The AKR1C3-activated prodrug OBI-3424 exerts profound in vivo efficacy against preclinical models of T-cell acute lymphoblastic leukemia (T-ALL); a Pediatric Preclinical Testing Consortium study

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1. Introduction
AKR1C3 inhibition favors tumor growth and proliferation and promotes disease progression.

2. Methods

2.1. Study Design and Analysis
Pediatric acute lymphoblastic leukemia (ALL) xenografts were established from clinical samples and characterized by preclinical testing (Suryan et al., 2016). All xenografts were derived from pediatric cases (BCP-ALL T-ALL) and genetically engineered to mimic the human leukemia transcriptome. The AKR1C3 expression level was significantly higher in ALL-11 versus the 86 different ALL PDXs (P<0.05). A significant reduction in leukemia bone marrow infiltration was observed in 8 of 9 xenografts.

2.2. Study Administration
OBI-3424 was tested at a dose of 2.5 mg/kg administered by intraperitoneal injection once weekly for 3 weeks. Since there is no murine equivalent of human AKR1C3, this dose of OBI-3424 was selected based on estimations to achieve exposure levels in mice that will be readily attainable in humans, and is well below the mouse maximum tolerated dose (MTD).

3. Results

3.1. AKR1C3 expression in T-cell acute lymphoblastic leukemia
AKR1C3 mRNA and protein expression, as well as its enzymatic activity, had previously been measured in 86 different pediatric patients' xenografts (PDXs). T-cell acute lymphoblastic leukemia (T-ALL) was selected as the primary disease model for further study because it is a monolineage acute leukemia with well-characterized pathogenic pathways with B-cell pre-treatment ALL (BCP-ALL) or T-ALL (Teichman et al., 2015).

3.2. AKR1C3 enzymatic activity significantly correlated with its protein expression levels (Figure 2), and both were significantly higher in T-ALL compared with BCP-ALL PDXs.

3.3. OBI-3424 exerted profound in vivo efficacy against preclinical models of T-ALL by OBI-3424 treatment was well tolerated at a dose that is estimated to achieve exposure levels in mice that will be readily achievable in humans.

4. Conclusions and Discussion
OBI-3424 may represent a novel treatment approach for aggressive and chemotherapy-resistant T-ALL in pediatric clinical trials.

5. References

More Information
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Figure 1. Structure of OBI-3424

Figure 3. AKR1C3 protein expression in metaphase and ALL-T-ALL PDX cells. AKR1C3 protein was quantified by immunodetection and AKR1C3 enzymatic activity by fluorometric assay. Expression was measured on untreated (A), and AKR1C3 treated (B) ALL-T-ALL PDX cells (Manesh et al., 2015).

Figure 4. Effects of OBI-3424 on leukemia infiltration into the femoral BM of mice engrafted with T-ALL xenografts (ALL-11/EV). The proportion of human leukemia cells in specific femoral bone marrow regions was determined by fluorometric assay, as described previously (Jamieson et al., 2015).

Figure 5. Responses of ALL PDXs to OBI-3424 treatment. Responses, l.r.; treated; local, median of each group; arrows, days of treatment.

Figure 6. Effects of OBI-3424 on leukemia infiltration into the femoral BM of mice engrafted with T-ALL xenografts (ALL-11/EV). The proportion of human leukemia cells in specific femoral bone marrow regions was determined by fluorometric assay, as described previously (Jamieson et al., 2015).

Figure 7. Responses of ALL-11/EV control and OBI-3424 treated BM leukemic cells, treated; blue lines, median cell count of each group; arrows, days of treatment.

Figure 8. Waterfall plot depicting the maximum decrease from baseline levels of human leukemia cells in the murine peripheral blood in response to OBI-3424 treatment. Each symbol represents a single mouse. Bars represent the median cell count. The graph is ranked in ascending order.