AVENANCE: subgroup analysis of patients with advanced urothelial carcinoma with histological variants from a real-world study of avelumab first-line maintenance

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SCOPE

- **We present a subgroup analysis of patients with histological variants from AVENANCE, an ongoing real-world, ambispective (retrospective and prospective) study evaluating the effectiveness and safety of avelumab first-line (1L) maintenance in patients with advanced urothelial carcinoma (UC) in France**

CONCLUSIONS

- **Real-world data from AVENANCE provide evidence of the effectiveness and safety of avelumab 1L maintenance in patients with advanced UC with histological variants that had not progressed following 1L platinum-based chemotherapy**
- **To our knowledge, this is the first analysis of avelumab 1L maintenance in this patient population**
- **These subgroup data are consistent with findings in the overall AVENANCE population[1] and further support the recommendation of avelumab 1L maintenance as standard of care in patients with advanced UC following disease control with 1L platinum-based chemotherapy, including those with histological variants**

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BACKGROUND

- Histological variants of UC are tumors that arise from within the urothelium but have some component of morphology that is not urothelial (ie, nonpure UC)[2]
  - Tumors with histological variants can be mixed or have a predominant histological subtype (ie, pure variant)
    - Approximately 10%-25% of bladder cancers have nonpure UC histology[2-4]
  - These tumors are often underdiagnosed and aggressive, and are frequently excluded from prospective clinical trials,[2,3] representing an unmet medical need
- In the phase 3 JAVELIN Bladder 100 trial (NCT02603432), avelumab 1L maintenance + best supportive care (BSC) significantly prolonged overall survival (OS) vs BSC alone in patients with advanced UC that had not progressed with 1L platinum-based chemotherapy[5,6]
  - After ≥2 years of follow-up in all patients, median OS (measured from randomization) was 23.8 vs 15.0 months, respectively (hazard ratio [HR], 0.76 [95% CI, 0.63-0.91]; p=0.0036), and median progression-free survival (PFS) was 5.5 vs 2.1 months (HR, 0.54 [95% CI, 0.46-0.64]; p<0.0001)[6]
  - In a post hoc analysis, median OS with the full JAVELIN Bladder regimen (1L platinum-based chemotherapy followed by avelumab 1L maintenance) was 29.7 months[7]
  - Trial results led to the recommendation of avelumab 1L maintenance as standard of care in international treatment guidelines[8-10]
- AVENANCE (NCT04822350) is an ongoing real-world study evaluating the effectiveness and safety of avelumab 1L maintenance in patients with advanced UC in France
  - Previous results have shown the clinical activity and acceptable safety profile of avelumab 1L maintenance in a large cohort of patients (N=593) from a heterogeneous population[1]
    - Median OS from the start of avelumab treatment was 20.7 months (95% CI, 17.1 months-not estimable [NE]), and the 12-month OS rate was 65.4% (95% CI, 61.0%-69.4%)
    - Median PFS from the start of avelumab treatment was 5.7 months (95% CI, 5.3-7.0 months)
    - The safety profile was consistent with that observed in other studies of avelumab monotherapy[11]; no new safety concerns were identified

METHODS

- AVENANCE is an ongoing multicenter, ambispective, noninterventional study
- Eligible patients have locally advanced or metastatic UC that has not progressed with 1L platinum-based chemotherapy (ie, ongoing complete response, partial response, or stable disease) and have previous, ongoing, or planned avelumab 1L maintenance treatment
- Data collection started on 13 July 2021, and data cutoff for this analysis was 31 May 2023
- The primary endpoint is OS from the start of avelumab treatment
- Secondary endpoints include PFS from the start of avelumab treatment, duration of treatment, and safety
- Effectiveness and safety were analyzed in patients who had received ≥1 dose of avelumab
- Patients with histological variants (mixed UC with variants [UC-V] and pure variants [PV]) were analyzed
- Data reported here are preliminary and analyses are ongoing

RESULTS

- 44 of 594 patients in AVENANCE had histological variants
- Baseline characteristics of and tumor histology in patients with histological variants are shown in **Table 1**
  - Tumor histology was UC-V (including epidermoid and micropapillary) in 29 patients (65.9%) and PV in 15 (34.1%)
  - The most common 1L platinum-based chemotherapy regimen was carboplatin + gemcitabine (UC-V, n=17 [58.6%]; PV, n=11 [78.6%])
- As of the data cutoff (31 May 2023), median follow-up from start of avelumab 1L maintenance (by reverse Kaplan-Meier estimation) was 22.5 months (95% CI, 19.4-28.3 months) in all patients with histological variants, 21.5 months (95% CI, 18.8 months-NE) in patients with UC-V, and 24.4 months (95% CI, 14.7-29.4 months) in patients with PV

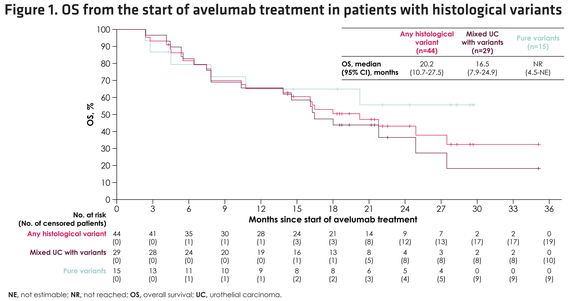
Table 1. Baseline characteristics and tumor histology

	Any histological variant (n=44)	Mixed UC with variants (n=29)	Pure variants (n=15)
Age, median (Q1-Q3), years	73.8 (67.4-79.4)	74.3 (65.0-79.8)	73.8 (68.0-79.1)
Sex, n (%)			
Male	34 (77.3)	24 (82.8)	10 (66.7)
Female	10 (22.7)	5 (17.2)	5 (33.3)
Location of primary tumor, n (%)			
Bladder	38 (86.4)	26 (89.7)	12 (80.0)
Upper tract	6 (13.6)	3 (10.3)	3 (20.0)
Tumor histology, n (%)			
UC with variant*	29 (65.9)	29 (100)	0
Epidermoid carcinoma	5 (11.4)	0	5 (33.3)
Pure adenocarcinoma	1 (2.3)	0	1 (6.7)
Pure small cell neuroendocrine carcinoma	1 (2.3)	0	1 (6.7)
Other	8 (18.2)	0	8 (53.3)
ECOG PS at start of 1L chemotherapy, n (%)			
0	9 (25.0)	5 (19.2)	4 (40.0)
1	17 (47.2)	14 (53.8)	3 (30.0)
2	10 (27.8)	7 (26.9)	3 (30.0)
Missing	8	3	5
Tumor status at start of 1L chemotherapy, n (%)			
Locally advanced	2 (4.7)	1 (3.4)	1 (7.1)
Metastatic	41 (95.3)	28 (96.6)	13 (92.9)
Missing	1	0	1
Presence of visceral metastasis at start of 1L chemotherapy, n (%)	**n=41**	**n=28**	**n=13**
Yes	36 (87.8)	25 (89.3)	11 (84.6)
No	5 (12.2)	3 (10.7)	2 (15.4)
Type of 1L chemotherapy, n (%)			
Cisplatin + gemcitabine	8 (18.6)	7 (24.1)	1 (7.1)
Carboplatin + gemcitabine	28 (65.1)	17 (58.6)	11 (78.6)
MVAC	4 (9.3)	4 (13.8)	0
Other	3 (7.0)	1 (3.4)	2 (14.3)
Missing	1	0	1
No. of 1L chemotherapy cycles, median (range)	5 (3-10)	5 (3-10)	6 (4-7)
Response to last chemotherapy, n (%)			
Complete response	9 (20.9)	7 (24.1)	2 (14.3)
Partial response	27 (62.8)	16 (55.2)	11 (78.6)
Stable disease	7 (16.3)	6 (20.7)	1 (7.1)
Missing	1	0	1

Percentages reported were calculated using the denominator of patients with available data for each characteristic.
1L, first line; **MVAC**, methotrexate, vinblastine, doxorubicin, and cisplatin; **UC**, urothelial carcinoma.
*Includes micropapillary, epidermoid, and other variant types.

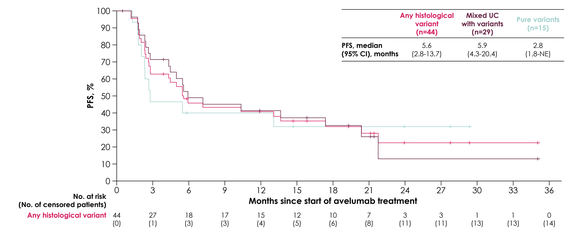
- Median duration of treatment was 5.1 months (95% CI, 2.8-13.4 months) in all patients with histological variants, 5.7 months (95% CI, 3.7-17.4 months) in patients with UC-V, and 5.1 months (95% CI, 1.4-24.0 months) in patients with PV
- At data cutoff, 12 of 44 patients (27.3%) were still receiving treatment
  - In the 32 patients who had discontinued, reasons were disease progression (n=24 [75.0%]), adverse event (AE; n=4 [12.5%]), death (n=2 [6.3%]), patient's decision (n=1 [3.1%]), and other (n=1 [3.1%])
- Median OS in all 44 patients with histological variants was 20.2 months (95% CI, 10.7-27.5 months) (**Figure 1**), with a 12-month OS rate of 65.3% (95% CI, 49.1%-77.4%)
  - Median OS was 16.5 months (95% CI, 7.9-24.9 months) in patients with UC-V and not reached (95% CI, 4.5 months-NE) in patients with PV
- Median PFS in all 44 patients with histological variants was 5.6 months (95% CI, 2.8-13.7 months) (**Figure 2**)
  - Median PFS was 5.9 months (95% CI, 4.3-20.4 months) in patients with UC-V and 2.8 months (95% CI, 1.8 months-NE) in patients with PV
- 20 patients (45.5%) reported receiving subsequent treatment

Figure 1. OS from the start of avelumab treatment in patients with histological variants



NE, not estimable; **NR**, not reached; **OS**, overall survival; **UC**, urothelial carcinoma.

Figure 2. PFS from the start of avelumab treatment in patients with histological variants



NE, not estimable; **PFS**, progression-free survival; **UC**, urothelial carcinoma.

- A summary of safety data is presented in **Table 2**
  - Any-grade treatment-emergent AEs (TEAEs) occurred in 37 patients with histological variants (84.1%), including serious TEAEs in 22 (50.0%)
    - The most common TEAE of any grade was asthenia (n=11 [25.0%]) (**Table 3**)
  - Any-grade treatment-related and treatment-emergent AEs (TRAEs) occurred in 24 patients with histological variants (54.5%), including serious TRAEs in 5 (11.4%)
    - One patient (2.3%) had a TRAE that led to death (attributed to pneumonia)

Table 2. Summary of AEs

Patients, n (%)	Any histological variant (n=44)	Mixed UC with variants (n=29)	Pure variants (n=15)
TEAE*	37 (84.1)	23 (79.3)	14 (93.3)
Serious TEAE	22 (50.0)	14 (48.3)	8 (53.3)
TEAE leading to temporary/permanent discontinuation	23 (52.3)	14 (48.3)	9 (60.0)
TEAE leading to death	11 (25.0)	9 (31.0)	2 (13.3)
TRAE	24 (54.5)	16 (55.2)	8 (53.3)
Serious TRAE	5 (11.4)	5 (17.2)	0
TRAE leading to temporary/permanent discontinuation	15 (34.1)	10 (34.5)	5 (33.3)
TRAE leading to death	1 (2.3)	1 (3.4)	0

AE, adverse event; **TEAE**, treatment-emergent adverse event; **TRAE**, treatment-related and treatment-emergent adverse event; **UC**, urothelial carcinoma.
*AEs were considered "treatment emergent" if their start date was on or after avelumab initiation.

Table 3. Most common TEAEs of any grade

Patients, n (%)	Any histological variant (n=44)	Mixed UC with variants (n=29)	Pure variants (n=15)
Any TEAE	37 (84.1)	23 (79.3)	14 (93.3)
Asthenia	11 (25.0)	9 (31.0)	2 (13.3)
Intentional product misuse	11 (25.0)	7 (24.1)	4 (26.7)
Diarrhea	9 (20.5)	6 (20.7)	3 (20.0)
Neoplasm progression	7 (15.9)	6 (20.7)	1 (6.7)
Constipation	6 (13.6)	3 (10.3)	3 (20.0)
Pruritis	6 (13.6)	3 (10.3)	3 (20.0)
COVID-19	5 (11.4)	5 (17.2)	0
Urinary tract infection	5 (11.4)	1 (3.4)	4 (26.7)
Arthralgia	4 (9.1)	2 (6.9)	2 (13.3)
Nausea	4 (9.1)	2 (6.9)	2 (13.3)
Anemia	3 (6.8)	3 (10.3)	0
General physical health deterioration	3 (6.8)	2 (6.9)	1 (6.7)
Hematuria	3 (6.8)	2 (6.9)	1 (6.7)
Pelvic pain	3 (6.8)	1 (3.4)	2 (13.3)
Peripheral neuropathy	3 (6.8)	1 (3.4)	2 (13.3)
Not coded	7 (15.9)	4 (13.8)	3 (20.0)

Table shows TEAEs of any grade occurring in ≥5% of all patients with histological variants.
TEAE, treatment-emergent adverse event; **UC**, urothelial carcinoma.

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DISCLOSURES P. Barthélémy has served in consulting or advisory roles for Amgen, Bristol Myers Squibb, Ipsen, Janssen-Cilag, Merck, MSD, and Pfizer; has received travel and accommodations expenses from Astellas Pharma, Bristol Myers Squibb, Ipsen, Janssen-Cilag, MSD, and Pfizer; and has received honoraria from Astellas Pharma, Bristol Myers Squibb, Ipsen, Janssen-Cilag, Merck, MSD, Novartis, Pfizer, and Seagen. **Y. Loriot** has served in consulting or advisory roles for Astellas Pharma, Bristol Myers Squibb, Immunomedics, Janssen, Janssen (institution), Loxo/Lilly, Merck, MSD, MSD (institution), Pfizer, Roche, Seagen, and Taiho Pharmaceutical; has received travel and accommodations expenses from Astellas Pharma, Janssen Oncology, MSD, Roche, and Seagen; and has received institutional research funding from Astellas Pharma, Basilea, Bristol Myers Squibb, Exelixis, Gilead Sciences, Incyte, Janssen Oncology, Merck, MSD, Nektar, Pfizer, Roche, Sanofi, Seagen, and Taiho Pharmaceutical. **A. Fléchon** has received travel and accommodations expenses from AAA HealthCare, Astellas Pharma, Bayer, Bristol Myers Squibb, Ipsen, Janssen-Cilag, MSD, Pfizer, Roche/Genentech, and Sanofi/Aventis; and has received honoraria from AAA HealthCare, Astellas Pharma, Bayer, Bristol Myers Squibb, Ipsen, Janssen-Cilag, MSD, Pfizer, Roche/Genentech, and Sanofi/Aventis. **M. Gross-Goupil** has served in consulting or advisory roles for Amgen, Astellas Pharma, AstraZeneca, Bristol Myers Squibb, EISAI, Ipsen, Janssen-Cilag, Merck, MSD, and Pfizer; has received travel and accommodations expenses from Astellas Pharma, Bristol Myers Squibb, Ipsen, Janssen-Cilag, Merck, MSD, and Pfizer; and has provided speakers services for Astellas Pharma, AstraZeneca, Bristol Myers Squibb, EISAI, Ipsen, and Janssen-Cilag. **E. Voog** has nothing to declare. **J.-C. Eymard** has served in consulting or advisory roles for Astellas Pharma, Ipsen, Janssen, and Sanofi; and has received institutional research funding from Bristol Myers Squibb, Ipsen, and Pfizer. **V. Lorgis** has nothing to declare. **D. Pouessel** has served in consulting or advisory roles for Astellas Pharma, AstraZeneca, MSD, and Pfizer; has provided speakers services for Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Ipsen, Janssen, Merck, MSD, and Pfizer; has received travel and accommodations expenses from MSD and Pfizer; and has received institutional research funding from MSD. **L. Francois** has received honoraria for boards from Ipsen, Janssen, Merck, MSD, and Pfizer. **C. Sajous** has served in consulting or advisory roles for Bristol Myers Squibb, Dalichi Sankyo, Lilly, Merck, and Pfizer; and has received travel and accommodations expenses from Merck and Pfizer. **D. Chocteau** has nothing to declare. **A. Guillot** has nothing to declare. **J. Long** has nothing to declare. **E. Amela** has nothing to declare. **C. Josse** reports employment with eXYSTAT and has received institutional research funding from Pfizer. **M.-N. Solbes** reports employment with Merck Santé S.A.S., Lyon, France, an affiliate of Merck KGaA. **P. Lambert** reports employment with Pfizer. **C. Thibault** has served in consulting or advisory roles for AAA, AstraZeneca, Bristol Myers Squibb, Ipsen, Merck, MSD, and Pfizer; has provided speakers services for Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Ipsen, Janssen, MSD, and Sanofi; and has received institutional research funding from AstraZeneca and Sanofi.

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