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# Avelumab first-line (1L) maintenance for advanced urothelial carcinoma (UC): analysis of clinical and genomic subgroups from the JAVELIN Bladder 100 trial

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JAVELIN Bladder 100

## SCOPE

- **This analysis reports overall survival (OS) and progression-free survival (PFS) in previously unreported clinical and genomic subgroups from the phase 3 JAVELIN Bladder 100 trial, which investigated avelumab 1L maintenance + best supportive care (BSC) vs BSC alone in patients with advanced UC that had not progressed with 1L platinum-based chemotherapy**

## CONCLUSIONS

- **An OS and PFS benefit was seen with avelumab 1L maintenance + BSC vs BSC alone across several subgroups of interest, including patients with:**
  - **Upper or lower tract disease**
  - **Metastatic disease, unresectable locally advanced (LA) disease, or lymph node–only disease**
  - **PD-L1+ tumors who received 1L gemcitabine + carboplatin**
  - **Tumor genomic subtypes defined by The Cancer Genome Atlas (TCGA),[1] except luminal**
- **Analysis of key immune biomarkers by TCGA subtype did not predict benefit with avelumab 1L maintenance**
- **These data further support avelumab 1L maintenance as a standard of care for patients with advanced UC that has not progressed with 1L platinum-containing chemotherapy**

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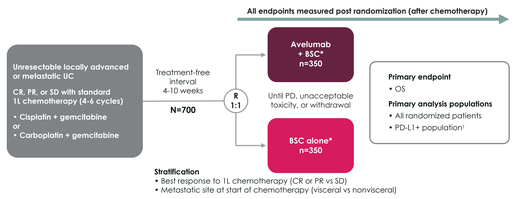
## BACKGROUND

- In the phase 3 JAVELIN Bladder 100 trial, avelumab 1L maintenance + BSC significantly prolonged OS and PFS vs BSC alone in patients with advanced UC that had not progressed with 1L platinum-based chemotherapy
  - Median OS was 21.4 vs 14.3 months, respectively; hazard ratio (HR), 0.69 (95% CI: 0.56, 0.86; 1-sided p=0.0005)[2]
  - OS benefit was previously shown in all analyzed subgroups, including patients who received cisplatin + gemcitabine or carboplatin + gemcitabine as 1L chemotherapy[3]
- Based on the results of this study, avelumab 1L maintenance was approved in the USA, Canada, Europe, Japan, and several other countries for the treatment of patients with LA or metastatic UC who are progression free following platinum-based chemotherapy[4,5]
  - Avelumab 1L maintenance is recommended as a standard of care in US and European guidelines for both cisplatin-eligible and cisplatin-ineligible patients, irrespective of PD-L1 status, based on level 1 evidence[6-8]
- Some immune checkpoint inhibitors were granted approval as 1L monotherapy for cisplatin-ineligible patients with PD-L1+ tumors and have shown similar OS to gemcitabine + carboplatin chemotherapy based on cross-trial comparisons[9-11]
- To further explore outcomes with avelumab 1L maintenance, we report post hoc analyses of the JAVELIN Bladder 100 trial in additional subgroups of interest:
  - Previously unreported clinical subgroups
  - TCGA genomic subtypes

## METHODS

- JAVELIN Bladder 100 (NCT02603432) enrolled patients with LA or metastatic UC that had not progressed with 1L chemotherapy (4-6 cycles of gemcitabine + cisplatin or carboplatin)
- Patients were randomized to receive 1L maintenance avelumab + BSC or BSC alone until disease progression, unacceptable toxicity, or withdrawal (**Figure 1**)
- The primary endpoint was OS, assessed in all randomized patients and in patients with PD-L1+ tumors
- Post hoc analyses were performed in exploratory subgroups defined by:
  - Site of primary tumor: upper vs lower urinary tract
  - Type of advanced disease: metastatic or unresectable LA disease prior to chemotherapy, or lymph node–only disease post chemotherapy
  - TCGA subtype: basal squamous, luminal, luminal infiltrated, or luminal papillary[1]
- Patients with PD-L1+ tumors who received 1L gemcitabine + carboplatin were also analyzed as a specific population of interest

**Figure 1. JAVELIN Bladder 100 phase 3 study design**




Data cutoff, October 21, 2019

**1L**, first line; **BSC**, best supportive care; **CR**, complete response; **OS**, overall survival; **PR**, partial response; **PD**, progressive disease; **R**, randomization; **SD**, stable disease; **UC**, urothelial carcinoma.

*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable.

†Assessed using the Ventana SP263 assay.

## RESULTS

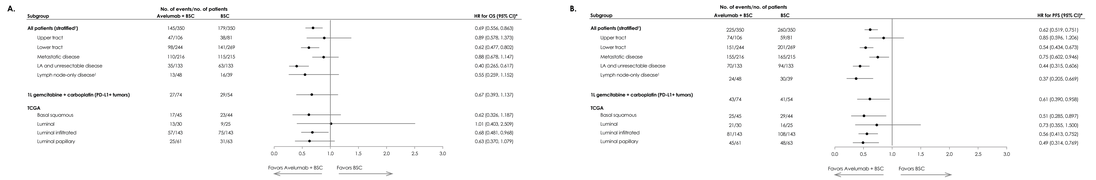
- Baseline characteristics were generally balanced between arms in subgroups of interest (**Table 1**)
- Longer OS and PFS were observed with avelumab + BSC vs BSC alone, irrespective of site of primary tumor or type of advanced disease, with a greater difference between arms in patients with lower tract primary tumors, unresectable LA disease, or lymph node–only disease post chemotherapy; however, the number of patients and events was small in some subgroups (**Figure 2**)
- Longer OS and PFS were observed with avelumab + BSC vs BSC alone in patients with PD-L1+ tumors who received 1L gemcitabine + carboplatin, and findings were consistent with the overall JAVELIN Bladder 100 trial population (**Figures 2** and **3**)
- OS and PFS analyses favored avelumab + BSC vs BSC alone in all TCGA subtypes except luminal, although numbers of patients were small in some subtypes (**Figure 4**)
- PD-L1 expression on tumor cells and CD8+ cells in the total tumor area were higher in basal squamous vs other TCGA subtypes (**Figure 5**)

**Table 1. Baseline characteristics of clinical subgroups**

| | Site of primary tumor | | | | Type of advanced disease | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Upper urinary tract | | Lower urinary tract | | Metastatic | | Unresectable LA disease prior to chemotherapy | | Lymph node only post chemotherapy | | PD-L1+, 1L gemcitabine + carboplatin | |
| n (%) | Avelumab + BSC (n=106) | BSC (n=81) | Avelumab + BSC (n=244) | BSC (N=269) | Avelumab + BSC (n=216) | BSC (n=215) | Avelumab + BSC (n=133) | BSC (n=133) | Avelumab + BSC (n=48) | BSC (n=39) | Avelumab + BSC (n=74) | BSC (n=54) |
| **Age** | | | | | | | | | | | | |
| <65 years | 43 (40.6) | 26 (32.1) | 86 (35.2) | 81 (30.1) | 90 (41.7) | 63 (29.3) | 39 (29.3) | 42 (31.6) | 17 (35.4) | 15 (38.5) | 19 (25.7) | 6 (11.1) |
| ≥65 years | 63 (59.4) | 55 (67.9) | 158 (64.8) | 188 (69.9) | 126 (58.3) | 152 (70.7) | 94 (70.7) | 91 (68.4) | 31 (64.6) | 24 (61.5) | 55 (74.3) | 48 (88.9) |
| **ECOG PS** | | | | | | | | | | | | |
| 0 | 70 (66.0) | 50 (61.7) | 143 (58.6) | 161 (59.9) | 133 (61.6) | 131 (60.9) | 80 (60.2) | 78 (58.6) | 33 (68.8) | 20 (51.3) | 39 (52.7) | 31 (57.4) |
| ≥1 | 36 (34.0) | 31 (38.3) | 101 (41.4) | 108 (40.1) | 83 (38.5) | 84 (39.1) | 53 (39.8) | 55 (41.4) | 15 (31.3) | 19 (48.7) | 35 (47.3) | 23 (41.6) |
| **Type of advanced disease** | | | | | | | | | | | | |
| Visceral | 62 (58.5) | 49 (60.5) | 129 (52.9) | 142 (52.8) | 156 (72.2) | 156 (72.6) | 34 (25.6) | 34 (25.6) | 12 (25.0) | 12 (30.8) | 30 (40.5) | 22 (40.7) |
| Nonvisceral | 44 (41.5) | 32 (39.5) | 115 (47.1) | 127 (47.2) | 60 (27.8) | 59 (27.4) | 99 (74.4) | 99 (74.4) | 36 (75.0) | 27 (69.2) | 44 (59.5) | 32 (59.3) |
| **1L chemotherapy regimen** | | | | | | | | | | | | |
| Gemcitabine + cisplatin | 51 (48.1) | 49 (60.5) | 132 (54.1) | 157 (58.4) | 112 (51.9) | 125 (58.1) | 71 (53.4) | 79 (59.4) | 24 (50.0) | 26 (66.7) | 0 | 0 |
| Gemcitabine + carboplatin | 51 (48.1) | 27 (33.3) | 96 (39.3) | 95 (35.3) | 93 (43.1) | 75 (34.9) | 53 (39.8) | 47 (35.3) | 21 (43.8) | 13 (33.3) | 74 (100.0) | 54 (100.0) |
| **Best response to 1L chemotherapy** | | | | | | | | | | | | |
| CR or PR | 74 (69.8) | 59 (72.8) | 179 (73.4) | 193 (71.7) | 158 (73.1) | 152 (70.7) | 94 (70.7) | 98 (73.6) | 31 (64.6) | 26 (66.7) | 55 (74.3) | 35 (64.8) |
| SD | 32 (30.2) | 22 (27.2) | 65 (26.6) | 76 (28.3) | 58 (26.9) | 63 (29.3) | 39 (29.3) | 35 (26.3) | 17 (35.4) | 13 (33.3) | 19 (25.7) | 19 (35.2) |
| **PD-L1 status** | | | | | | | | | | | | |
| Positive | 44 (41.5) | 35 (43.2) | 145 (59.4) | 134 (49.8) | 101 (46.8) | 96 (44.7) | 88 (66.2) | 72 (54.1) | 36 (75.0) | 24 (61.5) | 74 (100.0) | 54 (100.0) |
| Negative | 54 (50.9) | 30 (37.0) | 85 (34.8) | 101 (37.5) | 102 (47.2) | 91 (42.3) | 37 (27.8) | 40 (30.1) | 10 (20.8) | 11 (28.2) | 0 | 0 |
| Unknown | 8 (7.5) | 16 (19.8) | 14 (5.7) | 34 (12.6) | 13 (6.0) | 28 (13.0) | 8 (6.0) | 21 (15.8) | 2 (4.2) | 4 (10.3) | 0 | 0 |

**1L**, first line; **BSC**, best supportive care; **CR**, complete response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **LA**, locally advanced; **PR**, partial response; **SD**, stable disease.

**Figure 2. Forest plots of (A) OS and (B) PFS based on BICR in subgroups of interest**



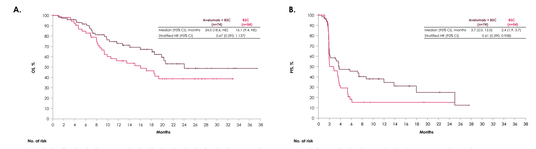

**1L**, first line; **BICR**, blinded independent central review; **BSC**, best supportive care; **HR**, hazard ratio; **OS**, overall survival; **PFS**, progression-free survival; **TCGA**, The Cancer Genome Atlas.

*HRs and CIs were calculated using a Cox proportional hazards model.

†Stratified by best response to 1L chemotherapy (complete or partial response vs stable disease) and metastatic disease site (visceral vs nonvisceral).

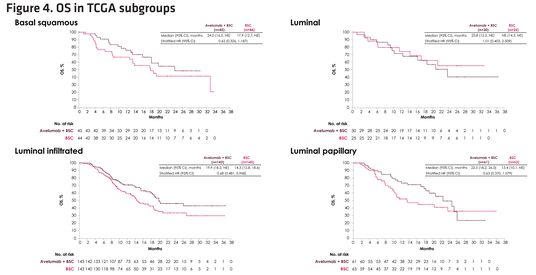
‡Post chemotherapy.

**Figure 3. OS (A) and PFS (B) in patients with PD-L1+ tumors who received 1L gemcitabine + carboplatin**



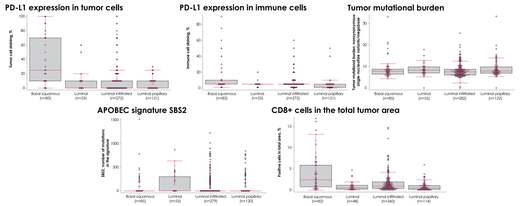

**1L**, first line; **BSC**, best supportive care; **HR**, hazard ratio; **NE**, not estimable; **OS**, overall survival; **PFS**, progression-free survival.

**Figure 4. OS in TCGA subgroups**




**BSC**, best supportive care; **HR**, hazard ratio; **NE**, not estimable; **OS**, overall survival; **TCGA**, The Cancer Genome Atlas.

**Figure 5. Biomarker expression in TCGA subtypes**




**TCGA**, The Cancer Genome Atlas.

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