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DRB, RT: Conceptualization, Methodology, Formal analysis, Investigation, Data Curation, Writing- Original Draft, Writing-Review and Editing. **GIL**: Statistical Analysis. **DM, LND, NT, NA, RZ, AB, JB, DP, JK, TJ, VK, JM, MM, AF, JJ, YZ, AD, ARV, MRC, DC, LAB, ID, CCC, RMB, DM, RM, TS, SG, EY, ATR:** Investigation, Writing- Review and Editing. **ARK, PG:** Conceptualization, Methodology, Validation, Investigation, Resources, Writing- Review and Editing, Supervision.

Declaration of Competing Interest
None.

Response and outcomes of maintenance avelumab after platinum-based chemotherapy (PBC) in patients with advanced urothelial carcinoma (aUC): 'real world' experience

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Abstract

Micro-Abstract: Based on JAVELINBladder100 trial, avelumab maintenance was approved for patients with advanced urothelial carcinoma (aUC) without progression on first-line platinum-based chemotherapy. We examined patient characteristics, prognostic factors and outcomes in patients who received avelumab switch maintenance in a "real-world" *(outside trials)* setting. Our results appear similar with those from the clinical trial and recent "real world" studies.

Background: Platinum-based chemotherapy (PBC) followed by avelumab switch maintenance in non-progressors is standard first line (1L) treatment for advanced urothelial carcinoma (aUC). We describe clinical features and outcomes in a 'real-world' cohort treated with avelumab maintenance for aUC.

Methods: This was a retrospective cohort study of patients (pts) who received 1L switch maintenance avelumab after no progression on PBC for aUC. We calculated progression-free survival (PFS) and overall survival (OS) from initiation of maintenance avelumab. We also described OS and PFS for specific subsets using Cox regression and observed response rate (ORR).

Results: A total of 108 pts with aUC from 14 sites treated with maintenance avelumab were included. There was a median of 6 weeks (1–30) from end of PBC to avelumab initiation; median follow-up time from avelumab initiation was 8.8 months (1–42.7). Median [m]PFS was 9.6 months (95%CI 7.5–12.1) and estimated 1-year OS was 72.5%. CR/PR (vs SD) to 1L PBC (HR=0.33, 95%CI 0.13–0.87) and ECOG PS 0 (vs 1), (HR=0.15, 95%CI 0.05–0.47) were

associated with longer OS. The presence of liver metastases was associated with shorter PFS (HR=2.32, 95%CI 1.17–4.59). ORR with avelumab maintenance was 28.7% (complete response 17.6%, partial response 11.1%), 29.6% stable disease, 26.9% progressive disease as best response (14.8% best response unknown).

Conclusions: Results seem relatively consistent with findings from JAVELIN Bladder100 trial and recent "real world" studies. Prior response to platinum-based chemotherapy, ECOG PS 0, and absence of liver metastases were favorable prognostic factors. Limitations include the retrospective design, lack of randomization and central scan review, and possible selection/confounding biases.

Keywords

avelumab; anti-PD(L)1; bladder cancer; urinary tract cancer; urothelial carcinoma

Introduction

Bladder cancer is one of the most common malignancies with estimated 81,180 new cases and 17,100 deaths in United States in 2022 (1). Advanced urothelial carcinoma (aUC) which is defined as locally advanced / unresectable, or metastatic UC, is the most aggressive stage and is associated with poor quality of life and short survival (2). Standard of care first line (1L) induction treatment is platinum-based chemotherapy (PBC) for platinum-eligible patients with aUC (3). This is followed by switch maintenance avelumab for those without progression on/after PBC.

The benefit of switch maintenance avelumab was demonstrated in the landmark phase 3 JAVELIN Bladder (JB) 100 trial, which investigated switch maintenance avelumab (anti-PD-L1) plus best supportive care (BSC) compared to BSC alone in patients with aUC without progression after 4–6 cycles of PBC (4, 5). Maintenance avelumab resulted in significantly prolonged overall survival (OS) and progression-free survival (PFS) leading to level I evidence and approval by regulatory agencies in several countries, including FDA approval on June 30, 2020 (6).

We conducted a multicenter retrospective cohort study to examine the "real word" (outside clinical trials) patient characteristics and clinical outcomes with avelumab switch maintenance. We also examined outcomes of specific subgroups to investigate potential prognostic factors. We hypothesized that our data would align with what was reported in the JB 100 trial.

Methods

Study design and data collection

This is a retrospective cohort study which has been conducted according to the STROBE guidelines for cohort studies (7). After obtaining institutional review board (IRB) approval and with respect to the Declaration of Helsinki ethical principles (8), we conducted a retrospective study including patients from academic centers from the United States and Europe. Eligible patients for this study were identified through a larger cohort, previously described, in which data of patients who received immune checkpoint inhibitor (ICI) for

aUC have been collected (9–17). Each institution independently identified consecutive patients through provider-driven and electronic health record search algorithms. Data collection and storage was performed using the web-based, secure, and standardized REDCap capture tools hosted at the Institute of Translational Sciences at the University of Washington (18, 19). Data was collected using a pre-specified web-based form and included demographic/baseline characteristics, cancer-related information, treatment details and clinical outcomes. Assessment of response was based on the report of the investigators.

Eligibility Criteria

We included adult patients with aUC who received 1L switch maintenance avelumab after induction PBC (cisplatin or carboplatin-based regimens). Patients were excluded if they had received avelumab for progressive disease (PD) or in cases that they received other regimens between PBC and avelumab. Patients who received (neo)adjuvant ICI (as standard of care or experimental) were considered eligible if they received switch maintenance avelumab as standard of care. Patients with mixed urothelial histology were included, but those with pure non-urothelial carcinoma were excluded.

Endpoints

Primary endpoints included OS and PFS from the start of avelumab maintenance. For both OS and PFS, we investigated specific subsets and potential prognostic factors. In particular, we investigated the following subsets: sex (male or female), smoking history (ever or never smoker), primary tumor site (upper tract [ureter or renal pelvis] or lower tract [bladder or urethra]), histology (pure or mixed UC), platinum (cisplatin or carboplatin), number of cycles of PBC received (4 or >4), presence of liver metastases at PBC start (yes or no), ECOG PS at PBC start (0 or 1), best response to PBC (Complete response [CR]/partial response [PR] or stable disease [SD]), weeks from PBC end to avelumab initiation (3 or 4–10; >10 or 4–10). We also examined the response rate, disease control rate (SD), primary progression rate with avelumab maintenance and calculated the observed response rate (ORR) (PR+CR) as well as the reasons for avelumab discontinuation. Response to avelumab was investigator-assessed without central scan review.

Statistical Analysis

Baseline characteristics were summarized using descriptive statistics. We calculated OS and PFS using the Kaplan Meier method. OS was calculated from the initiation of avelumab maintenance until the date of death, and PFS was calculated from the date of avelumab initiation until the date of investigator-assessed clinical and/or radiographic disease progression or death. In both OS and PFS, patients who did not have an event were censored at the date of last follow-up. We also calculated the estimated OS rate at 1 year. Univariate cox proportional-hazards models were used for our subset analyses. All statistical analyses were performed using R version 4.1.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

We identified 108 eligible patients from a total of 1,514 patients in our database. Included patients were from 14 centers and had received 1L avelumab maintenance after no progression on PBC for aUC. Baseline characteristics can be found in Table 1. Median age was 69 years, most patients were White (92.6%), male (80.6%) with lower tract primary (85.2%); 71 patients (65.7%) received cisplatin-based chemotherapy. One patient had received neoadjuvant nivolumab for localized muscle invasive bladder cancer (MIBC) and two patients received adjuvant nivolumab for MIBC.

At the time of PBC start, 13 (12%) patients had liver metastases, 51 (47.2%) had ECOG PS 0 and 41 (38%) ECOG PS 1 (16 unknown). The median time from avelumab maintenance initiation to the last follow up was 8.8 months (min-max: 1–42.7). The median time interval between the last chemotherapy dose and avelumab maintenance initiation was 6 weeks (min-max: 1–30). At the time of the analysis, 48 patients (44.4%) were still on avelumab maintenance and among the 60 (55.6%) patients who had discontinued avelumab, 46 (76.7%) had radiographic and/or clinical progression, 6 (10%) had a treatment-related adverse event (TRAE) and 8 (13.3%) discontinued treatment due to other reasons, including treatment holiday or completion, death, loss to follow up, and other unrelated to avelumab treatment (Table 2).

At last follow-up 76 (70.3%) patients were alive, 30 (27.8%) patients had died, and two (1.9%) patients had unknown vital status. Median OS was not reached, but the landmark OS rate at 1 year was 72.5% (CI: 63.2–83.1%), median PFS was 9.6 months (95%CI 7.5–12.1) (Figure 1). Results after examining specific subsets of interest regarding OS and PFS can be found in Table 3. We found that response to PBC (CR/PR) vs SD (HR=0.33, 95%CI 0.13–0.87) as best response to PBC as well as ECOG PS 0 vs 1 at PBC initiation (HR=0.15, 0.05–0.47) were associated with longer OS. We also found that patients with liver metastases at the time of PBC initiation had shorter PFS vs patients without liver metastases (HR=2.32, 95%CI 1.17–4.59) (Figures 2 and 3). Notably, response to PBC and ECOG PS did not have a statistically significant impact on PFS on avelumab. Sex, smoking history, site of primary tumor, pure vs mixed histology, type of platinum agent used, number of cycles of PBC and the time interval from PBC end to avelumab initiation were not significantly associated with OS or PFS.

Among all 108 patients treated with avelumab maintenance, CR and PR as best observed response were reported in 19 (17.6%) patients and 12 (11.1%) patients, respectively (ORR 28.7% of all patients) (Table 2); 32 additional patients (29.6%) had SD and 29 patients (26.9%) had progression as best response. Response to avelumab maintenance was unknown for 16 patients due to mortality, loss to follow-up or no documented evaluation.

Discussion

In this multi-institutional retrospective study, we aimed to examine the "real-world" data of patients who received 1L avelumab switch maintenance after no progression on PBC for aUC. Our results support the key findings of the JB 100 trial findings, showing an

estimated OS at 1 year (72.5% alive) but higher ORR and median PFS in patients with aUC who received avelumab maintenance relative to JB 100 trial data. Moreover, we found that response to PBC and ECOG PS 0 were associated with longer OS and the absence of liver metastases was associated with longer PFS in patients receiving avelumab maintenance. Our findings also align well with other "real world" studies discussed below, while a few others are ongoing, e.g. PATRIOT-II (20). Impaired ECOG PS (2) and liver metastases have been associated with worse outcomes according to a new survival prognostic model in patients with aUC, which align and lend credibility to our results (10).

In line with our findings (mPFS 9.6 months and 12-months OS 72,5%), results from other studies aiming to describe "real-world" data, such as READY and AVENANCE studies, corroborate the favorable outcomes and support the avelumab maintenance strategy (20–23). In the READY study in the Italian population, the 12-months PFS was 38.9% and the median PFS 6.6 months. The 12-month OS rate was 69.1% (95%CI 64.4%–73.6%) (22). Moreover, in the AVENANCE study in the French population, median PFS was 5.7 months and the 1-year OS rate 64.8% (23)

An important question has been whether the number of induction PBC cycles and platinum agent (cisplatin vs carboplatin) may affect outcomes with switch maintenance avelumab. According to our results, no significant difference was found between the number of cycles (4 vs >4 cycles) of PBC and survival with avelumab neither the platinum agent. In the same pattern, data from published studies did not show a significant association between the number of 1L PBC cycles and outcomes with maintenance avelumab (24, 25). The DISCUS trial (EudraCT number 2021–001975-17) in Europe will help elucidate if receiving 3 cycles of induction chemotherapy followed my switch maintenance avelumab results in better quality of life (based on patient-reported outcomes) whilst maintaining similar levels of efficacy compared to 6 cycles of induction PBC (26).

Interestingly, our study showed 28.7% ORR to avelumab, which is higher than the reported 9.7% ORR with avelumab in JB 100 (16 patients with no response evaluation were included in the denominator). This discrepancy may likely be attributed to the limitation of using retrospective chart review rather than central scan review to guide response assessment A recent Japanese study also examined "real-world" data with 1L avelumab maintenance after no progression on PBC in 27 patients (27). According to that study, 16 patients (59%) had disease control including CR, PR, or SD as best response (27). It is hard to ascertain in this setting whether response should be attributed to avelumab maintenance and/or to prior PBC. The JB 100 trial and 'real-world' studies (e.g. READY, AVENANCE), did not show significant PFS benefit based on best response to PBC (4, 22, 23).

In our study, only 6% of patients discontinued avelumab due to a TRAE, which aligns well with data from JB100 trial. However, we did not rigorously collect the incidence, type, and grade of TRAEs. Data regarding avelumab toxicity from the READY study reported that grade 3–4 TRAEs were observed in 7.1% (22). A similarly low rate of high grade TRAEs (10.3%) was reported in the AVENANCE study (23). The incidence of grade 3–4 TRAEs with avelumab monotherapy has been low, while rare events might occur (28). In the Japanese study, 12 patients (44%) experienced immune related adverse events of any grade;

one patient (3.7%) had a grade 3 TRAE leading to avelumab discontinuation (27). Data from the JB 100 trial showed that the survival benefit with avelumab maintenance was not associated with significant detriment in patient reported outcomes and the quality of life of patients (25).

Data from the long-term follow up analysis of the JB 100 trial confirms the survival benefit in patients who received avelumab maintenance (29). Biomarker analysis investigated the potential use of several candidate biomarkers (e.g. PD-L1, TMB, APOBEC, other gene signatures, mutations in DNA damage response [DDR] etc.) as prognostic or predictive tools in this setting; however, such molecular biomarkers are not used in clinical practice for selection of patients for avelumab maintenance (30). Interestingly, despite the JB100 trial outcomes reported and the level I evidence, results from a recent abstract showed a relatively modest uptake of avelumab maintenance in practice (31); this may be possibly due to the awareness regarding the data and/or patient preference to avoid long-term therapy burden.

As switch maintenance has been identified as a successful treatment approach for patients with aUC, other agents have been investigated or are currently undergoing investigation in this setting. A randomized phase II trial investigating switch maintenance pembrolizumab after achieving at least SD on 1L induction PBC showed prolonged PFS with pembrolizumab vs BSC (median 5.4 vs 3 months, respectively HR=0.65) without significant OS benefit (32). ATLANTIS is a randomized multi-arm phase II biomarker-directed umbrella trial of 1L switch maintenance therapy after response or SD to induction PBC in aUC (33, 34). There was no benefit with switch maintenance cabozantinib vs placebo (33), whereas switch maintenance rucaparib showed longer median PFS vs placebo (35.3 vs 15.1 weeks) in patients with DDR gene alterations, which was a hypothesis-generating result (34). Other ongoing maintenance therapy trials include JAVELIN Bladder Medley, a phase Ib/II, multi-arm trial that aims to evaluate switch maintenance avelumab alone vs avelumab plus sacituzumab govitecan (anti-body drug conjugate against TROP-2), avelumab plus M6223 (an anti T-cell-immune-receptor) and avelumab plus NKTR-255 (a novel recombinant human IL-15) (35). The MAIN-CAV study is a phase III trial evaluating maintenance cabozantinib plus avelumab vs avelumab alone (36), and the TALASUR is a phase II trial investigating maintenance talazoparib (PARP-inhibitor) plus avelumab (37). These and other ongoing studies, e.g. TROPHY U-01 (NCT03547973) and PRESERVE 3 (NCT04887831) can help further refine the optimal switch maintenance strategy for aUC.

Limitations of our study include the moderate sample size, the relatively limited number of events and the retrospective design which is characterized by lack of randomization and of central scan review, with potential selection and confounding biases. Furthermore, the involvement of multiple institutions can lead to slightly different clinical practices (e.g. imaging scheduled intervals, which can affect PFS) as well as interpretation of scan review regarding therapy response or SD vs progression. Further, while our study aimed to investigate "real-world" outcomes, contributing sites are academic centers, so application of results to broader community practice settings may be relatively limited. We also did not evaluate quality of life, patient reported outcomes and molecular biomarker data.

Despite inherent limitations, to our knowledge this is one of the first analyses of "real world" data after the approval of 1L switch maintenance avelumab in aUC, aiming to complement clinical trial data. Our results support the data from JB100 and align with other recent "real world" studies.

Acknowledgements

Abbreviations

1L	First Line
APOBEC	Apolipoprotein B mRNA-editing enzyme catalytic polypeptide
aUC	Advanced Urothelial carcinoma
BSC	Best supportive care
CI	Confidence Interval
CR	Complete response
DDR	DNA Damage Response
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FDA	Food and Drug Administration
HR	Hazard Ratio
JB	JAVELIN Bladder
IRB	Institutional review board
ITT	Intent-to-treat
MIBC	Muscle invasive bladder cancer
Mo	Months
ORR	Observed response rate

OS	Overall survival
PBC	Platinum-based chemotherapy
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TMB	Tumor mutational burden
TRAE	Treatment-related adverse event

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Clinical Practice Points

- Avelumab has been approved in several countries with level I evidence as first line maintenance therapy in patients with advanced urothelial carcinoma (aUC) without progression on platinum-based chemotherapy (PBC) based on the JAVELINBladder100 (JB100) trial, which showed longer overall and progression-free survival (OS, PFS) with switch maintenance avelumab plus best supportive care (BSC) vs BSC alone.

- We conducted a retrospective cohort study investigating patient characteristics, prognostic factors and outcomes in patients treated with avelumab switch maintenance after no progression on first line PBC for aUC in the "real-world" setting (outside clinical trials).

- Our results support JB100 trial data; we noted higher response rate and longer median PFS (9.6 months) with avelumab maintenance and an estimated 73% OS rate at 1st year, which align with recent "real world" studies in this setting.

- We also found that response (vs stable disease) to PBC, better performance status and absence of liver metastasis were favorable prognostic factors.

- Limitations include retrospective nature, lack of randomization and of central scan review, as well as possible selection and confounding biases.
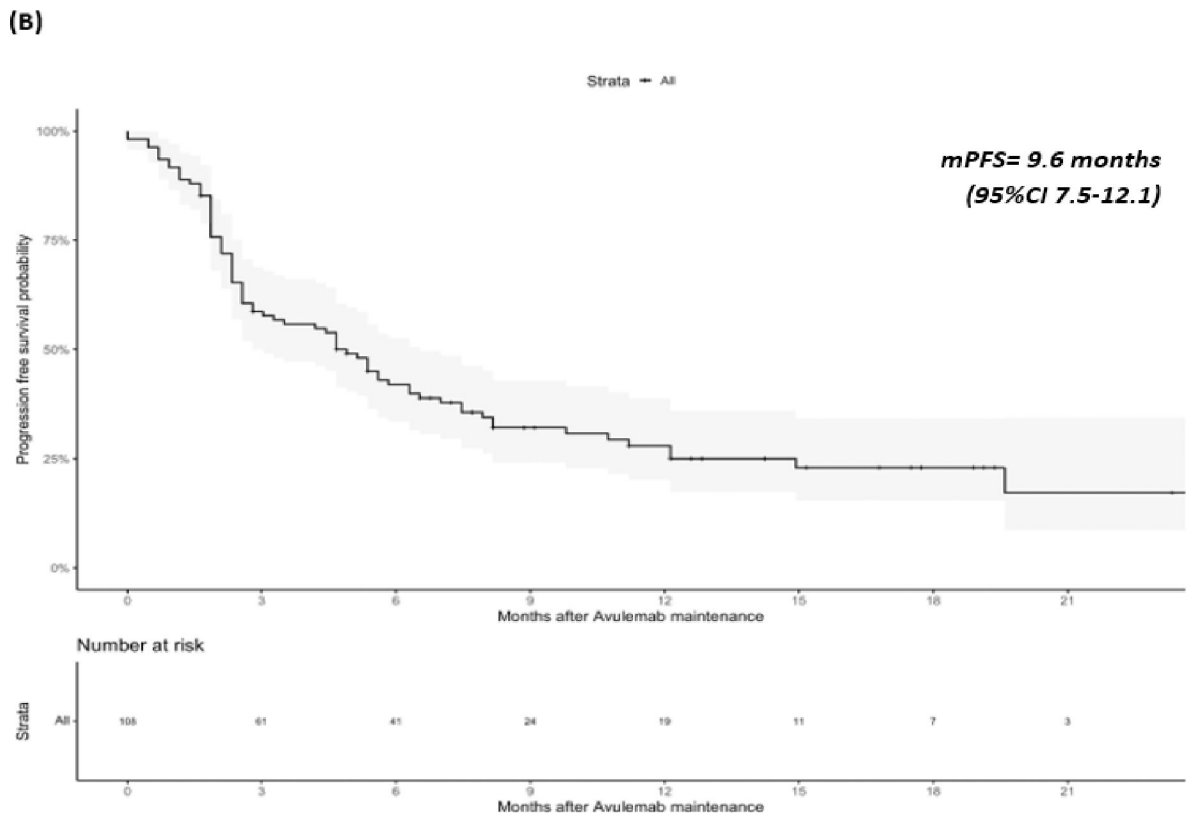
(A)

(B)

Strata — All

mPFS= 9.6 months
(95%CI 7.5-12.1)
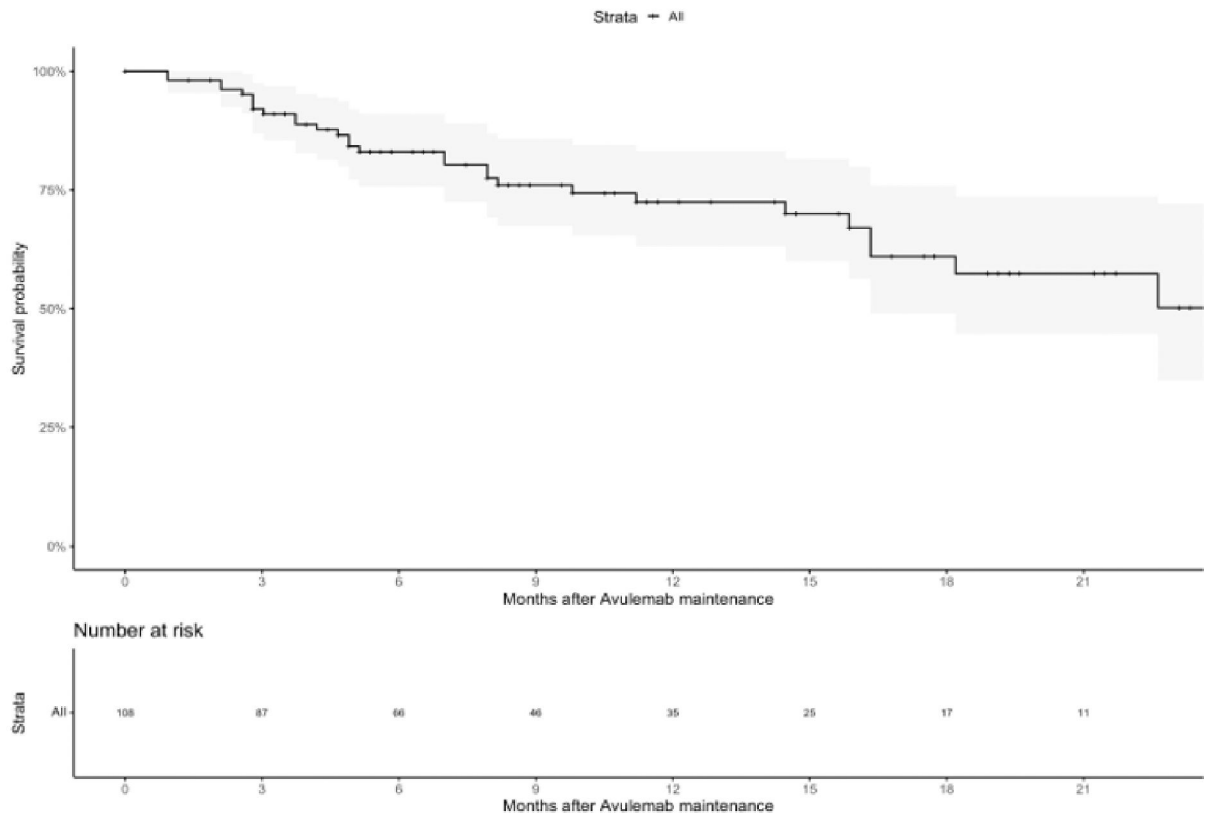
Figure 1:
Overall Survival (OS) (A) and Progression Free Survival (PFS) (B) for the entire population.
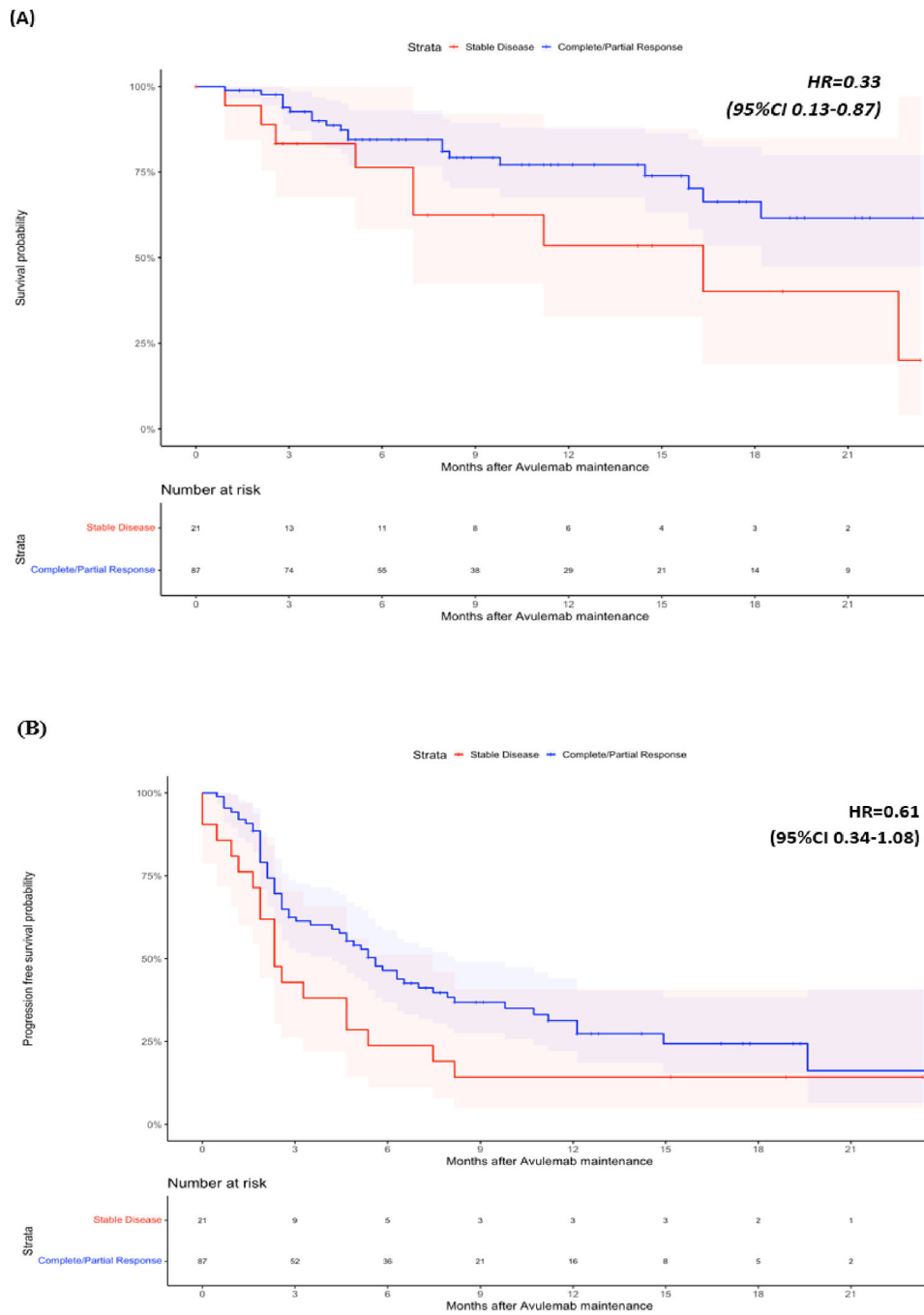
(A)

(B)

Figure 2:

Overall Survival (OS) (A) and Progression Free Survival (PFS) (B) of subjects stratified by best response to Platinum Based Chemotherapy.
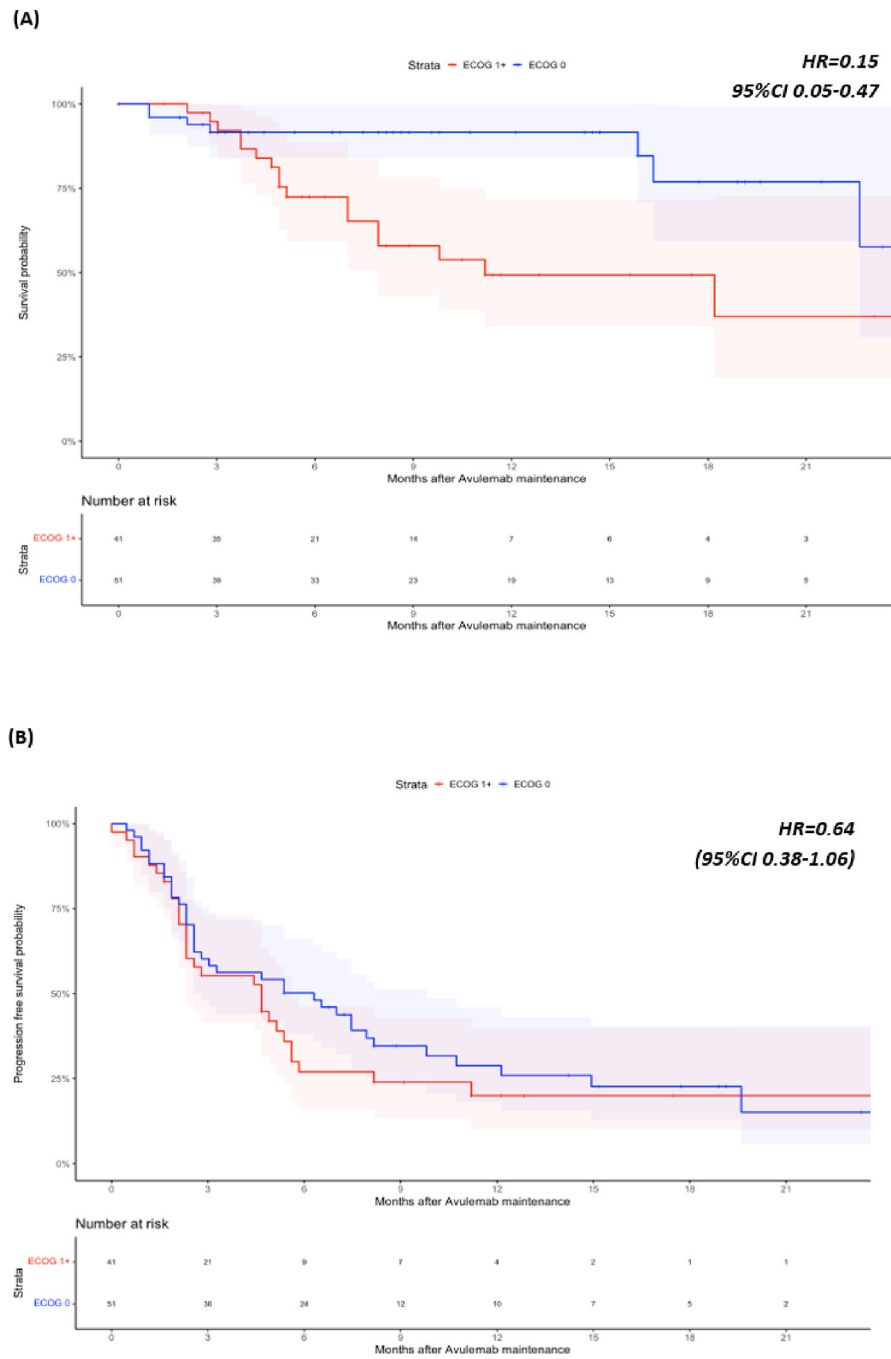
(A)

(B)

Figure 3:
Overall Survival (OS) (A) and Progression Free Survival (PFS) (B) of subjects stratified by ECOG Performance Status (PS)

Table 1:

Baseline characteristics of patients who received avelumab maintenance.

	Overall population (N=108) n (%)
Age of cancer diagnosis	69 [31.3, 96.2] *
Sex	
Male	87 (80.6)
Female	21 (19.4)
Race	
White	100 (92.6)
Not white	6 (5.6)
Unknown	2 (1.9)
Smoking history	
Yes	63 (58.3)
No	43 (39.8)
Missing	2 (1.9)
Tumor site	
Lower urinary tract	92 (85.2)
Upper urinary tract	16 (14.8)
Pure UC histology	
Yes	85 (78.7)
No	23 (21.3)
ECOG PS at PBC start	
0	51 (47.2)
1	38 (35.2)
2	3 (2.8)
Missing	16 (14.8)
Cycles of 1L PBC	
>4 cycles	62 (57.4)
4 cycles	42 (38.9)
Missing	4 (3.7)
Liver metastases	
No	95 (88)
Yes	13 (12)
Weeks from last PBC to avelumab initiation	
3 weeks	18 (16.7)
4–10 weeks	76 (70.3)
>10 weeks	14 (13)
Platinum agent	
Carboplatin	37 (34.3)

	Overall population (N=108) n (%)
Cisplatin	71 (65.7)
Best response to PBC	
Complete Response	18 (16.7)
Partial Response	69 (63.9)
Stable Disease	21 (19.4)

PBC: Platinum Based Chemotherapy

*
 Median [Min, Max]

Table 2:

Response and outcomes to avelumab maintenance treatment

	(N=108)
Best response to Avelumab maintenance	
Complete Response	19 (17.6)
Partial Response	12 (11.1)
Stable Disease	32 (29.6)
Progressive Disease	29 (26.9)
Unknown [*]	16 (14.8)
Overall Response Rate (ORR) %	28.7%
Reason of avelumab discontinuation	
Clinical Progression	12 (11.1)
Radiographic Progression	34 (31.5)
Toxicity	6 (5.6)
Other	8 (7.4)
Patient still on treatment	48 (44.4)

[*] Most of those patients did not have response evaluation or were lost to follow-up

Table 3:

Hazard ratios (HR) for Overall Survival (OS) and Progression-free survival (PFS) for specific subsets

Variable	OS		PFS	
	HR	*95%CI*	*HR*	*95%CI*
Sex (Female vs Male)	1.76	0.68–4.50	1.29	0.70–2.36
Smoking History (No vs Yes)	0.70	0.27–1.78	0.94	0.57–1.55
Upper vs Lower tract	1.19	0.33–4.29	1.32	0.64–2.74
Histology (pure vs mixed UC)	1.09	0.37–3.21	0.91	0.52–1.57
PBC Regimen (Cis vs Carbo)	2.25	0.88–5.77	1.58	0.90–2.76
Cycles of PBC (4 vs >4)	0.80	0.30–2.15	1.13	0.67–1.91
Liver mets at start of PBC (Yes vs No)[*]	1.06	0.35–3.18	2.32	1.17–4.59
ECOG PS (0 vs 1) at start of PBC[*]	0.15	0.05–0.47	0.64	0.38–1.06
Best response to PBC (CR/PR vs SD)[*]	0.33	0.13–0.87	0.61	0.34–1.08
Weeks from PBC end to avelumab initiation (3 vs 4–10)	1.46	0.48–4.41	1.59	0.84–3.00
Weeks from PBC end to avelumab initiation (>10 vs 4–10)	0.59	0.13–2.75	0.44	0.19–1.05

CI: Confidence Interval, CR: Complete Response, ECOG PS: Eastern Cooperative Oncology Group Performance Status, Mets: Metastases, OS: Overall Survival, HR: Hazard Ratio, PBC: Platinum-based Chemotherapy, PFS: Progression-Free Survival, PR: Partial Response, SD: Stable disease

[*]Significant variables (a = 0.05)