

**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 Pembrolizumab (MK3475). 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. The safety phase has been completed in all strata as of version 12 of this 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

Pembrolizumab (MK3475) 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 Pembrolizumab (MK3475) 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 Pembrolizumab (MK3475), 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.

## **Objectives:**

### **Primary Objectives**

- a. Recurrent, progressive or refractory diffuse intrinsic pontine glioma (DIPG), non-brainstem high grade glioma (NB-HGG), ependymoma and medulloblastoma (Strata A, B, D and E).
  - To establish the safety and describe adverse effects associated with administration of the adult recommended dose of Pembrolizumab (MK3475) in each stratum separately.
  - To estimate the sustained objective response rate, (CR + PR, sustained for at least 9 weeks) associated with Pembrolizumab (MK3475) treatment for pediatric patients with recurrent, progressive or refractory DIPG, NB-HGG, Ependymoma or medulloblastoma. This assessment will be done separately for each stratum (Strata A, B, D and E).
- b. Hypermutated brain tumors
  - To establish the safety and describe adverse effects associated with administration of the adult recommended dose of Pembrolizumab (MK3475) in pediatric patients with progressive or recurrent hypermutated tumors, including those with Constitutional Mismatch Repair Deficiency (CMMRD) syndrome.
  - To estimate the sustained response rate of pediatric patients with progressive or recurrent hypermutated NB-HGG, including those with CMMRD syndrome, treated with Pembrolizumab (MK3475).
  - To determine changes in the immunophenotypic profile of PD-1<sup>hi</sup> CD8<sup>+</sup> T cells from serial peripheral blood samples obtained before and during treatment with Pembrolizumab (MK3475) in pediatric patients with hypermutated brain tumors, including those with CMMRD syndrome.

### **Secondary Objectives**

- a. Recurrent, progressive or refractory diffuse intrinsic pontine glioma (DIPG) and non-brainstem high grade glioma (NB-HGG), ependymoma or medulloblastoma (Strata A, B, D and E)
  - To assess the relationship between outcome (response and progression free survival) and potential biomarkers including PD-L1 expression, patient immunophenotype, RNA signature profile, mutational profile, tumor gene expression profile and circulating tumor DNA (ctDNA).
  - To estimate the duration of objective response in patients with measurable disease at baseline and estimate progression-free/event-free/overall survival for patients in each stratum treated with Pembrolizumab (MK3475).
  - To evaluate PD-L1 expression on archival tissue obtained from pediatric patients with eligible primary CNS tumors.
  - To examine the ability of quantitative MR spectroscopy and diffusion/weighted imaging/ADC mapping to provide early assessment of tumor behavior and specifically distinguish pseudoprogression/tumor inflammation from tumor progression.
  - To explore the use of serial MR permeability (DCE) and MR perfusion (DSC) to determine if elevated rCBV and ktrans can distinguish pseudoprogression/tumor inflammation from tumor progression in tumors treated on this protocol.

- To characterize biomarkers, patient immunophenotyping, mutational load (as determined by whole exome sequencing), the tumor gene expression profile and ctDNA in patients receiving Pembrolizumab (MK3475).

b. Hypermutated brain tumors

- To estimate the duration of objective response, progression-free survival/event free survival and document overall survival of pediatric patients with progressive or recurrent hypermutated NB-HGG, including those with CMMRD syndrome, treated with Pembrolizumab (MK3475).
- To estimate the PFS of all patients enrolled on Stratum C and sustained objective response rate of pediatric patients with hypermutated progressive low grade gliomas including those with CMMRD, treated with Pembrolizumab (MK3475).
- To categorize the T-cell receptor repertoire in PD-1<sup>+</sup> cells obtained from peripheral blood or from tumor tissue, when available, before and after treatment with Pembrolizumab (MK3475) in pediatric patients treated in stratum C (hypermutated brain tumors)
- To define the specificity of T-cell receptors against tumor antigens identified in objective 1.2.9.
- To characterize functional features of T-cell populations after Pembrolizumab (MK3475) treatment and relate these findings to epigenetic programs within these cells

## **Patient Selection:**

All subjects must meet the following inclusion and exclusion criteria based on the stratum on which the patient is enrolled. Please carefully review each criterion noted below and ensure the stratum specific criteria have been fulfilled prior to enrollment. No exceptions will be given. Imaging studies to establish eligibility must be done within three (3) weeks prior to enrollment. All other clinical evaluations to establish eligibility must be done within 7 days prior to enrollment.

## **Inclusion Criteria for Strata A, B, D and E**

### Tumor

Patient must have one of the following diagnoses to be eligible:

**Stratum A, currently closed to enrollment:** Patients must have a recurrent, progressive or refractory DIPG following radiation therapy with or without chemotherapy.

- 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 B: Patients must have a histologically confirmed diagnosis of a non-brainstem high-grade glioma (NB-HGG) that is recurrent, progressive or refractory following therapy which included radiotherapy. Spinal primary disease is eligible

Stratum D: Patients must have a histologically confirmed diagnosis of ependymoma that is recurrent, progressive or refractory following therapy which included radiotherapy.

Stratum E: Patients must have a histologically confirmed diagnosis of medulloblastoma that is recurrent, progressive or refractory following therapy which included radiotherapy.

### Available Pre-trial Tumor Tissue:

Patients must have adequate pre-trial FFPE tumor material available for use in the Biology studies mutational analysis and genome wide sequencing for each stratum.

- Patients with DIPG who have tissue available are requested to submit similar tissue as patients in other strata; however, this is not required for eligibility.

### Disease status:

All subjects must have measurable disease in 2-dimensions on MRI scan of the brain. Disease should be consistently measured with the two largest perpendicular dimensions.

### Age

Patient must be  $\geq 1$  but  $\leq 18$  years of age at the time of enrollment during the safety portion, which is complete as of version 12. Patients  $< 22$  may be enrolled during the efficacy portion of the study.

### Prior Therapy

Patients **must** have received prior radiation therapy and/or chemotherapy and recovered from the acute treatment related toxicities (defined as  $\leq$  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.

### *Myelosuppressive chemotherapy:*

Patients must have received their last dose of known myelosuppressive anticancer therapy at least three (3) weeks prior to study enrollment or at least six (6) weeks if prior nitrosourea.

### *Investigational/Biologic Agent:*

- Biologic or investigational agent (anti-neoplastic):

Patient must have received their last dose of the investigational or biologic agent  $\geq 7$  days prior to study enrollment.

- For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration must be discussed with and approved by the study chair.

- Monoclonal antibody treatment and/or agents with prolonged half-lives:

Patient must have recovered from any acute toxicity potentially related to the agent and received their last dose of the agent  $\geq 28$  days prior to study enrollment.

### *Immunotherapy:*

Patient must have completed immunotherapy (e.g. tumor vaccines, oncolytic viruses. etc.) at least 42 days prior to enrollment.

### *Radiation:*

Patients must have had their last fraction of:

- Craniospinal irradiation  $\geq 3$  months prior to enrollment.
- Other substantial bone marrow irradiation  $\geq 6$  weeks prior to enrollment
- Local palliative XRT (small port)  $\geq 2$  weeks

### *Stem Cell Transplant*

Patient must be:

$\geq 12$  weeks since autologous bone marrow/stem cell transplant prior to enrollment

### Surgery

Patients must be fully recovered from all acute effects of prior surgical intervention.

### Inclusion of Women and Minorities

Both males and females of all races and ethnic groups are eligible for this study.

### Neurologic Status

Patients with neurological deficits should have deficits that are completely stable for a minimum of 1 week (7 days) prior to enrollment.

### Performance Status

Karnofsky Performance Scale (KPS for  $> 16$  years of age) or Lansky Performance Score (LPS for  $\leq 16$  years of age) assessed within two weeks of enrollment must be  $\geq 70$ . Patients who are unable to walk because of neurologic deficits, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

### Organ Function

Patients must have adequate organ and marrow function as defined below:

- Absolute neutrophil count  $\geq 1000$  cells/ $\mu$ L
- Platelets  $\geq 75,000$  cells / $\mu$ L (unsupported, defined as no platelet transfusion within 7 days)
- Hemoglobin  $\geq 8$ g/dl (may receive transfusions)
- Total bilirubin  $\leq 1.5$  times institutional upper limit of normal (ULN)
- ALT(SGPT)  $\leq 3$  x institutional upper limit of normal
- Albumin  $\geq 2$  g/dl
- Serum creatinine based on age/gender as noted in Table 4. Patients that do not meet the criteria below but have a 24hour Creatinine Clearance or GFR (radioisotope or iothalamate)  $\geq 70$  ml/min/1.73 m<sup>2</sup> are eligible.

Table 4

| Serum Creatinine for Age/Gender |                                  |        |
|---------------------------------|----------------------------------|--------|
|                                 | Maximum Serum Creatinine (mg/dl) |        |
| Age                             | Male                             | Female |
| 1 to < 2 years                  | 0.6                              | 0.6    |
| 2 to < 6 years                  | 0.8                              | 0.8    |
| 6 to < 10 years                 | 1                                | 1      |
| 10 to < 13 years                | 1.2                              | 1.2    |
| 13 to < 16 years                | 1.5                              | 1.4    |
| $\geq 16$ years                 | 1.7                              | 1.4    |

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

- Pulmonary function - Pulse oximetry > 93% on room air and no evidence of dyspnea at rest.

#### HIV Infection

HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial

#### Growth Factors

Patients must be off all colony-forming growth factor(s) for at least 1 week prior to registration (e.g. filgrastim; sargramostim; erythropoietin). 2 weeks must have elapsed for long-acting formulations.

#### Steroid Use

Patients must be willing to use brief courses (at least 72 hours) of steroids as directed for potential inflammatory side effects of the therapy if recommended by their treating physician.

#### Pregnancy Status

Female subjects of childbearing potential must not be pregnant or breast-feeding. Female patients of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Pregnant women are excluded from this study because Pembrolizumab (MK3475) is an agent with the potential for teratogenic effects. Because there is unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with Pembrolizumab (MK3475), breastfeeding should be discontinued if the mother is to be treated with Pembrolizumab

(MK3475).

### Pregnancy Prevention

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.

### Informed Consent

The patient or parent/guardian is able to understand the consent and is willing to sign a written informed consent document, inclusive of assent where appropriate, according to institutional guidelines.

## **Exclusion Criteria for Strata A, B, D and E**

### Concurrent Illness

- Patients with active autoimmune disease or documented history of autoimmune disease/syndrome that requires ongoing systemic steroids or systemic immunosuppressive agents, except
  - Patients with vitiligo or resolved asthma/atopy
  - Patients with hypothyroidism stable on hormone replacement or Sjogren's syndrome
- History of or ongoing pneumonitis or significant interstitial lung disease  
**Note:** This would include non-infectious pneumonitis that required steroid use.
- Patients with any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction), that in the opinion of the investigator would compromise the patient's ability to tolerate protocol therapy, put them at additional risk for toxicity or would interfere with the study procedures or results.
- Patients with other current malignancies.
- Patients with known hypermutated brain tumors including those with CMMRD and Lynch syndrome are ineligible for enrollment in Strata A, B, D and E.
- Patients who have received a solid organ transplant.

### Presence of Bulky Tumor

Patients with bulky tumor on imaging are ineligible. Treating physicians are encouraged to contact the Study Chair to request a rapid central imaging review to confirm fulfillment of these eligibility criteria, if they have concerns.

Bulk tumor is defined as:

- Tumor with evidence of clinically significant uncal herniation or midline shift
- Tumor with diameter of >5cm in one dimension on T2/FLAIR
- Tumor that in the opinion of the site investigator, shows significant mass effect in either the brain or spine
- Multi-focal/ Metastatic disease:  
**Note:** Multiple foci of enhancement in a single FLAIR abnormality is permissible and will not exclude the subject
  - Patients with multi-focal parenchymal disease are ineligible
  - Patients with leptomeningeal metastatic disease are eligible. This includes disease that is discrete from the primary lesion but that has a radiographic appearance consistent with leptomeningeal spread, rather than likely trans-parenchymal spread.
  - **Strata B, D and E** – Patients whose tumor has a significant component involving the brainstem or with significant fourth ventricular compression are ineligible.

### Concurrent therapy

Patients who are receiving any other anti-cancer or investigational drug therapy are ineligible.

### Infectious Diseases

Patients who have a known active Hepatitis B or Hepatitis C infection are ineligible. Patient must have documented evidence of negative tests for the presence of Hepatitis B surface antigen and Hepatitis C (anti-HCV antibody OR Hep C RNA-qualitative).

### Recent Live Vaccination

Patients who have received the last vaccination of a live vaccine  $\leq 30$  days prior to enrollment are ineligible. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and must meet timeline for live vaccine.

### Allergy

Patients with a history severe ( $\geq$ Grade 3) hypersensitivity reaction to a monoclonal antibody are ineligible.

### Prior Therapy

Patients who have received previous therapy with an anti-CTLA4, anti-CD137, anti-PD-L1 or anti-PD-1 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

- Patients who have received agents that are considered CD40L agonists are eligible. Sites should contact the study PI with any questions related to other agents which are felt to specifically target T-cell co-stimulation or checkpoint pathways to discuss the impact on eligibility.

### Seizures

Patients with uncontrolled seizures defined as seizures that require regular use of rescue medications or in the opinion of the investigator require increasing doses of antiepileptic medications or would compromise the ability to tolerate study therapy or interfere with protocol therapy or procedures. Patients with seizures that are well controlled are eligible and may be on antiepileptic medications if on a stable dose.

### Concomitant Medications

Patients may not be on immunosuppressive therapy, including corticosteroids (with the exception of physiologic replacement, defined as 0.75mg/m<sup>2</sup>/day dexamethasone equivalent) at time of enrollment. However, patients who require intermittent use of bronchodilators or local steroid injections will not be excluded from the study.

## **Inclusion Criteria Stratum C**

### Diagnosis of Hypermutated Brain Tumors

Patients with brain tumors and increased tumor mutation burden as determined by

- Confirmed diagnosis of CMMRD syndrome by CLIA-certified germline gene sequencing OR
- Confirmation of high mutation burden by whole genome/exome sequencing performed in a

CLIA-certified laboratory and/or the use of Foundation One next generation sequence panel or another CLIA approved targeted sequencing lab with publicly available correlations between number of mutations found in the panel and mutations per megabase and/or genome. For protocol purposes a high mutation burden will be defined as at least 180 non-synonymous coding-region mutations by whole exome/genome sequencing (well above two standard deviations of the number of median similar mutations described in pediatric CNS cancers) AND/OR a high tumor mutation burden (TMB) or intermediate TMB based on the reporting parameters of the panel. TMB parameters provided for the Foundation One panel are as follows: high TMB is  $\geq 20$  mutations per megabase and intermediate TMB is between 6 to 19 mutations per megabase OR

- Confirmed diagnosis of Lynch syndrome by CLIA-certified germline gene sequencing. Patients with Lynch syndrome will not be accounted for in primary objective 1.1.3 unless their tumors are determined to have the minimum number of mutations described above but they will still be eligible for this study.
  - Low-grade tumors in patients with CMMRD or Lynch syndrome do not have to reach the threshold of 100 mutations for study inclusion.

#### Tumor Type

Patients must have a histologically confirmed primary brain tumor that is recurrent, progressive or refractory. Inclusion criteria encompasses all types of brain tumors (e.g. gliomas, embryonal tumors or any other type of brain tumor as long as other eligibility criteria are met.

- Patients with high-grade gliomas are eligible for this clinical trial at least 2 weeks after completion of radiotherapy independent of tumor progression/recurrence as long as they are not enrolled on any other therapeutic clinical trial and there is macroscopic residual disease

Patients with other concomitant tumors associated with CMMRD and Lynch syndrome including gastrointestinal polyps/adenomas and carcinomas, lymphomas and leukemias will be eligible as long as they are not requiring anticancer therapy directed against these other cancers and meet all other eligibility criteria.

#### Available Pre-trial Tumor Tissue:

Patients must have adequate pre-trial FFPE tumor material available and be willing to provide a blood sample for use in the genome wide sequencing studies. While tissue is required for Genome-wide sequencing of tumor and germline samples, patients will be deemed eligible for the study with a minimum of approximately 10 unstained slides for the planned analysis.

#### Disease status:

Subjects must have measurable disease in 2-dimensions on MRI scan of the brain and/or spine with the exception allowed for non-progressed HGGs noted in Section 3.3.2. Disease should be consistently measured with the two largest perpendicular dimensions.

#### Age

Patient should be <30 years at the time of enrollment.

#### Prior Therapy

Patients **must** have received prior radiotherapy and/or chemotherapy with the following exceptions:

- Patients with secondary CNS cancers after a previous medical problem/malignancy who cannot receive full dose of radiotherapy (>50Gy) as long as they meet all other eligibility criteria
- Patients with progressive low-grade gliomas and CMMRD or Lynch syndrome

Patients must have recovered from the acute treatment related toxicities (defined as  $\leq$  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.

The required intervals for prior therapy are identical to those noted below except for patients with HGG who have not experienced disease progression.

*Myelosuppressive chemotherapy:*

Patients must have received their last dose of known myelosuppressive anticancer therapy at least three (3) weeks prior to study enrollment or at least six (6) weeks if prior nitrosourea.

*Investigational/Biologic Agent:*

- Biologic or investigational agent (anti-neoplastic):

Patient must have received their last dose of the investigational or biologic agent  $\geq 7$  days prior to study enrollment.

- For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration must be discussed with and approved by the study chair.

- Monoclonal antibody treatment and/or agents with prolonged half-lives:

Patient must have recovered from any acute toxicity potentially related to the agent and received their last dose of the agent  $\geq 28$  days prior to study enrollment

*Immunotherapy:*

Patient must have completed immunotherapy (e.g. tumor vaccines, oncolytic viruses. etc.) at least 42 days prior to enrollment.

*Radiation*

Patients except as noted in the Prior Therapy section noted above must have had their last fraction of:

- Craniospinal irradiation  $\geq 3$  months prior to enrollment.
- Other substantial bone marrow irradiation  $\geq 6$  weeks prior to enrollment
- Local palliative XRT (small port)  $\geq 2$  weeks

*Stem Cell Transplant*

Patient must be:

- $\geq 12$  weeks since autologous bone marrow/stem cell transplant prior to enrollment
- $\geq 5$  years since allogeneic stem cell transplant prior to enrollment with no evidence of active graft vs. host disease.

*Surgery*

Patients must be fully recovered from all acute effects of prior surgical intervention.

Inclusion of Women and Minorities

Both males and females of all races and ethnic groups are eligible for this study.

### Neurologic Status

Patients with neurological deficits should have deficits that are completely stable for a minimum of 1 week (7 days) prior to enrollment.

### Performance Status

Karnofsky Performance Scale (KPS for > 16 years of age) or Lansky Performance Score (LPS for ≤ 16 years of age) assessed within two weeks of enrollment must be ≥ 60. Patients who are unable to walk because of neurologic deficits, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

### Organ Function

Patients must have adequate organ and marrow function as defined below:

- Absolute neutrophil count ≥1000 cells/μL
- Platelets ≥75,000 cells/μL (unsupported, defined as no platelet transfusion within 7 days)
- Hemoglobin ≥8g/dl (may receive transfusions)
- Total bilirubin ≤1.5 times institutional upper limit of normal (ULN)
- ALT(SGPT) ≤3 x institutional upper limit of normal
- Albumin ≥2 g/dl
- Serum creatinine based on age/gender as noted in Table 5. Patients that do not meet the criteria below but have a 24hour Creatinine Clearance or GFR (radioisotope or iothalamate) ≥ 70 ml/min/1.73 m<sup>2</sup> are eligible.

Table 5

| Serum Creatinine for Age/Gender |                                  |        |
|---------------------------------|----------------------------------|--------|
|                                 | Maximum Serum Creatinine (mg/dl) |        |
| Age                             | Male                             | Female |
| 1 to < 2 years                  | 0.6                              | 0.6    |
| 2 to < 6 years                  | 0.8                              | 0.8    |
| 6 to < 10 years                 | 1                                | 1      |
| 10 to < 13 years                | 1.2                              | 1.2    |
| 13 to < 16 years                | 1.5                              | 1.4    |
| ≥ 16 years                      | 1.7                              | 1.4    |

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

- Pulmonary function - Pulse oximetry > 93% on room air and no evidence of dyspnea at rest.

### HIV Infection

HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial

### Growth Factors

Patients must be off all colony-forming growth factor(s) for at least 1 week prior to registration (e.g. filgrastim; sargramostim; erythropoietin). 2 weeks must have elapsed for long-acting formulations.

### Steroid Use

Patients must be willing to use brief courses (at least 72 hours) of steroids as directed for potential

inflammatory side effects of the therapy if recommended by their treating physician.

### Pregnancy Status

Female subjects of childbearing potential must not be pregnant or breast-feeding. Female patients of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Pregnant women are excluded from this study because Pembrolizumab (MK3475) is an agent with the potential for teratogenic effects. Because there is unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with Pembrolizumab (MK3475), breastfeeding should be discontinued if the mother is to be treated with Pembrolizumab (MK3475).

### Pregnancy Prevention

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.

### Informed Consent

The patient or parent/guardian is able to understand the consent and is willing to sign a written informed consent document, inclusive of assent where appropriate, according to institutional guidelines.

## **Exclusion Criteria for Stratum C**

### Diagnosis

Patients with diffuse intrinsic pontine or other brainstem high-grade glioma and those with primary spinal cord tumors.

### Presence of Bulky Tumor

Patients with bulky tumor on imaging are ineligible. Treating physicians are encouraged to contact the Study Chair to request a rapid central imaging review to confirm fulfillment of these eligibility criteria, if they have concerns.

Bulky tumor is defined as:

- Tumor with any evidence of clinically significant uncal herniation or midline shift
- Tumor with diameter of >5cm in one dimension on T2/FLAIR except for those patients with HGG treated following irradiation without signs of tumor progression. For the latter group, a maximum diameter of contrast enhancing solid or necrotic tumor and of T2/FLAIR abnormality will be 5 cm and 8 cm, respectively.
- Tumor that in the opinion of the site investigator, shows significant mass effect
- Metastatic disease:

Patients with  $\leq 5$  separate foci of metastatic disease not causing mass effect on adjacent parenchyma and each measuring less than 0.5 cm in maximum diameter will be eligible for this arm of the study. Patients with diffuse linear leptomeningeal spread are not eligible for this arm of the study.

- Multi-focal disease:

Patients with multi-focal parenchymal disease will be eligible for Stratum C if the sum of the product of the maximum perpendicular diameters of all measurable non-contiguous lesions is less than 16 cm<sup>2</sup> based on the T2/FLAIR abnormality.

- Multi-focal disease in patients with HGG treated following irradiation without signs of tumor progression at the time of enrollment will be eligible for Stratum C if the sum of the product of the maximum perpendicular diameters of all measurable non-contiguous lesions is less than 25cm<sup>2</sup> based on the T2/FLAIR abnormalities.

In such cases, a minimum of 2 and a maximum of 5 “target” non-contiguous lesions will be selected. The lower size limit of the target lesion(s) should be at least twice the thickness of the slices showing the tumor to decrease the partial volume effect (e.g., 8 mm lesion for a 4mm slice).

#### Concurrent Illness

- Patients with active autoimmune disease or documented history of autoimmune disease/syndrome that requires ongoing systemic steroids or systemic immunosuppressive agents, except
  - Patients with vitiligo or resolved asthma/atopy
  - Patients with hypothyroidism stable on hormone replacement or Sjogren’s syndrome
- History of or ongoing pneumonitis or significant interstitial lung disease
 

Note: This would include non-infectious pneumonitis that required steroid use.
- Patients with any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction), that in the opinion of the investigator would compromise the patient’s ability to tolerate protocol therapy, put them at additional risk for toxicity or would interfere with the study procedures or results.
  - Exception to this is the presence of gastrointestinal polyps/adenomas and non-metastatic carcinomas, and history of any previous malignancies in patients with CMMRD and Lynch syndrome which will be allowed in this study.
- Patients who have received a solid organ transplant.

#### Concurrent therapy

Patients who are receiving any other anti-cancer or investigational drug therapy are ineligible.

#### Infectious Diseases

Patients who have a known active Hepatitis B or Hepatitis C infection are ineligible. Patient must have documented evidence of negative tests for the presence of Hepatitis B surface antigen and Hepatitis C (anti-HCV antibody OR Hep C RNA-qualitative).

#### Recent Live Vaccination

Patients who have received the last vaccination of a live vaccine  $\leq 30$  days prior to enrollment are ineligible. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and must meet timeline for live vaccine.

#### Allergy

Patients with a history severe ( $\geq$ Grade 3) hypersensitivity reaction to a monoclonal antibody are ineligible.

### Prior Therapy

Patients who have received previous therapy with an anti-CTLA4, anti-CD137, anti-PD-L1 or anti-PD-1 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

- Patients who have received agents that are considered CD40L agonists are eligible. Sites should contact the study PI with any questions related to other agents which are felt to specifically target T-cell co-stimulation or checkpoint pathways to discuss the impact on eligibility.

### Seizures

Patients with uncontrolled seizures defined as seizures that require regular use of rescue medications or in the opinion of the investigator require increasing doses of antiepileptic medications or would compromise the ability to tolerate study therapy or interfere with protocol therapy or procedures. Patients with seizures that are well controlled are eligible and may be on antiepileptic medications if on a stable dose.

### Concomitant Medications

Patients may not be on immunosuppressive therapy, including corticosteroids (with the exception of physiologic replacement, defined as  $\leq 0.75$  mg/m<sup>2</sup>/day dexamethasone equivalent) at time of enrollment. However, patients who require intermittent use of bronchodilators or local steroid injections will not be excluded from the study.