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RESEARCH ARTICLE

Avelumab maintenance in advanced urothelial carcinoma: real-world data from Northern Spain (AVEBLADDER study)

Marta Sotelo[1] · Mireia Pelaez[2] · Laura Basterretxea[3] · Estrella Varga[4] · Ricardo Sánchez-Escribano[5] · Eduardo Pujol Obis[6] · Carmen Santander[7] · Mireia Martínez Kareaga[8] · Mikel Arruti Ibarbia[9] · Inmaculada Rodríguez Ledesma[10] · Carlos Álvarez Fernández[11] · Pablo Piedra[4] · Verónica Calderero Aragón[12] · Nuria Lainez[4] · Juan Antonio Verdún Aguilar[13] · Irene Gil Arnáiz[14] · Ricardo Fernández[15] · Cristina Mazas[2] · Ignacio Duran[1]

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Abstract

Background Before the incorporation of enfortumab vedotin with pembrolizumab, the standard of care for patients with locally advanced or metastatic urothelial carcinoma who do not progress after platinum-based chemotherapy was avelumab maintenance therapy, as demonstrated by the JAVELIN 100 trial. However, real-world European data remain scarce.

Patients and Methods AVEBLADDER is a retrospective study conducted at 14 hospitals in Northern Spain, including patients with locally advanced or metastatic urothelial carcinoma diagnosed between January 2021 and June 2023. Outcomes of overall survival (OS) and progression-free survival (PFS) were analyzed for patients treated with platinum-based chemotherapy, with and without subsequent avelumab maintenance therapy. non-avelumab patients. Median PFS was 11.33 months (95% CI: 10–13.6) with avelumab and 6.43 months (95% CI: 6–7.6) without. One-year OS probabilities were 81.6% vs. 45.6% ($p < 0.001$) in the avelumab and non-avelumab groups, respectively. No unexpected toxicities were reported.

Conclusions Despite proven survival benefits, avelumab uptake in real-world practice is limited by barriers like access, reimbursement, and awareness. These findings align with JAVELIN 100 and underscore the need for further real-world studies to address treatment disparities.

Keywords Avelumab · Locally advanced/metastatic urothelial cancer · Treatment outcomes · Real-world data

Introduction

Bladder cancer is the 10 th most common cancer worldwide with an estimated 573,000 new cases and 213,000 deaths in 2020, showing higher incidence rates in men and in developed regions such as Europe. In Europe, bladder cancer represents one of the most frequently diagnosed cancers, with the highest incidence rates observed in Southern and Western Europe, largely attributed to smoking and occupational exposures as significant risk factors [1, 2]. Bladder

✉ Ignacio Duran
ignaciojose.duran@scsalud.es

1 Hospital Universitario Marqués de Valdecilla and IDIVAL, Santander, Spain
2 Universidad Europea del Atlántico, Santander, Spain
3 Hospital Universitario de Donostia, Donostia, Spain
4 Hospital Universitario de Navarra, Pamplona, Spain
5 Hospital Universitario de Valladolid, Valladolid, Spain
6 Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain
7 Hospital Universitario Miguel Servet, Zaragoza, Spain
8 Hospital Universitario de Araba-Txagorritxu, Araba, Spain
9 Hospital Galdakao-Usansolo, Bizkaia, Spain
10 Hospital Universitario de Burgos, Burgos, Spain
11 Hospital Universitario Central de Asturias, Oviedo, Spain
12 Hospital Universitario San Jorge, Huesca, Spain
13 Hospital de Alcañiz, Teruel, Spain
14 Hospital Reina Sofía de Tudela, Navarra, Spain
15 Hospital Universitario de Cruces, Bilbao, Spain

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cancer remains one of the most frequently diagnosed cancers in Spain. In 2024, it is estimated that there will be 22,097 new cases of bladder cancer, making it one of the top five most common cancers in the country, following colorectal, breast, lung, and prostate cancers [3].

Platinum-containing chemotherapy for 4–6 cycles stands as the established treatment for individuals with locally advanced or metastatic urothelial carcinoma (mUC) [4]. While this treatment leads to disease control (either response or stabilization), in about 75–80% of patients, most will experience disease progression within nine months. This results in limited survival, around 14–15 months for cisplatin-based regimens and 9–10 months for those with carboplatin [5, 6].

Until recently, no novel agent had improved survival when added concurrently to platinum-based chemotherapy in the first-line treatment of mUC. Pembrolizumab or atezolizumab combined with chemotherapy did not significantly improve overall survival [7, 8]. Avelumab emerged as a new option as switch-maintenance therapy as ICIs could be more effective after tumor reduction by chemotherapy [9, 10]. In the JAVELIN Bladder 100 study, avelumab was compared to best supportive care in patients with locally advanced or mUC who had already benefited from first-line chemotherapy. Avelumab showed a significant reduction in the risk of with a median survival of 21.4 months compared to 14.3 months with supportive care. This effect was even more pronounced in patients whose tumors expressed PD-L1 [11]. Based on this data, avelumab received FDA approval in 2020 and EMA approval in 2021 for the treatment on first-line maintenance in mUC patients whose disease had not progressed following first-line platinum-based chemotherapy [12, 13]. A recent article with two years of follow-up from the JAVELIN 100 study confirmed that benefit without unexpected signs of toxicity [14].

First-line treatment options have changed with FDA approval in December 2023 and by the European Commission in August 2024, of enfortumab vedotin and pembrolizumab for patients with locally advanced or mUC [15, 16]. In addition, in March 2024, the FDA approved the use of nivolumab in combination with cisplatin and gemcitabine for patients with unresectable or mUC based on the results of the checkmate 901 study, marking a major breakthrough in immunotherapy-chemotherapy combinations [17, 18]. These trials collectively underscore the evolving landscape of immunotherapy in advanced or metastatic urothelial carcinoma and the promising role of avelumab.

In Spain avelumab was approved in June 2022, previously accessible through compassionate use programs, and granted reimbursement specifically for patients with locally advanced or mUC who have benefited from platinum-based chemotherapy, initially only in those whose tumors express PD-L1 until September 2023 when that limitation was eliminated. Yet as of today, though, we lack real-world data that would enable us to assess the actual use, effectiveness, and safety of this medication in clinical practice outside of controlled clinical studies.

The aim of this study was to characterize the health outcomes, treatment regimens, and clinical characteristics of patients with locally advanced or mUC in Northern Spain, with a particular focus on the appropriate use of avelumab as maintenance therapy in eligible patients.

Patients and methods

Study design and population

This retrospective cohort study (AVEBLADDER) included adult patients (≥ 18 years) with the following inclusion criteria: diagnosed with advanced or mUC, candidates for systemic treatment, data between January 1 st, 2021 and June 30 th, 2023 (study inclusion period) and treated in one of the 14 centers of Northern Spain. Patients were followed until death, loss to follow-up, or the study's end (November 30, 2023). Clinical data was gathered from electronic health records.

Study aims

To analyze real-world data on the patterns of use of avelumab maintenance in patients with locally advanced or mUC treated in Northern Spain.

Data collection

Epidemiological (demographic characteristics: age, gender, risk factors); histological subtype, tumor extension and management, sites of metastasis, and type of systemic treatment received. Radiologic response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. In patients who achieved a complete response after first-line chemotherapy and showed no evidence of disease in subsequent imaging, the response was categorized as non-evaluable in accordance with the methodology used in the JAVELIN Bladder 100 trial. Safety data were also collected."

Statistical analysis

Patients' demographics and other study characteristics have been analyzed using descriptive statistics for categorical and quantitative (continuous) variables. Continuous variables have been described using the mean, median, standard deviation, minimum, and maximum, as well as the lower and upper quartiles. Categorical variables have been described

using their frequency distribution, as well as the 95% CI for the variables related to the main objective of the study. Median overall survival (OS) and progression-free survival (PFS) were determined using the Kaplan–Meier method. Specific OS and PFS analyses calculated from the initiation of avelumab maintenance therapy, following the same methodology used in the JAVELIN Bladder 100 study. Dedicated graphs illustrating these findings have been generated and are now included in the manuscript. In addition, overall OS and PFS analyses calculated from the time of diagnosis to the event (death or progression) across the entire study population, comparing outcomes between patients who received avelumab and those who did not. The statistical analysis has been carried out using the statistical package Libre R, version 4.3.1.

Results

Patient data

A total of 443 patients from 14 centers located in Northern Spain were enrolled. Twenty patients were excluded (7 did not meet the inclusion criteria [patients with locally advanced or mUC diagnosed between January 1, 2021, and June 30, 2023] and 17 did not receive treatment). Finally, a total of 419 patients were included in the analysis.

Patients' characteristics

A total of 80% of the patients were male. The median age at diagnosis was 71 years. The most common location for the primary tumor in the study population is the lower urinary tract (bladder and urethra) (83.1%). The most frequent histology was urothelial (94%). 45% of the patients had had advanced disease at the time of diagnosis**.** Visceral or bony metastases were present in 73% of patients, while 27% had lymph node-only disease. Around ninety percent of the patients were active (26%) or previous smokers (60%) and 32% referred drinking habits. According to Galsky criteria, 58% of the population was classified as unfit (Table 1). At the end of the study period, 53.7% of patients (n = 225) had died, and 46.3% (n = 194) were still alive. Of the living patients, 13% (n = 25) are disease-free, which represents 6% of the total population. Among the deceased patients, 88.5% (n = 199) died from UC, 9% (n = 20) from other causes including sepsis, respiratory, cardiac, and cerebrovascular diseases, and 2.67% (n = 6) died from unknown reasons. The mean follow-up duration was 11.1 months (95% CI: 10.3 to 11.9), and the median follow-up was 9 months.

Table 1 Baseline demographic and clinical characteristics

Variables	Total N = 419	Avelumab patients N = 85
Median age, IQR	71 (42–88)	72 (42–88)
Gender, n (%)		
Male	336 (80.2%)	72 (84.3%)
Female	83 (19.8%)	13 (15.3%)
ECOG PS, n (%)		
0	76 (18.1%)	24 (28.2%)
1	238 (56.8%)	51 (60.0%)
≥ 2	99 (23.7%)	8 (9.4%)
Not available	6 (1.4%)	2 (2.3%)
Creatinine clearance, n (%)		
< 60 ml/min	193 (46.1%)	35 (41.2%)
≥ 60 ml/min	226 (53.9%)	50 (58.8%)
Tumor histology, n (%)		
Urothelial	399 (93.8%)	81 (95.3%)
Squamous cell carcinoma	11 (2.6%)	0 (0.0%)
Small cell carcinoma	3 (0.7%)	0 (0.0%)
Adenocarcinoma	3 (0.7%)	0 (0.0%)
Other variants	9 (2.1%)	4 (4.7%)
Disease stage at diagnosis, n (%)		
Locally advanced/metastatic	190 (45.3%)	41 (48.2%)
Muscle invasive	165 (39.4%)	25 (29.4%)
Non-muscle invasive	64 (15.3%)	20 (22.3%)
Location primary tumor, n (%)		
Lower urinary tract	344 (82.1%)	77 (90.6%)
Upper urinary tract	71 (16.9%)	8 (9.4%)
Both upper and lower urinary tract	4 (1.0%)	0 (0.0%)
Most frequent metastatic location[a], n (%)		
Only lymph nodes	114 (27.2%)	34 (40%)
Visceral metastases	305 (72.8%)	51 (60%)
Galsky classification, n (%)		
Unfit	243 (58.0%)	39 (45.9%)
Fit	176 (42.0%)	46 (54.1%)
PD-L1 status, n (%)		
Positive	95 (22.7%)	59 (69.4%)
Negative	101 (24.1%)	5 (5.9%)
Not available	223 (53.2%)	21 (24.7)

[a]A more detailed breakdown of visceral metastasis distribution is provided in the main text

Treatment characteristics and outcomes

Figure 1 represents a Sankey diagram that depicts the treatments received in first, second, and subsequent lines.

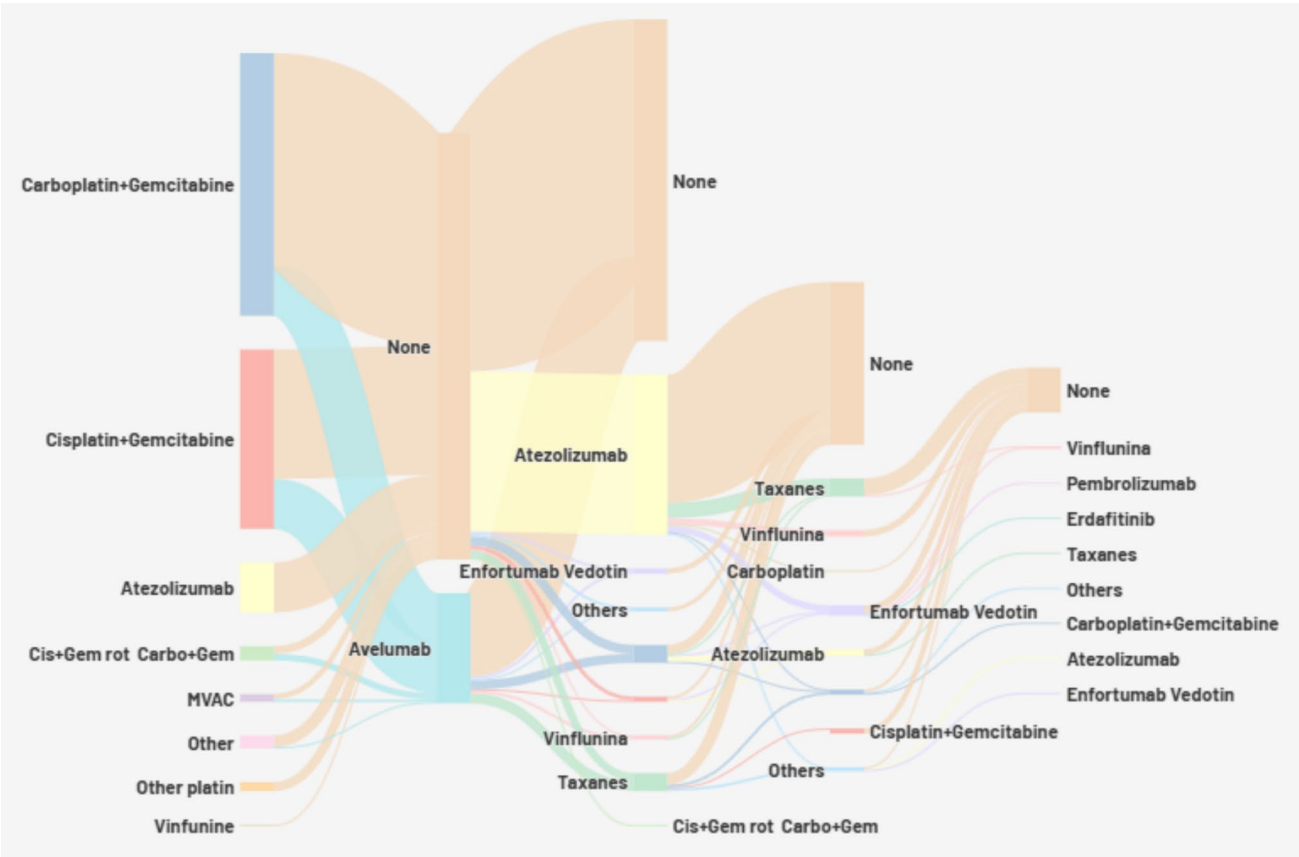


Fig. 1 Sankey diagram: treatments received in first, second, and subsequent lines

First line treatment

A total of 370 patients (88%) received chemotherapy-based treatments, 39 patients received anti-PD-L1 antibody atezolizumab (9.3%), and 10 patients (2.4%) received other treatments as first-line therapy. Patients completing platinum-based treatment (n = 347) received an average of 4.25 cycles (SD 1.57), with a median of 4 cycles (range: 1 to 10 cycles). The percentage of patients receiving ≥ 4 cycles was 71%.

Complete responses were seen in 6.7% of cases overall, with higher rates in the other platinum-based group (28.6%). Partial responses occurred in 38.7% of cases, particularly with cisplatin + gemcitabine (47.1%) and MVAC (50%). Stable disease was observed in 16.0%, while progressive disease occurred in 26.0%. Instances of not evaluable or no response occurred in 10.5% of cases, and undocumented responses were rare at 2.1% overall (Table 2).

Avelumab maintenance treatment

In the study population, 229 patients (62%) who achieved non-progression with platinum-based chemotherapy, defined as any response (complete or partial) or stable disease, were identified as candidates for avelumab maintenance therapy. Of these, 85 patients (37%) received avelumab. The reasons for not receiving avelumab among eligible patients included negative PD-L1 status (53 patients, 36.5%), lack of access or reimbursement (32 patients, 22.1%), progression after first-line therapy prior to avelumab initiation (23 patients, 15.9%), patient decisions (3 patients, 2.1%) and other reasons, mainly exitus (34 patients, 23.4%). Baseline characteristics of these 85 patients who received avelumab maintenance therapy are presented in Table 1.

At the time of analysis, 47 patients (55%) were still receiving avelumab treatment. Among those who discontinued avelumab (n = 39), the most common reasons were disease progression (64.1%) and toxicity (23.0%). The median number of avelumab cycles received was 7.5 (range: 1–49 cycles). For discontinued patients, the median number of cycles was 6 (range: 1–29). The best responses to avelumab were as follows: CR: 7 (8.2%), PR: 12 (14.1%), SD: 22 (25.9%), and PD: 17 (20.0%).

Table 2 First line treatment and best response achieved

Treatment	N (%)	CR	PR	SD	PD	NE/NR	ND
Cisplatin + Gemcitabine	140 (33.4%)	11 (7.9%)	66 (47.1%)	19 (13.6%)	33 (23.6%)	10 (7.1%)	1 (0.7%)
Carboplatin + Gemcitabine	205 (48.9%)	9 (4.4%)	72 (35.1%)	39 (19.0%)	56 (27.3%)	23 (11.2%)	6 (2.9%)
Cisplatin + Gemcitabine, switching to Carboplatin + Gemcitabine	11 (2.6%)	2 (18.2%)	3 (27.3%)	2 (18.2%)	3 (27.3%)	1 (9.1%)	0 (0.0%)
MVAC	6 (1.4%)	0 (0.0%)	3 (50.0%)	0 (0.0%)	3 (50.0%)	0 (0.0%)	0 (0.0%)
Other Platinum-Based	7 (1.7%)	2 (28.6%)	1 (14.3%)	1 (14.3%)	0 (0.0%)	3 (42.9%)	0 (0.0%)
Atezolizumab	39 (9.3%)	2 (5.1%)	13 (33.3%)	4 (10.3%)	12 (30.8%)	7 (17.9%)	1 (2.6%)
Vinflunine	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100%)
Other	10 (4.0%)	2 (20.0%)	4 (40.0%)	2 (20.0%)	2 (20.0%)	0 (0.0%)	0 (0.0%)
Total	**419 (100%)**	**28 (6.7%)**	**162 (38.7%)**	**67 (16.0%)**	**109 (26.0%)**	**44 (10.5%)**	**9 (2.1%)**

Bold value indicates data from all patients enrolled

MVAC methotrexate (M), vinblastine (V), Adriamycin (A) (= doxorubicin) and cisplatin (C)

*others: carboplatin (n = 1), carboplatin + etoposide (n = 3), carboplatin + taxol (n = 1), carboplatin + radiotherapy (n = 1); cisplatin + sacitizumab govitecan (n = 1)

Second line treatment

A total of 168 patients (40.1%) of the total population received second-line treatment. Patients were categorized into three groups based on their first-line treatment and avelumab maintenance status: Group 1: Patients who received platinum-based first-line chemotherapy followed by avelumab maintenance (n = 21); Group 2: Patients who received platinum-based first-line chemotherapy but did not receive avelumab maintenance (n = 135); Group 3: Patients who received atezolizumab as first-line therapy (n = 7). Six additional patients received second-line treatment but did not fit into these three groups. Table 3A summarizes the treatments received in each group. In Group 1, response rates included 9.6% complete response, 19.0% partial response, and 19.0% stable disease, while progressive disease occurred in 28.6% of cases. In Group 2, complete response was observed in 1.5% of cases, partial response in 11.9%, and stable disease in 19.2%. Progressive disease was recorded in 43.7% of patients, and 20.7% of patients were either not evaluable or had no response. Data was unavailable for 3.0% of patients.

Third line treatment

Among patients who received second-line treatment (n = 168), 25% (n = 41) progressed to third-line therapy. Patients were categorized into two groups based on their first-line treatment and avelumab maintenance status: Group 1: Patients who received platinum-based first-line chemotherapy followed by avelumab maintenance (n = 7); Group 2: Patients who received platinum-based first-line chemotherapy but did not receive avelumab maintenance (n = 32). Table 3B summarizes the treatments received in each group. In Group 1, third-line treatments included carboplatin-gemcitabine (28.6%), taxane-based therapy (14.3%), and enfortumab vedotin (28.6%). In Group 2, taxane-based therapies were the most common (37.5%), followed by enfortumab vedotin (15.6%) and vinflunine (15.6%). Progressive disease was observed in the majority of cases.

Fourth line treatment

Among patients who received third-line treatment (n = 41), 20% (n = 9) progressed to fourth-line therapy. Patients were categorized into two groups based on their first-line treatment and avelumab maintenance status: Group 1: Patients who received platinum-based first-line chemotherapy followed by avelumab maintenance (n = 1); Group 2: Patients who received platinum-based first-line chemotherapy but did not receive avelumab maintenance (n = 8). Table 3C summarizes the treatments received in each group. In Group 1, the sole patient received carboplatin-gemcitabine, achieving a partial response. In Group 2, fourth-line treatments included vinflunine (25.0%), enfortumab vedotin (12.5%), and pembrolizumab (12.5%), among others.

Outcomes

Among patients who received avelumab maintenance, the mean OS from the start of avelumab was 17.35 months (SD 1.25; range, 14.9–19.8), and the median OS was 22.00 months (SD 3.53; range, 14.6–29.4). These values are comparable to the JAVELIN Bladder 100 trial, which reported a median OS of 23.8 months (95% CI, 19.9–28.8) (Fig. 2). For PFS calculated from the initiation of avelumab, the mean duration was 6.13 months (SD 1.2; range, 3.78–8.49), and the median PFS was 4.0 months (SD 0.39; range, 3.2–4.8).

Table 3 Second and subsequent lines of systemic treatment

3 A) Second Line Systemic treatments	Group 1 (n = 21)	Group 2 (n = 135)	Group 3 (n = 7)
Atezolizumab	–	123 (91.1%)	–
Carboplatin-gemcitabine	7 (33.3%)	5 (3.7%)	1 (14.3%)
Cisplatin-gemcitabine	1 (4.8%)	1 (0.7%)	1 (14.3%)
Taxane	8 (38.1%)	4 (3.0%)	2 (28.6%)
Enfortumab vedotin	2 (9.5%)	–	2 (28.6%)
Vinflunine	2 (9.5%)	1 (0.7%)	–
Neratinib	1 (4.8%)	–	–
Topotecan	–	1 (0.7%)	–
Erdafitinib		–	1 (14.3%)

3B) Third Line Systemic treatments	Group 1 (n = 7)	Group 2 (n = 32)
Atezolizumab	–	5 (15.6%)
Carboplatin-gemcitabine	2 (28.6%)	2 (6.3%)
Cisplatin-gemcitabine	1 (14.3%)	–
Taxane	1 (14.3%)	12 (37.5%)
Enfortumab vedotin	2 (28.6%)	5 (15.6%)
Carboplatin	1 (14.3%)	1 (3.1%)
Vinflunine	–	5 (15.6%)
Erdafitinib	–	1 (3.1%)
Docetaxel-carboplatin		1 (3.1%)

3 C) Fourth Line Systemic treatments	Group 1 (n = 1)	Group 2 (n = 8)
Carboplatin + gemcitabine	1 (100.0%)	–
Atezolizumab		1 (12.5%)
Cisplatin		1 (12.5%)
Taxane		1 (12.5%)
Enfortumab vedotin		1 (12.5%)
Vinflunine		2 (25.0%)
Erdafitinib		1 (12.5%)
Pembrolizumab		1 (12.5%)

GROUP 1: Patients who received platinum in the first line and completed avelumab

GROUP 2: Patients who received platinum in the first line but did not receive avelumab

GROUP 3: Patients who received atezolizumab in the first line

(Fig. 3).These findings are also consistent with the median PFS of 5.5 months (95% CI, 4.2–7.2) reported in JAVELIN Bladder 100.

In addition to this subgroup analysis, we also present OS and PFS calculated from the time of diagnosis to the respective event (death or disease progression) across the full study cohort (Figs. 4 and 5). Among the study population, patients treated with avelumab had a median OS of 28 months (95% CI: 23.1 to NA), compared to 11 months (95% CI: 9 to 13) for patients who were eligible but did not receive avelumab. The one-year survival probability was 81.6% in the avelumab group compared to 45.6% in the non-avelumab group ($p < 0.001$). Similarly, the median PFS was 11.33 months (95% CI: 10–13.6) for avelumab-treated patients compared to 6.43 months (95% CI: 6–7.6) for those who did not receive avelumab (Fig. 3), with one-year PFS probabilities of 42.0% and 23.8%, respectively ($p < 0.001$). In our cohort, 45% of patients were PD-L1-positive. As disease advanced, the proportion of patients transitioning to subsequent treatment lines decreased: 62% of patients achieved non-progression with platinum-based chemotherapy and were candidates for avelumab, while 40% transitioned to second-line therapy, 25% to third-line, and 20% to fourth-line therapy. No unexpected toxicities were reported.

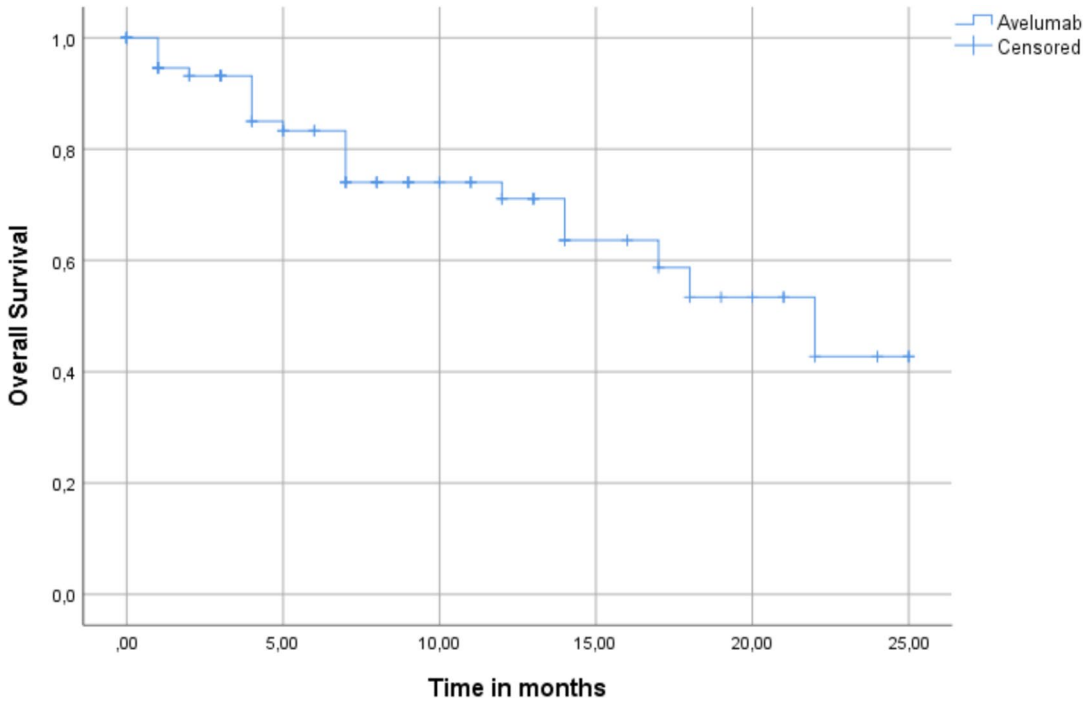
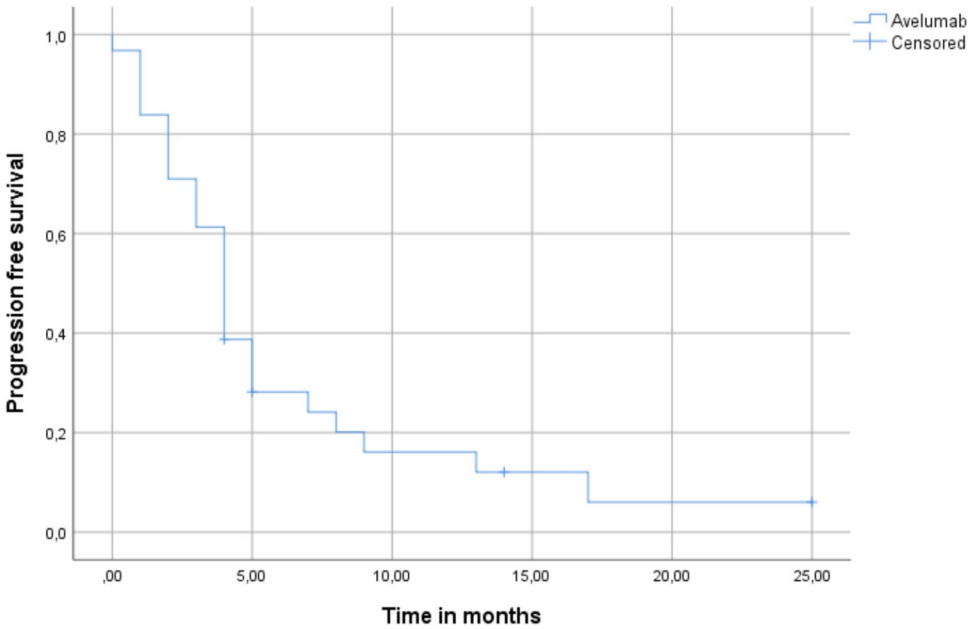


Fig. 2 Overall Survival from the initiation of Avelumab in treated patients

Fig. 3 Progression-free survival from the initiation of Avelumab in treated patients



Discussion

For over 40 years, platinum-based regimens were the primary treatments demonstrating survival benefits for mUC, yielding a median OS of approximately 14 months and a five-year survival rate of 5–15%. While cisplatin-based chemotherapy remains the standard first-line treatment, many patients are ineligible for cisplatin, necessitating alternatives like carboplatin and gemcitabine. The introduction of avelumab has transformed the treatment landscape, establishing a new paradigm of first-line maintenance therapy in patients with mUC. Approved by the FDA in 2020 and the EMA in 2021, avelumab was shown in the JAVELIN

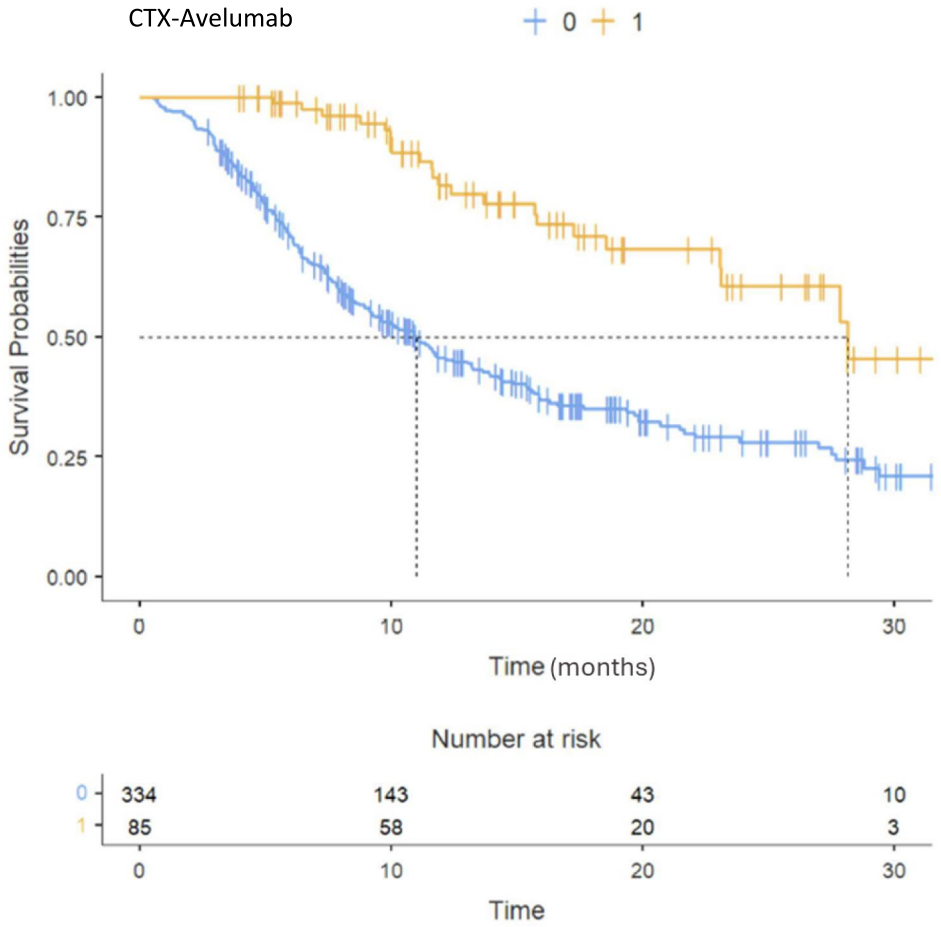


Fig. 4 Overall survival

Bladder 100 trial to significantly improve both OS and PFS compared to best supportive care alone [11]. Consequently, avelumab maintenance therapy post-platinum chemotherapy is now strongly recommended in several clinical guidelines. Recent data by Sridhar et al., provide an analysis of OS from the initiation of first-line chemotherapy in the JAVELIN study, revealing results that are strikingly consistent with our findings [19, 20]. Our study's median OS of 28 months in patients receiving avelumab aligns closely with these data, further validating the real-world applicability of the JAVELIN Bladder 100 trial outcomes.

Despite these advancements, real-world evidence remains critical to understanding the practical application of avelumab outside of controlled clinical trials. Our AVEBLADDER study conducted in Northern Spain aimed to fill this gap by providing real-world evidence on avelumab's therapeutic benefits, patient-reported outcomes, tolerability, and toxicity management in maintenance therapy for mUC. In our cohort, a substantial proportion of patients (45%) were PD-L1-positive, a factor that likely contributed to the observed survival benefits with avelumab. This finding mirrors the JAVELIN Bladder 100 trial, where patients with PD-L1-positive tumors exhibited a greater OS benefit, with an HR of 0.56 [19]. However, this raises an important question about the extent to which PD-L1 positivity may have influenced our results, as well as the generalizability of these outcomes to broader patient populations. Our study found that patients receiving avelumab maintenance had a median OS of 28 months, compared to 11 months for those who did not receive avelumab. This finding is consistent with the JAVELIN Bladder 100 trial, where avelumab improved OS and PFS. It is important to clarify that our reported median PFS of 11.33 months reflects the time from diagnosis, not from the start of avelumab maintenance. When analyzed from the initiation of avelumab, our median PFS was 4.0 months, which aligns more closely with the 5.5 months reported in the JAVELIN Bladder 100 trial. Regarding PD-L1 status, although only 45% of our full cohort were PD-L1-positive, among patients who actually received avelumab, 69.4% were

Fig. 5 Progression free survival

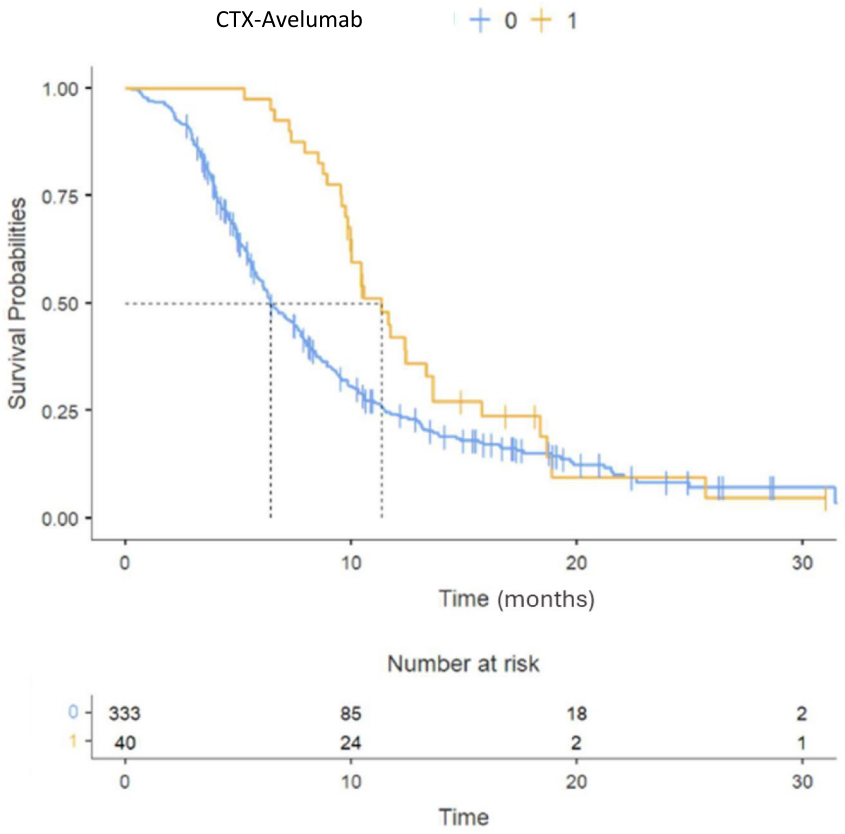


Table 4 Real World Data Studies of Avelumab maintenance treatment: Main efficacy results and comparison with Javelin Bladder 100 clinical trial. 11, 11–26

Study	Median OS	Median PFS	Key Findings	Comparison with JAVELIN Bladder 100
JAVELIN Bladder 100 [11]	21.4 months (not reached)	8.4 months (95% CI: 7.3–9.6)	Significant improvement in OS and PFS with avelumab maintenance versus BSC alone	HR for OS: 0.69 (95% CI 0.50–0.93); HR for PFS: 0.62 (95% CI 0.46–0.84)
Spanish Study (AVEBLADDER)	28 months	6.8 months	OS and PFS improvements with avelumab, but lower uptake due to access/reimbursement issues	Comparable PFS; higher OS compared to JAVELIN Bladder 100
French Study (AVENANCE) [21]	18.4 months	5.7 months	Median OS and PFS are consistent with JAVELIN; broader patient demographic	OS slightly shorter and PFS consistent with JAVELIN
Italian Study (READY) [22]	26.2 months	7.6 months	Confirmed survival benefit; well-tolerated	Higher OS; similar PFS
US and European Study [23]	Not reported	9.6 months	Identified prognostic factors; good PFS and OS rates	PFS and OS similar to JAVELIN; identifies additional prognostic factors
German Study [24]	13.4 months	6.2 months	Moderate AEs; shorter OS compared to JAVELIN, similar PFS	OS shorter than JAVELIN; PFS similar
Japanese Study (J-AVENUE) [25]	Not reported	6.1 months	Similar PFS to JAVELIN; slightly shorter median time to treatment failure	PFS consistent with JAVELIN; slightly lower compared to JAVELIN
Korean Study [26]	Not analyzed	7.9 months	Clinical activity with moderate AEs; no detailed OS data (only one patient died)	PFS similar to JAVELIN; OS not reported

PD-L1-positive. This enrichment may have contributed to improved treatment outcomes.

Comparative real-world data from other studies offer additional context (Table 4) [21–26]. Compared to the JAVELIN Bladder 100 trial, our cohort showed a higher objective response rate (22% vs 14.3%) and lower rate of progressive disease (20% vs 29%). Several factors may contribute to these differences, including patient selection and the real-world setting. Additionally, in our cohort, 6% of patients had an unknown ORR status, 18% did not undergo response evaluation (including those who progressed before assessment), and 7% were deemed non-evaluable. These elements may have led to an apparent increase in response rate and decrease in PD frequency. The French AVENANCE study reported a median OS of 18.4 months and a median PFS of 5.7 months with avelumab. While this supports the efficacy of avelumab, it indicates a slightly shorter PFS compared to our findings, potentially reflecting a broader patient demographic [21]. The Italian study, known as READY, was a prospective investigation involving 414 patients enrolled in a compassionate use program. This study reported a median overall survival (OS) of 26.22 months and a median progression-free survival (PFS) of 7.63 months, demonstrating that avelumab was well-tolerated and had a manageable safety profile [22]. The findings of this study align with the JAVELIN trial results, confirming the survival benefit of avelumab in a real-world Italian population. The US and European study reported a median PFS of 9.6 months and a one-year OS of 72.5%, which aligns with both our study and the JAVELIN trial. Notably, this study identified prognostic factors such as prior response to platinum-based chemotherapy and ECOG performance status that were associated with better outcomes, which aligns with our observations [23]. Conversely, the German study reported a median OS of 13.4 months and a median PFS of 6.2 months, with moderate adverse event rates but a higher proportion of patients experiencing progression during treatment, resulting in shorter survival compared to the JAVELIN trial [24]. The J-AVENUE study from Japan found a median PFS of 6.1 months and a median time to treatment failure of 4.6 months, similar to our study's PFS of 6.8 months [25]. These results support the JAVELIN trial's conclusions, although the reported PFS was slightly shorter, potentially reflecting regional variations. In Korea, real-world data showed a median PFS of 7.9 months and a lower rate of adverse events, though the shorter follow-up period and lack of detailed OS data limit direct comparisons [26]. Nonetheless, the median PFS aligns with the JAVELIN trial and our findings.

Our study faced two notable limitations. First, the uptake of avelumab was lower than anticipated, primarily due to negative PD-L1 status and access/reimbursement challenges, as in Spain, access and reimbursement were only guaranteed for PD-L1–positive patients for a period of time. The substantial proportion of patients with negative PD-L1 status reduced eligibility for avelumab, impacting its adoption. Furthermore, while avelumab maintenance therapy has demonstrated robust efficacy, its uptake in real-world practice remains limited due to challenges such as access, reimbursement policies, and physician awareness. The transition from first-line chemotherapy to avelumab maintenance is a critical period, with many eligible patients failing to initiate maintenance therapy due to progression or logistical barriers. These findings emphasize the need for interventions to improve access to avelumab and optimize patient management during this transition phase. Additional limitations include the retrospective design, which may introduce selection bias and limit the ability to control for confounding variables; the relatively short follow-up period, which may have restricted the observation of long-term outcomes; and the small sample size, which limits the generalizability of our findings and reduces the statistical power to detect more subtle effects.

Future research should address unresolved questions, such as the comparative benefits of avelumab maintenance following different platinum-based regimens and the optimal duration of the treatment-free interval before initiating avelumab. Furthermore, the role of PD-L1 status as a predictive biomarker for avelumab efficacy warrants further investigation to better stratify patients and personalize treatment approaches.

In conclusion, our findings provide robust real-world evidence supporting the efficacy and safety of avelumab as a first-line maintenance therapy for mUC. The consistency between our results and those of the JAVELIN Bladder 100 trial, particularly in PD-L1-positive patients, underscores the value of avelumab in improving survival outcomes for this population.

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Data availability Not applicable.

Declarations

Conflict of interest Astellas has contributed a grant to support a portion of the program's cost, but they have not exerted any influence or input on the research program.

Ethical approval The study was approved by the Institutional Review Board and Ethics Committee of all the participant centers.

Informed consent Informed consent was obtained whenever required by the Spanish Law.

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