Preclinical In Vivo Activity of the Menin Inhibitor Ziftomenib (KO-539) in Pediatric KMT2A-Rearranged Acute Lymphoblastic Leukemia

Catherine D Falkenstein, BS,1 Lisa M Niswander, MD PhD,1 Linda Kessler, BA,2 Blake Tomkinson, PhD MBA,2 Francis Burrows, PhD,2 and Sarah K Tasiian, MD,1,3

1 Division of Oncology and Center for Childhood Cancer Research, Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania
2 Kura Oncology, San Diego, California and Boston, Massachusetts
3 Department of Pediatrics and Abramson Cancer Center, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Introduction

- Chemotherapy resistance and subsequent relapse remain a major cause of childhood leukemia mortality, particularly for infants with KMT2A-rearranged B-acute lymphoblastic leukemia (ALL).
- KMT2A is a histone lysine N-methyltransferase involved in Hox-family and MEIS1 gene regulation.
- Recent preclinical and early clinical studies have reported successful targeting of the menin scaffold protein within KMT2A fusion complexes in adults with KMT2A-rearranged acute leukemias.

Hypothesis

The selective menin inhibitor ziftomenib (KO-539) will have potent activity in preclinical patient-derived xenograft models of infant and non-infant pediatric KMT2A-rearranged ALL and could enhance chemosensitivity in these often-chemoresistant leukemias.

Methods

- We measured the ability of ziftomenib to inhibit in vitro viability in KMT2A-rearranged and KMT2A wild-type ALL cell lines using Cell Titer Glo assays.
- In vivo activity of ziftomenib as monotherapy or in combination with chemotherapy was assessed in luciferase+ ALL cell line xenograft models and in 8 patient-derived xenograft (PDX) models of de novo or relapsed KMT2A-R ALL harboring various 5' fusion partners.
- NSG mice engrafted with human KMT2A-rearranged ALL cells were randomized to treatment with vehicle, ziftomenib, vincristine, dexamethasone, ziftomenib + vincristine, or ziftomenib + dexamethasone.
- Human CD45+ CD19+ cell counts were measured weekly via retro-orbital venous bleeding and in end-study murine spleens via quantitative flow cytometry.

Results

Figure 1. Ziftomenib preferentially inhibits in vitro viability of KMT2A-rearranged ALL. KMT2A-rearranged ALL (SEM, KOPN8, HB11119) and KMT2A wild-type (NALM-6) cell lines were treated with escalating doses of ziftomenib or vehicle control in vitro for 7 days. Cell Titer Glo analysis was performed to assess cell viability. Data were normalized to vehicle-treated cells as mean with standard deviation. Half-maximal inhibitory concentrations (IC50) of ziftomenib were calculated. Statistical analysis was performed with two-way ANOVA with Tukey’s post-test for multiple comparisons. *p<0.05.

Figure 2. Ziftomenib potently inhibits in vivo leukemia proliferation in KMT2A-r rearranged ALL. (A-H) NSG mice were injected with primary KMT2A-rearranged ALL cells and passed for serial engraftment. Tertiary PDX models were treated with 150 mg/kg ziftomenib (zifto) via oral gavage daily 5 days/week, vincristine (vcr, 0.1 mg/kg intraperitoneally once weekly, dexamethasone (dex) 1 mg/kg intraperitoneally daily x 5 days/week, zifto + vcr, or zifto + dex for 3-6 weeks (depending upon rate of ALL progression in control animals) as designated by arrows. Statistical analysis was performed with two-way ANOVA (blood data) or one-way ANOVA (spleen data) with Dunnett’s post-test for multiple comparisons using ziftomenib monotherapy (red) as the comparator. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. Lack of asterisk indicates non-significance.

Conclusions & Future Directions

- We observed preferential in vitro sensitivity to ziftomenib of KMT2A-R ALL cell lines versus a KMT2A wild-type ALL cell line.
- Ziftomenib treatment of infant, non-infant pediatric, and young adult KMT2A-rearranged ALL PDX models induced significant inhibition of in vivo leukemia proliferation compared to vehicle treatment.
- Combination of ziftomenib with vincristine or dexamethasone further enhanced reduction of human ALL disease burden.
- Additional preclinical studies of ziftomenib in combination with other chemotherapies or immunotherapies are warranted.
- Based upon early clinical safety and tolerability data for ziftomenib in adult patients and our pediatric-specific data described here, a phase 1 clinical trial of ziftomenib in combination with multi-agent chemotherapy for children with relapsed/refractory KMT2A-R leukemias is planned.

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