Acute Lymphoblastic Leukemia (ALL) and E1lan (XPO1/CRM1)

While the overall 5-year survival rate for children with ALL is now approximately 90% (Segal et al., 2019), children with certain high-risk subtypes experience a far less favorable outcome.

- E1lan (XPO1/CRM1) plays a central role in the export of proteins from the nucleus, including those with tumour suppressor and growth regulatory activity, such as p53, p21, BCL-2, and STAT3 (Segal et al., 2019).
- As E1lan protein expression is upregulated in several leukemia subtypes, including B-cell ALL (Thaepet et al., 2014), XPO1 presents a promising therapeutic target for pediatric ALL.

Development of E1lanx by Karyopharm Therapeutics

Elanexor (KPT-8602) is a second-generation Selective Inhibitor of Nuclear Export (SINE) that specifically blocks XPO1 cargo interactions and exhibits improved tolerability in animal models compared to the first-generation SINE, selinexor (KPT-330) (Elshin et al., 2015).

Elanexor has demonstrated activity in vitro and in vivo activity against preclinical models of chronic lymphoblastic leukemia, B-cell lymphoma, and acute myeloid leukemia (Elshin et al., 2015; Hing et al., 2015).

Elanexor is currently in a phase III clinical trial for adults with multiple myeloma and other relapsed/refractory cancer indications (NCT04597910).

Study Objective

The objective of this study was to evaluate the in vivo activity of elanexor against the PTCF preclinical models of pediatric ALL patient-derived xenografts (PDXs) in a single mouse trial (SMT) format.

2. Study Methods

Study Design and Analysis

- 90 pediatric ALL PDXs were previously established from direct patient explants via tail vein injection of NOD/SCID or NSG mice. The PDXs develop as models of systemic disease (Lock et al., 2002; Richmond et al., 2015).
- For the SMT, 1 NSG mouse per PDX was inoculated via tail vein injection and treatment began at the % human CD45+ cells (%HC45+ in mice wherein peripheral blood (PB) reagent 2% ± 1). The baseline level of the %HC45+ in each mouse serves as its own control.
- Elanexor was provided by Karyopharm Therapeutics Inc. and administered via oral gavage at a dose of 12.5 mg/kg, daily for 5 days for an intended 4 weeks.
- Events were defined when the %HC45+ in the PB was increased, or the animal exhibited leukemic-related morbidity associated with high-level leukemic infiltration (>50%) of at least 2 major organs.
- The objective response measures (ORMs) are as described by Houghton et al. (2004) with minor modifications:
  - PD1: progressive disease 1, when the %HC45+ in PB was never <1% and event was reached or before Day 14.
  - PD2: progressive disease 2, when the %HC45+ in PB was never <1% and event was reached after Day 14 but before Day 42.
  - SD: stable disease for the %HC45+ in PB was never <1% and the mouse did not reach event during the study period.
  - PR: partial response, the %HC45+ in PB was <1% once during the study period.
  - CR: complete response, the %HC45+ in PB was <1% for at least 2 consecutive weekly readings during the study period.
- For the conventional study, the in vivo efficacy of elanexor was previously assessed against 12 PDXs alongside a vehicle control group (vehicle, 0.9% NaCl solutions) and compared to SMT data by linear regression analysis.
- Summary plots portray the treatment period and event-free survival (EFS) of individual mice. The length of each bar is proportional to the EFS, and the hatched area indicates the drug treatment period.
- The Kaplan-Meier method compared the EFS mice between leukemia subtypes.
- Waterfall plots represent the percentage ratio of the minimal %HC45+ cells in the PB at any point in time after treatment initiation relative to the %HC45+ at Day 0.

3. Results

3.1. In vivo activity of elanexor as a single agent against 90 PDXs

Table 1. In vivo activity of elanexor as a single agent against 90 PDXs.

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3.2. EFS days post treatment initiation

Figure 2. Kaplan-Meier curves of mouse EFS over time in response to elanexor treatment. Each PDX is grouped by subtype, and the dotted line indicates the end of the treatment period.

Figure 3. Correlation between ORMs of 12 ALL PDXs in response to elanexor treatment assessed by conventional or SMT testing formats. Solid and dashed lines represent linear regression and 95% confidence intervals, respectively.

4. Discussion and Conclusions

Elanexor exhibited broad single-agent in vivo activity against a range of ALL subtypes, eliciting prolonged protracted delay and objective responses in >50% of the PDXs tested in either the conventional or SMT format, although only a minority (14%) achieved MCR responses.

Elanexor exhibited good single-agent in vivo activity against a range of ALL subtypes, eliciting prolonged protracted delay and objective responses in >50% of the PDXs tested in either the conventional or SMT format, although only a minority (14%) achieved MCR responses.

The SMT format correlated highly with conventional drug testing, providing a strong rationale for the use of SMTs in assessing drug efficacy across a broad range of PDXs.

5. References

Doll, J., Bembenek, A., Conley, A.S., Nuclear export inhibitor KPT-8602 is highly active against leukemia subtypes, and demonstrates therapeutic potential against xenograft models of ALL. Blood (2013) 120(23) 4398-4405.


More Information

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