Enfortumab Vedotin Plus Pembrolizumab Compared to Pembrolizumab and Standard Chemotherapy: Birds of a Feather Flock Together in Urothelial Cancer

Clinical Medicine Insights: Oncology
Volume 19: 1–3

DOI: 10.1177/11795549251321147

Adriana Guarino[1], Matteo Santoni[2], Martina Catalano[1] and Giandomenico Roviello[1]

[1]Department of Health Sciences, University of Florence, Florence, Italy. [2]Oncology Unit, Macerata Hospital, Macerata, Italy.

KEYWORDS: Clinical trials, combination therapy, drug development, medical oncology, PD-1 inhibitors, immunotherapy

RECEIVED: November 26, 2024. **ACCEPTED:** January 12, 2025.

TYPE: Editorial

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Giandomenico Roviello, Department of Health Sciences, University of Florence, Florence 50134, Italy. Email: giandomenico.roviello@unifi.it

Urothelial carcinoma (UC) ranks as the most common cancer in the Western countries.[1] Historically, its treatment has relied on platinum-based chemotherapy regimens as the first-line therapy for metastatic urothelial carcinoma (mUC) and as a perioperative strategy for locally advanced disease.[2] Typically, 4 to 6 cycles of platinum-based chemotherapy administered, with treatment compliance and toxicity profiles guiding the evaluation of outcomes. Patients who achieve an objective response rate (ORR), including complete response, partial response, or disease stability, following platinum-based chemotherapy may qualify for maintenance therapy with avelumab, an anti-programmed cell death 1 (PD-L1) antibody. Evidence from the JAVELIN Bladder 100 trial demonstrated that avelumab significantly improved progression-free survival (PFS), overall survival (OS), and efficacy compared to best supportive care (BSC) alone.[3] For patients whose disease progress during or after chemotherapy, pembrolizumab, an anti-PD-1 antibody, serves as second-line treatment option. Its efficacy was established in the KEYNOTE-045 trial.[4] In addition, the IMvigor211 study supported an evidence of efficacy of atezolizumab (an anti PD-L1 antibody) as a second-line therapy.[2]

More recently, transformative data from the EV-302 study highlighted the potential of enfortumab vedotin (EV), a conjugated antibody directed against nectin-4, in combination with pembrolizumab.[5] The combination therapy (Figure 1) showed substantial improvements in both OS and PFS, with statistically significant benefits for patients with untreated mUC. Specifically, patients receiving EV and pembrolizumab had a median OS of 31.5 months compared to 16.1 months for the chemotherapy group, representing a 53% reduction in the risk of death. Similarly, median PFS was 12.5 months with EV and pembrolizumab vs 6.3 months with chemotherapy, corresponding to a 55% reduction in the risk of progression or death. Secondary endpoints as subgroup analyses, stratified by tumor location (bladder vs upper tract), type of platinum-based chemotherapy (cisplatin vs carboplatin), PD-L1 expression levels, and the presence of hepatic metastases, consistently support the superiority of EV and pembrolizumab combination over chemotherapy alone. These findings are particularly notable as they reinvigorate the role of immunotherapy in first-line treatment setting for mUC. Previous studies evaluating the combination of immunotherapy with first-line platinum chemotherapy have yielded mixed results. For example, the KEYNOTE-361 trial[6] found that pembrolizumab combined with chemotherapy did not significantly improve PFS (median PFS of 8.3 months with pembrolizumab plus chemotherapy vs 7.1 months with chemotherapy alone) or OS (median OS of 17.0 vs 14.3 months, respectively). Furthermore, pembrolizumab alone demonstrated similar OS compared to chemotherapy (15.6 months vs 14.3 months, respectively).

Interestingly, despite the comparable baseline characteristics of patients in EV-302 and KEYNOTE-361 (Table 1), the outcome of pembrolizumab differs markedly on its combination partner:

> In fact, the combination of EV and pembrolizumab achieved a longer median PFS (12.5 vs 8.3 months) and a longer median OS (31.5 vs 17 months) compared to the pembrolizumab-chemotherapy combination in KEYNOTE-361. This data is particularly relevant, especially regarding survival outcomes, which were nearly doubled.

Other parameter of efficacy such as the response rate of tumor is better for the combination of EV and pembrolizumab. This discrepancy suggests a synergistic effect between EV and pembrolizumab.

Proposed mechanisms for this synergy include the potential immunomodulatory effects of nectin-4 inhibition and the capacity of antibody-drug conjugates to stimulate immune activation. Nonetheless, it is essential to carefully consider the toxicity profile of EV and the comorbidities of individual patients when selecting candidates for combination therapy.

In conclusion, the EV and pembrolizumab combination represents a significant advancement in the survival outcomes of mUC patients. Future research should focus on identifying

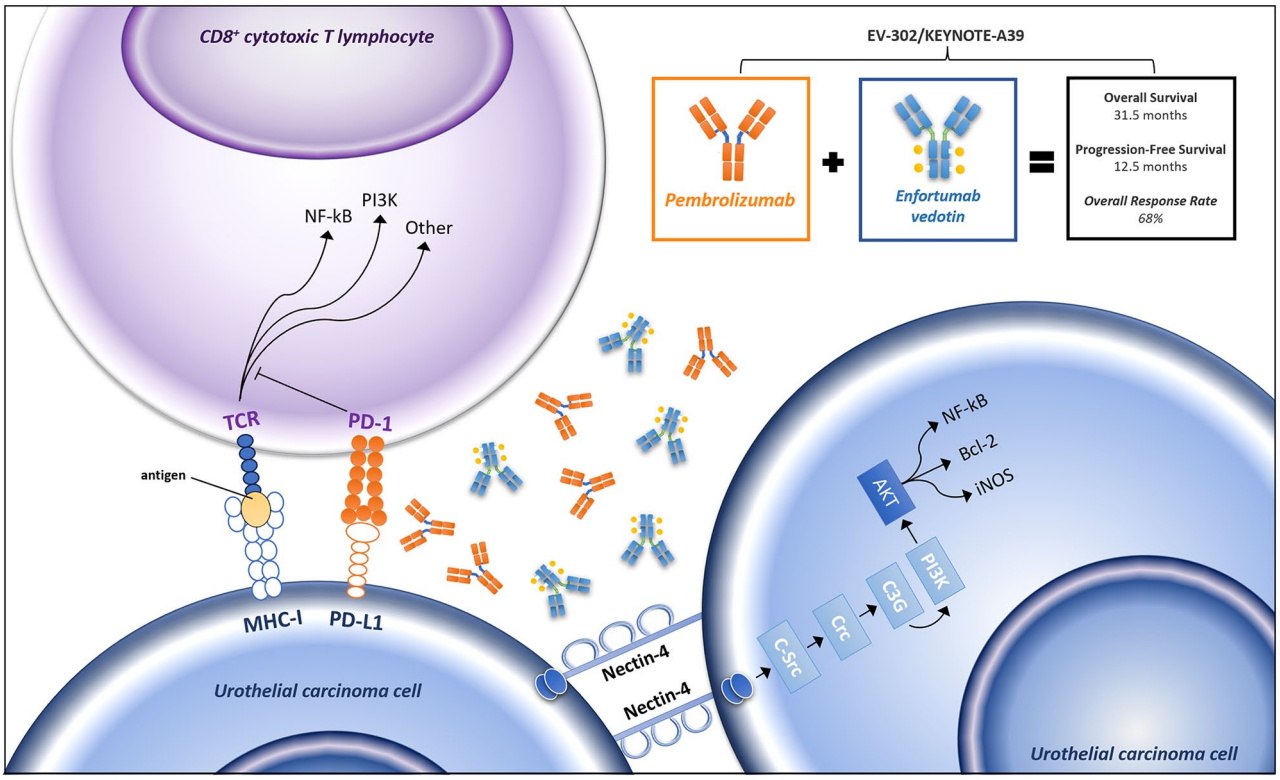

Figure 1. Effective drugs in metastatic urothelial carcinoma—the figure is drawn by the authors.

Table 1. Best response, PFS, and OS according to the experimental and control arm.

	MEDIAN AGE (YEARS)	MALE PTS (%)	ECOG PERFORMANCE STATUS SCORE = 2 (%)	PRIMARY SITE OF ORIGIN OF DISEASE: UPPER TRACT (%)	LIVER METASTASES (%)	MEDIAN FOLLOW-UP MONTHS	RR N (%)	MEDIAN PFS MONTHS (95% CI)	MEDIAN OS MONTHS (95% CI)
KEYNOTE-361 (1:1:1)									
Pembrolizumab plus chemotherapy (n = 351)	69 (62-75)	272 (78)	23 (7)	64 (18)	78 (22)	31.7[a]	192 (54.7)	8.3 (7.5-8.5)	17.0 (14.5-19.5)
Pembrolizumab monotherapy (n = 307)	68 (61-74)	228 (36)	25 (8)	65 (25)	65 (21)		93 (32.3)	NA	15.6 (12.1-17.9)
Control arm: chemotherapy alone (n = 352)	69 (61-75)	262 (74)	22 (6)	82 (23)	74 (21)		158 (44.9)	7.1 (6.4-7.9)	14.3 (12.3-16.7)
EV-302 (1:1)									
Enfortumab vedotin–pembrolizumab (n = 442)	69 (37-87)	344 (77.8)	15 (3.4)	135 (30.5)	100 (22.6)	17.2[b]	296 (67.7)	12.5 (10.4-16.6)	31.5 (25.4-NR)
Control arm chemotherapy (n = 444)	69 (22-91)	336 (75.7)	11 (2.5)	104 (23.4)	99 (22.3)		196 (44.4)	6.3 (6.2-6.5)	16.1 (13.9-18.3)

[a]At final analysis, median follow-up is defined as the time from randomization to data cutoff on April 29, 2020.
[b]As of August 8, 2023, the median duration of follow-up for survival.

biomarkers and elucidating resistance mechanisms to refine the clinical application of this promising therapeutic approach.

Author Contributions

GR and MC made a substantial contribution to the concept or design of the work; or acquisition, analysis, or interpretation of data. AG and MS drafted the article or revised it critically for important intellectual content. All authors approved the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

ORCID iD

Giandomenico Roviello https://orcid.org/0000-0001-5504-8237

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin*. 2021;71:7-33.
2. Roviello G, Santoni M, Sonpavde GP, Catalano M. The evolving treatment landscape of metastatic urothelial cancer. *Nat Rev Urol*. 2024;21:580-592. doi:10.1038/s41585-024-00872-0
3. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. *N Engl J Med*. 2020;383:1218-1230. doi:10.1056/NEJMoa2002788
4. Bellmunt J, de Wit R, Vaughn DJ, et al; KEYNOTE-045 Investigators. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med*. 2017;376:1015-1026. doi:10.1056/NEJMoa1613683
5. Powles T, Valderrama BP, Gupta S, et al; EV-302 Trial Investigators. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. *N Engl J Med*. 2024;390:875-888. doi:10.1056/NEJMoa2312117
6. Powles T, Csőszi T, Özgüroğlu M, et al; KEYNOTE-361 Investigators. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22:931-945. doi:10.1016/S1470-2045(21)00152-2