# Avelumab (Bavencio®) as monotherapy for the first-line maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma

## General information [1]

| Drug description [2] | Indication |
|---|---|
| Avelumab is an anti–PD-L1 antibody. | Avelumab is indicated as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum-based chemotherapy. |

## Current treatment

- ❖ Combination platinum-based chemotherapy is the standard of care for first-line treatment of advanced UC in patients who are suitable candidates for platinum-based therapy [2].
- ❖ Currently NICE does not recommend any maintenance treatment option for patients with locally advanced or metastatic UC that did not progress during or following completion of first-line chemotherapy [3].

## Regulatory status

### EMA [1]

**Approval status for this indication**: On 10 December 2020, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Bavencio®.

The CHMP adopted a new indication as follows:

- ❖ Bavencio® is indicated as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic UC who are progression-free following platinum-based chemotherapy.

**Other indications**:

- ❖ Bavencio® is indicated as monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC).
- ❖ Bavencio® in combination with axitinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).

✓ **Medicine under additional monitoring**

### FDA [4, 5]

**Approval status for this indication**: On 30 June 30 2020, the FDA approved avelumab (Bavencio®) for maintenance treatment of patients with locally advanced or metastatic UC that has not progressed with first-line platinum-containing chemotherapy.

**Other indications**: Avelumab is a PD-L1 blocking antibody indicated for:

- ❖ MCC:
  - Adults and paediatric patients 12 years and older with metastatic MCC (indication approved under accelerated approval).
- ❖ UC:
  - Patients with locally advanced or metastatic UC who:
    - o have disease progression during or following platinum-containing chemotherapy.
    - o have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- ❖ RCC:
  - First-line treatment, in combination with axitinib, of patients with advanced RCC.

## Costs

**10 ml Bavencio®** concentrate for solution for infusion 20 mg/ml = € 908.00 (ex-factory price) [6]

JAVELIN Bladder 100 trial patients in the avelumab group received avelumab at a dose of 10 mg/kg of body weight (IV, every 2 weeks) [2]. Assuming an average body weight of 80 kg, 800 mg avelumab would be needed for one dose → € 3,632.00/dose. Median duration of treatment in the avelumab group was 24.9 weeks.

## Study characteristics [2, 7-9]

| Trial name | *n* | Intervention (I) | Comparator (C) | PE | Characteristics | Biomarker | Funding | Publication(s) |
|---|---|---|---|---|---|---|---|---|
| JAVELIN Bladder 100 NCT02603432 | 700 | maintenance therapy with avelumab (at a dose of 10 mg/kg of body weight, administered IV every 2 weeks) + BSC | BSC alone | OS in the overall population and the PD-L1–positive population | international, open-label, randomized, phase 3 trial | - | Pfizer and Merck | [2] |

## Efficacy (I vs. C)

**OS at 1 year** (measured from randomization): 71.3% (95% CI, 66.0-76.0) vs. 58.4% (95% CI, 52.7-63.7)
**Median OS:** 21.4 m (95% CI, 18.9-26.1) vs. 14.3 m (95% CI, 12.9-17.9), HR for death 0.69 (95% CI, 0.56-0.86; repeated CI, 0.54-0.92; p=0.001)
**OS in the PD-L1–positive population at 1 year**: 79.1% (95% CI, 72.1-84.5) vs. 60.4% (95% CI, 52.0-67.7), HR 0.56 (95% CI, 0.40-0.79; repeated CI, 0.39-0.94; p<0.001)

## Safety (I vs. C)

**Grade ≥3 AEs**: n=163/344 (47.4%) vs. n=87/345 (25.2%)
**Serious TEAEs:** n=96/344 (27.9%) vs. n=69/345 (20.0%)
**Serious treatment-related TEAE:** n=31/344 (9.0%) vs. n=0/345 (0.0%)
**Immune-related AE:** n=101/344 (29.4%) vs. n=5/345 (1.4%)
**TEAE leading to death**: n=4/344 (1.2%) vs. n=24/345 (7.0%)

| | |
|---|---|
| **Median OS among patients with PD-L1–negative tumors**: 18.8 m (95% CI, 13.3-22.5) vs. 13.7 m (95% CI, 10.8-17.8); HR 0.85 (95% CI, 0.62-1.18)<br>**Median PFS In the overall population**: 3.7 m (95% CI, 3.5-5.5) vs. 2.0 m (95% CI, 1.9-2.7); HR 0.62 (95% CI, 0.52-0.75)<br>**Median PFS in the PD-L1–positive population:** 5.7 m (95% CI, 3.7-7.4) vs. 2.1 m (95% CI, 1.9-3.5); HR 0.56 (95% CI, 0.43-0.73)<br>**Median PFS in patients with PD-L1–negative tumors:** 3.0 m (95% CI, 2.0-3.7) vs. 1.9 m (95% CI, 1.9-2.1); HR 0.63 (95% CI, 0.47-0.85)<br>**QoL:** not reported | **Treatment-related TEAE leading to death**: n=1/344 (0.3%) vs. 0<br>**Discontinuation[1]:** n=42/344 (11.9%) vs. n=0/345 (0.0%)<br>**Treatment-related TEAE leading to discontinuation of study drug**: n=33/344 (9.6%) vs. n=0/345 (0.0%)<br>Death was attributed by the investigator to the toxicity of trial treatment in two patients (0.6%) in the avelumab group[2]. |

**ESMO-MCBS version 1.1[3]**

| Scale | Int. | Form | MG ST | MG | HR (95% CI) | Score calculation | PM | Toxicity | QoL | AJ | FM |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Original | NC | 2a | >12 m ≤24 m | OS: +7.1 m | 0.69 (0.56-0.86) | HR≤70 AND gain ≥5 m | 4 | x | NA | x | 4 |
| Adapted | NC | 2a | >12 m ≤24 m | OS: +7.1 m | 0.69 (0.56-0.86) | HR≤70 AND gain ≥5 m | 4 | grade≥3 AEs: +22.2% discontinuation: +9.6% | NA | -1 | 3 |

**Risk of bias (study level)**

| Adequate generation of randomisation sequence | Adequate allocation concealment | Blinding | Selective outcome reporting unlikely | Other aspects which increase the risk of bias | **Risk of bias** |
|---|---|---|---|---|---|
| yes | yes | no, open-label | unclear[4] | yes[5] | unclear |

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Abbreviations: AE=adverse event, AJ=adjustment, BSC=best supportive care, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HR=hazard ratio, I=intervention, Int.=intention, m=months, MCC=Merkel cell carcinoma, MG=median gain, n=number of patients, NA=not available, NICE=National Institute for Health and Care Excellence, OS=overall survival, PD-L1=programmed cell death ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, RCC=renal cell carcinoma, SAE=serious adverse event, ST=standard treatment, TEAEs=treatment-emergent adverse events, UC=urothelial carcinoma.

## References:


1. European Medicines Agency (EMA). Medicines. Bavencio. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/bavencio-0.
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5. U.S. Food and Drug Administration (FDA). FDA approves avelumab for urothelial carcinoma maintenance treatment. [Available from: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-avelumab-urothelial-carcinoma-maintenance-treatment.
6. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/.
7. Supplement to: Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med 2020;383:1218-30.
8. Protocol for: Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med 2020;383:1218-30.


[1] Discontinuation due to AE(s)

[2] 1 patient had sepsis after a urinary tract infection and possible central venous catheter infection after receiving 11 infusions of avelumab. The other patient had an ischemic stroke 100 days after receiving a single dose of avelumab and after disease progression and AEs of limb venous thrombosis, pulmonary embolism, and acute myocardial infarction.

3 The ESMO-MCBS evaluation is based on the overall study population.

[4] JAVELIN Bladder 100 trial is ongoing until 06/2022

[5] Industry-sponsored; A professional medical writer funded by the sponsors assisted with manuscript preparation.

9. U.S. National Library of Medicine, ClinicalTrials.gov. A Study Of Avelumab In Patients With Locally Advanced Or Metastatic Urothelial Cancer (JAVELIN Bladder 100) [Available from: https://clinicaltrials.gov/ct2/show/NCT02603432.