PEDIATRIC PRECLINICAL TESTING PROGRAM (PPTP) EVALUATION OF THE NON-CAMPTOTHECIN TOPOISOMERASE 1 TARGETED AGENT GENZ-644282

ABSTRACT

Background: Genz-644282, a non camptothecin topoisomerase 1 poison, was developed from a lead compound identified in a screen for inhibitors of PARP-1 (poly (ADP-ribose)polymerase-1) (1,2). In vitro, Genz-644282 is a potent inhibitor of topoisomerase 1 (TOP1) at micromolar concentrations. Non-commercially available ABCG2 transgenic xenografts (ARCl11,B6 mice) also differentiated from other camptothecin derivatives in that it was not a substrate for the ABCG2 drug transporter.

Objective: The PPTP includes a molecularly characterized in vitro panel of cell lines (n=27) and in vivo panel of xenografts (n=18) derived from both pediatric and adult solid tumors and childhood acute lymphoblastic leukemia (ALL). Genz-644282 (provided by Merck) was tested in a concentration-response exposure to drug. A median of 1 cycle of treatment (T/C) was analyzed for the tumor volume measure; and 3) a time to event (4-fold increase in tumor volume) measure based on the median event-free survival (EFS) of treated and control animals for each xenograft.

Methods: The PPTP includes a molecularly characterized in vitro panel of cell lines (n=27) and in vivo panel of xenografts (n=18) derived from both pediatric and adult solid tumors and childhood acute lymphoblastic leukemia (ALL). Genz-644282 (provided by Merck) was tested in a concentration-response exposure to drug. A median of 1 cycle of treatment (T/C) was analyzed for the tumor volume measure; and 3) a time to event (4-fold increase in tumor volume) measure based on the median event-free survival (EFS) of treated and control animals for each xenograft.

Results: In vitro Genz-644282 exerted potently cytotoxic activity with a median IC50 of 1.19 mM (range 0.19 – 22.3 mM). In vivo at 4 mg/kg (MTD) for two cycles, Genz-644282 induced complete regressions in 7/18 models including tumor volumes for all responsive xenografts to topotecan. Doxorubicin exposure (1 cycle of treatment) against 3 tumor lines from hematopoietic tumor models showed Genz-644282 induced complete or partial regressions of tumor volumes. In vivo, Genz-644282 was adequately tolerated at the highest dose / schedule tested (4 mg/kg MWF for 2 weeks). The ratio of the median relative IC50 for the panel to each individual cell line’s relative IC50 represents the mean diameter.

CONCLUSIONS

- Genz-644282 demonstrated potent cytotoxicity in vitro with Ymin values approaching 0% for almost all cell lines.
- The median relative IC50 for Genz-644282 (1.2 nM) was ~6.8-fold lower than that for topotecan.
- The ALL cell lines had the lowest IC50 values, while the rhabdomyosarcoma cell lines had the highest.
- Genz-644282 was adequately tolerated at the highest dose / schedule tested (4 mg/kg MWF for 2 weeks), with toxicity in ~12% of treated animals. Genz-644282 at the 4 mg/kg dose caused MCR of all tumor lines irrespective of their sensitivity to topotecan.
- The dose response relationship was determined against 3 models having the least sensitivity to topotecan (NB4, NCI-H157, and MIA PaCa-2) administered 4 times at a 1:2:4:8 dilution to determine the minimum effective dose level. Genz-644282 induced CR or MCR in each of these models at 2 mg/kg and above. However, 1 mg/kg there was progressive growth for each model, suggesting a narrow dose range response, typical of cytotoxic agents that target topoisomerase I.
- Genz-644282 demonstrated a high level of activity at the 2 mg/kg dose level, inducing regressions in 8 of 18 models evaluated at this dose (46%), including models that are intrinsically insensitive to topotecan.
- Objective responses at 2 mg/kg were most commonly observed for sarcoma models, with 4 of 5 osteosarcoma xenografts achieving objective responses at this dose level.
- How accurately these data translate into clinical activity will depend on the PPTP. Genz-644282 in Phase I dose escalation study in advanced solid tumors is currently underway. The poster will be available at pptp.nchresearch.org

IN V ITRO & IN VIVO TESTING METHODS

- Genz-644282 was provided to the PPTP by Genzyme Corporation. Testing was supported by NIH RO1CA130555 and NICHD 5R01HD034851.

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