Rovalpituzumab tesirine (Rova-T) as a therapeutic agent for neuroendocrine prostate cancer

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Background: The Notch ligand Delta like ligand 3 (DLL3) is aberrantly expressed on the cell surface of small cell lung cancer (SCLC), and the DLL3-antibody drug conjugate, Rova-T, has shown promise for patients with SCLC (Rudin et al, Lancet Onc 2017). Neuroendocrine prostate cancer (NEPC) is a histologic subtype of advanced prostate cancer with limited therapeutic options. Based on clinical and molecular similarities with SCLC, we investigated expression of DLL3 and the use of Rova-T in NEPC.

Methods: We evaluated mRNA and/or protein expression of DLL3 in a cohort of 395 patients (535 samples) ranging from benign prostate (BEN), localized prostate adenocarcinoma (PCA), castration resistant adenocarcinoma (CRPC-Adeno), and NEPC and correlated with pathologic and genomic features. Prostate cancer cell lines and patient-derived organoids were treated with Rova-T (SC16LD6.5) *in vitro* and *in vivo.*

Results: DLL3 was expressed at the mRNA and/or protein level in 0/143 BEN (0%), 4/266 PCA (1%), 8/76 CRPC-Adeno (10%), 33/50 NEPC (66%). DLL3 IHC was of higher intensity in NEPC and co-localized with classical NE marker expression (SYP, CGA). DLL3 was amongst the most differentially expressed genes by RNA-seq in NEPC versus CRPC-Adeno ($p = < 0.0001$, fold change = 71), correlated with ASCL1 expression ($r = 0.88$) and RB1 genomic loss (83%), and inversely with AR expression. Although treatment with the Notch inhibitor DAPT suppressed Notch target gene expression in NEPC, DAPT did not have significant effect on cellular proliferation. siRNA knockdown of DLL3 or DAPT did not alter AR signaling or NE markers. Rova-T (SC16LD6.5) was active in DLL3-positive NEPC cell lines and xenografts with an IC50 of 580pM compared to the control IgG1LD6.5 (IC50 = 6.3nM), whereas CRPC-Adeno lines were insensitive.

Conclusions: DLL3 is a cell surface protein aberrantly expressed in the majority of NEPC and a subset of CRPC-Adeno, and is not expressed in primary prostate cancer or benign tissues. The DLL3 antibody-drug conjugate Rova-T demonstrates preferential preclinical activity in NEPC compared to prostate adenocarcinoma. These data support further investigation of Rova-T as a potential therapeutic agent for NEPC. A phase I trial with dedicated NEPC arm is currently accruing patients (NCT02709889).

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