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# Sex Differences in Enfortumab Vedotin Efficacy and NECTIN-4 Levels in Metastatic Urothelial Cancer

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**Background**

Antibody-drug conjugates (ADCs) represent an emerging class of anti-cancer therapies. Enfortumab vedotin (EV), a NECTIN-4–targeting ADC, has recently been integrated into the treatment landscape for urothelial cancer (UC). Prior subgroup analyses suggest sex may influence treatment efficacy – a factor often underexplored in research. To investigate this, we conducted a multi-center real-world data analysis, complemented by translational research, to gain deeper insight into this disparity.

**Methods**

Clinical outcomes were collected from the ARON2-EV retrospective study. Kaplan–Meier and log-rank tests were used for analysis. TCGA data for patients diagnosed with T2-T4a UC were

analyzed for NECTIN-4 expression, sex differences, smoking status, molecular subtypes and regulating pathways.

**Results**

454 patients with metastatic UC treated with EV across 51 centers in 18 countries were included. Overall survival was 13.6 months in males vs 7.7 months in females ($p<.001$), consistent after stratification by ECOG status, tumor histology, smoking status and prior therapy. Males also had longer time on-treatment (13.3 vs 7.4 months, $p<.001$). Objective response rate was similar (45% in males vs 36% in females), but primary refractory rates differed significantly (26% vs 44%, respectively, $p=.008$). NECTIN-4 expression was higher in men compared to women ($p<.001$), an effect that was augmented in smokers. Women were more often diagnosed with basal histology, which exhibits lower NECTIN-4 expression; However, differences persisted even after stratification by molecular subtype ($p=.002$). NECTIN-4 expression was most strongly associated with estrogen response gene set ($p<.001$), and smoking was found to reduce estrogen levels specifically in women.

**Conclusions**

Females appear to benefit less from EV treatment, potentially due to lower Nectin-4 expression driven by molecular subtype, mutational signatures, and the differential impact of smoking on estrogen levels. As ADCs continue to emerge as a novel class of therapy, these findings of an ADC with sex differences underscore the importance of evaluating the influence of sex on ADC efficacy and toxicity in clinical trials.

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