Avelumab first-line maintenance for advanced urothelial carcinoma: long-term follow-up results from the JAVELIN Bladder 100 trial

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JAVELIN Bladder 100

SCOPE

- **We report long-term data from the JAVELIN Bladder 100 trial, which compared avelumab first-line (1L) maintenance + best supportive care (BSC) vs BSC alone in patients with advanced urothelial carcinoma (UC) that had not progressed with 1L platinum-containing chemotherapy**

CONCLUSIONS

- **Long-term follow-up from the JAVELIN Bladder 100 trial (≥2 years in all patients) continues to show prolonged overall survival (OS) and progression-free survival (PFS) with avelumab 1L maintenance + BSC vs BSC alone**
  - **OS rates at 2 years were 49.8% in the avelumab + BSC arm vs 38.4% in the BSC alone arm; 2-year PFS rates were 23.4% vs 7.1%, respectively**
  - **OS was prolonged with avelumab 1L maintenance despite a high proportion of patients treated with BSC alone receiving a subsequent anticancer drug therapy (avelumab + BSC, 52.9%; BSC, 72.0%), particularly PD-1/PD-L1 inhibitors (11.4% vs 53.1%)**
- **Long-term safety of avelumab 1L maintenance was demonstrated, with 19.5% of patients receiving ≥2 years of treatment and a low rate of discontinuation due to treatment-related adverse events (TRAEs)**
  - **No new safety signals were identified**
- **These results further support the recommendation of avelumab 1L maintenance as standard of care for patients with advanced UC that has not progressed with 1L platinum-containing chemotherapy**

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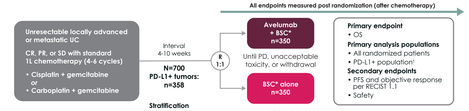
BACKGROUND

- In the JAVELIN Bladder 100 trial, avelumab 1L maintenance + BSC significantly prolonged OS vs BSC alone in patients with advanced UC that had not progressed with 1L platinum-containing chemotherapy[1]
  - In the initial analysis (data cutoff, October 21, 2019), median OS was 21.4 vs 14.3 months, respectively (hazard ratio [HR], 0.69 [95% CI, 0.56-0.86]; 2-sided p=0.001)
- Subsequently, avelumab 1L maintenance was approved in various countries worldwide for the treatment of patients with locally advanced or metastatic UC who are progression free following platinum-containing chemotherapy
- Avelumab 1L maintenance is now considered standard of care in international treatment guidelines[2-5]
- We report updated JAVELIN Bladder 100 data from an exploratory analysis with ≥2 years of follow-up in all patients (additional 19 months of median follow-up from the initial analysis), enabling assessment of longer-term efficacy and safety

METHODS

- In the phase 3 JAVELIN Bladder 100 trial (NCT02603432), enrolled patients had unresectable locally advanced or metastatic UC that had not progressed with 4-6 cycles of 1L gemcitabine + cisplatin or carboplatin
- Patients were randomized 1:1 to receive avelumab 1L maintenance + BSC or BSC alone after an interval of 4-10 weeks from the end of 1L chemotherapy (**Figure 1**)
- The primary endpoint was OS, assessed from randomization in all patients and patients with PD-L1+ tumors
  - For these long-term follow-up analyses, PFS analysis was based on investigator assessment
- Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03

Figure 1. JAVELIN Bladder 100 study design[1]



1L, first line; **BSC**, best supportive care; **CR**, complete response; **OS**, overall survival; **PD**, progressive disease; **PFS**, progression-free survival; **PR**, partial response; **R**, randomization; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumors version 1.1; **SD**, stable disease; **UC**, urothelial carcinoma.
*BSC (eg, antibiotics, nutritional support, hydration, and 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.
†PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively (Ventana SP263 assay).

RESULTS

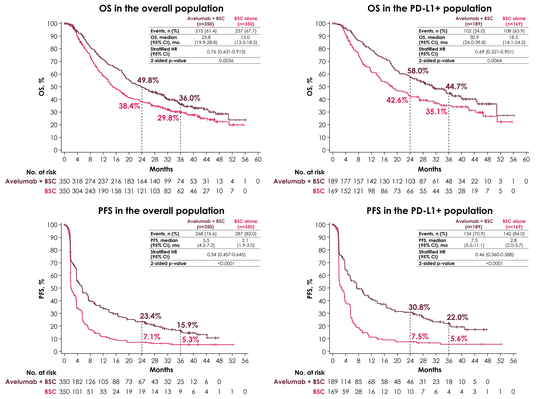
- Baseline characteristics are shown in **Table 1**
- At data cutoff (June 4, 2021), median follow-up in all randomized patients was 38.0 months (95% CI, 36.1-40.5) with avelumab + BSC and 39.6 months (95% CI, 36.2-41.7) with BSC alone
- Treatment was ongoing in 43 patients (12.3%) in the avelumab + BSC arm and 10 (2.9%) in the BSC alone arm
- The most common reason for treatment discontinuation in both arms was disease progression (avelumab + BSC, 59.7%; BSC, 78.6%)
- Median duration of avelumab treatment was 25.3 weeks (range, 2.0-216.0)
  - 67 patients (19.5%) had received ≥2 years of avelumab treatment
- OS was prolonged in the avelumab + BSC arm vs BSC alone arm in all patients and patients with PD-L1+ tumors (**Figure 2A** and **2B**)
  - In the overall population, median OS was 23.8 months (95% CI, 19.9-28.8) in the avelumab + BSC arm vs 15.0 months (95% CI, 13.5-18.2) in the BSC alone arm (HR, 0.76 [0.631-0.915])
- OS favored avelumab + BSC vs BSC alone across subgroups (**Figure 3**), and a similar OS benefit was seen across subgroups defined by best response to 1L chemotherapy (**Table 2**)
- Restricted mean survival time in the overall population was 28.8 months (95% CI, 16.6-31.0) in the avelumab + BSC arm vs 24.1 months (95% CI, 21.9-26.3) in the BSC alone arm (2-sided p=0.0029)
  - In the PD-L1+ population, restricted mean survival time was 32.4 months (95% CI, 29.4-35.4) vs 26.4 months (95% CI, 23.2-29.7), respectively (2-sided p=0.0080)
- Investigator-assessed PFS was also prolonged with avelumab + BSC vs BSC alone (**Figure 2C** and **2D**)

Table 1. Baseline characteristics

	All patients (N=700)		PD-L1+ population (n=358)	
	Avelumab + BSC (n=350)	BSC alone (n=350)	Avelumab + BSC (n=189)	BSC alone (n=169)
Age, years				
Median (range)	68 (37-90)	69 (32-89)	70 (37-90)	70 (32-84)
Site of primary tumor, n (%)*				
Upper tract	106 (30.3)	81 (23.1)	44 (23.3)	35 (20.7)
Lower tract	244 (69.7)	269 (76.9)	145 (76.7)	134 (79.3)
Site of metastasis at start of chemotherapy, n (%)				
Visceral	191 (54.6)	191 (54.6)	88 (46.6)	79 (46.7)
Nonvisceral	159 (45.4)	159 (45.4)	101 (53.4)	90 (53.3)
PD-L1 status, n (%)				
Positive	189 (54.0)	169 (48.3)	189 (100)	169 (100)
Negative	139 (39.7)	131 (37.4)	0	0
Unknown	22 (6.3)	50 (14.3)	0	0
1L chemotherapy regimen, n (%)				
Gemcitabine + cisplatin	183 (52.3)	206 (58.9)	101 (53.4)	98 (58.0)
Gemcitabine + carboplatin	147 (42.0)	122 (34.9)	74 (39.2)	54 (32.0)
Gemcitabine + cisplatin + carboplatin†	20 (5.7)	20 (5.7)	14 (7.4)	15 (8.9)
Not reported	0	2 (0.6)	0	2 (1.2)
Best response to 1L chemotherapy, n (%)				
CR	90 (25.7)	89 (25.4)	60 (31.7)	53 (31.4)
PR	163 (46.6)	163 (46.6)	79 (41.8)	75 (44.4)
SD	97 (27.7)	98 (28.0)	50 (26.5)	41 (24.3)

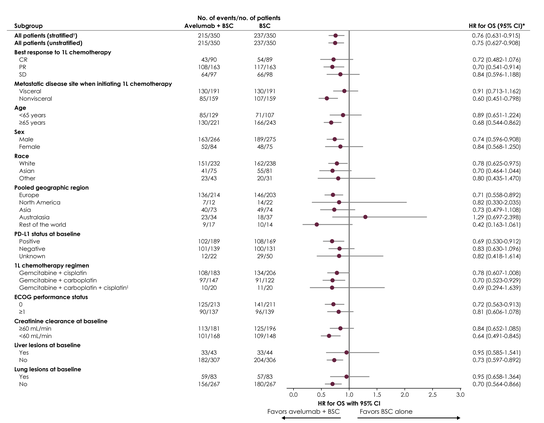
Data cutoff, October 21, 2019.
1L, first line; **BSC**, best supportive care; **CR**, complete response; **PR**, partial response; **SD**, stable disease.
*The upper tract was defined as the renal pelvis or ureter, and the lower tract as the bladder, urethra, or prostate gland.
†Patients who switched platinum regimens while receiving 1L chemotherapy.

Figure 2. OS and investigator-assessed PFS in the overall population and the PD-L1+ population



BSC, best supportive care; **HR**, hazard ratio; **OS**, overall survival; **PFS**, progression-free survival.

Figure 3. Subgroup analysis of OS in the overall population



1L, first line; **BSC**, best supportive care; **CR**, complete response; **ECOG**, Eastern Cooperative Oncology Group; **HR**, hazard ratio; **OS**, overall survival; **PR**, partial response; **SD**, stable disease.
*HRs and CIs were calculated using a Cox proportional hazards model.
†Stratified by best response to 1L chemotherapy (CR or PR vs SD) and metastatic disease site when initiating 1L chemotherapy (visceral vs nonvisceral).
‡Patients who switched platinum regimens while receiving 1L chemotherapy.

Table 2. OS in subgroups defined by best response to 1L chemotherapy in the overall population

	Median OS (95% CI), months		
	Avelumab + BSC	BSC alone	HR (95% CI)
Best response to 1L chemotherapy			
Complete response (n=179)	39.8 (28.5-NE)	26.8 (18.5-33.6)	0.72 (0.482-1.076)
Partial response (n=326)	19.2 (16.0-23.8)	12.8 (10.3-14.8)	0.70 (0.541-0.914)
Stable disease (n=195)	22.3 (18.2-28.8)	14.0 (10.6-19.6)	0.84 (0.596-1.188)

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

- More patients in the BSC alone arm than in the avelumab + BSC arm received a subsequent anticancer drug therapy, commonly PD-1/PD-L1 inhibitors (**Table 3**)
- In patients with ≥12 months of treatment with avelumab + BSC (n=118):
  - Any-grade treatment-emergent AEs (TEAEs) with onset after ≥12 months occurred in 102 patients (86.4%), including grade ≥3 TEAEs in 56 (47.5%) (**Table 4**)
  - Any-grade TRAEs with onset after ≥12 months occurred in 59 patients (50.0%), including grade ≥3 TRAEs in 14 (11.9%)
  - The most common TEAEs with onset after ≥12 months of treatment with avelumab + BSC were urinary tract infection and diarrhea (n=15 [12.7%] each) (**Table 5**)
- 1 patient (0.8%) had a TRAE after ≥12 months of treatment with avelumab + BSC that led to death (attributed to immune-mediated nephritis by the treating investigator)

Table 3. Subsequent anticancer therapy

	All patients (N=700)		Subgroup that received subsequent therapy (n=437)		Subgroup that discontinued study treatment due to PD (n=484)	
	Avelumab + BSC (n=350)	BSC alone (n=350)	Avelumab + BSC (n=185)	BSC alone (n=252)	Avelumab + BSC (n=209)	BSC alone (n=275)
Discontinued and received subsequent drug therapy, n (%)	185 (52.9)	252 (72.0)	185 (100)	252 (100)	158 (75.6)	225 (81.8)
PD-1 or PD-L1 inhibitor	40 (11.4)	186 (53.1)	40 (21.6)	186 (73.8)	27 (12.9)	166 (60.4)
FGFR inhibitor	10 (2.9)	13 (3.7)	10 (5.4)	13 (5.2)	10 (4.8)	11 (4.0)
Any other drug	177 (50.6)*	156 (44.6)†	177 (95.7)	156 (61.9)	151 (72.2)	139 (50.5)
Study treatment ongoing, n (%)	43 (12.3)	10 (2.9)	–	–	–	–

BSC, best supportive care; **FGFR**, fibroblast growth factor receptor; **PD**, progressive disease.
*The most common other drugs received were gemcitabine (n=87), carboplatin (n=66), paclitaxel (n=60), vinflunine (n=46), and cisplatin (n=37).
†The most common other drugs received were gemcitabine (n=67), paclitaxel (n=59), carboplatin (n=48), cisplatin (n=28), and vinflunine (n=22).

Table 4. Summary of AEs overall and with onset after ≥12 months of treatment with avelumab + BSC

	Avelumab + BSC	
Events, n (%)	Onset after ≥12 months of treatment (n=118)*	Onset at any time (n=344)†
TEAE of any grade	102 (86.4)	338 (98.3)
Grade ≥3 TEAE	56 (47.5)	185 (53.8)
TRAE of any grade	59 (50.0)	269 (78.2)
Grade ≥3 TRAE	14 (11.9)	67 (19.5)
Serious TEAE	28 (23.7)	105 (30.5)
Serious TRAE	6 (5.1)	35 (10.2)
TEAE leading to interruption of avelumab	43 (36.4)	156 (45.3)
TEAE leading to discontinuation	13 (11.0)	49 (14.2)
TRAE leading to discontinuation	12 (10.2)	40 (11.6)
TEAE leading to death	3 (2.5)	7 (2.0)
TRAE leading to death	1 (0.8)	2 (0.6)
Infusion-related reaction of any grade	4 (3.4)	75 (21.8)

AE, adverse event; **BSC**, best supportive care; **TEAE**, treatment-emergent adverse event; **TRAE**, treatment-related adverse event.
*Patients with ≥12 months of treatment.
†All treated patients.

Table 5. Most common TEAEs with onset after ≥12 months of treatment with avelumab + BSC

	Avelumab + BSC (n=118)	
Events, n (%)	Any grade	Grade ≥3
Any TEAE	102 (86.4)	56 (47.5)
Urinary tract infection	15 (12.7)	3 (2.5)
Diarrhea	15 (12.7)	1 (0.8)
Arthralgia	14 (11.9)	1 (0.8)
Back pain	14 (11.9)	0
Cough	14 (11.9)	0
Pruritus	14 (11.9)	0
Nasopharyngitis	12 (10.2)	0

Table shows TEAEs of any grade occurring in ≥10% of patients with ≥12 months of treatment.
BSC, best supportive care; **TEAE**, treatment-emergent adverse event.

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