Poster #66

Benchmarking Maintenance Therapy Survival in First-Line Advanced Urothelial Carcinoma Using Disease Modeling

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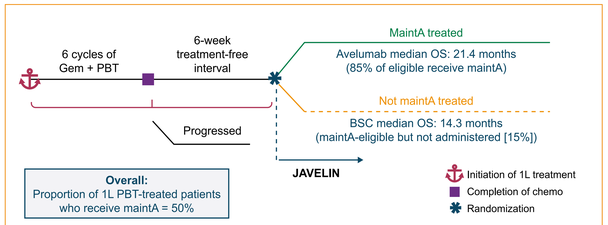
Background and Objective

- Maintenance avelumab (maintA) following first-line (1L) therapy in patients with advanced urothelial carcinoma (aUC) prolonged overall survival (OS) in the JAVELIN Bladder 100 trial.[1]
- MaintA is the new standard of care for patients with aUC who have no evidence of disease progression following 1L platinum-based therapy (PBT) in the NCCN[2] and ESMO treatment guidelines with level 1 evidence.[3]
  - However, differences in study design mean the survival benefit of maintA cannot be compared with that of other 1L therapies using conventional methods such as network meta-analyses.[4]
- JAVELIN measured OS from initiation of maintA among a subgroup of the overall aUC 1L-treated population with receipt of maintA based on a conditional eligibility.[1]
  - Patients received maintA if they had no disease progression (complete response, partial response, or stable disease) after 4–6 cycles of gemcitabine (Gem) + PBT and following a treatment-free interval of 4–10 weeks (**Figure 1**).

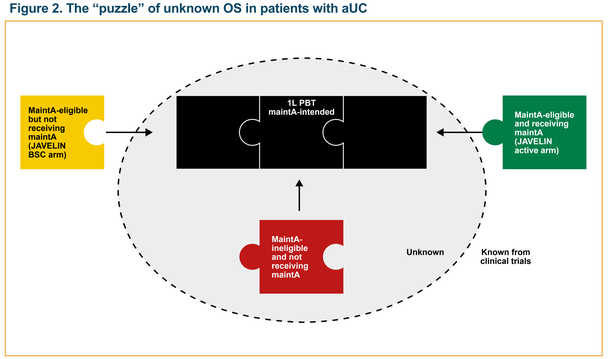
Figure 1. Estimation of OS for maintA measured from the initiation of 1L PBT: model inputs



1L, first-line; BSC, best supportive care; Gem, gemcitabine; maintA, maintenance avelumab; OS, overall survival; PBT, platinum-based therapy.

- Patients who progressed on or immediately following PBT were not included in JAVELIN; as a result, the OS of the maintA-ineligible subgroup and of the overall population of patients treated with 1L PBT with the intention to receive maintA (1L PBT maintA-intended) is unknown (**Figure 2**).
- To address this, we used disease modeling to estimate the OS of patients with aUC who received 1L treatment, including both maintA-eligible and -ineligible patients, measured from initiation of 1L PBT to align OS in patients receiving maintA with the common initiation point, so as to benchmark with other 1L clinical trials.

Figure 2. The "puzzle" of unknown OS in patients with aUC



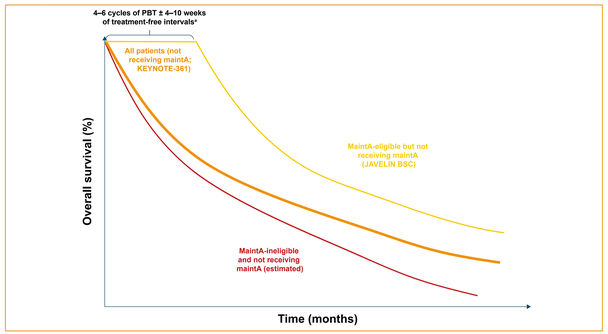
Overall survival in patients treated with 1L PBT with the intention to receive maintA (1L PBT maintA-intended) is unknown but can be modeled from known data from the "MaintA-eligible but not receiving maintA" population from the JAVELIN BSC arm (yellow) and the "MaintA-eligible and receiving maintA" population from the JAVELIN active arm (green), together with unknown data from the "MaintA-ineligible and not receiving maintA" population (red) estimated in this analysis.

1L, first-line; aUC, advanced urothelial carcinoma; BSC, best supportive care; maintA, maintenance avelumab; OS, overall survival; PBT, platinum-based therapy.

Methods

- We developed a simulated cohort to estimate OS from initiation of 1L PBT in patients with aUC who received maintA and those who did not, to simulate OS in all patients with aUC treated with 1L PBT with the intention to receive maintA (1L PBT maintA-intended; **Figure 2**).
  - The 1L PBT maintA-intended population consists of maintA-eligible patients who may or may not receive maintA.
  - Non-receipt of maintA consists of patients ineligible for maintA and patients eligible for maintA but, due to patient/provider decision-making, do not choose to receive maintA treatment.
- To estimate the OS of patients with aUC who were maintA-ineligible and not receiving maintA, we used the known OS of the overall aUC population informed by KEYNOTE-361,[5] and the known OS of patients who were maintA-eligible but not receiving maintA, informed by the JAVELIN best supportive care (BSC) arm[1] (**Figure 3**).

Figure 3. Estimation of the OS of patients with aUC not treated with maintA (maintA-ineligible, or eligible and not treated)



All patients not receiving maintA consists of patients from the KEYNOTE-361[5] control arm who were treated with PBT without subsequent maintA and includes both maintA-ineligible and maint-eligible patients.

[a]The horizontal portion of the maintA-eligible (not receiving maintA) line reflects the eligibility criteria of JAVELIN and shows the 5.6-month run-in (accounting for 6 PBT cycles and a nominal 6-week treatment-free interval) time interval during which a patient must remain progression-free between PBT and the start of maintA treatment in the JAVELIN trial.[1]

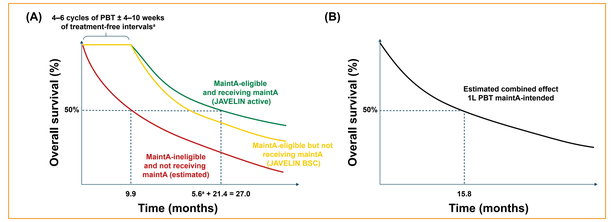
aUC, advanced urothelial carcinoma; maintA, maintenance avelumab; OS, overall survival; PBT, platinum-based therapy.

- The proportion of patients who were eligible for maintA was estimated from progression-free survival (PFS) data from the control arm of KEYNOTE-361.[5]
  - Considering this PFS curve between 4–7 months (aligning to at least 4 cycles of PBT and a treatment-free period of 4–10 weeks), there was a range of 55–84% of patients who remained progression-free.
  - For this model, we estimate that 57% (corresponding to the likely scenario of 6 cycles of PBT and a 6-week treatment-free interval) would be progression-free and eligible for maintA.
- JAVELIN included a maintA-treated arm, from which we assumed that 85% of eligible patients received maintA, and a BSC arm, from which we assumed that 15% of maintA-eligible patients did not receive maintA; with these assumptions based on the authors' (MG and TP) clinical experience.
- Key inputs to the model to estimate OS were taken from JAVELIN, with the BSC arm providing data on patients eligible for maintA but not receiving maintA, and the active arm providing data on patients receiving maintA (**Figure 1**).
  - In the JAVELIN active arm (receiving maintA), median OS was 21.4 months.
  - In the JAVELIN BSC arm (not receiving maintA), median OS was 14.3 months.
  - Due to the conditional eligibility of the maintA cohort, patients with stable disease received maintA leading to improved OS, whereas those with progressive disease were ineligible for maintA, contributing to shorter OS.
- As illustrated in **Figure 2**, the unsolved puzzle of OS in the 1L PBT maintA-intended cohort, measured from initiation of 1L PBT, was estimated from: (1) the maintA-eligible but not receiving maintA population from the JAVELIN BSC arm; (2) the maintA-eligible and receiving maintA population from the JAVELIN active arm; and (3) the maintA-ineligible and not receiving maintA population estimated in this analysis (**Figure 3**).
  - As JAVELIN[1] and KEYNOTE-361[5] data were available for the subgroup of 1L PBT-treated patients receiving Gem + carboplatin (carbo), we also conducted analyses within this subgroup; however, as data for the Gem + cisplatin subgroup were not available from KEYNOTE-361[5], we were not able to conduct the analysis in that subgroup.
- Scenario analyses were conducted using OS inputs from the control arms of other contemporary clinical trials such as IMvigor130[6] and DANUBE[7] in addition to the base case (KEYNOTE-361[5]).

Results

- The model estimated that approximately 50% of the 1L PBT-treated population received maintA; based on 57% of patients being maintA-eligible multiplied by the assumption that 85% of maintA-eligible patients received maintA.
- Our approach estimated a median OS of 9.9 months for the maintA-ineligible and not receiving maintA cohort, compared with 27.0 months for the maintA-eligible and receiving maintA cohort (**Figure 4A**).
- Combined, the estimated median OS of 1L PBT maintA-intended patients was 15.8 months (**Figure 4B**).
- As an illustrative comparison, the estimated combined effect on OS of 1L Gem + PBT followed by maintA was 15.8 months compared with 14.3 months (95% confidence interval [CI]: 12.3–16.7) with Gem + PBT only, as reported in the control arm of KEYNOTE-361.[5]
- In the subgroup analysis in patients treated with Gem + carbo (assumed to be cisplatin-ineligible), estimated OS was 13.5 months with Gem + carbo with maintA, compared with 12.3 months (95% CI: 10.0–15.5) with Gem + carbo only in KEYNOTE-361.[5]

Figure 4. Estimated OS in 1L PBT maintA-intended patients with aUC from initiation of 1L PBT



(A) OS in maintA-eligible patients not receiving maintA from the JAVELIN BSC arm (yellow), OS in maintA-eligible patients receiving maintA from the JAVELIN active arm (green), and the estimated OS in maintA-ineligible patients not receiving maintA (red) were used to calculate (B) the combined OS in 1L PBT maintA-intended patients (black).

[a]Includes 5.6-month run-in period in which no patient mortality was reported.

1L, first-line; aUC, advanced urothelial carcinoma; BSC, best supportive care; maintA, maintenance avelumab; OS, overall survival; PBT, platinum-based therapy.

- Scenario analysis found that varying the proportion of eligible patients with aUC in the 1L PBT maintA-intended cohort who received maintA between 20% and 50% led to a median OS range of 12.5–15.8 months (**Table 1**).
  - If the percentage of the 1L PBT maintA-intended population receiving maintA was increased to 67% (ie, 100% of eligible patients received maintA without any treatment-free period), then the estimated OS was 16.5 months.

Table 1. Scenario analysis of proportion of 1L PBT maintA-intended population who received maintA

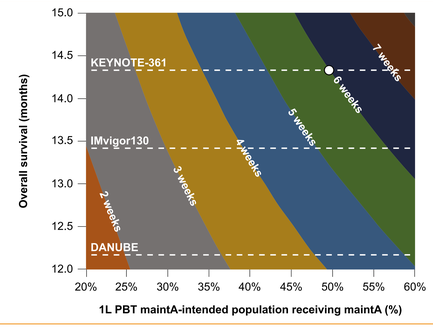
	Percentage of 1L PBT maintA-intended population who received maintA (proportion who were eligible × proportion who received maintA)			
Survival outcomes[a]	**20%**	**30%**	**40%**	**50%**
KEYNOTE-361[5] (14.3 mOS) (7.1 mPFS – 57% eligible[b])	**14.9 pop mOS** Δ0.6 (33% of eligible)	**15.2 pop mOS** Δ0.9 (50% of eligible)	**15.5 pop mOS** Δ1.2 (66% of eligible)	**15.8 pop mOS** Δ1.5 (83% of eligible)
IMvigor130[6] (13.4 mOS) (6.3 mPFS – 53% eligible[b])	**13.9 pop mOS** Δ0.5 (35% of eligible)	**14.2 pop mOS** Δ0.8 (53% of eligible)	**14.4 pop mOS** Δ1.0 (71% of eligible)	**14.7 pop mOS** Δ1.3 (88% of eligible)
DANUBE[7] (12.1 mOS) (6.7 mPFS – 55% eligible[b])	**12.5 pop mOS** Δ0.4 (34% of eligible)	**12.7 pop mOS** Δ0.6 (51% of eligible)	**12.9 pop mOS** Δ0.8 (68% of eligible)	**13.1 pop mOS** Δ1.0 (85% of eligible)

[a]OS and PFS outcomes reported in months. For each cell, the "% of eligible" represents the proportion of the patients eligible for maintA who receive maintenance therapy. [b]Proportion of 1L-treated patients eligible for maintA (not progressed) at the time of maintA-eligibility assessment (5.6 months). Δ Difference in mOS between a 1L-chemotherapy population and a 1L chemotherapy with maintA-availability population.

1L, first-line; maintA, maintenance avelumab; mOS, median overall survival; mPFS, median progression-free survival; PBT, platinum-based therapy; pop, population.

- If key baseline assumptions (% of eligible patients receiving maintA and median OS following Gem + PBT) were varied, the survival benefit of 1L Gem + PBT followed by maintA relative to Gem + PBT alone among 1L PBT maintA-intended patients was shown to vary between 2 and 8 weeks (or approximately 0.5–2 months; **Figure 5**).

Figure 5. Contour plot of population-level OS impact across included clinical trials[1,5-7,a]



[a]By varying the proportion of the 1L PBT maintA-intended population receiving maintA (x-axis) and varying the mOS associated with PBT between 12.0 and 15.0 months (y-axis), the survival benefit from maintA ranged from 2 to 8 weeks (shown in colored bands). mOS for included clinical trials is shown by the dotted lines. The white dot highlights the expected survival benefit of 6 weeks from KEYNOTE-361 if 50% of patients received maintA (compared with 5 weeks from IMvigor130 and 4 weeks from DANUBE).

1L, first-line; maintA, maintenance avelumab; mOS, median overall survival; PBT, platinum-based therapy; OS, overall survival.

Limitations

- OS data are based on published data from 1L clinical trials, which may overestimate real-world outcomes.
- The proportion of patients moving onto maintA is estimated using PFS curves from contemporary 1L trials; real-world data will be needed to validate these estimates.
- A lack of patient-level data meant that simplifying assumptions were made for the statistical modeling of OS in the maintA-ineligible subpopulation.
  - However, this was necessary as existing trials, including JAVELIN,[1] did not enroll patients from 1L initiation.
  - Because of a lack of patient-level data, estimates were conservative, with fewer patients potentially receiving maintA in clinical practice.
- Subgroup analyses, including those reported for the Gem + carbo subgroup, are subject to limitations due to sample size and the characteristics of the patient population studied.

Conclusions

- Patients who receive maintA have a longer median OS from the initiation of 1L PBT (27.0 months) compared with patients who are not eligible or do not receive maintA (9.9 months).
- Our simulation model suggests that 50% of 1L PBT-treated patients with aUC will not receive maintA, regardless of their eligibility.
- The estimated median OS in 1L PBT maintA-intended patients was 15.8 months at a population level, which is a small improvement compared with the 14.3-month OS with Gem + PBT alone, demonstrating continuing unmet need in the overall 1L aUC population even following the introduction of this new standard of care.
- Patients treated with Gem + carbo at 1L show less OS gain from maintA treatment than patients receiving Gem + PBT, highlighting even greater unmet need in this subgroup of patients.

References

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HSW and ZH are employees of, and own stock in, Seagen Inc.
BB and JT are employees of Curta Inc., paid consultants to Seagen Inc. in connection with this study.
EL is an employee of Astellas Pharma Inc.
TP is a paid consultant for Incye, has received consultancy fees, and research funding from Astellas, AstraZeneca, Bristol Myers Squibb, Eisai, EMD Serono, Exelixis, F. Hoffmann-La Roche, Ipsen Biopharm Limited, Johnson & Johnson, Merck, MSD, Novartis, Pfizer, and Seagen Inc.; and has received travel costs from AstraZeneca, F. Hoffmann-La Roche, Ipsen Biopharm Limited, MSD, and Pfizer.

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