Primary analysis of post-marketing surveillance data for avelumab maintenance therapy in patients with curatively unresectable urothelial carcinoma in Japan

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CONCLUSIONS

- **In post-marketing surveillance (PMS) of avelumab maintenance therapy in patients with curatively unresectable urothelial carcinoma (UC) treated in clinical practice in Japan (N=453), the observed safety and effectiveness were consistent with results from the phase 3 JAVELIN Bladder 100 trial and real-world studies in other countries[1-7]**
  - **The PMS population was heterogeneous and included patients who would have been excluded from JAVELIN Bladder 100,[1] including patients with Eastern Cooperative Oncology Group performance status ≥2 (3.8%) or stage III disease (6.2%)**
- **The safety profile of avelumab was consistent with previous reports,[1-5] and no additional safety concerns were identified**
  - **The most common any-grade prespecified adverse drug reactions (ADRs) were infusion reactions (IRs) and thyroid dysfunction, which were observed in comparable proportions to JAVELIN Bladder 100 (IR in 11.7% vs infusion-related reaction in 21.5%; thyroid dysfunction in 7.3% vs 16.6%, respectively)[1]**
- **Median time to treatment failure (TTF) from the start of avelumab treatment was 4.6 months (95% CI, 3.8-5.3 months)**
- **The 12-month overall survival (OS) rate (77.9%) was comparable to the 12-month OS rates reported in the JAVELIN Bladder 100 trial (71.3%) and other real-world studies (65.6%-72.5%)[5-7]**
- **56.6% of patients discontinued avelumab maintenance therapy and received next-line therapy, which included chemotherapy, enfortumab vedotin, and pembrolizumab**
- **Overall, results from the PMS demonstrate the acceptable safety, tolerability, and effectiveness of avelumab maintenance therapy in a heterogeneous population and support its continued use in clinical practice in Japan**

PLAIN LANGUAGE SUMMARY

- Based on results from the JAVELIN Bladder 100 clinical trial, avelumab maintenance is considered a standard therapy for people with advanced urothelial cancer that disappeared, shrank, or stopped growing with chemotherapy
- In this study, investigators looked at people in Japan with advanced urothelial cancer who received avelumab maintenance therapy in routine clinical practice, outside of a clinical trial
- Avelumab was safe and worked well across groups of people who had different characteristics or differences in their chemotherapy treatment
  - The most common side effects were infusion reaction and thyroid dysfunction
  - 78% of people were still alive after 12 months of avelumab treatment
- Overall, these results provide more support for using avelumab maintenance therapy in people with advanced urothelial cancer in clinical practice in Japan

BACKGROUND

- In the phase 3 JAVELIN Bladder 100 trial, avelumab first-line (1L) maintenance therapy + best supportive care (BSC) significantly prolonged OS and progression-free survival (PFS) vs BSC alone in patients with unresectable locally advanced or metastatic UC that had not progressed with 1L platinum-based chemotherapy[1,2]
  - After ≥2 years of follow-up in all patients, median OS was 23.8 vs 15.0 months (hazard ratio [HR], 0.76 [95% CI, 0.63-0.91]; p=0.0036), and median PFS was 5.5 vs 2.1 months (HR, 0.54 [95% CI, 0.46-0.64]; p<0.0001), respectively[2]
  - The long-term safety of avelumab 1L maintenance was also demonstrated
  - Results from JAVELIN Bladder 100 led to the approval of avelumab 1L maintenance therapy worldwide, and it is recommended in international treatment guidelines based on level 1 evidence[8-11]
- In a post hoc subgroup analysis from JAVELIN Bladder 100, efficacy and safety results in patients enrolled in Japan (n=73) were generally consistent with those reported in the overall population[12]
  - Median OS was 24.7 vs 18.7 (unstratified HR, 0.81 [95% CI, 0.41-1.58]), and median PFS was 5.6 vs 1.9 months (unstratified HR, 0.63 [95% CI, 0.36-1.11])
- In Japan, avelumab maintenance therapy was approved for patients with curatively unresectable UC who were progression free after prior chemotherapy in February 2021, and it is recommended in Japanese Urological Association treatment guidelines[6]
- Because a limited number of patients in JAVELIN Bladder 100 trial were enrolled in Japan (avelumab + BSC arm, n=36),[7] PMS was performed in accordance with Good Post-marketing Study Practice to obtain real-world data from patients receiving avelumab maintenance therapy in clinical practice
- Here we report results from the primary analysis of PMS of avelumab maintenance therapy in Japan
  - The primary objective was to evaluate the safety of avelumab maintenance, and the secondary objective was to evaluate effectiveness

METHODS

- This prospective, multicenter, noninterventional PMS evaluated all patients with curatively unresectable UC who received ≥1 dose of avelumab maintenance therapy in Japan between February 2021 and December 2021
  - The observation period was ≤52 weeks from the first dose of avelumab
  - This PMS was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR: UMIN 43435) and was carried out in accordance with the Good Postmarketing Study Practice Ministerial Ordinance in Japan
  - Data were collected by case report forms. The approval of the ethical committee/institutional review board and informed consent was obtained based on requirements of each institution
- Safety data were collected for prespecified ADRs included in safety specifications defined in the Japanese Risk Management Plan as well as hematuria and urinary tract infection that were deemed to be associated with avelumab. ADRs were aggregated by system organ class and preferred term and were presented as overall frequency and percentages, worst grade, and time of onset
- Effectiveness data, including TTF and OS, were estimated using the Kaplan-Meier method (including medians and rates) and 95% CIs were calculated

RESULTS

- Of 465 case report forms collected across 213 medical facilities, 453 were evaluable for safety and effectiveness at data cutoff (6 March 2024); patients who did not provide informed consent for publication (n=9) or received off-label avelumab (n=3) were excluded
- Median duration of avelumab maintenance therapy was 5.1 months (IQR, 2.3-12.0 months)
- Prior platinum-based chemotherapy was gemcitabine + cisplatin in 267 patients (58.9%); gemcitabine + carboplatin in 163 (36.0%); and dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin ([dd]MVAC) in 9 (2.0%) (**Table 1**)
- The number of prior treatment cycles overall and in subgroups of patients with complete response, partial response, or stable disease after prior chemotherapy are shown in **Figure 1**
  - Overall, 284 patients (62.7%) received 4-6 prior cycles of chemotherapy, with most patients receiving 4 cycles of prior chemotherapy (175 patients [38.6%])

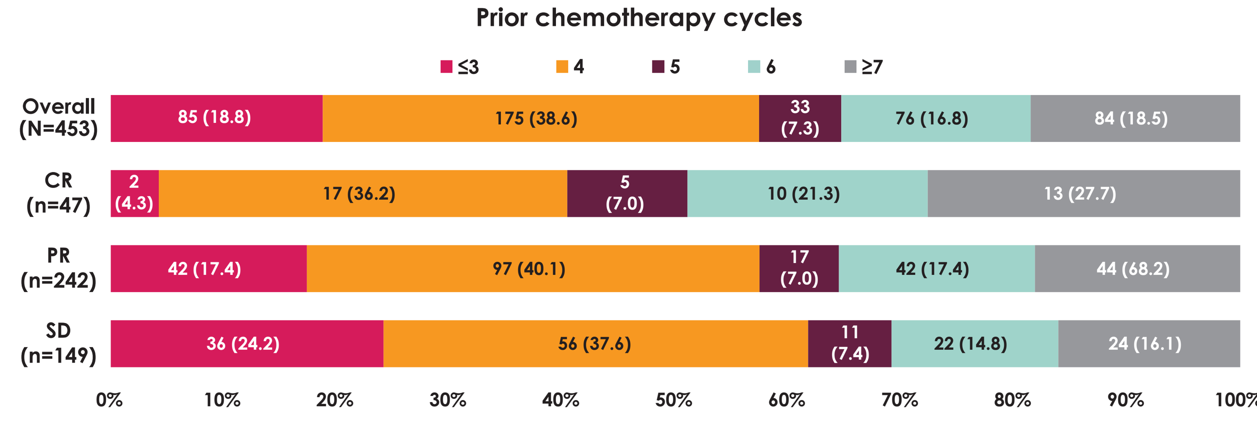
Table 1. Patient baseline characteristics at the start of avelumab maintenance therapy

Baseline characteristics	N=453
Age, median (range), years	73.0 (21-91)
≤64, n (%)	75 (16.6)
65-74, n (%)	198 (43.7)
≥75, n (%)	180 (39.7)
BMI, median (range), kg/m²	22.8 (9.8-33.9)
Sex, n (%)	
Male	333 (73.5)
Female	120 (26.5)
ECOG PS, n (%)	
0	325 (71.7)
1	111 (24.5)
≥2	17 (3.8)
Primary tumor site, n (%)	
Bladder	244 (53.9)
Upper tract	209 (46.1)
Metastatic lesion, n (%)	
No	44 (9.7)
Yes*	409 (90.3)
Site of metastatic lesion, n (%)	
Lung	109 (26.7)
Bone	55 (13.4)
Liver	39 (9.5)
Lymph node	309 (75.6)
Other	51 (11.3)

Baseline characteristics	N=453
Disease stage, n (%)†	
III	28 (6.2)
IV	404 (89.2)
Comorbidity, n (%)‡	
Renal impairment	166 (36.6)
Hepatic impairment	12 (2.6)
Interstitial lung disease	6 (1.3)
Autoimmune disease	4 (0.9)
Other disease	188 (41.5)
Prior treatment, n (%)‡	
Surgery	333 (73.5)
Radiation therapy	63 (13.9)
Prior chemotherapy regimen, n (%)§	
Gemcitabine + cisplatin	267 (58.9)
Gemcitabine + carboplatin	163 (36.0)
(dd)MVAC	9 (2.0)
BOR to prior chemotherapy, n (%)‖	
CR	47 (10.4)
PR	242 (53.4)
SD	149 (32.9)
Treatment-free interval, n (%)§	
<4 weeks	204 (45.0)
4 to <6 weeks	96 (21.2)
6 to <8weeks	67 (14.8)
8 to 10 weeks	26 (5.7)
>10 weeks	60 (13.2)

BMI, body mass index; **BOR**, best overall response; **CR**, complete response; **(dd)MVAC**, dose-dense methotrexate, vinblastine, doxorubicin; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **PR**, partial response; **SD**, stable disease.
*Patients with ≥1 metastatic lesion were included. †Data were unavailable in 21 patients. ‡Patients with ≥1 category were included. §Data were unavailable in 14 patients. ‖Data were unavailable in 15 patients. §Time between the last dose of chemotherapy and first dose of avelumab.

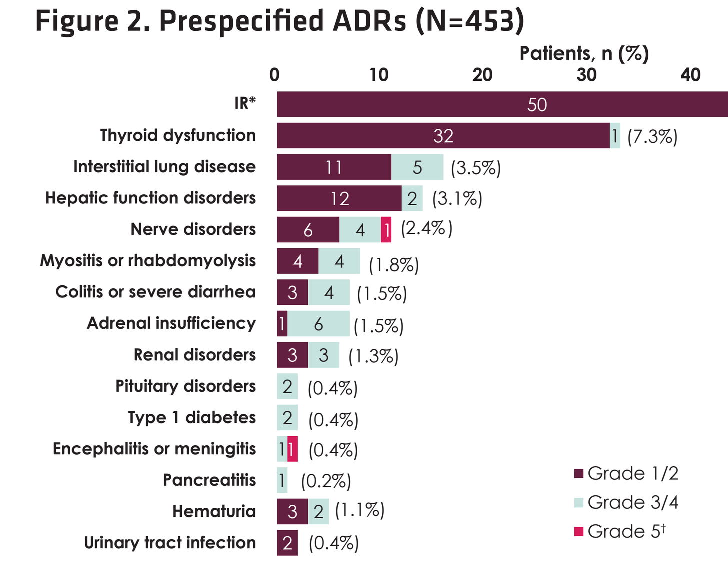
Figure 1. Number of prior chemotherapy cycles prior to starting avelumab maintenance therapy by BOR to chemotherapy (N=453)



BOR data were missing or unavailable in 15 patients (3.3%).
BOR, best overall response; **CR**, complete response; **PR**, partial response; **SD**, stable disease.
*Percentages may not total 100% due to rounding.

- Any-grade prespecified ADRs were observed in 144 patients (31.8%) and were grade ≥3 in 35 (7.7%) (**Figure 2**)
  - The most common any-grade prespecified ADRs (≥5.0% of patients) were IR in 53 patients (11.7%) and thyroid dysfunction in 33 patients (7.3%)
  - The most common grade 3/4 prespecified ADRs (≥1.0% of patients) were adrenal insufficiency in 6 patients (1.3%) and interstitial lung disease in 5 patients (1.1%)
  - One grade 5 prespecified ADR was observed in 1 patient (noninfective encephalitis), which was categorized as a prespecified ADR of both nerve disorder and encephalitis
- Median TTF was 4.6 months (95% CI, 3.8-5.3 months) and the 12-month TTF rate was 25.9% (95% CI, 21.4%-30.7%) (**Figure 3A**)
- The 6- and 12-month OS rates were 89.2% (95% CI, 86.0%-91.8%) and 77.9% (95% CI, 73.7%-81.5%), respectively (**Figure 3B**)

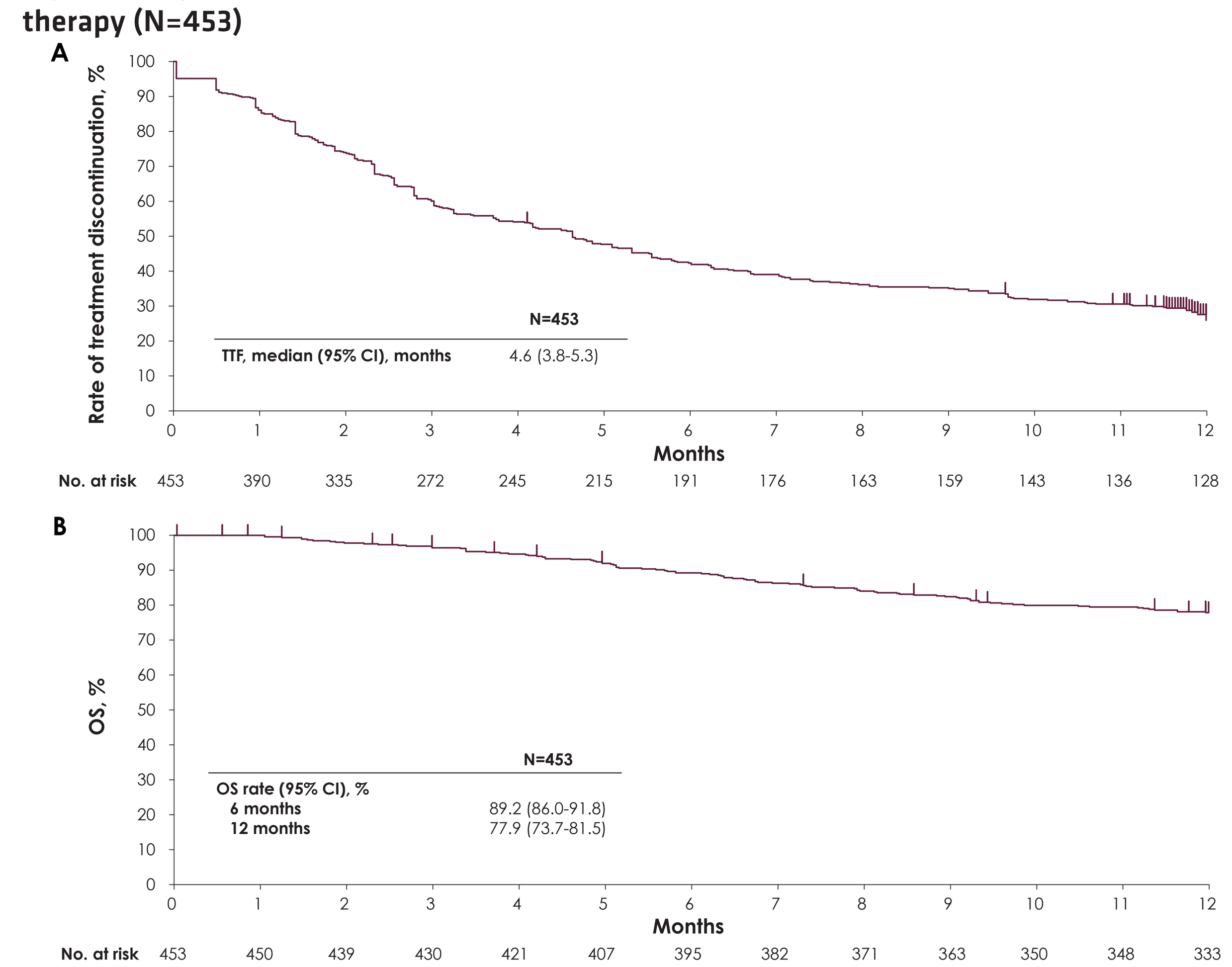
Figure 2. Prespecified ADRs (N=453)



	n (%)
Any-grade prespecified ADRs	144 (31.8)
Grade ≥3 prespecified ADRs	35 (7.7)
ADR leading to death	1 (0.2)
Any-dose steroid treatment	38 (8.4)
High-dose steroid treatment‡	19 (4.2)
Administered for IR	4 (0.9)
Administered for ADR other than IR	15 (3.3)

ADR, adverse drug reaction **IR**, infusion reaction.
*IR includes infusion-related reaction, chills, and pyrexia.†One grade 5 ADR was observed in 1 patient (noninfective encephalitis), which was categorized as a prespecified ADR of both nerve disorder and encephalitis. ‡Patients received ≥40 mg total daily dose of prednisone or equivalent.

Figure 3. Kaplan-Meier analysis of (A) TTF* and (B) OS from start of avelumab maintenance therapy (N=453)



OS, overall survival; **TTF**, time to treatment failure.
*Time from start of avelumab treatment to end of avelumab treatment for any reason.

- At data cutoff, 128 patients (28.3%) were still receiving avelumab treatment (**Table 2**)
  - Of the 325 patients (71.7%) who discontinued avelumab, the most common reason was disease progression in 225 patients (49.7%), followed by prespecified ADRs in 32 (7.1%)
- 184 patients (56.6% of 325 patients who discontinued avelumab) received subsequent treatment; 154/225 patients (68.4%) who discontinued because of disease progression and 13/32 (40.6%) who discontinued because of prespecified ADRs received subsequent treatment (**Table 3**)
- The most common next-line treatments were gemcitabine + cisplatin in 53 patients (16.3% of 325 patients who discontinued avelumab), enfortumab vedotin in 44 (13.5%), gemcitabine + carboplatin in 34 (10.5%), and pembrolizumab in 30 (9.2%)
- Corticosteroid treatment was administered for prespecified ADRs in 38 of 453 total patients (8.4%), of whom 19 (4.2%) received high-dose corticosteroid treatment (≥40 mg total daily dose of prednisone or equivalent) (**Figure 2**)

Table 2. Treatment disposition

	N=453
Avelumab treatment ongoing, n (%)	128 (28.3)
Avelumab treatment discontinued, n (%)	325 (71.7)
Reason for discontinuation, n (%)*	
Disease progression	225 (49.7)
Prespecified ADRs	32 (7.1)
Surgery	7 (1.5)
Patient preference	25 (5.5)
Death	4 (0.9)
Transfer to another hospital	5 (1.1)
Other	32 (7.1)

ADR, adverse drug reaction.
*Patients with >1 reason for discontinuation are included in >1 row.

Table 3. Next-line subsequent treatment after discontinuation of avelumab maintenance therapy

	Patients who discontinued avelumab maintenance therapy (n=325)*	Reason for discontinuation	
		Progressive disease (n=225)	Prespecified ADRs (n=32)
Received subsequent anticancer drug treatment, n (%)	184 (56.6)†	154 (68.4)‡	13 (40.6)§
Type of subsequent treatment received, n (%)			
Chemotherapy	109 (33.5)	89 (39.6)	8 (25.0)
Gemcitabine + cisplatin	53 (16.3)	43 (19.1)	3 (9.4)
Gemcitabine + carboplatin	34 (10.5)	29 (12.9)	3 (9.4)
Chemotherapy (other combination)	14 (4.3)	13 (5.8)	1 (3.1)
Chemotherapy (monotherapy)	8 (2.5)	4 (1.8)	1 (3.1)
Enfortumab vedotin	44 (13.5)	39 (17.3)	3 (9.4)
Pembrolizumab	30 (9.2)	25 (11.1)	2 (6.3)
Other	1 (0.3)	1 (0.4)	0

ADR, adverse drug reaction.
*Includes 68 patients who discontinued for reasons other than disease progression or prespecified ADRs. †Includes 17 patients who discontinued for reasons other than disease progression or prespecified ADRs; percentage calculated using total number of patients who discontinued avelumab (n=325). ‡Percentage calculated using total number of patients who discontinued avelumab due to disease progression (n=225). §Percentage calculated using total number of patients who discontinued treatment due to prespecified ADRs (n=32).

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DISCLOSURES E. Kikuchi has served in consulting or advisory roles for Astellas Pharma, AstraZeneca, Bristol Myers Squibb-Ono Pharmaceutical, Chugai Pharmaceutical, Janssen, Merck, MSD, and Pfizer; speakers bureau participation for Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb-Ono Pharmaceutical, Chugai Pharmaceutical, Janssen, Kissei Pharmaceutical, Kyorin, Kyowa Kirin International, Merck, MSD, Nippon Kayaku, Nippon Shinyaku, Pfizer, Sanofi, Taiho Pharmaceutical, and Takeda; and has received institutional research funding from Chugai Pharmaceutical, Kissei Pharmaceutical, Kyorin, Kyowa Kirin International, Nippon Kayaku, Nippon Shinyaku, Otsuka, Sanofi, Taiho Pharmaceutical, and Takeda. **M. Nagata** has reported speakers services for Janssen and Sanofi. **T. Ito, M. Sato, M. Morita, M. Ogi,** and **M. Kajita** report employment by Merck Biopharma Co., Ltd., Tokyo, Japan, an affiliate of Merck KGaA. **H. Nishiyama** has reported speakers bureau participation for Astellas Pharma, Bristol Myers Squibb, Merck, MSD, and Ono Pharmaceutical; and has received research funding from Astellas Pharma and Chugai Pharmaceutical. **ACKNOWLEDGMENTS** This work was supported by Merck Biopharma Co., Ltd., Tokyo, Japan, an affiliate of Merck KGaA (CrossRef Funder ID: 10.13039/100009945) and was previously conducted under an alliance between Merck and Pfizer. Editorial support was provided by Nucleus Global and was funded by Merck.

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