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Landscape analysis and oncologic outcomes in advanced urothelial carcinoma (UC) by NECTIN4 RNA expression.

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Background: Advanced UC is a devastating disease, however recent advances with antibody drug conjugates (ADCs), including enfortumab vedotin (EV), have improved outcomes significantly. Currently no biomarkers are clinically available to predict response to therapy. We hypothesized that benefit from EV may correlate with mRNA expression of NECTIN4, the gene encoding the relevant cell surface antigen for EV. Therefore, we performed a landscape analysis of NECTIN4 in advanced UC and correlated expression with oncologic outcomes. **Methods:** Bladder and upper tract UC samples were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA (592 genes or whole exome) and NovaSeq on RNA (whole transcriptome). UC samples were stratified by NECTIN4 mRNA levels into four quartiles. Tumor mutational burden (TMB) totaled somatic nonsynonymous mutations per tumor (high >10 mut/Mb). Insurance claims data were used to calculate survival outcomes using Kaplan-Meier estimates. Overall survival (OS) was calculated from the date of sample collection and date of treatment initiation to date of last follow up. Time on treatment (TOT) was calculated from date of treatment initiation to date of last treatment.Survival analysis was performed between top and bottom quartiles of NECTIN4 expression. **Results:** A total of 6,395 patient samples were analyzed [n=4335 from primary tumor (3496 bladder/urethra, 839 upper tract), n= 2060 from metastases]. Expression of NECTIN4 was associated with higher rates of mutations in FGFR3 (18.9% vs 6.9%), ERBB2 (11.8% vs 5.9%), pTERT (77.3% vs 62.6%), CCNE1 (5.6% vs 1.7%), SDHC (8.3% vs 0.6%) and with TMB-H status (46.2% vs 35.8%) but lower rates of TP53 mutations (54.6% vs 67.7%). NECTIN4 expression positively correlated with expression of TACSTD2 (TROP2), ERBB2 (HER2) and SLITRK6. Interestingly, NECTIN4 expression inversely correlated with PDL1 expression by IHC (22c3, 26.9% vs 59.2%). Similar findings were found when analysis was performed by primary bladder versus primary upper tract, as well as primary versus metastatic site. NECTIN4 expression was associated with longer OS in the overall population, and improvement in TOT (HR 0.53) and OS (HR 0.67) for patients treated with EV (Table). NECTIN4 expression was not associated with benefit with anti-PD1/L1 therapy. **Conclusions:** In the largest study investigating NECTIN4 expression in UC, we demonstrate co-expression of TACSTD2 (TROP2), ERBB2 (HER2) and SLITRK6 with NECTIN4. Expression of NECTIN4 correlated with favorable prognosis and predicted benefit from EV. NECTIN4 RNA expression could be a potential biomarker for selecting patients for treatment with EV. Further validation is required. Research Sponsor: None.

	Bottom Quartile NECTIN4	Top Quartile NECTIN4	HR
OS (N=1969)	13.8m	21.1m	0.76**
OS (Did not receive EV) (N=1561)	15.7m	22.1m	0.79**
TOT-EV (N=236)	2.7m	4.3m	0.53**
OS-EV (N=255)	12.9m	18.0m	0.67*

*P-value<0.05; **P-value <0.001