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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1. Introduction
- The outcome for many high-risk subtypes of pediatric acute lymphoblastic leukemia (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 (1.9 ST-64) false discovery rate (0.02), [Houghton 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 3 weeks.
- Study design and analysis:
  - ABCB1 mRNA expression in pediatric ALL PDxs was quantified by RNAseq (https://pedcbioportal.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 tariquidar. Rh123 was measured by flow cytometry.
  - E7130 and vincristine were evaluated in 10 ETP-ALL PDxs. Each PDx was intravenously inoculated into 6-8 immune-deficient (NSG) mice per treatment group (2-5 x 10^6 cells/mouse). Lock et al., (Blood, 2002).
- Engraftment and drug responses were evaluated by enumerating the proportion of CD45+ cells in the peripheral blood (%huCD45+) at weekly intervals.
  - An event was defined as ≥25% huCD45+ cells in peripheral blood (PB), or when the mouse exhibited leukemia-related morbidity associated with high-level leukemic infiltration (≥50% huCD45+) at least 2 major organs.
  - The Kaplan-Meier method was used to determine event-free survival (EFS) between control and treated groups.
- Treatment responses were monitored using Objective Response Measures (ORMs) modeled after stringent clinical criteria, which was assessed at Day 42 post treatment initiation (Houghton et al., 2007).
- PD1 - progressive disease 1, %huCD45 in PB never drops below 1% and reaches event before the end of the study, with an EFS ≤ 200% of median control EFS.
- PD2 - progressive disease 2, %huCD45 in PB never drops below 1% and reaches event before the end of the study, with an EFS ≤ 200% of median control EFS.
- CR = complete response, %huCD45 in PB < 1% for 2 consecutive weeks and event is not reached by Day 42.
- MCR = maintained complete response, %huCD45 in PB < 1% for at least 2 consecutive weeks after treatment completion and event is not reached by Day 42.
- Waterfall plots represent the ratio of the minimal %huCD45 in the PB at any point after treatment initiation relative to the %huCD45 at Day 0.

3. Results
- E7130 was evaluated 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.
- E7130 displayed comparable efficacy against all PDxs, with no apparent correlation with ABCB1 expression.
- Additional studies are necessary to determine whether E7130 represents an alternative to vincristine for the treatment of pediatric ALL with high ABCB1 gene expression.

4. Discussion and Conclusions
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5. References

More Information
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Table 1: In-vivo activity of E7130 and Vincristine against ETP-ALL PDxs. E7130: mg/kg; vincristine: mg/kg; CR: complete response; MCR: maintained complete response; PD: progressive disease. CR efficacy was evaluated in 10 ETP-ALL PDxs (1.97 NA; 0.081 mg/kg) administered intravenously once a week for 3 weeks. The right panels represent EFS of individual mice per treatment group. E7130 was generally well tolerated in NSG mice, with maximum average weight loss of 2.7-11.7% in the groups treated with the highest dose compared with 3.2-12.7% in the vincristine treated groups. E7130 (0.09 mg/kg) significantly (P<0.05) delayed the disease progression of all 6 PDxs (T/C 10.5-41.3 days, T/C 1.8-6.9) and elicited objective responses in 2/8 PDxs (1 CR, 1 MCR). The higher dose of E7130 (0.135 mg/kg) significantly delayed the progression of all 6 evaluable PDxs (T/C 18.1-48.5 days, T/C 2.3-8.6) and elicited 4 objective responses (1 CR, 3 MCRs). In contrast, vincristine significantly delayed the progression of 3/8 PDxs (T/C 3.5-37.7 days, T/C 1.3-6.4) and elicited only 2 objective responses (1 CR, 1 MCR).