### The Nicotinamide Phosphoribosyltransferase (NAMPT) Inhibitor, OT–82, Exhibits In Vitro and In Vivo Efficacy Against Patient-Derived Xenograft Models of High-Risk Acute Lymphoblastic Leukemia

**A Report from the Pediatric Preclinical Testing Consortium**

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**INTRODUCTION**

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer and although children with ALL are cured, certain subtypes have significant relapse risk. Against this background, there is a pressing need for alternative strategies to target resistant/all refractory ALL. The nicotinamide phosphoribosyltransferase (NAMPT) is a novel target that has been associated with ALL disease progression. The potential therapeutic effects of NAMPT inhibition in preclinical ALL models were investigated in this study. NAMPT inhibition presents a potential therapeutic strategy for targeting ALL. In the present study, the novel NAMPT inhibitor OT–82, exhibits antiproliferative effects in preclinical ALL models, was validated in its efficacy in a panel of preclinical ALL models and identified potential PAR and NAD-dependent protein interactors.

**AIMS**

- Evaluate the efficacy of OT–82 in cell lines derived from ALL. Drugs were evaluated in HER2, ETS, and ALL–8 ALL cell lines.
- Investigate the effect of OT–82 in Xenograft models of ALL (Doxil, CU1, LAm-1, and ALL–1).

**METHODS**

In vitro drug sensitivity studies

Cell viability, cell proliferation, and spleen weight were determined for ALL cell lines after incubation with OT–82 (0–100 nM) for 48 hours. The half-maximal effective concentration (EC50) was calculated. Colony, where sensitivity is defined as an EC50 > 100 nM, an additive effect as EC50 = 10–100 nM, and a sensitive effect as EC50 < 10 nM.

In vivo drug sensitivity studies

Pediatric ALL (PDX) previously established in our lab at the Children’s Cancer Institute (CCI) was used. The PDXs were treated with oral OT–82 (0–100 mg/kg) per day for 7 days. The single-agent treatment of the single-agent treatment for 7 days in mice bearing the ALL–8 xenograft (OR = 0.2, 95% CI = 0.1–0.4) was effective in reducing the tumor burden.

**RESULTS**

OT–82 demonstrated in vivo efficacy against a diverse panel of pediatric ALL PDXs

**SUMMARY OF FINDINGS**

- OT–82 as a single agent demonstrated low nanomolar (nM) IC50 values in vitro with leukemia cell lines and significant anti-leukemia activity as a single agent against a diverse panel of pediatric ALL PDXs, in vivo. OT–82 treatment elicited objective responses in 11/13 (85%) of ALL PDXs with matched clinical responses in 4/13 (30%).

- Pharmacological studies suggest that modification of RPA and/or equivalent regulators do not correlate with OT–82 response in the evaluated PDXs, and further studies into identifying markers of OT–82 response are ongoing.

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