**1. Introduction**

Aldo-keto reductase family 1 member C3 (AKR1C3) belongs to a superfamily of oxidoreductases that are broadly expressed in human tissues. AKR1C3 enzymatic activity was measured by SN34037-sensitive coumberol formation in cell lysates via tail vein injection of NOD/SCID or NSG mice, and modeled systemic disease (Suryani et al., 2014).

**2. Study Methods**

**Drug 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 to achieve systemic exposure levels in mice that will be lethal to healthy mice.

**Study Design and Analysis**

- Pediatric acute lymphoblastic leukemia (ALL) PDXs were established from donor ex vivo expanded T-cell acute lymphoblastic leukemia (T-ALL) and B-cell acute lymphoblastic leukemia (BCP-ALL) patient samples, and engineered with selective advantages (Djuric et al., 2014).
- AKR1C3 enzymatic activity was measured in a large panel of patient-derived xenografts (PDXs) from pediatric patients presenting with T-cell acute lymphoblastic leukemia (T-ALL); a Pediatric Preclinical Testing Consortium study (Suryani et al., 2014).
- AKR1C3 mRNA and protein expression, as well as its enzymatic activity, had previously been measured in a large panel of human T-cell acute lymphoblastic leukemia (T-ALL) PDX samples using a novel fluorometric assay (Evans et al., 2014).

**3. Results**

**3.1. AKR1C3 expression in T-cell acute lymphoblastic leukemia (T-ALL)**

AKR1C3 mRNA and protein expression, as well as its enzymatic activity, had previously been measured in a large panel of human T-cell acute lymphoblastic leukemia (T-ALL) PDX samples using a novel fluorometric assay (Evans et al., 2014).

**3.2. Effect of OBI-3424 on leukemia infiltration into the femoral bone marrow of mice engrafted with T-ALL PDXs**

Figure 6. Effects of OBI-3424 on leukemia infiltration into the femoral BM of mice engrafted with T-ALL PDXs. In vivo efficacy against a broad range of T-ALL PDXs derived predominantly from patients who experienced aggressive and fatal disease. OBI-3424 treatment was well tolerated at a dose that is estimated to achieve exposure levels in mice that will be lethal to healthy mice.

**3.3. Expression of selected endometrioid carcinoma patient samples**

Table 1. Relative Expression of AKR1C3 mRNA in Patient-Derived T-ALL-ALL-11/EV, EFS T/ C, average minimum huCD45% for treated group; T/ C, total number of mice entering experiment; Median response, difference in median time-to-event (days); DOD, number of mice in analysis; EFS, event-free survival; EFS T, event-free survival for treated groups; Events were defined as the proportion of human CD45+ cells (%huCD45+) in the peripheral blood (PB) post treatment initiation or at event (whichever occurred first) in control and OBI-3424-treated animals. Waterfall plots represent the percentage ratio of the minimal %huCD45+ cells in the PB at any point in time after treatment initiation to the %huCD45+ at Day 0 (baseline).

**Figure 8. Waterfall plot depicting the maximum decrease from baseline levels of human leukemic cells in the mouse peripheral blood in response to OBI-3424 treatment. Each symbol represents a single mouse. Bars represent the median of each group; arrows, days of treatment.

**4. Conclusions and Discussion**

**5. References**

Kathryn Evans1, Tara Pritchard1, Raymond Yung1, Stephen W. Erickson2, Yuelong Guo2, Jianxin Duan3, Beverly A. Teicher4, Malcolm A. Smith4, Richard B. Lock1.

**A novel fluorometric assay for aldo-keto reductase family 1 member C3 (AKR1C3) expression in human tissues**

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More Information

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**Abstract**

Kathryn Evans1, Tara Pritchard1, Raymond Yung1, Stephen W. Erickson2, Yuelong Guo2, Jianxin Duan3, Beverly A. Teicher4, Malcolm A. Smith4, Richard B. Lock1.

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AKR1C3 is a nitro-benzene prodrug of 17β-hydroxysteroid dehydrogenase and prostaglandin F synthase. OBI-3424 is a nitro-benzene prodrug of N-acetylsaliclylic acid.

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**3. Results (continued)**

Figure 9. Table of relative expression of AKR1C3 in pediatric ALL PDXs treated with OBI-3424 in vivo.

**4. Conclusions and Discussion**

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