Figure 3].

## DISCUSSION

PD-1/PDL-1 inhibitors are undoubtedly the most exciting addition to the therapeutic armamentarium of AdUCs, a field which has not witnessed major breakthroughs for almost three decades. The experience with these new class of agents is short, though they have demonstrated some promise by achieving better ORR in the participants with high PD-1/PDL-1 expression in the tumor tissue, in both, cisplatin-based regimen failure and cisplatin ineligibility. However, when the patients were treated irrespective of their tumor PD-1/PDL-1 expression status, the response rate was only marginally higher in the PD-1/PDL-1 treatment group in the second-line settings (18.2% vs. 12.6%,

**Table 3: Common drug-related adverse events reported in the included clinical trials of programmed cell death-1/programmed cell death ligand-1 inhibitors in advanced urothelial malignancy**

| Study ID | Drug | Any AE* | Grade-1/2 AE | Grade-3/4/5 AE | Death due to AE | AE leading to Rx discontinuation | Fatigue | Infusion-related reactions | Asthenia | Arthralgia | Nausea | Decreased appetite | Diarrhea | Vomiting | Pyrexia | Constipation, gastrointestinal | Skin rash | Pruritus | Anaemia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PD-1 inhibitors as second-line standalone agent** | | | | | | | | | | | | | | | | | | | |
| Sharma-2016 (*n*=78) | Nivolumab | 81 | 59 | 22 | 2.56 | 3 | 36 | NR | NR | 12 | 13 | NR | NR | NR | NR | 1 | 18 | 29 | 10 |
| Sharma-2017 (*n*=270) | Nivolumab | 64 | 46 | 17 | 1 | 5 | 17 | NR | 5 | NR | 7 | 8 | 9 | NR | 6 | 9 | 6 | 9 | NR |
| Bellmunt-2017 (*n*=266) | Pembrolizumab | 61 | 46 | 15 | 1.5 | 5.6 | 15 | 0.8 | 6 | NR | 11.3 | 8.6 | 10.1 | NR | NR | 5.7 | NR | 19.5 | 4.2 |
| **PDL-1 inhibitors as second-line standalone agent** | | | | | | | | | | | | | | | | | | | |
| Rosenberg-2016 (*n*=310) | Atezolizumab | 85 | 69 | 16 | 0 | 4 | 30 | NR | NR | 8 | 14 | 13 | 8 | 6 | 9 | 2 | 7 | 10 | 4 |
| Powles-2018 (*n*=459) | Atezolizumab | 69 | NR | 20[b] | 1 | 3 | 17 | NR | 13 | NR | 10 | 12 | 11 | 3 | 9 | 6 | 9 | 12 | 7 |
| Apolo-2017 (*n*=44) | Avelumab | 66 | 59.1 | 6.8 | 0 | 9.1 | 20.5 | 20.5 | 11.4 | NR | 11.4 | 4.5 | 9.1 | NR | NR | NR | 9.1 | 6.8 | NR |
| Masard-2016 (*n*=61) | durvalumab | 69 | 64 | 4.9 | 0 | 1.6 | 13.1 | 3.2 | 6.6 | 6.6 | 6.6 | 8.2 | 9.8 | NR | 6.6 | NR | NR | 3.3 | NR |
| Powles-2017 (*n*=191) | Durvalumab | 68 | 61[a] | 6.8 | 1 | 1.6 | 19.4 | 1 | NR | 5.8 | 6.8 | 9.4 | 8.4 | NR | 5.8 | NR | 7.3 | 5.2 | 1.5 |
| **PD-1 inhibitors as first-line agent in cisplatin-ineligible** | | | | | | | | | | | | | | | | | | | |
| Balar-2017(a) (*n*=370) | Pembrolizumab | 62 | 46 | 14[c]1[d]0.2[e] | 0.2 | 5 | 17 | NR | 5.2 | 2.2 | 7.2 | 9.2 | 8 | NR | 4.2 | 2.2 | 9.2 | 14.2 | 2.2S |
| **PDL-1 inhibitors as first-line agent in cisplatin-ineligible** | | | | | | | | | | | | | | | | | | | |
| Balar-2017(b) (*n*=119) | Atezolizumab | 66 | 50 | 16[b] | 0.8 | 8 | 30 | NR | 3 | 4 | 5 | 9 | 12 | 5 | 5 | NR | 5 | 11 | 5 |

Data are represented as percentage of the events of AEs in the study population. *Any AE includes AEs of all grades (1-5). [a]Any grade, [b]Grade-3/4, [c]Grade-3, [d]Grade-4, [e]Grade-3/4/5. AE = Adverse events, NR = Not reported

**Table 4: Immune-related adverse events reported in the included clinical trials of programmed cell death-1/programmed cell death ligand-1 inhibitors in advanced urothelial malignancy**

| Study ID | Drug | CNS (encephalitis/ aseptic meningitis/ hypophysitis/) | Eye Uvitis | Thyroiditis/ parathyroiditis | Breathing difficulty/ pneumonitis | Liver (hepatitis)/ autoimmune hepatitis) | Kidney (nephritis) | Adrenal insufficiency | Pancreatitis/ autoimmune diabetes/ rheumatoid arthritis | Colitis | Mucositis | vasculitis | Peripheral neuritis/ | Hematological (anemia, thrombocytopenia, neutropenia) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PD-1 inhibitors as second-line standalone agent** | | | | | | | | | | | | | | |
| Sharma *et al.*, 2016[20] (*n*=270) | Nivolumab | NR | NR | 8 | 4 | 4 | 3 | NR | NR | 9 | NR | NR | NR | NR |
| Sharma *et al.*, 2017[21] (*n*=78) | Nivolumab | 2 | NR | NR | 5 | 24 | 1 | NR | 6 | 1 | NR | NR | NR | 15 |
| Bellmunt *et al.*, 2017[27] (*n*=266) | Pembrolizumab | 1.2 | NR | 11 | 6.4 | NR | 1.6 | 0.8 | NR | 3.4 | NR | NR | 1.2 | 0.4 |
| **PDL-1 inhibitors as second-line standalone agent** | | | | | | | | | | | | | | |
| Rosenberg *et al.*, 2016[22] (*n*=310) | Atezolizumab | NR | NR | NR | 12 | 4 | NR | NR | NR | 2 | NR | NR | NR | NR |
| Powles *et al.*, 2018[28] (*n*=459) | Atezolizumab | 4 | NR | NR | 4 | NR | NR | NR | NR | NR | 3 | NR | NR | 6.2 |
| Apolo *et al.*, 2017[25] (*n*=44) | Avelumab | NR | 2.3 | 6.8 | 2.3 | 6.8 | NR | NR | 2.3 | NR | NR | NR | NR | NR |
| Massard *et al.*, 2016[24] (*n*=61) | Durvalumab | NR | NR | NR | NR | NR | 1.6 | NR | NR | NR | NR | NR | NR | NR |
| Powles *et al.*, 2017[23] (*n*=191) | Durvalumab | NR | NR | NR | 3.6 | 21.6 | 1 | NR | NR | NR | NR | NR | NR | 1.5 |
| **PD-1 inhibitors as first-line agent in cisplatin-ineligible** | | | | | | | | | | | | | | |
| Balar *et al.*, 2017 (a)[29] (*n*=370) | Pembrolizumab | 1.8 | 0.27 | 1.81 | 2.54 | 14.16 | 3.89 | 1.54 | 6.08 | 2.27 | 1.35 | 0.27 | NR | 2.27 |
| **PDL-1 inhibitors as first-line agent in cisplatin-ineligible** | | | | | | | | | | | | | | |
| Balar *et al.*, 2017 (b)[30] (*n*=119 | Atezolizumab | NR | NR | 10 | 6 | 14 | 2 | NR | NR | 1 | NR | 1 | NR | 11 |

Figures are expressed are in percentages of the total participants; Miscellaneous AEs include: hypersensitivity, multiple organ dysfunction syndrome, infection (Influenza-like illness, upper respiratory tract infection, pneumonia, urinary tract infection), muscle spasm, muscle weakness, back pain, facial paralysis, lichen planus, hyperhidrosis, tumor flare, stomatitis, myalgia, abdominal pain, decreased weight. PD-1 = Programmed cell death-1, PDL-1 = Programmed cell death ligand-1, NR = Not reported, CNS = Central nervous system

respectively compared to that of chemotherapy) and in the first-line setting in cisplatin ineligible (ORR in PD-1/PDL-1 treatment group was 23.78%; no comparative data for alternative chemotherapy).

We also evaluated the OS and PFS, since ORR is not universally regarded as the best indicator of anti-cancer drug efficacy, even though the FDA recognizes it as a valid surrogate marker for drug approvals in short-term single-arm clinical trial when there is an unmet need.[15] The median PFS does not appear to be better with PD-1/PDL-1 inhibitors compared to the second-line chemotherapy (1.5–2.9–3.3–4.0 months). The median PFS was found to be similar with PD-1/PDL-1 inhibitors, in first-line and second-line setting (1.5–2.9 vs. 2.0–2.7 months) in the single arm studies. However, the available data indicates that the median OS may be longer with use of these agents as compared to second-line chemotherapy (7.9–18.2 vs. 7.4–8.0 months). Nevertheless, we consider the evidence as weak as it was inconsistent across the studies.[27,28] Moreover, the possibility of a selection bias in an open label single arm early phase clinical trials cannot be ruled out. Of the two RCTs, *Powles et al.* did not find any difference between PFS and OS,[28] but *Bellmunt et al.* did report a marginal increase in OS with PD-1/PDL-1 inhibitors although the PFS was similar to chemotherapy[27]. This could be due to the non-stringent entry criteria (the patients in the PD-1/PDL-1 treatment groups did not have a cutoff for tumor PDL-1 expression to enter into the clinical trial) or a purely drug specific effect. Overall, there was a notable heterogeneity in the clinical response to the drugs.

It is also unclear at this point, whether the short-term benefit with PD-1/PDL-1 inhibitors would translate into long-term survival benefit if the patients are treated irrespective of the PDL-1 expression status in the tumor tissue. Further, the remaining period of survival beyond the PFS (till the total period of survival, which is reported be 6–16 months or more), may be burdened with the long-term imAE induced by these drugs, further compromising the quality of life. These drugs are expensive; hence a modest gain in PFS with an extended OS with poor quality of life, is likely to reduce quality-adjusted life years (QALY) gained along with an added cost of treatment. None of the clinical trials included in this systematic review and meta-analysis addressed this issue. The QOL as well as QALY are important outcomes which need to be considered before these drugs are designated as the standard of care.

In terms of efficacy outcomes when stratified by PDL-1 expression status, PDL-1 expression on the tumor cells alone or immune cells alone with a cutoff of 1% failed to predict ORR consistently. Even when the cutoff for expression was increased to 5%, there was an inconsistent indication for predictability of response.[22,25,28] CPS seems to have emerged as a better predictor of response to treatment

with PD-1/PDL-1 inhibitors in all settings.[23,24,29] However, this biomarker was employed only in studies evaluating pembrolizumab but not the other agents. None of the studies mentioned how many of the patients had null expression status, and their outcomes. Currently, it is believed that lack of expression of PDL-1 should not preclude treatment with these agents as some of the patients with negative expression have also exhibited responses.[34] It could have been interesting to compare the outcomes in PD-1/PDL-1-negative versus positive patients, with respect to safety and survival. Another limitation is that four different testing methods have been developed parallel to the development of PD-1/PDL-1 inhibitors either as companion or complementary diagnostic test. However, skepticism has been expressed over the interchangeability of the tests, as they may differ in their sensitivities.[12,34,35] In addition, there are concerns over the dynamic and heterogeneous nature of the PDL-1 expression, which may vary in different regions of the tumor and between the primary tumor and the metastatic lesions.[36-38] The data on PDL-1 testing as a prognostic and predictive biomarker are still evolving. Although there is no consensus at present regarding the best PDL-1 testing method and the cutoff to define positivity, CPS as a predictive biomarker needs further validation in a larger cohort of patients and across all the approved agents.

PD-1/PDL-1 inhibitors have been proposed to be better tolerated due to their targeted action unlike the other immune checkpoint inhibitors such as CTLA-4. CTLA-4 targets the cytotoxic T-lymphocyte antigen reducing the T-cell function at a proximal step unlike the PD-1/PDL-1, which inhibit the T-lymphocyte function at a later stage, which may explain their better tolerability.[39] In this systematic review, approximately 70% of the patients reported treatment-related AEs and about one-fourth of them were serious in nature, though the rate of treatment discontinuation was only 5%–10%. It is worth appreciating that the median duration of treatment was as short as 2.8–3.6 months (reported only in 5 studies); but the total duration of treatment ranged from 0 to 35.5 months. Thereby meaning that the majority of the patients could not tolerate the drug beyond 3–4 months, which itself indicates poor tolerability. Some of the patients could tolerate therapy for as long as 35.5 months, however, it is unclear whether it is the general health of the patients (ECOG performance status) or PDL-1 positivity status or the response to the disease that determines tolerability to the drug. These details have not been reported in the published literature. Similarly, it is unclear at this time that if a dose-response relationship exists for the AEs.

The imAEs were as high as 21% and included several organ systems. Skin rash was the commonest and first to appear, but other more severe ones affecting critical neuroendocrine organs appeared over a period of weeks to months. The course of these imAEs and their association with dose of PD-1/PDL-1 inhibitors is unknown. There is no consensus at this time, whether their onset is an indication to stop further treatment. The available evidence is also inadequate to suggest whether the imAEs have a bearing with the extent of PDL-1 expression similar to efficacy or not. Moreover, there is no data on the adverse effects in tumors without PD-1/PDL-1 expression, which could have helped us to understand the true expression of imAEs. The iatrogenic AEs such as arthralgia and myalgia may also potentially compromise the quality of life during the extended period of survival. Further research is also required to characterize the imAEs and define strategies to manage them effectively. Moreover, all the included studies involved management of UCs as a whole, while tumors at specific sites such as upper tract urothelial tumors or bladder urothelial tumors might have differential effects and efficacy and this could also be one of the future areas of further investigation.

Several biomarkers like the TCGA subtypes (basal subtype-1 and luminal-II); higher tumor mutation load and higher expression of CD8, CXCL9, CXCL10, interferon-□ seem to predict better response to the PD-1/PDL-1 inhibitors. However, the data are available from limited number of studies and only for two of the agents. Therefore, further exploration of molecular markers is required to generalize the use of biomarkers for this class of agents. There are several ongoing studies with combination of targeted therapies; concurrent radiotherapy; with extensive biomarker evaluation that may reveal some interesting findings in the future.[40-49]

In this systematic review, we were unable to apply Grading of Recommendation Assessment, Development, and Evaluation[50] to rate the quality of evidence since the risk of bias for eight of the ten included studies could not be assessed due to unavailability of a validated tool. Drugs and biologic agents being developed for advanced stages of malignancy are invariably tested in nonrandomized single arm interventional studies, where there is no control arm. This is a more intuitive study design in this scenario than a RCT. Since the new drug approvals and subsequent treatment of patients are based on the data obtained from such studies, there is an unmet need to devise an instrument (tool) and validate it to assess the of risk of bias in randomized single arm interventional studies to improve the robustness of systematic review process.

Future research is required to address several aspects of PD-1/PDL-1 inhibitor use in AdUC. Assays for the assessment of PD1/PD-L1 expression on both tumor cells and immune cells need to be standardized. It is imperative to characterize the responder profile with biomarkers upfront before therapy initiation to maximize the benefits obtained.

The optimum duration of therapy, discontinuation criteria and imAEs also need more investigation. The impact on the quality of life of the patients who respond to therapy and have long OS even with disease progression need more clarity to make an informed choice about the treatment. The health economics aspects of treatments also need to be better understood.

## CONCLUSIONS

PD-1/PDL-1 inhibitors appear to be promising in the treatment of AdUCs with higher PDL-1 expression and the concept of a cutoff value for the same is still evolving. CPS may be considered as a potentially reliable biomarker for predicting response to these agents but need further validation as a universal biomarker for making treatment decisions. Caution needs to be exercised until more data are available on the long-term imAEs and further studies are required to prove their worthiness as a standard of care.

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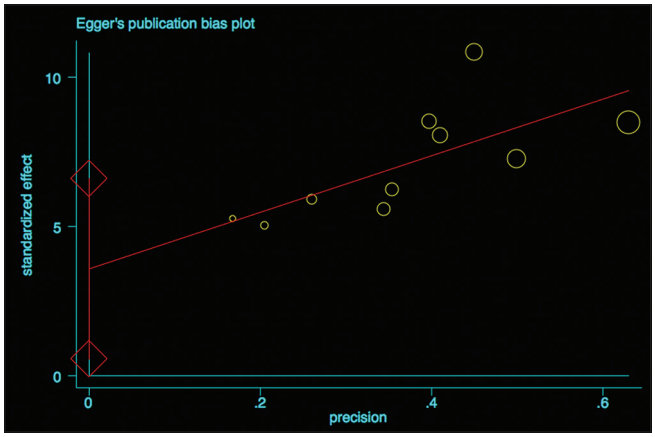
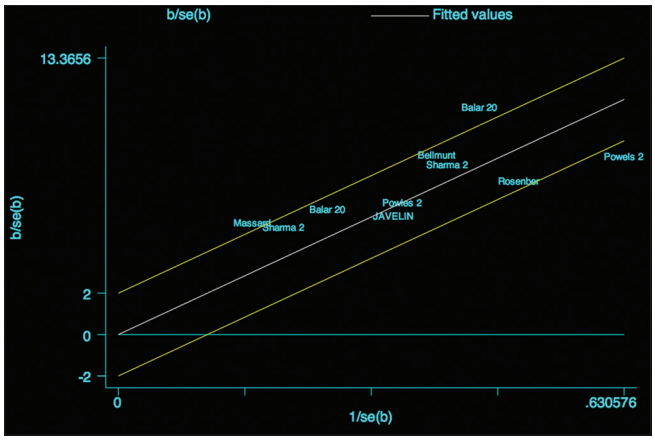
Note: Supplementary tables are available online at www.indianjurol.com


**Supplementary Figure 1:** Risk of bias




**Supplementary Figure 2:** Egger's plot for publication bias




**Supplementary Figure 3:** Galbraith plot for heterogeneity

**Supplementary Table: Search strategy**

| |
|---|
| 1. PubMed |
| Search (((((((urothelial carcinoma) OR metastatic urothelial carcinoma) OR urinary bladder carcinoma) OR bladder cancer) OR metastatic bladder cancer)) AND ((((programmed death ligand 1 inhibitors) OR PD-L1 inhibitors) OR programmed death receptor 1 inhibitors) OR PD-1 inhibitors)) AND ((((((((((((((((nivolumab) OR atezolizumab) OR pembrolizumab) OR durvalumab) OR avelumab) OR OPDIVO) OR ONO-4538) OR BMS-936558) OR MDX1106) OR TOCENTRIQ) OR MPDL3280A) OR IMFINZI) OR MEDI4736) OR BEVANCIO) OR MSB0010718C) OR KEYTRUDA) OR MK-3475)) AND ((clinical trial) OR trials) |
| Search (clinical trial) OR trials |
| Search ((((((((((((((((nivolumab) OR atezolizumab) OR pembrolizumab) OR durvalumab) OR avelumab) OR OPDIVO) OR ONO-4538) OR BMS-936558) OR MDX1106) OR TOCENTRIQ) OR MPDL3280A) OR IMFINZI) OR MEDI4736) OR BEVANCIO) OR MSB0010718C) OR KEYTRUDA) OR MK-3475 |
| Search (((programmed death ligand 1 inhibitor) OR PD-L1 inhibitors) OR programmed death receptor 1 inhibitor) OR PD-1 inhibitors |
| Search ((((urothelial carcinoma) OR metastatic urothelial carcinoma) OR urinary bladder carcinoma) OR bladder cancer) OR metastatic bladder cancer |
| Search metastatic bladder cancer |
| Search bladder cancer |
| Search urinary bladder carcinoma |
| Search metastatic urothelial carcinoma |
| Search urothelial carcinoma |

The searches were updated on May 22, 2018

## 2. The Cochrane Library

| ID | Search | Hits |
|---|---|---|
| #1 | urothelial carcinoma | |
| #2 | metastatic urothelial carcinoma | |
| #3 | urinary bladder carcinoma | |
| #4 | bladder cancer | |
| #5 | metastatic bladder cancer | |
| #6 | #1 or #2 or #3 or #4 or #5 | |
| #7 | programmed death ligand 1 inhibitors | |
| #8 | PD-L1 inhibitors | |
| #9 | programmed death receptor inhibitors | |
| #10 | PD-1 inhibitors | |

#11 #7 or #8 or #9 or #10
#12 nivolumab
#13 atezolizumab
#14 pembrolizumab
#15 durvalumab
#16 avelumab
#17 OPDIVO
#18 ONO-4538
#19 MDX 1106
#20 TECENTRIQ
#21 BMS 936558
#22 MPDL 3280A
#23 IMFINZI
#24 MEDI 4736
#25 BEVANCIO
#26 MSB 0010718C
#27 KEYTRUDA
#28 MK-3475
#29 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28
#30 clinical trial
#31 trials
#32 #30 or #31
#33 #6 and #11 and #29 and #32

The searches were updated on 22/05/2018

## 3. OVID

| | |
|---|---|
| 33 | 6 and 11 and 29 and 32 |
| 32 | or/30-31 |
| 31 | trial {Including Limited Related Terms} |
| 30 | clinical trial {Including Limited Related Terms} |
| 29 | or/12-28 |
| 28 | MK-3475 {Including Limited Related Terms} |
| 27 | KEYTRUDA {Including Limited Related Terms} |
| 26 | MSB 0010718C {Including Limited Related Terms} |
| 25 | BEVANCIO {Including Limited Related Terms} |
| 24 | MEDI 4736 {Including Limited Related Terms} |
| 23 | IMFINZI {Including Limited Related Terms} |
| 22 | MPDL 3280A {Including Limited Related Terms} |
| 21 | BMS 936558 {Including Limited Related Terms} |
| 20 | TECENTRIQ {Including Limited Related Terms} |
| 19 | MDX 1106 {Including Limited Related Terms} |
| 18 | ONO-4538 {Including Limited Related Terms} |
| 17 | OPDIVO {Including Limited Related Terms} |
| 16 | Avelumab {Including Limited Related Terms} |
| 15 | Durvalumab {Including Limited Related Terms} |
| 14 | Pembrolizumab {Including Limited Related Terms} |
| 13 | Atezolizumab {Including Limited Related Terms} |
| 12 | Nivolumab {Including Limited Related Terms} |
| 11 | or/7-10 |
| 10 | PD-1 inhibitors {Including Limited Related Terms} |
| 9 | Programmed death receptor inhibitors {Including Limited Related Terms} |
| 8 | PD-L1 inhibitors {Including Limited Related Terms} |
| 7 | Programmed death ligand inhibitors {Including Limited Related Terms} |
| 6 | or/1-5 |
| 5 | Metastatic bladder cancer {Including Limited Related Terms} |
| 4 | Bladder cancer {Including Limited Related Terms} |
| 3 | Urinary bladder carcinoma {Including Limited Related Terms} |
| 2 | Metastatic urothelial carcinoma {Including Limited Related Terms} |
| 1 | 'Urothelial carcinoma'.mp. [mp=tx, bt, ti, ab, ct, sh, ot, nm, hw, fx, kf, px, rx, an, ui, ds, on, sy] |

The searches were updated on 22/05/2018

## 1)EMBASE:

#8 AND #13 AND #31 AND #34
#34
#32 OR #33
#33
'trial'/exp OR 'trial'
#32
'clinical trial'/exp OR 'clinical trial'
#31
#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30
#30
'mk-3475'/exp OR 'mk-3475'
#29
'keytruda'/exp OR 'keytruda'
#28
'msb 0010718c'/exp OR 'msb 0010718c'
#27
'bevancio'

#26
'medi 4736'/exp OR 'medi 4736'
#25
'imfinzi'/exp OR 'imfinzi'
#24
'mpdl 3280 a'/exp OR 'mpdl 3280 a'
22
#23
'tecentriq'/exp OR 'tecentriq'
#22
'mdx 1106'/exp OR 'mdx 1106'
#21
'bms-936558'/exp OR 'bms-936558'
#20
'ono-4538'/exp OR 'ono-4538'
#19
'opdivo'/exp OR 'opdivo'
#18
'avelumab'/exp OR 'avelumab'
#17
'durvalumab'/exp OR 'durvalumab'
#16
'pembrolizumab'/exp OR 'pembrolizumab'
#15
'atezolizumab'/exp OR 'atezolizumab'
#14
'nivolumab'/exp OR 'nivolumab'
#13
#9 OR #10 OR #11 OR #12
#12
'pd-1 inhibitors'
#11
'programmed death receptor inhibitors'
#10
'pd-l1 inhibitors'
#9
'programmed death ligand inhibitors'
#8
#2 OR #4 OR #5 OR #6 OR #7
#7
'metastatic bladder cancer'/exp OR 'metastatic bladder cancer'
#6
'bladder cancer'/exp OR 'bladder cancer'
#5
'urinary bladder carcinoma'/exp OR 'urinary bladder carcinoma'
#4
'metastatic urothelial carcinoma'/exp OR 'metastatic urothelial carcinoma'
#3
'urothelail carcinoma'
#2
'urothelial carcinoma'/exp OR 'urothelial carcinoma'
urothelial AND ('carcinoma'/exp OR carcinoma)  #1

The searches were updated on 22/05/2018