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Evaluation of Bortezomib against Childhood Tumor Models by the Pediatric Preclinical Testing Program (PPTP)

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Abstract

Previous studies have validated the use of xenografts derived from childhood cancers as models that can identify drugs known to be active against their respective clinical diseases. Importantly, these models have correctly identified novel agents that have prospectively been shown to have significant activity in phase I and 2 clinical trials in children. Because cancer in children is relatively rare, and only limited numbers of clinical trials can be undertaken, a need exists for preclinical models representing key characteristics and upon gene expression profiles similar to their respective clinical disease. Importantly, these models have correctly identified novel agents that have prospectively been shown to have significant activity in children with solid tumors.

These data will be publicly available.

PPTP Tumor Panels and Test Sites

- Rhabdomyosarcoma (n=6) and Ewing sarcoma (n=3)
- Dr. Peter Houghton (St. Jude Children’s Research Hospital)
- Neuroblastoma (n=6)
- Dr. John Maris (Children’s Hospital of Philadelphia)
- Osteosarcoma (n=6)
- Dr. Richard Gorlick (Albert Einstein College of Medicine)
- Acute lymphoblastic leukemia (n=8)
- Dr. Richard Lock (Children’s Cancer Institute Australia)
- Brain tumors, Glioblastoma (n=4)
- Dr. Henry Friedman (Duke University Medical Center)
- Brain tumors, Non-glioblastoma (n=6)
- Dr. Peter Houghton (St. Jude Children’s Research Hospital)
- Kidney cancers (n=4)
- Dr. Peter Houghton (St. Jude Children’s Research Hospital)
- In vivo panel (n=23)
- Dr. Patrick Reynolds (Children’s Hospital of Los Angeles)

Gene expression profiles and chromosome copy number abnormalities are being determined for each of the PPTP lines. These data will be publicly available.

Bortezomib & Vincristine Activity: PPTP in Vivo Lines

- Bortezomib activity: • No objective responses or stable disease in solid tumor lines • ALL lines (n=4): 1 MCR and 2 CR
- Vincristine activity: • Response in ALL solid tumor lines, including: • Wilms tumor (n=6): 1CRR & 1MR • Rhabdomyosarcoma (n=6): 1MCR, 1CR & 1 PR • Glioblastoma (n=4): 1MCR • Osteosarcoma (n=6): 1MCR & 1CR

Methods for PPTP in Vivo Testing

Stage 1 testing involves testing an agent across the entire PPTP panel of childhood cancer xenograft lines at 1 mg/kg twice weekly based on PPTP studies using adult preclinical models. If activity is observed in Stage 1 testing, then further testing in Stage 2 can address, as appropriate, the dose-response curve for antitumor activity, PK/PD studies, and drug combination studies. Procedures for Stage 1 testing are provided below.

- Solid tumor testing: For each xenograft line, 10 mice bearing SC tumors initiated treatment when the xenograft was 3 cm in diameter. Two percutaneous tumor diameters were measured at either every 3 or twice weekly intervals with digital vernier calipers. Assessing tumors to be spherical, volumes were calculated from the formula V = (4/3)πr³, where r represents the mean diameter.

- Progression free survival (PFS) is defined as the time from initiating therapy until disease progression, death, or last follow-up.

- Objective regression is defined as a ≥75% reduction in tumor volume for ≥4 weeks, based on the two percutaneous tumor diameters measured at every 3 or twice weekly intervals.

- Preradiation testing is provided in D960/IFH/36 in 96 weeks to detect the presence of CD45 positive cells and thereby identify novel agents. Tumors were selected based upon their growth characteristics and upon gene expression profiles similar to their respective clinical disease.

- Approximately 12 agents per year can be evaluated by the PPTP. To calibrate the system we then evaluated vincristine, a standard cytotoxic agent used as a component of multiple protocols. Vincristine ($1 mg/kg of 6 weeks) elicited objective regressions in 1/6 kidney tumors/rhabdoid tumors, 3/6 rhabdomyosarcoma, 0/2 Ewing sarcoma (primary/relapse) and 3/6 Ewing sarcoma (diagnosis).

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DISCUSSION & CONCLUSIONS

- Stage 1 testing results for bortezomib suggest that this agent warrants further evaluation for pediatric ALL. Data from one additional ALL line will be included in the final Stage 1 report.
- Activity of bortezomib is reported to occur commonly in pediatric ALL, providing a potential mechanism for bortezomib activity in this disease. The combination of bortezomib, dexamethasone, & doxorubicin has been evaluated in children with myeloma and there is interest in evaluating this combination in children with ALL.
- In the bortezomib testing of bortezomib, this provides no leads for the use of bortezomib in children with solid tumors.
- The antitumor activity of vincristine observed against the ALL, rhabdomyosarcoma, and Wilms tumor was expected, given the activity of these agents in children with these tumors.
- The responses to vincristine observed against the osteosarcoma lines were unexpected. Though vincristine has been used in treating children with osteosarcoma, its single agent activity is considered to be limited.
- Studies are in progress to identify associations between the gene expression profiles of the xenograft lines and their responsiveness to bortezomib and vincristine. Patterns of gene expression associated with activity could be clinically relevant, if similar patterns are present in patient responses to these agents.

This initial PPTP experiment demonstrates the feasibility of testing of agents across a relatively large panel of childhood cancer xenograft lines, with one agent initiating testing each month. Future agents to be tested will address molecular targets as Src family kinases, VEGFR, histone deacetylase, ErbB family kinases, mTOR, and Bcl-2 family inhibitors of apoptosis.