Pediatric Preclinical Testing Consortium Evaluation of the Novel Anti-Microtubule Drug E7130 in Xenograft Models of Early T-Cell Precursor Acute Lymphoblastic Leukemia

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Pediatric Preclinical Testing Consortium

1. Introduction

- The outcome for many high-risk subtypes of pediatric acute lymphoblastic leukemia (ALL) such as early T-cell precursor ALL (ETP-ALL) can be poor.
- Standard-of-care drugs used in multi-agent treatment protocols for ALL (including vincristine) are substrates for the ATP-dependent drug efflux pump P-glycoprotein (P-gp), encoded by the ABCB1 gene.
- ETP-ALL is characterized by poor early response to conventional induction treatment and expresses significantly higher levels of the ABCB1 gene compared with typical T-ALL (1 ST-64 false discovery rate 0.029, P=0.005, Zhang et al, 2012).
- E7130 is a novel anti-microtubule agent with low affinity for P-gp compared with other anti-microtubule drugs such as vincristine. E7130 has shown significant preclinical activity against patient-derived xenograft (PDX) models of adult malignancies. Therefore it was of interest to test E7130 against the PFTC ETP-ALL PDXs.

2. Study Methods

Agent administration:
- E7130 was provided by Eisai Inc. and tested at 2 dose levels (0.09 and 0.135 mg/kg) administered intravenously once a week for 3 weeks.
- Vincristine was evaluated at 1 mg/kg administered intraperitoneally once a week for 5 weeks.

Study design and analysis:
- ABCB1 mRNA expression in pediatric ALL PDXs was quantified by RNAseq (https://edpbiopenportal.org) and qRT-PCR.
- Activity of P-gp was measured by the Rhodamine-123 (Rh123) efflux assay in the absence or presence of the P-gp inhibitor tariquet. Intracellular Rh123 was measured by flow cytometry.
- E7130 and vincristine were evaluated using Objective Response Measures (ORMs) modeled after stringent clinical criteria, which monitored treatment response using Objective Response Measures (ORMs).
- An event was defined as ≥ 25% huCD45+ cells in the peripheral blood for each treatment group. Lighter colored lines represent individual mouse %huCD45+ (1 MCR, 1 MCR).

3. Results

Figure 3. Engraftment and EFS of pediatric ETP-ALL PDXs in response to E7130 and vincristine. (A) Tumor burden across different PDX models in response to E7130 and vincristine. (B) Cumulative incidence of relapse in response to E7130 and vincristine. (C) EFS for treated group; median response, median response evaluation; ORM, Objective Response Measure.

Table 1: Engraftment of all ETP-ALL PDXs with high ABCB1 expression. (A) Tumor burden across different PDX models in response to E7130 and vincristine. (B) Cumulative incidence of relapse in response to E7130 and vincristine. (C) EFS for treated group; median response, median response evaluation; ORM, Objective Response Measure.

4. Discussion and Conclusions

- E7130 was tested at two dose levels against 6 ETP-ALL PDXs, which were selected based on differential levels of ABCB1 gene expression.
- A statistically significant delay of leukemic progression was observed in all evaluable PDXs at both doses of E7130 compared to control.
- Vincristine was less effective against the PDXs with high ABCB1 expression, although the difference only approached significance.

5. References

- MCR = maintained complete response, CCR = continuous complete response.