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Effectiveness and safety of avelumab first-line maintenance in locally advanced or metastatic urothelial carcinoma: a systematic literature review and meta-analysis

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CONCLUSIONS

- The global real-world evidence (RWE) identified in this systematic literature review (SLR) and meta-analysis demonstrates the effectiveness and acceptable safety profile of avelumab first-line maintenance (1LM) treatment in patients with locally advanced or metastatic urothelial carcinoma (la/mUC) outside of clinical trials
- Data from routine clinical practice were comparable with results from the JAVELIN Bladder 100 randomized trial, despite heterogeneity and limited follow-up
- The findings of this study provide further evidence of the established clinical benefit of avelumab 1LM across a broad range of patients, including older patients, those with high metastatic tumor burden, and those with Eastern Cooperative Oncology Group performance status (ECOG PS) >1
- These data support the recommendation of avelumab 1LM for the treatment of patients with la/mUC that has not progressed following 1L platinum-based chemotherapy (PBC)
- Further research on treatment options beyond 1L is warranted to determine optimal treatment sequencing for patients with la/mUC

PLAIN LANGUAGE SUMMARY

- Real-world studies provide information about how well drugs work outside of clinical trials
- Avelumab is a recommended treatment for people with advanced urothelial cancer whose cancer has disappeared, shrank, or stopped growing with chemotherapy
- In this study, researchers looked at real-world studies of people with advanced urothelial cancer treated with avelumab after chemotherapy. They wanted to see if avelumab treatment worked well outside of clinical trials and how many people had side effects
- Researchers analyzed data from more than 2,600 people in 45 different real-world studies. They found that people treated with avelumab in these studies had similar benefits and side effects to people treated in clinical trials
- Overall, these results provide more evidence showing that avelumab treatment after chemotherapy is effective for a wide variety of people with advanced urothelial cancer, and that side effects are acceptable

BACKGROUND

- The phase 3 JAVELIN Bladder 100 randomized controlled trial (RCT) demonstrated prolonged overall survival (OS) and progression-free survival (PFS) with avelumab 1LM + best supportive care vs best supportive care alone in patients with la/mUC that had not progressed following 1L PBC[1]
- Based on JAVELIN Bladder 100 results, guidelines recommend avelumab 1LM as a treatment option for patients with la/mUC without progression following PBC[2,3]
- RWE is needed to assess whether the outcomes of RCTs are generalizable to the wide variety of patients encountered in clinical practice (ie, those whose characteristics are outside the strict inclusion and exclusion criteria of RCTs)[4,5]
- We conducted an SLR and meta-analysis to summarize global RWE on the effectiveness, safety, and tolerability of avelumab 1LM in patients with la/mUC, and assess how these data compare with those from the JAVELIN Bladder 100 trial

METHODS

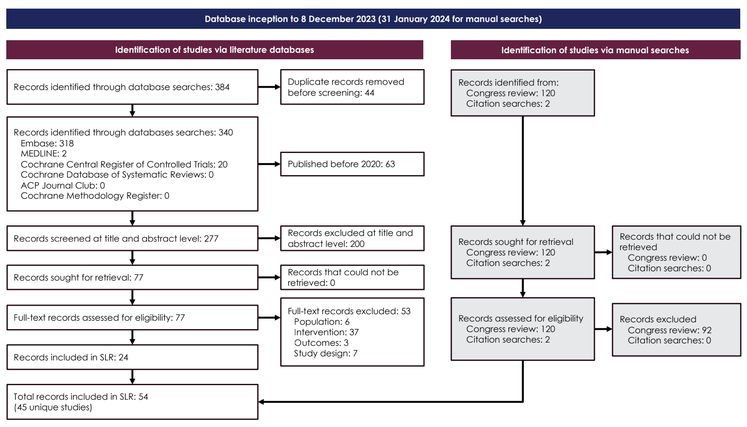
SLR

- The SLR was conducted according to reporting and methodological standards outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and the Cochrane Handbook for Systematic Reviews of Interventions[6,7]
- Studies published since 1 January 2020 were retrieved from MEDLINE, Embase, and Cochrane databases up to 8 December 2023, and through gray literature/conference searches up to 31 January 2024
- Only studies reporting treatment patterns, patient characteristics, and efficacy or safety outcomes related to avelumab 1LM were included, with no language restrictions applied. Editorials, notes, and nonsystematic reviews were excluded
- Literature screening was performed by 2 independent reviewers, and conflicts were resolved by a third independent reviewer. Data from included studies were extracted by 1 reviewer and assessed by a second reviewer for consistency and accuracy
- Quality assessment was performed using the Newcastle-Ottawa Scale (NOS) for full-text journal articles or conference abstracts with available posters or slides[8]

Meta-analysis

- The meta-analysis was conducted for pooled 12-month landmark OS or PFS from the start of avelumab 1LM for proportions using R function metaprop in the meta package (version 6.5-0), using a generalized linear mixed model with logit link for pooling[9]
- Pooled event rates with 95% CIs were estimated using fixed-effect and random-effects models

Figure 1. PRISMA flow diagram



ACP, American College of Physicians; **PRISMA**, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **SLR**, systematic literature review.

Table 1. Patient characteristics

Characteristic	Reporting studies, n/N (%)	Weighted mean across RWE (range)	JAVELIN Bladder 100 data (ITT)
Age, median, years	22/45 (49)	71 (65-74)*	68
Male, %	21/45 (47)	78 (63-83)	76
Primary tumor location and histology, %			
Upper tract	18/45 (40)	26 (8-50)	30
Pure urothelial carcinoma	7/45 (16)	88 (65-100)	87
Metastatic site, %			
Visceral	10/45 (22)	63 (30-78)†	55
Liver	12/45 (27)	14 (4-17)	12
Lung	9/45 (20)	25 (19-42)	24
ECOG PS, %			
0	15/45 (33)	44 (10-100)	61
1	14/45 (31)	37 (6-85)	39
0/1	16/45 (36)	81 (67-100)	100‡
Type of 1L PBC, %			
Cisplatin + gemcitabine	11/45 (24)	38 (25-70)	52
Carboplatin + gemcitabine	11/45 (24)	51 (25-75)	42
Response to 1L PBC, %			
CR	13/45 (28)	15 (5-25)	26
PR	13/45 (28)	57 (33-68)	47
SD	15/45 (33)	27 (11-48)	28

1L, first line; **CR**, complete response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ITT**, intention to treat; **PBC**, platinum-based chemotherapy; **PR**, partial response; **RWE**, real-world evidence; **SD**, stable disease.
*Weighted mean of median ages reported in each study. †Most studies reported a proportion of 30% to 44%, except for RAVE-Bladder (63%) and AVENANCE (78%). However, in the AVENANCE study, bone metastases were counted as visceral metastases, and all other studies either did not provide a definition of visceral metastases or did not include bone metastases in this definition. ‡99.8% (1/350 patients had ECOG PS of 2).

RESULTS

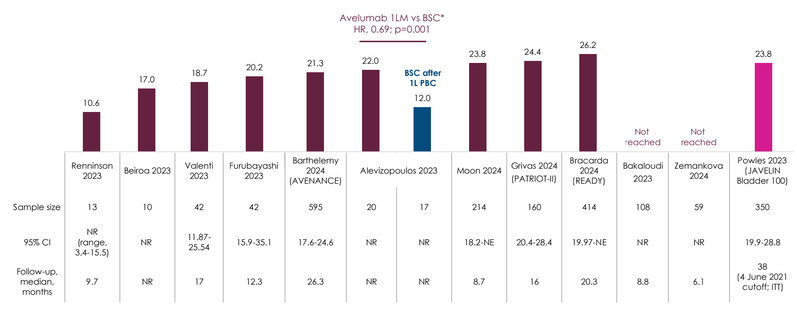
Study and patient characteristics

- The SLR identified 54 publications reporting 45 unique studies and comprising 2,656 patients treated with avelumab 1LM (**Figure 1**)
- Included studies were most commonly conducted in the US (15/45), Europe (13/45; France, Germany, Italy, Spain, and the UK), or Japan (5/45)
- Of 28 studies assessable for quality, the quality score was high (NOS ≥7) in 13 (46%), moderate (NOS 5 or 6) in 8 (29%), and low (NOS ≤4) in 7 (25%); 17 studies were only published in abstract form and thus had insufficient information for quality assessment
- Patient characteristics were heterogeneous across studies, with ages typically older than patients in the JAVELIN Bladder 100 population (**Table 1**)
- The majority of patients were male and had an ECOG PS of 0/1
- Most patients received second-line therapy, the most common of which was enfortumab vedotin (36% of patients)

Effectiveness and safety

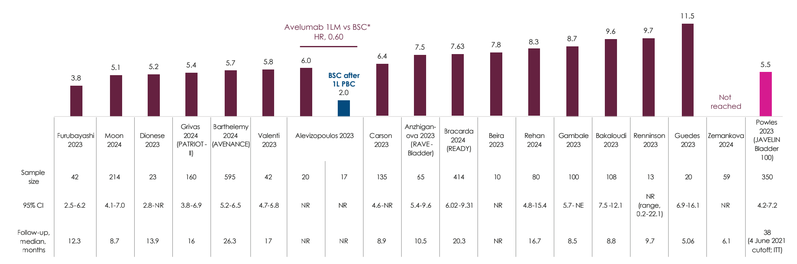
- Median OS from start of avelumab 1LM in RWE studies ranged from 10.6 to 26.2 months vs 23.8 months in JAVELIN Bladder 100 (**Figure 2**; **Table 2**)
- Median PFS from start of avelumab 1LM ranged from 3.8 to 11.5 months vs 5.5 months in JAVELIN Bladder 100 (**Figure 3**; **Table 2**)
- 12-month OS and PFS rates were comparable to those in the JAVELIN Bladder 100 trial (**Figures 4** and **5**)
- RWE studies demonstrated the favorable safety profile of avelumab 1LM with an acceptable rate of adverse events and discontinuation, in line with clinical trial data (**Table 2**)

Figure 2. Median OS (months) from start of avelumab 1LM



1L, first line; **1LM**, first-line maintenance; **BSC**, best supportive care; **HR**, hazard ratio; **ITT**, intention to treat; **NE**, not estimable; **NR**, not reported; **OS**, overall survival; **PBC**, platinum-based chemotherapy; **PFS**, progression-free survival.
*In this study, BSC was given to patients who were offered avelumab 1LM but refused it.

Figure 3. Median PFS (months) from start of avelumab 1LM

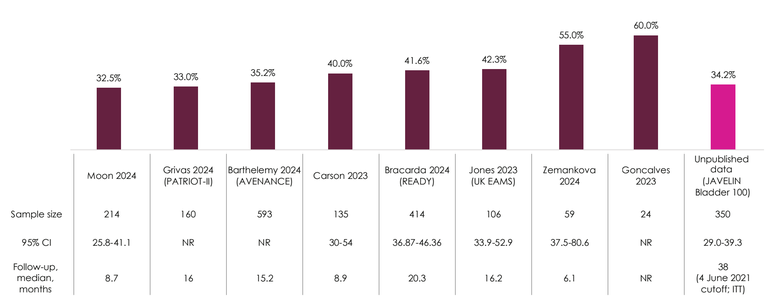


1L, first line; **1LM**, first-line maintenance; **BSC**, best supportive care; **HR**, hazard ratio; **ITT**, intention to treat; **NE**, not estimable; **NR**, not reported; **PBC**, platinum-based chemotherapy; **PFS**, progression-free survival.
*In this study, BSC was given to patients who were offered avelumab 1LM but refused it.

Figure 4. Landmark 12-month OS from start of avelumab 1LM

1L, first line; **1LM**, first-line maintenance; **BSC**, best supportive care; **ITT**, intention to treat; **NR**, not reported; **OS**, overall survival; **PBC**, platinum-based chemotherapy.
*In this study, BSC was given to patients who were offered avelumab 1LM but refused it.
†Powles T, et al (2020) reports the landmark 12-month OS rate from start of avelumab 1LM as 71.3% as of data cutoff on 21 October 2019.[1]

Figure 5. Landmark 12-month PFS from start of avelumab 1LM



1LM, first-line maintenance; **ITT**, intention to treat; **NR**, not reported; **PFS**, progression-free survival.

Table 2. Clinical outcomes and safety

	RWE median outcome across studies	RWE outcome, range	RWE FU, median, months	JAVELIN Bladder 100 (ITT; FU >19 months; 21 October 2019 cutoff)[1]	JAVELIN Bladder 100 (ITT; median FU, 38 months; 4 June 2021 cutoff)[10]
Duration of avelumab 1LM	4.8 months	3.8-7.1 months	NR	24.9 weeks (5.7 months)	5.8 months
OS from start of avelumab 1LM					
Median	21.3 months	10.6-26.2 months	16.0	21.4 months	23.8 months
12-month rate	71%	57.5%-90.0%	10.5	71%	72%
PFS from start of avelumab 1LM					
Median	7.0 months	3.8-11.5 months	10.5	3.7 months	5.5 months*
12-month rate	41%	32.5%-60.0%	15.2	NR	34%*
Response during avelumab 1LM					
CR	3%	0%-19%	13.8	6%	7%*
PR	12%	2%-26%	12.3	4%	7%*
SD	38%	11%-70%	12.3	13%	21%*
Serious AEs					
Treatment emergent	37%	23%-71%	16.7	28%	31%
Treatment related	8%	6%-10%	16.7	9%	10%
Grade ≥3 AEs	8%	1%-50%	14.6	47%	54%
Discontinuation due to AEs	9%	4%-17%	9.9	12%	14%

1LM, first-line maintenance; **AE**, adverse event; **CR**, complete response; **FU**, follow-up; **ITT**, intention to treat; **NR**, not reported; **OS**, overall survival; **PFS**, progression-free survival; **PR**, partial response; **SD**, stable disease; **RWE**, real-world evidence.
*Investigator assessed.

STRENGTHS AND LIMITATIONS

Strengths

- Multiple databases and conference proceedings were searched to ensure comprehensive inclusion of RWE
- The "population, intervention, comparison, results, and study design" approach enabled strict criteria to be used to identify studies
- 2 reviewers were involved at every stage of the SLR to ensure quality in compliance with best practices
- Specific studies were identified through a well-balanced search strategy for specificity and sensitivity
- The transparent search strategy enables reproducibility of results
- The absence of language, geography, or observational study type restrictions ensured comprehensive data collection

Limitations

- Analyses were not based on individual patient data
- Despite attempts to avoid overlapping data, the possibility of double counting of patients from the same country/database cannot be excluded
- Some studies were published as abstracts only and therefore provided limited data
- Many studies included a small sample size and had short follow-up
- Observational studies investigating OS may have been subject to immortal time bias
- The possibility of selection bias in comparative studies cannot be excluded
- Study heterogeneity precludes comparison between studies, and the results of this analysis are not adjusted and therefore descriptive only

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