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CADTH PCODR FINAL CLINICAL GUIDANCE REPORT

Clinical Report

Avelumab (Bavencio)

(EMD Serono - Pfizer Alliance)

Indication: for the first-line maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma whose disease has not progressed with first-line platinum-based induction chemotherapy.

Service Line:	CADTH pCODR Clinical Guidance Report
Version:	Final
Publication Date:	March 23, 2021
Report Length:	113 Pages

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AE	adverse event
BSC	best supportive care
BICR	blinded independent central review
CGP	Clinical Guidance Panel
CI	confidence interval
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DOR	duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EQ-5D-3L	European Quality of Life Scale, 5-Dimensions, 3-Level
FBISI	Functional Assessment of Cancer Therapy Bladder Cancer Symptom Index - 7 Item Version
HR	hazard ratio
ITT	intention to treat
IV	intravenous
KM	Kaplan-Meier
MID	minimally important difference
MRI	magnetic resonance imaging
NCCN-FACT	National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy
NCI	National Cancer Institute
NE	not estimable
NR	not reported
ORR	objective response rate
OS	overall survival
PAG	Provincial Advisory Group
PD	progressive disease
PD-L1	programmed death-ligand 1

pERC	pCODR Expert Review Committee
PFS	progression free survival
PR	partial response
PRO	patient reported outcome
QoL	quality of life
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
TTD	time to deterioration
TTR	time to response
UC	urothelial carcinoma
VAS	visual analogue scale

1 Guidance In Brief

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding avelumab (Bavencio) for the first-line maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) whose disease has not progressed with first-line platinum-based induction chemotherapy. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature conducted by the Clinical Guidance Panel (CGP) and the CADTH Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group (PAG); and input from Registered Clinicians.

The systematic review is fully reported in Sections 6. A background of Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input, a summary of submitted Provincial Advisory Group Input, and a summary of submitted Registered Clinician Input, and are provided in Sections 2, 3, 4, and 5 respectively. No supplemental issues were identified.

1.1 Introduction

The objective of this review is to evaluate the efficacy and safety of avelumab (Bavencio) plus best supportive care (BSC) for adult patients with locally advanced or metastatic UC whose disease has not progressed with first line platinum-based induction chemotherapy. Avelumab was granted a Health Canada Notice of Compliance (NOC) for this indication on December 10, 2020.[1]

Avelumab is a fully human immunoglobulin G1 (IgG1) monoclonal antibody directed against programmed death ligand (PD-L1). When avelumab binds PD-L1, interactions between PD-L1 and programmed death 1 (PD-1) and B7 are blocked, which removes the suppressive effects of PD-L1 on cytotoxic CD8+ T-cells; this results in the restoration of anti-tumour T-cell responses, ultimately leading to decreased tumour growth.[2] The recommended dosing for avelumab is 10 mg/kg as a one-hour IV infusion once every two weeks.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The CADTH systematic review included one randomized controlled trial (RCT), the JAVELIN Bladder 100 trial.[3] A summary of the trial and its results are provided below.

JAVELIN Bladder 100

The JAVELIN Bladder 100 trial is an international, multicenter, randomized, open-label, parallel arm phase III trial comparing the efficacy and safety of maintenance treatment with avelumab plus BSC versus BSC alone in adult patients with unresectable locally advanced or metastatic UC after completion of first-line platinum-based chemotherapy (gemcitabine plus cisplatin or gemcitabine plus carboplatin) without evidence of disease progression.[3] Patients were enrolled from 197 sites across 29 countries.[3] Eligible patients included adults

(≥18 years) with histologically confirmed, unresectable locally advanced or metastatic UC with an ECOG PS of 0 or 1 and documented stage IV disease measured according to RECIST v1.1 criteria before having received first-line chemotherapy. First-line chemotherapy must have been either gemcitabine plus cisplatin or gemcitabine plus carboplatin, and patients must have received four to six cycles of treatment with chemotherapy. Patients must not have experienced disease progression (i.e., they must have had an ongoing complete response, partial response, or stable disease) per RECIST v1.1 criterion. Before beginning study treatment, patients must have been treatment-free for four to ten weeks. Patients must also have had a tumour specimen obtained either recently or in archive, and have had adequate hematologic, hepatic, and renal function.[3] Key exclusion criteria included receipt of adjuvant or neoadjuvant systemic therapy within a year of receiving study treatment, contraindication for immune checkpoint inhibitors, previous exposure to immune checkpoint inhibitors, or progressive disease per RECIST v1.1 criteria.

Patients were randomized in a 1:1 ratio to receive either avelumab plus BSC or BSC alone. Randomization was stratified according to:

- Patients' response to first-line chemotherapy (CR or PR versus SD)[3]
- Metastatic site at initiation of first-line chemotherapy (visceral versus non-visceral; patients with unresectable locally advanced disease, including bone metastasis, were included in the non-visceral disease stratum)[3]

Randomization was centrally allocated across all study centres using an Interactive Response Technology (IRT) system. Site personnel, which included the study coordinator or specified designee, entered or selected information including but not limited to user's identification and password, the protocol number, patient identifiers and demographic information, and stratification factors. Treatment assignment of patients was then provided to the site personnel.[3] The JAVELIN Bladder 100 trial was open-label and therefore investigators and patients were aware of treatments administered. Disease progression was determined and confirmed by an expedited independent blinded central review (BICR) based on radiological assessments (CT/MRI scans) from pre-chemotherapy and post-chemotherapy confirmatory scan(s).[3]

The primary endpoint of the trial was OS, assessed in both the Overall and PD-L1 Positive Populations. OS was defined as the time from the date of randomization to the date of death due to any cause. Patients last known to be alive were censored at the date of last contact. [3] The null hypothesis of the JAVELIN Bladder 100 trial was that avelumab plus BSC maintenance therapy was not better than BSC alone; therefore, a one-sided test for superiority was performed against the null hypothesis with an alpha of 0.025. [3] The type 1 error rate was maintained at or below the one-sided alpha by allocating an alpha of 0.015 to the OS comparison in the Overall Population, and an alpha of 0.01 to the OS comparison in the PD-L1 Positive Population. To preserve the overall type 1 error rate and determine efficacy boundaries, a group-sequential design with a Lan-DeMets (O'Brien-Fleming) alpha spending function was used. To accept the alternative hypothesis of this trial (that avelumab plus BSC maintenance is superior to BSC alone), statistical significance in either the Overall or PD-L1 Positive Populations must have been observed via stratified log-rank test for OS. The study would be considered positive if the stratified log rank test for OS was significant at the respective adjusted levels at the interim or at the final analyses, for either of the two co-primary populations.[3] Secondary endpoints of the trial included PFS, ORR, TTR, DOR, DC.

Efficacy outcomes were analyzed in the intention-to-treat (ITT) population; i.e., all randomized patients were analyzed according to their assigned treatment groups. Two co-primary populations of interest were evaluated in the JAVELIN Bladder 100 trial[3]:

- Overall Population: all patients who underwent randomization
- PD-L1 Positive Population: patients with PD-L1 positive tumours.

One pre-specified interim analysis was planned for each co-primary populations; the interim analyses was conducted at the same time for both co-primary populations. The interim analysis was planned to occur after an estimated 74% of events (315 patients with documented disease progression per BICR assessment or death) in the Overall Population and 66.7% of events (146 patients with documented disease progression pre BICR assessment or death) in the PD-L1 Positive Population.[3] An independent data and safety monitoring committee reviewed results of the interim analysis on December 20, 2019 and it was determined that the efficacy boundaries for OS in the Overall Population ($p<0.0053$) and the PD-L1 Positive Population ($p<0.0014$) had been crossed, and therefore the analyses were considered as final.[3]

A total of 700 patients met the requirements and were enrolled in the JAVELIN Bladder 100 trial (350 patients in each treatment group in the Overall Population). Within the PD-L1 Positive Population,189 patients were randomized to the avelumab plus BSC group and 169 patients were randomized to the BSC group.[3] In the Overall Population, the baseline characteristics were similar for both treatment groups. The median age was 68 years (range, 37-90) in the avelumab plus BSC group and 69 years (range, 32-89) in the BSC group.[3] Most patients were 65 years of age or older (avelumab plus BSC: 63.1%; BSC: 69.4%). A slightly lower proportion of patients were between 66 and 74 years of age in the avelumab plus BSC group (38.9%) compared to the BSC group (46.6%). Most patients were White (avelumab plus BSC: 66.3%; BSC: 68.0%) males (avelumab plus BSC: 76.0%; BSC: 78.6%), recruited from Europe (avelumab plus BSC: 61.1%; BSC: 58.0%), and belonged to the ethnic group categorized as not Hispanic or Latino (avelumab plus BSC: 81.7%; BSC: 85.1).[4] Baseline demographic characteristics were similarly reported in the PD-L1 Positive Population.[4]

In the Overall Population, the same proportions of patients were reported to have visceral (54.6%) and non-visceral (45.4%) site of baseline metastasis before receipt of chemotherapy in both treatment groups. More patients had a complete or partial response to first-line chemotherapy (avelumab plus BSC: 72.3%; BSC: 72.0%) versus patients who had a stable disease (avelumab plus BSC: 27.7%; BSC: 28.0%). Overall, 54.0% of patients in the avelumab plus BSC group and 48.3% of patients in the BSC group had PD-L1 positive status tumours. A smaller proportion of patients had tumours with unknown PD-L1 status in the avelumab plus BSC group (6.3%) compare to the BSC group (14.3%). Slightly less patients received gemcitabine plus cisplatin as their first-line chemotherapy regimen in the avelumab plus BSC group compared to the BSC group (52.3% versus 58.9%, respectively), and more patients received gemcitabine plus carboplatin in the avelumab plus BSC group (42.0% versus 34.9%, respectively). A greater proportion of patients had an upper tract tumour as the primary site of the disease in the avelumab plus BSC group (30.3%) compared to the BSC group (23.1%).[3] The median time from initial diagnosis of UC to the date of first study treatment was 11.5 months in the avelumab plus BSC group and 12.8 months in the BSC group.[4]

In the PD-L1 Positive Population, baseline characteristics were balanced across treatment groups. Most patients had either a CR or PR to their first-line chemotherapy (avelumab plus

BSC: 73.5%; BSC: 75.7%). A slightly lower proportion of patients had visceral disease (avelumab plus BSC: 46.6%; BSC: 46.7%), versus non-visceral disease (53.4% and 53.3%, respectively).[3] Most patients had an ECOG PS of 0 (avelumab plus BSC: 60.3%; BSC: 63.3%) or 1 (39.2% and 36.1%, respectively).[4] Most patients also had the primary site of their tumour in the lower tract (avelumab plus BSC: 76.7%; BSC: 79.3%).[3] The median time from initial diagnosis of UC to the date of first study treatment was 13.3 months for the avelumab plus BSC group and 10.2 months for the BSC group.[4] Compared to the Overall Population, a greater proportion of patients in the PD-L1 Positive Population had baseline metastasis in non-visceral sites (53.4% in the avelumab plus BSC group and 53.3% in the BSC group) than in visceral sites (46.6% for both treatment groups).[3]

The median duration of treatment among all treated patents was 24.9 weeks (range, 2.0-159.9) in the avelumab plus BSC group compared to 13.1 weeks (range, 0.1-155.6) in the BSC group.[3] The longer median duration of treatment in the avelumab plus BSC group was stated by the sponsor to be mainly driven by the earlier PFS time in the BSC group.[4] For patients randomized to receive maintenance treatment with avelumab, pre-medication 30 to 60 minutes prior to the avelumab infusion was mandatory for the first four infusions. The most frequent pre-medications reported were analgesics (99.4%) and an antihistamine for systemic use (100%).[4]

Efficacy

The results of the primary and secondary endpoints from the JAVELIN Bladder 100 trial were based on a median follow-up for OS was greater than 19.6 (95% CI: 18.0 to 20.6) months for patients in the avelumab plus BSC group and 19.2 (95% CI: 17.4 to 21.6) months for patients in the BSC group in the Overall Population. The median follow-up for OS was 18.3 (95% CI: 16.0 to 20.2) months and 20.0 months (95% CI: 17.1 to 22.2) for the avelumab plus BSC and BSC groups, respectively, in the PD-L1 Positive Population.[4]

In the Overall Population, the median OS was longer in the avelumab plus BSC group at 21.4 months (range, 18.9-26.1) compared to the BSC group which had a median OS of 14.3 months (range, 12.9-17.9)[3]. The stratified HR for death was 0.69 (95%CI 0.56-0.86;), indicating a 31% reduction in risk of death and statistically significantly in favour of maintenance treatment with avelumab plus BSC.[3] Results for OS in the PD-L1 Positive Population were similar to results observed in the Overall Population; median OS in the avelumab plus BSC group was not estimable (NE) (range, 20.3 to NE) compared to 17.1 months (range, 13.5 to 23.7) in the BSC group,[3]. The stratified HR for death was statistically significantly in favour of the avelumab plus BSC group resulting in a 44% reduction in risk of death compared to patients in the BSC group (HR=0.56, 95%CI 0.40 to 0.79).

Secondary endpoints assessed by BICR, including PFS, ORR, DCR, and TTR, also demonstrated superior treatment efficacy with avelumab plus BSC maintenance treatment over BSC alone:

- PFS
  - The median PFS was 3.7 months (95% CI: 3.5 to 5.5) in the avelumab plus BSC group compared to 2.0 months (95% CI: 1.9 to2.7) in the BSC group (HR=0.62; 95% CI: 0.52 to 0.75).[3] In the PD-L1 Positive Population, the median PFS was 7.5 months (95% CI: 5.5 to11.2) and 2.8 months (95% CI: 2.0 to 3.7) in the avelumab plus BSC group and the BSC group, respectively (HR=0.43; 95% CI 0.33 to 0.55).[4]

- ORR
  - In the Overall Population, a greater proportion of patients in the avelumab plus BSC group had a confirmed objective response compared to the BSC group, with 9.7% of patients (95% CI: 6.8 to 13.3) and 1.4% of patients (95% CI: 0.5 to 3.3) in the avelumab plus BSC group and the BSC groups respectively (stratified odds ratio [OR] : 7.46; 95% CI: 2.82 to 24.45). Results for overall response in the PD-L1 Positive Population were similar to those of the Overall Population; 13.8% of patients (95% CI: 9.2 to 19.5) in the avelumab plus BSC group and 1.2% of patients (95% CI: 0.1 to 4.2) in the BSC group had a confirmed objective response, respectively (stratified OR : 12.70; 95% CI: 3.16 to 114.12).[3]
- DCR
  - In the Overall Population, the proportion of patients with a best overall response was greater in the avelumab plus BSC group than the BSC group (41.1% versus 27.4%, respectively). Similarly in the PD-L1 Positive Population, 43.9% of patients in the avelumab plus BSC group had a best overall response compared to 27.8% of patients in the BSC group.[3]
- TTR
  - In the Overall Population, the median TTR was the same in both treatment groups at two months (avelumab plus BSC group: range, 1.7 to 16.4 months; BSC group: range, 1.8 to 7.0 months). In the PD-L1 Positive Population, the median TTR was 2.0 months (range, 1.7-16.4) in the avelumab plus BSC group and 2.8 months (range, 1.8-3.8) in the BSC group.[3]

Patient Reported Outcomes - NCCN-FACT FBISI and the EQ-5D-5L

Health-related quality of life (HRQoL) was assessed using the following tools: the National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy (NCCN-FACT) FACT-Bladder Cancer Symptom Index (FBISI) and EuroQol 5 Dimensions 5- levels (EQ-5D-5L) and Visual Analogue Scale (VAS).[3] For the Overall Population, completion rates for both the FBISI and EQ-5D-5L for both treatment groups of the trial were reported to be >90% for the majority of the treatment period.[5] After cycle 18, the number of patients eligible for completion was less than 50 patients.[4] For the PD-L1 Positive Population, completion rates for both questionnaires were also similar to those of the Overall Population for both treatment groups.[4]

In the Overall Population, the mean FBISI-18 total score at baseline in the avelumab plus BSC group was [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]) in the BSC group. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* During on treatment assessments with sufficient data from at least 10 patients (through cycle 31 for the avelumab plus BSC group and cycle 25 for the BSC group) FIBISI-18 total scores showed improvement (i.e., better HRQoL) in both treatment groups.[4] In the Overall Population, changes in the FIBISI-18 total and subscale scores from baseline were similar between the avelumab plus BSC group and the BSC group. Results of the PD-L1 Positive Population were similar to those of the Overall Population.[5]

The FBISI DRS-P subscale was used to measure TTD in both co-primary populations, which corresponded to an MID of a decrease of three points or greater from baseline in scores for two consecutive assessments.[4] The median TTD was not reached (95% CI: 13.9 months to not reached) in the avelumab plus BSC group, and was 13.8 months (95% CI: 12.9 months

to not reached) in the BSC group (HR=1.26; 95% CI: 0.90 to 1.77).[5] Similar results were observed for the PD-L1 Positive Population; in the avelumab plus BSC group, median TTD was [redacted] (95% CI: [redacted]) versus a median TTD of [redacted] months in the BSC group (95% CI: [redacted]) (HR = [redacted]; 95% CI: [redacted]).[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

In the Overall Population, the mean EQ-5D-5L score at baseline in the avelumab plus BSC group was [redacted] (95% CI: [redacted]) and was [redacted] (95% CI: [redacted]) in the BSC group. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* During on treatment assessments with sufficient data from at least 10 patients (through cycle 31 for the avelumab plus BSC group and cycle 25 for the BSC group) EQ-5D-5L scores showed improvement (i.e., better health state) in both treatment groups.[4]In the Overall Population, the mean VAS scores at baseline were similar in the avelumab plus BSC and BSC groups at [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]), respectively. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* During on treatment assessments with sufficient data from at least 10 patients (through cycle 31 for the avelumab plus BSC group and cycle 25 for the BSC group), VAS scores increased (i.e., better health state) for both treatment groups.[4] Changes from baseline were similar between both the avelumab and BSC groups in the EQ-5D-5L index and VAS scores. Similar results were observed for the PD-L1 Positive Population.[5] In the Overall Population and the PD-L1 Positive Population, EQ-5D-5L and VAS results were similar between both treatment groups similar using a mixed model analysis.[4]

Harms

In general, adverse events (AEs) of all types occurred more frequently among patients in the avelumab plus BSC group compared to patients in the BSC group.

AEs of any grade occurred more frequently in the avelumab plus BSC group versus the BSC group (98.0% versus 77.7%, respectively); occurrence of any AE was reported no more frequently than in 17.7% of patients. Grade 3 or higher AEs occurred more frequently in the avelumab plus BSC group compared to the BSC group (47.4% versus 25.2%, respectively). The most commonly occurring grade 3 or higher AEs in the avelumab plus BSC group compared to the BSC group were urinary tract infection (4.4% versus 2.6%) and anemia (3.8% versus 2.9%).[3] Serious AEs (SAEs) occurred in 96 patients (27.9%) in the avelumab plus BSC group and 69 patients (20.0%) in the BSC group. The most common SAE was urinary tract infection, occurring in 16 patients (4.7%) in the avelumab plus BSC group and seven patients (2.0%) in the BSC group.[3]

Treatment-related AEs of any grade occurred in a total of 266 patients (77.3%) in the avelumab plus BSC group and in four patients (1.2%) in the BSC group. The most common treatment-related AEs in the avelumab plus BSC group were pruritus (13.7%), hypothyroidism (10.5%), diarrhea (10.2%) and infusion-related reactions (10.2%). None of

these treatment-related AEs occurred in the BSC group. Treatment-related AEs of grade 3 or higher were reported in 57 patients (16.6%) the avelumab plus BSC group. Of these three patients (0.9%) experienced a grade 4 treatment related AE. No patients in the BSC group experienced a grade 3 or higher treatment related AE.[3]

An immune-related AE of any grade was reported in 101 patients (29.4%) in the avelumab plus BSC group and in five patients (1.4%) in the BSC group.[3,4] Grade 3 immune-related AEs occurred in 24 patients (7.0%) in the avelumab plus BSC group and one patient (0.3%) in the BSC group.[3,4] There were no occurrences of grade 4 or 5 immune-related AEs. In the avelumab plus BCS group, most immune-related AEs were thyroid disorders (n = 41; 12.2%); the most common immune-related AEs of any grade to occur were hypothyroidism (10.2%) and rash (4.9%).[3] Grade 3 or higher immune-related AEs occurred in 24 patients (7.0%) in the avelumab plus BSC group, and one patient (0.3%) in the BSC group.[3,4] A total of 31 patients (9.0%) received high-dose glucocorticoids (≥40 mg total daily dose of prednisone or equivalent) after having an immune-related AE.[3] Serious immune-related AEs occurred in [redacted] patients ([redacted]%) in the avelumab plus group, most commonly due to colitis which occurred in [redacted] patients ([redacted]%). [redacted] ([redacted]%) in the BSC group experienced a serious immune-related AE which was due to diabetes mellitus.[4] Discontinuation of treatment due to immune-related AEs occurred in [redacted] patients ([redacted]%) in the avelumab plus BSC group, most commonly due to an immune-related AE was an alanine aminotransferase increase, occurring in [redacted]% of patients.[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Infusion related reactions (referring to the composite category) occurred in 74 patients (21.5%) in the avelumab plus BSC group, and in no patients in the BSC group, with the most commonly occurring reacting being related to infusion related reactions (10.2%), followed by chills (6.4%) and pyrexia (5.2%). Three patients (0.9%) experienced grade 3 or higher infusion related reactions. Serious infusion related reactions in the avelumab plus BSC group were reported in [redacted] patients ([redacted]%), all of whom discontinued receiving study treatment with avelumab. Patients first experiencing an infusion related reaction typically did so following their first or second infusion of avelumab; only [redacted] patients experienced an infusion related reaction for the first time during a later infusion.[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Deaths were mainly due to progression of disease, occurring in [redacted] patients ([redacted]%) in the avelumab plus BSC group versus [redacted] patients ([redacted]%) in the BSC group.[4] Based on investigator assessment, [redacted] patients ([redacted]%) in the avelumab plus BSC group experienced death related to toxicity of trial treatment. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* One of the patients experienced sepsis following a urinary tract infection and possible central venous catheter infection after having received 11 infusions of avelumab. The second patient did from an ischemic occurring stroke 100 days

after having received one dose of avelumab and after disease progression and AEs of limb venous thrombosis, pulmonary embolism and acute myocardial infarction.[3]

Limitations and Potential Sources of Bias

A complete list of limitations and sources of bias are available in section 6 of this report. A summary of the major limitations and sources of bias are summarized below:

- The JAVELIN Bladder 100 trial was conducted using an open-label study design, which is susceptible to reporting and performance biases. Patients and investigators were aware of the study drug assigned, which can introduce the potential to bias results and outcomes in favour of the active treatment if the assessor (investigator or patient) believes the study drug is likely to provide a benefit. This limits the robustness of the efficacy results. The sponsor justified the use of an open-label study design as avelumab is administered to patients via one-hour infusion; the use of a placebo equivalent in a double-blind placebo-controlled trial would have involved administration of an intravenous placebo which may have introduced patients randomized to the BSC group to risks, including injection site reactions; the sponsor indicated that patients randomized to the BSC group would not have benefit from such a procedure. Further, as patients receiving avelumab required premedication with an H1 blocker and paracetamol prior to infusion to limit incidence and severity of infusion-related reactions, patients randomized to the BSC group would also be required to receive placebo equivalents; the sponsor indicated that providing such treatments would be unnecessary to patients randomized to the BSC group of the trial. [3] Therefore, the lack of blinding may have introduced bias affecting the performance, measurement and reporting of clinical outcomes (i.e., safety and efficacy) in the context of both the patients and investigators. However, randomization was performed centrally using an IRT system, and a BICR was implemented to mitigate biases associated with assessment of outcomes, such as PFS and ORR. Further, disease progression was based on objective diagnostic criteria (RECIST v1.1) and radiological assessments, including CT or MRI scans. Biases pertaining to an open-label study design likely continued to exist; however, they may not have impacted patients' treatment assignment or the trial outcomes due to the IRT system for randomization, objective diagnostic testing criteria and BICR assessment of outcomes.
- In addition to the bias that an open-label design introduces to reporting safety and/or efficacy outcomes, the measurement of PROs may also be biased favouring maintenance treatment with the investigational therapy (avelumab plus BSC) over the control group in the trial (BSC alone) as patients remained aware of their treatment assignment. Completion of PRO questionnaires may have been influenced by patients' knowledge of their assigned treatment and this should be taken into account when interpreting results from PRO questionnaires. MID of 3 points was prespecified for the FBlSI HRQoL tool in the trial. However, there was no prespecified MID established for the EQ-5D-5L or VAS tools, and results for these questionnaires were not reported based on MID between treatment groups. MID is a useful calculation to determine whether differences in HRQoL observed between trial groups are clinically relevant. Without a MID, results for the EQ-5D-5L and VAS tools may be interpreted only based on changes in HRQoL observed from baseline throughout the trial. The sponsor noted that data from patients for the EQ-5D were primarily collected to calculate utility values for economic models.[6] The sponsor also noted that a MID has been established for UK-utility scores ranging from 0.09 to 0.12 for the EQ-5D-5L and 7 to 12 for the VAS for all cancers.[6,7] As no MID was prespecified for analysis of the EQ-5D-5L and VAS, results were not reported or interpreted this way.
- In the analysis of OS, censoring occurred on the date patients were last known to be alive. A large proportion of patients were censored in the analysis of OS; censoring of patients occurred in [redacted]% of patients in the avelumab plus BSC group and 49% of patients in the BSC group. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the*

Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed). The large amount of censoring may inflate the benefit observed in the avelumab plus BSC group. In addition, analysis of OS did not account for patients who may have received subsequent therapies. Few patients in the avelumab plus BSC group ([redacted]%) received at least one type of subsequent anti-cancer therapy versus patients in the BSC group ([redacted]%). *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* Patients in the BSC group more frequently received at least one anti-cancer drug therapy than patients in the avelumab plus BSC group (61.7% versus 42.3%, respectively).[4] Patients in the BSC group most commonly received a subsequent PD-1 or PD-L1 inhibitor (43.7%) which may underestimate the results of OS as patients receiving subsequent therapy will receive additional benefit from treatment. Overall, analyses of OS were confounded in ways which could have both over- and underestimated the treatment benefit of avelumab plus BSC. Despite the biases associated with the analysis of OS, numerous sensitivity analyses of OS continued to support the primary results of OS which demonstrate improved survival for patients who received avelumab plus BSC maintenance treatment.[4]

- Analysis of PROs was dependent on completion of PRO questionnaires by patients. For the FBISI, completion of the entire questionnaire was less than [redacted]% of patients during all cycles, and from cycle 2, substantially fewer patients in the BSC group were eligible to complete the FBISI questionnaire (n=[redacted]), than the avelumab plus BSC group (n=[redacted])[5]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* In addition, after cycle 19, few patients (<50) were eligible for completion of both the FBISI and the EQ-5D questionnaires. Therefore, the number of patients included in the calculation of mean changes from baseline decreased over the course of treatment during the trial, introducing uncertainty in the results of the PROs. Further, the analysis of TTD was conducted based on FBISI DRS-P results. It was noted that results of TTD may be biased in favour of the avelumab plus BSC maintenance group, as events of progression or death were not considered deterioration events in the KM analysis resulting in greater censoring of patients in the avelumab plus BSC group versus the BSC group.[5] Although, in general a large number of patients were censored in the analysis for TTD ([redacted]% of patients in the avelumab plus BSC group and [redacted]% of patients in the BSC group), mainly due to patients ongoing in the trial without experiencing an event ([redacted]% versus [redacted]%, respectively).[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* KM analysis of TTD revealed a median TTD of 13.8 months (95% 12.9-NE) in the BSC group and a median TTD of NE (95%CI 13.9-NE) in the avelumab plus BSC group, with results favouring the BSC group (HR=1.26, 95%CI 0.90-1.77). A post-hoc analysis of TTD based on death or decline in DRS-P was also conducted for TTD and favoured the avelumab plus BSC group over the BSC group, resulting in a HR of 0.84 (95% CI: 0.68 to 1.03; P=0.089).[5] As the analysis of TTD was reported to be biased for the avelumab plus BSC group, the results suggest that attention to the deterioration and physical state of patients may be warranted with maintenance treatment with avelumab plus BSC.

Table 1: Highlights of Key Outcomes

	Overall Population		PD-L1 Positive Population	
	Group (N=350)	Group (N=350)	Group (N=189)	Group (N=169)
Primary Endpoint				
OS, median, months (95% CI)	21.4 (18.9 to 26.1)	14.3 (12.9 to 17.9)	NE (20.3 to NE)	17.1 (13.5 to 23.7)
HR (95%CI)	0.69 (0.56 to 0.86)		0.56 (0.40 to 0.79)	
1-sided p-value 2-sided p-value	0.0005 0.0010		0.0003 0.0007	
Secondary Endpoints				
PFS, median, months (95% CI)	3.7 (3.5 to 5.5)	2.0 (1.9 to 2.7)	5.7 (3.7 to 7.4)	2.1 (1.9 to 3.5)
HR (95%CI)	0.62 (0.52 to 0.75)		0.56 (0.43 to 0.73)	
1-sided p-value 2-sided p-value	<0.0001 <0.0001		<0.0001 <0.0001	
ORR, n responders	34	5	26	2
% (95% CI)	9.7 (6.8 to 13.3)	1.4 (0.5 to 3.3)	13.8 (9.2 to 19.5)	1.2 (0.1 to 4.2)
Confirmed BOR, n (%)				
Complete response	21 (6.0)	3 (0.9)	18 (9.5)	1 (0.6)
Partial response	13 (3.7)	2 (0.6)	8 (4.2)	1 (0.6)
Stable disease	44 (12.6)	46 (13.1)	19 (10.1)	23 (13.6)
Non-complete response or non-progressive disease	66 (18.9)	45 (12.9)	38 (20.1)	22 (13.0)
Progressive disease	130 (37.1)	169 (48.3)	59 (31.2)	82 (48.5)
Could not be evaluated	76 (21.7)	85 (24.3)	47 (24.9)	40 (23.7)
DCR, n (%)	144 (41.1)	96 (27.4)	83 (43.9)	47 (27.8)
Harms Outcome, n (%)	**Group (N=344)**	**Group (N=345)**		
AE (any grade)	337 (98.0)	268 (77.7)	NR	NR
Grade ≥3 AE	163 (47.4)	87 (25.2)	NR	NR
TRAE (any grade)	266 (77.3)	4 (1.2)	NR	NR
Grade ≥3 TRAE	57 (16.6)	0	NR	NR
SAE	96 (27.9)	69 (20.0)	NR	NR
AEs leading to dose reduction of avelumab	1 (0.3)	0	NR	NR
AEs leading to interruption of avelumab	140 (40.7)	0	NR	NR
AEs leading to discontinuation of study drug	41 (11.9)	0	NR	NR
irAE	101 (29.4)	5 (1.4)	NR	NR
IRR	74 (21.5)	0	NR	NR

AE = adverse event, BOR = best overall response, BSC = best supportive care, CI = confidence interval, HR = hazard ratio, irAE = immune related adverse event, IRR = immune related reaction, NR = not reported, PD-L1 = programmed death-ligand 1, SD = standard deviation, TRAE = treatment-related adverse event, WDAE = withdrawal due to adverse event

*HR < 1 favours avelumab plus BSC group

Source: Clinical Study Report[4], Powles et al. 2020[3]

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

One input was provided by Bladder Cancer Canada (BCC), for the review of avelumab for the first-line maintenance treatment of patients with locally advanced or metastatic UC whose disease has not progressed with first-line platinum-based induction chemotherapy.

BCC gathered information from two sources: an online survey and a one-to-one patient interview. The online survey was conducted between September 8, 2020 and September 18, 2020. This survey included 45 patients and three caregivers. Of the 48 completed surveys, 34 respondents were from Canada, three were from the US, one was from Brazil, one was from Kenya, and seven respondents chose not to answer where they were from. Patients were diagnosed in the following years: 6 in 2020, 9 in 2019, 5 in 2018, 9 in 2017, 5 in 2016, 10 from 2010 to 2015, and 4 in 2009 or earlier. A total of 28 respondents had been diagnosed with muscle-invasive UC and 20 had been diagnosed with locally advanced or metastatic UC. Two patients that were surveyed had treatment experience with avelumab, and one of these patients participated in a one-to-one 40-minute phone interview.

Currently, there is no approved maintenance treatment for patients with locally advanced or metastatic UC whose disease has not progressed with platinum-based chemotherapy. These patients currently receive best supportive care. The most commonly reported symptoms of UC were blood in the urine, fatigue, difficulty urinating and a burning sensation during urination. Previously used treatments reported by respondents were gemcitabin, cisplatin, carboplatin, pembrolizumab, durvalumab, atezolizumab, docetaxel, methotrexate, doxorubicin, paclitaxel and enfortumab. The most frequently reported side-effects of current treatments were fatigue, loss of appetite, nausea, low blood cell counts, hair loss, constipation, and neuropathy. A few patients also reported that the disease and current treatments have caused a financial burden due to increased travel and accommodation costs, drug costs, and loss of income due to work absence. Out of the two patients that reported being treated with avelumab, one reported mild to moderate side-effects and was able to complete the full course the treatment. The other patient reported that they initially experienced few side-effects but had to discontinue the treatment after six months due to a sudden onset of side-effects. However, both patients concluded that they would recommend avelumab to other patients. Overall, patients value preventing disease recurrence, controlling progression, and maintaining their quality of life. Most patients reported that they would tolerate moderate to severe adverse effects if a treatment controlled disease progression or prevented recurrence. BCC strongly recommends the reimbursement of avelumab as it addresses an unmet need and aligns with patient values.

Of note, quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient groups.

Provincial Advisory Group (PAG) Input

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Place in therapy and sequencing with currently available treatments including other immune checkpoint inhibitors
- Eligibility in patients unable to receive or complete induction platinum chemotherapy

Economic factors:

- Unclear treatment duration

Registered Clinician Input

One joint clinician input was provided from two medical oncologists. One oncologist provided input on behalf of Ontario Health (Cancer Care Ontario) GU Drug Advisory Committee, and the other was an oncologist was practicing in at an Ontario health centre.

Overall, the clinicians providing input felt that the patient population in the reimbursement request aligns with the need identified in their clinical practice. They would use avelumab maintenance therapy in patients who have received first line platinum-containing regimen and experienced stable disease or regression. The clinicians felt that avelumab fulfills an unmet need for maintenance treatment following good response to platinum-based induction chemotherapy. Currently, these patients are monitored and given best supportive care. In the event of disease progression, patients are treated with pembrolizumab. Avelumab maintenance therapy would be a replacement of pembrolizumab in these patients.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

Comparison with Other Literature

The CADTH Clinical Guidance Panel and the CADTH Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of Generalizability of Evidence for Maintenance Treatment with Avelumab plus Best Supportive Care

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td>Population</td><td>ECOG PS</td><td>The JAVELIN Bladder 100 trial enrolled patients with an ECOG PS of 0 or 1. However, a total of four patients with an ECOG PS of 2 (n=1) or 3 (n=3) were included in the trial.[3]
<table>
<tr><th>ECOG PS</th><th>Avelumab Group[a] n (%)</th><th>Control Group[b] n (%)</th></tr>
<tr><td>0</td><td>213 (60.9)</td><td>211 (60.3)</td></tr>
</table></td><td>Do the trial results apply to patients with worse performance status?</td><td>The trial results are generalizable to patients with an ECOG PS of ≤2. Given that a worse PS (i.e., ECOG PS of 3) may be due to the effects of chemotherapy of chemotherapy treatment and not due to cancer symptoms, it may be reasonable that the results of the trial be generalizable</td></tr>
</table>

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		1: 136 (28.9) / 136 (38.9) 2: 1 (0.3) / 0 3: 0 / 3 (0.9) 4: 0 / 0 NR: 0 / 0		to patients with and ECOG PS of 3, however clinical judgment would need to be exercised.
	Measurable disease	Patients were enrolled in the trial if they had measurable disease based on RECIST v1.1 criteria.[3]	Are trial results generalizable to patients without measurable disease?	The CGP considered the trial data generalizable to patients with incurable urothelial cancer of predominantly transitional histology without formally measurable manifestations of their cancer, as long as there was no evidence of disease progression on or after 1st-line chemotherapy.
Comparator	Best supportive care	In the JAVELIN Bladder 100 trial, BSC was provided to patients as deemed appropriate by the treating physicians, but could include treatment with antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including palliative radiotherapy). BSC did not include any anti-tumour therapies; although, local radiotherapy of isolated lesions with palliative intent was acceptable.[3]	Is this definition of BSC in the trial applicable to how Canadian patients receiving BSC may be treated? Is there any expected variation of how BSC is provided to patients across different institutions or countries?	The included countries have practice patterns similar to those of Canada. The trial results may be applied to Canadian patients.
Outcomes	Appropriateness of Primary and Secondary Outcomes	Primary outcome: OS Secondary outcomes: PFS, ORR, TTR, DOR, DCR, safety, PROs[3]	Were the primary and secondary outcomes appropriate for the trial design?	The selection of endpoints in the trial were appropriate and of clinical relevance.
Setting	Countries participating in the trial	The JAVELIN Bladder 100 trial was conducted in 197 sites across 29 countries within North America, Europe, Asia, Australasia and the Rest of the World.[3] A total of [redacted] Canadian patients were enrolled in the study: [redacted] patients from Ontario and [redacted] from Quebec.[8]	Are there any known potential differences in the practice patterns between other countries that the other trial was conducted in and Canada?	The included countries have practice patterns similar to those of Canada. The trial results may be applied to Canadian patients.
Comparator	Best supportive care	In the JAVELIN Bladder 100 trial, BSC was provided to patients as deemed appropriate by the treating physicians, but could include treatment with antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including palliative	Is this definition of BSC in the trial applicable to how Canadian patients receiving BSC may be treated? Is there any expected variation of how	The included countries have practice patterns similar to those of Canada. The trial results may be applied to Canadian patients.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		radiotherapy). BSC did not include any anti-tumour therapies; although, local radiotherapy of isolated lesions with palliative intent was acceptable.[3]	BSC is provided to patients across different institutions or countries?	

Avelumab Group: Patients were treated with avelumab (10 mg/kg every two weeks) plus best supportive care

Control Group: Patients were treated with best supportive care

BSC = best supportive care; CGP = clinical guidance panel; ECOG PS = Eastern Cooperative Oncology Group performance status; DCR = disease control rate;

DOR = duration of response; NR = not reported; ORR = overall response rate; OS – overall survival; PFS = progression-free survival; PRO = patient-reported outcomes;

RECISR = Response evaluation criteria in solid tumors; TTR = time-to-tumour response.

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

1.2.4 Interpretation

Burden of Illness and Need

Although 1st-line platinum-based combination chemotherapy has reasonably high objective response rates and is associated with improved overall survival, and 2nd-line immunotherapy with pembrolizumab has modestly improved overall survival, virtually all patients with recurrent, metastatic or locally advanced incurable urothelial cancer die from it (Bellmunt NEJM 2017). Improved treatment options for these patients are needed and highly relevant, as urothelial cancer remains an important cause of cancer death in Canada with approximately 2500 deaths annually. The effectiveness of immunotherapy as 2nd-line treatment has led to investigation of immunotherapy-based 1st-line treatment strategies for incurable urothelial cancer in at least 6 RCTs that have now completed enrollment and continue to report results. The value of conducting RCTs was confirmed when unfavorable survival outcomes were observed early in two trials in a subset of patients with low tumor PD-L1 expression receiving monotherapy with either pembrolizumab or atezolizumab. Subsequently, a US FDA warning about use of monotherapy PD-1/PD-L1 inhibitors based on tumor PD-L1 expression was announced, as several of these agents had been approved as monotherapy for the treatment of 1st-line cisplatin ineligible incurable urothelial cancer based on uncontrolled data.

To date only the JAVELIN Bladder 100 trial (n=700) has reported improved overall survival with the addition of 1st-line immunotherapy. This RCT randomized patients achieving objective tumor response or at least stable disease with standard gemcitabine/platinum chemotherapy to either maintenance therapy with the PD-L1 inhibitor avelumab plus best supportive care [BSC] or BSC alone and will be discussed further as the main focus of this report (Powles NEJM 2020). Overall survival was not improved in the DANUBE RCT (n=1004) with tremelimumab plus durvalumab compared to chemotherapy (Powles ESMO 2020). In the KEYNOTE-361 RCT (n=1010) overall survival was not improved with the addition of pembrolizumab to chemotherapy compared to chemotherapy alone (Alva ESMO 2020). As well, overall survival was not improved with single agent durvalumab, pembrolizumab, or atezolizumab in PD-L1 overexpressing patients compared to chemotherapy in these trials and the IMvigor 130 RCT (Galsky Lancet 2020). In the latter RCT (n=1213) improved PFS and a trend to improved OS were reported with the addition of the PD-L1 inhibitor atezolizumab to chemotherapy compared to gemcitabine/platinum alone. Further follow up of the OS trend observed in this RCT is warranted. The Checkmate-901 RCT (n=897) comparing ipilimumab plus nivolumab and nivolumab plus chemotherapy to

gemcitabine/platinum alone, and the NILE RCT (n=885) comparing durvalumab plus chemotherapy (with or without tremelimumab) to gemcitabine/platinum chemotherapy have yet to report results. The targeted agents enfortumab vedotin and erdafitinib are also under study in RCTs in the 1st-line treatment of incurable urothelial cancer.

Effectiveness

The results of the JAVELIN Bladder 100 RCT are the most important treatment advance in the first-line treatment of incurable bladder cancer in 20 years. The most important observation was that patients lived longer on average when they received maintenance avelumab after clinical response or non-progression after 4-6 cycles of gemcitabine/platinum chemotherapy than patients treated with chemotherapy plus BSC alone. Median overall survival was increased by 50% (21.4 months versus 14.3 months) with mortality reduced 31% over the course of the trial (hazard ratio [HR] for death, 0.69; 95% confidence interval [CI], 0.56 to 0.86; P = 0.001). For every 8 patients treated with avelumab, 1 more was alive at one year (71.3% versus 58.4%). OS benefit appeared to be present regardless of tumor PD-L1 expression, although subgroups analysis suggested a more modest OS effect in tumors with absent PD-L1 expression. This survival benefit was achieved without deleterious effects on HRQoL. With one exception, there was no difference in changes from baseline over the course of the trial in PROs using the NCCN-FACT FBISI-18 Total and Disease Related Symptoms-Physical Scores, and EQ-5D-5L. Time to deterioration in the FBISI-18 Disease Related Symptoms-Physical Score (defined as ≥3 points decrease prior to end of treatment) did appear improved in the avelumab group (not reached versus 13.8 months). By RECIST 1.1 criteria, the objective tumor response rate was improved with avelumab (9.7% versus 1.4%). Median PFS was also improved with the addition of avelumab (3.7 months versus 2.0 months; PFS HR, 0.62; 95% CI, 0.52 to 0.75). An improvement in overall survival and disease control without deleterious effects on HRQoL is very important and relevant to patients.

Safety

77.3% of patients treated with avelumab were reported to have had treatment-related adverse events, 16.6% of these were grade 3 or higher, 9.0% were considered serious, and 2 were fatal (0.6%). In the avelumab group, 11.9 % had adverse events led to discontinuing treatment, 29.4% had an adverse event categorized as being immune-related (7.0% grade 3), and 9.0% received high-dose corticosteroid treatment for immune-related toxicity. The immune-mediated adverse effects were typical of those seen with PD-1/PD-L1 inhibitors with the most frequent of these being thyroid disorders (12.2%). A unique observation with avelumab was a relatively high rate of acute infusion reactions (21.5%). These are typically uncommon with PD-1/PD-L1 inhibitors and although usually not severe and amenable to premedication, such events are potentially disruptive in a busy chemotherapy suite and negatively impact the patient experience. Notwithstanding the inconvenience of acute infusion reactions, the use of avelumab in this setting appears very safe with low rates of severe adverse effects including immune-mediated effects and this is highly relevant to patients.

Limitations and Generalizability

Enrollment was limited to adult patients with urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra that showed predominantly transitional-cell features and was unresectable or metastatic. Disease measurable by RECIST 1.1 criteria, no evidence of disease progression on or after 4-6 cycles of first-line gemcitabine/platinum chemotherapy,

and a treatment-free interval of 4-10 weeks since the last dose of chemotherapy were required. Patients had ECOG PS 0 or 1 and adequate organ function. Patients with adjuvant or neoadjuvant systemic therapy within the preceding 12 months, contraindications for or previous exposure to immune checkpoint inhibitors, known CNS metastases requiring steroids, active infection requiring systemic therapy, diagnosis of prior immunodeficiency or organ transplant requiring immunosuppressive therapy, HIV or AIDS-related illness, and a variety of other serious medical conditions were excluded.

Strengths of the trial included overall survival as a co-primary endpoint, and that a high proportion of patients in the control arm received 2nd-line treatment at progression (61.7%) including immune checkpoint inhibitors (43.7%). Conversely, in current practice some might consider a 2nd-line PD-1 exposure rate less than 50% a weakness. The collection and reporting of HRQoL data are also a strength. A common practice in oncology trials but weakness of the trial design was lack of use of placebo blinding of investigators and patients to receipt of maintenance avelumab. This raises potential for ascertainment bias that could lead to earlier initiation of 2nd-line therapy in the control arm. As well, patients known to be receiving immune checkpoint inhibitor therapy are often continued on treatment despite evidence of tumor growth due to the possibility of “pseudo-progression” from tumor inflammation. The CGP considered the potential effect of these on the efficacy results uncertain.

JAVELIN Bladder 100 was an international trial, however, despite most of the patients enrolled in Europe with a minority in North America, the CGP considered the results valid for generalization to Canadian patients. It is important to note that patients with stable disease were eligible for this trial. Stable disease by RECIST 1.1. criteria allow up to <20% increase in the sum of measurable lesions on or after treatment.

The CGP considered these data generalizable to patients with incurable urothelial cancer of predominantly transitional histology without formally measurable manifestations of their cancer, as long as there was no evidence of disease progression on or after 1st-line chemotherapy. The JAVELIN Bladder 100 results should not be generalized to patients with predominantly non-transitional histologies. However, the favorable safety profile suggested that avelumab was a reasonable choice in patients with ECOG 2 performance status.

The realities of clinical practice may require a longer period of recovery prior to initiating avelumab; however, the CGP recommends that this not exceed 12 weeks. In real world practice some patients may receive alternative non-platinum chemotherapy, and the CGP considered maintenance therapy with avelumab reasonable for these patients, provided they have received a minimum of 12 weeks (e.g. 4 or more cycles) of treatment and had not shown evidence of progressive disease on or after treatment.

Patients with potentially curable urothelial cancer, those who have received adjuvant or neoadjuvant systemic therapy within 12 months, and those who have had prior treatment with PD-1/PD-L1 inhibitors or who have received 2nd-line chemotherapy for incurable disease should not be considered candidates for avelumab maintenance therapy.

As the optimal duration of chemotherapy exposure required to realize optimal benefit from avelumab is unclear, patients receiving less than 4 cycles of chemotherapy due to intolerance could be considered candidates for avelumab provided no evidence of disease progression has occurred on or after treatment. However, as this could also encourage inadequate exposure to chemotherapy, the reasons for shortened chemotherapy exposure should be clearly justified.

The CGP considered weight-based dosing of avelumab up to 800 mg q2weeks a reasonable extrapolation. However, CGP does not recommend less frequent dosing schedules until more data supporting the safety and efficacy of these are available.

The optimal treatment for patients with tumor progression despite avelumab maintenance therapy is uncertain. Treatment with pembrolizumab is not recommended. Participation in clinical trials or treatment with standard chemotherapy agents should be considered.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to avelumab as maintenance therapy in the treatment of incurable advanced or metastatic urothelial cancer for patients with response or lack of progression on or after 4-6 cycles of 1st-line gemcitabine/platinum chemotherapy and no prior immune checkpoint inhibitor therapy based on one high-quality randomized controlled trial that demonstrated a clinically and statistically significant benefit in overall survival benefit for avelumab compared with best supportive care. On average deleterious effects on HRQoL were not reported and adverse event profiles with avelumab therapy were acceptable for patients and clinicians. In making this conclusion, the Clinical Guidance Panel considered:

- These results are also generalizable to patients without measurable disease, those of slightly poorer performance status (ECOG 2), those receiving non-platinum chemotherapy, and those starting treatment up to 12 weeks after chemotherapy.
- Ongoing clinical trials are studying immune checkpoint inhibitors in the 1st-line setting in cisplatin-eligible and –ineligible patients. Until the results of these trials are available, the optimal use of immunotherapy in the 1st-line setting remains undefined.
- There is currently no evidence to support the use of a second-line immune checkpoint inhibitor following first-line avelumab maintenance, given they work through similar mechanisms of action.

Table 3: CADTH Clinical Guidance Panel Response to Provincial Advisory Group Implementation Questions

PAG Implementation Questions	CGP Response
Eligible Patient Population	
In view of the characteristics of the patient population and exclusion criteria in the JAVELIN Bladder 100 trial, PAG is seeking clarity on whether the following patients would be eligible for treatment with avelumab: • Patients on alternative non-platinum chemotherapy (e.g., gemcitabine/paclitaxel) due to intolerance or contraindications.	• The realities of clinical practice may require a longer period of recovery prior to initiating avelumab; however, the CGP recommended that this not exceed 12 weeks. In real world practice some patients may receive alternative non-platinum chemotherapy, and the CGP considered maintenance therapy with avelumab reasonable for these patients, provided they have received a minimum 12 weeks of treatment (4-6 cycles) of treatment and had not shown evidence of progressive disease on or after treatment.
• Patients having experienced prior adjuvant or neoadjuvant systemic therapy within the past 12 months and who are candidates for re-treatment with chemotherapy in the advanced setting.	• The CGP felt that patients with potentially curable urothelial cancer, those who have received adjuvant or neoadjuvant systemic therapy within 12 months, and those who have had prior treatment with PD-1/PD-L1 inhibitors or who have received 2nd-line chemotherapy for incurable disease should not be considered candidates for avelumab maintenance therapy. Pembrolizumab is currently approved for second-line treatment in this space.
• Patients who experience intolerance and are unable to complete at least 4 cycles of platinum-based chemotherapy as first-line treatment.	• As the optimal duration of chemotherapy exposure required to realize optimal benefit from avelumab is unclear, the CGP felt that patients receiving less than 4 cycles of chemotherapy due to intolerance could be considered candidates for avelumab provided no evidence of disease progression has occurred on or after treatment. However, as this could also encourage inadequate exposure to chemotherapy, the reasons for shortened chemotherapy exposure should be clearly justified.
PAG seeks to understand if there are histologies other than transitional cell in UC and if so, whether they would they qualify for avelumab.	The CGP considered these data generalizable to patients with incurable urothelial cancer of predominantly transitional histology without formally measurable manifestations of their cancer, as long as there was no evidence of disease progression on or after 1st-line chemotherapy. The JAVELIN Bladder 100 results should not be generalized to patients with predominantly non-transitional histologies.
Implementation Factors	
The recommended dose of avelumab is 10 mg/kg body weight by intravenous infusion over 60 minutes every two weeks in four-week cycles. It is proposed that the drug should continue to be administered until disease progression or unacceptable toxicity. PAG seeks advice on a definition of progression and related criteria for discontinuation.	In the JAVELIN Bladder 100 trial, disease progression was determined by BICR assessment based on RECIST v1.1 criterion. Radiological tumour assessments were conducted at baseline (within 28 days prior to randomization), at 8 weeks after randomization, every eight weeks for 12 months from randomization, and every 12 weeks thereafter until documented disease progression regardless of whether patients then received subsequent anti-cancer therapy. The CGP felt that in clinical practice, radiological tumour assessments are more commonly performed every 12 weeks (compared to the more frequent assessments performed in the trial).

PAG Implementation Questions	CGP Response
PAG noted that the use of single-use 200 mg vials may result in wastage, particularly in low volume or rural institutions where vial sharing is not feasible and weight-based dosing is utilized. For a 70 kg patient, the 10 mg/kg dose would be 700 mg which requires four vials to be used; the unused portion (100 mg) would be discarded if vial sharing cannot occur. PAG remarked that a fixed dose of 800 mg avelumab was used in some clinical trials and was approved by the FDA. PAG seeks advice on implementing weight-based dosing up to a maximum of 800 mg, as it would minimize waste and be consistent with how nivolumab and pembrolizumab are currently implemented.	The CGP noted that weight-based dosing would be reasonable to minimize wastage.
PAG commented that the Q2W schedule has potential impacts on chemotherapy room utilization, nursing resources, and patient commitment to treatment schedule. Consequently, PAG seeks evidence and guidance on administering avelumab on a different schedule (e.g., every 4 weeks) for patient convenience and to minimize visits to the cancer treatment centre.	The CGP noted that there is no evidence to support a different dosing schedule. Additionally, there is the concern of an increased risk for infusion related reactions if less administration schedules lead to patients receiving larger doses of avelumab.
Sequencing and Priority of Treatment	
PAG is seeking guidance on the appropriate place in therapy of avelumab for UC and on sequencing with other drugs for this condition. PAG seeks to understand what options would be available after failure of avelumab. On that subject, PAG raised the question of the appropriateness of subsequent immune checkpoint inhibitors in case of progression on avelumab maintenance, and whether it would preferable to give avelumab for maintenance or wait and give pembrolizumab to patients who progress.	The CGP noted that there is currently no evidence to support the use of a second-line immune checkpoint inhibitor following first-line avelumab maintenance, given they work through similar mechanisms of action. There remains a lack of evidence-based therapies for these patients, however chemotherapy and clinical trials may be appropriate. In terms of whether it would preferable to give avelumab for maintenance or wait and give pembrolizumab to patients who progress, the CGP noted that the JAVELIN Bladder 100 clinical trial investigated whether patients treated with avelumab plus BSC had better outcomes than patients treated with BSC only. Given the results of the trial, the CGP felt that it would be preferable to give avelumab for maintenance therapy rather than wait and give pembrolizumab to patients who progress.
If subsequent anti-PD1 therapy is permitted, PAG would like to determine the minimum progression free interval to qualify for such therapy (e.g., patients who progress during or within 6 months of stopping avelumab would not be eligible for further anti-PD1 therapy).	The CGP noted that patients who progressed on avelumab maintenance treatment should not be treated with subsequent anti-PD1 therapy. For patients who stop treatment with avelumab for reasons related to infusion reaction or unrelated to progression after a short duration of exposure (i.e., <6 months) and who then experience disease progression after a progression free interval of >6 months, subsequent treatment with pembrolizumab may be considered.
PAG mentioned that patients may interrupt avelumab maintenance for personal reasons and seeks guidance (adequacy, timing, etc.) on restarting avelumab therapy in case of disease progression or giving pembrolizumab instead.	The CGP noted that treatment with avelumab should only be continued if disease is still in remission. If the disease had progressed, then the patient would be moved on to the next line of treatment for their disease.
Companion Diagnostic Testing	
PAG would like confirmation that PD-L1 testing is not required and that no PD-L1 expression subgroup derives a distinct benefit from avelumab.	The CGP noted that PD-L1 testing is not required. The results of the JAVELIN Bladder 100 trial showed a positive effect of avelumab treatment in the overall population, and that these results were not limited just to patients who were PD-L1 positive.

CGP = Clinical Guidance Panel; PAG = Provincial Advisory Group; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1; UC = urothelial carcinoma.

2 Background Clinical Information

2.1 Description of the Condition

Two-thousand five hundred Canadians died of urothelial cancer in 2019, making it the eight most common cause of cancer death, and fifth most common in males. Urothelial cancer typically arises in the bladder but may develop in the urothelium lining the renal pelvis, ureter, and proximal and prostatic urethra as well. In North America, urothelial cancer is usually related to chronic exposure of the urothelium to carcinogens from tobacco use. Other risk factors include recurrent urinary tract infections, indwelling catheters, previous exposure to chemotherapy drugs such as cyclophosphamide, and exposure to certain chemicals in manufacturing dyes, paint and leather. In tropical countries, chronic infections due to schistosomiasis are the major cause of urothelial cancers. Patients typically present with painless gross hematuria, and often initially have low- grade superficial bladder tumors treated effectively with local excision and intravesical therapies. However, superficial bladder tumors often recur, and a subset of these patients progress to develop high-grade muscle-invasive urothelial cancer requiring more definitive treatment such as radical cystectomy or chemoradiation with or without adjunctive systemic chemotherapy.

2.2 Accepted Clinical Practice

Patients may develop incurable metastatic or locally advanced urothelial carcinoma not amenable to curative local therapy, either de novo or following definitive local therapy. For these patients, treatment of symptomatic disease may require optimized analgesic therapy, palliative radiation, relief of urinary obstruction, bone targeted agents, and even palliative surgery in rare cases. However, controlling the underlying cancer usually requires systemic drug therapy. Urothelial cancer is considered sensitive to chemotherapy and many chemotherapy agents have demonstrated single agent activity. Combination cisplatin-based chemotherapy is considered the standard of care and has been shown to improve OS. However, as many as 50% of patients may be considered “cisplatin ineligible” based on factors such as performance status, poor cardiac or renal function, and neuropathy. Gemcitabine/cisplatin is the most commonly used combination chemotherapy in Canada, with substitution of carboplatin for cisplatin in those considered cisplatin ineligible. Single-agent gemcitabine may also be used in the latter scenario. Dose intense methotrexate/vinblastine/doxorubicin/cisplatin (M-VAC) + G-CSF and paclitaxel/gemcitabine/cisplatin have higher tumor response rates but greater toxicity than gemcitabine/cisplatin and may be used in patients able to tolerate more rigorous treatment.

Patients with urothelial cancers arising outside the bladder are treated similarly to those arising within the bladder cancer although the prognosis is generally worse. Objective tumor response rates are approximately 50% with gemcitabine/cisplatin, 40% with gemcitabine/carboplatin, and 30% with gemcitabine monotherapy. All patients eventually progress. For patients progressing with metastatic disease on or within 12 months of receiving platinum-based chemotherapy, immunotherapy with the PD-1 inhibitor pembrolizumab is typically offered. This practice is based on the results of the KEYNOTE-045 trial which reported superior tumor response and improved overall survival with less toxicity with pembrolizumab compared to standard single-agent chemotherapy with either vinflunine, docetaxel or paclitaxel. This supported further testing of immunotherapy in the 1st-line setting, and at least six RCTs comparing standard chemotherapy (usually gemcitabine/cisplatin) to immunotherapy alone, in combination, or in sequence with

chemotherapy have been completed and some of these results have been reported. Immunotherapy drugs studied include CTLA-4 inhibitors (ipilimumab, tremelimumab), PD-1 inhibitors (nivolumab, pembrolizumab), and PD-L1 inhibitors (durvalumab, atezolizumab, avelumab). Most of these trials are also including cisplatin ineligible patients by allowing use of gemcitabine/carboplatin as control treatment. Early in the conduct of two of these RCTs unfavorable outcomes were noted in patients with low tumor PD-L1 expression receiving monotherapy with either pembrolizumab or atezolizumab. The trials were amended to close these treatment arms and an FDA warning about use of monotherapy PD-1 or PD-L1 inhibitors was announced, as several PD-1 and PD-L1 inhibitors had been approved by the US FDA as monotherapy for the treatment of 1st-line cisplatin ineligible incurable urothelial cancer based on uncontrolled data. An antibody drug conjugate, enfortumab vedotin, and an FGFR tyrosine kinase inhibitor, erdafitinib, are also under study in ongoing randomized trials for the 1st-line treatment of metastatic urothelial cancer.

3 Summary of Patient Advocacy Group Input

One input was provided by Bladder Cancer Canada (BCC), for the review of avelumab for the first-line maintenance treatment of patients with locally advanced or metastatic UC whose disease has not progressed with first-line platinum-based induction chemotherapy.

BCC gathered information from two sources: an online survey and a one-to-one patient interview. The online survey was conducted between September 8, 2020 and September 18, 2020. This survey included 45 patients and three caregivers. Of the 48 completed surveys, 34 respondents were from Canada, three were from the US, one was from Brazil, one was from Kenya, and seven respondents chose not to answer where they were from. Patients were diagnosed in the following years: 6 in 2020, 9 in 2019, 5 in 2018, 9 in 2017, 5 in 2016, 10 from 2010 to 2015, and 4 in 2009 or earlier. A total of 28 respondents had been diagnosed with muscle-invasive UC and 20 had been diagnosed with locally advanced or metastatic UC. Two patients that were surveyed had treatment experience with avelumab, and one of these patients participated in a one-to-one 40-minute phone interview.

Currently, there is no approved maintenance treatment for patients with locally advanced or metastatic UC whose disease has not progressed with platinum-based chemotherapy. These patients currently receive best supportive care. The most commonly reported symptoms of UC were blood in the urine, fatigue, difficulty urinating and a burning sensation during urination. Previously used treatments reported by respondents were gemcitabin, cisplatin, carboplatin, pembrolizumab, durvalumab, atezolizumab, docetaxel, methotrexate, doxorubicin, paclitaxel and enfortumab. The most frequently reported side-effects of current treatments were fatigue, loss of appetite, nausea, low blood cell counts, hair loss, constipation, and neuropathy. A few patients also reported that the disease and current treatments have caused a financial burden due to increased travel and accommodation costs, drug costs, and loss of income due to work absence. Out of the two patients that reported being treated with avelumab, one reported mild to moderate side-effects and was able to complete the full course the treatment. The other patient reported that they initially experienced few side-effects but had to discontinue the treatment after six months due to a sudden onset of side-effects. However, both patients concluded that they would recommend avelumab to other patients. Overall, patients value preventing disease recurrence, controlling progression, and maintaining their quality of life. Most patients reported that they would tolerate moderate to severe adverse effects if a treatment controlled disease progression or prevented recurrence. BCC strongly recommends the reimbursement of avelumab as it addresses an unmet need and aligns with patient values.

Of note, quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient groups.

3.1 Condition and Current Therapy Information

3.1.1 Patients Experiences

Almost half of the respondents (48%, n=23) received platinum-based chemotherapy, and the remaining respondents either did not or did not recall. Of the 23 patients, 18 achieved disease improvement or stabilization from this treatment. The most frequently reported cancer symptoms by the survey respondents were blood in urine (49%), fatigue (38%),

difficulty urinating (22%), and a burning sensation during urination (20%). Approximately 11 to 15% of patients also reported abdominal pain, nausea, shortness of breath, and loss of appetite. Four patients reported that they had no symptoms prior to diagnosis and before treatments started. Several patients believed their symptoms were caused by the cancer treatments and/or stress related to their diagnosis and not directly caused by their UC.

3.1.2 Patients' Experiences with Current Therapy

Of the 45 patient respondents, 39 specified the treatments they had undergone. Treatments included: gemcitabine (n=22, 56%), cisplatin (n=30, 77%), carboplatin (n=7, 18%), pembrolizumab (n=9, 23%), durvalumab (n=3, 8%), atezolizumab (n=3, 8%), docetaxel (n=2, 5%), methotrexate (n=2, 5%), doxorubicin (n=2, 5%), avelumab (n=2, 5%), paclitaxel (n=1, 3%), and enfortumab (n=1, 3%).

BCC noted that most patient comments regarding current therapies focused on their adverse effects that accompanied the therapy. The most frequently reported adverse effects were fatigue (66%), loss of appetite (36%), nausea (34%), low blood cell counts (30%), hair loss (28%), constipation (26%), and neuropathy (26%). Patients indicated that fatigue and nausea were the most difficult to tolerate. Comments from patients regarding their experiences with current therapies included:

"Some residual peripheral neuropathy post treatment. General fatigue during treatment. Anemia took some time to resolve after treatment. Overall I tolerated treatment quite well".

"I experienced fatigue and loss of appetite for several days following infusion. Loss of hair after second round. Extreme bone pain was said to be from injections to boost immunity. I was determined to beat it so I had to remain as positive as possible throughout."

Two full chemo treatments, one with radiation. Very tired and loss of appetite.

"Exhausting, traumatic, depleting. Pre-existing kidney disease with borderline GFRs made the treatment very difficult; required split doses and extra IV hydration with every treatment. Only made it through 2 rounds of chemo; severe neutropenia, organ stress.'

"Extreme fatigue to point I was no longer self sufficient."

Few patients reported difficulty accessing current treatments. However, they did report the following challenges: travel distance (n=4), treatment cost (n=3), and parking and travel costs (n=4). Respondents reported additional financial challenges such as accommodation costs and low income caused by absences from work. Six patients required financial assistance due to the cost of UC or its treatments. Comments from patients regarding their experiences accessing current therapies included:

"Immunotherapy was going to be way beyond my budget but again, I was lucky to be offered free treatment as one of a study."

"I was fortunate to have family and friends step up to get me to my treatments. The cancer clinic I had treatments at is about 45 minutes from home. Without these wonderful volunteers I'm not sure what I would have done. I do realize, however, that the distance to travel for me is way less than many needing treatment."

"Had to travel 4 hours one way but managed."

"I am financially secure and reside within 10 minutes of most of my treatments. But it is not difficult to understand how many of the above captioned costs could be a burden for low income patients and those who must travel from out of town for treatment. I was a volunteer driver for the Canadian Cancer Society and it is abundantly clear that there are hundreds, if not thousands of patients who suffer extreme financial hardships in transportation alone.'

3.1.3 Impact on Caregivers

Three of the 48 respondents were caregivers. Challenges reported by these respondents included travel distance, treatment cost, parking and travel costs, accommodation costs, and low income due to work absences. Below is a quote from a caregiver regarding the challenges associated with UC and current treatments:

"As a caregiver I had to use my vacation time and also had to take some unpaid time off from my work. If we had access to homecare I would not have to use my own resources."

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for New Therapies

The most important expectation by respondents for new therapies was prevention of disease recurrence, followed by control of disease progression, maintenance of quality of life and a reduction in symptoms. Most respondents (n=44, 92%) indicated they would tolerate side effects from drugs that can control disease progression or prevent recurrence. The following are some patient comments regarding improved outcomes:

"Any effort that delays disease progression enhances the possibilities of progress being made in finding drugs to control, decrease or eradicate the disease."

"Given the poor prognosis of stage IV, the goal was controlling the disease and prolonging the quality of life."

3.2.2 Patient Experiences to Date

Two respondents that were diagnosed with locally advanced or metastatic UC had treatment experience with avelumab. One patient was previously treated with cisplatin and atezolizumab, and one patient was previously treated with cisplatin and gemcitabine.

One patient experienced mild to moderate side effects that they felt were tolerable and was able to complete the full course of avelumab treatment. The second patient had a sudden onset of severe adverse effects after six months of treatment and stopped avelumab treatment as a result.

BCC asked the patients to rate changes to their quality of life on avelumab compared to other treatments they have received. The patient who completed the full cycle of the treatment reported that their quality of life was approximately the same while the other reported that it was better in the first six months of treatment, but after that the that side-effects/quality of life became worse and the patient had to stop the treatment as a result.

Adverse effects reported by one patient were skin rash, joint pain, lack of energy, nausea and cough. The other patient reported fatigue, lack of energy, constipation, back pain decreased appetite, loss of taste, muscle cramping, dry mouth and shortness of breath.

BCC asked patients to rate how the side effects of avelumab have affected their lives. Both respondents responded that the side-effects had the biggest impact on their ability to exercise, perform chores and fulfill family obligations. Below are some patient comments:

"My treatment started out positively for the first six months with very few side-effects but ended with sudden severe side-effects. Currently waiting to have CT next week which will tell me whether or not my disease has stabilized or improved. If my CT shows improvement the side-effects will be worth the benefit."

"I have an inoperable tumour so treatment options are invaluable"

Neither patient had difficulty accessing their bi-weekly treatments. Both patients indicated that they would recommend avelumab to other patients based on their own experiences with the treatment.

3.3 Companion Diagnostic Testing

Not applicable.

3.4 Additional Information

BCC provided some additional comments for CADTH's consideration. BCC reported that despite bladder cancer being the fifth most common cancer in Canada, there are limited treatment options for patients with locally advanced or metastatic disease. The five-year survival rate for stage IV bladder cancer is approximately 5%. BCC feels that the results of the phase III Javelin trial are clinically significant, and avelumab would provide patients with an additional treatment option that can improve overall survival.

4 Summary of Provincial Advisory Group (PAG) Input

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the CADTH website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) participating in CADTH. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Place in therapy and sequencing with currently available treatments including other immune checkpoint inhibitors
- Eligibility in patients unable to receive or complete induction platinum chemotherapy

Economic factors:

- Unclear treatment duration

Please see below for more details.

4.1 Currently Funded Treatments

The standard first line treatment for patients with locally advanced or metastatic urothelial carcinoma (UC) is platinum-based induction chemotherapy. Some patients who are not candidates for platinum chemotherapy may receive alternate chemotherapy (e.g., gemcitabine and paclitaxel). Pembrolizumab is currently funded in patients with relapsed disease following first-line therapy. There is currently no maintenance treatment following good response to induction chemotherapy; patients are being monitored and given best supportive care. PAG noted that the JAVELIN Bladder 100 trial compared avelumab to placebo, which would be a relevant comparator in this clinical context.

4.2 Eligible Patient Population

The reimbursement request is for the first-line maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) whose disease has not progressed with first-line platinum-based induction chemotherapy. In view of the characteristics of the patient population and exclusion criteria in the JAVELIN Bladder 100 trial, PAG is seeking clarity on whether the following patients would be eligible for treatment with avelumab:

- Patients on alternative non-platinum chemotherapy (e.g., gemcitabine/paclitaxel) due to intolerance or contraindications.
- Patients having experienced prior adjuvant or neoadjuvant systemic therapy within the past 12 months and who are candidates for re-treatment with chemotherapy in the advanced setting.
- Patients who experience intolerance and are unable to complete at least 4 cycles of platinum-based chemotherapy as first-line treatment.

PAG seeks to understand if there are histologies other than transitional cell in UC and if so, whether they would they qualify for avelumab.

PAG noted that the JAVELIN Bladder 100 study started avelumab within 10 weeks of completion of chemotherapy and seeks to confirm if this would be the maximum interval between end of induction chemotherapy and initiation of avelumab maintenance. Should the drug be reimbursed, PAG identified a potential time-limited need to cover patients currently on observation after first-line chemotherapy and who received the latter beyond the maximum allowed wait period.

PAG noted potential indication creep in the following scenarios:

- Patients who did not achieve a clinical complete response or partial response following upfront chemotherapy.
- Patients treated with prior immunotherapy.
- Patients ineligible for treatment with first line chemotherapy.
- Use as induction therapy rather than maintenance.
- Use as maintenance after second line chemotherapy.
- Use as maintenance after adjuvant platinum-based chemotherapy.
- Patients who had less than four cycles of chemotherapy due to intolerance (if the evidence is not generalizable to them).

4.3 Implementation Factors

The recommended dose of avelumab is 10 mg/kg body weight by intravenous infusion over 60 minutes every two weeks (Q2W) in four-week cycles. It is proposed that the drug should continue to be administered until disease progression or unacceptable toxicity. PAG seeks advice on a definition of progression and related criteria for discontinuation.

PAG noted that the use of single-use 200 mg vials may result in wastage, particularly in low volume or rural institutions where vial sharing is not feasible and weight-based dosing is utilized. For a 70 kg patient, the 10 mg/kg dose would be 700 mg which requires four vials to be used; the unused portion (100 mg) would be discarded if vial sharing cannot occur. PAG remarked that a fixed dose of 800 mg avelumab was used in some clinical trials and was approved by the FDA. PAG seeks advice on implementing weight-based dosing up to a maximum of 800 mg, as it would minimize waste and be consistent with how nivolumab and pembrolizumab are currently implemented.

PAG commented that the Q2W schedule has potential impacts on chemotherapy room utilization, nursing resources, and patient commitment to treatment schedule. Consequently, PAG seeks evidence and guidance on administering avelumab on a different schedule (e.g., every 4 weeks) for patient convenience and to minimize visits to the cancer treatment centre.

PAG noted that for the indication under review, avelumab is an additional therapy after chemotherapy. As a result, additional resource will be required for drug preparation and administration. Incremental resources would also be required to monitor and treat infusion reactions, immune related adverse effects and other toxicities associated with immunotherapies. Additionally, PAG identified the need for premedication with an antihistamine and acetaminophen prior to the first four infusions of avelumab.

Avelumab would be administered in an outpatient chemotherapy center for appropriate administration and monitoring of toxicities. PAG noted that these centres already use avelumab for Merkel cell carcinoma and are thus familiar with the product. Intravenous chemotherapy drugs would be fully funded in all jurisdictions for eligible patients, which is an enabler for patients. However, in some areas, patients would need to travel far to an outpatient chemotherapy center, which would be a barrier for these patients.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on the appropriate place in therapy of avelumab for UC and on sequencing with other drugs for this condition. PAG seeks to understand what options would be available after failure of avelumab. On that subject, PAG raised the question of the appropriateness of subsequent immune checkpoint inhibitors in case of progression on avelumab maintenance, and whether it would preferable to give avelumab for maintenance or wait and give pembrolizumab to patients who progress. If subsequent anti-PD1 therapy is permitted, PAG would like to determine the minimum progression free interval to qualify for such therapy (e.g., patients who progress during or within 6 months of stopping avelumab would not be eligible for further anti-PD1 therapy). PAG mentioned that patients may interrupt avelumab maintenance for personal reasons and seeks guidance (adequacy, timing, etc.) on restarting avelumab therapy in case of disease progression or giving pembrolizumab instead.

4.5 Companion Diagnostic Testing

PAG would like confirmation that PD-L1 testing is not required and that no PD-L1 expression subgroup derives a distinct benefit from avelumab.

4.6 Additional Information

None.

5 Summary of Registered Clinician Input

One joint clinician input was provided from two medical oncologists. One oncologist provided input on behalf of Ontario Health (Cancer Care Ontario) GU Drug Advisory Committee, and the other was an oncologist was practicing in at an Ontario health centre.

Overall, the clinicians providing input felt that the patient population in the reimbursement request aligns with the need identified in their clinical practice. They would use avelumab maintenance therapy in patients who have received first line platinum-containing regimen and experienced stable disease or regression. The clinicians felt that avelumab fulfills an unmet need for maintenance treatment following good response to platinum-based induction chemotherapy. Currently, these patients are monitored and given best supportive care. In the event of disease progression, patients are treated with pembrolizumab. Avelumab maintenance therapy would be a replacement of pembrolizumab in these patients.

Please see below for details from the clinician input.

5.1 Current Treatment(s)

The clinicians stated that the standard first-line treatment for patients with locally advanced or metastatic UC is platinum-based induction chemotherapy. Upon progression, toxicity, or non-response to platinum-based chemotherapy, pembrolizumab is usually the funded and standard second-line therapy. Other options in the second- and third-line settings are alternate single agent and combination chemotherapy regimens (e.g. carboplatin, paclitaxel, and gemcitabine).

5.2 Eligible Patient Population

The clinicians noted that the eligible patient population aligns with the reimbursement request. They would use avelumab to treat patients who received first-line platinum-based chemotherapy and experienced stable disease or regression. Treatment with avelumab with would begin immediately after completing chemotherapy (usually 4-8 cycles) as opposed to monitoring for progression of disease and then starting on pembrolizumab as a second line agent. The clinicians also noted that avelumab maintenance therapy represents an unmet need.

The clinicians did not identify any subgroups beyond the study population that they would use the new treatment in. They also did not identify any subgroups within the study population that the new treatment should be limited to.

5.2.1 In some clinical trials, avelumab is being administered as a flat 800 mg dose every 2 weeks. Is it reasonable to implement avelumab dosing as 10 mg/kg up to a cap of 800 mg every 2 weeks to minimize drug waste, in line with how nivolumab and pembrolizumab are currently implemented?

The clinicians agreed that it would be reasonable to implement avelumab dosing as 10 mg/kg up to a cap of 800 mg every two weeks.

5.2.2 Is there any evidence to administer avelumab on a different schedule (e.g., every 4 weeks) for patient convenience and to minimize visits to the cancer treatment centre?

The clinicians noted that there is growing evidence that administering avelumab every four weeks is an appropriate schedule. They support this schedule as it would minimize visits and would be more convenient for patients.

5.2.3 Is there evidence to inform whether avelumab maintenance can be administered to patients who are in response following non-platinum-based chemotherapy in the first-line setting for advanced bladder cancer?

The clinicians stated that, at present and to their knowledge, there is no evidence to inform whether avelumab maintenance can be administered to patients who are in response following non-platinum-based chemotherapy in the first-line setting for advanced bladder cancer. However, they felt that the response to avelumab after chemotherapy is not likely to depend on the type of chemotherapy regimen given before it is initiated, and that the biology would support its effect regardless of which treatment was given in the first-line setting (i.e. platinum- or non-platinum-based chemotherapy).

5.3 Relevance to Clinical Practice

The clinicians did not report experience with avelumab but noted that most clinicians in Ontario have experience with other immunotherapy agents (e.g. durvalumab, pembrolizumab) in this patient population. They noted that contraindications for avelumab treatment would be there same as contraindications for other immunotherapy agents. The clinicians indicated they would use avelumab in patients that would otherwise have been eligible for the trial (JAVELIN Bladder 100). Avelumab maintenance therapy would be different than pembrolizumab therapy because they would not wait for disease progression to initiate avelumab treatment.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

The clinicians would initiate avelumab maintenance therapy after the completion of first-line chemotherapy for advanced disease in patients who have not progressed. Avelumab maintenance therapy would be a replacement of pembrolizumab for these patients.

5.4.1 What is the recommended therapy for patients who progress on avelumab?

The clinicians indicated that the recommended therapy for patients who progress on avelumab would include second-line chemotherapy (e.g. paclitaxel, etc.), best supportive care, participatiom in a clinical trial, and/or compassionate FGFR therapy (if they are positive for FGFR alteration as part of a patient support program).

5.4.2 Is there evidence on the use of pembrolizumab after progression on avelumab?

The clinician noted that there is no evidence on the use of pembrolizumab after progression on avelumab.

5.4.3 If a patient is intolerant to avelumab and must stop treatment, is there evidence and/or inclination to use pembrolizumab upon progression? If the reason for stopping is not intolerance or disease progression, is it more appropriate to re-start avelumab at the time of progression?

The clinicians indicated that switching to pembrolizumab would be appropriate and reasonable if the toxicity was an infusion reaction. Otherwise, they would not use pembrolizumab in these patients.

5.4.4 If subsequent anti-PD1 therapy is permitted, what would be the minimum progression free interval to qualify for such therapy? (e.g., patients who progress during or within 6 months of stopping avelumab would not be eligible for further anti-PD1 therapy).

The clinicians noted that if avelumab was discontinued for reasons other than progression, anti-PD1 therapy upon progression could be allowed regardless of the progression free interval. If an interval needed to be in place, the clinician felt that three to four months should be sufficient.

5.4.5 Would you prefer to give maintenance therapy with avelumab or treatment in second line with pembrolizumab?

The clinician felt that avelumab maintenance therapy would be preferred in most cases because patients with urothelial cancers often progress quickly. They felt that using pembrolizumab upon progression may be more challenging and less effective for weaker and sicker patients.

5.4.6 Under what circumstances should maintenance avelumab not be offered?

The clinicians indicated that avelumab should not be offered under the usual circumstances that would exclude a patient from receiving any immunotherapy agent.

5.4.7 Is there an optimal duration of treatment with avelumab maintenance? How does a physician determine when to stop maintenance therapy?

The clinician noted the optimal duration of avelumab maintenance therapy has not yet been determined, however, they estimated that it likely will be at least two years.

5.4.8 Can patients take a treatment break after a number of cycles with stable disease, and if so, is there a minimum number of cycles that should be administered, and is there a timeframe after which patients can resume avelumab upon disease progression?

The clinician providing input noted that this is a possibility, but this cannot be determined based on the current body of evidence.

5.4.9 What is an appropriate timeline to start avelumab maintenance therapy on a time-limited basis for patients who have already completed platinum-based chemotherapy at the time of implementation?

The clinician noted that the appropriate timeline to start avelumab maintenance therapy is not well defined by the available research, however they estimated that avelumab should be started within six months of platinum-based chemotherapy completion, if CT scans shows ongoing stability/response of the disease.

5.4.10 How frequently should patients be monitored for disease progression on maintenance?

The clinicians suggested that patients should be monitored in the usual manner as with other funded therapies, which is serial imaging every 3 to 4 months optimally.

5.5 Companion Diagnostic Testing

Not applicable.

6 Systematic Review

6.1 Objectives

To evaluate the efficacy and safety of avelumab plus BSC for the treatment of adult patients with locally advanced or metastatic UC whose disease has not progressed with first line platinum-based induction chemotherapy.

No supplemental questions or comparison with other literature relevant to the CADTH review and to the Provincial Advisory Group were identified while developing the review protocol.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the CADTH Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the CADTH Methods Team are provided in Appendix A.

Table 4: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes

Published or unpublished RCTs
 	
In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of avelumab should be included.
	Adult patients with locally advanced or metastatic UC whose disease has not progressed with first line pt-based induction chemotherapy
	
	Subgroups:
	• Site of metastases (visceral, non-visceral)
	• Site of primary tumour (upper tract, lower tract)
	• Presence of poor prognostic factors
	  ○ ECOG PS (0, ≥1)
	  ○ Presence of liver metastasis
	  ○ Presence of anemia
	• PD-L1 (positive, negative)
	• Age (≥65 years, <65 years)
	• Sex (male, female)
	• First-line chemotherapy regimen
	• BOR to first-line therapy (CR, PR, SD)
		Avelumab + BSC[a]	BSC[a]	**OS**
				PFS
				DOR
				ORR
				TTR
				DOR
				DCR
				HRQoL
				
				Safety
				• AEs
				• SAEs
				• Immune related AEs

Abbreviations: BOR = best overall response; BSC=best supportive care; CR = complete response; DCR = disease control rate; DOR = duration of response; OS = overall survival; ORR = overall response rate; PFS = progression-free survival; pt = platinum; PR = partial response; RCT = randomized controlled trial; SD = stable disease; TTR = time-to-tumour response; UC = urothelial carcinoma.

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

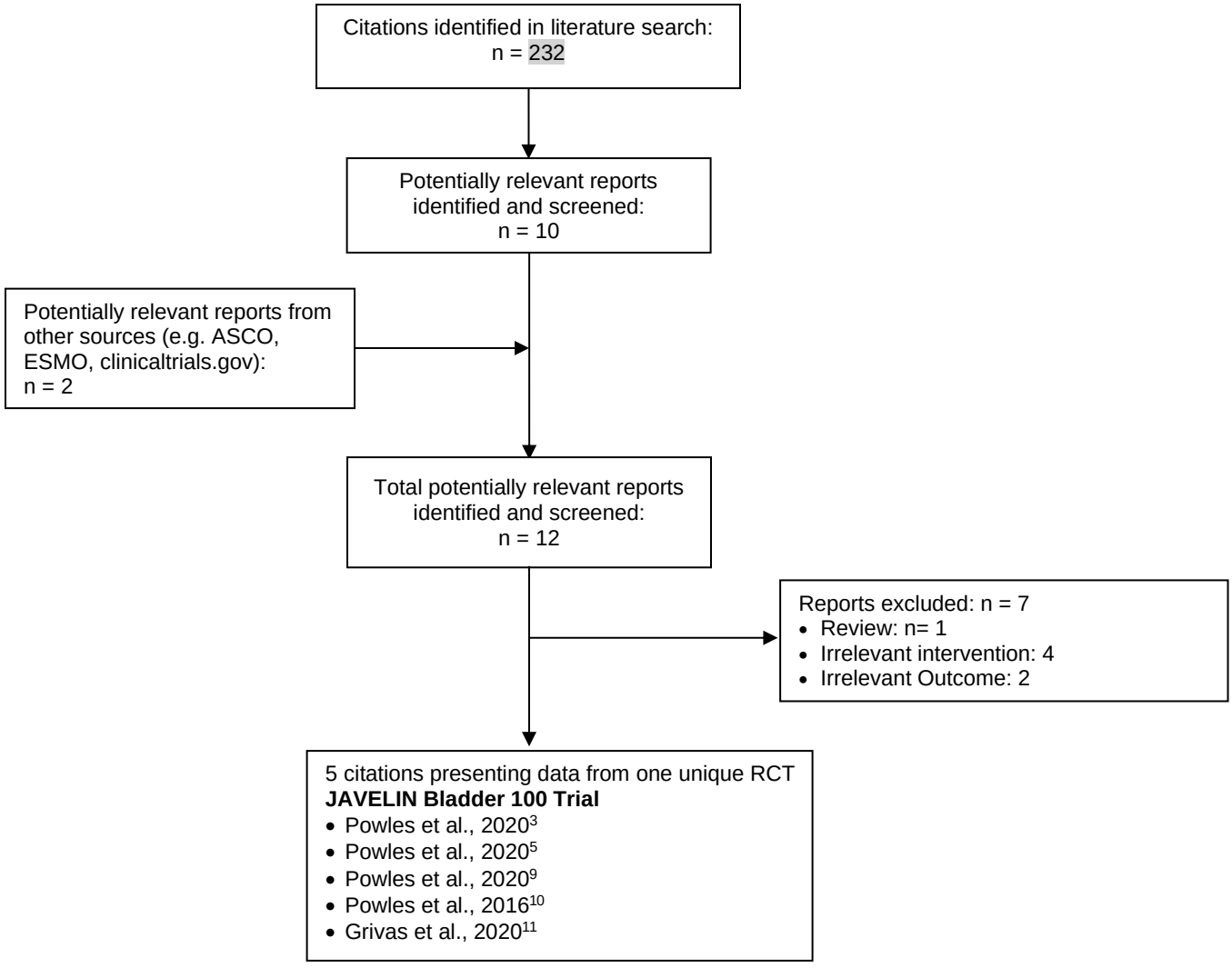
[a] Treatment with antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including palliative radiotherapy)

6.3 Results

6.3.1 Literature Search Results

Of the 12 potentially relevant reports identified, 5 studies[3,5,9-11] were included in the CADTH systematic review and 7 studies were excluded[12-18]. Studies were excluded because they were a review[12], or included an irrelevant intervention[13,14,17,18] or outcome[15,16].

Figure 1: Flow Diagram for Study Selection



Note: Additional data related to the Javelin Bladder 100 trial were also obtained through requests to the Sponsor by CADTH[19]

6.3.2 Summary of Included Studies

One open-label, phase III randomized trial, the JAVELIN Bladder 100 trial, was identified and met the systematic review protocol criteria. Key characteristics of the study including study design, eligibility criteria, intervention details, and trial outcomes are summarized in Table 5.

6.3.2.1 Detailed Trial Characteristics

Table 5: Summary of Trial Characteristics of the JAVELIN Bladder 100 Trial

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: JAVELIN Bladder 100 NCT02603432 Characteristics: Phase III, multicentre, multinational, randomized (1:1), open-label, parallel-arm trial n= 700 randomized (avelumab plus BSC: n = 350; BSC: n = 350) n= 689 treated (avelumab plus BSC: n = 344; BSC: n = 345) **Settings:** 197 sites across 29 countries (Argentina, Australia, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Greece, Hong Kong, Hungary, India, Israel, Italy, Japan, Republic of Korea, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Russian Federation, Serbia, Spain, Sweden, Taiwan, United Kingdom, United States) **Patient Enrolment Dates:** Final Analysis: data cut-off: October 21, 2019 **Funding:** Pfizer	**Key Inclusion Criteria:** Adult patients aged ≥18 years (≥ 20 years in Japan)[3] Histologically confirmed, unresectable locally advanced or metastatic urothelial carcinoma[3] Documented stage IV disease (according to American Joint Committee on Cancer-International Union for Cancer Control tumour-node-metastasis system, 7th edition) that was measurable according to the RECIST v1.1, before the receipt of first-line chemotherapy[3] No disease progression after the receipt of four to six cycles of first-line chemotherapy with gemcitabine plus cisplatin or gemcitabine plus carboplatin, with a treatment-free interval of four to ten weeks since the last dose of chemotherapy[3] ECOG PS 0 or 1[3] Recently obtained or archival tumour specimen[3] Estimated life expectancy of at least 3 months[3] Adequate renal function (creatinine clearance ≥30 mL/min), bone marrow function (absolute neutrophil count ≥1,500/mm^3 or ≥1.5x10^9/L; platelets ≥100,00/mm^3 or ≥100x10^9/L; hemoglobin ≥9g/dL [may have been transfused]), and liver function (total serum bilirubin ≤1.5 x ULN; aspartate aminotransferase and alanine aminotransferase ≤1.5 x ULN)[3] **Key Exclusion Criteria:** Receipt of adjuvant or neoadjuvant systemic therapy within the preceding 12 months of randomization[3]	**Intervention**: Avelumab plus BSC Avelumab at 10 mg/kg as a 1-hour IV infusion once every two weeks plus BSC (described below) **Comparator:** BSC - as deemed appropriate by the treating physician: • Including treatment with antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including palliative radiotherapy). • Not including any active anti-tumour therapies (local radiotherapy of isolated lesions with palliative intent were acceptable)	**Primary:** OS **Secondary:** • PFS • ORR • TTR • DOR • DCR • Safety (AEs, laboratory abnormalities, vital signs) • Pharmacokinetics • Immunogenicity (anti drug antibody, neutralizing antibody against nivolumab) • Tumour tissue biomarkers (e.g., PD-L1, tumor-infiltrating CD8+ T lymphocytes) • PROs (EQ-5D, NCCN-FACT FBSI) **Exploratory:** Other biomarkers

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	Contraindication for or previous exposure to immune checkpoint inhibitors[3] Progressive disease per RECIST v1.1 on or after first-line chemotherapy Major surgery ≤four weeks or major radiation therapy ≤two weeks prior to randomization (Previously received palliative radiotherapy [≤10 fractions] to metastatic lesions was permitted such that it was completed at least 48 hours prior to randomization) [3] Known CNS metastases requiring steroids. Patients with previously diagnosed CNS metastases were eligible if they completed their treatment and recovered from any acute side effects of radiation or surgery before randomization. Patients must also have discontinued corticosteroid treatment for the CNS metastases for at least four weeks and must have been neurologically stable[3] Active infection requiring systemic therapy, diagnosis of prior immunodeficiency or organ transplant requiring immunosuppressive therapy, HIV or AIDS-related illness, HBV, HCV, other acute or chronic medical conditions (i.e., colitis, IBS, pneumonitis), psychiatric conditions, or any of the following within the previous six months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack, deep vein thrombosis or symptomatic pulmonary embolism[3] Known prior or suspected hypersensitivity to study drugs or any component in their formulations[3]		

AEs = adverse events; BSC = best supportive care; DCR = disease control rate; DOR = duration of response; ECOG PS = Easter Cooperative Oncology Group performance score; EQ-5D = EuroQol 5-Dimensions; NCCN-FACT-FBISI = National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy-Bladder Symptom Index; ORR = objective response rate; OS = overall survival; PFS = progression free survival; PRO = patient reported outcome; RECIST = Response Evaluation Criteria in Solid Tumors; TTR = time to response; ULN = upper limit of normal .

Source: Powles et al. 2020[3]; Clinical Study Protocol[3]

a) Trial

The JAVELIN Bladder 100 trial is an international, multicenter, randomized, open-label, parallel arm phase III trial comparing the efficacy and safety of maintenance treatment with avelumab plus BSC versus BSC alone in adult patients with unresectable locally advanced or metastatic UC after completion of first-line platinum-based chemotherapy (gemcitabine

plus cisplatin or gemcitabine plus carboplatin) without evidence of disease progression.[3] Patients were enrolled from 197 sites across 29 countries, including [redacted] patients from Canada ([redacted] patients from Ontario and [redacted] patients from Quebec).[3,8] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Trial Design

Screening, Eligibility Criteria and Randomization: Key eligibility criteria are reported in Table 5. Briefly, eligible patients included adults (≥18 years) with histologically confirmed, unresectable locally advanced or metastatic UC with an ECOG PS of 0 or 1. Patients must have had documented stage IV disease measured according to RECIST v1.1 criteria before having received first-line chemotherapy. First-line chemotherapy must have been either gemcitabine plus cisplatin or gemcitabine plus carboplatin, and patients must have received four to six cycles of treatment with chemotherapy. Patients must not have experienced disease progression (i.e., they must have had an ongoing complete response, partial response, or stable disease) per RECIST v1.1 criterion. Before beginning study treatment, patients must have been treatment-free for four to ten weeks. Patients must also have had a tumour specimen obtained either recently or in archive, and have had adequate hematologic, hepatic, and renal function.[3] Key exclusion criteria included receipt of adjuvant or neoadjuvant systemic therapy within a year of receiving study treatment, contraindication for immune checkpoint inhibitors, previous exposure to immune checkpoint inhibitors, or progressive disease per RECIST v1.1 criteria.

The study design of the JAVELIN Bladder 100 trial is depicted in Figure 2. Patients were randomized in a 1:1 ratio to receive either avelumab plus BSC or BSC alone. Randomization was stratified according to:

- Patients' response to first-line chemotherapy (CR or PR versus SD)[3]
- Metastatic site at initiation of first-line chemotherapy (visceral versus non-visceral; patients with unresectable locally advanced disease, including bone metastasis, were included in the non-visceral disease stratum)[3]

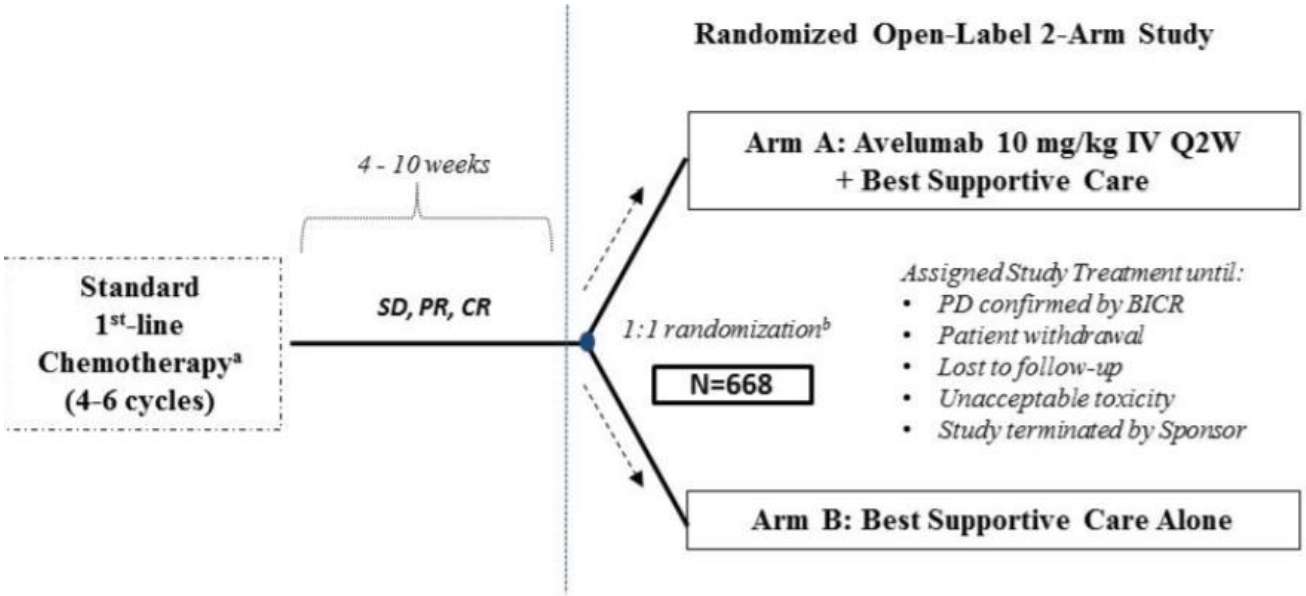
Randomization was centrally allocated across all study centres using an Interactive Response Technology (IRT) system. Site personnel, which included the study coordinator or specified designee, entered or selected information including but not limited to user's identification and password, the protocol number, patient identifiers and demographic information, and stratification factors. Treatment assignment of patients was then provided to the site personnel.[3]

Post-chemotherapy confirmatory scans must have been performed within 28 days prior to randomization to assess response status following first-line chemotherapy. Pre- and post-chemotherapy scans must have been performed and be readily available during screening and must have been submitted for independent central review before randomization for review and assessment of patient eligibility.[3]

The JAVELIN Bladder 100 trial was open-label and therefore investigators and patients were aware of treatments administered. In order to mitigate biases which may arise from determining disease progression in patients, disease progression was determined and confirmed by an expedited independent blinded central review (BICR) based on radiological

assessments (CT/MRI scans) from pre-chemotherapy and post-chemotherapy confirmatory scan(s).[3]

Figure 2: JAVELIN Bladder 100 Study Design



a. Allowed first-line chemotherapy regimens are gemcitabine + cisplatin or gemcitabine + carboplatin.
b. Randomization must occur at least 4 and not more than 10 weeks after the last dose of first-line chemotherapy and will be stratified by: best response on 1st-line therapy (CR or PR vs. SD) and metastatic disease site (visceral vs. non-visceral).

BICR = Blinded Independent Central Review; CR = complete response; IV = intravenous; PD = progressive disease; PR = partial response; Q2W = every 2 weeks; SD = stable disease

Source: Clinical Study Protocol[3]

Efficacy outcomes were analyzed in the intention-to-treat (ITT) population; i.e., all randomized patients were analyzed according to their assigned treatment groups. Two co-primary populations of interest were evaluated in the JAVELIN Bladder 100 trial[3]:

- Overall Population: all patients who underwent randomization
- PD-L1 Positive Population: patients with PD-L1 positive tumours.

In addition to the two primary efficacy populations used in the JAVELIN Bladder 100 trial for assessment of efficacy endpoints, a safety population was also used for assessment of safety data. The safety population included all patients who received at least one dose of avelumab in the avelumab plus BSC group, and all patients who completed the Cycle 1, Day 1 visit in the BSC group. The Per-Protocol Analysis set of patients was also used to conduct sensitivity analyses of efficacy endpoints, and included patients who received at least one dose of study drug, or who only received BSC, and who did not have any major protocol deviations expected to impact the primary objectives of the trial.[3]

Biomarker Assessments: Tumour tissues, including archival tumour tissues, if available, were collected from patients to support the investigation and, as appropriate, the clinical validation of biomarkers which may predict response to treatment. End of Treatment (EOT) tumour tissue from a *de novo* biopsy should also have been obtained unless clinically contraindicated to support an investigation of mechanisms of resistance. Collection of

banked blood biospecimen from all patients was conducted at baseline, on treatment and EOT/withdrawal to support exploratory investigation of possible markers predictive of clinical benefit, pharmacodynamic markers and/or markers of intrinsic or acquired resistance.[3]

PD-L1 status assessment of the tumours was conducted at baseline. Assessment of PD-L1 expression was conducted via the Ventana PD-L1 assay (SP263, Ventana Medical Systems). PD-L1 positive status was based on patients having met at least one of the following criteria:[3]

- At least 25% of tumour cells stained for PD-L1
- At least 25% of immune cells stained for PD-L1 if more than 1% of the tumour area contained immune cells
- 100% of immune cells stained for PD-L1 if no more than 1% of the tumour area contained immune cells

Disease Assessments: Radiological tumour assessments were conducted at baseline (within 28 days prior to randomization), at 8 weeks after randomization, every eight weeks for 12 months from randomization, and every 12 weeks thereafter until documented disease progression regardless of whether patients then received subsequent anti-cancer therapy. Tumour assessments were based on RECIST v1.1 criteria for secondary endpoints and Immune-related RECIST for exploratory endpoints. Tumour assessments included all known or suspected disease sites, and may have included the chest, abdomen, pelvis CT or MRI scans.[3]

All radiographic images from the time of the most recent tumor assessment prior to first-line chemotherapy until documented disease progression were submitted to a BICR. Radiological tumour assessments were also conducted when disease progression was suspected (i.e., symptomatic deterioration). Assessments of complete or partial response must have been confirmed with repeated imaging performed at least four weeks after initial documentation of response. If radiologic imaging revealed PD, tumour assessments were repeated after at least four weeks to confirm disease progression. In the absence of clinical deterioration, patients with PD were to remain on the study treatment until PD was confirmed by BICR.[3] Among patients with a history of brain metastases or for patients in whom brain metastases were suspected, imaging of the head was required at baseline. For patients with brain metastases at baseline, brain scans must have been included in subsequent tumour assessments; otherwise, they were conducted only as clinically indicated. Bone scans revealing bone lesions at baseline were further assessed via CT or MRI per local practice and then re-assessed by CT or MRI per the tumour assessment schedule as an alternative to bone scans. Bone scans were only repeated as needed during the study as clinically needed, at the time of a complete response confirmation, and at every other tumour assessment visit (every 16 weeks) if considered local standard of care.[3]

Patients were followed for survival until death, end of the study, or if the patient withdrew consent, whichever came first and regardless of whether patients initiated new anti-cancer therapy. Patients were followed for 90 days after receiving their last dose of study treatment or until they initiated a new anti-cancer treatment. After this period, patients entered the long-term follow-up where and were followed every three months (±14 days) for survival, ECOG PS, tumour assessments and new anti-cancer treatment either at the investigative site or via telephone contact.[3]

Study Endpoints and Statistical Analysis

Efficacy Outcomes

The primary endpoint of the trial was OS, assessed in both the Overall and PD-L1 Positive Populations. OS was defined as the time from the date of randomization to the date of death due to any cause. Patients last known to be alive were censored at the date of last contact.[3]

The null hypothesis of the JAVELIN Bladder 100 trial was that avelumab plus BSC maintenance therapy was not better than BSC alone; therefore, a one-sided test for superiority was performed against the null hypothesis with an alpha of 0.025.[3] The type 1 error rate was maintained at or below the one-sided alpha by allocating an alpha of 0.015 to the OS comparison in the Overall Population, and an alpha of 0.01 to the OS comparison in the PD-L1 Positive Population. To preserve the overall type 1 error rate and determine efficacy boundaries, a group-sequential design with a Lan-DeMets (O'Brien-Fleming) alpha spending function was used. To accept the alternative hypothesis of this trial (that avelumab plus BSC maintenance is superior to BSC alone), statistical significance in either the Overall or PD-L1 Positive Populations must have been observed via stratified log-rank test for OS. The study would be considered positive if the stratified log rank test for OS was significant at the respective adjusted levels at the interim or at the final analyses, for either of the two co-primary populations.[3]

OS time associated with each treatment arm were summarized using the Kaplan-Meier (KM) method and displayed graphically where appropriate. Confidence intervals (CIs) for the 25th, 50th and 75th percentiles were reported. The Cox proportional hazards model was fitted to compute the treatment hazard ratios and the corresponding 95% CI.[3]

Secondary efficacy endpoints of the trial included the following outcomes assessed by both the BICR and by the investigator:

- **Progression free survival (PFS):** PFS was defined as the time from randomization to the date of first documentation of objective progression of disease or death due to any cause, whichever occurs first. PFS data were censored on the date of patients' last adequate tumour assessment for patients who did not have an event (PD or death), for patients who started a new anti-cancer therapy prior to an event, or for patients with an event after two or more missing tumour assessments. Patients who did not have a baseline tumour assessment or who did not have any post-baseline tumour assessments were censored on the day of randomization, with a duration of 1 day, unless death occurred on or before the time of the second planned tumour assessment in which case the death was considered an event.[3]
- **Objective response rate (ORR):** Objective response was recorded from randomization until disease progression or death from any cause. Patients were considered to have achieved an objective response if they sustained a CR or PR according to RECIST v1.1 criteria (otherwise, patients were considered non-responders in the ORR analysis). Complete and partial response must have been confirmed by repeat assessments performed within four weeks after the criteria for response were met. Patients who did not have adequate data for tumour assessment (i.e., no baseline assessment or no follow-up assessments) were considered non-responders in the ORR analysis. OR was estimated in each arm by dividing the number of patients with CR or PR by the number of patients randomized to the respective treatment group. The corresponding exact 2-sided 95% CIs were provided by treatment arm. In addition, the best overall response for each patient was summarized by treatment arm.[3]
- **Time to tumour response (TTR):** TTR was analyzed in patients with an objective response per RECIST v1.1 criterion and was defined as the time from randomization to

first documentation of objective tumour response (CR or PR). TTR was summarized descriptively (i.e., number of events, mean, median, standard deviation, minimum, maximum) by treatment group.[3]

- **Duration of response (DOR)**: DOR was analyzed in patients with an objective response per RECIST v1.1 criteria and was defined as the time from the first documentation of objective tumour response (CR or PR) to the first documentation of objective tumour progression or death due to any cause, whichever occurred first. Censoring rules for DOR were the same as those described above for PFS. DOR was summarized by treatment group using the KM method and, where appropriate, displayed graphically. The median and its associated 95% CIs were reported.[3]
- **Disease Control (DC):** DC was defined as a CR, PR, or SD according to RECIST v1.1 criterion, and was recorded from randomization until disease progression or death due to any cause. The disease control rate (DCR) and DCR at 24 weeks on each randomized treatment group was estimated by dividing the number of patients with CR, PR, or SD overall by the number of patients randomized to each treatment group. Corresponding exact two-sided 95% CIs were reported for DCR.[3]

The ITT population was used for the assessment of efficacy endpoints. The KM method was applied for the analyses of OS and PFS. Two-sided repeated CIs were constructed for the HR to account for the group-sequential design in the analysis of OS; unadjusted 95% CIs were also calculated. Exact two-sided CIs for objective response according to treatment group were calculated by the Clopper-Pearson method. The Mantel-Haenszel method was used to calculate stratified odds ratios (OR); this method was stated to be analogous to logistic regression.

Sensitivity Analyses: Three sensitivity analyses were conducted for OS to assess the robustness of the primary results, and these analyses were considered exploratory. Two of the sensitivity analyses were prespecified in the protocol: 1) an unstratified analysis of OS; and 2) analysis of OS using the Per-Protocol Set (PPS) of patients. The sensitivity analyses used the same data cut-offs and methods for p-values, HRs and 95% CIs as the primary analysis.[3] The third sensitivity analysis was conducted based on patients' actual stratification values, as 9.6% of patients were randomized under the incorrect stratification value. Based on a protocol amendment, this sensitivity analysis was removed, but was nonetheless calculated.[4]

Patient Reported Outcomes – NCCN-FACT FBISI, EQ-5D-5L and VAS

PROs were assessed via the National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy (NCCN-FACT) FACT-Bladder Cancer Symptom Index (FBISI) and EuroQol 5 Dimensions 5- levels (EQ-5D-5L) and Visual Analogue Scale (VAS). The questionnaires were administered to patients on day 1 of each treatment cycle, at the end of treatment or withdrawal from the trial, and at the 30- 60- and 90-day follow-up visits. Summary statistics (including mean, standard errors, median, range and 95% CIs) of absolute scores were reported for all of the FBISI subscales and the EQ-5D VAS scale. Mean change of absolute scores from baseline and associated 95% CIs were also reported. Line charts which depicted the means and mean changes of questionnaire items and subscales were also provided for each treatment group. Additional exploratory analyses, including repeated measures mixed effects modeling and analyses of patients who experienced a CR were conducted.[3]

The NCCN-FACT FBISI was developed to be part of the Functional Assessment of Chronic Illness Therapy (FACIT) system with input from the FDA and validated in bladder cancer patients. The FBISI was created using input from oncologists and patients and was

designed to be a stand-alone instrument to measure symptoms and quality of life in patients with UC. A minimally important difference (MID) of ≥3 points from baseline on the FACT scales was used as according to literature by Yost & Eton[20]; this difference would correlate with change in disease symptoms and status. Symptoms subscale improvement was also defined as an increase of at least 3 points in the mean FBISI-DRS-P subscale score of the FBISI. To test the robustness of the MID of 3 points, sensitivity analyses using 2 and 4 points were also explored. Within- and between-group comparisons to baseline were conducted to assess symptom improvement among treatment groups.[3] The Disease Related Symptoms subscale of the FBlSI (FBISI-DRS-P) uses a subset of symptoms from the FBISI which are related to symptoms specific to UC; this subscale was used to determine the time to deterioration (TTD). TTD was defined as the time from first dose (baseline) to the first time the patient's score shows a 3-point or higher increase in the FBISI-DRS-P subscale. KM plots were used to display deterioration over time and a log-rank test was used to compare TTD between treatment groups. Patients were censored at the last time they completed a subscale assessment if they had not deteriorated. Comparisons for each co-primary population were performed at the nominal 0.0125 one-sided significance level. The Brookmeyer Crowley method was used to provide the median time and associated two-sided 95% CIs.[3]

The EQ-5D is a six-item questionnaire assessing health status through a single index or utility value. The two components of the EQ-5D are the Health State Profile (EQ-5D-5L) and the VAS. The Health State Profile has individuals rate their level of problems on a five-level scale (none to extreme/unable) in five areas (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The VAS allows patients to rate their overall health status on a scale from 0 (worst imaginable) to 100 (best imaginable). Patients' overall scores can range from 0 to 1 with lower scores indicating higher levels of dysfunction. [3]

Safety Outcomes

Safety outcomes were assessed in the safety analysis set. Safety analysis involved assessment of adverse events (AEs) which were graded according to NCI CTCAE version 4.03.[3] Patients were followed for safety every 30 days (±3 days) through 90 days after receiving their last dose of study treatment or until they initiated a new anti-cancer treatment. During the period of post-treatment safety follow-up (beyond the 30 days through 90 days after final administration of study treatment), any AEs that were thought by the investigator to have been related to the study drug were recorded. AEs of special interest to investigators were considered to be any AE suspected of being an immune-related AE due to treatment of avelumab.[3]

Sample Size

The target sample size of the trial was 668 patients; with at least 50% (334 patients) with confirmed PD-L1 positive tumours.[3] The following assumptions were made when determining sample size for the trial[3]:

- The median OS is 12 months for patients in both primary populations receiving BSC alone after first-line chemotherapy.
- The median OS is assumed to be 17.1 months for patients in the Overall Population receiving avelumab plus BSC after first-line chemotherapy.
- The median OS is assumed to be 18.5 months for patients in the PD-L1 Positive Population receiving avelumab plus BSC after first-line chemotherapy.
- A 5% drop-out rate was assumed for OS on either treatment group.

- A non-uniform patient accrual accomplished over a 28-month period.
- Follow-up for approximately 11 months post-randomization of the final patient in the trial.

A data cut-off for the primary OS analysis was pre-specified to occur after the target number of events had been reached in both co-primary populations and the last randomized patient in the study had been followed for a period of at least 12 months post-randomization.[3]

For the analysis of OS in the Overall Population, an estimated 425 deaths were required to provide the trial with 93% power for detection of a hazard ratio (HR) of 0.7 via one-sided log-rank test at a significance level of 0.015 and a 2-look group-sequential design with Lan-DeMets (O'Brien-Fleming) alpha-spending function to determine the efficacy boundary and a Gamma Family (-8) β-spending function to determine the non-binding futility boundary.[3]

For the analysis of OS in the PD-L1 Positive Population, an estimated 219 deaths would provide the trial with 80% power to detect a HR of 0.65 via one-sided log-rank test at a significance level of 0.01 and a 2-look group-sequential design with Lan-DeMets (O'Brien-Fleming) alpha-spending function to determine the efficacy boundary and a Gamma Family (-8) β-spending function to determine the non-binding futility boundary.[3] The protocol of the JAVELIN Bladder 100 trial prespecified the use of one-sided p values; however, two-sided p values were also reported.

Interim Analysis

One pre-specified interim analysis was planned for each co-primary populations and was performed at the same time for the following reasons:[3]

- Allow for early stopping of the trial for futility
- Allow for early stopping of the trial for efficacy
- Assess safety of avelumab
- Potentially adjust the sample size

Analyses for both co-primary populations at the time of the pre-specified interim analysis required the following conditions: an estimated 74% of events (315 patients with documented disease progression per BICR assessment or death) in the Overall Population and 66.7% of events (146 patients with documented disease progression pre BICR assessment or death) in the PD-L1 Positive Population.[3] The efficacy and futility boundaries for the co-primary populations at the interim analysis are listed in Table 6. An independent data and safety monitoring committee reviewed results of the interim analysis on December 20, 2019 and it was determined that the efficacy boundaries for OS in the Overall Population ($p<0.0053$) and the PD-L1 Positive Population ($p<0.0014$) had been crossed, and therefore the analyses were considered as final.[3]

Table 6: Stopping Boundaries for Overall Survival

Population	Number of Events	Efficacy		Futility	
		Z scale	p-value (one-sided)	Z scale	p-value (one-sided)
All patients	315	z < -2.595	p <0.005	z > -0.789	p >0.215
PD-L1-positive	146	z < -2.947	p <0.002	z > -0.397	p >0.346

Source: Clinical Study Protocol[3]

Protocol Amendments

The final protocol was dated October 29, 2015. A total of five amendments were made to the protocol of the JAVELIN Bladder 100 trial over the course of the study.[21] Protocol amendments are summarized in Table 7.

Table 7: Protocol Amendments of the JAVELIN Bladder 100 Trial

Amendment Date	Summary of Changes
Amendment 1 December 17, 2015	• Clarification of management of immune related adverse events for avelumab • Addition of treatment discontinuation rule for avelumab (discontinuation of avelumab for patients with ASL/ALT >3 x ULN with concurrent elevation of total bilirubin >2 x ULN without another obvious cause). • Revision of inclusion criteria to allow for enrollment of patients with creatinine clearance (CrCl) ≥30 mL/min (changed from ≥50 mL/min). • Removal of time to deterioration as a formal comparison between treatment groups to avoid inflation of overall type I error. • Correction of the interim analysis to reflect that the timing of this analysis was dependent on events based on deaths and not on disease progression. • Patient withdrawal due to disease progression changed to be assessed by investigator rather than by BICR.
Amendment 2 March 24, 2016	• Added an HIV screening test unless not permitted by local laws and regulations and exclusion of HIV positive patients. • Clarification that exclusion criteria pertaining to severe or chronic medical conditions which would make a patient inappropriate for entry into the trial include, but were not limited to, those conditions listed. Also, an addition that patients with pulmonary fibrosis were also to be excluded. • Clarification of stopping rules for efficacy and futility.
Amendment 3 December 16, 2016	• **An expedited BICR for investigator assessed disease progression was added to mitigate potential for bias.** • **Removal of the requirement for central eligibility review of first-line chemotherapy response.** • **Per United States FDA request, addition of relevant measurement and screening procedures and management guidelines for assessment of the utility of serum troponin in early detection of myocarditis, a rare and potentially fatal risk associated with avelumab and other checkpoint inhibitors. The additions included: mandatory measurement of cardiac troponin levels at screening and at each clinic visit ending on Cycle 4 Day 1 (i.e., for a total of 12 weeks), and as clinically indicated; and management guidelines for myocarditis.** • Clarification that testing procedures for detection of disease progression are to be conducted at each tumour assessment time point and for all patients. • Screening for brain metastases was changed to occur only for patients with a history of brain metastases or for whom brain metastases are suspected, as asymptomatic brain metastases are infrequent in this study population. • Extension of the adverse event collection period from 30 days to 90 days after the last administration of study drug.

Amendment Date	Summary of Changes
	• **Clarification to eligibility criteria that first-line chemotherapy must have been completed between four and ten weeks prior to randomization.** • Clarification to exclusion criteria that patients must not have received prior systemic therapy within 12 months of randomization.
Amendment 4 March 28, 2019	• Due to lack of standardization, immune-related Response Criteria (irRECSIT) was removed as an exploratory endpoint and required study assessment. • **Revision related to the management of avelumab-related toxicity to require premedication for only the first four infusions of avelumab.** • Clarification that reporting of adverse events and concomitant medications for the best supportive care group were to end 90 days after the end of treatment rather than 90 days after the last dose of study drug.
Amendment 5 February 13, 2020	• Addition of information pertaining to crossover from the best supportive care group to the avelumab plus best supportive care group.

*Bolded amendments were considered to have affected the conduct of the trial by the sponsor.

Analyses of clinical and safety data were conducted as specified in the statistical analysis plan of the trial. While not included in the sponsor's list of amendments, the following changes were made to the statistical analyses:

- Regarding subgroup analyses based on Pooled Geographic Region: the original planned analysis stated that categories of a subgroups with a low number of patients (<5% of the randomized population) would be pooled, or in cases where no meaningful pooling can be performed, the category may not be summarized. However, the subgroup of patients from North America and the Rest of the World accounted for 4.9% and 4.4% of randomized patients, respectively; these subgroups were not pooled as the subgroup of patients from North America was nearly 5% and was considered a clinically meaningful subgroup.[4]
- Regarding subgroup analysis based on first-line chemotherapy regimen: an additional subgroup level was included for patients who received all three chemotherapy agents (gemcitabine, carboplatin and cisplatin), as more than 5% of the randomized population had received this regimen.[4]
- Regarding the Safety Population: The Safety Population included all patients who received at least one dose of avelumab in the avelumab group, or who completed cycle 1 on day 1 visit in the control group. In addition to these, patients in the control group who did not complete cycle 1 on day 1 but completed subsequent visits prior to the end of the treatment period were also included in the safety analysis set.[4]

Funding

In an alliance between Pfizer and Merck Healthcare KGaA/EMD Serono, both companies agreed to develop and commercialize avelumab; both companies are also sponsoring studies investigating the use of avelumab for various tumour types. Pfizer sponsored the JAVELIN Bladder 100 trial. Investigators contracted by, and under the direction of, Pfizer managed and conducted the trial, and were responsible for adhering to the study procedures described in the protocol.[4]

b) Populations

A total 1005 patients were assessed for eligibility between May 11, 2016 and June 4, 2019, with 700 meeting the requirements and enrolled in the trial (350 patients in each treatment group in the Overall Population). Within the PD-L1 Positive Population,189 patients were randomized to the avelumab plus BSC group and 169 patients were randomized to the BSC

group. The most common reason for patients being excluded from enrollment was due to screen failure (87.5%) and other reasons included no longer meeting eligibility criteria (6.9%), patients having withdrawn consent (3.6%), death (1%) and other reasons (1%).[3] Baseline characteristics for both the Overall Population and PD-L1 Positive Population are summarized in Table 8.

Demographic Characteristics

In the Overall Population, the baseline characteristics were similar for both treatment groups. The median age was 68 years (range, 37-90) in the avelumab plus BSC group and 69 years (range, 32-89) in the BSC group.[3] Most patients were 65 years of age or older (avelumab plus BSC: 63.1%; BSC: 69.4%). A slightly lower proportion of patients were between 66 and 74 years of age in the avelumab plus BSC group (38.9%) compared to the BSC group (46.6%). Most patients were White (avelumab plus BSC: 66.3%; BSC: 68.0%) males (avelumab plus BSC: 76.0%; BSC: 78.6%), recruited from Europe (avelumab plus BSC: 61.1%; BSC: 58.0%), and belonged to the ethnic group categorized as not Hispanic or Latino (avelumab plus BSC: 81.7%; BSC: 85.1).[4]

In the PD-L1 Positive Population, demographic characteristics were similar across both treatment groups.[3] The median age was 70 years in both treatment groups (range, 37-90 in the avelumab plus BSC group; range, 32-84 in the BSC group). A greater proportion of patients were 65 years of age or older (avelumab plus BSC: 67.2%; BSC: 71.0%). Most patients were White (avelumab plus BSC: 64.0%; BSC: 70.4%), categorized as not Hispanic or Latino (avelumab plus BSC: 80.4%; BSC: 86.4%), and recruited from Europe (avelumab plus BSC: 58.2%; BSC: 60.4%).[4]

Disease Characteristics

In the Overall Population, the same proportions of patients were reported to have visceral (54.6%) and non-visceral (45.4%) site of baseline metastasis before receipt of chemotherapy in both treatment groups. More patients had a complete or partial response to first-line chemotherapy (avelumab plus BSC: 72.3%; BSC: 72.0%) versus patients who had a stable disease (avelumab plus BSC: 27.7%; BSC: 28.0%). Overall, 54.0% of patients in the avelumab plus BSC group and 48.3% of patients in the BSC group had PD-L1 positive status tumours. A smaller proportion of patients had tumours with unknown PD-L1 status in the avelumab plus BSC group (6.3%) compare to the BSC group (14.0%). For the first-line chemotherapy regimen received by patients, slightly less patients received gemcitabine plus cisplatin in the avelumab plus BSC group compared to the BSC group (52.3% versus 58.9%, respectively), and more patients received gemcitabine plus carboplatin in the avelumab plus BSC group (42.0% versus 34.9%, respectively). Of note, a greater proportion of patients had an upper tract tumour as the primary site of the disease in the avelumab plus BSC group (30.3%) compared to the BSC group (23.1%).[3] The median time from initial diagnosis of UC to the date of first study treatment was 11.5 months in the avelumab plus BSC group and 12.8 months in the BSC group.[4]

In the PD-L1 Positive Population, baseline characteristics were balanced across treatment groups. Most patients had either a CR or PR to their first-line chemotherapy (avelumab plus BSC: 73.5%; BSC: 75.7%). A slightly lower proportion of patients had visceral disease (avelumab plus BSC: 46.6%; BSC: 46.7%), versus non-visceral disease (53.4% and 53.3%, respectively).[3] Most patients had an ECOG PS of 0 (avelumab plus BSC: 60.3%; BSC: 63.3%) or 1 (39.2% and 36.1%, respectively).[4] Most patients also had the primary site of their tumour in the lower tract (avelumab plus BSC: 76.6%; BSC: 79.3%).[3] The median time from initial diagnosis of UC to the date of first study treatment was 13.3 months for the

avelumab plus BSC group and 10.2 months for the BSC group.[4] Compared to the Overall Population, a greater proportion of patients in the PD-L1 Positive Population had baseline metastasis in non-visceral sites (53.4% in the avelumab plus BSC group and 53.3% in the BSC group) than in visceral sites (46.6% for both treatment groups).[3]

Table 8: Baseline Characteristics of Patients in the JAVELIN Bladder 100 Trial

	Overall Population			PD-L1 Positive Population		
	Avelumab+BSC (N=350)	BSC (N=350)	Total (N=700)	Avelumab+BSC (N=189)	BSC (N=169)	Total (N=358)
Age (years), n (%)						
<65 years	129 (36.9)	107 (30.6)	236 (33.7)	62 (32.8)	49 (29.0)	111 (31.0)
≥65 years	221 (63.1)	243 (69.4)	464 (66.3)	127 (67.2)	120 (71.0)	247 (69.0)
65-<75	136 (38.9)	163 (46.6)	299 (42.7)	72 (38.1)	73 (43.2)	145 (40.5)
75-<85	80 (22.9)	78 (22.3)	158 (22.6)	51 (27.0)	47 (27.8)	98 (27.4)
≥85 years	5 (1.4)	2 (0.6)	7 (1.0)	4 (2.1)	0	4 (1.1)
n [1]	350	350	700	189 169	189 169	358
Mean (SD)	67.2 (9.52)	67.7 (9.20)	67.5 (9.36)	68.2 (9.87)	68.0 (9.71)	68.1 (9.78)
Q1	61.00	62.00	62.00	62.00	62.00	62.00
Median	68.00	69.00	69.00	70.00	70.00	70.00
Q3	74.00	74.00	74.00	75.00	75.00	75.00
Range (min, max)	(37.0, 90.0)	(32.0, 89.0)	(32.0, 90.0)	(37.0, 90.0)	(32.0, 84.0)	(32.0, 90.0)
Race, n (%)						
Black or African American	2 (0.6)	0	2 (0.3)	1 (0.5)	0	1 (0.3)
American Indian or Alaska Native	0	0	0	0	0	0
Asian	75 (21.4)	81 (23.1)	156 (22.3)			
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
White	232 (66.3)	238 (68.0)	470 (67.1)	121 (64.0)	119 (70.4)	240 (67.0)
Other	21 (6.0)	15 (4.3)	36 (5.1)	12 (6.3)	7 (4.1)	19 (5.3)
Unknown	20 (5.7)	16 (4.6)	36 (5.1)	13 (6.9)	10 (5.9)	23 (6.4)
Gender, n (%)						
Male	266 (76.0)	275 (78.6)	541 (77.3)	145 (76.7)	129 (76.3)	274 (76.5)
Female	84 (24.0)	75 (21.4)	159 (22.7)	44 (23.3)	40 (23.7)	84 (23.5)
Ethnicity, n (%)						
Hispanic or Latino	18 (5.1)	12 (3.4)	30 (4.3)	9 (4.8)	3 (1.8)	12 (3.4)
Not Hispanic or Latino	286 (81.7)	298 (85.1)	584 (83.4)	152 (80.4)	146 (86.4)	298 (83.2)
Not reported	42 (12.0)	36 (10.3)	78 (11.1)	24 (12.7)	18 (10.7)	42 (11.7)
Unknown	4 (1.1)	4 (1.1)	8 (1.1)	4 (2.1)	2 (1.2)	6 (1.7)
Pooled Geographic Region, n (%)						
North America	12 (3.4)	22 (6.3)	34 (4.9)	8 (4.2)	8 (4.7)	16 (4.5)

	Overall Population			PD-L1 Positive Population		
	Avelumab+BSC (N=350)	BSC (N=350)	Total (N=700)	Avelumab+BSC (N=189)	BSC (N=169)	Total (N=358)
Europe	214 (61.1)	203 (58.0)	417 (59.6) 1	110 (58.2)	102 (60.4)	212 (59.2)
Asia	73 (20.9)	74 (21.1)	147 (21.0)	40 (21.2)	31 (18.3)	71 (19.8)
Australasia	34 (9.7)	37 (10.6)	71 (10.1)	20 (10.6)	24 (14.2)	44 (12.3)
Rest of the World	17 (4.9)	14 (4.0)	31 (4.4)	11 (5.8)	4 (2.4)	15 (4.2)
Best response to first-line chemotherapy (IRT)						
CR or PR	253 (72.3)	252 (72.0)	505 (72.1)	139 (73.5)	128 (75.7)	267 (74.6)
SD	97 (27.7)	98 (28.0)	195 (27.9)	50 (26.5)	41 (24.3)	91 (25.4)
Site of metastasis (IRT)						
Visceral	191 (54.6)	191 (54.6)	382 (54.6)	88 (46.6)	79 (46.7)	167 (46.6)
Non-Visceral	159 (45.4)	159 (45.4)	318 (45.4)	101 (53.4)	90 (53.3)	191 (53.4)
Histopathological classification						
Carcinoma	306 (87.4)	292 (83.4)	598 (85.4)	163 (86.2)	137 (81.1)	300 (83.8)
Carcinoma with Squamous	16 (4.6)	26 (7.4)	42 (6.0)	8 (4.2)	13 (7.7)	21 (5.9)
Carcinoma with Glandular	6 (1.7)	9 (2.6)	15 (2.1)	3 (1.6)	6 (3.6)	9 (2.5)
Carcinoma with Variant	22 (6.3)	22 (6.3)	44 (6.3)	15 (7.9)	13 (7.7)	28 (7.8)
Other	0	1 (0.3)	1 (0.1)	0	0	0
ECOG performance status						
0	213 (60.9)	211 (60.3)	424 (60.6)	114 (60.3)	107 (63.3)	221 (61.7)
1	136 (38.9)	136 (38.9)	272 (38.9)	74 (39.2)	61 (36.1)	135 (37.7)
2	1 (0.3)	0	1 (0.1)	1 (0.5)	0	1 (0.3)
3	0	3 (0.9)	3 (0.4)	0	1 (0.6)	1 (0.3)
4	0	0	0	0	0	0
Not reported	0	0	0	0	0	0
PD-L1 Status						
Positive	189 (54.0)	169 (48.3)	358 (51.1)	189 (100.0)	169 (100.0)	358 (100.0)
Negative	139 (39.7)	132 (37.7)	271 (38.7)	0	0	0
Unknown	22 (6.3)	49 (14.0)	71 (10.1)	0	0	0

The denominator to calculate percentages is N, the number of patients in the Overall Population within each treatment group.

Baseline is defined as the last assessment on or prior to randomization for patients randomized but not dosed, and the last assessment on or prior to first dose of study treatment for patients randomized and dosed.

Source: Clinical Study Report[4]

Prior Treatments

To be eligible for the JAVELIN Bladder 100 trial, patients must have had between four and six cycles of gemcitabine plus cisplatin and/or gemcitabine plus carboplatin as first line treatment. Other first line chemotherapy regimens were not permitted. Within both the Overall Population and PD-L1 Population, the mean and median durations of treatment for each chemotherapy regimen were similar between both treatment groups.[4] In the Overall

Population, gemcitabine plus cisplatin was the more common chemotherapy regimen having been received by 52.3% in the avelumab plus BSC group and 58.9% of patients in the BSC group. Prior therapy with carboplatin and gemcitabine regimen had been received by 42.0% of patients in the avelumab plus BSC group and 34.9% of patients in the BSC group. Gemcitabine plus cisplatin and carboplatin combination had been received by 5.7% of patients in both treatment groups.[4] The characteristics of first-line chemotherapy regimens were similar for patients in the PD-L1 Positive Population; the most common first-line chemotherapy regimen was gemcitabine plus cisplatin (53.4% in the avelumab plus BSC group and 58.0% in the BSC group), followed by gemcitabine plus carboplatin (39.2% and 32.0%, respectively) and gemcitabine plus carboplatin and cisplatin (7.4% and 8.9%, respectively) (data not displayed).[4]

In the Overall Population, most patients had received at least one prior anticancer therapy, including drug therapy, radiation and therapy, other than first-line chemotherapy (83.7% in the avelumab plus BSC group and 81.7% in the BSC group) (Table 9). Of these patients, most had reported having had at least one prior anticancer surgery (80.9% in the avelumab plus BSC group and 78.0% in the BSC group). In the avelumab plus BSC group, 20.9% of patients reported at least one prior anticancer drug therapy versus 24.0% in the BSC group. At least one prior anticancer radiotherapy was reported for 13.7% of patients in each treatment group.[4]

In the PD-L1 Positive Population, similar frequencies of anti-cancer therapies were reported between both treatment groups. At least one prior anti-cancer therapy was reported by 87.8% of patients in the avelumab plus BSC group and 79.9% of patients in the BSC group. The most frequent type of prior anti-cancer therapy was surgery (85.7% in the avelumab plus BSC group and 75.1% in the BSC group), followed by drug therapy (23.3% and 21.9%, respectively) and radiotherapy (15.3% and 11.8%, respectively).[4]

Analgesics, antithrombotic agents, drugs for acid related disorders, agents acting on the renin-angiotensin system, lipid modifying agents, psycholeptics, calcium channel blockers, ophthalmologicals and urologicals were reported to be the most frequent anatomical therapeutic chemical level 2 (ATC2) class of prior medications received by patients in the Overall Population.[4]

Table 9: Prior Anti-Cancer Therapies in the JAVELIN Bladder 100 Trial – Overall Population

N, %	Overall Population		PD-L1 Positive Population	
	Avelumab plus BSC Group N=350	BSC Group N=350	Avelumab plus BSC Group N=350	BSC Group N=350
First-line chemotherapy regimen				
Cisplatin	0	0	0	0
Gemcitabine	0	0	0	0
Cisplatin+Gemcitabine	183 (52.3)	206 (58.9)	101 (53.4)	98 (58.0)
Carboplatin+Gemcitabine	147 (42.0)	122 (34.9)	74 (39.2)	54 (32.0)
Carboplatin+Cisplatin+Gemcitabine	20 (5.7)	20 (5.7)	14 (7.4)	15 (8.9)
Not reported	0	2 (0.6)	0	2 (1.2)
Patients with at least one type of prior anti-cancer therapy				
Yes	293 (83.7)	286 (81.7)	166 (87.8)	135 (79.9)
No	56 (16.0)	59 (16.9)	22 (11.6)	32 (18.9)

N, %	Overall Population		PD-L1 Positive Population	
	Avelumab plus BSC Group N=350	BSC Group N=350	Avelumab plus BSC Group N=350	BSC Group N=350
Not reported	1 (0.3)	5 (1.4)	1 (0.5)	2 (1.2)
Type of prior anti-cancer therapy [1]				
Drug	**73 (20.9)**	**84 (24.0)**	**44 (23.3)**	**37 (21.9)**
Neoadjuvant	26 (7.4)	26 (7.4)	23 (12.2)	14 (8.3)
1 regimen	21 (6.0)	22 (6.3)	19 (10.1)	11 (6.5)
≥2 regimens	5 (1.4)	4 (1.1)	4 (2.1)	3 (1.8)
Adjuvant	37 (10.6)	48 (13.7)	17 (9.0)	20 (11.8)
1 regimen	28 (8.0)	36 (10.3)	16 (8.5)	16 (9.5)
≥2 regimens	9 (2.6)	12 (3.4)	1 (0.5)	4 (2.4)
Advanced/metastatic	0	0	0	0
Radiotherapy	48 (13.7)	48 (13.7)	29 (15.3)	20 (11.8)
Curative	18 (5.1)	20 (5.7)	13 (6.9)	7 (4.1)
Palliative	31 (8.9)	29 (8.3)	17 (9.0)	13 (7.7)
Surgery	283 (80.9)	273 (78.0)	162 (85.7)	127 (75.1)
Curative	229 (65.4)	232 (66.3)	127 (67.2)	106 (62.7)
Palliative	78 (22.3)	72 (20.6)	51 (27.0)	34 (20.1)
Prior anti-cancer drug therapy regimens [2]				
0 regimens	276 (78.9)	264 (75.4)	144 (76.2)	132 (78.1)
1 regimen	57 (16.3)	67 (19.1)	38 (20.1)	30 (17.8)
2 regimens	12 (3.4)	13 (3.7)	6 (3.2)	6 (3.6)
3 regimens	4 (1.1)	2 (0.6)	0	0
≥4 regimens	0	2 (0.6)	0	1 (0.6)
Not reported	1 (0.3)	2 (0.6)	1 (0.5)	0
Patients with prior locoregional disease/recurrence anti-cancer drug therapy	11 (3.1)	12 (3.4)	4 (2.1)	5 (3.0)
0 regimens	0	0	0	0
1 regimen	7 (2.0)	9 (2.6)	2 (1.1)	3 (1.8)
2 regimens	3 (0.9)	3 (0.9)	2 (1.1)	2 (1.1)
3 regimens	1 (0.3)	0	0	0
≥4 regimens	0	0	0	0

[1] Subjects are counted once in each category but may be counted in multiple categories

[2] Includes the overall number of regimens in neoadjuvant, adjuvant, advanced/metastatic or locoregional disease/recurrence drug therapies.

Prior anti-cancer drug therapy does not include first-line chemotherapy.

Source: Clinical Study Report[4]

c) Interventions

Investigational Therapy

The avelumab plus BSC group of the JAVELIN Bladder 100 trial received avelumab plus BSC. Avelumab maintenance therapy was administered at a dose of 10 mg/kg of body weight as a one-hour intravenous infusion every two weeks. An antihistamine and

acetaminophen (i.e., 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent) were given to patients in the avelumab plus BSC group of the trial approximately 30 to 60 minutes before the first four avelumab infusions to lessen the occurrences of infusion-related reactions, which have been identified to be important risks for avelumab; modifications of these medications was based on local treatment standards and guidelines, as appropriate as long as it did not include systemic corticosteroids.[3] Dose reductions for avelumab were not permitted; although, an omittance of subsequent infusions of avelumab were permitted if there were persistent AEs.[3]

BSC was provided to patients according to local practice on the basis of the clinical judgement of the treating physician and the patient's condition. BSC included antibiotic agents, nutritional support, hydration, and pain management. BSC did not include or permit the administration of systemic therapies; however, patients were permitted to receive palliative local radiotherapy for isolated lesions.[3]

Patients received the investigational therapy until confirmation of disease progression in absence of clinical deterioration based on the following criteria:[3]

- Absence of clinical signs and symptoms (including worsening of laboratory values) of disease progression
- No decline in ECOG PS
- Absence of rapid progression of disease by radiographic imaging
- Absence of progressive tumour at critical anatomical sites (i.e., cord compression) requiring urgent alternative medical intervention

Treatment with avelumab may have been resumed if repeat imaging no longer indicated the patient as having progressive disease, but instead indicated a CR, PR, or SD compared to the initial scan. If repeat imaging confirmed PD, was discontinued. However, at the clinical judgement of the investigator, patients with PD may have continued to be have been treated with avelumab, such that the patient was thought to continue to experience clinical benefit.[3]

Patients who stopped treatment with avelumab and who then subsequently experienced radiologic disease progression were eligible for re-treatment with avelumab at the discretion of the investigator and after discussion with the sponsor's medical monitor. These patients were eligible for re-treatment if they had not received any cancer treatment other than BSC since their last dose of avelumab, if they did not meet the safety withdrawal criteria, and if the trial was still open.[3] However, no patients were retreated with avelumab.[19]

Comparator Group

The comparator group of the trial received BSC alone in the same manner as was provided to patients in the avelumab plus BSC group. Treatment for all patients continued until disease progression, unacceptable toxicity, withdrawal of consent, or if any other criterion for withdrawal occurred.[3]

Treatment Modification: Modifications of avelumab infusions were dependent mainly upon severity of infusion related reactions. A summary of treatment modifications for avelumab depending on severity of infusion-related reactions is reported in Table 10. Additional modifications were specified for patients who experienced grade 2 infusion related reactions that did not improve or worsen after implementing specified modifications; treatment with corticosteroids was permitted at the discretion of the investigator, and the infusion of avelumab was not to be resumed for that dose. The next dose of avelumab for these

patients may have included the addition of H2-blocker antihistamines (i.e., famotidine or ranitidine), meperidine, or ibuprofen to the mandatory premedication. Prophylactic steroids were not permitted to address infusion related reactions.[4]

Modifications of avelumab were also dependent on severity of immune-related AEs. Management of avelumab depending on immune-related AEs involved initial management of immune-related AEs as well as follow-up management to monitor the improvement or worsening of symptoms. Management of immune-related AEs due to avelumab treatment were pre-specified in the protocol for the JAVELIN Bladder 100 trial. Separate guidelines were provided for management of gastrointestinal, dermatological, pulmonary, hepatic, endocrine immune-related AEs; guidelines were specified by severity based on CTCAE v4 criteria, and included management guidelines at initial assessment as well as during follow-up.[4]

Table 10: Treatment Modification for Symptoms of Avelumab Infusion-Related Reactions in the JAVELIN Bladder 100 Trial

NCI CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild • Mild transient reaction; infusion interruption not indicated; intervention not indicated.	• Decrease the avelumab infusion rate by 50%* and monitor closely for any worsening.
Grade 2 – moderate • Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.	• Temporarily discontinue avelumab infusion. • Resume infusion at 50% of previous rate* once infusion-related reaction has resolved or decreased to at least Grade 1 in severity. Monitor closely for any recurrence or worsening.
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. • Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the avelumab infusion immediately and disconnect infusion bag and tubing from the patient. • Subjects have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.

IV=intravenous, NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events, NSAIDs=nonsteroidal anti-inflammatory drugs.
*If the avelumab infusion rate has been decreased by 50% due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed at the next scheduled infusion, at the Investigator's discretion, the infusion rate may be returned to baseline at subsequent infusions.

Source: Clinical Study Protocol[3]

Dose Exposure

The median duration of treatment among all treated patents was 24.9 weeks (range, 2.0-159.9) in the avelumab plus BSC group compared to 13.1 weeks (range, 0.1-155.6) in the BSC group (Table 11).[3] The longer median duration of treatment in the avelumab plus BSC group was stated by the sponsor to be mainly driven by the earlier PFS time in the BSC group.[4]

Table 11: Exposure to Study Treatment in the JAVELIN Bladder 100 Trial - Safety Population

[1] Duration of avelumab treatment is defined as Duration (weeks) = (last dose date of avelumab – first dose date of avelumab + 14)/7

[2] Duration of BSC treatment is defined as Duration (weeks) = (end date of BSC – start date of BSC + 1)/7.

[3] The descriptive summary statistics are calculated based on n, the number of subjects who have received at least one dose of the study drug.

Source: Clinical Study Report[4]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

The dose intensity of avelumab in the Safety Population of the avelumab plus BSC group is summarized in (Table 12). The median dose intensity of avelumab received by patients was 17.6 mg/kg per 4-week cycle (Range, 1.6-20.4). The median relative dose intensity for patients receiving avelumab was 88.2% (range, 8.00-102.1).[4]

Table 12: Dose Intensity of Avelumab in the JAVELIN Bladder 100 Trial – Safety Population

	Avelumab+BSC (N=344)
Cumulative dose (mg/kg) [1]	
n	344
Mean (SD)	182.6 (161.58)
Q1	60.0
Median	112.6
Q3	266.7
Range (min, max)	(1.6, 787.7)
Dose intensity (mg/kg/4-week cycle) [2]	
n	344
Mean (SD)	16.9 (2.56)
Q1	16.0
Median	17.6
Q3	18.7
Range (min, max)	(1.6, 20.4)
Relative dose intensity (%) [3]	
n	344
Mean (SD)	84.6 (12.82)
Q1	80.0
Median	88.2
Q3	93.5
Range (min, max)	(8.0, 102.1)

[1] Cumulative dose (mg/kg) = sum of all doses (mg/kg) of avelumab.

[2] Dose intensity (mg/kg/4-week cycle) = [overall cumulative dose (mg/kg)] / [(intended duration of avelumab treatment (weeks)/4]

[3] Relative dose intensity (%) = 100 × [dose intensity (mg/kg/4-week cycle)] / [20 (mg/kg/4-week cycle)] The descriptive summary statistics are calculated based on n, the number of subjects who have received at least one dose of avelumab.

Source: Clinical Study Report[4]

The dose modifications of avelumab in the Safety Population of the avelumab plus BSC group are summarized in Table 13. Over half of patients (54.1%) did not require any dose delays (i.e. dose was administered within three days of scheduled administration). Of the 45.9% of patients requiring dose delays, most were delays of seven days or greater (37.8%), while the remaining where delays between four to six days (8.1%).[4] Overall, 11 patients receiving avelumab required dose reductions, with 10 of these patients requiring only one dose reduction and one patient who required two dose reductions. At least one infusion rate reduction of at least 50% was required in 32 (9.3%) patients; of these patients, 22 (6.4%) required four or more reductions, while the remaining patients required one (n=7, 2.0%), two (n=1, 0.3%), or three (n=2, 0.6%) infusion rate reductions. A total of 16 patients (4.7%) required dose interruptions (an infusion interruption was defined as an infusion that was stopped and re-started on the same day). Of these, most required only one infusion interruption of avelumab (n=14, 4.1%), and the remaining patients two patients (0.6%) required two infusion interruptions of avelumab. No patients required three or more infusion interruptions.[4]

Table 13: Dose Modifications of Avelumab in the JAVELIN Bladder 100 Trial – Safety Population

	Avelumab+BSC (N=344) n (%)
Duration of dose delays [1]	
No Delay	186 (54.1)
0 days	81 (23.5)
1 - 3 days	105 (30.5)
Dose delays	158 (45.9)
4 - 6 days	28 (8.1)
≥7 days	130 (37.8)
1 day	43 (12.5)
2 days	35 (10.2)
3 days	27 (7.8)
4 days	16 (4.7)
5 days	9 (2.6)
6 days	3 (0.9)
7-13 days	32 (9.3)
14-20 days	58 (16.9)
21-27 days	8 (2.3)
≥28 days	32 (9.3)
Subjects with at least one dose reduction [2]	11 (3.2)
1 reduction	10 (2.9)
2 reductions	1 (0.3)
3 reductions	0
≥4 reductions	0
Subjects with at least one infusion rate reduction of 50% or more [3]	32 (9.3)
1 infusion rate reduction	7 (2.0)
2 infusion rate reductions	1 (0.3)
3 infusion rate reductions	2 (0.6)
≥4 infusion rate reductions	22 (6.4)
Subjects with at least one infusion interruption [4]	16 (4.7)
1 infusion interruption	14 (4.1)
2 infusion interruptions	2 (0.6)
3 infusion interruptions	0
≥4 infusion interruptions	0

[1] Dose delay is the difference between the actual time between two consecutive non-zero doses and the planned time between the same two consecutive non-zero doses. A delay of 1-3 days is not counted as a delay.

[2] Dose reduction is defined as actual non-zero dose < 90% of the planned dose.

[3] Infusion rate reduction is defined as decrease in the infusion rate by 50% or more compared to the first infusion rate.

[4] An infusion interruption is defined as an infusion that is stopped and re-started on the same day.

[5] The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.

Source: Clinical Study Report[4]

Pre-Medications for Avelumab Infusions

For patients randomized to receive maintenance treatment with avelumab, pre-medication 30 to 60 minutes prior to the avelumab infusion was mandatory for the first four infusions. The most frequent pre-medications reported were analgesics (99.4%) and an antihistamine for systemic use (100%).[4]

Concomitant Treatments

Per protocol, concomitant surgery and radiation therapy were permitted for palliative reasons. Concomitant medications were analyzed using the Safety Population of the JAVELIN Bladder 100 trial. A total of 336 patients (97.7%) and 316 patients (91.5%) in the avelumab plus BSC and BSC groups, respectively, used a concomitant medication during the trial. A similar proportion of patients in the avelumab plus BSC (4.9%) and BSC (4.1%) groups received concomitant palliative radiation therapy, and a greater proportion of patients in the BSC group (3.5%) than the avelumab plus BSC group (1.7%) received concomitant anti-cancer surgery (Table 14).[4]

Table 14: Concomitant Treatments in the JAVELIN Bladder 100 Trial – Safety Population

	Avelumab plus BSC group	BSC group
Anti-cancer surgery	**6 (1.7)**	**12 (3.5)**
Bladder operation	1 (0.3)	0
Cancer surgery	0	1 (0.3)
Cranial operation	0	1 (0.3)
Hip arthroplasty	0	1 (0.3)
Jejunostomy	0	1 (0.3)
Pelvic exenteration	0	1 (0.3)
Transurethral bladder resection	3 (0.9)	8 (2.3)
Urinary cystectomy	1 (0.3)	0
Urostomy	1 (0.3)	1 (0.3)
Radiation therapy	**17 (4.9)**	**15 (4.1)**
Curative	0	1 (0.3)
Palliative	17 (4.9)	14 (4.1)
Medications	**336 (97.7)**	**316 (91.6)**

Source: Clinical Study Report[4]

Subsequent Therapy

In the Overall Population, anticancer therapies of any type were reported less frequently among patients in the avelumab plus BSC group ([redacted]%) compared to patients in the BSC group ([redacted]%). A similar proportion of patients in in the avelumab plus BSC and BSC groups discontinued treatment without receiving any subsequent therapy ([redacted]% and [redacted]%, respectively (Table 15).[4,19] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* A smaller proportion of patients had received subsequent anticancer drug therapy in the avelumab plus BSC group (42.3%) compared to the BSC group (61.7%) the most common subsequent anticancer drug therapy in the BSC group was any PD-1 or PD-

L1 inhibitor, having been administered to 6.3% in the avelumab plus BSC group and to 43.7% of patients in the BSC group. Any other drug therapy was provided to 40.0% and 34.0% of patients in the avelumab plus BSC group and the BSC group, respectively (Table 15).

Within the PD-L1 Positive Population, similar to the Overall Population, fewer patients received a subsequent anticancer drug therapy in the avelumab plus BSC group (36.0%) compared to the BSC group (64.5%) (Table 15). A PD-1 or PD-L1 inhibitor was administered to 5.3% of patients in the avelumab plus BSC group and to 47.9% of patients in the BSC group. Other drug therapies were administered to 35.4% and 33.7% of patients in the avelumab plus BSC and BSC groups, respectively.[3]

The proportion of patients receiving subsequent anticancer radiotherapy ([redacted]% and [redacted]% in the avelumab plus BSC group and the BSC group, respectively) and surgery ([redacted]% and [redacted]%, respectively) were similar between both treatment groups in the Overall Population; with most patients receiving subsequent anticancer radiotherapy as a palliative treatment.[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* A similar proportion of patients in in the avelumab plus BSC and BSC groups discontinued treatment without receiving any subsequent therapy (33.4% and 30.9%, respectively).[19]

Table 15: Summary of Subsequent Anti-Cancer Therapies in the JAVELIN Bladder 100 Trial – Overall Population

	Overall Population		PD-L1 Positive Population	
	Avelumab plus BSC N=350	BSC N=350	Avelumab plus BSC N=189	BSC N=169
Patients with at least one type of follow-up anti-cancer therapy				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]
Patients with at least one follow-up anti-cancer drug therapy				
Yes	148 (42.3)	216 (61.7)	68 (23.0)	109 (64.5)
No	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]
Any PD-1 or PD-L1 inhibitor	22 (6.3)	153 (43.7)	10 (5.3)	81 (47.9)
FGFR inhibitor	9 (2.6)	8 (2.3)	3 (1.6)	4 (2.4)
Any other drug therapy	140 (40.0)	119 (34.0)	67 (35.4)	57 (33.7)
Patients with at least one follow-up anti-cancer radiotherapy				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]
Patients with at least one follow-up anti-cancer radiotherapy [1]				
Curative	[redacted]	[redacted]	[redacted]	[redacted]
Palliative	[redacted]	[redacted]	[redacted]	[redacted]

	Overall Population		PD-L1 Positive Population	
	Avelumab plus BSC N=350	BSC N=350	Avelumab plus BSC N=189	BSC N=169
Patients with at least one follow-up anti-cancer surgery				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up anti-cancer drug therapy regimens [2]				
0 regimens	[redacted]	[redacted]	[redacted]	[redacted]
1 regimen	[redacted]	[redacted]	[redacted]	[redacted]
2 regimens	[redacted]	[redacted]	[redacted]	[redacted]
3 regimens	[redacted]	[redacted]	[redacted]	[redacted]
≥4 regimens	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]

Follow-up anti-cancer therapies as recorded in the Follow-up Cancer Therapy, Follow-up Radiation Therapy and Follow-up Surgery CRF pages

The denominator to calculate the percentages is N, the number of patients in the Overall Population within each treatment group.

[1] Patients are counted once per category but may be counted in multiple categories

[2] Includes the overall number of regimens in neoadjuvant, adjuvant, advanced/metastatic or locoregional disease/recurrence drug therapies

Source: Clinical Study Report[4], Checkpoint Question Responses November 27th, 2020[19]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Crossover was not permitted within the JAVELIN Bladder 100 trial. However, at the pre-specified interim analysis the primary endpoint of OS demonstrated superiority in both co-primary populations; based on this, a recommendation was made from an External-Data Monitoring Committee that remaining patients in the BSC group be offered crossover to avelumab if they met the eligibility criteria specified in the amended trial protocol. A protocol amendment was made on February 13, 2020 to address this crossover. At the time of the interim analysis, 26 patients in the BSC group were eligible for crossover; confirmation from the sponsor indicated that only one patient in the BSC group had crossed over to receive avelumab.[19]

d) Patient Disposition

Disposition of patients in the JAVELIN Bladder 100 trial are reported in Table 16. At the time of the data cut-off (October 21, 2019), 85 patients (24.3%) in the avelumab plus BSC group and 26 patients (7.4%) in the BSC group were still receiving trial treatment. Treatment discontinuation occurred for 265 patients (75.7%) in the avelumab plus BSC group and 324 patients (92.6%) in the BSC group. The most common reasons for discontinuation in the avelumab plus BSC group included progressive disease (54.0%), AEs (11.1%), and withdrawal of consent (4.6%). The most common reasons for discontinuation in the BSC group included progressive disease (75.1%), withdrawal of consent (8.3%) and death (4.0%).[3]

Patients who had discontinued study treatment were able to go into a follow-up phase or a long-term follow-up phase; patients were able to do this if they had received either a subsequent anti-cancer therapy at the end of their treatment or at their own request. The disposition of these patients in the follow-up and long-term follow-up phases is reported in Table 16.[4] For patients who entered the follow-up phase, the primary reason for

discontinuation of follow-up was listed as ‘other’ (16.9% and 17.4% in the avelumab plus BSC group and the BSC group, respectively), followed by death (4.6% and 5.4%, respectively). For patients entering long-term follow-up, the primary reason for discontinuation of long-term follow-up was death (35.1% in the avelumab plus BSC group and 41.1% in the BSC group). In the avelumab plus BSC group, 20% of patients were in the follow-up phase and 26.3% of patients were in the long-term follow-up phase at the time of the data cut-off. In the BSC group, 1.1% of patients were in the follow-up phase and 32.9% of patients were in the long-term follow-up phase.[4]

Table 16: Patient Disposition of the JAVELIN Bladder 100 Trial

Patient Disposition, n (%)	Overall Population		PD-L1 Positive Population	
	Avelumab plus BSC	BSC	Avelumab plus BSC	BSC
Patients randomized	350 (100.0)	350 (100.0)	189 (100.0)	169 (100.0)
Received treatment[a]	344	345	NR	NR
Received no treatment	6	5	NR	NR
Completed Treatment	165 (76.4)	160 (74.1)	NR	NR
Trial phase: End of Treatment				
Discontinued Treatment	265 (75.7)	324 (92.6)	131 (69.3)	156 (92.3)
Progressive disease	189 (54.0)	263 (75.1)	84 (44.4)	126 (74.6)
Adverse events	39 (11.1)	2 (0.6)	26 (13.8)	1 (0.6)
Withdrew consent	16 (4.6)	29 (8.3)	7 (3.7)	12 (7.1)
Death	5 (1.4)	14 (4.0)	3 (1.6)	8 (4.7)
Physician's decision	5 (1.4)	7 (2.0)	4 (2.1)	6 (3.6)
Global deterioration of health[b]	4 (1.1)	6 (1.7)	2 (1.1)	1 (0.6)
No longer meets eligibility criteria	3 (0.9)	0	1 (0.5)	0
Lost to follow-up	2 (0.6)	2 (0.6)	2 (1.1)	1 (0.6)
Non-compliance with study drug	1 (0.3)	0	1 (0.5)	0
Other reasons	1 (0.3)	1 (0.3)	1 (0.5)	1 (0.6)
Still on treatment	85 (24.3)	26 (7.4)	58 (30.7)	13 (7.7)
Trial phase: Follow-up				
Patients entering follow-up	147 (42.0)	134 (38.3)	73 (38.6)	68 (40.2)
Discontinued	78 (22.3)	84 (24.0)	35 (18.5)	40 (23.7)
Reason for discontinuation				
Death	16 (4.6)	19 (5.4)	5 (2.6)	6 (3.6)
Withdrew consent	2 (0.6)	4 (1.1)	2 (1.1)	2 (1.2)
Lost to follow-up	1 (0.3)	0	0	0
Other	59 (16.9)	61 (17.4)	28 (14.8)	32 (18.9)
Completed	62 (17.7)	46 (13.1)	36 (19.0)	26 (15.4)
Ongoing	7 (2.0)	4 (1.1)	2 (1.1)	2 (1.2)
Trial phase: Long-Term Follow-Up				
Patients entering long-term follow-up	221 (63.1)	268 (76.6)	114 (60.3)	135 (79.9)
Discontinued	129 (36.9)	153 (43.7)	57 (30.2)	72 (42.6)
Reasons for discontinuation				
Death	123 (35.1)	144 (41.1)	53 (28.0)	68 (40.2)
Withdrew consent	4 (1.1)	4 (1.1)	2 (1.1)	2 (1.2)
Lost to follow-up	2 (0.6)	5 (1.4)	2 (1.1)	2 (1.2)
Ongoing	92 (26.3)	115 (32.9)	57 (30.2)	63 (37.3)

BSC = best supportive care; NR=not reported.

[a] Avelumab plus BSC group: included patients who received at least one dose of avelumab plus best supportive care. BSC: included patients who completed Cycle 1 on Day 1.

[b] Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumour assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Source: Clinical Study Report[4], Clinical Study Protocol[3]

Protocol Deviations

Major protocol deviations were pre-specified and included the following: patients who were dosed on the study despite not satisfying the inclusion criteria, patients who developed withdrawal criteria whilst on the study but were not withdrawn, patients who received the wrong treatment or an incorrect dose, patients who received an excluded concomitant medication, and/or deviations from Good Clinical Practice.[22]

A list of potentially important protocol deviations is reported in Table 17. Potentially important protocol deviations occurred in [redacted]% in the avelumab plus BSC group and [redacted]% in the BSC group. Potentially important protocol deviations in the avelumab plus BSC group were mainly due to issues related to informed consent ([redacted]%), inclusion/exclusion criteria ([redacted]%) or concomitant medications ([redacted]%). Potentially important protocol deviations in the BSC group were mainly due to inclusion/exclusion criteria ([redacted]%), issues related to informed consent ([redacted]%) and randomization ([redacted]%).[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

There were higher proportion of protocol deviations related to inclusion/exclusion criteria in the BSC group than the avelumab plus BSC group; large differences between groups were mainly due to deviations related to patients receiving their prior first-line chemotherapy of between 4 and 6 cycles of gemcitabine plus cisplatin and/or carboplatin ([redacted] in the avelumab plus BSC group and [redacted]% in the BSC group), patients without progressive disease per RECIST v1.1 criteria following of first-line chemotherapy as determined by BICR ([redacted]% versus [redacted]%, respectively), provision of recent formalin-fixed paraffin-embedded tumour tissue block or slides obtained within 24 months prior to randomization no intervening chemotherapy ([redacted]% versus [redacted]%, respectively), and dosing of patients even though a procedure/lab/assessment required for determination of eligibility was not completed or results were not available ([redacted]% versus [redacted]%, respectively).[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Protocol deviations related to inclusion/exclusion criteria were mainly related to randomization were concerning randomization of patients under the incorrect strata. In the avelumab plus BSC group, [redacted] patient ([redacted]%) was incorrectly randomized under the wrong stratification of patient's response to first-line chemotherapy (CR or PR versus SD) and metastatic site at imitation of first-line chemotherapy (visceral versus non-visceral), [redacted] patients ([redacted]%) under the incorrect stratification of response to first-line chemotherapy , and eight patients ([redacted]%) under incorrect metastatic site at initiation of first-line chemotherapy; randomization under the incorrect strata in the BSC group occurred in [redacted] patients ([redacted]%), [redacted] patients ([redacted]%), and [redacted] patients ([redacted]%), respectively.[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

To note, the sponsor conducted a sensitivity analysis for OS based on the potentially important protocol deviations associated with randomization of the IRT system; [redacted]% of patients in the avelumab plus BSC group and [redacted]% of patients in the BSC group had a potentially important protocol deviation associated with randomization where patients were randomized under the wrong stratification factor (CR/PR versus SD and/or visceral versus non-visceral disease). *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* The sensitivity analysis was done based on actual stratification that was documented for patients, and revealed that the result based on IRT-entered randomization stratification factors were similar to results of the sensitivity analysis.[4]

Table 17: Potentially Important Protocol Deviations

N (%)	Avelumab plus BSC group N=350	BSC group N=350	Total N=700
Patients with potentially important deviations			
Concomitant medications			
Inclusion/exclusion criteria			
Informed consent			
Investigational product			
Procedures/tests			
Protocol specific discontinuation criteria			
Randomization			

BSC = best supportive care.

Data Source: Clinical Study Report[4]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

e) Limitations/Sources of Bias

Overall, the JAVELIN Bladder 100 trial was a well-conducted randomized trial with two treatment arms. The objective of the trial was to compare the efficacy and safety of maintenance treatment with avelumab plus BSC versus BSC alone in adult patients with unresectable locally advanced or metastatic UC after completion of first-line platinum-based chemotherapy.

As per the CGP, the comparator arm of the trial, which included BSC only, was appropriate given that current standard of care involves BSC only or observation. The statistical analyses of this trial involved estimates based on a one-sided alpha, testing for superiority of avelumab plus BSC over BSC alone. The use of one-sided alpha allowed for increased power of the statistical tests used in the trial (i.e., higher probability of rejecting the null hypothesis due to larger rejection region toward one direction versus a two-tailed test which considers smaller rejection areas in either positive or negative directions). The primary endpoint for analysis in the JAVELIN Bladder 100 trial was OS in the Overall Population and the PD-L1 Positive Population. To preserve the overall type 1 error rate, a group-sequential design with a Lan-DeMets (O'Brien Fleming) alpha spending function was used, whereby a one-sided alpha of 0.015 and 0.01 were allocated for analysis of OS in the Overall and PD-L1 Positive Population, respectively. Overall, the methods used to conduct the JAVELIN Bladder 100 trial were considered appropriate.

The CADTH Methods Team identified the following limitations and potential sources of bias that should be considered when interpreting the trial results:

Study Design

- The JAVELIN Bladder 100 trial was conducted using an open-label study design, which is susceptible to reporting and performance biases. Patients and investigators were aware of the study drug assigned, which can introduce the potential to bias results and outcomes in favour of the active treatment if the assessor (investigator or patient) believes the study drug is likely to provide a benefit. This limits the robustness of the efficacy results. The sponsor justified the use of an open-label study design as avelumab is administered to patients via one-hour infusion; the use of a placebo equivalent in a double-blind placebo-controlled trial would have involved administration of an intravenous placebo which may have introduced patients randomized to the BSC

group to risks, including injection site reactions; the sponsor indicated that patients randomized to the BSC group would not have benefit from such a procedure. Further, as patients receiving avelumab required premedication with an H1 blocker and paracetamol prior to infusion to limit incidence and severity of infusion-related reactions, patients randomized to the BSC group would also be required to receive placebo equivalents; the sponsor indicated that providing such treatments would be unnecessary to patients randomized to the BSC group of the trial.[3] Therefore, the lack of blinding may have introduced bias affecting the performance, measurement and reporting of clinical outcomes (i.e., safety and efficacy) in the context of both the patients and investigators. However, randomization was performed centrally using an IRT system, and a BICR was implemented to mitigate biases associated with assessment of outcomes, such as PFS and ORR. Further, disease progression was based on objective diagnostic criteria (RECIST v1.1) and radiological assessments, including CT or MRI scans. Biases pertaining to an open-label study design likely continued to exist; however, they may not have impacted patients' treatment assignment or the trial outcomes due to the IRT system for randomization, objective diagnostic testing criteria and BICR assessment of outcomes.

- In addition to the bias that an open-label design introduces to reporting safety and/or efficacy outcomes, the measurement of PROs may also be biased favouring maintenance treatment with the investigational therapy (avelumab plus BSC) over the control group in the trial (BSC alone) as patients remained aware of their treatment assignment. Completion of PRO questionnaires may have been influenced by patients' knowledge of their assigned treatment and this should be taken into account when interpreting results from PRO questionnaires. MID of 3 points was prespecified for the FBISI HRQoL tool in the trial. However, there was no prespecified MID established for the EQ-5D-5L or VAS tools, and results for these questionnaires were not reported based on MID between treatment groups. MID is a useful calculation to determine whether differences in HRQoL observed between trial groups are clinically relevant. Without a MID, results for the EQ-5D-5L and VAS tools may be interpreted only based on changes in HRQoL observed from baseline throughout the trial. The sponsor noted that data from patients for the EQ-5D were primarily collected to calculate utility values for economic models.[6] The sponsor also noted that a MID has been established for UK-utility scores ranging from 0.09 to 0.12 for the EQ-5D-5L and 7 to 12 for the VAS for all cancers.[6,7] As no MID was prespecified for analysis of the EQ-5D-5L and VAS, results were not reported or interpreted this way.
- The sponsors funded the trial and were involved in several aspects of the study conduct, including the study design, data analysis, data interpretation, and writing of the reports. The extent to which the sponsors' involvement may have influenced the results and reporting of the trial is unknown.
- Patients included in the JAVELIN Bladder 100 trial were enrolled based on strict eligibility criteria. The rigorous inclusion and exclusion criteria limit the applicability of trial results to the patient population included in the trial. External validity of trial results to other patients with UC who do not strictly fall under the eligibility of the trial may be limited. However, based on input from the CGP, baseline characteristics of patients included in the trial were not uncommon to patients who may be treated in clinical practice. Based on the trial design and results reported, clinicians should be able to judge for which patients avelumab plus BSC maintenance can be appropriately prescribed to provide clinical benefit. Comments from the CGP regarding generalizability of avelumab plus BSC maintenance are reported in Table 3.

Protocol Deviations and Amendments

- Upon review of potentially important protocol deviations by the CADTH Methods Team, it was determined that protocol deviations pertaining to inclusion/exclusion criteria, which occurred more frequently in the BSC alone group, had the potential to negatively bias outcomes of clinical efficacy against the maintenance with BSC alone. However, as

these protocol deviations occurred in somewhat low frequency (<5%), it is overall unclear how such protocol deviations may have influenced patient outcomes.

- Two protocol amendments potentially impacting the trial were dated for December 16, 2016, approximately one year after the final protocol for the JAVELIN Bladder 100 trial was approved:

    1. The protocol was amendment to provide a clarification regarding eligibility criteria for patients enrolled within the trial; patients must have completed first-line chemotherapy between four and ten weeks prior to randomization. This amendment was considered by the sponsor to have impacted the conduct of the trial in a significant manner which could influence trial results depending on whether patients had been randomized into the trial earlier than four weeks post completion of first-line chemotherapy, or for greater than ten weeks post completion of first-line chemotherapy. The sponsor confirmed that 35 patients were enrolled who did not complete first-line chemotherapy within the four to ten week timeframe. However, a review of these 35 patients by the CADTH Methods Team revealed that there was no significant deviation in time frame for completing first-line therapy, as most patients completed first-line chemotherapy at just under four works (between 2.9 to 3.9 weeks) or just over ten weeks (10.1 to 19 weeks). Only one patient was enrolled who completed first-line chemotherapy after greater than 11.6 weeks.[6] Therefore, as a small proportion of patients who did not complete first-line chemotherapy within four to ten weeks were enrolled, and since most patients fell close within the eligibility window for completion of first-line chemotherapy, it is expected that the impact of this amendment is minimal. In addition, another trial amendment also made at this time removed the requirement for central eligibility review of first-line chemotherapy response.

    2. The protocol was amended to include an expedited BICR for investigator-assessed disease progression to mitigate potential biases. Prior to the date of the amendment (December 16, 2016), 24 patients were enrolled, seven of whom were deemed progressed by the investigator and seven of whom were deemed progressed by BICR; of these patients deemed progressed by both investigator and BICR, there was agreement for six of the patients.[6] Therefore, this protocol amendment is expected to have a minimal impact on efficacy analyses.

Statistical Analyses and Assessment of Outcomes

- Efficacy estimates in subgroups, while pre-specified per protocol, were not powered to detect difference and were limited due to small sample sizes. Also, adjustments for multiplicity for subgroup analyses were not conducted. The lack of adjustment may increase the likelihood of type 1 error, resulting in an increased likelihood of detecting a treatment effect when one may not be present. Therefore, results for subgroup analyses should be considered exploratory and should be interpreted with caution.

- Assessment for violation of the proportional hazards assumption was conducted based on the Schoenfeld's residual test and by plotting log(-log(OS)) versus log(time) within each randomization stratum. The tests revealed that there was no violation of the proportional hazards assumption for either the Overall or PD-L1 Positive Population, except under the stratification factors of '*SD*' for the variable of patients best response to first-line chemotherapy and '*visceral'* for the variable of metastatic disease.[4] Otherwise, proportional hazard assumptions for the strata of '*CR or PR*' with '*visceral*' and '*non-visceral*' disease were valid. However, results for OS were also summarized using the restricted mean survival time (RMST) method, which supported the primary analysis of OS favouring maintenance treatment with avelumab plus BSC over BSC alone.[4]

- In the analysis of OS, censoring occurred on the date patients were last known to be alive. A large proportion of patients were censored in the analysis of OS; censoring of patients occurred in 59% of patients in the avelumab plus BSC group and 49% of patients in the BSC group. The large amount of censoring may inflate the benefit

observed in the avelumab plus BSC group. In addition, analysis of OS did not account for patients who may have received subsequent therapies. Few patients in the avelumab plus BSC group ([redacted]%) received at least one type of subsequent anti-cancer therapy versus patients in the BSC group ([redacted]%). *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* Patients in the BSC group more frequently received at least one anti-cancer drug therapy than patients in the avelumab plus BSC group (61.7% versus 42.3%, respectively).[4] Patients in the BSC group most commonly received a subsequent PD-1 or PD-L1 inhibitor (43.7%) which may underestimate the results of OS as patients receiving subsequent therapy will receive additional benefit from treatment. Overall, analyses of OS were confounded in ways which could have both over- and underestimated the treatment benefit of avelumab plus BSC. Despite the biases associated with the analysis of OS, numerous sensitivity analyses of OS continued to support the primary results of OS which demonstrate improved survival for patients who received avelumab plus BSC maintenance treatment.[4]

- Efficacy analyses were conducted in two co-primary populations, including the Overall Population and the PD-L1 Positive Population. However, the study was not stratified by PD-L1 status, which may introduce bias and confounding during the assessment of efficacy outcomes in this population. An analysis of OS was conducted among the subgroup of patients with PD-L1 negative status enrolled within the trial, which consisted of 271 patients (38.7%) in total with no differences in baseline characteristics between the treatment groups. Analysis of OS in PD-L1 negative patients continued to support improved outcomes for patients who received avelumab plus BSC compared versus BSC alone (unstratified HR = 0.86; 95% CI: 0.62 to 1.18). Subgroup analyses of PFS (unstratified HR = 0.63; 95% CI: 0.48 to 0.85) and ORR (unstratified OR = 8.0; 95% C:, 1.04 to 357.6) for PD-L1 negative patients also favoured treatment with avelumab plus BSC.[4] In addition, the sponsor conducted sensitivity analyses for OS which included analyses based on stratification of PD-L1 status, and another based on stratification of PD-L1 status, patients' response to first line chemotherapy and metastatic disease site; both of these sensitivity analyses continued to show improved benefit in the avelumab plus BSC group over the BSC group, with hazard ratios for death of [redacted] (95% CI, [redacted]) and [redacted] (95% CI, [redacted]), respectively.[4] Therefore, the benefit observed with avelumab plus BSC over BSC may not completely driven by the results observed in the PD-L1 positive patients. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

- Analysis of PROs was dependent on completion of PRO questionnaires by patients. For the FBISI, completion of the entire questionnaire was less than [redacted]% of patients during all cycles, and from cycle 2, substantially fewer patients in the BSC group were eligible to complete the FBISI questionnaire (n=[redacted]), than the avelumab plus BSC group (n=[redacted])[5]. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* In addition, after cycle 19, few patients (<50) were eligible for completion of both the FBISI and the EQ-5D questionnaires. Therefore, the number of patients included in the calculation of mean changes from baseline decreased over the course of treatment during the trial, introducing uncertainty in the results of the PROs. Further, the analysis of TTD was conducted based on FBISI DRS-P results. It was noted that results of TTD may be biased in favour of the avelumab plus BSC maintenance group, as events of progression or death were not considered deterioration events in the KM analysis resulting in greater censoring of patients in the avelumab plus BSC group versus the

BSC group.[5] Although, in general a large number of patients were censored in the analysis for TTD ([redacted]% of patients in the avelumab plus BSC group and [redacted]% of patients in the BSC group), mainly due to patients ongoing in the trial without experiencing an event ([redacted]% versus [redacted]%, respectively).[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* KM analysis of TTD revealed a median TTD of 13.8 months (95% 12.9-NE) in the BSC group and a median TTD of NE (95%CI 13.9-NE) in the avelumab plus BSC group, with results favouring the BSC group (HR=1.26, 95%CI 0.90-1.77). A post-hoc analysis of TTD based on death or decline in DRS-P was also conducted for TTD and favoured the avelumab plus BSC group over the BSC group, resulting in a HR of 0.84 (95% CI: 0.68 to 1.03; P=0.089).[5] As the analysis of TTD was reported to be biased for the avelumab plus BSC group, the results suggest that attention to the deterioration and physical state of patients may be warranted with maintenance treatment with avelumab plus BSC.

- For the analysis of PFS, patients receiving any other anti-cancer therapy were censored, and this outcome was not treated as an event. As per the FDA, this is considered a biased censoring rule, and generally starting another treatment before PD should be considered as an event. The CADTH Methods Team requested that the sponsor conduct sensitivity analysis of PFS which did not sensor for patient who started a new anti-cancer therapy prior to an event and who had two or more missing tumour assessments. The sponsor provided sensitivity analyses of PFS following EMA guidelines which considered all events of PD and deaths as events regardless of missing assessments or timing of the event. Results supported the primary analysis of PFS and showed a lower risk of progression or death for patients randomized to the avelumab plus BSC group in the Overall Population (HR=[redacted]; 95% CI: [redacted]) and the PD-L1 Positive Population (HR=[redacted]; 95% CI: [redacted]).[6] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

The results of for the JAVELIN Bladder 100 trial are summarized in Table 18. At the time of data cut-off, in the Overall Population, the median follow-up for OS was greater than 19.6 (95% CI: 18.0 to 20.6) months for patients in the avelumab plus BSC group and 19.2 (95% CI: 17.4 to 21.6) months for patients in the BSC group. In the PD-L1 Positive Population, the median follow-up for OS was 18.3 (95% CI: 16.0 to 20.2) months and 20.0 months (95% CI: 17.1 to 22.2) for the avelumab plus BSC and BSC groups, respectively.[4]

Table 18: Summary of Primary and Secondary Efficacy Endpoints (ITT population)

	Overall population		PD-L1 Positive Population	
	Avelumab plus BSC Group N=350	BSC Group N=350	Avelumab plus BSC Group N=189	BSC Group N=169
Overall Survival Median, months (95%CI)	21.4 (18.9 to 26.1)	14.3 (12.9 to 17.9)	NE (20.3 to NE)	17.1 (13.5 to 23.7)
Median OS follow-up, months (95% CI)	19.6 (18.0 to 20.6)	19.2 (17.4 to 21.6)	18.3 (16.0 to 20.2)	20.0 (17.1 to 22.2)
Events, n (%)	145 (41.4)	179 (51.1)	61 (32.3)	82 (48.5)
Hazard ratio (95% CI) 1-sided p-value 2-sided p-value	0.69 (0.56 to 0.86) 0.0005 0.0010		0.56 (0.40 to 0.79) 0.0003 0.0007	
Progression-free Survival Median, months (95%CI)	3.7 (3.5 to 5.5)	2.0 (1.9 to 2.7)	5.7 (3.7 to 7.4)	2.1 (1.9 to 3.5)
Median PFS follow-up, months (95% CI)	15.1 (11.2 to 16.7)	13.0 (8.3 to 19.4)	13.8 (11.0 to 16.6)	14.1 (7.5 to 19.4)
Events, n (%)	225 (64.3)	260 (74.3)	109 (57.7)	130 (76.9)
Hazard ratio (95% CI) 1-sided p-value 2-sided p-value	0.62 (0.52 to 0.75) <0.0001 <0.0001		0.56 (0.43 to 0.73) <0.0001 <0.0001	
Objective Response				
Confirmed objective response, % (95% CI)	9.7 (6.8 to 13.3)	1.4 (0.5 to 3.3)	13.8 (9.2 to 19.5)	1.2 (0.1 to 4.2)
Stratified odds ratio (95% CI)	7.46 (2.82 to 24.45)		12.70 (3.16 to 114.12)	
Confirmed best overall response, n (%)				
Complete response	21 (6.0)	3 (0.9)	18 (9.5)	1 (0.6)
Partial response	13 (3.7)	2 (0.6)	8 (4.2)	1 (0.6)
Stable disease	44 (12.6)	46 (13.1)	19 (10.1)	23 (13.6)
Non-complete response or non-progressive disease	66 (18.9)	45 (12.9)	38 (20.1)	22 (13.0)
Progressive disease	130 (37.1)	169 (48.3)	59 (31.2)	82 (48.5)
Could not be evaluated	76 (21.7)	85 (24.3)	47 (24.9)	40 (23.7)
Disease control, n (%)	144 (41.1)	96 (27.4)	83 (43.9)	47 (27.8)
Time to objective response, months (range)	2.0 (1.7 to 16.4)	2.0 (1.8 to 7.0)	2.0 (1.7 to 16.4)	2.8 (1.8 to 3.8)

BSC = best supportive care; CI = confidence interval; PD-L1 = programmed death-ligand 1.

Source: Clinical Study Report[4], Powles et al. 2020[3]

Primary Outcome: Overall Survival

In the Overall Population, the median OS was longer in the avelumab plus BSC group at 21.4 months (range, 18.9-26.1) compared to the BSC group which had a median OS of 14.3 months (range, 12.9-17.9),[3] with 145 patients (41.4%) and 179 patients (51.1%) experiencing an OS event[4] in each treatment group, respectively (Table 19). The stratified HR for death was 0.69 (95%CI 0.56-0.86;), indicating a 31% reduction in risk of death and statistically significantly in favour of maintenance treatment with avelumab plus BSC. OS of patients at 1 year was also greater in the avelumab plus BSC group than the BSC group, with 71.3% (95%CI 66.0-76.0) of patients and 58.4% (95%CI 52.7-63.7) surviving at one year in each group, respectively.[3]

Results for OS in the PD-L1 Positive Population were similar to results observed in the Overall Population (Table 19). Median OS in the avelumab plus BSC group was not estimable (NE) (range, 20.3 to NE) compared to 17.1 months (range, 13.5 to 23.7) in the BSC group,[3] with 61 patients (32.3%) and 82 patients (48.5%) with an OS event in each treatment group, respectively.[4] The stratified HR for death was statistically significantly in favour of the avelumab plus BSC group resulting in a 44% reduction in risk of death compared to patients in the BSC group (HR=0.56, 95%CI 0.40 to 0.79;). At one year, OS of patients was 79.1% (95%CI 72.1 to 84.5) in the avelumab plus BSC group and 60.4% (95%CI 52.0 -67.7) in the BSC group.[3] KM plots for OS in both analysis populations are displayed in Figure 3.

Table 19: Summary of Overall Survival in Overall Population and PD-L1 Positive Population

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.

[1] Includes subjects deemed to be lost to follow-up by the Investigator and subjects with last follow-up > 16 weeks prior to data cutoff (21OCT2019).

[2] CIs are derived using the log-log transformation with back transformation to untransformed scale.

[3] CIs are calculated using Brookmeyer and Crowley method.

[4] Stratified by best response to first-line chemotherapy (CR or PR vs. SD), metastatic disease site (visceral vs. nonvisceral). IRT stratification values used.

[5] Cox proportional hazard model used.

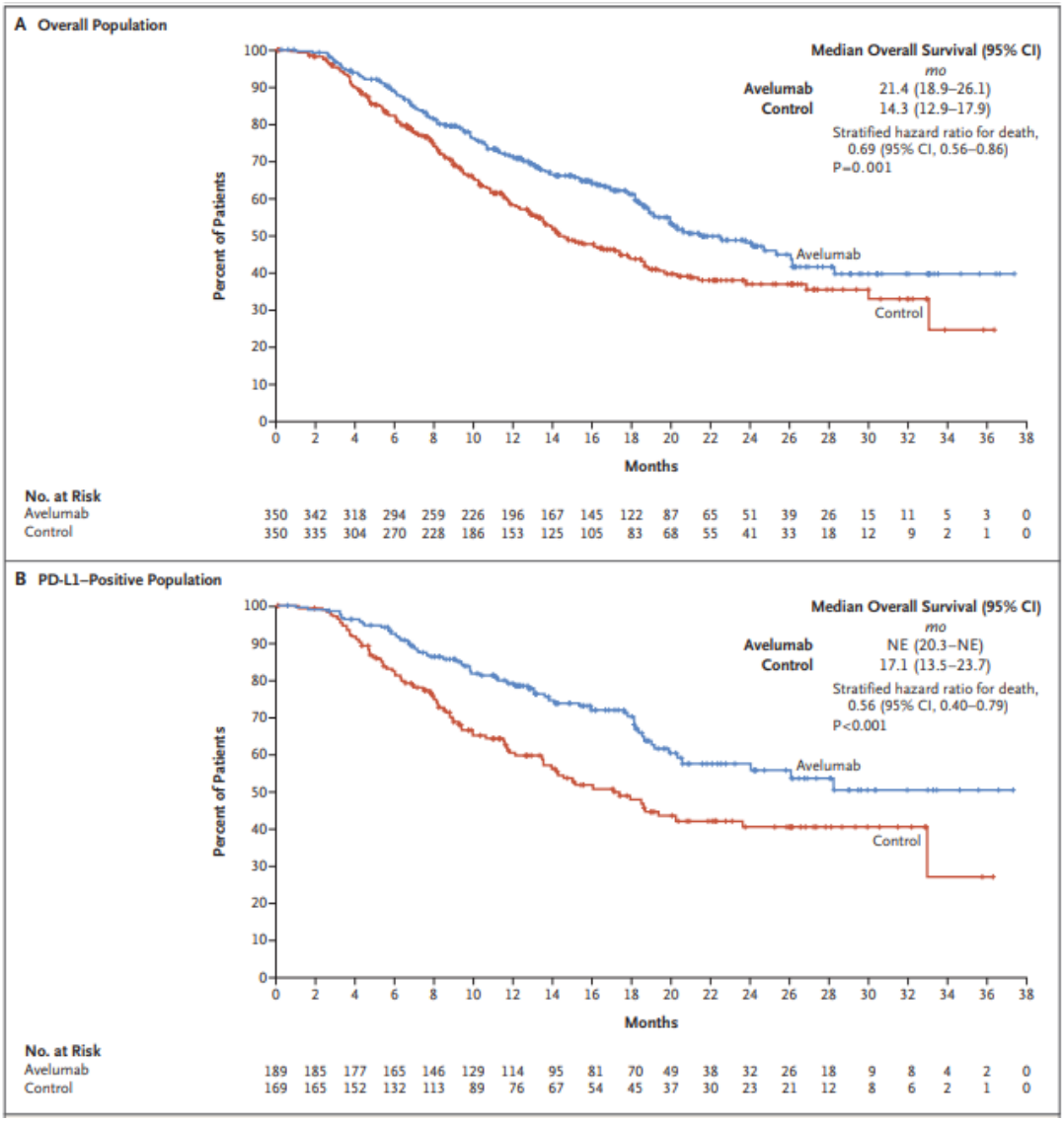
[6] Repeated confidence interval method used to take into account the group-sequential nature of the design.

[7] Log-rank test is used.

Source: Clinical Study Report[4]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Figure 3: Overall Survival in Overall Population and PD-L1 Positive Population



CI = confidence interval; NE = not estimable; PD-L1 = programmed cell death ligand 1

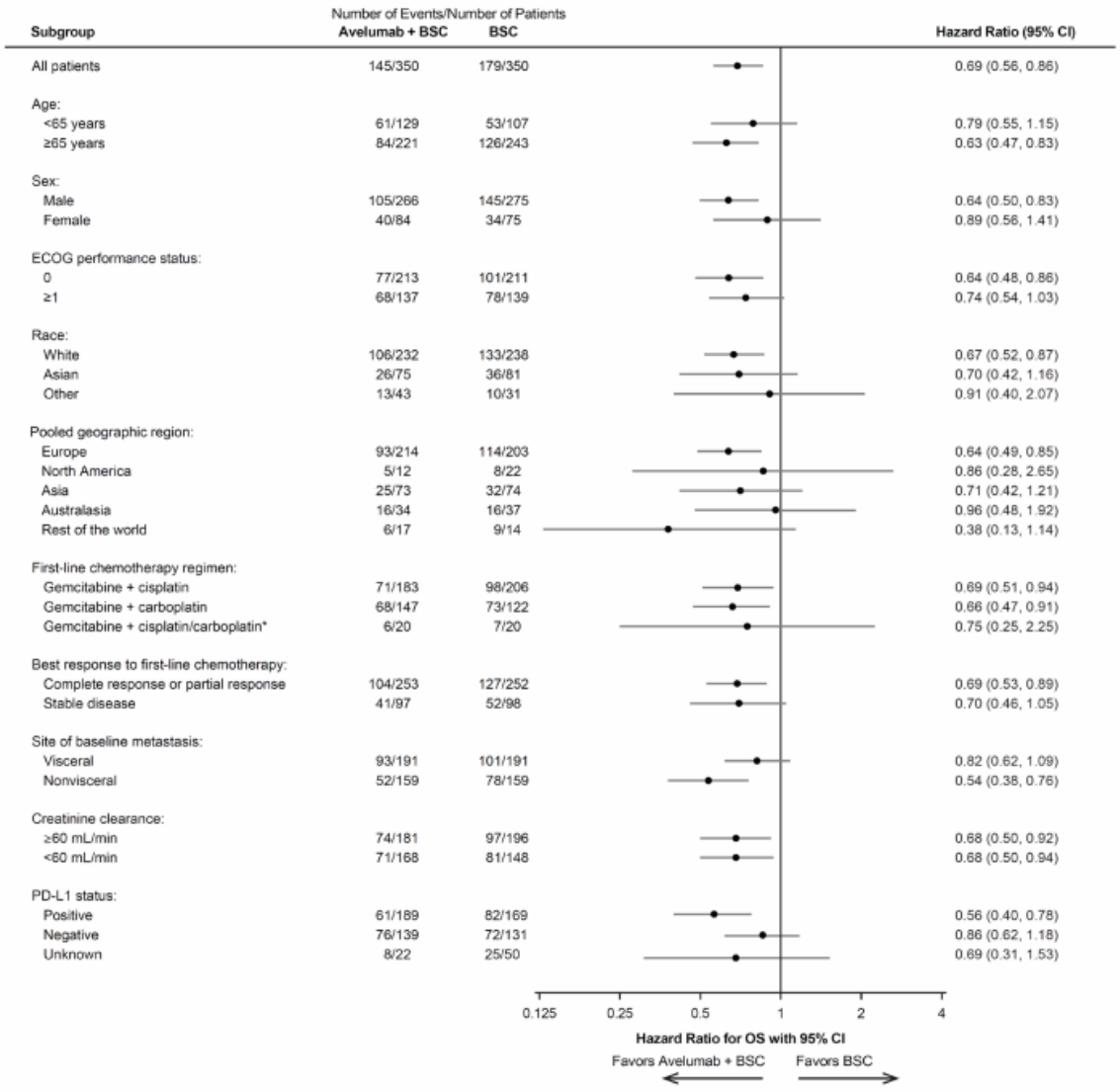
Tick marks indicate censored data

Source: From the New England Journal of Medicine, Powles T et al, avelumab maintenance therapy for advanced or metastatic urothelial carcinoma, 383, pages 1218-30. Copyright ©2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[3]

OS in pre-specified subgroups: The results of some of these analyses were consistent with the overall OS results; a statistically significant longer OS in the avelumab plus BSC versus BSC alone was found except in the following subgroups: age *'< 65 years'*, sex *'female'*, ECOG PS *'≥1'*, race *'Asian'* and *'Other'*, pooled geographic region *'North America'*, *'Asia'*, *'Australasia'*, and *'Rest of the World'*, first-line chemotherapy regimen *'gemcitabine plus cisplatin/carboplatin'*, best response to first-line therapy *'stable disease'*, and PD-L1 status *'negative'* and *'unknown'* (Figure 4). These subgroup analyses were not powered to

detect statistically significant differences between treatment groups and may have been limited by the small sample sizes of some subgroups.[3]

Figure 4: Subgroup Analysis of Overall Survival in Overall Population



All analyses shown are unstratified except for the analysis in all patients.

*Includes patients who switched platinum regimens while receiving first-line chemotherapy.

Source: From the New England Journal of Medicine, Powles T et al, avelumab maintenance therapy for advanced or metastatic urothelial carcinoma, 383, pages 1218-30. Copyright ©2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[3]

Sensitivity Analyses: Results of the sensitivity analysis of OS using the Per-Protocol Set, patients' actual stratification values, and unstratified sensitivity analyses supported the primary OS results (Table 20).[4] A third sensitivity analysis was conducted based on patients' actual stratification values, as 9.6% of patients were randomized under the incorrect stratification value. Based on a protocol amendment, this sensitivity analysis was removed; nonetheless, the results for this sensitivity analysis were calculated and supported the

primary analysis for OS favouring maintenance treatment with avelumab plus BSC over BSC alone.[4]

Table 20: Sensitivity Analyses for Overall Survival

	Overall Population	PD-L1 Positive Population
Per-Protocol Set		
HR (95% CI)	[redacted]	[redacted]
1-sided p-value	[redacted]	[redacted]
Unstratified analysis		
HR (95% CI)	[redacted]	[redacted]
1-sided p-value	[redacted]	[redacted]
Actual strata of patients (CRF-derived)		
HR (95% CI)	[redacted]	[redacted]
1-sided p-value	[redacted]	[redacted]

Source: Clinical Study Report[4]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Secondary Endpoints

Progression Free Survival: In the Overall Population, the median PFS was 3.7 months (95% CI: 3.5 to 5.5) in the avelumab plus BSC group compared to 2.0 months (95% CI: 1.9 to 2.7) in the BSC group (Table 21).[3] A total of 225 patients (64.3%) and 260 patients (74.3%) experienced a PFS event in the avelumab plus BSC group and the BSC group, respectively.[4] The stratified HR for disease progression or death was 0.62 (95% CI: 0.52 to 0.75), indicating a 38% reduction in the risk of progression or death and a statistically significant improvement favouring maintenance treatment with avelumab plus BSC over BSC alone (Figure 5).[3]

In the PD-L1 Positive Population, the median PFS was 5.7 months (95% CI: 3.7 to 7.4) in the avelumab plus BSC group compared to 2.1 months (95% CI: 1.9 to 3.5) in the BSC group (Table 21).[3] A total of 109 patients (57.7%) in the avelumab plus BSC group and 130 patients (76.9%) in the BSC group experienced a PFS event.[4] The stratified HR for disease progression or death was 0.56 (95% CI: 0.43 to 0.73), indicating a 44% reduction in the risk of progression or death and a statistically significant improvement in the avelumab plus BSC group over the BSC group (Figure 5).[3]

PFS was also assessed via investigator and supported similar results of PFS as assessed by BICR in both co-primary populations (results not displayed). In the Overall Population, the median PFS in the avelumab plus BSC group was [redacted] months (95% CI: [redacted]) and was [redacted] months (95% CI: [redacted]) in the BSC group. The stratified HR was [redacted] (95% CI: [redacted]), favouring treatment with avelumab plus BSC. In the PD-L1 Positive Population, the median PFS was [redacted] months (95% CI: [redacted]) and [redacted] months (95% CI: [redacted]) in the avelumab plus BSC group and the BSC group, respectively, with a stratified HR of [redacted] (95% CI [redacted]).[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Table 21: Summary of Progression Free Survival in Overall Population and PD-L1 Positive Population

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.

[1] CIs are derived using the log-log transformation with back transformation to untransformed scale.

[2] CIs are calculated using Brookmeyer and Crowley method.

[3] Stratified by best response to first-line chemotherapy (CR or PR vs. SD), metastatic disease site (visceral vs. non-visceral). IRT stratification values used.

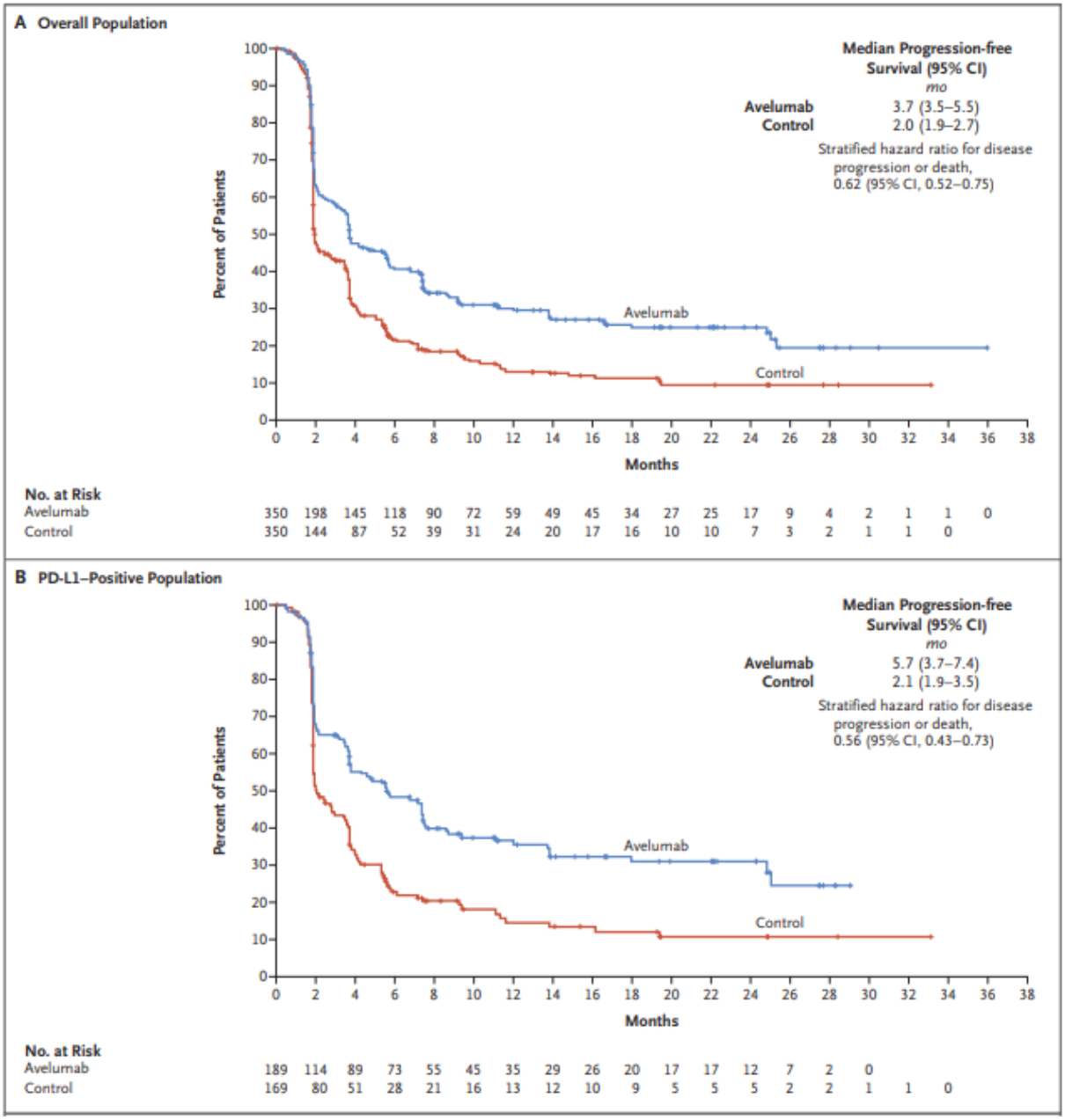
[4] Cox proportional hazard model used.

[5] Log-rank test is used.

Source: Clinical Study Report[4]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Figure 5: Progression Free Survival in the Overall Population and PD-L1 Positive Population



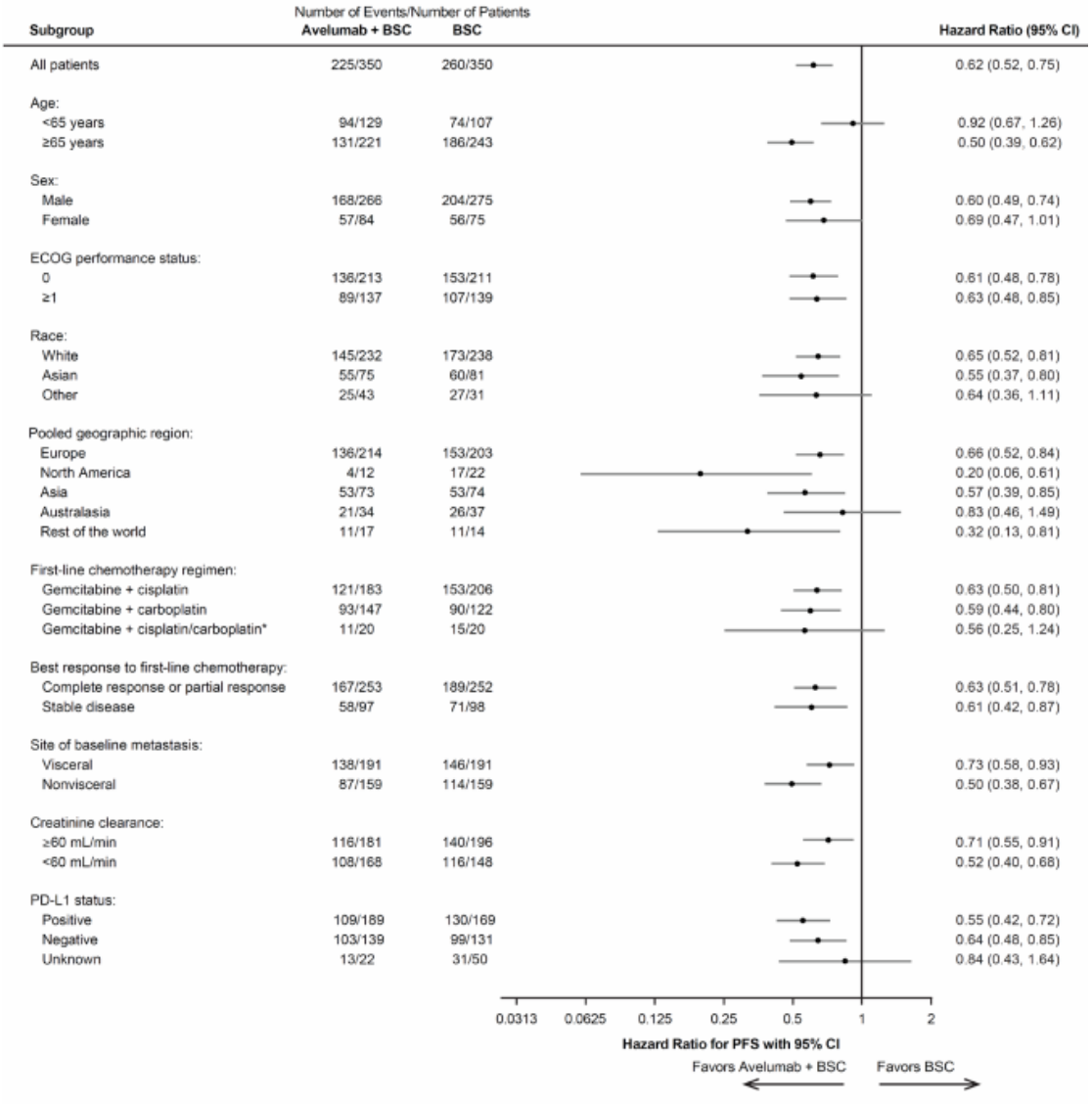
Progression was assessed by blinded independent central review according to the Response Evaluation Criteria in Solid Tumours, version 1.1

Tick marks indicate censored data

Source: From the New England Journal of Medicine, Powles T et al, avelumab maintenance therapy for advanced or metastatic urothelial carcinoma, 383, pages 1218-30. Copyright ©2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[3]

PFS in pre-specified subgroups: The results of some of these analyses were consistent with the overall PFS results; a statistically significant longer OS in the avelumab plus BSC versus BSC alone was found except in the following subgroups: age *'< 65 years'*, sex *'female'*, race *'Other'*, pooled geographic region *'Australasia'*, first-line chemotherapy regimen *'gemcitabine plus cisplatin/carboplatin'*, and PD-L1 status *' 'unknown'* (Figure 6). These subgroup analyses were not powered to detect statistically significant differences between treatment groups and may have been limited by the small sample sizes of some subgroups.[3]

Figure 6: Subgroup Analysis of Progression Free Survival in the Overall Population



All analyses shown are unstratified except for the analysis in all patients.

*Includes patients who switched platinum regimens while receiving first-line chemotherapy.

Source: From the New England Journal of Medicine, Powles T et al, avelumab maintenance therapy for advanced or metastatic urothelial carcinoma, 383, pages 1218-30. Copyright ©2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[3]

Objective Response Rate: In the Overall Population, a greater proportion of patients in the avelumab plus BSC group had a confirmed objective response compared to the BSC group, with 9.7% of patients (95% CI: 6.8 to 13.3) and 1.4% of patients (95% CI: 0.5 to 3.3) in the avelumab plus BSC group and the BSC groups respectively (stratified OR : 7.46; 95% CI: 2.82 to 24.45), per BICR assessment (Table 22). More patients in the avelumab plus BSC group showed either a complete or partial response compared to the BSC group (9.7% versus 1.5%, respectively). Patients with either stable disease or who had a non-complete response or non-progressive disease were similar across both treatment groups. Fewer patients had a reported disease progression in the avelumab plus BSC group (37.1%) compared to the BSC group (48.3%). Results for overall response in the PD-L1 Positive Population were similar to those of the Overall Population.[3]

Table 22: Overall Response in the Overall Population and PD-L1 Positive Population per BICR Assessment

Table 2. Responses in the Overall Population and the PD-L1–Positive Population.*

Variable	Overall Population			PD-L1–Positive Population		
	Avelumab Group (N=350)	Control Group (N=350)	Stratified Odds Ratio (95% CI)	Avelumab Group (N=189)	Control Group (N=169)	Stratified Odds Ratio (95% CI)
Confirmed objective response (95% CI) — %	9.7 (6.8–13.3)	1.4 (0.5–3.3)	7.46 (2.82–24.45)	13.8 (9.2–19.5)	1.2 (0.1–4.2)	12.70 (3.16–114.12)
Confirmed best overall response — no. (%)						
Complete response	21 (6.0)	3 (0.9)		18 (9.5)	1 (0.6)	
Partial response	13 (3.7)	2 (0.6)		8 (4.2)	1 (0.6)	
Stable disease	44 (12.6)	46 (13.1)		19 (10.1)	23 (13.6)	
Non–complete response or non–progressive disease†	66 (18.9)	45 (12.9)		38 (20.1)	22 (13.0)	
Progressive disease	130 (37.1)	169 (48.3)		59 (31.2)	82 (48.5)	
Could not be evaluated	76 (21.7)‡	85 (24.3)§		47 (24.9)¶	40 (23.7)‖	
Disease control — no. (%)**	144 (41.1)	96 (27.4)		83 (43.9)	47 (27.8)	
Median time to objective response (range) — mo	2.0 (1.7–16.4)	2.0 (1.8–7.0)		2.0 (1.7–16.4)	2.8 (1.8–3.8)	

* An objective response was defined as a complete or partial response. Objective responses were assessed by blinded independent central review according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and indicated the change in tumors as compared with baseline at randomization (i.e., the change during chemotherapy was not considered). In patients with a complete response after chemotherapy, the best overall response was noted as "could not be evaluated" if no evidence of disease at baseline was detected after randomization or as "progressive disease" if disease progression occurred after randomization; these patients could not have had a best overall response of complete response, partial response, stable disease, or non–complete response or non–progressive disease after randomization. Percentages may not total 100 because of rounding.

† This category of response is defined by RECIST, version 1.1, and refers to persistence of one or more nontarget lesions in patients with nontarget lesions only.

‡ Reasons that the response could not be evaluated were the following: no evidence of disease at baseline (in 52 patients), no postbaseline assessments owing to other reasons (in 18), stable disease occurring less than 6 weeks after randomization (in 2), progressive disease occurring more than 12 weeks after randomization (in 2), no postbaseline assessments owing to early death (in 1), and new anticancer therapy started before the first postbaseline assessment (in 1).

§ Reasons that the response could not be evaluated were the following: no evidence of disease at baseline (in 50 patients), no postbaseline assessments owing to other reasons (in 17), stable disease occurring less than 6 weeks after randomization (in 8), no postbaseline assessments owing to early death (in 4), new anticancer therapy

started before the first postbaseline assessment (in 3), progressive disease occurring more than 12 weeks after randomization (in 2), and all postbaseline assessment had an overall response of "could not be evaluated" (in 1).

¶ Reasons that the response could not be evaluated were the following: no evidence of disease at baseline (in 31 patients), no postbaseline assessments owing to other reasons (in 12), stable disease occurring less than 6 weeks after randomization (in 1), no postbaseline assessments owing to early death (in 1), new anticancer therapy started before the first postbaseline assessment (in 1), and progressive disease occurring more than 12 weeks after randomization (in 1).

‖ Reasons that the response could not be evaluated were the following: no evidence of disease at baseline (in 28 patients), no postbaseline assessments owing to other reasons (in 5), stable disease occurring less than 6 weeks after randomization (in 3), progressive disease occurring more than 12 weeks after randomization (in 2), no postbaseline assessments owing to early death (in 1), and new anticancer therapy started before the first postbaseline assessment (in 1).

** Disease control was defined as a best overall response of complete response, partial response, stable disease, or non–complete response or non–progressive disease.

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Disease Control Rate: In the Overall Population, the proportion of patients with a best overall response was greater in the avelumab plus BSC group than the BSC group (41.1% versus 27.4%, respectively) (Table 18**)**. Similarly in the PD-L1 Positive Population, 43.9% of patients in the avelumab plus BSC group had a best overall response compared to 27.8% of patients in the BSC group.[3]

Time to Response: In the Overall Population, the median TTR was the same in both treatment groups at two months (avelumab plus BSC group: range, 1.7 to 16.4 months; BSC group: range, 1.8 to 7.0 months) (Table 18). In the PD-L1 Positive Population, the median TTR was 2.0 months (range, 1.7-16.4) in the avelumab plus BSC group and 2.8 months (range, 1.8-3.8) in the BSC group.[3]

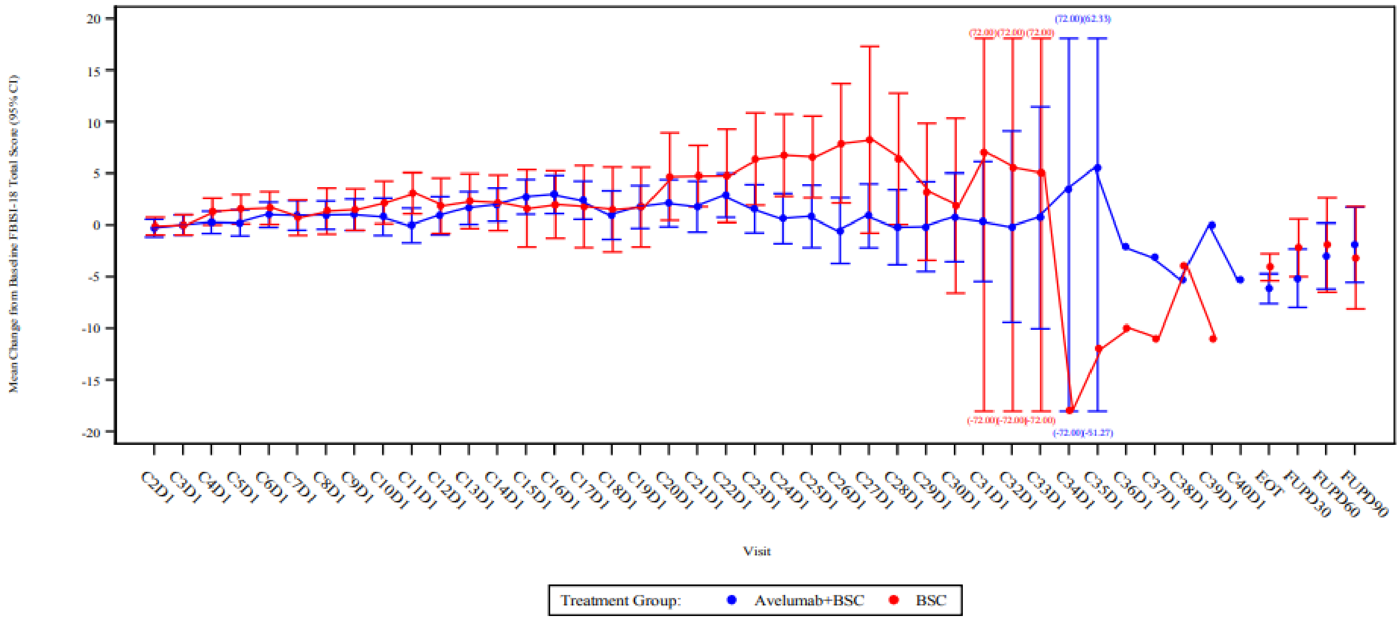
Quality of Life

PROs were assessed via the NCCN-FACT FBISI and the EQ-5D-5L. For the Overall Population, completion rates for both the FBISI and EQ-5D-5L for both treatment groups of the trial were reported to be >90% for the majority of the treatment period.[5] For the FBISI-18 questionnaire, the proportion of patients completing the entire questionnaire (answering all questions) was <[redacted]% during all cycles. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* After cycle 18, the number of patients eligible for completion was less than 50 patients. Also, it should be noted that after cycle 19 there were less than 50 patients eligible for completion of the EQ-5D-5L questionnaires; although, completion of the entire questionnaire was conducted by most patients during each cycle (<90%), except for cycle 32 where [redacted] of [redacted] patients ([redacted]%) completed the entire questionnaire.[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* For the PD-L1 Positive Population, completion rates for both questionnaires were also similar to those of the Overall Population for both treatment groups.[4]

NCCN-FACT FBISI-18: In the Overall Population, the mean FBISI-18 total score at baseline in the avelumab plus BSC group was [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]) in the BSC group. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* During on treatment assessments with sufficient data from at least 10

patients (through cycle 31 for the avelumab plus BSC group and cycle 25 for the BSC group) FIBISI-18 total scores showed improvement (i.e., better HRQoL) in both treatment groups.[4] In the Overall Population, changes in the FIBISI-18 total (Figure 7) and subscale scores (Figure 8) from baseline were similar between the avelumab plus BSC group and the BSC group. Results of the PD-L1 Positive Population were similar to those of the Overall Population.[5] Mixed model analysis for the FBlSI-18 during on treatment assessments revealed similar results between both treatment groups.[5]

Figure 7: Summary of FBISI-18 Total Score Change from Baseline (Overall Population)



Number of Subjects at Risk

Avelumab+BSC	310	269	240	202	178	160	144	132	123	120	103	96	87	80	67	63	57	47	42	43	38	35	33	25	22	20	18	17	11	10	6	4	2	2	1	1	1	1	1	192	68	56	37
BSC	297	223	155	120	109	85	68	55	49	47	43	36	32	28	26	23	21	18	16	16	15	14	10	11	6	5	7	6	5	2	2	2	1	1	1	1	1	1	0	238	57	30	30

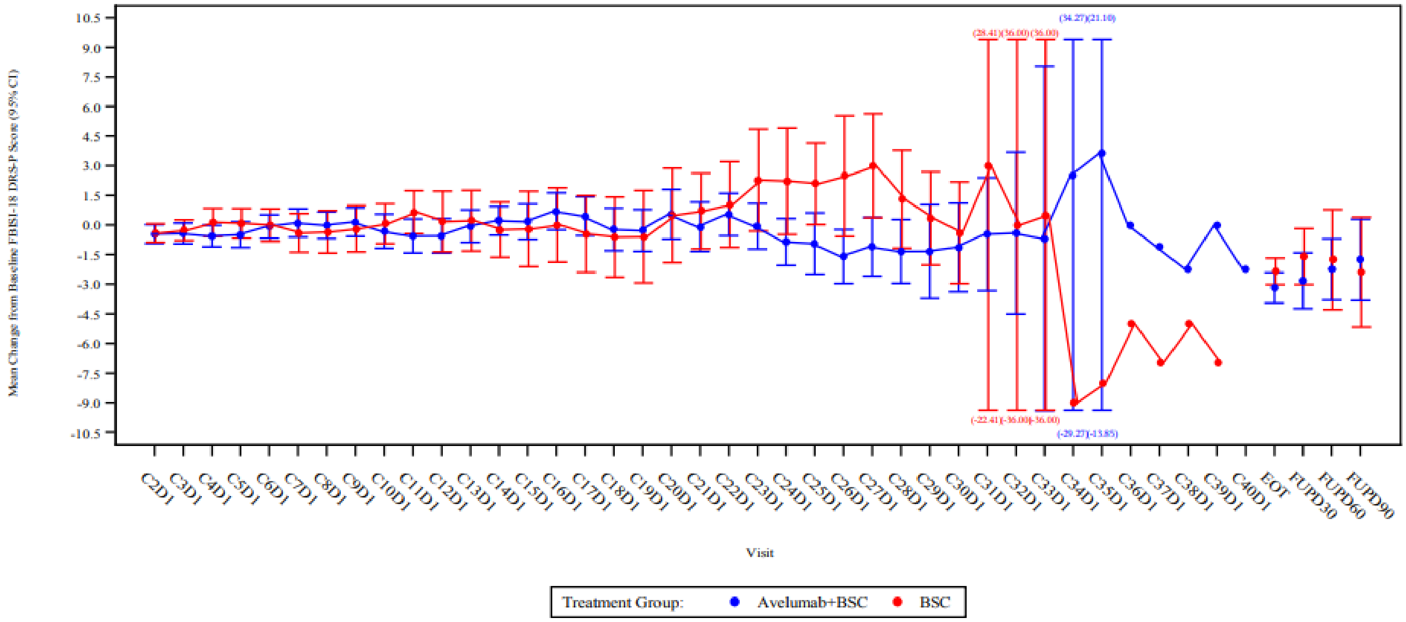
Baseline is the last non-missing measurement prior to randomization or, if not available, prior to the first dose of study treatment. Higher FBISI-18 Total scores mean better health state.

Unscheduled visits are excluded from the analysis. Cycle 1 Day 1 post-dose assessments are not baseline assessments, therefore, are excluded from the analysis.

PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADCA Output File: ./B9991001/B9991001_CSR/adca_ttsch_f001 Date of Generation: 14JAN2020 (06:02) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019

Source: Clinical Study Report[4]

Figure 8: Summary of FBISI-18 Disease Related Symptoms-Physical Score Change from baseline (Overall Population)



Number of Subjects at Risk

Avelumab+BSC	310	269	239	202	178	160	144	132	123	120	103	96	87	80	67	63	57	47	42	43	38	35	33	25	22	20	18	17	11	10	6	4	2	2	1	1	1	1	1	192	68	56	37
BSC	297	224	155	121	109	85	68	55	49	47	43	36	32	28	26	23	21	18	16	16	15	14	10	11	6	5	7	6	5	2	2	2	1	1	1	1	1	1	0	238	57	30	30

Baseline is the last non-missing measurement prior to randomization or, if not available, prior to the first dose of study treatment. Higher FBISI-18 DRS-P scores mean less disease related physical symptoms.

Unscheduled visits are excluded from the analysis. Cycle 1 Day 1 post-dose assessments are not baseline assessments, therefore, are excluded from the analysis.

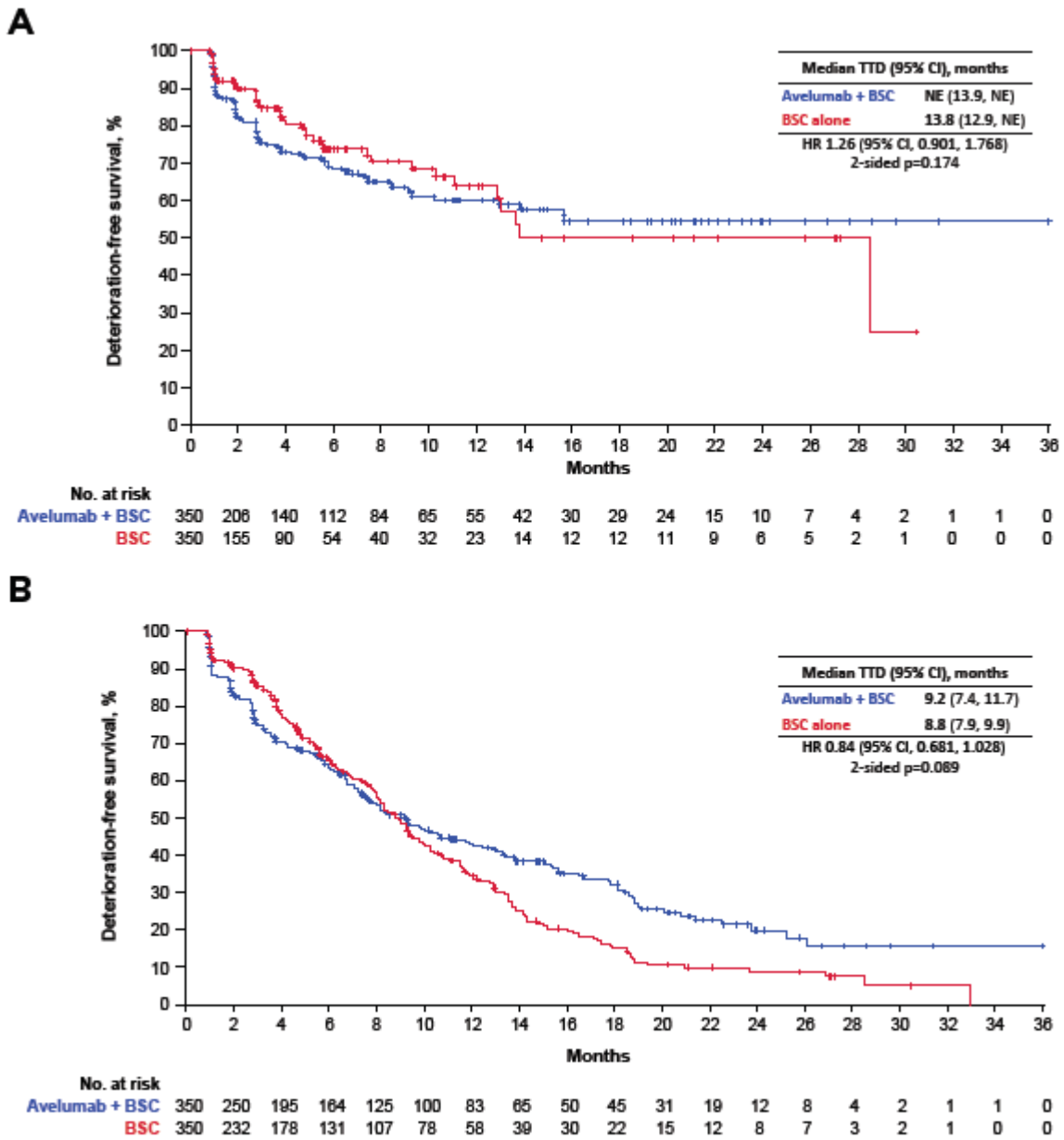
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADCA Output File: ./B9991001/B9991001_CSR/adca_drspch_f001 Date of Generation: 14JAN2020 (05:08) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019

Source: Clinical Study Report[4]

The FBISI DRS-P was used to measure TTD in both co-primary populations, which corresponded to an MID of a decrease of three points or greater from baseline in scores for two consecutive assessments.[4] The median TTD was not reached (95% CI: 13.9 months to not reached) in the avelumab plus BSC group, and was 13.8 months (95% CI: 12.9 months to not reached) in the BSC group, corresponding to an HR of 1.26 (95% CI: 0.90 to 1.77) (Figure 9).[5] Similar results were observed for the PD-L1 Positive Population; in the avelumab plus BSC group, median TTD was [redacted] (95% CI: [redacted]) versus a median TTD of [redacted] months in the BSC group (95% CI: [redacted]). The HR for TTD in the PD-L1 Positive Population was [redacted] (95% CI: [redacted]).[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* A post-hoc analysis was conducted for TTD based on death or decline in DRS-P. The median TTD was 9.2 months in the avelumab plus BSC group versus 8.8 months in the BSC group (HR=0.84; 95% CI: 0.68 to 1.03); results were similar for the PD-L1 Positive Population. Sensitivity analyses of TTD in FBISI-18 DRS scores using MID thresholds of two points or

greater and four points or greater showed similar results to the primary analysis in both co-primary populations.

Figure 9: Kaplan-Meier Plot of Time to Deterioration (≥3 points decrease prior to end of treatment) in FBISI-18 DRS-P Scores (A) and DRS-P Scores or death (B) for Overall Population



NE, not estimable
Crossing of curves, inconsistency between HRs, and differences in median TTD suggest that HRs may be nonproportional; therefore results should be interpreted with caution

Source: Powles et al., 2020[23]

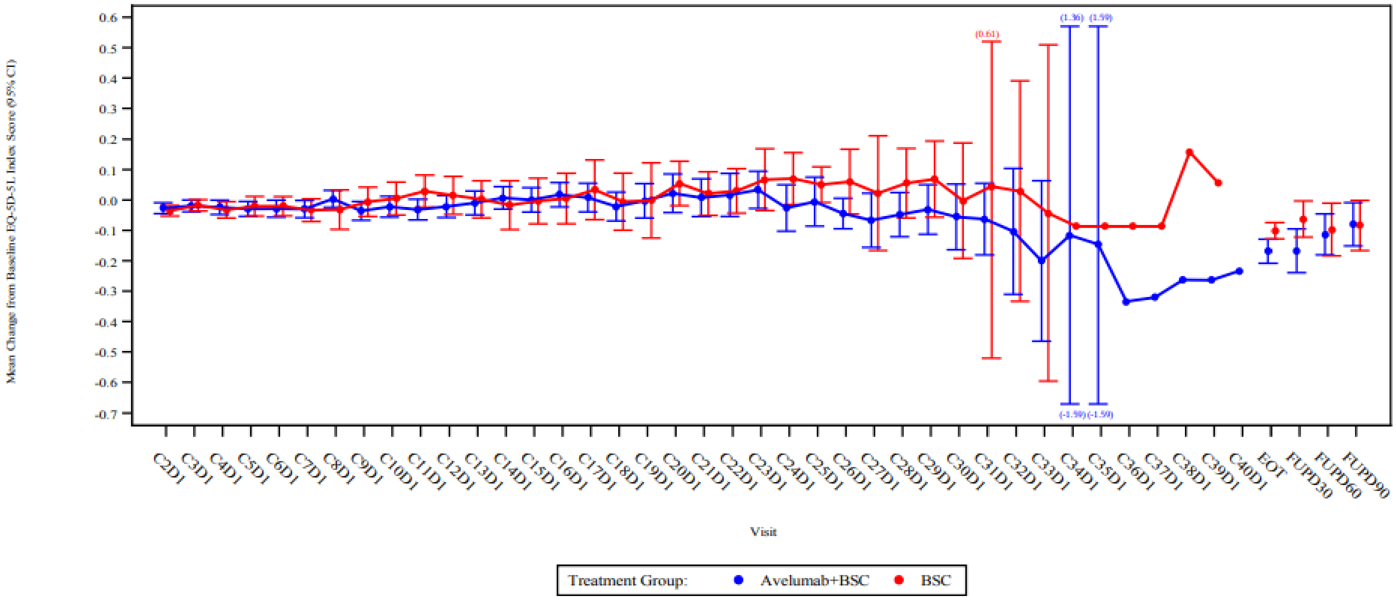
EuroQol 5 Dimensions (EQ-5D-5L and VAS): In the Overall Population, the mean EQ-5D-5L score at baseline in the avelumab plus BSC group was [redacted] (95% CI: [redacted]) and was [redacted] (95% CI: [redacted]) in the BSC group. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* During on treatment assessments with sufficient data from at least 10 patients (through cycle 31 for the avelumab plus BSC group and cycle 25 for the BSC group) EQ-5D-5L scores showed improvement (i.e., better health state) in both treatment groups.[4]

In the Overall Population, the mean VAS scores at baseline were similar in the avelumab plus BSC and BSC groups at [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]), respectively. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* During on treatment assessments with sufficient data from at least 10 patients (through cycle 31 for the avelumab plus BSC group and cycle 25 for the BSC group), VAS scores increased (i.e., better health state) for both treatment groups.[4] Changes from baseline were similar between both the avelumab and BSC groups in the EQ-5D-5L index (

Figure 10) and VAS scores (Figure 11). Similar results were observed for the PD-L1 Positive Population.[5]

In the Overall Population and the PD-L1 Positive Population, EQ-5D-5L and VAS results were similar between both treatment groups similar using a mixed model analysis.[4]

Figure 10: Summary of EQ-5D-5L Index Score Change from Baseline by Visit (Overall Population)



Number of Subjects at Risk

	C2D1	C3D1	C4D1	C5D1	C6D1	C7D1	C8D1	C9D1	C10D1	C11D1	C12D1	C13D1	C14D1	C15D1
Avelumab+BSC	310	273	244	208	181	164	144	134	124	120	103	97	88	81
BSC	298	221	154	123	111	84	67	55	49	47	43	34	32	28

	C16D1	C17D1	C18D1	C19D1	C20D1	C21D1	C22D1	C23D1	C24D1	C25D1	C26D1	C27D1	C28D1	C29D1
Avelumab+BSC	70	65	58	49	44	44	40	37	35	27	24	21	19	18
BSC	26	23	21	18	16	16	15	14	10	11	6	5	7	6

	C30D1	C31D1	C32D1	C33D1	C34D1	C35D1	C36D1	C37D1	C38D1	C39D1	C40D1	EOT	FUPD30	FUPD60	FUPD90
Avelumab+BSC	12	11	6	4	2	2	1	1	1	1	1	193	69	58	38
BSC	5	2	2	2	1	1	1	1	1	1	0	238	56	30	30

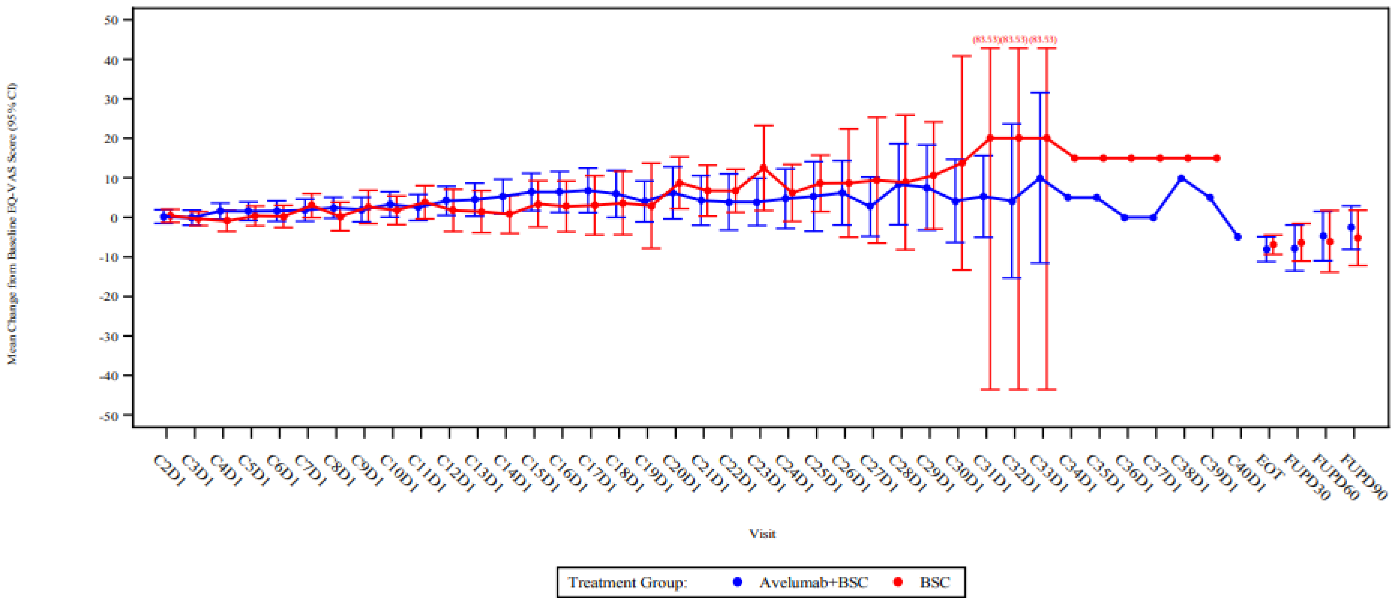
Baseline is the last non-missing measurement prior to randomization or, if not available, prior to the first dose of study treatment. Higher index scores mean better health state.

Unscheduled visits are excluded from the analysis. Cycle 1 Day 1 post-dose assessments are not baseline assessments, therefore, are excluded from the analysis.

PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADE5 Output File: ./B9991001/B9991001_CSR/ade5_f006a Date of Generation: 14JAN2020 (08:22) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019

Source: Clinical Study Report[4]

Figure 11: Summary of EQ-5D-5L-Visual Analogue Scale Change from Baseline by Visit (Overall Population)



Number of Subjects at Risk

Avelumab+BSC	304	270	244	207	183	161	147	133	125	120	103	96	87	80	70	64	57	48	43	43	40	36	34	27	24	21	19	18	12	11	6	4	2	2	1	1	1	1	1	193	67	58	38
BSC	292	220	151	120	109	84	66	53	48	46	42	35	32	27	25	23	20	17	16	16	14	13	10	10	6	5	6	5	4	2	2	2	1	1	1	1	1	1	0	234	55	30	30

Baseline is the last non-missing measurement prior to randomization or, if not available, prior to the first dose of study treatment. Higher EQ-VAS scores mean better health state.

Unscheduled visits are excluded from the analysis. Cycle 1 Day 1 post-dose assessments are not baseline assessments, therefore, are excluded from the analysis.

PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADE5 Output File: ./B9991001/B9991001_CSR/ade5_f005a Date of Generation: 14JAN2020 (08:18) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019

Source: Clinical Study Report[4]

Harms Outcomes

An overall summary of the incidence of AEs in the Javelin Bladder 100 trial is provided in Table 23. In general, AEs of all types occurred more frequently among patients in the avelumab plus BSC group compared to patients in the BSC group.

AEs resulting in treatment interruption of avelumab were reported in 140 (40.7%) of patients in the avelumab plus BSC group, with the most commonly occurring reason being due to urinary tract infection (3.5%). A dose reduction of avelumab due to an AE occurred in one patient (0.3%) and this was a result of asthenia. AEs resulting in both treatment interruption and a dose reduction of avelumab did not occur.[4]

AEs leading to discontinuation of treatment were reported in 11.9% of patients in the avelumab plus group, and in no patients in the BSC group. Infusion related reactions occurring in 4 patients (1.2%) were the most common cause of treatment discontinuation, followed by lipase increased and troponin-T increased (n=3 patients, 0.9% each).[4]

Table 23: Summary of Adverse Events in the JAVELIN Bladder 100 Trial

Number (%) of Subjects	Avelumab plus BSC N=344 n (%)	BSC N=345 n (%)
Subjects with treatment-related AEs	266 (77.3)	4 (1.2)
Subjects with grade ≥ 3 treatment-related AEs	57 (16.6)	0
Subjects with serious AEs	96 (27.9)	69 (20.0)
Subjects with serious treatment-related AEs	31 (9.0)	0
Subjects with AEs leading to dose reduction of Avelumab	1 (0.3)	0
Subjects with AEs leading to interruption of Avelumab	140 (40.7)	0
Subjects with AEs leading to discontinuation of study drug	41 (11.9)	0
Subjects with treatment-related AEs leading to discontinuation of study drug	33 (9.6)	0
Subjects with AEs leading to death	4 (1.2)	24 (7.0)
Subjects with treatment-related AEs leading to death	1 (0.3)	0
Subjects with immune-related adverse events (irAEs)	101 (29.4)	5 (1.4)
Subjects with infusion-related reactions (IRRs)	74 (21.5)	0

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.

MedDRA v22.1 coding dictionary and CTCAE version 4.03 applied.

Source: Clinical Study Report[4]

AEs of any grade occurred more frequently in the avelumab plus BSC group versus the BSC group (98.0% versus 77.7%, respectively), although none occurred more frequently than in 17.7% of patients (Table 24). The most commonly occurring AEs of any grade in the avelumab plus BSC group compared to the BSC group were fatigue (17.7% versus 1.7%), pruritus (17.2% versus 0.3%), urinary tract infection (17.2% versus 4.4%), diarrhea (16.6% versus 0.6%), arthralgia (16.3% versus 0.6%), asthenia (16.3% versus 0%), constipation (16.3% versus 0.6%), and back pain (16.0 versus 1.2%%).[3]

Grade 3 or higher AEs occurred more frequently in the avelumab plus BSC group compared to the BSC group (47.4% versus 25.2%, respectively) (Table 24). The most commonly occurring grade 3 or higher AEs in the avelumab plus BSC group compared to the BSC group were urinary tract infection (4.4% versus 2.6%) and anemia (3.8% versus 2.9%).[3]

Table 24: Adverse Events in the JAVELIN Bladder 100 Trial

Event	Avelumab Group (N=344)		Control Group (N=345)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	337 (98.0)	163 (47.4)	268 (77.7)	87 (25.2)
Fatigue	61 (17.7)	6 (1.7)	24 (7.0)	2 (0.6)
Pruritus	59 (17.2)	1 (0.3)	6 (1.7)	0
Urinary tract infection	59 (17.2)	15 (4.4)	36 (10.4)	9 (2.6)
Diarrhea	57 (16.6)	2 (0.6)	17 (4.9)	1 (0.3)
Arthralgia	56 (16.3)	2 (0.6)	19 (5.5)	0
Asthenia	56 (16.3)	0	19 (5.5)	4 (1.2)
Constipation	56 (16.3)	2 (0.6)	31 (9.0)	0
Back pain	55 (16.0)	4 (1.2)	34 (9.9)	8 (2.3)
Nausea	54 (15.7)	1 (0.3)	22 (6.4)	2 (0.6)
Pyrexia	51 (14.8)	1 (0.3)	12 (3.5)	0
Decreased appetite	47 (13.7)	1 (0.3)	23 (6.7)	2 (0.6)
Cough	44 (12.8)	1 (0.3)	16 (4.6)	0
Vomiting	43 (12.5)	4 (1.2)	12 (3.5)	2 (0.6)
Hypothyroidism	40 (11.6)	1 (0.3)	2 (0.6)	0
Rash	40 (11.6)	1 (0.3)	4 (1.2)	0
Anemia	39 (11.3)	13 (3.8)	23 (6.7)	10 (2.9)
Hematuria	36 (10.5)	6 (1.7)	37 (10.7)	5 (1.4)
Infusion-related reaction	35 (10.2)	3 (0.9)	0	0

* The safety population included all the patients in the avelumab group who received at least one dose of avelumab and all the patients in the control group who completed the cycle 1, day 1, visit. Shown are the adverse events of any grade and from any cause that occurred in at least 10% of these patients and the adverse events of grade 3 or higher and from any cause that occurred in at least 5% of these patients.

Source: From the New England Journal of Medicine, Powles T et al, avelumab maintenance therapy for advanced or metastatic urothelial carcinoma, 383, pages 1218-30. Copyright ©2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[3]

Serious Adverse Events: SAEs occurred in 96 patients (27.9%) in the avelumab plus BSC group and 69 patients (20.0%) in the BSC group (Table 25). The most common SAE was urinary tract infection, occurring in 16 patients (4.7%) in the avelumab plus BSC group and seven patients (2.0%) in the BSC group.[3]

Table 25: Summary of the Most Common Serious Adverse Evens (Safety Population)

	Avelumab Plus BSC (N=344)	BSC Alone (N=345)
	no. (%)	
Patients with any event	96 (27.9)	69 (20.0)
Urinary tract infection	16 (4.7)	7 (2.0)
Acute kidney injury	6 (1.7)	6 (1.7)
Hematuria	5 (1.5)	2 (0.6)
Infusion-related reaction	4 (1.2)	0
Pain	4 (1.2)	1 (0.3)
Sepsis	4 (1.2)	1 (0.3)
Atrial fibrillation	3 (0.9)	1 (0.3)
Back pain	3 (0.9)	1 (0.3)
Disease progression	3 (0.9)	16 (4.6)
Hydronephrosis	3 (0.9)	1 (0.3)
Ileus	3 (0.9)	1 (0.3)
Pyelonephritis	3 (0.9)	3 (0.9)
Vomiting	3 (0.9)	0
Blood CPK increased	2 (0.6)	0
Colitis	2 (0.6)	0
Constipation	2 (0.6)	0
Dyspnea	2 (0.6)	1 (0.3)
Kidney infection	2 (0.6)	0
Myocardial infarction	2 (0.6)	0
Pyrexia	2 (0.6)	1 (0.3)
Vascular device infection	2 (0.6)	0
Abdominal pain	1 (0.3)	3 (0.9)
Anemia	1 (0.3)	2 (0.6)
Basal cell carcinoma	1 (0.3)	2 (0.6)
Urosepsis	1 (0.3)	2 (0.6)
Syncope	0	2 (0.6)
Tumor pain	0	2 (0.6)
Urinary tract obstruction	0	2 (0.6)

BSC, best supportive care; CPK, creatine phosphokinase.

Source: From the New England Journal of Medicine, Powles T et al, avelumab maintenance therapy for advanced or metastatic urothelial carcinoma, 383, pages 1218-30. Copyright ©2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[3]

Treatment-Related Adverse Events: A summary of treatment-related AEs is reported in Table 26. Treatment-related AEs of any grade occurred in a total of 266 patients (77.3%) in the avelumab plus BSC group and in four patients (1.2%) in the BSC group. The most common treatment-related AEs in the avelumab plus BSC group were pruritus (13.7%), hypothyroidism (10.5%), diarrhea (10.2%) and infusion-related reactions (10.2%). None of these treatment-related AEs occurred in the BSC group. Treatment-related AEs of grade 3 or higher were reported in 57 patients (16.6%) the avelumab plus BSC group. Of these patients, three patients (0.9%) experienced a grade 4 treatment related AE. No patients in the BSC group experienced a grade 3 or higher treatment related AE.[3]

Table 26: Treatment Related Adverse Events in the JAVELIN Bladder 100 Trial

Preferred Term	Avelumab + BSC (N=344)		BSC (N=345)	
	All Grades (n %)	Grade ≥ 3 (n %)	All Grades (n %)	Grade ≥ 3 (n %)
Subjects with events	266 (77.3)	57 (16.6)	4 (1.2)	0
Pruritus	47 (13.7)	1 (0.3)	0	0
Hypothyroidism	36 (10.5)	1 (0.3)	0	0
Diarrhoea	35 (10.2)	0	0	0
Infusion related reaction	35 (10.2)	3 (0.9)	0	0
Asthenia	34 (9.9)	0	0	0
Fatigue	33 (9.6)	1 (0.3)	0	0
Rash	25 (7.3)	1 (0.3)	0	0
Chills	24 (7.0)	0	0	0
Nausea	24 (7.0)	1 (0.3)	0	0
Arthralgia	23 (6.7)	1 (0.3)	0	0
Pyrexia	23 (6.7)	0	0	0
Hyperthyroidism	21 (6.1)	0	0	0
Dry skin	18 (5.2)	0	0	0
Amylase increased	15 (4.4)	7 (2.0)	0	0
Lipase increased	13 (3.8)	10 (2.9)	0	0

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
Subjects reporting more than one adverse event (AE) within a preferred term are counted only once in that preferred term.
For subjects reporting more than one AE within a preferred term, the AE with maximum grade is included in the table.
Sorted in descending order of the frequency of PTs by all grades in Avelumab + BSC arm.
MedDRA (v22.1) coding dictionary and CTCAE version 4.03 applied.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADAE Output File: ./B9991001/B9991001 CSR/adae s999a trtrel Date of Generation: 14JAN2020 (04:48) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019
Table 14.3.1.3.15 is for Pfizer internal use.

Source: Clinical Study Report[4]

Immune-Related Adverse Events: Immune-related AEs occurring in the avelumab plus BSC group are reported in

Table 27. An immune-related AE of any grade was reported in 101 patients (29.4%) in the avelumab plus BSC group and in five patients (1.4%) in the BSC group.[3,4] Grade 3 immune-related AEs occurred in 24 patients (7.0%) in the avelumab plus BSC group and one patient (0.3%) in the BSC group.[3,4] There were no occurrences of grade 4 or 5 immune-related AEs.

In the avelumab plus BCS group, most immune-related AEs were thyroid disorders (n = 42; 12.2%); the most common immune-related AEs of any grade to occur were hypothyroidism (10.2%) and rash (4.9%).[3] Grade 3 or higher immune-related AEs occurred in 24 patients (7.0%) in the avelumab plus BSC group, and one patient (0.3%) in the BSC group.[3,4] A total of 31 patients (9.0%) received high-dose glucocorticoids (≥40 mg total daily dose of prednisone or equivalent) after having an immune-related AE.[3]

Serious immune-related AEs occurred in [redacted] patients ([redacted]%) in the avelumab plus group, most commonly due to colitis which occurred in [redacted] patients ([redacted]%). [redacted] ([redacted]%) in the BSC group experienced a serious immune-related AE which was due to diabetes mellitus.[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Discontinuation of treatment due to immune-related AEs occurred in [redacted] patients ([redacted]%) in the avelumab plus BSC group. The most common cause of treatment discontinuation due to an immune-related AE was an alanine aminotransferase increase, occurring in [redacted]% of patients.[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Table 27: Immune-Related Adverse Events in Patients Treated with Avelumab plus BSC (Safety Analysis Population)

Cluster and Preferred Term	Avelumab+BSC (N=344)		BSC (N=345)	
	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
Subjects with events	101 (29.4)	24 (7.0)	5 (1.4)	1 (0.3)
IMMUNE-RELATED ENDOCRINOPATHIES: THYROID DISORDERS	42 (12.2)	1 (0.3)	2 (0.6)	0
Hypothyroidism	35 (10.2)	1 (0.3)	1 (0.3)	0
Hyperthyroidism	16 (4.7)	0	1 (0.3)	0
Autoimmune thyroiditis	2 (0.6)	0	0	0
Autoimmune hypothyroidism	1 (0.3)	0	0	0
Blood thyroid stimulating hormone increased	1 (0.3)	0	0	0
Thyroiditis	1 (0.3)	0	0	0
Thyroxine free decreased	1 (0.3)	0	0	0
IMMUNE-RELATED RASH	35 (10.2)	5 (1.5)	1 (0.3)	0
Rash	17 (4.9)	1 (0.3)	0	0
Rash maculo-papular	8 (2.3)	1 (0.3)	0	0
Pruritus	7 (2.0)	0	1 (0.3)	0
Erythema	2 (0.6)	1 (0.3)	0	0
Purpura	2 (0.6)	0	0	0
Rash erythematous	2 (0.6)	0	0	0
Drug eruption	1 (0.3)	1 (0.3)	0	0
Erythema multiforme	1 (0.3)	1 (0.3)	0	0
Lichen planus	1 (0.3)	0	0	0
Rash papular	1 (0.3)	0	0	0
Rash pruritic	1 (0.3)	0	0	0
OTHER IMMUNE-RELATED ADVERSE EVENTS: OTHER	9 (2.6)	2 (0.6)	0	0
Psoriasis	3 (0.9)	0	0	0
Vitiligo	2 (0.6)	0	0	0
Arthritis	1 (0.3)	0	0	0
Dermatitis psoriasiform	1 (0.3)	0	0	0
Oligoarthritis	1 (0.3)	1 (0.3)	0	0
Polyarthritis	1 (0.3)	0	0	0
Rheumatoid arthritis	1 (0.3)	1 (0.3)	0	0

IMMUNE-RELATED PNEUMONITIS	7 (2.0)	1 (0.3)	0	0
Pneumonitis	5 (1.5)	1 (0.3)	0	0
Interstitial lung disease	2 (0.6)	0	0	0
IMMUNE-RELATED NEPHRITIS AND RENAL DYSFUNCTION	6 (1.7)	1 (0.3)	0	0
Nephritis	3 (0.9)	0	0	0
Renal failure	3 (0.9)	1 (0.3)	0	0
Tubulointerstitial nephritis	1 (0.3)	0	0	0
IMMUNE-RELATED COLITIS	5 (1.5)	3 (0.9)	0	0
Colitis	3 (0.9)	2 (0.6)	0	0
Diarrhoea	2 (0.6)	0	0	0
Enteritis	1 (0.3)	1 (0.3)	0	0
Proctitis	1 (0.3)	0	0	0
IMMUNE-RELATED HEPATITIS	5 (1.5)	5 (1.5)	0	0
Alanine aminotransferase increased	3 (0.9)	3 (0.9)	0	0
Aspartate aminotransferase increased	2 (0.6)	2 (0.6)	0	0
Autoimmune hepatitis	1 (0.3)	1 (0.3)	0	0
Hepatotoxicity	1 (0.3)	1 (0.3)	0	0
IMMUNE-RELATED ENDOCRINOPATHIES: ADRENAL INSUFFICIENCY	3 (0.9)	0	0	0
Adrenal insufficiency	3 (0.9)	0	0	0
IMMUNE-RELATED ENDOCRINOPATHIES: TYPE 1 DIABETES MELLITUS	3 (0.9)	3 (0.9)	1 (0.3)	1 (0.3)
Hyperglycaemia	3 (0.9)	3 (0.9)	0	0
Diabetes mellitus	0	0	1 (0.3)	1 (0.3)
IMMUNE-RELATED PANCREATITIS	2 (0.6)	1 (0.3)	0	0
Autoimmune pancreatitis	1 (0.3)	1 (0.3)	0	0
Pancreatitis	1 (0.3)	0	0	0
OTHER IMMUNE-RELATED ADVERSE EVENTS: MYOSITIS	2 (0.6)	2 (0.6)	0	0
Myositis	2 (0.6)	2 (0.6)	0	0
OTHER IMMUNE-RELATED ADVERSE EVENTS: GUILLAIN-BARRE SYNDROME	1 (0.3)	1 (0.3)	0	0
Miller Fisher syndrome	1 (0.3)	1 (0.3)	0	0
OTHER IMMUNE-RELATED ADVERSE EVENTS: UVEITIS	1 (0.3)	0	1 (0.3)	0
Uveitis	1 (0.3)	0	1 (0.3)	0

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.

Subjects reporting more than one adverse event (AE) within a preferred term are counted only once in that preferred term.

Subjects reporting multiple preferred terms within the same cluster are counted only once within each cluster.

For subjects reporting more than one AE within a cluster or preferred term, the AE with maximum grade are included in the table. Sorted in descending order of the frequency of clusters and PTs within cluster for all grades in the Avelumab+BSC arm.

MedDRA v22.1 coding dictionary and CTCAE version 4.03 applied.

Source: Clinical Study Report[4]

Infusion-Related Reactions: A summary of the infusion related reactions is provided in Table 28. Infusion related reactions (referring to the composite category) occurred in [redacted] patients ([redacted]%) in the avelumab plus BSC group, and in no patients in the BSC group, with the most commonly occurring reacting being related to infusion related reactions (10.2%), followed by chills ([redacted]%) and pyrexia ([redacted]%). Three patients (0.9%) experienced grade 3 or higher infusion related reactions. Serious infusion related reactions in the avelumab plus BSC group were reported in [redacted] patients ([redacted]%), all of whom discontinued receiving study treatment with avelumab. Patients first experiencing an infusion related reaction typically did so following their first or second infusion of avelumab; only [redacted] patients experienced an infusion related reaction for the first time during a later infusion.[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Table 28: Summary of Infusion Related Reactions

Source: Clinical Study Report[4]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

Death: A summary of deaths occurring during the JAVELIN Bladder 100 trial are reported in Table 29. Deaths were mainly due to progression of disease, occurring in [redacted] patients ([redacted]%) in the avelumab plus BSC group versus [redacted] patients ([redacted]%) in the BSC group.[4] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* Based on investigator assessment, two patients (0.6%) in the avelumab plus BSC group experienced death related to toxicity of trial treatment. One of the patients experienced sepsis following a urinary tract infection and possible central venous catheter infection after having received 11 infusions of avelumab. The second patient did from an ischemic occurring stroke 100 days after having received one dose of avelumab and after disease progression and AEs of limb venous thrombosis, pulmonary embolism and acute myocardial infarction.[3]

Table 29: Summary of Deaths

Source: Clinical Study Report[4]

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).

6.4 Ongoing Trials

No ongoing trials were identified as being relevant to this review.

7 Supplemental Questions

No supplemental questions were identified as being relevant to this review.

8 Comparison with Other Literature

The CADTH CGP and the CADTH Method Team did not identify other relevant literature as supporting information for this review.

9 About this Document

This Clinical Guidance Report was prepared by the CADTH Urothelial Carcinoma Clinical Guidance Panel and supported by the CADTH Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on avelumab for patients with UC. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant CADTH Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

CADTH considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the Procedures for the CADTH pan-Canadian Oncology Drug Review.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

Appendix 1: Literature Search Strategy and Detailed Methodology

1. Literature search via Ovid platform

Database(s): Cochrane Central Register of Controlled Trials August 2020, Embase 1974 to 2020 September 30, Ovid MEDLINE(R) ALL 1946 to September 29, 2020

Search Strategy:

#	Searches	Results
1	(avelumab* or bavencio* or MSB-0010718C or MSB0010718C or MSB-0010682 or MSB0010682 or MSB-10682 or MSB10682 or MSB-10718C or MSB10718C or PF-068346635 or PF06834635 or PF-6834635 or PF6834635 or KXG2PJ551I).ti,ab,ot,kf,kw,hw,nm,rn.	3274
2	Carcinoma, Transitional Cell/ or Urinary bladder neoplasms/ or Ureteral neoplasms/ or Urethral neoplasms/	87503
3	((urologic* or urothel* or urinary tract or bladder or uretra* or urethra* or ureter* or (transitional adj3 cell*) or transitional epithel* or renal pelvis or uroepitheli* or uro-epitheli* or urogenital* or uro-genital* or vesical* or uretal*) and (tumor* or tumour* or cancer* or carcinoma* or malignan* or metasta* or adenocarcinoma* or adeno-carcinoma* or neoplas*)).ti,ab,kf,kw.	272278
4	or/2-3	287370
5	1 and 4	559
6	5 use cctr	31
7	5 use medall	103
8	*avelumab/ or (avelumab* or bavencio* or MSB-0010718C or MSB0010718C or MSB-0010682 or MSB0010682 or MSB-10682 or MSB10682 or MSB-10718C or MSB10718C or PF-068346635 or PF06834635 or PF-6834635 or PF6834635).ti,ab,kw,dq.	1788
9	Transitional Cell Carcinoma/ or Urinary tract carcinoma/ or exp bladder cancer/ or exp ureter cancer/ or exp urethra cancer/ or urinary tract cancer/	162451
10	((urologic* or urothel* or urinary tract or bladder or uretra* or urethra* or ureter* or (transitional adj3 cell*) or transitional epithel* or renal pelvis or uroepitheli* or uro-epitheli* or urogenital* or uro-genital* or vesical* or uretal*) and (tumor* or tumour* or cancer* or carcinoma* or malignan* or metasta* or adenocarcinoma* or adeno-carcinoma* or neoplas*)).ti,ab,kw,dq.	271036
11	or/9-10	302608
12	8 and 11	349
13	12 use oemezd	228
14	13 not (conference review or conference abstract).pt.	139
15	7 or 14	242
16	limit 15 to english language	234
17	6 or 16	265
18	remove duplicates from 17	174
19	13 and (conference review or conference abstract).pt.	89
20	limit 19 to english language	89
21	limit 20 to yr="2015 -Current"	88
22	18 or 21	262

2. Cochrane Central Register of Controlled Trials (CENTRAL) (searched via Ovid)

3. Grey literature search via:

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

World Health Organization
http://apps.who.int/trialsearch/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Health Canada's Clinical Trials Database
https://health-products.canada.ca/ctdb-bdec/index-eng.jsp

The European Clinical Trial Register
https://www.clinicaltrialsregister.eu/ctr-search/search

Search: Bavencio/avelumab, urothelial carcinoma

Select international agencies including:

US Food and Drug Administration (FDA)
https://www.fda.gov/

European Medicines Agency (EMA)
https://www.ema.europa.eu/

Search: Bavencio/avelumab, urothelial carcinoma

Conference abstracts:

American Society of Clinical Oncology (ASCO)
https://www.asco.org/

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

Search: Bavencio/avelumab, urothelial carcinoma — last five years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[24]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Bavencio (avelumab) and urothelial carcinoma.

No filters were applied to limit the retrieval by study type. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of January 20, 2021.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[25] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry, Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials, Health Canada Clinical Trials Database, and the European Clinical Trials Registry), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

One member of the CADTH Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team made the final selection of studies to be included in the review.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the CADTH Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. [Cite tools used for quality assessment of included studies]. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and CADTH:

- The Methods Team wrote a summary of background clinical information, a systematic review of the evidence, interpretation of the systematic review, and summaries of evidence for supplemental questions.
- The CADTH Clinical Guidance Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- CADTH wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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