Avelumab First-Line Maintenance for Locally Advanced or Metastatic Urothelial Carcinoma: Results From the Real-World US PATRIOT-II Study

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Abstract

In this study, researchers studied 160 people with advanced urothelial cancer in the US receiving avelumab maintenance treatment. These people had already received platinum chemotherapy, and their disease had either gone away, become smaller, or stopped growing. The efficacy and safety of avelumab treatment in these people were comparable to findings from a previous clinical trial and other real-world studies.

Introduction: In JAVELIN Bladder 100, avelumab first-line maintenance (1LM) improved overall survival (OS) and progression-free survival (PFS) in patients with locally advanced/metastatic urothelial carcinoma (la/mUC) without progression following 1L platinum-based chemotherapy (PBC) versus best supportive care. PATRIOT-II describes real-world outcomes with avelumab 1LM. **Patients and Methods:** This observational, retrospective study of avelumab 1LM in US community/academic centers used medical record data collected from avelumab initiation for ≥12 months to assess survival, safety, and healthcare resource utilization; analyses are descriptive. **Results:** The study included 160 patients from 37 centers (median age, 70 years; 77% male). Avelumab 1LM was initiated at a median of 4 weeks (IQR 3-6) after PBC completion. Median follow-up from avelumab 1LM was 16 months (IQR 11-21). At study end, 19.4% of patients continued avelumab; 73.7% had discontinued due to progression, adverse events (AEs), or performance status deterioration. Median PFS and OS from avelumab initiation were 5.4 months (95% CI, 3.8-6.9) and 24.4 months (95% CI, 20.4-28.4), respectively. Grade ≥3 treatment-related AEs (TRAEs) occurred in 15 patients (9.4%); 35 (21.9%) had any-grade immune-related AEs, and 23 (14.3%) received high-dose systemic corticosteroids for AEs. Forty-four patients (27.5%) were hospitalized during the avelumab treatment period, of whom 13 (8.1%) were hospitalized due to TRAEs. Limitations of this study include a small sample size, potential selection bias, and missing/unknown data. **Conclusion:** These results align with the JAVELIN Bladder 100 clinical trial and other real-world studies, supporting avelumab 1LM use in patients with la/mUC without progression following 1L PBC.

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Abbreviations: 1L, first line; 1LM, first-line maintenance; 2L, second line; AE, adverse event; BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; ED, emergency department; EV, enfortumab vedotin; HCRU, healthcare resource utilization; irAE, immune-related adverse event; la/mUC, locally advanced/metastatic urothelial carcinoma; OS, overall survival; PBC, platinum-based chemotherapy; PFS, progression-free survival; PD-L1, programmed death ligand 1; TRAE, treatment-related adverse event; UC, urothelial carcinoma.

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Take Home Message

- PATRIOT-II is a retrospective study of avelumab first-line maintenance treatment in patients with advanced urothelial carcinoma in the US who were progression free following platinum-based chemotherapy.
- The real-world effectiveness and safety of avelumab first-line maintenance treatment was consistent with findings from the JAVELIN Bladder 100 clinical trial and other real-world studies.
- These results support avelumab first-line maintenance as the standard of care for patients with advanced urothelial carcinoma without progression following platinum-based chemotherapy.

Introduction

Urothelial carcinoma (UC) accounts for ≈90% of all bladder cancers, with an incidence rate in the US of ≈18.2 per 100,000 per year.[1,2] The 5-year overall survival (OS) rate in US patients with locally advanced or distant metastatic UC (la/mUC) is about 40% and <10%, respectively.[1] Despite high initial response rates with first-line (1L) platinum-based chemotherapy (PBC), durable responses are rare; most patients have relatively early progression, often with clinical deterioration that may impact the ability to receive salvage systemic therapy.[1,3-6]

Avelumab is the first immunotherapy to demonstrate clinically meaningful and statistically significant improvement in OS as a 1L maintenance (1LM) treatment for patients with la/mUC without progression following 1L PBC. Avelumab received US Food and Drug Administration (FDA) approval in June 2020 based on the JAVELIN Bladder 100 phase 3 trial (NCT02603432). In the trial, patients with la/mUC that had not progressed following 4-6 cycles of PBC were randomized to receive avelumab 1LM plus best supportive care (BSC) or BSC alone.[7] After ≥2 years of follow-up, median OS (23.8 vs. 15.0 months) and progression-free survival (PFS; 5.5 vs. 2.1 months) were significantly improved with avelumab 1LM plus BSC versus BSC alone, respectively.[8] The significant survival benefit was independent of platinum agent received (cisplatin or carboplatin), whether response versus stable disease was achieved with PBC, or the number of PBC cycles.[9] Avelumab demonstrated an acceptable safety profile with no new safety concerns or significant detriments in quality of life.[8,10,11]

Our study aimed to examine real-world patient characteristics, treatment patterns, clinical outcomes, and healthcare resource utilization (HCRU) in an observational cohort of patients with la/mUC who received avelumab 1LM after no progression on PBC.

Patients and Methods

Setting and Patients

This retrospective study included adult patients with histologically confirmed la/mUC treated in 37 academic centers and community-based sites in the US. The study design is summarized in Figure 1 and detailed methods are provided in the Supplement. Briefly, eligible patients had la/mUC that had not progressed with 1L PBC and had received avelumab 1LM. Data were sourced from site-collected data and the EMOL Health data warehouse, an aggregator of healthcare data from electronic medical records, clinical trials, and patient monitoring systems.[12]

Data and Statistical Methods

Data collected at baseline included patient demographics, clinical parameters at PBC initiation, and treatment information (including response assessment to 1L PBC). Patients were followed up via medical record review for ≥12 months post avelumab 1LM initiation. PFS and OS were estimated using the Kaplan-Meier method and were measured from avelumab initiation until progression or death for PFS and until death for OS. OS was also measured from the start of PBC as an exploratory endpoint. Hazard ratios and 95% CIs for PFS and OS from initiation of avelumab were calculated in prespecified subgroups using univariate Cox regression. Treatment-related adverse events (TRAEs) were captured from date of avelumab 1LM initiation, were coded and graded using the Medical Dictionary for Regulatory Activities, and the preferred term was reported. The following were considered high-dose corticosteroids: prednisone 1 to 2 mg/kg/day or equivalent, prednisone 40 mg/day, dexamethasone 6 mg/day, methylprednisolone 32 mg/day, or hydrocortisone 160 mg/day. HCRU per person-year was reported as hospitalizations and emergency department (ED) visits related to UC and treatment complications in both the PBC treatment period (time between initiation of PBC and avelumab) and avelumab treatment period (time between initiation and discontinuation of avelumab plus 90 days or initiation of second-line [2L] therapy).

Results

Baseline and Treatment Characteristics

A total of 160 patients from 37 geographically dispersed oncology practices and community and academic centers in the US were enrolled. Of these, 70 patients (43.8%) were captured from the EMOL Health data warehouse. Demographics and clinical characteristics of patients at baseline are reported in Table 1. Most patients were White (n = 143 [89.4%]) and had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0/1 at PBC initiation (n = 121 [75.6%]). A total of 77 patients (48.1%) had tumors tested for programmed death ligand 1 (PD-L1) expression (Supplemental Table 1); 44/160 patients (27.5%) had PD-L1+ tumors. Metastatic disease at la/mUC diagnosis was observed in 119 patients (74.3%), with lymph nodes, bone, lung, and liver being the most common metastatic sites. 1L PBC was carboplatin based in 60 (37.5%) and cisplatin based in 100 patients (62.5%), including dose-dense methotrexate/vinblastine, doxorubicin, and cisplatin in 7 (4.4%). Patients received a median of 4 cycles (IQR 3-6) of PBC. Best observed response to PBC was complete or partial response in 130 patients (81.3%) and stable disease in 17 (10.6%), with the remainder unknown.

Patients started avelumab 1LM at a median of 4 weeks (IQR 3-6) following PBC completion. Avelumab was administered intravenously every 2 weeks at a dose of 800 mg in 130 patients (81.3%) or 10 mg/kg in 30 (18.8%). Patients received a median of 9 avelumab doses (IQR 5-26). Median follow-up from avelumab 1LM initiation was 16 months (IQR 11-21). At the end of follow-up, 31 patients (19.4%) were still on avelumab, and 129 (80.6%) had permanently discontinued due to progression (n = 63 [39.4%]), any AEs (n = 22 [13.8%]), medical comorbidity or ECOG PS deterioration (n = 3 [1.9%]), or drug cost, patient choice, or the COVID-19 pandemic (n = 1 each; others had missing

Table 1 Patient Demographics and Baseline Characteristics

	All Patients ($N = 160$)
Age, median (range), years	70 (40-90)
Sex, *n* (%)	
Male	123 (76.9)
Female	37 (23.1)
Race, *n* (%)	
White	143 (89.4)
Black	5 (3.1)
Asian	4 (2.5)
American Indian/Alaskan native	1 (0.6)
Other/unknown	7 (4.4)
Ethnicity, *n* (%)	
Hispanic or Latino	7 (4.4)
Not Hispanic or Latino	125 (78.1)
Unknown	28 (17.5)
ECOG PS, *n* (%)	
0	68 (42.5)
1	53 (33.1)
≥2	12 (7.5)
Unknown	27 (16.9)
Tumor location, *n* (%)	
Upper tract	49 (30.6)
Lower tract	78 (48.8)
Both	5 (3.1)
Unknown	28 (17.5)
PD-L1 status, *n* (%)	
Positive	44 (27.5)
Negative	33 (20.6)
Unknown	83 (51.9)
Site of distant metastasis at start of 1L PBC, *n* (%)	
Visceral[a]	70 (43.8)
Nonvisceral	51 (31.9)
None	23 (14.3)
Unknown	16 (10.0)
Creatinine clearance, *n* (%)	
≥60 mL/min	64 (40.0)
<60 mL/min	66 (41.3)
Unknown	30 (18.8)
1L PBC regimen, *n* (%)	
Cisplatin	100 (62.5)
Cycles, median (IQR)	4 (3-6)
Carboplatin	60 (37.5)
Cycles, median (IQR)	5 (4-6)
Best response to 1L PBC, *n* (%)	
Complete response or partial response	130 (81.3)
Stable disease	17 (10.6)
Unknown	13 (8.1)

Percentages may not total 100 because of rounding.
Abbreviations: 1L = first line; ECOG PS = Eastern Cooperative Oncology Group performance status; PBC = platinum-based chemotherapy; PD-L1 = programmed death ligand 1.
[a] Does not include bone metastasis.

reason). Of 129 patients who discontinued avelumab, 88 (68.2%) received a 2L therapy, most commonly enfortumab vedotin (EV; $n = 63$ [71.6%]), or gemcitabine plus cisplatin/carboplatin ($n = 10$ [11.4%]), pembrolizumab ($n = 6$ [6.8%]), or erdafitinib ($n = 5$ [5.7%]).

Survival Endpoints

Median PFS from start of avelumab 1LM was 5.4 months (95% CI, 3.8-6.9) (Figure 2) and median OS was 24.4 months (95% CI, 20.4-28.4) (Figure 3). Median PFS from start of avelumab 1LM was 5.5 months (95% CI, 3.6-7.4) in patients who had received cisplatin and 5.3 months (95% CI, 2.7-7.9) in patients who had received carboplatin (Supplemental Figure 1). In this selected population without progression after 1L PBC (exploratory analysis), median OS was 30.5 months (95% CI, 23.4-37.6) from the start of PBC (Supplemental Figure 2). At last follow-up, 66 patients (41.3%) were deceased, and 94 (58.8%) were alive. No patients died from a TRAE. Hazard ratios for PFS and OS (exploratory analysis) from initiation of avelumab in specific subgroups are presented in Table 2.

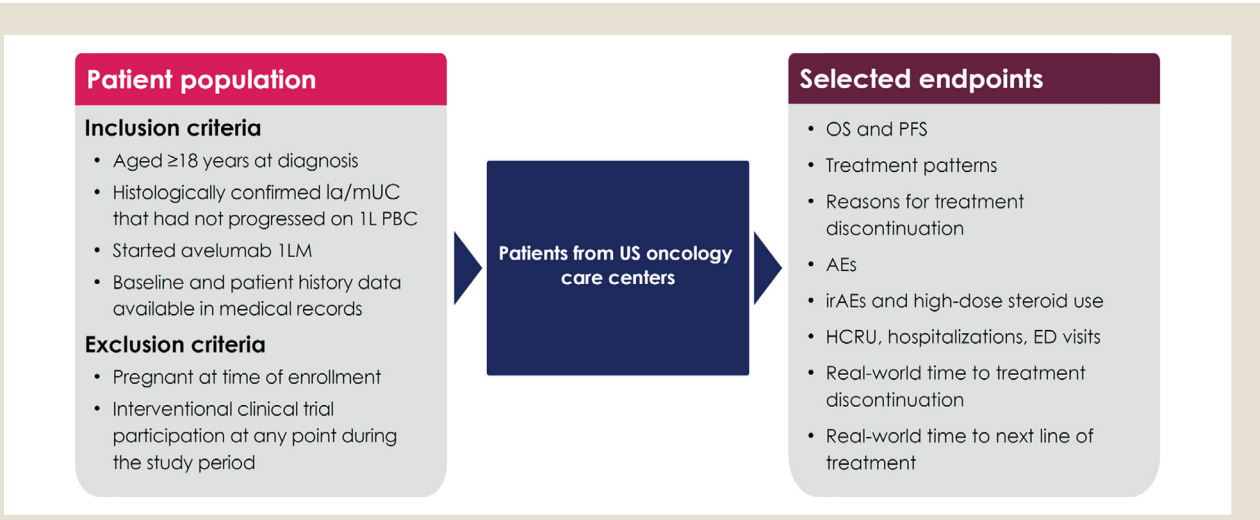
Adverse Events

TRAEs related to avelumab occurred in 62 patients (38.8%); 15 (9.4%) had grade ≥3 TRAEs, 35 (21.9%) had any-grade immune-related AEs (irAEs), 23 (14.3%) received high-dose systemic steroids, 13 (8.1%) were hospitalized due to TRAEs, and 16 (10.0%) discontinued therapy due to TRAEs (Table 3). The most commonly observed any-grade TRAEs were fatigue and hypothyroidism ($n = 7$ each [4.4%]), anemia, infusion-related reaction, and nausea ($n = 6$ each [3.8%]), elevated creatinine ($n = 5$ [3.1%]) and diarrhea and rash ($n = 4$ each [2.5%]). The most common irAEs were hypothyroidism ($n = 7$ [4.4%]) and rash ($n = 4$ [2.5%]) (Supplemental Table 2).

Healthcare Resource Utilization

During the avelumab treatment period, 44 patients (27.5%) were hospitalized for a mean of 11.5 days per person-year. Hospi-

Figure 1 PATRIOT-II study design.



Abbreviations: 1L, first line; 1LM, first-line maintenance; AE, adverse event; ED, emergency department; HCRU, healthcare resource utilization; irAE, immune-related adverse event; la/mUC, locally advanced or metastatic urothelial carcinoma; OS, overall survival; PBC, platinum-based chemotherapy; PFS, progression-free survival.

Table 2 Subgroup Analyses – Hazard Ratios for PFS and OS

	All Patients ($N = 160$)			
	PFS		OS	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
ECOG PS (0 vs. ≥1) at start of PBC	0.88	0.59-1.31	0.61	0.36-1.03
High-dose corticosteroids for irAEs (yes vs. no)	0.78	0.48-1.28	0.75	0.37-1.52
PBC agent (cisplatin vs. carboplatin)	0.86	0.58-1.26	1.05	0.63-1.74
No. of cycles of PBC (≤4 vs. >4)	1.11	0.77-1.60	1.01	0.62-1.65
Site of metastases (visceral vs. nonvisceral)	1.50	0.96-2.32	1.77	0.99-3.17
Liver metastases at start of PBC (yes vs. no)	1.04	0.63-1.71	1.18	0.64-2.19
Interval between end of PBC and avelumab initiation (≤4 vs. >4 weeks)	1.04	0.73-1.50	0.80	0.49-1.30

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; irAE = immune-related adverse event; OS = overall survival; PBC = platinum-based chemotherapy; PFS = progression-free survival.

Figure 2 Progression-free survival (PFS) from the start of avelumab first-line maintenance (1LM).
*Date of progression was missing for one patient. Progression was unknown for three patients; patients were censored at the most recent follow-up date.

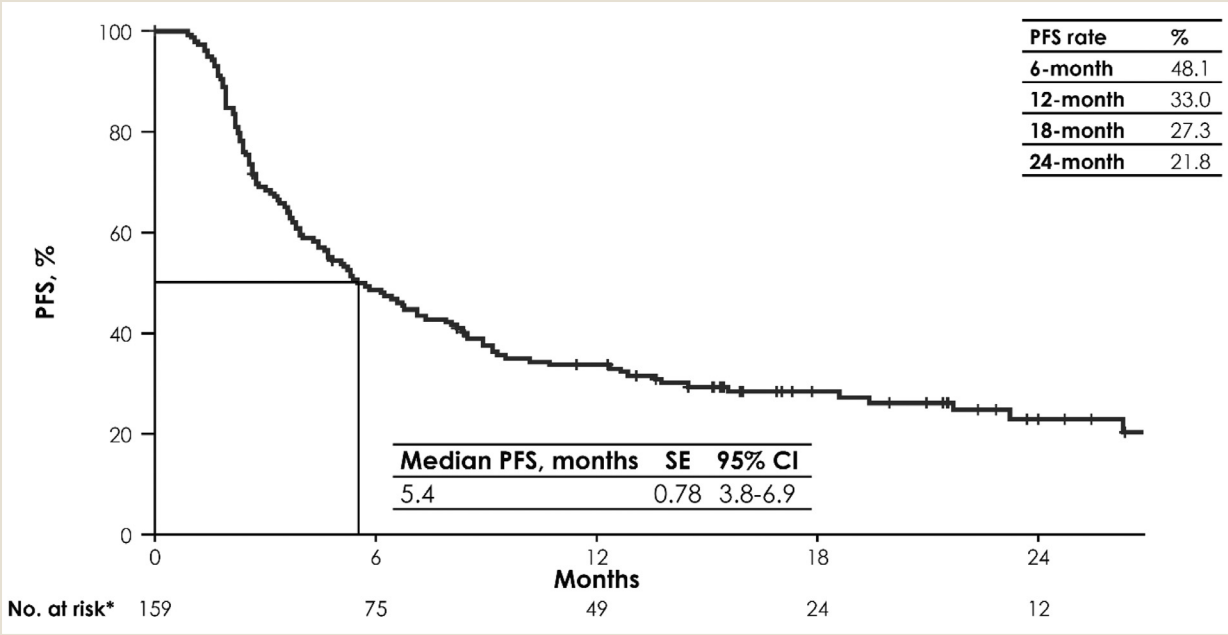


Figure 3 Overall survival (OS) from the start of avelumab first-line maintenance (1LM).

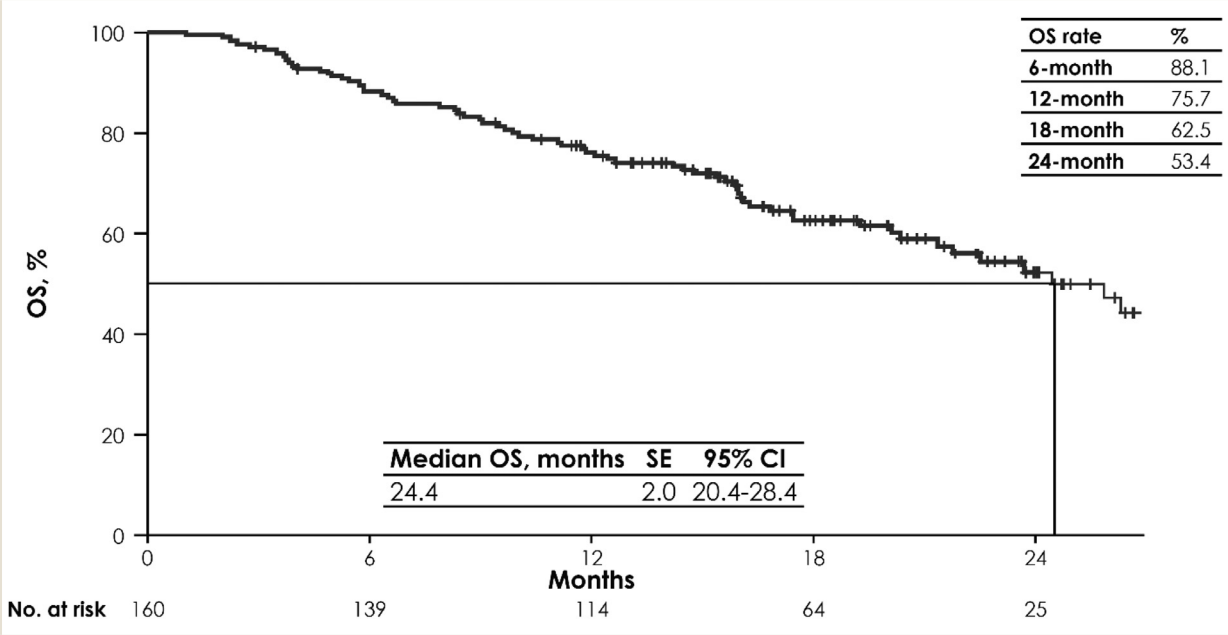


Table 3 Summary of Long-Term Safety for Avelumab Maintenance

	All Patients ($N = 160$)
Any TRAE, *n* (%)	62 (38.8)
Time to onset from avelumab initiation, mean (SD), days	95 (127)
Median (range), days	56 (0-793)
Grade ≥3 TRAE, *n* (%)	15 (9.4)
Any immune-related AE, *n* (%)	35 (21.9)
Time to onset from avelumab initiation, mean (SD), days	146 (173)
Median (range), days	91 (0-793)
Therapy stopped due to any TRAE, *n* (%)	16 (10.0)
Therapy delayed due to any TRAE, *n* (%)	20 (12.5)
Received steroid due to any TRAE (including topical), *n* (%)	36 (32.1)
Received high-dose systemic steroid due to any TRAE, *n* (%)	23 (14.3)
TRAE outcome, *n* (%)	$N = 165$[a]
Resolved	105 (63.6)
Unresolved at last follow-up	32 (19.4)
Resolved with sequelae	2 (1.2)
Unknown	26 (15.8)
Duration of TRAE, days[b]	$N = 165$[a]
Mean (SD)	97 (151)
Median (range)	31 (0-657)
Hospitalized due to TRAE, *n* (%)	
Yes	13 (8.1)
No	147 (91.9)

Abbreviations: AE = adverse event; TRAE = treatment-related adverse event.
[a] N represents number of AEs, duplicated in data file.
[b] Most recent follow-up date used if unresolved.

tal admission was due to TRAEs in 13 patients (8.1%); the remainder were related to cancer progression, surgical procedures, and medical comorbidities. During the PBC treatment period, 25 patients (15.6%) were hospitalized for a mean of 3 days per person-year. During the avelumab and PBC treatment periods, respectively, 12 (7.5%) and 11 (6.9%) patients had an ED visit (Supplemental Table 3).

Discussion

PATRIOT-II examined real-world treatment patterns, clinical outcomes, and HCRU prior to and during avelumab 1LM in patients with la/mUC in routine clinical practice in the US. Baseline factors, treatment patterns, and response to PBC were consistent with usual therapy paradigms in the 1L induction setting in clinical trials and real-world data.[10,13] Real-world OS and PFS from the initiation of avelumab 1LM in PATRIOT-II were consistent with findings from JAVELIN Bladder 100. In this selected population, the exploratory median OS measured from the start of 1L PBC in this study was comparable to long-term data from JAVELIN Bladder 100 (30.5 and 29.7 months, respectively).[14]

Our findings align with those of other real-world studies of patients treated with avelumab 1LM in the US, Europe, and Asia. In a study of 108 patients in US academic medical centers, median PFS from start of avelumab 1LM was 9.6 months, with a median follow-up of 8.8 months, and the 12-month OS rate was 72.5%.[15] In a study using the US Flatiron database, median OS and PFS in 214 patients from start of avelumab 1LM were 23.8 and 5.1 months, respectively, with median follow-up of 8.7 months.[16] In the AVENANCE ambispective study of 595 patients in France, median OS and PFS from start of avelumab 1LM were 21.3 and 5.7 months, respectively, with median follow-up of 26.3 months.[17] In the READY study, a compassionate use program of 414 patients in Italy, median OS and PFS from start of avelumab 1LM were 26.2 and 7.6 months, respectively, with median follow-up of 20.2 months.[18] In exploratory analyses the median OS from start of 1L PBC in patients without progression with 1L PBC was 26.5 and 30.9 months for the AVENANCE and READY studies, respectively.[18] In a study in Japan, a subgroup analysis of 27 patients found that 11 (41%) had an investigator-assessed objective response to avelumab 1LM.[19] Finally, an expanded access study in Korea had results consistent with those of JAVELIN Bladder 100.[20]

We observed that approximately 3 in 4 patients were either still on avelumab or received 2L treatment in PATRIOT-II, similar to findings in the AVENANCE study.[17] In PATRIOT-II, with a median follow-up of 16 months, 19% of patients were still on avelumab treatment at the end of the study, while 19.5% received ≥2 years of avelumab treatment in JAVELIN Bladder 100.[8] Eighty-eight patients (55%) received a 2L treatment in PATRIOT-II; of these, 72% received 2L EV, which is greater than 55% in the US Flatiron study. In Flatiron, outcomes for 2L EV were consistent

with those of the EV-301 trial, with median PFS and OS of 4.9 and 11.2 months, respectively.[16,21] These results were corroborated by the UNITE real-world study examining outcomes from start of 2L EV after progression on avelumab 1LM (median PFS and OS of 7.0 and 13.3 months, respectively).[22]

Similar to other studies, subgroup analyses did not show a significant difference in OS benefit based on the number of PBC cycles (>4 vs. ≤4) or platinum agent received (cisplatin vs. carboplatin).[10,13] Our study did not assess subgroup outcomes based on PD-L1 expression levels because they are not routinely measured in clinical practice. However, an exploratory analysis of candidate biomarkers (eg, PD-L1, tumor mutational burden, and APOBEC) in JAVELIN Bladder 100 did not identify a clinically useful biomarker.[23]

The rate of TRAEs related to avelumab in this study was lower than in JAVELIN Bladder 100 (38.8% vs. 78.2%), likely because documentation of AE occurrence, type, severity, and association with treatment relied on data from medical records.[8] Grade ≥3 TRAEs were reported in 9.4% of patients, consistent with 10.3% reported in AVENANCE[24] but slightly higher than 7.1% reported in READY.[18] In this study, any-grade irAEs were reported in 21.9% of patients, which is lower than the 32.3% and 44% reported in JAVELIN Bladder 100 and the Japanese real-world study, respectively.[8,19] Avelumab treatment was discontinued due to a TRAE in 16 patients (10.0%) in this study, in line with JAVELIN Bladder 100, in which TRAEs led to avelumab discontinuation in 10.2% of patients after ≥12 months of follow-up. No new safety concerns were observed.

The economic impact of cancer care includes HCRU, including inpatient hospital care and ED visits. This is currently the only study to examine hospitalizations and ED visits in both the PBC and avelumab periods in patients with la/mUC initiating avelumab 1LM without progression on PBC. In this study, HCRU, both hospitalizations (including length of stay) and incidence of ED visits, was higher during and 90 days after the avelumab treatment period than during the 1L PBC treatment period. This is likely due to the impact of several potential unmeasured confounders, including cancer progression, complications of subsequent therapies, and clinical deterioration over time, as we measured HCRU for ≤3 months after avelumab was discontinued. In a study based on US Medicare data, 78%-83% of patients initiating PBC required hospitalization over a 4-year follow-up period. However, that study was conducted prior to the availability of avelumab 1LM and did not specifically analyze HCRU while receiving PBC versus subsequent therapies or surveillance in the BSC period.[25] Grivas et al.[26] examined all-cause HCRU associated with the management of select severe AEs in patients receiving chemotherapy or anti–PD-(L)1 agents as 1L treatment for advanced UC. HCRU, particularly hospitalization, was significantly higher in patients with the most severe AEs. However, data from that study were generated prior to the use of avelumab 1LM, and no adequately powered comparison of HCRU data between chemotherapy and anti–PD-(L)1 agents was feasible.

Recently, additional 1L combination treatments have been included in clinical guidelines for la/mUC.[27] The combination of EV plus pembrolizumab received FDA approval regardless of cisplatin eligibility based on significantly improved PFS and OS versus PBC in the phase 3 EV-302 trial.[5] For cisplatin-eligible patients, nivolumab plus gemcitabine-cisplatin followed by nivolumab maintenance received FDA approval based on significantly improved PFS and OS versus gemcitabine plus cisplatin in the phase 3 CheckMate-901 trial.[6,28] In addition to these new recommended treatment options, avelumab 1LM remains a standard of care in patients with la/mUC without progression on PBC, especially in countries with no access to these combinations or for patients ineligible for or with contraindications to the aforementioned combination regimens.

Limitations of this study include a relatively small sample size and the inherent limitations of real-world data, which lack central imaging review and are subject to missing/unknown data, potential selection bias, and confounding factors due to the lack of randomization. As a retrospective study, data collection relied on medical records, limiting the collection of additional data not contained in a medical record, potentially introducing bias as the accuracy and completeness of the data in medical charts may vary widely. Events that occurred outside the provider's institution may potentially be undercounted. This may impact parameters such as AEs, reports of which may not be routinely solicited in the same manner and granularity as in prospective clinical trials. Also, HCRU is subject to underreporting, as utilization incurred outside the practice setting may not be fully accounted. Lastly, as molecular biomarkers are not used in clinical practice for selection of patients for avelumab 1LM, PD-L1 expression was not reported for many patients. When PD-L1 data were reported, results were not formally evaluated based on each assay's scoring system and cutoffs. Finally, OS analyses from 1L PBC need to be interpreted with caution because of immortal-time bias since only patients on 1LM are included.

Conclusion

Our retrospective US study of 160 patients adds to the growing body of real-world data that consistently supports avelumab 1LM as an effective and safe therapy for patients with la/mUC without progression following 1L PBC. In a rapidly evolving treatment landscape, further research is needed to evaluate the real-world effectiveness and toxicity of recently approved therapies.

Clinical Practice Points

- Avelumab is standard of care for first-line maintenance treatment in patients with advanced urothelial carcinoma who receive first-line cisplatin- or carboplatin-based chemotherapy without cancer progression. Approval was based on the JAVELIN Bladder 100 phase 3 trial, which showed that avelumab + best supportive care (BSC) significantly prolonged overall survival (OS) and progression-free survival (PFS) versus BSC alone in platinum-treated patients without cancer progression.
- In this retrospective real-world US study, patients with advanced urothelial carcinoma treated with avelumab first-line maintenance had similar outcomes to those in the JAVELIN Bladder 100 trial and other real-world studies.
- The incidence of treatment-related adverse events was lower in this study compared with JAVELIN Bladder 100 but consistent with other real-world studies.

- Healthcare resource utilization (HCRU), including hospitalizations, length of hospital stay, and incidence of emergency department visits, was higher during and after avelumab treatment than during platinum-based chemotherapy treatment. This was likely due to the impact of several potential unmeasured confounders, including cancer progression, complications of subsequent therapies, and clinical deterioration over time, as we measured HCRU for ≤3 months after avelumab was discontinued.
- Limitations of this study include a small sample size, potential selection and confounding biases, lack of randomization and central scan review, and missing/unknown data.
- In the context of recent approvals of other new first-line treatment regimens, avelumab maintenance remains the standard of care for cisplatin-eligible or -ineligible patients with advanced urothelial carcinoma who previously received and had no progression on induction platinum-based chemotherapy in updated international treatment guidelines.

Disclosure

In the last 2 years, P. Grivas has served in consulting or advisory roles for AbbVie, Aadi Biosciences, Asieris Pharmaceuticals, Astellas Pharma, AstraZeneca, Bicycle Therapeutics, Bristol Myers Squibb, CG Oncology, Fresenius Kabi, G1 Therapeutics, Gilead Sciences, ImmunityBio, Janssen, Merck & Co., Kenilworth, NJ, Pfizer, Roche, Strata Oncology, and the healthcare business of Merck KGaA, Darmstadt, Germany; and has received institutional research funding from Acrivon Therapeutics, ALX Oncology, Bristol Myers Squibb, G1 Therapeutics, Genentech, Gilead Sciences, Merck & Co., Kenilworth, NJ, Mirati Therapeutics, QED Therapeutics, and the healthcare business of Merck KGaA, Darmstadt, Germany.

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Supplementary materials

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References

1. National Cancer Institute. SEER Cancer Stat Facts: Bladder Cancer. Accessed August 12, 2024. https://seer.cancer.gov/statfacts/html/urinb.html.
2. Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA, Barsouk A. Epidemiology of bladder cancer. *Med Sci (Basel)*. 2020;8:15.
3. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol*. 2023;41:3881–3890.
4. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. *J Clin Oncol*. 2012;30:191–199.
5. Powles T, Valderrama BP, Gupta S, et al. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. *N Engl J Med*. 2024;390:875–888.
6. van der Heijden MS, Sonpavde G, Powles T, et al. Nivolumab plus gemcitabine–cisplatin in advanced urothelial carcinoma. *N Engl J Med*. 2023;389:1778–1789.
7. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. *N Engl J Med*. 2020;383:1218–1230.
8. Powles T, Park SH, Caserta C, et al. Avelumab first-line maintenance for advanced urothelial carcinoma: results from the JAVELIN Bladder 100 trial after ≥2 years of follow-up. *J Clin Oncol*. 2023;41:3486–3492.
9. Grivas P, Park SH, Voog E, et al. Avelumab first-line maintenance therapy for advanced urothelial carcinoma: comprehensive clinical subgroup analyses from the JAVELIN Bladder 100 phase 3 trial. *Eur Urol*. 2023;84:95–108.
10. Sridhar SS, Powles T, Climent Duran MA, et al. Avelumab first-line maintenance for advanced urothelial carcinoma: analysis from JAVELIN Bladder 100 by duration of first-line chemotherapy and interval before maintenance. *Eur Urol*. 2024;85:154–163.
11. Grivas P, Kopyltsov E, Su PJ, et al. Patient-reported outcomes from JAVELIN Bladder 100: avelumab first-line maintenance plus best supportive care versus best supportive care alone for advanced urothelial carcinoma. *Eur Urol*. 2023;83:320–328.
12. EMOL Health. The successful integration of information technology and patient-based oncology data. Accessed March 5, 2024. https://learnmore.emolhealth.com/.
13. Bellmunt J, Chang J, Pavilack-Kirker M, et al. Evaluating real-world characteristics of patients with advanced urothelial carcinoma eligible for avelumab maintenance therapy: a multicountry retrospective medical chart review. *Clin Genitourin Cancer*. 2023;21:459–466.
14. Sridhar SS, Powles T, Gupta S, et al. Avelumab first-line (1L) maintenance for advanced urothelial carcinoma (UC): long-term follow-up from the JAVELIN Bladder 100 trial in subgroups defined by 1L chemotherapy regimen and analysis of overall survival (OS) from start of 1L chemotherapy. *J Clin Oncol*. 2023;41 Abstract 508.
15. Bakaloudi DR, Talukder R, Lin GI, et al. Response and outcomes of maintenance avelumab after platinum-based chemotherapy (PBC) in patients with advanced urothelial carcinoma (aUC): "real world" experience. *Clin Genitourin Cancer*. 2023;21:584–593.
16. Moon HH, Kearney M, Mahmoudpour SH, et al. Real-world (rw) treatment patterns, sequencing, and outcomes in patients (pts) with locally advanced or metastatic urothelial carcinoma (la/mUC) receiving avelumab first-line maintenance (1LM) in the US. *J Clin Oncol*. 2024;42 Abstract 605.
17. Barthelemy P, Loriot Y, Thibault C, et al. Updated results from AVENANCE: real-world effectiveness of avelumab first-line maintenance (1LM) in patients (pts) with advanced urothelial carcinoma (aUC) and analysis of subsequent treatment. *J Clin Oncol*. 2024;42 Abstract 561.
18. Antonuzzo L, Maruzzo M, De Giorgi U, et al. READY: REAl-world Data from an Italian compassionate use program of avelumab first-line maintenance for locallY advanced or metastatic urothelial carcinoma. *ESMO Real World Data Digi Oncol*. 2024;5:100068.
19. Miyake M, Shimizu T, Oda Y, et al. Switch-maintenance avelumab immunotherapy following first-line chemotherapy for patients with advanced, unresectable or metastatic urothelial carcinoma: the first Japanese real-world evidence from a multicenter study. *Jpn J Clin Oncol*. 2023;53:253–262.
20. Park SH, Rah SY, Seo HK, Keam B, Oh ES, Lee J-L. First results of a Korean expanded access program of avelumab first-line maintenance in patients with locally advanced or metastatic urothelial carcinoma. Poster presented at 15th Annual Meeting of the Korean Society of Medical Oncology & 2022 International Congress; Seoul, Korea; September 1-2. 2022.
21. Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. *N Engl J Med*. 2021;384:1125–1135.
22. Nizam A, Jindal T, Jiang CY, et al. Outcomes in patients (pts) with advanced urothelial carcinoma (aUC) treated with enfortumab vedotin (EV) after switch maintenance avelumab (MAv) in the UNITE study. *J Clin Oncol*. 2024;42 Abstract 537.
23. Powles T, Sridhar SS, Loriot Y, et al. Avelumab maintenance in advanced urothelial carcinoma: biomarker analysis of the phase 3 JAVELIN Bladder 100 trial. *Nat Med*. 2021;27:2200–2211.
24. Barthelemy P, Loriot Y, Flechon A, et al. AVENANCE: subgroup analysis of patients (pts) with advanced urothelial carcinoma (aUC) with histological variants from a real-world (RW) study of avelumab first-line maintenance (1LM). *Ann Oncol*. 2023;34 Abstract 2379P.
25. Bilen MA, Robinson SB, Schroeder A, et al. Clinical and economic outcomes in patients with metastatic urothelial carcinoma receiving first-line systemic treatment (the IMPACT UC I study). *Oncologist*. 2023;28:790–798.
26. Grivas P, DerSarkissian M, Shenolikar R, Laliberte F, Doleh Y, Duh MS. Healthcare resource utilization and costs of adverse events among patients with metastatic urothelial cancer in USA. *Future Oncol*. 2019;15:3809–3818.
27. Powles T, Bellmunt J, Comperat E, et al. ESMO Clinical Practice Guideline interim update on first-line therapy in advanced urothelial carcinoma. *Ann Oncol*. 2024;35:485–490.
28. Opdivo (nivolumab). Prescribing information. Bristol-Myers Squibb; 2024.