

Rovalpituzumab tesirine as a therapeutic agent for neuroendocrine prostate cancer

Loredana Puca^{1,2}, Katie Gavyert³, Verena Sailor^{2,3}, Vincenza Conteduca^{1,3}, Etienne Dardenne⁴, Michael Sigouros¹, Kumiko Isse⁵, Megan Kearney⁶, Aram Vosoughi⁴, Heng Pan², Samaneh Motanagh⁴, Judy Hess¹, Andrea Sboner², Yuzhuo Wang⁶, Ryan Dittamore⁶, David Rickman⁴, David M Nanus¹, Scott T Tagawa¹, Olivier Elemento², Juan Miguel Mosquera^{2,4}, Laura Saunders⁵, Himisha Beltran^{1,2*}

1 Division of Medical Oncology, Weill Cornell Medicine. New York, NY

2 Caryl and Israel Englander Institute for Precision Medicine, New York Presbyterian Hospital-Weill Cornell Medicine. New York, NY

3 Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy.

4 Department of Pathology, Weill Cornell Medicine. New York, NY

5 AbbVie Stemcentrx LLC

6 Epic Sciences, San Diego, California

7 University of British Columbia, Vancouver BC, Canada

Background: Delta-like protein 3 (DLL3) is expressed on the surface of small cell lung cancer (SCLC) tumor-initiating cells, and the DLL3-targeted antibody-drug conjugate, Rovalpituzumab tesirine (Rova-TTM; SC16LD6.5), has shown promise for patients with SCLC. Neuroendocrine prostate cancer (NEPC) is an emerging late stage subtype of castration resistant prostate cancer with limited therapeutic options. Based on clinical and molecular similarities with SCLC, we investigated expression of DLL3 and the use of Rovalpituzumab tesirine in NEPC xenografts.

Methods: We evaluated mRNA and/or protein expression of DLL3 in a cohort of 423 patients (735 samples) ranging from benign prostate (BEN), localized prostate adenocarcinoma (PCA), castration resistant adenocarcinoma (CRPC), and castration resistant NEPC and correlated with pathologic and genomic features. mRNA was assessed by RNAseq and Nanostring. Protein was assessed by immunohistochemistry (DLL3 SP347 antibody). Prostate cancer cell lines, organoids and tissue were engrafted in mice and treated with SC16LD6.5 in vivo.

Results:

DLL3 was expressed at the mRNA and/or protein level in 0/144 Benign (0%), 6/320 (1.88%) PCA, 14/119 (11.76%) CRPC and 81/114 (73.6%) NEPC samples. DLL3 IHC was of higher intensity in NEPC and co-localized with classical neuroendocrine (NE) markers. DLL3 was amongst the most differentially expressed genes by RNA-seq in NEPC versus CRPC ($p < 0.0001$, fold change=71), and positively correlated with ASCL1 expression ($r = 0.92$) and RB1 genomic loss (83%), and inversely with AR expression ($r = -0.3$). siRNA knockdown of DLL3 did not alter AR signaling or NE score in vitro. In vivo treatment of the NEPC, NCI-H660, and LTL352 xenografts expressing DLL3 with vehicle, IgG1LD6.5, or SC16LD6.5 (intraperitoneal single dose) showed complete responses to SC16LD6.5 with no recurring tumors after 35 days; while the tumor developed from the CRPC line, DU145, and WCM1262 PDOX which do not express DLL3, continued growing despite the treatment and were sacrificed when tumors reached the maximum size allowed by our IACUC protocol.

Conclusions: DLL3 is expressed on the surface of the majority of NEPC cases evaluated, in a subset of metastatic castration resistant prostate adenocarcinoma (CRPC-Adeno) and minimal to no expression in localized prostate cancer or benign prostate tissue. Modulation of DLL3 expression does not appear to affect AR or NEPC signaling in cell lines. SC16LD6.5 (Rova-T) demonstrates preferential preclinical activity in NEPC that express DLL3 compared to CRPC-adenocarcinoma that are DLL3 negative in vitro and in vivo. A Phase 1 Basket trial investigating Rova-T is now open with a dedicated NEPC arm (NCT02709889).

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