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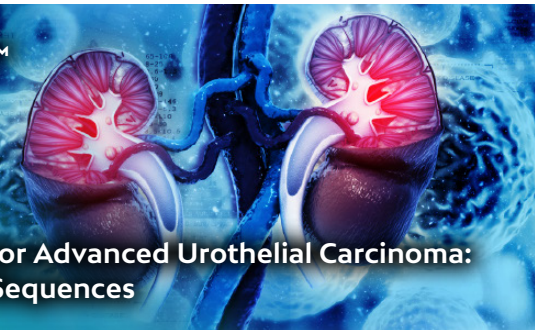

Real-World Effectiveness of Avelumab First-Line Maintenance for Advanced Urothelial Carcinoma: Updated Results from AVENANCE in the Context of Treatment Sequences

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Independent expert commentary by Associate Professor Andrew Weickhardt

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Abbreviations used in this review:

ADC = antibody-drug conjugate; **BSC** = best supportive care; **ESMO** = European Society for Medical Oncology; **ICIs** = immune checkpoint inhibitors; **NCCN** = National Comprehensive Cancer Network; **OS** = overall survival; **PD-L1** = programmed death-ligand 1; **PD-1** = programmed cell death protein; **PFS** = progression-free survival; **RCT** = randomised controlled trial; **RECIST** = Response Evaluation Criteria in Solid Tumours; **TEAE** = treatment-emergent adverse event.

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This review summarises and discusses the latest results from AVENANCE, an ongoing prospective study of the real-world effectiveness of avelumab as first-line maintenance therapy for advanced urothelial carcinoma, with a focus on subsequent (second-line) treatment. The overall results support international guidelines recommending avelumab first-line maintenance as a standard of care in patients with advanced urothelial carcinoma that has not progressed with first-line platinum-containing chemotherapy. At follow-up of 26.5 months, median overall survival (OS) from the start of avelumab first-line maintenance was 21.3 months and in subgroup analyses OS from the start of avelumab first-line maintenance was 31.3 months in patients who received second-line treatment with an antibody-drug conjugate (ADC). Results from exploratory analyses suggest that patients who receive first-line platinum-containing chemotherapy without disease progression followed by avelumab first-line maintenance and second-line treatment with an ADC may achieve survival of more than 3 years on average.

Introduction

Bladder cancer is one of the most commonly diagnosed malignancies, with the majority being urothelial carcinomas.[1,2]

The therapeutic landscape for advanced urothelial carcinoma has undergone rapid evolution in the past five or so years with the arrival of multiple targeted therapy agents and immune-checkpoint inhibitors (ICIs) as potential treatment options in both first- and second-line settings.[3,4]

Despite the arrival of these novel therapies, platinum-containing chemotherapy remains the backbone of first-line therapy for the majority of patients with advanced urothelial carcinoma. The monoclonal antibody ICI avelumab was, however, approved in 2020 by the FDA as first-line maintenance treatment for patients with locally advanced or metastatic urothelial carcinoma.[5]

Avelumab is a fully human monoclonal antibody that blocks the interaction between programmed death-ligand 1 (PD-L1) on tumour cells and programmed cell death protein 1 (PD-1) on T cells, B cells, and antigen-presenting cells.[6] By blocking the PD-1/PD-L1 interaction avelumab inhibits immunosuppression within the tumour microenvironment, which results in reduced tumour growth.

Due to its high mutational burden and genomic instability, urothelial carcinoma is considered to be a type of immunogenic cancer hence providing the rationale for investigating the use of ICIs in cases of advanced urothelial carcinoma that have progressed following first-line platinum-containing chemotherapy.[2]

Study background

Switch maintenance is a treatment strategy that involves the use of systemic treatments with different mechanisms of action, with the aim of prolonging or even enhancing the clinical benefits achieved with first-line anti-cancer therapy.[2]

The FDA approval of avelumab as a first-line maintenance therapy for locally advanced or metastatic urothelial carcinoma was based on data from the JAVELIN Bladder 100 international phase 3 trial,[5] which evaluated the efficacy and safety of avelumab as switch maintenance treatment in eligible patients with advanced urothelial carcinoma whose disease was stable or improved after first-line platinum-containing chemotherapy.[7]

In the JAVELIN Bladder 100 trial, avelumab as first-line maintenance plus best supportive care (BSC) was associated with a 7.1-month improvement in median overall survival (OS) compared with BSC alone (21.4 months [95% CI: 18.9–26.1] vs 14.3 months [95% CI: 12.9–17.9]) in patients with advanced urothelial carcinoma that had not progressed after first-line platinum-containing chemotherapy.[7] This was a statistically significant improvement in OS, representing a 31% reduction in the risk of death in the overall study population (HR 0.69; 95%CI: 0.56–0.86; p=0.001). In the subgroup of patients with PD-L1+ tumours, OS was also significantly (p<0.001) longer in patients who received avelumab plus BSC than in those who received BSC alone. The safety profile of avelumab plus BSC was consistent with that seen in prior studies of avelumab monotherapy, with no new safety signals observed.

Based on the findings of the JAVELIN Bladder 100 trial,[7] the JAVELIN Bladder anti-cancer regimen is a category 1 recommended regimen in the current NCCN and ESMO guidelines,[8,9] and the only regimen currently PBS reimbursed in Australia.

With avelumab first-line maintenance treatment having become the standard of care for advanced urothelial cancer stable or improved after first-line platinum-containing chemotherapy, based on evidence from the JAVELIN Bladder 100 trial, the efficacy and safety of the JAVELIN Bladder 100 regimen is now being evaluated in a heterogeneous advanced urothelial carcinoma patient population outside of a clinical setting in AVENANCE, an ongoing real-world study currently being conducted in France. Given the evolving treatment landscape, AVENANCE is also assessing patient survival with different treatment sequences.

Preliminary results already reported from AVENANCE at 11.4 months median follow-up indicated that real-world data for avelumab first-line maintenance in patients with advanced urothelial carcinoma support the clinical trial findings of the JAVELIN Bladder 100 trial.[10]

Updated results from AVENANCE were recently presented during a urothelial carcinoma poster session at the 2024 American Society of Clinical Oncology Genitourinary (ASCO GU) Cancers Symposium, which was held in San Francisco during 25–27 July 2024.[11] Data from analyses by subsequent (second-line) treatment and exploratory analyses of OS measured from start of first-line platinum-containing chemotherapy in this study population of patients without disease progression were also reported.

Expert comment

The AVENANCE real-world study was designed to offer clinicians supportive evidence regarding the use of avelumab as standard of care in responding/stable patients post-first-line platinum chemotherapy. While the JAVELIN Bladder 100 trial provided quality randomised data, I often wonder if the data applies to the same sort of patients seen in our clinics who are typically older and with comorbidities. Real-world outcomes of avelumab maintenance efficacy were needed to address this question.

Methods

Design

AVENANCE (NCT04822350) is an ongoing multicentre, ambispective (retrospective and prospective), non-interventional study designed to generate real-world data on the use of avelumab as a first-line maintenance treatment for patients with advanced or metastatic urothelial carcinoma.

Patients

Eligible patients were aged ≥18 years with locally advanced or metastatic urothelial carcinoma that had not progressed (i.e., ongoing complete response, partial response, or stable disease) following completion of first-line platinum-containing chemotherapy and previous (retrospective), ongoing (retrospective and prospective), or planned (prospective) avelumab first-line maintenance treatment.

Analyses

Data collection commenced on July 13, 2021, with patients being assessed and followed-up as per standard clinical practice (no study-specific visits were required). Additional follow-up and analysis is ongoing.

Primary endpoint: overall survival (OS) measured from the start of avelumab treatment.

Scondary endpoints: progression-free survival (PFS), duration of treatment, and safety.

Effectiveness population: all patients who received at least one dose of avelumab and met all eligibility criteria.

Safety population: all patients who received at least one dose of avelumab.

An exploratory analysis of OS data from the start of first-line chemotherapy was also performed. Patients whose start date for chemotherapy was not provided or was recorded as being on or after the date of avelumab initiation were excluded from the exploratory analysis.

Detailed analyses were also performed in the overall population and in subgroups defined by second-line treatment received after discontinuing avelumab first-line maintenance. Patients may have received second-line treatment within standard clinical practice, early access programmes, or clinical trials.

Expert comment

Real-world studies such as AVENANCE need to focus on harder objective endpoints such as OS, given the variability in data collection regarding response duration, use of Response Evaluation Criteria in Solid Tumours (RECIST), and follow-up. The primary endpoint of OS is therefore appropriate. Exploration of OS data timed from the commencement of first-line chemotherapy is of interest, given the recent publication of the EV-302 trial[1] and OS data reported from this study, taken from the commencement of first-line therapy. Note, however, the AVENANCE population reported in the exploratory population is different from EV-302, given that only responders and those with stable disease are included.

Reference: 1. Powles T, et al. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. N Engl J Med 2024;390:10:875-888.

Results

Of the 604 screened patients, a total of 595 patients were included in the effectiveness population and 596 were included in the safety population.

At data cutoff (December 7, 2023):

- Median follow-up duration from initiation of avelumab in the effectiveness population was 26.3 months.
- 125 patients (21%) were still receiving avelumab treatment.
- Reasons for avelumab discontinuation (reported in 469/470 patients) included disease progression (73%), adverse events (11%), death (9.4%), and other reasons (6.8%).
- Median duration of avelumab treatment was 5.6 months.
- 330 patients (55.5%) received second-line treatment after avelumab (70.2% of patients who discontinued avelumab) of which:
  - 62 (18.8%) received an antibody drug conjugate (ADC) treatment.
  - 81 (24.5%) received platinum-containing chemotherapy.
  - 163 (49.4%) received non-platinum-containing chemotherapy.
  - 24 (7.3%) received other treatments.

Patient survival measured from start of avelumab first-line maintenance treatment

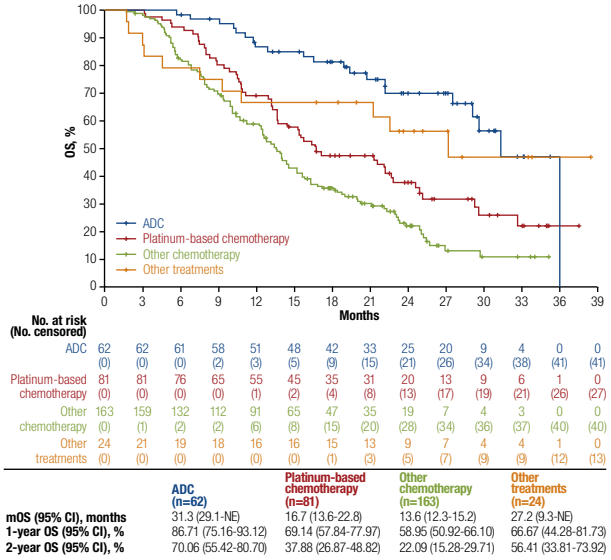
In the overall effectiveness population, median OS measured from the start of avelumab first-line maintenance treatment was 21.3 months (95% CI: 17.6–24.6):

- 1-year OS rate was 66.52% (95% CI: 62.53–70.19).
- 2-year OS rate was 45.89% (95% CI: 41.55–50.12).

Median PFS measured from start of avelumab treatment in the overall effectiveness population was 5.7 (95% CI: 5.2–6.5) months.

In the second-line treatment subgroups (**Figure 1**), median OS measured from the start of avelumab first-line maintenance treatment was:

- 31.3 months with ADC treatment.
- 16.7 months with platinum-containing chemotherapy.
- 13.6 months with non-platinum-containing chemotherapy.
- 27.2 months with other treatments.



	ADC (n=62)	Platinum-based chemotherapy (n=81)	Other chemotherapy (n=163)	Other treatments (n=24)
mOS (95% CI), months	31.3 (29.1-NE)	16.7 (13.6-22.8)	13.6 (12.3-15.2)	27.2 (9.3-NE)
1-year OS (95% CI), %	86.71 (75.16-93.12)	69.14 (57.84-77.97)	58.95 (50.92-66.10)	66.67 (44.28-81.73)
2-year OS (95% CI), %	70.06 (55.42-80.70)	37.88 (26.87-48.82)	22.09 (15.28-29.71)	56.41 (33.81-73.92)

Figure 1. OS from the start of avelumab first-line maintenance treatment in the second-line treatment groups.

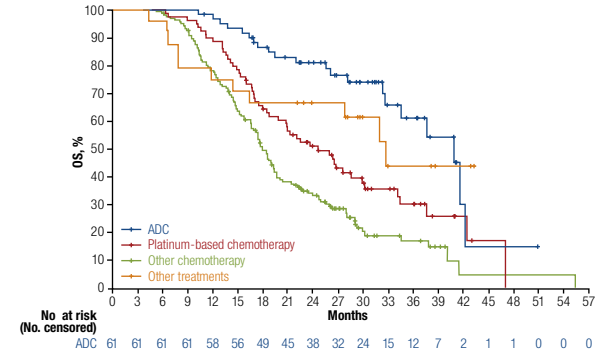
Patient survival measured from start of first-line chemotherapy

In the overall effectiveness population, median OS measured from the start of first-line chemotherapy was 26.5 months (95% CI: 23.4–30.1):

- 1-year OS rate was 79.16% (95% CI: 75.64–82.23).
- 2-year OS rate was 53.25% (95% CI: 49.02–57.30).

In the second-line treatment subgroups (**Figure 2**), median OS measured from the start of avelumab first-line maintenance treatment:

- 40.8 months (95% CI: 32.6–42.1) with ADC treatment.
- 24.5 months (95% CI: 19.8–29.8) with platinum-containing chemotherapy.
- 17.9 months (95% CI: 16.5–19.2) with non-platinum-containing chemotherapy.
- 32.6 months (95% CI: 14.3–not estimable) with other treatments.



	ADC (n=61)	Platinum-based chemotherapy (n=79)	Other chemotherapy (n=162)	Other treatments (n=24)
mOS (95% CI), months	40.8 (32.6-42.1)	24.5 (19.8-29.8)	17.9 (16.5-19.2)	32.6 (14.3-NE)
1-year OS (95% CI), %	96.69 (87.42-99.16)	88.61 (79.25-93.90)	78.17 (70.94-83.81)	75.00 (52.62-87.91)
2-year OS (95% CI), %	81.08 (68.40-89.06)	51.03 (39.39-61.53)	33.48 (26.12-40.99)	66.67 (44.28-81.73)

Figure 2. OS from the start of first-line chemotherapy in second-line treatment subgroups in the study population without disease progression after first-line chemotherapy.

Safety

Frequencies of different categories of treatment-emergent events (TEAEs) with avelumab first-line maintenance treatment in the overall safety population and second-line treatment subgroups are summarised in **Table 1**.

Table 1. Summary of TEAEs.

	Overall safety population (n=596)	2L treatment: chemotherapy (n=244)	2L treatment: ADC (n=62)	2L treatment: other (n=24)
TEAE, n (%)	507 (85.1)	201 (82.4)	55 (88.7)	20 (83.3)
Serious TEAE	305 (51.2)	147 (60.2)	36 (58.1)	12 (50.0)
TEAE leading to temporary/ permanent discontinuation	299 (50.2)	100 (41.0)	25 (40.3)	13 (54.2)
TEAE leading to death	199 (33.4)	107 (43.9)	18 (29.0)	6 (25.0)

Expert comment

Reassuringly, the AVENANCE data shows that patients treated with avelumab maintenance have similar outcomes to those documented in the JAVELIN Bladder 100 trial. Impressive OS rates. Similar PFS on avelumab with a median of 5.7 months. The data provided regarding the high OS in patients treated with an ADC (likely enfortumab vedotin) are especially encouraging in the Australian context, where access to enfortumab vedotin is currently restricted to this setting. This data reinforces the safety of maintenance avelumab and its position as the current accessible standard of care in Australia.

Study interpretation

The JAVELIN Bladder 100 trial has provided randomised controlled (RCT) evidence to support updates to international treatment guidelines,[8,9] which recommend maintenance avelumab if there is no progression on first-line platinum-containing chemotherapy.

However, RCTs of new medicines are not designed to detect all possible safety concerns and do not reflect how medicines are used in patients with complex needs.[12] Hence, following demonstration of drug efficacy and safety in RCTs, it is vital that real-world studies are conducted to evaluate how a new medicine, such as avelumab, is used in routine clinical practice to ensure its appropriate, effective, and safe use in a broader population.

The latest results from the ongoing real-world study AVENANCE support the findings of the JAVELIN Bladder 100 pivotal phase 3 trial in patients with advanced urothelial carcinoma that have not progressed with first-line platinum-containing chemotherapy and international guideline recommendations.

In AVENANCE, patients who received avelumab first-line maintenance treatment lived for an average of 21 months. Those who received subsequent treatment with an ADC lived for an average of 31 months and those subsequently treated with more platinum-containing therapy lived for an average of 17 months. When survival was measured from the start of first-line platinum-containing chemotherapy in this population without disease progression, OS was 26.5 months. Patients treated with avelumab followed by an ADC lived for an average of 41 months from the start of chemotherapy and patients treated with more platinum-containing chemotherapy after avelumab lived for an average of 24.5 months from the start of chemotherapy.

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Preliminary evidence of adoption of the new standard of care is provided by an assessment of treatment patterns and real-world patient outcomes in patients with advanced or metastatic urothelial carcinoma in the US following the approval of avelumab by the FDA in 2020.[13] The study found that most patients received standard-of-care platinum-containing chemotherapy in first-line with early uptake of avelumab as first-line maintenance therapy being observed.

A recent review of the treatment of advanced urothelial carcinoma in the Asia-Pacific region, including data suggesting that the efficacy and safety of avelumab first-line maintenance in patients from Asia and Australasia enrolled in the JAVELIN Bladder 100 trial were similar to results seen in the overall study population, prompted the authors to propose that avelumab first-line maintenance therapy should be considered as a standard-of-care in the Asia-Pacific region.[2]

Take-home messages

- With the development of targeted therapies and ICIs, the therapeutic treatment landscape for advanced urothelial carcinoma continues to evolve.
- The JAVELIN Bladder 100 phase 3 trial regimen of first-line platinum-containing chemotherapy followed by the PD-L1 inhibitor avelumab administered as switch-maintenance for patients with advanced urothelial carcinoma who have achieved at least stable disease is the current standard of care reimbursed in Australia.
- AVENANCE is an ongoing observational study assessing the real-word use of avelumab as first-line maintenance treatment in patients with advanced or metastatic urothelial carcinoma.
- The latest data reported from AVENANCE support the efficacy and safety of avelumab first-line maintenance treatment in real-world practice and indicate that:
  - Patients treated with first-line platinum-containing chemotherapy who then received avelumab as maintenance therapy lived for an average of 21 months.
  - Patients treated with first-line platinum-containing chemotherapy who then receive avelumab as maintenance therapy followed by an ADC could potentially live longer than 3 years on average.

Expert's concluding remarks

Real-world data shed a light on outcomes in patients that are underrepresented in clinical trials and reassures us that avelumab is efficacious and safe in maintaining responses in responding/stable patients post platinum chemotherapy with bladder cancer. However, sites that contribute to real-world data sets are usually large expert metropolitan academic centres that have their own selection bias. Nevertheless, avelumab remains the accessible standard of care for Australian patients with metastatic bladder cancer, especially in the context of being able to access enfortumab vedotin in the second line.

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