

A review of avelumab in locally advanced and metastatic bladder cancer

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Abstract: Urothelial carcinoma remains a devastating disease with a poor prognosis. Though immune therapy with *Bacillus Calmette–Guérin* (BCG) has been used for localized bladder cancer for years, only immune-checkpoint blockade with antiprogrammed cell-death 1 (anti-PD-1) and antiprogrammed cell-death ligand 1 (anti-PD-L1) inhibitors have demonstrated improvement in survival of patients with metastatic disease. Anti-PD-L1 antibody, avelumab, was recently given United States Food and Drug Administration (FDA) accelerated approval for the treatment of recurrent/metastatic urothelial carcinoma after failure of first-line chemotherapy, marking the fifth immune checkpoint inhibitor to be given FDA approval for the treatment of metastatic urothelial cancer. The following manuscript will review avelumab, its pharmacology, and the clinical experience that has led to its approval, as well as future plans for clinical development of avelumab for the treatment of urothelial cancer.

Keywords: urothelial cancer, avelumab, PD-L1, immune checkpoint

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Worldwide burden of bladder cancer

With over 430,000 new cases each year, bladder cancer (urothelial carcinoma, UC) is the ninth most common malignancy in the world, with the highest incidence being in Northern America and Europe and the lowest incidence in Asia, Latin America and the Caribbean. Older age, male sex, and environmental carcinogen exposure (smoking, industrial chemicals, arsenic, etc.) are known risk factors that not only increase the likelihood of development of UC¹ but affect its biology and clinical behavior, as well.² For the remainder of this article, we will focus on urothelial histology of UC.

Immunotherapy landscape in bladder cancer

UC is also unique in having one of the longest track records of responsiveness to immunotherapy. *Bacillus Calmette–Guérin* (BCG) was introduced as a treatment for nonmuscle invasive UC 40 years ago and continues to be a cornerstone of therapy to date.³ Since 2015, five immune-checkpoint inhibitors (CPIs) have been approved by the

United States Food and Drug Administration (FDA) for use in locally advanced or metastatic UC. These include two antiprogrammed cell-death 1 (anti-PD-1) agents (nivolumab and pembrolizumab), and three antiprogrammed cell-death ligand 1 (anti-PD-L1) agents (avelumab, atezolizumab and durvalumab).⁴

Because of differences in the setting of approval (untreated cisplatin-ineligible *versus* previously treated UC), pharmacokinetics (and hence dosing frequency), need for programmed cell-death ligand 1 (PD-L1) assessment, and toxicity profile, choosing the correct agent for a given patient is critical.

Avelumab overview

Avelumab (MSB0010718C) is a human immunoglobulin G1 (IgG1) monoclonal antibody targeting PD-L1. It received accelerated approval from the FDA in May 2017 for treatment of patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or within

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12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. It has also received accelerated approval for treatment of adults and pediatric (\geq age 12 years) patients with metastatic Merkel cell carcinoma.⁵

Preclinical development and pharmacokinetics of avelumab

Avelumab selectively blocks the interaction between programmed cell-death 1 (PD-1) and B7.1 (PD-L1) receptors, while still allowing interaction between PD-L2 and PD-1.⁵ This interaction then allows T-cell receptor activation and cell lysis. In vitro studies have shown that avelumab can lyse a range of human tumor cells in the presence of peripheral blood mononuclear cells consistent with this mechanism of action.⁶⁻⁹

Unlike currently available anti-PD-1 antibodies, avelumab's IgG1 Fc portion can bind Fc receptors to activate antibody-mediated cytotoxicity (ADCC). Indeed, preclinical data show that avelumab leads to potent cell killing in the presence of natural killer (NK) cells purified from either healthy donors or cancer patients.⁷⁻¹¹ ADCC has been demonstrated in several *in vitro* models, potentially suggesting two nonoverlapping mechanisms of action.^{6,8}

The pharmacokinetics of avelumab was studied in the JAVELIN solid tumor trial, a phase I trial with patients receiving doses ranging from 1 to 20 mg/kg every 2 weeks.^{12,13} The exposure of avelumab increased dose proportionally in the dose range of 3 to 20 mg/kg every 2 weeks. For all doses, the mean time to maximum concentration was within 1 h from the end of infusion. Steady-state concentrations of avelumab were reached after approximately 4 to 6 weeks (two to three cycles) of repeated dosing. Avelumab was primarily eliminated *via* proteolytic degradation and the terminal half-life was 6.1 days in patients receiving 10 mg/kg. No clinically meaningful differences in pharmacokinetics were observed for avelumab based on age, sex; mild, moderate or severe renal impairment (creatinine clearance 30 to 89 ml/min); and mild or moderate hepatic impairment [bilirubin less than or equal to three times the upper limit of normal (ULN)]. There are inadequate data for patients with severe hepatic impairment (bilirubin greater than three times ULN).

Clinical investigation of avelumab in bladder cancer

The above-mentioned JAVELIN trial [Clinical Trials.gov identifier: NCT01772004] was the pivotal trial examining the role of avelumab in locally advanced or metastatic UC. Adult patients with histologically confirmed locally advanced or metastatic UC were enrolled in two sequential cohorts: an initial cohort and an efficacy expansion cohort. Eligible patients were required to have disease progression after at least one previous platinum-based chemotherapy, or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

A pooled analysis of the patients in the UC cohorts of this trial was recently published.¹³ A total of 249 patients were enrolled including 58 (23%) with upper tract (renal pelvis or ureter) and 191 (77%) with lower tract (bladder or urethra) tumors. Only 13 (5%) patients were cisplatin ineligible. Of the 206 patients evaluable for PD-L1 expression level, 82 (33%) had PD-L1-positive tumors and 124 (50%) had PD-L1-negative tumors. Patients received avelumab 10 mg/kg by 1-h intravenous (IV) infusion every 2 weeks until the occurrence of disease progression, unacceptable toxicity, or other protocol-specified criteria for withdrawal. Median duration of treatment was 12.0 weeks [interquartile range (IQR) 6.0–19.7] and median follow up was 9.9 months (4.3–12.1). Objective response rate (ORR) was 17% [95% confidence interval (CI) 11–24], including nine (6%) complete responses and 18 (11%) partial responses by RECIST criteria. The disease control rate (proportion of patients with a complete response, partial response or stable disease) was 40% (64 of 161 patients). Median progression-free survival (PFS) was 6.3 weeks (95% CI 6.0–10.1). In patients with a confirmed response, median time to response was 11.4 weeks (IQR 5.9–17.4) and median duration of response was not reached by data cutoff (95% CI 42.1 weeks to not estimable). Most common reason for treatment discontinuation was disease progression, seen in 125 (50%) patients. Only 50 (20%) of 249 patients received anticancer treatment after discontinuing avelumab, including cytotoxic chemotherapy in 39 (16%) patients, kinase inhibitor in five (2%), antibody therapy in five (2%), and hormonal therapy in one (<1%). Median overall survival (OS) was 6.5 months (95% CI 4.8–9.5), and the 6-month OS rate was 53% (45–60).

Table 1. Response and survival according to PD-L1 status.

	PD-L1 positive (n = 63)	PD-L1 negative (n = 76)
Objective response (n, total)	15	10
ORR, rate [95% CI]	24% [14–36]	13% [7–23]
Median PFS, weeks [95% CI]	11.9 [6.1–18.0]	6.1 [5.9–8.0]
PFS at 6 months, rate [95% CI]	37% [25–49]	16 [9–26]
Median OS, months [95% CI]	8.2 [5.7–13.7]	6.2 [4.3–14.0]
OS at 6 months, rate [95% CI]	59% [45–70]	51% [39–62]

CI, confidence interval; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell-death ligand 1; PFS, progression-free survival.

Adverse event profile of avelumab

In the pooled analysis, adverse events of any grade occurred in 244 (98%) of 249 patients, including in 166 (67%) who had a treatment-related adverse event (TRAE). The most frequent TRAEs of any grade were infusion-related reaction (IRR) in 73 (29%) patients, and fatigue in 40 (16%) patients. All IRRs were grade ≤ 2 and occurred mostly during the first or second infusions. Only 21 (8%) of 249 patients had grade 3 or worse TRAEs, the most common of which were four with fatigue (2%), asthenia, elevated lipase, hypophosphatemia, and pneumonitis in two (1%) patients each. There were three grade 4 TRAE (elevated lipase and creatine phosphokinase concentrations, and hyperkalemia), and one treatment-related death, due to pneumonitis in a patient with ongoing treatment-unrelated *Clostridium difficile* colitis and diverticulitis. A total of 34 (14%) of 249 patients had immune-related adverse events (IRAE), mostly rash ($n = 12$; 10%) and hypothyroidism ($n = 9$; 4%). Avelumab was permanently discontinued after a TRAE in 14 (6%) patients: IRR and pneumonitis in two (1%) patients each, and adrenal insufficiency, acute kidney injury, arthralgia, diarrhea, raised concentrations of alkaline phosphatase, aspartate aminotransferase, gamma-glutamyl transferase and lipase, enterocolitis, fatigue, general physical health deterioration, Guillain-Barré syndrome, and rash in one (<1%) patient each.

Predictors for avelumab response

Tumor PD-L1 status: In the JAVELIN trial, a positive PD-L1 status was defined as >5% PD-L1 expression on tumor cells using the Dako PD-L1 IHC 73-10 pharmDx assay (Dako, Carpinteria, California, USA). A total of 206 patients were

evaluable for PD-L1 expression level. Nonevaluable samples ($n = 43$) were those that were missing, of poor quality due to insufficient tumor content or cellular preservation, or otherwise not available to provide results. A sum of 82 (33%) patients were classified as PD-L1 positive and 124 (50%) patients as PD-L1 negative. A summary of responses and survival in evaluable patients is summarized in Table 1.

Thus, similar to experience with other anti-PD-1/PD-L1 agents in UC, there's a trend toward higher ORR and improved PFS and OS in patients with positive PD-L1 status with avelumab therapy. Generalizability of this data is limited due to use of different PD-L1 assays and cutoffs, as well as lack of longer-term survival data in the UC cohorts of the JAVELIN SOLID TUMOR trial.

Tumor mutational burden: Ribonucleic acid sequencing (RNAseq) of RNA extracted from archival slides was performed. Tumor-specific mutations were then identified by combining tumor RNASeq data with germline nontumor whole-exome sequencing. Resulting mutations were analyzed with NetMHCpan (<http://www.cbs.dtu.dk/services/NetMHCpan-4.0>) to predict peptide binding to major histocompatibility complex molecules of known sequences. Potential neoantigens were weighted based on expression level.

In 29 analyzed samples, an exploratory *post hoc* analysis did not reach statistical significance for the association between increased mutational load and improved antitumor response ($p = 0.076$, Wilcoxon rank sum test; sample size 29). These results are not conclusive due to small sample size and methodological limitations.

Differences between avelumab and other immunotherapies approved in UC

Avelumab is a newer immunotherapy with a less robust track record of efficacy compared with its competitors. There are four other anti-PD-1/PD-L1 inhibitors that are currently FDA approved in the same setting as avelumab.¹⁴ While it is difficult to compare across different clinical trials, avelumab appears to have roughly similar activity against UCs to pembrolizumab and atezolizumab suggesting that this would be an appropriate choice of therapy in advanced UC patients. ADCC has been proposed as a potential mechanism that may differentiate avelumab from other immunotherapy agents in its class, but the efficacy data do not demonstrate added benefit due to this mechanism.

Safety profile of avelumab also appears comparable with other immunotherapy agents in its class except for potentially higher (though only grade ≤ 2) rates of infusion-related reactions. Grade 3 and grade 4 IRRs are rare with avelumab, occurring in 0.2% and 0.5% of all patients, respectively. In clinical trials, most patients received diphenhydramine (a first-generation antihistamine) and acetaminophen as a premedication, and the FDA avelumab prescribing information recommends this strategy for the first four infusions, to prevent IRR. The magnitude of benefit (IRR risk reduction) from this premedication regimen is not known for avelumab and this recommendation is based on the cumulative experience from other CPI therapies.

Management of IRRs is relatively straightforward: should a grade 1 or 2 IRR occur despite premedication, physicians can choose to either decrease the infusion rate, or interrupt and restart at a slower rate, in addition to administering supportive medications. Decreasing the dose of avelumab is not recommended, and treatment discontinuation is not required for grade ≤ 2 IRRs. Grade 3 or 4 IRRs require immediate and permanent discontinuation of avelumab infusion, administration of IV corticosteroids and close observation.¹⁵

Interestingly, avelumab has a shorter terminal half-life at 6.1 days compared with other CPIs (e.g. pembrolizumab, 26 days).¹⁴ Whether this translates into a decreased frequency of late (≥ 30 days after treatment discontinuation) IRAEs, or a shorter duration of systemic corticosteroid therapy for IRAE for avelumab-treated patients, is unknown.

Conclusions and future directions

It is clear from the above data that avelumab is an active agent in advanced UC. Avelumab is now available as a standard of care option for patients having failed one line of prior chemotherapy. However, pembrolizumab has an advantage over other CPIs including avelumab in this setting, as it is the only agent to have shown an OS benefit.¹⁶ Avelumab is given every 2 weeks rather than every 3 or 4 weeks for the others, and this might be considered less convenient from a patient perspective.

For these reasons, several trials have been initiated to explore avelumab in other settings for UC such as combination chemoimmunotherapy for muscle-invasive UC before cystectomy and previously untreated metastatic UC. Numerous other trials are exploring avelumab in combination with other CPI, as well as potentially immunostimulatory or immunomodulating therapies such as PARP inhibitor or multikinase inhibitor. Table 2 has a listing of ongoing clinical trials which will include patients with UCs. While many of these studies are early-phase combination studies for all solid tumors, there are several studies specifically studying patients with UCs. The vast majority of these studies will be reporting results in 2019–2020. Whether or not avelumab will emerge from one of these studies as a clear winner remains to be seen.

Another interesting and perhaps unique approach is the creation of a fusion protein containing avelumab. One such first-in-class bifunctional fusion protein, M7824 (MSB0011359C), comprising an anti-PD-L1 moiety based on avelumab fused to the extracellular domain of human transforming growth factor beta (TGF- β) receptor 2 has shown remarkable preclinical activity.¹⁷ A phase I clinical trial of this drug is currently ongoing and data from 19 heavily pretreated patients treated in the dose-escalation part was recently published.¹⁸ The drug showed good desired end-target activity, with saturation of peripheral PD-L1 and sequestration of any released plasma TGF- β 1, - β 2, and - β 3 at doses higher than 1 mg/kg. Side effects were manageable and maximally tolerated dose was not reached. There was early evidence of efficacy with one complete response (cervical cancer), two durable partial responses (PRs; pancreatic cancer and anal cancer), one near PR (cervical cancer). Enrollment in expansion cohorts is ongoing.

Given the breadth and depth of clinical and preclinical development, it is safe to say that

Table 2. Ongoing clinical trials and future directions of development in bladder cancer.

Trial name (ClinicalTrials.gov identifier)	Brief description	Completion by
JAVELIN medley: a study of avelumab in combination with other cancer immunotherapies in advanced malignancies (NCT02554812)	Phase Ib/II, open-label, multicenter, study of avelumab in combination with other immune modulators in adult patients with locally advanced or metastatic solid tumors Arm A: avelumab plus utomilumab (4-1BB agonist mAb) Arm B: avelumab plus PF-04518600 (OX40 agonist mAb) Arm C: avelumab plus PD 0360324 (M-CSF mAb) Arm D: avelumab plus utomilumab plus PF-04518600	May 2020
JAVELIN PARP medley: avelumab plus talazoparib in locally advanced or metastatic solid tumors (NCT03330405)	Phase Ib/II study to evaluate safety and antitumor activity of avelumab in combination with the poly (adenosine diphosphate ribose) polymerase (Parp) inhibitor talazoparib in patients with locally advanced or metastatic solid tumors	March 2020
JAVELIN Bladder 100: a study of avelumab in patients with locally advanced or metastatic urothelial cancer (NCT02603432)	Phase III, multicenter, randomized, open-label, parallel-arm study of avelumab plus best supportive care <i>versus</i> best supportive care alone as a maintenance treatment in patients with locally advanced or metastatic urothelial cancer whose disease did not progress after completion of first-line platinum-containing chemotherapy	July 2020
PAVE-1: a dose-escalation and confirmation study of PT-112 in advanced solid tumors in combination with avelumab (NCT03409458)	Phase Ib/IIa, open-label, multicenter, nonrandomized, dose-escalation study of PT-112, a novel platinum-pyrophosphate agent, in combination with avelumab in selected advanced solid tumors	May 2020
JAVELIN chemotherapy medley: safety and efficacy study of avelumab plus chemotherapy with or without other anticancer immunotherapy agents in patients with advanced malignancies (NCT03317496)	Phase Ib/II, open-label, multicenter, safety and clinical activity study of avelumab in combination cisplatin and gemcitabine in patients with cisplatin-eligible urothelial cancer (cohort A2).	October 2020
A study combining eribulin mesylate with avelumab in cisplatin-ineligible metastatic urothelial cell cancer patients (NCT03502681)	Phase Ib, open-label, with expansion cohort of combination therapy with eribulin mesylate and avelumab in platinum-ineligible urothelial carcinoma patients	June 2019
A combination of avelumab and taxane (AVETAX) for urothelial cancer (NCT03575013)	Phase Ib, open-label study of avelumab in combination with docetaxel after failure of first-line platinum-containing chemotherapy regimen	Not yet recruiting
JAVELIN medley VEGF: a study of avelumab in combination with axitinib in non-small cell lung cancer or urothelial cancer (NCT03472560)	Phase II, open-label, multi-institutional study of avelumab in combination with axitinib in cisplatin-ineligible patients	July 2020
Safety and efficacy study of avelumab plus chemotherapy with or without other anticancer immunotherapy agents in patients with advanced malignancies (NCT03317496)	Phase Ib/II, open-label, multi-institutional study of avelumab in combination with first-line platinum-based chemotherapy	October 2019
QUILT-3.048: NANT urothelial cancer vaccine: combination immunotherapy in subjects with urothelial cancer who have progressed on or after chemotherapy and PD-1/PD-L1 therapy (NCT03197571)	Phase Ib/II, open-label study of NANT urothelial cancer vaccine combination immunotherapy with avelumab in patients with urothelial cancer having failed prior anti-PD-1/PD-L1 therapies	January 2019

Table 2. (Continued)

Trial name (ClinicalTrials.gov identifier)	Brief description	Completion by
A window-of-opportunity trial: avelumab in nonmetastatic muscle-invasive bladder cancer (NCT03498196)	Pilot, open-label study of avelumab after TURBT of a muscle-invasive urothelial cancer prior to cystectomy	Not yet recruiting
Trial of intratumoral administration of recombinant vesicular stomatitis virus monotherapy and in combination with avelumab in patients with refractory solid tumors (NCT02923466)	Phase Ib study of combination intratumoral oncolytic virus with systemic avelumab in patients with advanced solid tumors	January 2019

PD-L1, programmed cell-death ligand 1; PFS, progression-free survival; TURBT, transurethral resection of bladder tumor; VEGF, vascular endothelial growth factor.

avelumab is likely to have a continued role in the management of patients with UC.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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