**PBTC-045**: A Safety and Preliminary Efficacy trial of MK-3475 (pembrolizumab; anti-PD-1) 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

**Abstract and Schema**

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 MK3475 (pembrolizumab). In the safety phase of the study, a cohort of up to 6 eligible patients per stratum will be enrolled initially at the starting dose level (2mg/kg q3 weeks) which is the recommended dose in adults. The first two courses (first 6 weeks) will be used as the safety evaluation period. Once a dose level is determined to be safe in a given stratum in the first 6 patients, we will begin the efficacy phase of the study.

Patients will enroll in one of five strata:
- Stratum A for patients with progressive, recurrent or refractory diffuse intrinsic pontine gliomas (DIPGs)-Currently closed to enrollment
- Stratum B for patients with progressive, recurrent or refractory non-brainstem high grade gliomas (NB-HGG).
- Stratum C for patients with hypermutated brain tumors, including those with constitutional mismatch-repair deficiency (CMMRD) syndrome
- Stratum D for patients with progressive, recurrent or refractory ependymoma
- Stratum E for patients with progressive, recurrent or refractory medulloblastoma

MK3475 (pembrolizumab) is supplied as an intravenous (IV) formulation. The starting dose level for this study is 2mg/kg given every 3 weeks (dose level 1). All patients will receive MK3475 (pembrolizumab) intravenously at a dose based on their assigned dose level on day 1 of each course. Treatment can be administered on an outpatient basis. 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.

The primary endpoints for the first phase of the study will be toxicity and safety monitoring of MK3475 (pembrolizumab), and for the second phase of the study will be to evaluate the efficacy of the regimen via objective response rate for Strata A-E.

Potential biomarkers will be measured and correlated to outcome, including PD-L1 and PD-1 tumor expression, patient immunophenotype, cytokine expression profiles, RNA signature
profile, mutational load, TCR-sequencing in tumor-infiltrating lymphocytes and peripheral blood mononuclear cells, circulating DNA (ctDNA) and tumor gene expression profile (all tumor-derived studies will be completed in strata B, C and E patients). These possible markers will define the immunologic phenotype of each patient, the response of the systemic immune system to PD-1 blockade, and potential tumor-derived derived predictors of response.

Quantitative MR spectroscopy and diffusion-weighted imaging will be obtained to attempt early prediction of tumor response and differentiation between pseudoprogression/tumor inflammation and progressive disease. Serial MR Permeability and MR perfusion will also be obtained to determine if elevated rCBV and ktrans can distinguish pseudoprogression/tumor inflammation from progression.