

Conference Abstracts

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ADC Target Signatures in Urothelial Carcinoma: A Transcriptomic Framework for Precision Therapy

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Abstract

Background

Nectin-4 targeting antibody drug conjugate (ADC) enfortumab vedotin (EV), in combination with pembrolizumab, is the first-line treatment for patients with metastatic or locally advanced urothelial cancer (UC). However, optimal treatment strategies for non-responders remain an unmet clinical need. We analyzed tumor transcriptomes to identify ADC target expression profiles with additional stratification by histologic subtype which may inform treatment selection for these patients.

Methods

We conducted a literature search to identify ADC targets approved or under investigation for UC. Molecular targets of interest included Nectin-4 (NECTIN4), Her2 (ERBB2), Trop-2 (TACSTD2), DLL3, B7-H3 (CD276), FGFR3, and PDL1 (CD274). We interrogated The Cancer Genome Atlas (TCGA) dataset, comprising tumors from 434 patients with UC. Hierarchical clustering was used to identify recurrent ADC target expression profiles. To validate our findings, we repeated the analysis on an independent cohort of 478 patients with UC from the Oncology Research Information Exchange Network (ORIEN). We also performed differential gene expression analysis between histological subtypes.

Results

Two mutually exclusive ADC target clusters were identified in TCGA with a similar pattern that was seen in ORIEN (Table 1, Figure 1). Differentially expressed ADC targets between histologic subtypes included: 1) Conventional urothelial carcinomas demonstrated higher expression of NECTIN4, FGFR3, ERBB2, and TACSTD2 relative to neuroendocrine and adenocarcinoma subtypes 2) Squamous cell carcinomas were enriched for EGFR, NECTIN4, and TACSTD2 3) Adenocarcinomas demonstrated increased ERBB3 expression 4) Neuroendocrine tumors showed increased DLL3

expression, although this did not reach statistical significance, likely due to limited sample size.

Conclusion

Through interrogation of TCGA and ORIEN data, we identified two mutually exclusive ADC target expression profiles in UC. Tumors lacking overexpression of NECTIN4, TACSTD2, or FGFR3 were enriched for DLL3, CD276 and CD274 expression, suggesting alternative ADC targets for non-responders to current therapies. These findings warrant prospective proteomic validation and may inform molecularly and histologically guided treatment selection beyond EV.

Table 1. ADC target clustering in TCGA and ORIEN cohorts

Data Clusters	TCGA Cohort	ORIEN Cohort
Cluster 1	Overexpressed: <i>ERBB2</i> , <i>FGFR3</i> , <i>NECTIN4</i> , <i>TACSTD2</i> . 70.2% (n = 318)	Overexpressed: <i>FGFR3</i> , <i>NECTIN4</i> , <i>TACSTD2</i>
Cluster 2	Overexpressed: <i>DLL3</i> , <i>CD276</i> , and <i>CD274</i> 29.8%, (n = 135)	Overexpressed: <i>DLL3</i> , <i>CD276</i> , <i>CD274</i> , <i>ERBB2</i>
Correlation	Negative Correlation, (Spearman rho = -0.40, p < 0.0001)	Negative Correlation (Spearman rho = -0.79, p < 0.0001)

Table 1: ADC target clustering in TCGA and ORIEN cohorts

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