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Simulated median overall survival of gemcitabine + carboplatin ± maintenance avelumab therapy or enfortumab vedotin + pembrolizumab in first-line treatment of la/mUC in patients ineligible for cisplatin using disease modeling

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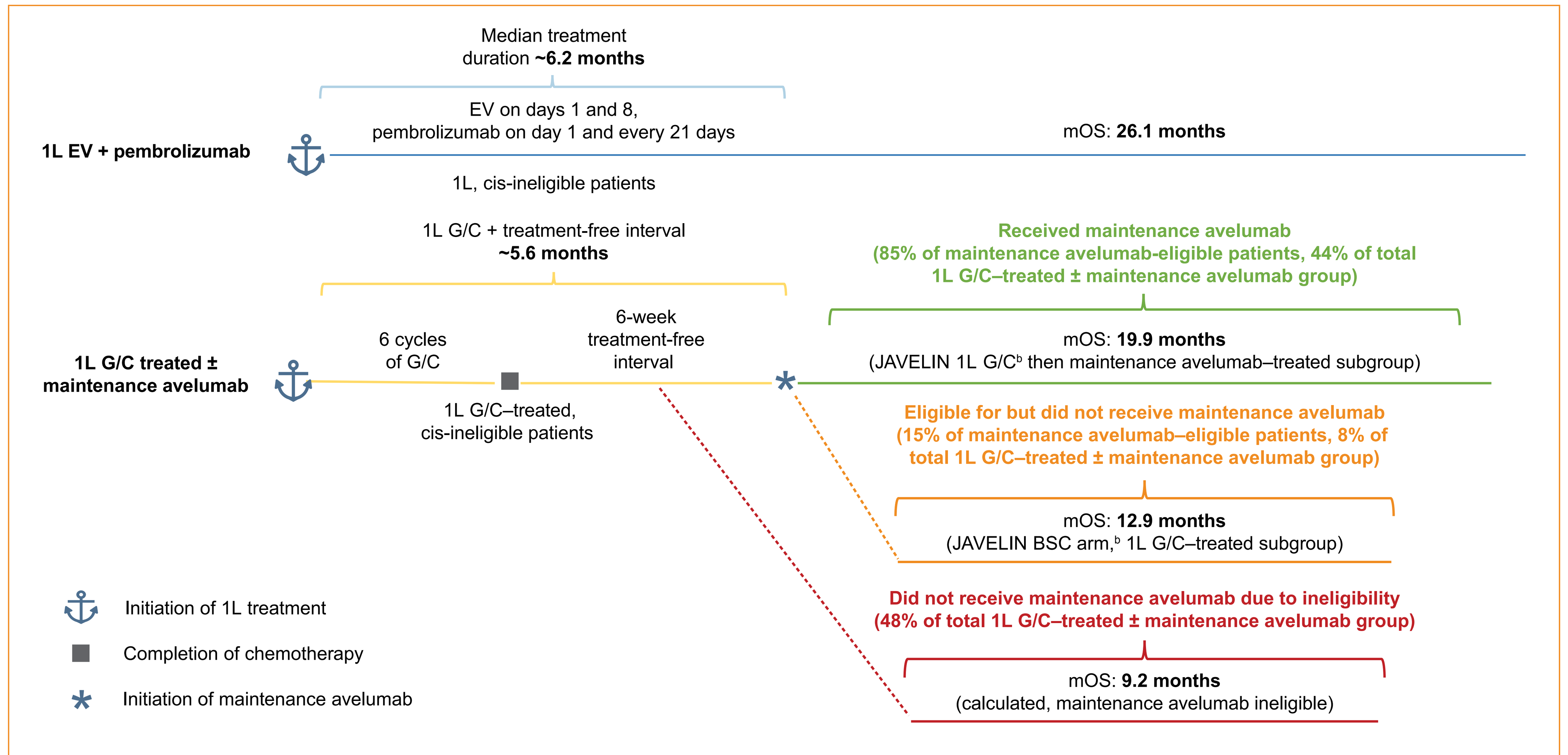
Background

- Maintenance avelumab treatment following first-line (1L) platinum-based therapy (PBT) prolonged overall survival (OS) in patients with locally advanced or metastatic urothelial carcinoma (la/mUC) in the JAVELIN Bladder 100 trial (JAVELIN).[1]
- Maintenance avelumab is now standard of care for patients with la/mUC who have no evidence of disease progression following 1L PBT, as per both the National Comprehensive Cancer Network® treatment guidelines and the European Society for Medical Oncology treatment guidelines.[2,3]
  - Recent real-world evidence suggests that only ~50% of patients with la/mUC who are cisplatin (cis) ineligible are eligible for maintenance avelumab, chiefly due to disease progression or death with 1L PBT.[4]
- Enfortumab vedotin (EV) + pembrolizumab was recently granted accelerated approval by the United States Food and Drug Administration for use as a 1L treatment in cis-ineligible patients with la/mUC based on efficacy data from the ongoing, multicohort phase 1/2 study EV-103.[5,6]
- EV + pembrolizumab is also being evaluated as a 1L treatment in both cis-eligible and cis-ineligible patients with la/mUC in the open-label, phase 3 study EV-302.
- As differences in trial design prevent indirect comparisons between JAVELIN Bladder 100, a maintenance study, and other studies of 1L therapies by traditional methods such as network meta-analysis, we used simulation modeling to estimate the impact of maintenance avelumab from the initiation of 1L therapy in cis-ineligible patients with la/mUC to contextualize outcomes with EV + pembrolizumab.[7]
  - This methodology has been used previously to benchmark the OS of patients with la/mUC who received or did not receive maintenance avelumab from initiation of 1L therapy.[8]

Methods

- A simulated cohort was developed to estimate median OS (mOS) from initiation of 1L gemcitabine + carboplatin (G/C) in cis-ineligible patients with la/mUC who:
  - *Received maintenance avelumab.*
  - *Eligible for but did not receive maintenance avelumab.*
  - *Did not receive maintenance avelumab due to ineligibility.*
- These estimates then were combined to provide an estimate of mOS in all patients with la/mUC who were cis ineligible and were treated with 1L G/C with the intention of receiving maintenance avelumab (1L G/C treated ± maintenance avelumab).
  - This estimated mOS then was compared descriptively with a simulated cohort of patients who received 1L EV + pembrolizumab.
  - In the base case, OS for patients treated with 1L G/C who were maintenance avelumab ineligible was calculated using OS data from the best supportive care arm of JAVELIN and the 1L G/C–treated (control) arm of KEYNOTE-361.[9,10]

Figure 1. Base case model OS inputs for the 1L EV + pembrolizumab and 1L G/C treated ± maintenance avelumab cohorts[a]



[a]mOS for each treatment measured from initiation of 1L therapy.
[b]mOS data taken from from JAVELIN trial.[1]

1L, first-line; BSC, best supportive care; cis, cisplatin; EV, enfortumab vedotin; G/C, gemcitabine + carboplatin; mOS, median overall survival; OS, overall survival.

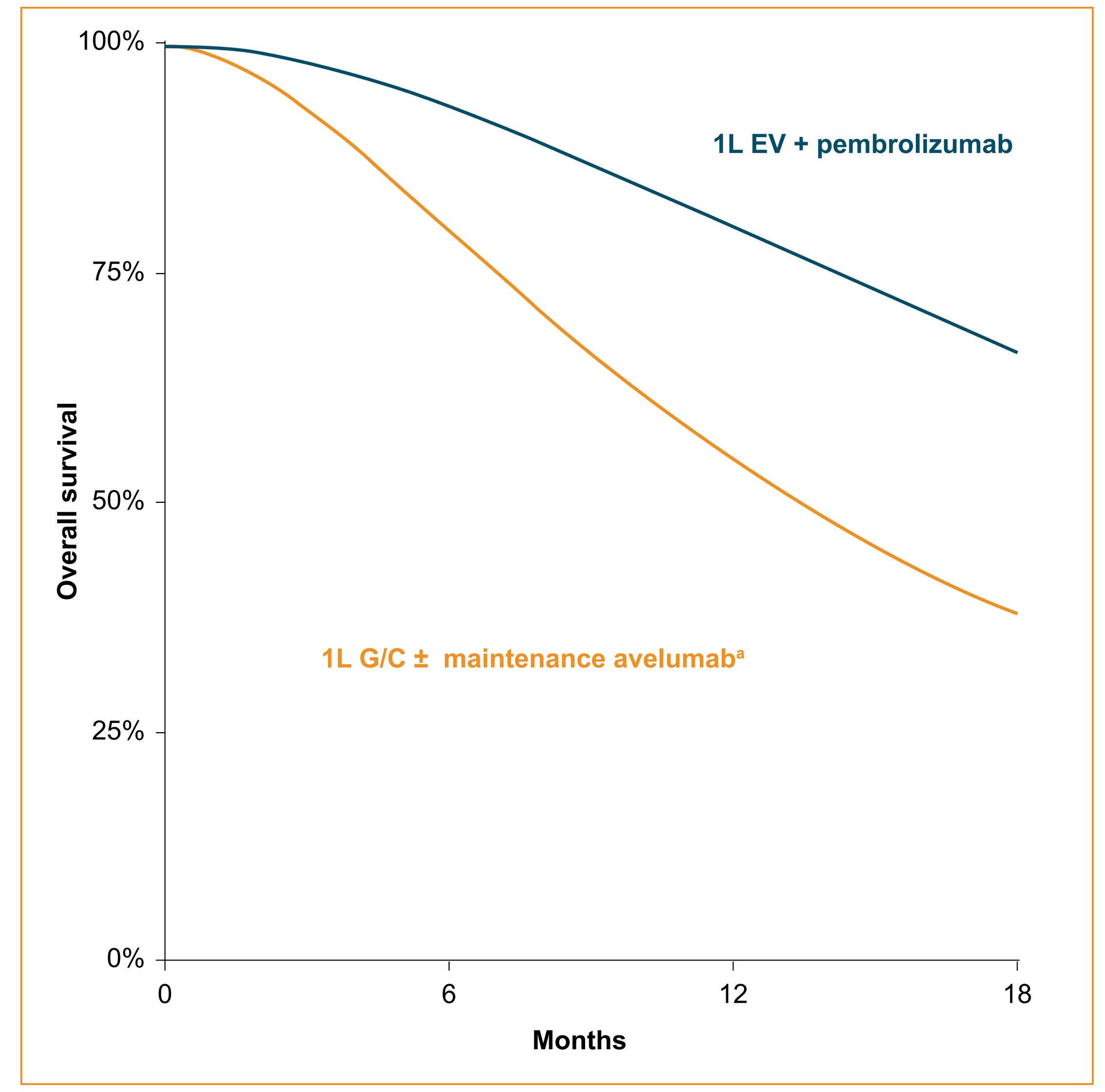
- Model inputs for the 1L EV + pembrolizumab group were from the EV-103 Dose Escalation/Cohort A trial.[11]
  - The 1L EV + pembrolizumab OS curve was digitized and fitted through standard parametric survival distributions. Based on statistical best fit, the log-logistic distribution was used to generate the simulated OS curve for 1L EV + pembrolizumab. The mOS for the 1L EV + pembrolizumab group was then estimated using this simulated OS curve.
- The model assumed that all patients in the 1L G/C–treated ± maintenance avelumab cohort received 6 cycles of G/C followed by a 6-week treatment-free interval, resulting in a time period of 5.6 months between 1L G/C initiation and maintenance avelumab initiation (**Figure 1**).
- The proportion of patients eligible for maintenance avelumab was estimated based on progression-free survival (PFS) data from the 1L G/C–treated (control) arm of KEYNOTE-361.[10]
  - Based on the PFS curve, 52% of patients were progression free at 5.6 months and were considered maintenance avelumab eligible.
- Based on the authors' (MDG, GPS, and TP) clinical experience, it was estimated that 85% of eligible patients would receive maintenance avelumab, so 44% of the total 1L G/C–treated ± maintenance avelumab cohort were estimated to receive maintenance (based on 52% of patients being maintenance avelumab eligible multiplied by the assumption that 85% of eligible patients received maintenance avelumab). Two sensitivity analyses were conducted to test the base case:
  - The first sensitivity analysis used the PFS curve for the 1L G/C–treated subgroup of the DANUBE study control arm to estimate the proportion of 1L G/C–treated patients eligible for maintenance avelumab (instead of the PFS curve for the 1L G/C–treated [control] arm of KEYNOTE-361).[12]
  - The second sensitivity analysis varied both the percentage of maintenance avelumab–eligible patients who received maintenance avelumab between 75% and 100% and the time period between 1L G/C treatment and starting maintenance between 3.7 and 6.5 months.
    - This range between 1L G/C treatment and maintenance was based on the lower and upper bounds of time spent on 1L treatment plus the treatment-free interval in the JAVELIN trial.[1]

Results

Base case

- Combined, the estimated mOS for the 1L G/C–treated ± maintenance avelumab cohort was 13.5 (95% CI: 11.1-16.1) months. This was based on the following mOS estimates for each patient subgroup.
  - 25.5 months for the received maintenance avelumab population.
  - 18.5 months for the eligible for but did not receive maintenance avelumab population.
  - 9.2 months for the did not receive maintenance avelumab due to ineligibility population.
- The estimated mOS for the 1L EV + pembrolizumab cohort was 26.5 (95% CI: 18.7-37.9) months (**Figure 2**) based on the simulated OS curve.

Figure 2. Base case. Estimated mOS



[a]The combined mOS in the 1L G/C ± maintenance avelumab cohort was calculated based on the weighted average hazard of the 3 patient subgroups together: 1) Received maintenance avelumab, 2) Eligible for but did not receive maintenance avelumab, 3) Did not receive maintenance avelumab due to ineligibility.

1L, first-line; EV, enfortumab vedotin; G/C, gemcitabine + carboplatin; mOS, median overall survival.

Sensitivity analyses

- Substituting the PFS curve from the 1L G/C–treated subgroup in the DANUBE trial control arm in place of data from the 1L G/C–treated (control) arm of KEYNOTE-361 resulted in an estimated mOS for the 1L G/C ± maintenance avelumab–treated cohort of 11.4 months, compared with 13.5 months in the base case.
- Varying the percentage of patients who were eligible for maintenance avelumab and who received maintenance avelumab treatment and varying the time period between 1L G/C and maintenance avelumab initiation had minimal impact on estimated mOS (range: 13.2-14.6 months) compared with the base case (13.5 months) (**Table 1**).
  - For example, if the time period between 1L G/C and maintenance avelumab initiation was reduced to 3.7 months (compared with 5.6 months in the base case), and the percentage of maintenance avelumab–eligible patients modeled to receive treatment was increased to 100%, then the resulting mOS was 14.6 months (versus 13.5 months in the base case).

Limitations

- As OS data inputs were taken from previously published clinical trials, OS estimates may not reflect real-world patient outcomes.
- The proportion of maintenance-eligible patients who received maintenance avelumab included in this model may not be reflective of real-world uptake; recent data suggest maintenance avelumab uptake may be lower in clinical practice.[13]

Table 1. Sensitivity analysis. Modeling the mOS of the 1L G/C ± maintenance avelumab–treated cohort across different treatment uptake scenarios and intervals between 1L G/C and maintenance initiation

% of maintenance avelumab eligible, modeled to receive treatment	Treatment interval between 1L G/C completion and maintenance avelumab initiation		
	3.7 months[a] 64% maintenance avelumab eligible	5.6 months[b] 52% maintenance avelumab eligible	6.5 months[c] 46% maintenance avelumab eligible
	mOS (months)		
75%	14.2	13.3	13.2
85%	14.3	13.5 (base case)	13.4
95%	14.5	13.6	13.5
100%	14.6	13.7	13.6

[a]Interval assumes 4 cycles of 1L G/C and 4 weeks of treatment-free interval, with maintenance avelumab eligibility based on the PFS curve of the 1L G/C–treated (control) arm of KEYNOTE-361.

[b]Base case assumption of 5.6-month interval, including 6 cycles of 1L G/C and 6 weeks of treatment-free interval, with maintenance avelumab eligibility based on the PFS curve of the 1L G/C–treated (control) arm of KEYNOTE-361.

[c]Interval assumes 6 cycles of 1L G/C and 10 weeks of treatment-free interval, with maintenance avelumab eligibility based on the PFS curve of the 1L G/C–treated (control) arm of KEYNOTE-361.

1L, first line; G/C, gemcitabine + carboplatin; mOS, median overall survival ; PFS, progression-free survival.

Conclusions

- This simulation model estimates that 1L EV + pembrolizumab may be associated with a longer mOS than 1L G/C ± maintenance avelumab in cis-ineligible patients with la/mUC.
- Sensitivity analyses were consistent with the base case mOS estimate, with mOS substantially longer with 1L EV + pembrolizumab than with 1L G/C ± maintenance avelumab in all additional analyses.
- While the findings of this model will need to be confirmed by the ongoing EV-302 clinical trial, this model may help illustrate the potential role of EV + pembrolizumab in 1L la/mUC therapy in the context of existing data from the JAVELIN Bladder 100 study.

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BB and JT are employees of Curta Inc. and paid consultants to Seagen Inc. in connection with this study.
MF was an employee of, and holds stock in, Seagen Inc.
ZH is an employee of, and owns stock in, Seagen Inc.
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