

## Experimental targeted therapy shows early promise against medulloblastomas

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Researchers from St. Jude Children's Research Hospital and the Pediatric Brain Tumor Consortium (PBTC) presented at the American Society of Clinical Oncology the findings of a pediatric brain tumor study using an experimental drug that targets the underlying genetic makeup of the tumor. The research focused on a new way to attack the tumors by blocking the Hedgehog pathway that is linked to approximately 20 percent of medulloblastomas.

The study is the first to report that the drug can be safely administered to children. The study also suggested that the drug is showing early signs of efficacy in this patient population, with some children still on treatment almost a year with no progression of disease. All the children on this study had medulloblastomas that persisted or returned despite standard treatment with radiation and <u>chemotherapy</u>. Recurrent medulloblastoma currently has a cure rate of less than 5 percent.

The researchers found that patients whose tumors had the Hedgehog molecular pathway activated appear to be some of the same patients who have responded to treatment in this trial, based on length of time on study. Investigators have observed tumor responses in similar young adult patients whose tumors had the Hedgehog molecular pathway activated. These early findings have given the green light for pediatric research to advance to a larger Phase II study scheduled to open later this year, and to increase the number of patients on the young adult study.

The Phase I study (PBTC -025) included 13 patients, 12 of them



evaluable, ranging in age from 4 to 21 years. All received one of two different doses of GDC-0449 daily for a minimum of 28 days and continued on treatment for as long as their disease remained stable. In addition to determining the safety and dosing of this <u>experimental drug</u> for children, the trial also conducted extensive research into pathologic and genomic methods for better identifying tumors that have the Hedgehog pathway activated.

"Medulloblastomas are the most common malignant brain tumors in children," said Amar Gajjar, M.D., co-chair of the St. Jude Department of Oncology and principal investigator of the PBTC trial. "The trend in treating children with these cancers is toward targeted therapies like this one, which block key signaling pathways and disable the cancer's ability to function or reproduce. We know that this Hedgehog pathway is important in the growth of these especially hard-to-treat tumors."

The PBTC has an ongoing Phase II trial in recurrent medulloblastomas in young adults (age 22 and older), with this same agent, which has recently been expanded to include more patients. A Phase II trial of GDC-0449's effectiveness against recurrent medulloblastomas in children (up to age 21) will start later this year based on the results of today's reported Phase I trial.

All of the PBTC trials are being sponsored by the Division of Cancer Treatment and Diagnosis, National Cancer Institute (NCI) under a Cooperative Research and Development Agreement Letter of Intent between NCI and Genentech, Inc.

St. Jude is home to the nation's largest research-based pediatric brain tumor program. St. Jude investigators have played a pivotal role in advancing understanding of the molecular missteps that give rise to medulloblastomas as well as seeking new, more targeted therapies to combat the tumors. St. Jude investigators have published evidence that



targeting the Hedgehog pathway eradicated medulloblastomas in laboratory models. During fetal development the Hedgehog pathway plays a central role in normal growth of the cerebellum. The cerebellum is located at the base of the skull and is the structure that helps coordinate movement and plays a role in mastering balance and other motor skills. Medulloblastomas begin in the cerebellum, and uncontrolled activity along this pathway is linked to several cancers, including basal cell skin cancer.

Provided by St. Jude Children's Research Hospital

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