KPT-330

- KPT-330 is an orally bioavailable Selective Inhibitor of Nuclear Export (SINE).
- KPT-330 binds covalently to the nuclear export protein XPO1 at Cys532 leading to irreversible inactivation.
- XPO1 exports over 200 proteins with specific nuclear export sequences.
- Cargo proteins include cancer-relevant proteins such as FOXO, IkB, PRB, p53, P73, P21, and p27.
- KPT-330 is in clinical trials for adults with cancer.

KPT-330 IN VITRO ACTIVITY

- The median relative IC50 (\text{IC}_{50}) for KPT-330 against PPTP cell lines was 125 nM (range 13.3 nM to >10 μM).
- KPT-330 induced Relative In/Out% values between -75% and -100% for most cell lines, consistent with a prominent cytotoxic effect.
- There were no significant differences in \text{IC}_{50} values by histotype, although there was a trend for greater sensitivity for the Ewing sarcoma cell lines (median \text{IC}_{50} = 57 nM) and lesser sensitivity for the neuroblastoma cell lines (median \text{IC}_{50} = 235 nM).
- The COMPARE-like plot illustrates the relative sensitivity of Ewing sarcoma cell lines (red bars) and lesser sensitivity of the neuroblastoma cell lines (blue bars).

COMPARE-Like plot for \text{IC}_{50} values for KPT-330

\[ \text{IC}_{50} \text{ values for KPT-330} = 2.35 \text{nM} \]

PPTP IN VITRO & IN VIVO TESTING METHODS

-in vitro: In vitro testing was performed using DRIMSCAN, a semi-automated fluorescence-based digital image microscopy system that quantifies viable (using fluorescein diacetate [FDA]) cell numbers in tissue culture multwell plates (Kang MH, et al. Pediatric Blood & Cancer 2015; 62: e233-245, 2011). Testing was for 96 hours at concentrations from 1.0 nM to 10.0 μM with replicates of 6-12 per data point. Data were analyzed by fitting a non-linear regression model-sigmoidal dose-response model to the response-relative fluorescence values vs. the concentration.

-in vivo: Standard PPTP methods for in vivo testing were employed (see www.pptp.org for complete methods). KPT-330 was tested in vivo using a dose of 10 mg/kg administered PO 3 times weekly (M/W/F) for a total of 4 consecutive cycles. The in vivo pharmacokinetic and toxicology evaluation was 9 wks.

Acute lymphoblastic leukemia testing: For each xenograft line, 8 mice were inoculated with 3-5 × 10^6 cells i.v. or s.c.

Solid tumor testing: For each xenograft line, 10 mice bearing SC tumors initiated treatment when the tumors were between 0.2-0.5 cm^3. Two perpendicular tumor diameters were measured at each time point and the mean tumor volume was calculated. Tumors were treated with KPT-330 when the tumor size at each time point was >100% of baseline.

The COMPARE-like plot illustrates the relative sensitivity of Ewing sarcoma cell lines (red bars) and lesser sensitivity of the neuroblastoma cell lines (blue bars).

KPT-330 IN VIVO ACTIVITY

- Solid tumor testing was performed using DIMSCAN, a semiautomatic system that allows the monitoring of tumor growth and treatment effects in the same mouse over time.

IN VIVO RESULTS AND CONCLUSIONS

- KPT-330 was well tolerated (0.9% mortality) at the dose (10 mg/kg PO) and schedule (M-W-F for 4 consecutive weeks) evaluated.
- KPT-330 induced tumor growth inhibition meeting criteria for intermediate or high EFS T/C activity (EFS T/C > 2) in 11 of 32 (34%) of solid tumor xenografts, most frequently for the Wilms tumor (2 of 3) and the Ewing sarcoma (4 of 4) panels.
- Three of 8 ALL xenografts met all criteria for intermediate or high EFS T/C activity.
- KPT-330 induced objective responses in 3 of 7 (42%) of solid tumor models, including two brain tumor xenografts, BT-60 (medulloblastoma) and BT-41 (ependymoma), as well as in 2 of 8 ALL xenografts (one B-cell and one T-cell ALL).

- Conclusions: KPT-330 shows tumor regression activity against selected PPTP solid tumor and ALL xenografts, and shows tumor growth inhibition for a larger number of models. Defining the relationship between KPT-330 systemic exposures in mice and humans will be important in assessing the clinical relevance of the PPTP in vivo results. Planned pharmacodynamic testing may provide insight into biological factors associated with responsiveness to KPT-330.