Pediatric Preclinical Testing Consortium (PPTC) evaluation of a DLL3-targeted antibody drug conjugate, rovalpituzumab tesirine, in neuroblastoma

Renata Sano¹, Kateryna Krystska², Matthew Tsang³, Stephen W. Erickson³, Beverly A. Techeľ², Kumiko Issé⁴, Hannah Ramoth⁵, Laura Saunders⁵, Malcolm A. Smith⁵, John M. Maris⁵, and Yael P. Mossé⁶
¹Children’s Hospital of Philadelphia, Philadelphia, PA; ²RTI International, Research Triangle Park, NC; ³National Cancer Inst., Bethesda, MD; ⁴Abbvie, North Chicago, IL; ⁵Abbvie, South San Francisco, CA

1. Introduction

Neuroblastoma is a neuroendocrine tumor of the developing sympathetic nervous system and accounts for 10% of all childhood cancer mortality. Given the variable origins of neuroblastomas, this cancer is characterized by expression of unique protein markers present not in normal tissues. Through an unbiased screen of RNA sequencing data, our group recently identified that the ligand delta-like 3 (DLL3) is robustly and differentially expressed on the cell surface of neuroblastomas and not on normal pediatric tissue.

DLL3 is a not fully elucidated member of the Delta-like/Notch signaling pathway, a signaling cascade that controls cell fate decisions in developing organs and in certain malignancies. Rova-T (SC16LD6.5) is an ADC targeting DLL3 composed of the recombinational antibody SC16 conjugated to the DNA damaging (DLL3-protic payload) (PBD) (drug toxin).

Clinical trials, Rova-T demonstrated antitumor activity in patients with small cell lung cancer (SCLC) and large cell neuroendocrine carcinomas (LCNEC) with high DLL3 protein expression.

Here, we characterize the expression of DLL3 in neuroblastoma patient derived xenografts (PDX), and define the efficacy of Rova-T in these models.

2. Study Methods

2.1. To assess DLL3 protein expression, we performed immunohistochemistry (IHC) on 12 PDXs from high-risk tumors in tissue culture.

2.1.1. Total and DLL3 cell surface expression in dissociated PDX tumors were assessed using immunoreactivity and flow cytometry, respectively.

2.1.2. The cytotoxic activity of Rova-T (10 nM to 10 μM) on ex vivo was determined in 8 dissociated PDXs using the Cell Titer Glo viability assay.

2.1.3. The in vivo activity of Rova-T was tested against four PDX models: Felix PDX, COG-N45, COG-452, and NB-1643. All four models were intratumorally inoculated to receive 5% glucose (water control), GqΔC6s or 0.1 μg SC16LD6.5 or 0.3 μg and 0.5 μg ml−1 events were defined as quadrupling the initial tumor volume. The Carr-Purcell-Meiboom-Gill (CPMG) pulse sequence was used to compare times to event between treated and control groups. Objective response categories were assigned as progressive disease (PD), which is sustained progressive disease without or with growth delay (PD2 or PD2+), stable disease (SD), partial response (PR), complete response (CR), and mixed complete response (mCR).

3. Results

3.1. DLL3 Cell Surface Expression

Figure 3. DLL3 is expressed in a large cohort of six xenograft samples. (A) Cell surface DLL3 expression using a flow cytometry assay. (B) DLL3 expression using immunoblotting of a large cell neuroendocrine cancer cell line.

3.2. Results (continued)

Figure 4. Ablation of DLL3 antibody is effectively inhibited. (A) Immunohistochemical staining used to detect DLL3 expression using immunohistochemistry in xenografts. (B) Rova-T, with isotype control, is stained with antibodies against DLL3 and SYP.

4. Conclusions

4.1. DLL3 is expressed in the plasma membrane in the majority of neuroblastoma PDXs. Rova-T displays cytotoxicity ex vivo and in tumor models. Rova-T is effectively inhibited in vivo. Rova-T induces an apoptosis and cell death.

Acknowledgments: Open access funding provided by Abbvie.

References: Available in original publication.