Sex Differences in Enfortumab Vedotin (EV) Efficacy and NECTIN-4 Levels in metastatic Urothelial Carcinoma (mUC)

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Introduction

• Sex differences significantly impact cancer incidence, biology and treatment outcomes, but remain underexplored for antibody-drug conjugates (ADCs). In UC, males have higher incidence, while females often present with more aggressive disease and poorer outcomes.

• EV, targeting NECTIN-4, has improved outcomes in mUC, yet large trials have not examined sex-based outcomes.

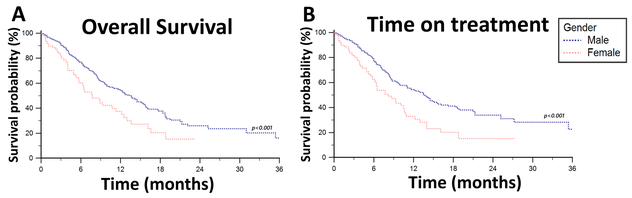
• Understanding sex disparities, is critical for optimizing care. We retrospectively analyzed EV efficacy in mUC, focusing on sex-based outcomes and potential molecular drivers, including NECTIN-4 expression, tumor subtypes and mutations.

Patients and Methods

• Retrospective analysis of outcomes in mUC patients treated with EV as an advanced-line treatment across 50 centers in 18 countries, including overall response rate (ORR), time on treatment (ToT), overall survival (OS), and duration of response (DoR) were stratified by sex, using RECIST v1.1 criteria.

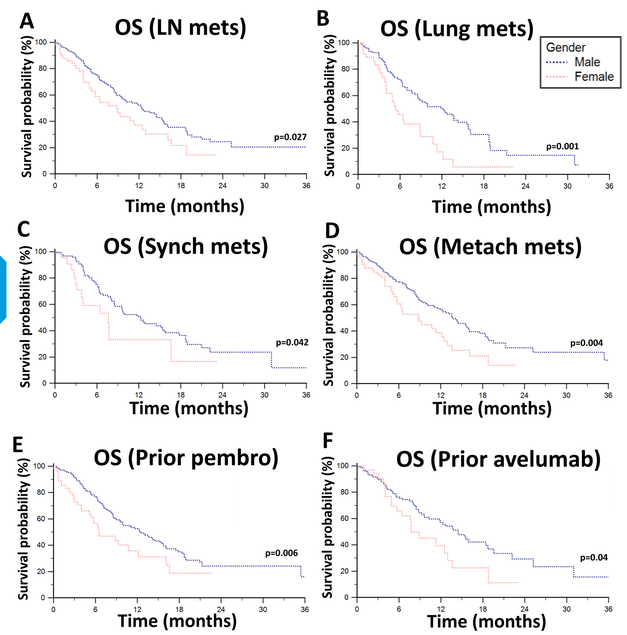
• NECTIN-4 expression and molecular pathways were analyzed in TCGA bladder cancer data via gene expression profiling, tumor subtyping, and hallmark pathway enrichment (ssGSEA).

OS and ToT in the overall cohort



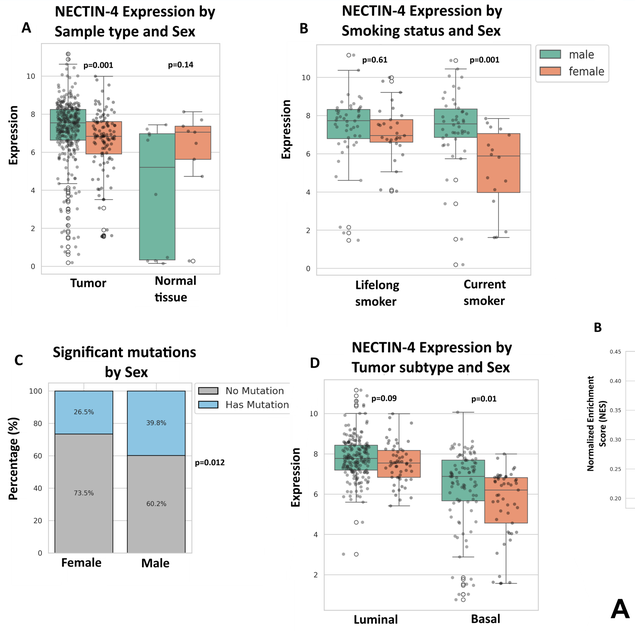
Kaplan-Meier curves of mUC patients stratified by sex (male: blue; female; pink) **A** Overall survival, **B** Time on treatment

OS across different clinic-pathological subgroups



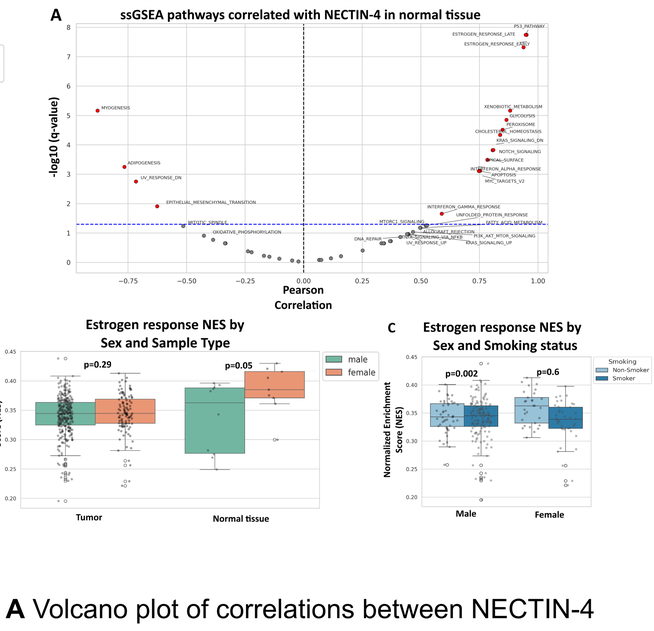
Kaplan-Meier curves of mUC patients stratified by sex (male: blue; female; pink) across different subgroups: **A** distant lymph node metastases, **B** lung metastases, **C** synchronous metastatic disease, **D** metachronous metastatic disease, **E** prior pembrolizumab, **F** prior avelumab

NECTIN-4 expression patterns in UC



NECTIN-4 mRNA expression (TCGA), stratified by sex (male: green; female; orange): **A** normal tissue vs. primary tumors, **B** smoking status, **C** mutation frequencies linked to NECTIN-4 expression, **D** molecular subtype

NECTIN-4-related gene expression signatures in UC



A Volcano plot of correlations between NECTIN-4 expression and ssGSEA in normal bladder tissue (TCGA); significant positive correlations (q<0.05) in red, **B** Box plots of estrogen response pathway enrichment by sex in normal tissue and tumors, **C** Box plots of estrogen response pathway enrichment by sex and smoking status

Conclusions

• In a large real-world cohort of mUC patients treated with EV, males had longer OS and ToT, while females showed higher rates of primary resistance and poorer survival despite similar baseline features.

• NECTIN-4 expression, associated with EV efficacy, was higher in male tumors, even after adjusting for molecular subtypes

• Smoking impacted NECTIN-4 and estrogen signaling, with female smokers showing reduced estrogen pathway activity, suggesting interplay between sex, environment, and tumor biology.

• Sex may independently associate with EV treatment outcomes, possibly driven by target expression, hormone pathways and smoking modulation, highlighting the need to include sex as a biological variable in future ADC trials.

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Acknowledgment: ARON Research Foundation ETS for its support and encouragement. All other co-authors: Jalal Baranseh, Enrique Grande, Sebastiano Buti, Francesco Massari, Fernando Sabino Marques Monteiro, Giandomenico Roviello, Cristian Lolli, Hideki Takeshita, Avivit Peer, Aristotelis Bamias.

Disclosure
First author, Tarek Taha, has no conflicts of interest to disclose.