

PBTC-045 - A SUMMARY FOR PATIENTS AND FAMILIES

Title: PBTC-045-A Safety and Preliminary Efficacy trial of MK-3475 (pembrolizumab; anti-PD-1) in Children with recurrent, progressive or refractory high-grade gliomas (HGG) and DIPGs

This is a brief summary of a clinical trial, a type of therapeutic research study. “You” refers to ‘you’ or ‘your child’ throughout this document. Clinical trials include only patients who choose to take part in the research study. Participation is entirely voluntary.

WHO MIGHT BE ELIGIBLE TO PARTICIPATE IN PBTC-045?

Patients must have a histologically confirmed diagnosis of recurrent, progressive or refractory non-brainstem high-grade glioma or diffuse intrinsic pontine glioma (DIPG) that is recurrent, progressive or refractory may be eligible for PBTC-045. Histologic diagnosis is not required for patients with typical imaging findings of DIPG (defined as patients with a diffuse expansile mass centered in and involving at least 2/3 of the pons.) Patients with brainstem tumors who have undergone biopsy with a diagnosis of high-grade glioma or diffuse infiltrating glioma may also be eligible. Patients must be between the ages of 1-18 for the safety portion and less than 22 years of age for the efficacy portion of the study. Patients **must** have received prior radiation therapy and/or chemotherapy and recovered from the acute treatment related toxicities (defined as < grade 1 if not defined in eligibility criteria) of all prior chemotherapy, immunotherapy or radiotherapy prior to entering this study. There is no upper limit to the number of prior therapies that is allowed. Patients must have received their last dose of known chemotherapy at least three 3 weeks prior to study enrollment or at least six 6 weeks if prior nitrosourea. Patient must have received their last dose of the investigational or biologic agent ≥ 7 days prior to study enrollment. Craniospinal radiation must have concluded 3 months prior to registration and Decadron dose should be stable or decreasing for at least 1 week prior to starting therapy.

Female patients may not be pregnant or nursing. Patients of childbearing or child fathering potential must be willing to use 2 methods of birth control or be surgically sterile or abstain from heterosexual activity while being treated on this study and for 4 months after the last dose of study medication. Patients’ medical and neurological condition must be stable for at least a week prior to participation in the trial.

Patients will need medical tests to assess whether they can participate in PBTC-045. These tests may include a medical history, physical examination, blood and urine tests and scans (MRI) of the brain and spine. Other tests may be required if doctors believe they are necessary. Approximately 33 children will take part in PBTC-045.

WHAT IS THE PURPOSE OF THIS STUDY?

The immune system has the capability to hinder and even eradicate tumor growth. Immune-mediated anti-tumor strategies may be superior to historical treatment options for children with recurrent non-brainstem high-grade glioma or DIPG. The potential advantages of leveraging the immune system in CNS tumors include potential durability of response, greater generalizability of approach, and potential communication across the blood-brain barrier. This is a two-phase safety and preliminary efficacy study. The first phase is a safety study to assess the dose limiting toxicities and defines a recommended phase II dose (RP2D) for MK-3475 (pembrolizumab).

MK-3475 is a monoclonal antibody that has produced impressive responses in heavily pre-treated solid tumors of the body in early clinical studies. The purpose of this research study is to investigate an experimental drug, MK-3475 in pediatric patients. The drug MK-3475 has been previously studied in adults, in a variety of tumors, but is not yet FDA approved. It is our hope the drug MK-3475 will be a safe and effective treatment for childhood brain tumors.

The purposes of the study, PBTC-045, are:

- To establish the safety and describe adverse effects associated with administration of the adult recommended dose of MK-3475 (pembrolizumab) in children with recurrent, progressive or

- refractory non-brainstem high grade glioma (NB-HGG) and diffuse intrinsic pontine glioma (DIPG).
- To estimate the sustained objective response rate associated with MK-3475 treatment for pediatric patients with recurrent, progressive or refractory NB-HGG or DIPG.
 - To assess the relationship between outcome (response and PFS) and potential biomarkers including PD-L1 expression, patient immunophenotype, RNA signature profile, and tumor gene expression profile.
 - To estimate the duration of objective response, progression-free/event-free survival and document overall survival for patients with NB-HGG and DIPG treated with MK-3475 (pembrolizumab).
 - To evaluate PD-L1 expression on archival tissue obtained from patients with non- brainstem high-grade glioma.

WHAT IS INVOLVED IN THIS STUDY?

Patients will receive MK-3475 (pembrolizumab) as a 30-minute IV infusion on an outpatient basis. Patients will receive MK3475 (pembrolizumab) intravenously at a dose based on their assigned dose level on day 1 of each course. Each course will be 3 weeks (21 days) in length. Subsequent courses will immediately follow with no break in the absence of toxicity or disease progression. Therapy may continue for 34 courses (approximately 2 years) in the absence of significant toxicity or disease progression.

Routine urine tests and blood tests will be performed prior to enrollment, weekly during the first two courses, prior to each infusion courses 3 through 34, and also at End of Treatment. Routine history and physical exams will continue to take place. Standard MRI brain with and without contrast will be obtained within 3 weeks prior to enrollment, every 3 courses through the first 18 courses and then every 4 courses until discontinuation or end of protocol therapy.

WHAT ARE THE RISKS OF PARTICIPATING IN PBTC-045?

Doctors watch study participants very carefully for any side effects or other problems. However, doctors do not know all the side effects that may occur. Side effects may be mild or very serious. The infusion of MK-3475, used in this research study, may affect how different parts of your body work such as your liver, kidneys, heart, and blood. Doctor will be testing your blood and will let you know if changes occur that may affect your health. Other medications may be given to lessen side effects. In some cases, side effects may be long lasting or may never go away. There is also a risk of death. Some of the common side effects of MK-3475 include fatigue and skin irritations (rash). Other less likely side effects include anemia, diarrhea, nausea, fever, edema, headache and cough.

There may be unknown risks and discomforts involved in participating in this or any clinical trial. The health care team may give participants medicines to help lessen side effects. Doctors will notify parents and patients immediately of any important information or treatment findings discovered during the study that may affect their willingness to continue to participate.

QUESTIONS ABOUT PBTC-045?

If you would like more information, please contact the PBTC member institution closest to you. You can also contact the doctor in charge of this study:

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OTHER INFORMATION IS AVAILABLE THROUGH

The National Cancer Institute's Cancer Information Service at 1-800-422-6237 or TTY: 1-800-332-8615 or through the National Cancer Institute's websites www.Cancer.gov and www.cancer.gov/clinicaltrials. There is additional accurate and reliable information at www.cancernet.org.