

PBTC-045 - A SUMMARY FOR PATIENTS AND FAMILIES

Title: PBTC-045 - A Safety and Preliminary Efficacy trial of Pembrolizumab (MK-3475) in children with recurrent, progressive or refractory diffuse intrinsic pontine glioma (DIPG), non-brainstem high-grade gliomas (NB-HGG), ependymoma, medulloblastoma or hypermutated brain tumors

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?

There are two categories of patients eligible to participate in PBTC-045;

1) Patients who have a histologically confirmed diagnosis of recurrent, progressive or refractory diffuse intrinsic pontine glioma (DIPG) non-brainstem high-grade glioma (NB-HGG), ependymoma, and medulloblastoma. 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 are also eligible. **Stratum A for recurrent, progressive or refractory DIPG is currently closed to accrual.**

2) Patients with histologically diagnosed brain tumors and increased tumor mutation burden including CMMRD syndrome or Lynch syndrome diagnosed by germline gene sequencing or whole genome/exome sequencing.

Patients enrolled in Stratum A, B, D or E must be less than 22 years of age for the efficacy portion of the study. Patients enrolled in Stratum C must be less than 30 years of age at enrollment. 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. Patients 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 dosages 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 who have a known active Hepatitis B or Hepatitis C infection, patients with a history of severe reactions to a monoclonal antibody, patients who previously received anti-CTLA4, anti-CD137, anti-PD-L1 or anti-PD-11 antibody or any other antibody or drugs targeting T-cell co-stimulation or checkpoint pathways and patients with uncontrolled seizures that require the regular use of rescue medications may not be eligible to participate in this study.

Patients' medical and neurological conditions 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 tests and scans (MRI) of the brain and spine. Other tests may be required if doctors believe they are necessary. Approximately 100 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 define a recommended phase II dose (RP2D) for Pembrolizumab (MK3475). Pembrolizumab (MK3475) is a monoclonal antibody that has produced 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, Pembrolizumab (MK3475), in pediatric patients. The drug Pembrolizumab (MK3475) has been previously studied in adults, in a variety of tumors, but is not yet FDA approved. It is our hope that Pembrolizumab (MK3475) will be a safe and effective treatment for childhood brain tumors.

The purposes of the study are:

- To establish the safety and describe adverse effects associated with administration of the adult recommended dose of Pembrolizumab (MK3475) in children with recurrent, progressive or refractory non-brainstem high grade glioma (NB-HGG), diffuse intrinsic pontine glioma (DIPG), ependymoma, or medulloblastoma that is recurrent, progressive or refractory.
- To estimate the sustained objective response rate associated with Pembrolizumab (MK3475) treatment for these tumors for at least 9 weeks.
- To assess the relationship between outcome (response and PFS) and potential biomarkers including PD-L1 expression, patient immunophenotypes, RNA signature profiles, and tumor gene expression profiles.
- To estimate the duration of objective responses, progression-free/event-free survival and document overall survival for patients with DIPG treated with Pembrolizumab (MK3475).
- 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 Pembrolizumab (MK3475) as a 30-minute IV infusion on an outpatient basis. Patients will receive Pembrolizumab (MK3475) 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 blood tests will be performed prior to enrollment, weekly during the first two courses, prior to each infusion during courses 3 through 34, and also at the end of the treatment. Routine history and physical exams will continue to take place. Standard brain MRIs with and without contrasts will be obtained within 3 weeks prior to enrollment, at the end of Course 2, then every 3 courses through the first 18 courses and then during every 4 courses until the discontinuation or end of the 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, the doctors do not know all the side effects that may occur. Side effects may be mild or very serious. The infusion of Pembrolizumab (MK3475), used in this research study, may affect how different parts of the body work, such as the liver, kidneys, heart, and blood. Doctors 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 Pembrolizumab (MK3475) include fatigue and skin irritations (rash). Other less likely side effects include anemia, diarrhea, nausea, fevers, edema, headaches and coughing.

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 doctors in charge of this study:

Strata B, D and E	Stratum C
Eugene Hwang, MD Children’s National Medical Center Washington, DC 20010 Telephone: 202-476-5046 Fax: 202-476-4304 Email: ehwang@childrensnational.org	Alberto Broniscer, MD Children’s Hospital of Pittsburgh Pittsburg, Pennsylvania 15224 Tel: 412 692-5056 FAX: 412 692-3412 Alberto.broniscer@chp.edu

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.