ABSTRACT #4585

Landscape analysis and oncologic outcomes in advanced urothelial carcinoma by NECTIN4 RNA expression

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Background

- Advanced urothelial carcinoma (UC) is a devastating disease, however recent advances with antibody drug conjugates (ADCs), including enfortumab vedotin (EV), have improved outcomes significantly.[1,2]
- Currently no biomarkers are clinically available to predict response to therapy EV.
- We hypothesized that benefit from EV may correlate with RNA 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

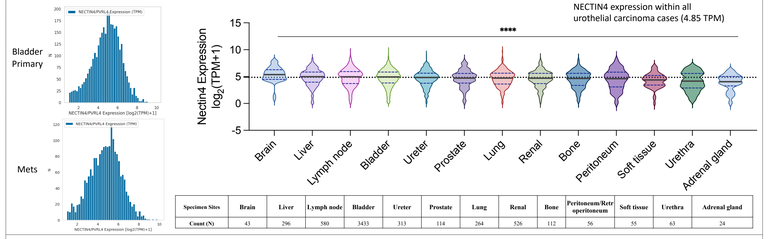
- Bladder and upper tract UC samples were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA (592 genes or whole exome) and NovaSeq on RNA (whole transcriptome).
- UC samples were stratified by *NECTIN4* RNA levels into four quartiles.
- Tumor mutational burden (TMB) totaled somatic 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 or 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. Hazard ratio (HR) was calculated using the Cox proportional hazards model, and P values were calculated using the log-rank test.
- Survival analysis was performed between top and bottom quartiles of NECTIN4 expression.
- Pairwise statistical analysis via Mann-Whitney U, Fisher's Exact, or Chi-square test was performed, as necessary.

Results

Table 1. Study Demographics

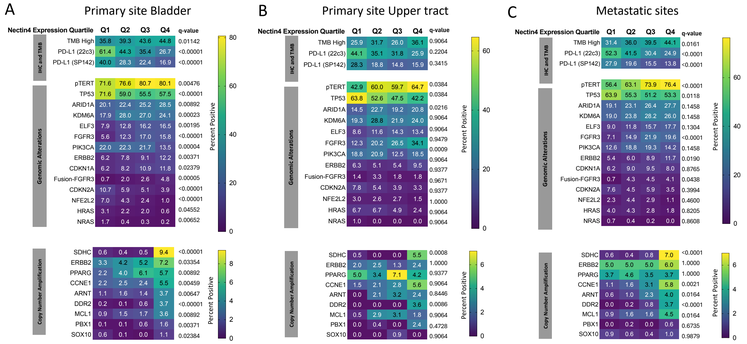
	Total (N)	NECTIN4_Q1	NECTIN4_Q2	NECTIN_Q3	NECTIN_Q4	Statistic	q-value
Count (N)	6395	1599	1598	1599	1599	N/A	N/A
Bladder/urethra	3496	829 (23.7%)	848 (24.3%)	882 (25.2%)	937 (26.8%)	N/A	N/A
Upper tract	839	208 (24.8%)	239 (28.5%)	224 (26.7%)	168 (20.0%)	N/A	N/A
Metastatic	2060	556 (27.0%)	515 (25.0%)	495 (24.0%)	494 (24.0%)	N/A	N/A
Median age, N [range]	72 [18->89]	72 [26 - >89]	72 [18 - >89]	73 [27 - >89]	72 [24 - >89]	Kruskal-Wallis	0.0654366
Male	4,596	67.5% (1080/1599)	70.6% (1128/1598)	73.4% (1173/1599)	76.0% (1215/1599)	Chi-square	1.88E-06
Female	1,799	32.5% (519/1599)	29.4% (470/1598)	26.6% (426/1599)	24.0% (384/1599)	Chi-square	1.88E-06

Figure 1 . NECTIN4 Expression across specimen sites of UC



Specimen Sites	Brain	Liver	Lymph node	Bladder	Ureter	Prostate	Lung	Renal	Bone	Peritoneum/Retroperitoneum	Soft tissue	Urethra	Adrenal gland
Count (N)	43	296	580	3433	313	114	264	326	112	56	55	63	24

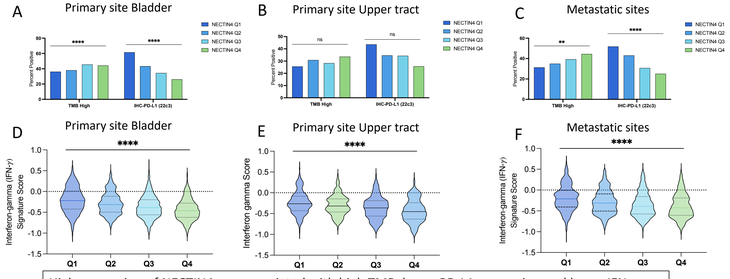
Figure 3: Genomic Landscape based on NECTIN4/PVRL4 Expression in UC



- TMB high threshold ≧ 10 Mutations Per Megabase
- Copy Number Amplified is defined as ≧6 copies

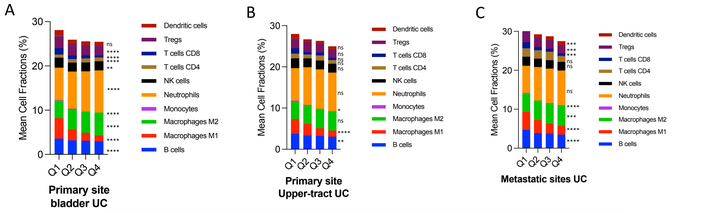
High expression of NECTIN4 was associated with higher rates of mutations in pTERT, ARID1A, FGFR3, ERBB2, among others, but lower rates of TP53 mutations.

Figure 4: Biomarker Prevalence and Nectin-4 expression



High expression of NECTIN4 was associated with high TMB, lower PD-L1 expression and lower IFN score

Figure 5: Association between NECTIN4 expression and the tumor immune cell microenvironment



High NECTIN4 expression is associated with lower mean immune cell fractions

Figure 6: Outcomes to systemic therapy by NECTIN4 expression

Figure 5a: Outcomes to enfortumab vedotin by NECTIN4 expression

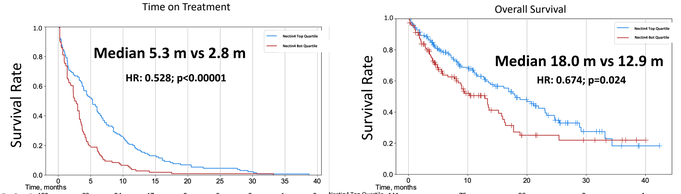


Figure 5b: Outcomes to anti-PD therapy by NECTIN4 expression in patients who have never received EV

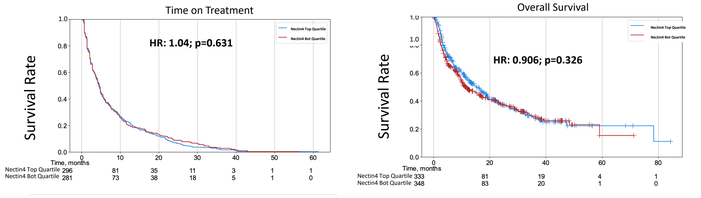


Figure 5c: Outcomes to platinum therapy by NECTIN4 expression in patients who have never received EV

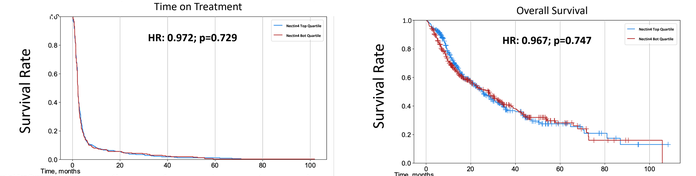
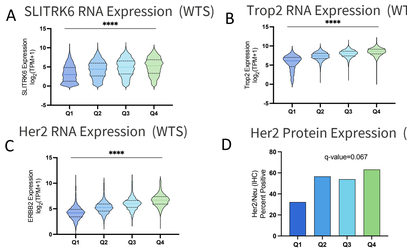


Figure 7: Association between NECTIN4 expression and TROP2, HER2, and SLITRK6 expression in urothelial carcinoma



Study Highlights

Nectin4 RNA expression is associated with improved outcomes for patients treated with EV, but not associated with clinical outcomes for patients treated with anti-PD or platinum based therapy.

Nectin4 expression may be a potential marker for selecting patients for treatment with EV.

Conclusions

- Here we present the largest analysis of NECTIN4 RNA expression for patients with urothelial carcinoma.
- High NECTIN4 expression was associated with higher rates of mutations in pTERT, ARID1A, FGFR3, ERBB2, CCNE1, SDHC but lower rates of TP53 mutations.
- NECTIN4 high expression was associated with high TMB and lower PD-L1 expression
- NECTIN4 expression was associated with co-expression of TACSTD2 (TROP2), ERBB2 (HER2) and SLITRK6.
- Expression of NECTIN4 correlated with favorable prognosis and predicted benefit from EV; however, NECTIN4 was not associated with outcomes for patients treated with anti-PD or platinum based therapies.
- NECTIN4 RNA expression may be a potential biomarker for selecting patients for treatment with EV.

References

1. Powles, Rosenberg, Sonpavde et al, NEJM, 2021
2. Powles, Valderrama, Gupta et al, NEJM, 2024

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