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Simulating the impact of first-line treatment choice on survival among patients with locally advanced/metastatic urothelial carcinoma considered cisplatin ineligible

Matthew D Galsky,[1] Guru P Sonpavde,[2] Brian Bloudek,[3] Mallory Farrar,[4] Zsolt Hepp,[4] Jack Timmons,[3] Ryan Dillon,[5] Thomas Powles[6]

[1]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, NY, USA; [2]AdventHealth Cancer Institute, Orlando, FL, USA; [3]Curta Inc., Seattle, WA, USA; [4]Seagen Inc., Bothell, WA, USA; [5]Astellas Pharma Inc., Northbrook, IL, USA; [6]Barts Cancer Institute, Queen Mary University of London, London, UK

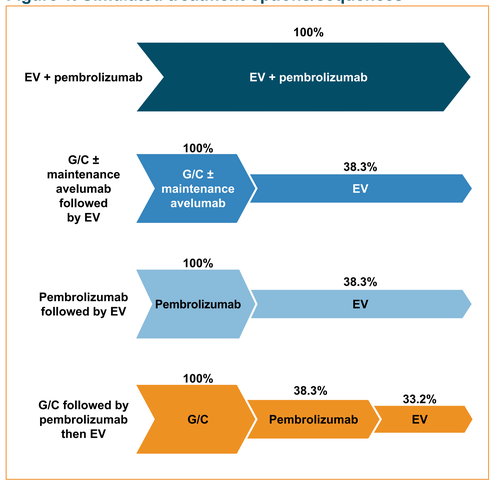
Background

- The rapidly evolving treatment landscape for locally advanced or metastatic urothelial carcinoma (la/mUC), together with challenges associated with differing trial designs, have limited direct comparisons of outcomes of different therapies and therapy sequences.
- Disease-state modeling can estimate the impact of various therapeutic sequences in the absence of head-to-head trials and ahead of the availability of real-world data.[1]
  - In addition, modeling can also be used to estimate the impact of treatment sequences that are unlikely to be investigated in a clinical trial.
- In this study, modeling was used to estimate median overall survival (mOS) among patients with la/mUC who were considered cisplatin (cis) ineligible and who were treated with 4 treatment options/sequences.

Methods

- mOS was estimated for a simulated cohort of treatment-naïve, cis-ineligible patients with la/mUC from initiation of 4 treatment options/sequences (**Figure 1**):
  1. Enfortumab vedotin (EV) + pembrolizumab.
  2. Gemcitabine + carboplatin (G/C) ± maintenance avelumab (includes those who received maintenance avelumab and those who did not, primarily due to ineligibility), followed by EV.
  3. Pembrolizumab followed by EV.
  4. G/C followed by pembrolizumab then EV.

Figure 1. Simulated treatment options/sequences[a]



[a]Percentages <100% are the proportions of patients receiving that treatment of those given the previous treatment in that option/sequence and are based on published real-world data on treatment rates for that line of treatment.[2]

EV, enfortumab vedotin; G/C, gemcitabine + carboplatin.

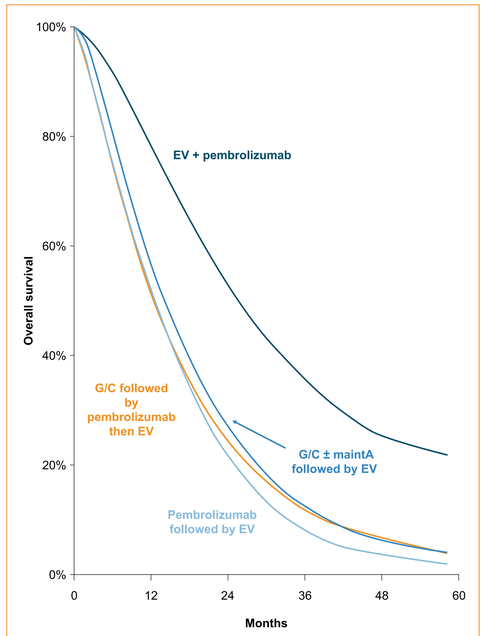
- For each treatment option/sequence, mOS was the composite Kaplan–Meier curve based on best-fit OS curves informed by published trials, and the treatment rate for each line of therapy was based on real-world data, using the previously published oncology simulation model framework.[1]
- Model inputs for the EV + pembrolizumab option/sequence were from the EV-103 Dose Escalation/Cohort A study.[3]
- Model inputs for the G/C ± maintenance avelumab followed by EV option/sequence were from the JAVELIN Bladder 100, KEYNOTE-361, and EV-301 studies.[4-6]
- Model inputs for the pembrolizumab followed by EV option/sequence were from the KEYNOTE-052 and EV-301 studies.[5,7]
  - EV-201 was considered as an alternative trial; however, the data were not selected for use in the base case because the study was a single-arm trial and had a smaller sample size than EV-301 had. These data were used in a separate sensitivity analysis.[8]
- Model inputs for the G/C followed by pembrolizumab then EV option/sequence were from the KEYNOTE-361, KEYNOTE-045, and EV-301 trials.[5,6,9]
- Progression from each treatment was based on progression-free survival curves of published trials and assumed all patients received first-line treatment.
- For each option/sequence, patients who did not receive a subsequent line of treatment stayed on the overall survival (OS) curve for their current treatment.
- In the base-case analysis, treatment rates during second line (2L) (38.3%) and third-line (3L) (33.2%) and attrition during treatment were based on published real-world data.[2]
- Two sensitivity analyses were conducted to investigate the robustness of the study's results:
  - The first sensitivity analysis varied 2L and 3L treatment rates for each treatment option/sequence between 20% and 60%. These utilization rates were chosen because they were thought to capture possible future treatment rates, which may differ from contemporary treatment patterns.
  - The second sensitivity analysis substituted data from the EV-301 trial with data from EV-201 Cohort 2, which comprised patients who were considered cis ineligible and had not received platinum-based chemotherapy prior to EV.[8]
    - These data were then used as scenarios to model OS for the pembrolizumab followed by EV treatment option/sequence.

Results

Model results. Base case

- The model generated an estimated mOS for each treatment option/sequence as follows:
  - 26.5 (95% credible interval [CrI]: 18.7-37.9) months for EV + pembrolizumab.
  - 14.4 (95% CrI: 12.4-16.4) months for G/C ± maintenance avelumab followed by EV.
  - 11.9 (95% CrI: 10.3-13.3) months for pembrolizumab followed by EV.
  - 12.7 (95% CrI: 10.9-14.7) months for G/C followed by pembrolizumab then EV (**Figure 2**).

Figure 2. Base case. Estimated mOS by treatment option/sequence received



Population	mOS (95% CrI)
EV + pembrolizumab	26.5 months (18.7-37.9)
G/C ± maintA followed by EV	14.4 months (12.4-16.4)
Pembrolizumab followed by EV	11.9 months (10.3-13.3)
G/C followed by pembrolizumab then EV	12.7 months (10.9-14.7)

CrI, credible interval; EV, enfortumab vedotin; G/C, gemcitabine/carboplatin; maintA, maintenance avelumab; mOS, median overall survival.

Table 1. Sensitivity analysis. Effect of 2L treatment rate on mOS for the treatment options/sequences: G/C ± maintenance avelumab followed by EV and pembrolizumab followed by EV

Treatment option/ sequence received	2L treatment rate					
	20%	30%	38.3% (base case)	40%	50%	60%
G/C ± maintenance avelumab followed by EV, mOS (months)	14.1	14.2	14.4	14.4	14.6	14.8
Pembrolizumab followed by EV, mOS (months)	11.2	11.6	11.9	11.9	12.3	12.7

2L, second-line; EV, enfortumab vedotin; G/C, gemcitabine + carboplatin; mOS, median overall survival.

Table 2. Sensitivity analysis. Effect of 3L treatment rate on mOS for the treatment option/sequence: G/C followed by pembrolizumab then EV

Treatment option/ sequence received	3L treatment rate					
	20%	30%	33.2% (base case)	40%	50%	60%
G/C followed by pembrolizumab then EV, mOS (months)	12.6	12.6	12.7	12.7	12.8	12.8

3L, third-line; EV, enfortumab vedotin; G/C, gemcitabine + carboplatin; mOS, median overall survival.

Model results. Sensitivity analyses

- Sensitivity analyses that varied treatment rates across 2L and 3L treatments between 20% and 60% resulted in small variations in mOS for modeled treatment options/sequences.
- mOS ranged from:
  - 14.1-14.8 months for G/C ± maintenance avelumab followed by EV (**Table 1**).
  - 11.2-12.7 months for pembrolizumab followed by EV (**Table 1**).
  - 12.6-12.8 months for G/C followed by pembrolizumab then EV (**Table 2**).
- Substituting data from the EV-301 trial with data from the EV-201 Cohort 2 trial resulted in a moderate improvement in patient mOS versus the base case for the pembrolizumab followed by EV sequence (14.3 [12.6-16.3] months versus 11.9 [10.3-13.3] months).

Limitations

- These analyses are limited by the small sample size of the EV + pembrolizumab group in the EV-103 Dose Escalation/Cohort A.
- OS data were based on previously published clinical trials, which may not reflect real-world patient outcomes.
  - There may be some differences in patient characteristics between treatment option/sequence received. In the G/C ± maintenance avelumab followed by EV and G/C followed by pembrolizumab then EV treatment options/sequences, G/C was taken as a marker of cis ineligibility, whereas in the pembrolizumab followed by EV treatment option/sequence, cis ineligibility in KEYNOTE-052 was confirmed by Galsky criteria.[10]
- A lack of data on attrition by treatment option/sequence meant that attrition for each line of therapy was assumed to be the same regardless of the previous treatment received; this may have led to underestimation of mOS with certain treatment options/sequences compared with real-world clinical practice where treatment uptake in subsequent lines may differ by prior line of therapy.
- Simulated treatment options/sequences have not been studied head to head in the clinical trial setting to date.

Conclusions

- Model results estimated longer mOS with EV + pembrolizumab (26.5 months) than with alternative treatment options/sequences starting with pembrolizumab or G/C (11.9-14.4 months).
- Sensitivity analyses varying the proportion of patients treated in 2L and 3L also supported these findings, as the estimated mOS of EV + pembrolizumab was longer than alternative treatment options/sequences.
- This analysis indicates the clinical value of selecting effective therapies at the point of first-line treatment initiation, rather than giving those same therapies in later lines. This analysis also highlights the importance of future longitudinal studies of alternative treatment options/sequences.

References

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BB and JT are employees of Curta Inc. and paid consultants to Seagen Inc. in connection with this study.
MF is a former employee of, and owns stock in, Seagen Inc.
ZH is an employee of, and owns stock in, Seagen Inc.
RD is an employee of, and owns stock in, Astellas Pharma Inc.
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Corresponding author: Matthew Galsky (matthew.galsky@mssm.edu)

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