Poster CO137

Are Standard Indirect Treatment Comparison Methods Suitable to Compare First-Line Vs Maintenance Therapies? An Assessment of Enfortumab Vedotin + Pembrolizumab Vs Avelumab in Locally Advanced/Metastatic Urothelial Carcinoma

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Objectives

- To perform a feasibility assessment using individual patient data (IPD) from EV-302 and aggregate-level data from JB-100 to assess the suitability of standard methods for an ITC of 1L EV+P versus PBC followed by avelumab maintenance in patients with la/mUC.
  - Outcomes of interest included PFS and OS.

Conclusions

- Differences in trial designs and populations between EV-302 and JB-100 preclude a scientifically robust and meaningful comparison through standard ITC methods.
  - The following between-study differences were identified:
    - Time of randomization (time-zero)
    - Timing of patient characteristics collection
    - Timing of endpoint assessment
    - Inclusion criteria (ECOG PS)
    - Patient characteristics that could bias relative treatment effects (geographic region, ECOG PS, liver metastases, lung metastases)
- Standard PAIC methods require that the index trial (EV-302) is aligned to the external target population trial (JB-100), so results will be representative of the JB-100 population (i.e., non-progressors following 1L PBC who are eligible for maintenance). The JB-100 population is a subset of the 1L treated population with survivorship bias and therefore not reflective of the FDA approved and NCCN/ESMO recommended population for EV+P.
- Therefore, standard PAIC methods are not suitable to estimate the comparative efficacy of 1L EV+P versus PBC with avelumab maintenance in patients with la/mUC.
  - Alternative non-standard ITC approaches that allow for time-zero adjustment and alignment of JB-100 with the EV-302 population could be explored.

Abbreviations

1L, first-line; BICR, blinded independent central review; BSC, best supportive care; CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; ESMO, European Society for Medical Oncology; EV+P, enfortumab vedotin + pembrolizumab; FDA, Food and Drug Administration; HR, hazard ratio; HTA, health technology assessment; IA, investigator assessment; IPD, individual patient data; ITC, indirect treatment comparison; ITT, intention to treat; la/mUC, locally advanced or metastatic urothelial carcinoma; NA, not applicable; NCCN, National Comprehensive Cancer Network; OS, overall survival; PAIC, population-adjusted indirect comparison; PBC, platinum-based chemotherapy; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; PS, performance status; R, randomization; RCT, randomized controlled trial; SD, stable disease.

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References

1. Astellas Pharma Inc. & Seagen Inc. https://www.astellas.com/en/news/28526.
2. Powles T, Park SH, et al. Annals of Oncology. 2023;34:S1340.
3. Powles TB, Perez Valderrama B, et al. The New England Journal of Medicine. 2024; 390(10).
4. Food and Drug Administration. Highlights of prescribing information: PADCEV. Revised 12/2023. Accessed March 2024.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Bladder Cancer; Version 3.2024 (April 16, 2024).
6. Powles T, Bellmunt J, et al. Annals of Oncology. 2024; doi:10.1016/j.annonc.2024.03.001.
7. Powles T, Park SH, et al. The New England Journal of Medicine. 2020; 383:1218-30.
8. Powles TB, Perez Valderrama B, et al. Annals of Oncology. 2023;34:S1340. doi:10.1016/j.annonc.2023.10.106.
9. Food and Drug Administration. Highlights of prescribing information: BAVENCIO. Revised 03/2024. Accessed March 2024.
10. European Medicines Agency. Bavencio European Public Assessment Report. Product number EMEA/H/C/004338. Revised 10/01/2024.
11. Goring S, Rogula B, et al. Value in Health. 2023;26(6, S4).
12. Cope S, Zhang J, et al. BMC medicine. 2014;12(1):1-17.
13. Sridhar SS, Powles T, et al. ASCO Genitourinary Cancers Symposium; February 16-18, 2023.

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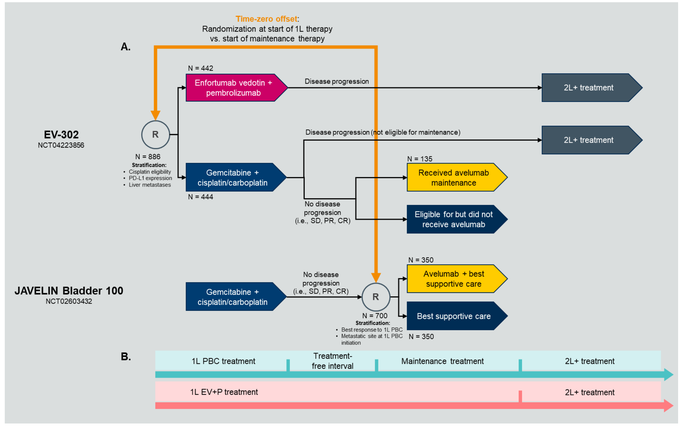
Background

- Enfortumab vedotin + pembrolizumab (EV+P) has been evaluated in a first-line (1L) locally advanced/metastatic urothelial carcinoma (la/mUC) population in the phase III randomized controlled trial (RCT) EV-302.
  - EV-302 met its dual primary endpoints of overall survival (OS) and progression-free survival (PFS) with EV+P demonstrating a significant benefit compared with gemcitabine + platinum-based chemotherapy (PBC).[1-3] These positive results led to EV+P being approved by the Food and Drug Administration (FDA)[4] and recommended as a preferred 1L treatment option for la/mUC regardless of cisplatin eligibility in both the National Comprehensive Cancer Network (NCCN)[5] and European Society for Medical Oncology (ESMO)[6] guidelines.
- Avelumab maintenance has been evaluated in the phase III RCT JAVELIN Bladder 100 (JB-100) in patients with la/mUC who did not have disease progression on or after 1L PBC.[7,8]
  - Based on results from JB-100, avelumab maintenance was approved by the FDA[9] and European Medicines Agency[10] for patients with la/mUC who have not progressed with 1L PBC. In the current ESMO guideline avelumab maintenance is a preferred treatment option in patients with no progression on 1L PBC regardless of cisplatin eligibility, while in the current NCCN guideline it is an "other recommended" option.[5,6]
- From a health technology assessment (HTA) perspective, 1L PBC followed by avelumab maintenance for non-progressors may be considered a relevant comparator for 1L EV+P. Beyond data from EV-302, where a subset (30.4%) of patients received avelumab maintenance following 1L PBC, there is no additional head-to-head clinical trial evidence comparing 1L EV+P vs. PBC followed by avelumab maintenance. An ITC could be considered to estimate the comparative efficacy between these treatments.
- However, the different trial designs of EV-302 and JB-100 present challenges for the application of standard ITC methods typically accepted in HTAs, and the treatment decisions made in clinical practice need to be considered in the context of patient selection (**Figure 1**).
  - A similar challenge with differences in "time zero" has been previously reported for resectable non-small cell lung cancer.[11]

Figure 1. Trial designs and treatment pathways. (A) EV-302 and JAVELIN Bladder 100 trial designs. **(B)** Overview of treatment pathways including 1L, maintenance, and subsequent treatment.



Methods

- A feasibility assessment was conducted using IPD from EV-302 and aggregate-level data from JB-100 to explore between-study differences in study/patient/treatment characteristics and outcomes.
  - The feasibility assessment process commonly used for network meta-analysis[12] was adapted for population-adjusted indirect comparison (PAIC) given the lack of common comparator between the two studies (**Figure 2**).
- The implications of feasibility assessment results on the application of PAIC methods typically accepted in HTAs were explored (i.e., matching-adjusted indirect comparison and simulated treatment comparison).
  - In standard PAIC methods, the index trial (EV-302) is matched to the external trial (JB-100) and results are representative of the JB-100 target population (i.e., non-progressors following 1L PBC who are eligible for maintenance).

Figure 2. Feasibility assessment process for population-adjusted indirect comparison

Are there between-study differences in terms of:

a) The distribution of study and patient characteristics that are expected to modify absolute or relative treatment effects?[a]
   - *Should patients from the index trial (EV-302) be excluded to align with inclusion criteria from the external study (JB-100)?*
   - *Should patient characteristic definitions from the index trial be adapted to align with the external study?*

b) Treatment and outcome definitions that are expected to modify relative treatment effects?
   - *Should index trial definitions be adapted to align with the external study?*

c) How the observed absolute effects are reported?
   - *Should index trial outcome reporting be adapted to align with the external study?*

Note: a) Effect modifiers were identified based on targeted literature review and clinical input.

Results

Between-study differences

Study design characteristics

- Patients in EV-302 were randomized before initiation of 1L therapy, while patients in JB-100 were randomized to maintenance therapy upon completion/discontinuation of 1L PBC (**Figure 1**).

Inclusion criteria

- EV-302 enrolled patients who had not received prior systemic therapy for la/mUC, while JB-100 enrolled a selected population of patients with la/mUC who had no disease progression after 4-6 cycles of 1L PBC and a treatment-free interval of 4-10 weeks since the last dose of chemotherapy.
- EV-302 enrolled patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2 prior to 1L therapy, while JB-100 enrolled patients with ECOG PS 0-1 after completion of 1L therapy.
  - The ECOG scores of JB-100 patients prior to 1L therapy are unknown.

Baseline patient characteristics

- All baseline characteristics were collected prior to 1L therapy in EV-302 but most characteristics in JB-100 were collected after completion of 1L therapy, although the site of metastases prior to 1L therapy was reported (**Table 1**).
- Between-study differences were observed in geographic region, ECOG PS, liver metastases, and lung metastases.
  - **Geographic region**: A greater proportion of patients in EV-302 were from North America than in JB-100, while more patients in JB-100 were from Europe; differences in geographic region may impact the availability of subsequent therapies (e.g., immunotherapies in second line).
  - **ECOG PS**: Fewer patients in EV-302 had an ECOG PS of 0 than JB-100, while more patients in EV-302 had an ECOG PS of 1, suggesting JB-100 patients may have an improved level of functioning.
    - In EV-302, only 3% of patients had an ECOG PS of 2. Despite JB-100 inclusion criteria restricting to ECOG PS 0-1, four patients (1%) with ECOG PS 2-3 were enrolled.
  - **Site of metastases prior to 1L therapy**: More patients in EV-302 had liver and lung metastases compared with JB-100, suggesting EV-302 patients may have had worse prognosis and as such the outcomes seen in EV-302 may be poorer.

Treatment characteristics

- In EV-302, EV+P was administered from the start of 1L, while in JB-100, avelumab was administered as maintenance therapy following 1L PBC in non-progressors**.**
- JB-100 required a 4-10-week treatment-free interval between completion of 1L PBC and initiation of maintenance (randomization), while in EV-302, avelumab maintenance could be used following completion and/or discontinuation of 1L PBC if locally available and if deemed appropriate by the investigator, so the timeframe of treatment-free interval was not specified for the control arm and was left to investigator discretion.
- More patients in JB-100 received subsequent anticancer drug therapies (52.9% in avelumab arm; 72.0% in BSC arm) than in EV-302 (29.0% in EV+P arm; 45.9% in chemotherapy arm) given a longer follow-up duration (median ≥38.0 months vs. 17.2 months, respectively), which should be considered when interpreting OS results.

Time of endpoint assessments, outcome definitions and observed treatment effects

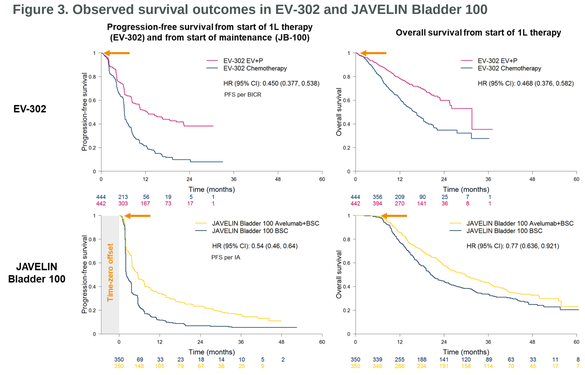
- Differences in time of randomization (time-zero) impacted endpoint assessment **(Figure 3)**.
- PFS was measured post-randomization from 1L therapy in EV-302 but post-randomization from maintenance therapy in JB-100.
  - PFS prior to maintenance therapy was not reported in JB-100 and although PFS for non-progressors who were randomized in JB-100 could be assumed, PFS is not known for patients who progressed on 1L PBC or who were not eligible for maintenance.
- Although OS curves from the start of 1L chemotherapy were available for both trials, EV-302 included all patients eligible for 1L PBC (prespecified analysis), while JB-100 only included non-progressors following 1L PBC (post-hoc analysis).

Table 1. Summary of key baseline patient characteristics

Characteristic (at baseline, unless otherwise stated)		EV-302		JAVELIN Bladder 100	
		EV+P (N=442)	Chemotherapy (N=444)	Avelumab + BSC (N=350)	BSC (N=350)
Age, years	Median (range)	69.0 (37-87)	69.0 (22-91)	68 (37-90)	69 (32-89)
Sex, n (%)	Male	344 (77.8)	336 (75.7)	266 (76.0)	275 (78.6)
Race, n (%)	White	308 (69.7)	290 (65.3)	232 (66.3)	238 (68.0)
	Asian	99 (22.4)	92 (20.7)	75 (21.4)	81 (23.1)
	Black/African American	3 (0.7)	7 (1.6)	2 (0.6)	0 (0.0)
	Other	5 (1.1)	8 (1.8)	21 (6.0)	15 (4.3)
	Unknown or not reported	27 (6.1)	47 (10.6)	20 (5.7)	16 (4.6)
Geographic region, n (%)	North America	**103 (23.3)**	**85 (19.1)**	**12 (3.4)**	**22 (6.3)**
	Europe	**172 (38.9)**	**197 (44.4)**	**214 (61.1)**	**203 (58.0)**
	Asia	123 (27.8)	107 (24.1)	73 (20.9)	74 (21.1)
	Australasia	12 (2.7)	15 (3.4)	34 (9.7)	37 (10.6)
	Rest of the world	32 (7.2)[a]	40 (9.0)[a]	17 (4.9)	14 (4.0)
ECOG PS, n (%)	0	**223 (50.5)**	**215 (48.4)[b]**	**213 (60.9)**	**211 (60.3)**
	1	**204 (46.2)**	**216 (48.6)[b]**	**136 (38.9)**	**136 (38.9)**
	2	15 (3.4)	11 (2.5)[b]	1 (0.3)	0 (0)
	3	--	--	0 (0)	3 (0.9)
Site of primary tumor, n (%)	Upper tract (renal pelvis or ureter)	135 (30.5)	104 (23.4)	106 (30.3)	81 (23.1)
	Lower tract (bladder, urethra, or prostate gland)	305 (69.0)	339 (76.4)	244 (69.7)	269 (76.9)
	Unknown	2 (0.5)	1 (0.2)	--	--
Site of metastases prior to 1L therapy, n (%)	Visceral[c]	318 (71.9)	318 (71.6)	191 (54.6)	191 (54.6)
	Bone[c]	81 (18.3)	102 (23.0)	--	--
	Liver	**100 (22.6)**	**99 (22.3)**	**43 (12.3)**	**44 (12.6)**
	Lung	**170 (38.5)**	**157 (35.4)**	**83 (23.7)**	**83 (23.7)**
	Non-visceral	124 (28.1)	126 (28.4)	159 (45.4)[d]	159 (45.4)[d]
	Lymph node only disease	103 (23.3)	104 (23.4)	--	--
	Not applicable[e]	21 (4.8)	22 (5.0)	--	--
PD-L1 expression, n (%)	Positive	254/438 (58.0)	254/439 (57.9)	189 (54.0)	169 (48.3)
	Negative	184/438 (42.0)	185/439 (42.1)	139 (39.7)	131 (37.4)
	Unknown	4/442 (0.90)	5/442 (1.13)	22 (6.3)	50 (14.3)
Cisplatin eligible, n (%)		240 (54.3)	242 (54.5)	--	--
1L chemo-therapy received, n (%)	Gemcitabine + cisplatin	NA	NA	183 (52.3)	206 (58.9)
	Gemcitabine + carboplatin	NA	NA	147 (42.0)	122 (34.9)
	Gemcitabine + cisplatin or carboplatin[f]	NA	NA	20 (5.7)	20 (5.7)
	Not reported	NA	NA	0 (0)	2 (0.6)
Creatinine clearance at baseline, n (%)	≥60 mL/min	249 (56.3)	257 (57.9)	181 (51.7)	196 (56.0)
	<60 mL/min	193 (43.7)	187 (42.1)	168 (48.0)	148 (42.3)

Notes: a) Rest of world includes Argentina and Russia; **b)** Two patients in EV-302 chemotherapy arm had ECOG data missing; **c)** More patients in EV-302 were classified as having visceral disease compared with JB-100; however, this was due to categorization of bone metastases as visceral disease in EV-302 but as non-visceral disease in JB-100; **d)** Non-visceral included patients with locally advanced disease in addition to patients with only non-visceral disease, including bone metastasis; **e)** Subjects had locally advanced disease without metastasis to lymph nodes or distant organs; **f)** Included patients who switched platinum regimens while receiving 1L chemotherapy.

Figure 3. Observed survival outcomes in EV-302 and JAVELIN Bladder 100



Notes: Arrows indicate differences in time of randomization (time-zero). Values under the curves represent the number of patients at risk. JB-100 survival curves were digitized from publications.[2,13]

Implications for ITC methods

- The main issue with respect to a comparison of EV+P and avelumab maintenance is one of patient selection.
  - Patients in EV-302 had not received prior systemic therapy for la/mUC and were randomized before initiation of 1L therapy, while JB-100 enrolled a selected population who had no disease progression following completion of 1L PBC and were randomized to maintenance therapy. As such, the JB-100 target population is a subset of the 1L treated population with survivorship bias; i.e., patients who had disease progression or died on/after 1L PBC were not enrolled in the trial.
  - Therefore, a simple comparison of outcomes with the two treatments would be subject to selection bias due to survivorship bias that exists due to time-zero offset.
- For standard ITC methods to be valid, the two populations must show sufficient overlap in the characteristics that affect treatment assignment; however, JB-100 required all patients to have no disease progression on/after 1L PBC (i.e., all patients were eligible for maintenance), while patients in EV-302 may have had disease progression on 1L PBC which precludes treatment with maintenance therapy (i.e., only a subset of EV-302 patients would be eligible for maintenance) (**Figure 1A**).
- Standard ITC methods also assume there are no differences between the trials in factors that could bias relative treatment effects; however, there were between-study differences in inclusion criteria and some patient characteristics (i.e., geographic region, ECOG PS, liver metastases, lung metastases). Although these differences could normally be adjusted using standard methods, this cannot be accounted for given the differences in patient selection.
- As a PAIC adjusts for between-study differences in baseline patient characteristics by aligning IPD from EV-302 (index trial) to aggregate-level data from JB-100 (external trial), results would be presented in a population similar to JB-100 (i.e., non-progressors following 1L PBC) which is not relevant to the 1L treatment initiation decision (**Figure 4**). The JB-100 population is a subset of the 1L treated population and therefore not reflective of the EV-302 target population for decision makers and/or clinicians who make 1L treatment initiation decisions with their patients.

Figure 4. Simplified overview of standard population-adjusted indirect comparison approach which is not suitable to estimate the comparative efficacy of 1L EV+P versus PBC with avelumab maintenance in patients with la/mUC given differences in patient selection