**TITLE: Rad3179-16 (MK-3475-423) Pilot Study of Pembrolizumab and Stereotactic Radio-Surgery (SRS) for Patients with Melanoma or Non-Small Cell Lung Cancer (NSCLC) Brain Metastases (BM)**

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## 1.0 TRIAL SUMMARY

| | |
|---|---|
| Abbreviated Title | SRS and Pembrolizumab for Melanoma and Non-Small Cell Lung Cancer (NSCLC) brain metastases (BM). |
| Trial Phase | *Pilot Study* |
| Clinical Indication | Melanoma and NSCLC Brain Metastases |
| Trial Type | Pilot study with three different radiation dose cohorts. |
| Type of control | None |
| Route of administration | Pembrolizumab delivered 200 mg IV every 3 weeks +/- 7 days for at least 2 years, or until progression. |
| Trial Blinding | N/A |
| Treatment Groups | All receive pembrolizumab 200 mg IV every 3 weeks +/- 7 days until progression or at least 2 years, with 3 altered radiation dose fractionation groups delivered during first cycle of pembrolizumab. |
| Number of trial subjects | 30 patients. |
| Estimated enrollment period | *2 years* |
| Description of enrollment | In 2013, we delivered SRS to 20 metastatic melanoma brain metastases patients and 27 NSCLC BM patients. In 2014, we delivered SRS to 14 and 26 patients, respectively. Assuming similar numbers over the next two years, and accruing 45% of patients, we anticipate around 30 patients to enroll.<br><br>These projected accrual numbers do not reflect the possibility of increased patient referrals from our satellite facilities, and/or increased regional/national referrals, once the trial is opened. We are also not aware of other potentially competing radiation SRS for melanoma and NSCLC brain metastases trials at our institution at this time. |
| Duration of Intervention | At least 12 months of Pembrolizumab, or until progression. |
| Duration of Evaluation | 3 year ( 2 yrs during accrual, and at least 1 year follow-up for last patient accrued on the study) |
| Estimated duration of trial | 3 years (2 years to accrue + 1 years to follow all patients) |
| Duration of Participation | 3 years |
| Study Center | Emory University. Atlanta, Georgia. |

## 2.0 TRIAL DESIGN/SCHEMA

### 2.1 Trial Overview

Pembrolizumab (i.e. anit-PD-1) and stereotactic radiosurgery (SRS) will be delivered concurrently. The safety and efficacy of this combination is not known. Preclinical data shows promise of this combination, but, has yet to be tested in humans with brain metastases. Pembrolizumab (**200 mg IV every 3 weeks +/- 7 days for at least 2 years, or until progression**) will be delivered on day 1 of cycle 1 and continued until at least 2 years or until disease progression per RECIST 1.1 (see Appendix II for RECIST Criteria). SRS will be delivered on day 2 or day 3 of cycle 1 (i.e. within 24-48 hours after anti-PD-1, with some flexibility allowed for SRS timing during cycle 1).

Three different radiation doses (**Table 1**) will be delivered during cycle 1, in combination with Pembrolizumab. All three radiation doses have different biological effectiveness doses (BED) for acute and late side effects, with Arm C being the most commonly used accepted arm; The **primary objective** will be to assess for dose limiting toxicity (i.e, ≥ **grade 3 CNS toxicity at 3 months**) when different radiation doses (**Table 1**) are delivered; Several secondary objectives will also be evaluated (**section 3.0**); The primary point of the trial (dose limiting toxicity) is ≥ radiation therapy oncology (RTOG) CNS grade 3 toxicity, as defined in the original RTOG 90-05 trial, used to arrive at the currently used safest single radiation dose fraction (**Arm C, Table 1**) schemes for radiosurgery (Shaw E, et al. Int. J. Rad. Onc. & Biol. 2000(47) 291-8); **Grade 3 CNS toxicity is defined as irreversible severe neurological symptoms as outpatient or inpatient requiring medication usage;** It is also possible that while changing the radiation dose levels, we may also find a radiation dose level that is also more immunogenic when combined with PD1 inhibitor; This optimal radiation dose may or may not be the same as that per RTOG 90-05; Preclinical data suggest that dose fraction sizes of 8-10 Gy may be more immunogenic compared with other dose fractionation regimens; This needs to be further evaluated in clinical trials;

All patients will have a baseline PET scan as well as a diagnostic CT chest, abdomen, and pelvis. All pre-treatment and post treatment imaging will be per standard of care for staging and surveillance purposes. They will also have a baseline brain MRI. Post SRS treatment, they will continue to have diagnostic brain MRI (at 6 weeks, and then every 3 months) as well as CT chest/abdomen/pelvis (every 3 months) per standard of care, to evaluate response and to monitor for any unexpected toxicity. Routine standard of care blood work (CBC, BMP, LDH, etc) will also be ordered at baseline and with all subsequent visits.

**Table 1 – Radiation Dose Arms**

| Group | Dose per fraction (Gy) | Number of Fractions | Acute BED | Chronic BED |
|---|---|---|---|---|
| A | 6 | 5 | 48 | 90 |
| B | 9 | 3 | 51.3 | 108 |
| C. tumor volume < 4cm$^3$ | 21 | 1 | 65.1 | 168 |
| tumor volume 4-14.15 cm$^3$ | 18 | 1 | 50.4 | 128 |

BED = biological equivalent dose. Acute BED is the biological equivalent dose for acute radiation responding tissue, which includes malignant cells. Chronic BED biological is the biologic equivalent dose for late radiation responding tissue, which includes normal brain tissue. Increasing chronic BED doses predicts higher risk of sub-acute and chronic toxicities.

### 2.2 Altered Radiation Dose Arms (See Figure 1, in Section 2.4);

This is a pilot study to look at the safety of concurrent PD-1 inhibitor and SRS for melanoma brain metastases using three different radiation arms currently used to treat brain metastases. An initial cohort of 6 patients will be enrolled on radiation arm A (6 Gy x 5) that has a lower biological effective doses (BED) for acute and chronic side effects (**Table 1**), radiation arm B (9 Gy x 3) which has the second lowest BED, and radiation arm C (21 Gy x 1 or 18 Gy x 1 based on tumor volume) which has the highest acute and chronic BED; Arm C is also the most commonly accepted standard of care regimens, and based on RTOG 90-05 radiation dose escalation trial.

The first 18 patients (6 per dose level) will be enrolled in sequence as follows:

Arm A: patient #1-6, Arm B: patient #7-12, Arm C: patient # 13-18;

There will be a 3 month interim waiting period after 6 patients are enrolled on a given radiation arm and analyzed for any undue early dose limiting toxicity (DLT); The DLT toxicity definition is similar to that defined in the RTOG 90-05 (i.e, **CNS grade 3 or more acute toxicity, which is considered irreversible severe neurological symptoms at 3 months requiring medications**); The time point of 3 months is typical of when all post SRS acute side effects are expected to resolve. Thus, having acute side effects requiring medication usage for irreversible severe symptoms at 3 months would be unusual.

The second 18 patients (6 per dose level) will be enrolled in a similar sequence as follows:

Arm A: Closed, Arm B: patient #25-30, Arm C: patient #31-36;

### 2.3 Acute Toxicity, Expansion Cohorts, and Late Toxicity Assessment:

Once 6 patients are enrolled on any given dose level, there will be a waiting period of 3 months (i.e, at time of second post SRS MRI assessment after pembrolizumab dose (i.e, 3 months after Day 1, cycle 1); This time point of 3 months and the dose limiting toxicity (i.e. grade 3 RTOG CNS toxicity) is based on similar timeline used on earlier trial to determine the safest radiation dose. Late toxicity (radionecrosis noted on MRI images will also be analyzed at 6 months and at 1 year, but will not be used to stop enrollment on any given dose arm.);

During this 3 month waiting period, the MRI images and the patients will be assessed for any

signs or symptoms of RTOG CNS toxicity as well as early manifestations of radionecrosis. ≥ Grade 3 CNS toxicity is the only DLT toxicity of principal concern. Patient can still be accrued on other dose arms during this waiting period, while data is being analyzed for safety concerns on a given radiation arm.

- If ≤ 2/6 patients develop a DLT on a given radiation arm, accrual on the particular dose arm will continue for another 6 patients for a total of 12 patients per dose arm. RTOG 90-05 used a 20% cutoff at 3 months as the DLT endpoint. We accept 2/6 (33%) based on a biological rationale that if there is slight increase in radiation toxicity, this may be offset by increased systemic responses through immune modulation of radiation when radiation is combined with anti PD-1 (see section 4.0 for biological rationale);
- If ≥3/6 patients develop a DLT on a given radiation dose arm, this arm will stop accrual and considered unsafe;

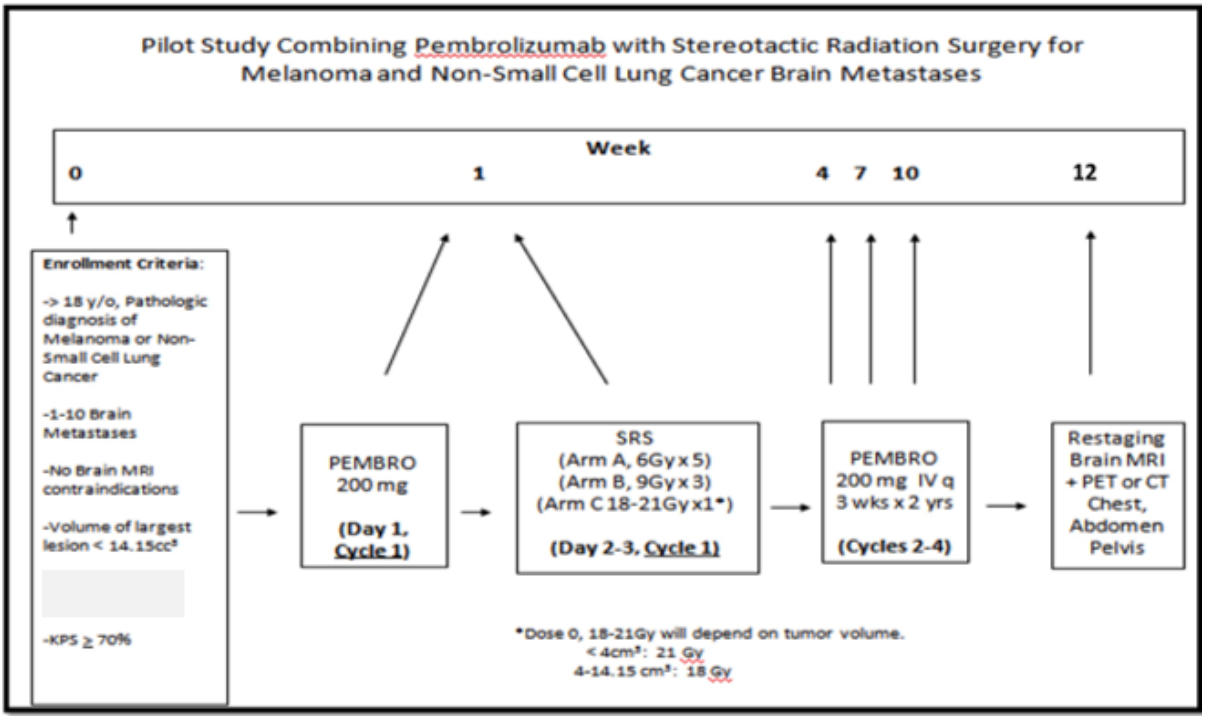
Late toxicity (i.e, toxicity starting after 3 months) will also be analyzed (a **secondary endpoint of trial**). The principal late toxicity of interest is symptomatic radiation necrosis. This is defined as radiographic (typically on MRI) changes consistent with radiation induced necrosis, and the patient also presenting with increased neurological symptoms. Symptomatic radiation necrosis will be recorded at 6 months and at 12 months;

- The radiation dose arm which meets the lowest DLT (i.e. ≥ Grade 3 CNS Toxicity at 3 months) and late toxicity (any radiation necrosis) endpoints, but also potentially provides higher overall systemic response rate and OS, will be considered the best radiation dose level that can be combined with pembrolizumab.
- Our published series of melanoma patients undergoing SRS alone had an average survival of 38% at 1 yr (Patel KR et al, American J. Clinic. Oncology. 2015, May 16. Epub); Our recent multi-institutional review in collaboration with Duke University suggested 1 yr overall survival of 78% for patients undergoing SRS and PD1 in combination (not published, accepted for annual presentation at American Society of Radiation Oncology Meeting, 2016). Thus, we suspect an improvement of 40% in OS compared with SRS alone. 12 patients on the most immunogenic arm (9Gy x 3), would be expected to have lowest acute and late toxicity, as well as potentially the highest OS benefit. We suspect that this may be the arm for a future trial. However, this has not been tested in any currently prospective manner.

Thus, the total enrollment will be 30 patients, and not less than 18.

### 2.4 Trial Schema

Figure 1: Trial Overview




## 3.0 OBJECTIVES, ENDPOINTS & HYPOTHESES

### 3.1 Primary Objective, Endpoint, & Hypothesis

#### 3.1.1 Primary Objective

a. To determine the safety of three different stereotactic radiosurgery (SRS) radiation arms in combination with pembrolizumab for melanoma and non-small cell lung cancer (NSCLC) brain metastasis (BM) patients.

#### 3.1.2 Primary Endpoint

a. RTOG grade 3 CNS toxicity at 3 months (the Dose Limiting Toxicity);

#### 3.1.3 Primary Endpoint Definitions

a. RTOG grade 3 CNS toxicity is defined as irreversible severe neurological symptoms requiring medications at 3 months;

#### 3.1.4 Primary Hypothesis

a. The primary hypothesis of this pilot study is that the use of concomitant SRS using

three different SRS radiation doses with pembrolizumab in melanoma and NSCLC BM patients will be a safe, well-tolerated regimen.

## 3.2 Secondary Objective(s), Endpoint(s) & Hypothesis(es)

### 3.2.1 Secondary Objectives

b. To evaluate intracranial outcomes – control of the treated lesion in the brain with SRS+ pembrolizumab (i.e. local control), development of additional sites of disease in the brain that were not initially treated with SRS (i.e. anywhere intra-cranial failure), intra-cranial progression free survival (local control of the area that received SRS and anywhere intra-cranial failure), extra-cranial disease response (overall progression free survival), rate of leptomeningeal dissemination, and overall survival.
c. To determine the overall response rate and overall survival of combination SRS and pembrolizumab compared to:
    i. SRS alone (historical control)
    ii. Pembrolizumab alone (historical control)

d. To evaluate treatment response at un-irradiated and extra-cranial sites (i.e. the abscopal effect) with all three arms;
e. To compare differences in potential immune biomarkers, pretreatment, during treatment, and post treatment;

### 3.2.2 Secondary Endpoints

a. Time to intracranial outcomes, including local recurrence, anywhere intra-cranial failure, leptomeningeal dissemination.
b. Overall survival time.
c. Overall response (intra-cranial and extra-cranial).
d. Difference in pre and post treatment serum immune biomarkers between the three different radiation arms (see biomarkers section);
e. Symptomatic radiation necrosis rates at 6 months and at 12 months;

### 3.2.3 Secondary Endpoint Definitions

a. Time to recurrence for each of the intracranial events will be measured from the first treatment on cycle 1, day 1 to the earlier of the recurrence event and/or last follow up/death.
b. Overall survival will be defined as time from first treatment on cycle 1, day 1 to the earlier of date of death and/or last follow up.
c. Overall response will be defined using RECIST and immune RECIST Criteria. Response will be measured for all metastatic sites and at un-irradiated sites (i.e. the abscopal effect).
    **d.** Several serum biomarkers will be analyzed (See section 12) to note any differences between the three arms.

e. Symptomatic radiation necrosis is defined as evidence of necrosis on MRI images (radiographic evidence or radionecrosis) and a patient having neurological symptoms attributed to the location where the radiosurgery was done (symptomatic); Secondary Hypotheses

### 3.2.4 Secondary Hypotheses

a. Using descriptive analyses, combination therapy will result in a higher median survival relative to a historical cohort treated with pembrolizumab alone or SRS alone.
b. Using descriptive analyses, combination therapy, relative to pembrolizumab alone cohort, will result in higher local control and intracranial control.
c. Using descriptive analyses, combination therapy, relative to the cohort treated with pembrolizumab alone, will result in a higher improved RECIST and immune RECSIT response rate.
d. We may see early difference in patients that develop enhanced abscopal response from those that do not, based on early biomarker analysis, and that this could potentially guide future therapy selection.
e. Radiation necrosis rates may be same, or better with altered dose fractionation compared with single fraction, especially when combined with concurrent PD1;

## 4.0 BACKGROUND & RATIONALE

### 4.1 Background

### 4.0.1 Brain Metastasis

In 2013, 10-30% of all adult cancer patients developed brain metastases, representing 170,000 newly diagnosed secondary brain malignancies in the United States [1]. While the highest number of BM arises from lung malignancies, stage IV melanoma has the highest relative proclivity – 50-75% – for developing brain metastases [2,3]. Among non-small cell lung cancer (NSCLC) and melanoma patients with documented brain metastases, intracranial lesions contribute to death in up to 95% of cases[4].

Survival rates for brain metastases patients vary according to each cancer subtype, but overall have been dismal [5]. Using 5 prospective RTOG studies with 1,960 brain metastases patients, Sperduto et al. developed a point scoring system to predict patient outcomes [6]. Applying this graded partitioning analysis (GPA) to a multi-institution retrospective database with 4,259 brain metastases patients, they developed a prognostic criteria for each of the main pathologic primary sites of metastases[7]. For newly diagnosed melanoma brain metastases (MBM) patients, two factors predicted survival: Karnofsky performance status (KPS) and the number of intracranial metastases; for NSCLC, age and presence of extracranial metastases also predicts for survival prognosis. The median survival for melanoma and NSCLC brain metastases is 6.7 months and 7.0 months respectively; the best prognosis risk group has a survival of 13.2 months and 14.8 months, respectively, while the worse risk prognosis group

has a survival of 3.4 and 3.0 months only. **Table 2** summarizes validated prognostic factors, risk groups, and outcomes for melanoma and NSCLC brain metastases patients.

**Table 2 – Median Survival of Brain Metastases patients stratified by histology and prognosis group**

| Primary Tumor Site of Brain metastases | Median survival (months) | Median survival within poorest prognosis group | Median survival with best prognosis group |
|---|---|---|---|
| NSCLC | 7.0 | 3.0 | 14.8 |
| Melanoma | 6.7 | 3.4 | 13.2 |

### 4.0.2 Stereotactic Radiation Surgery for Brain Metastasis

Historically, most traditional cytotoxic chemotherapies have a limited role in brain metastasis, in part due to blood brain barrier (BBB) limiting penetration[8]. As a result, the standard of care for brain metastasis includes surgery and/or radiation therapy. Although very effective for symptomatic control, Kocher et al. demonstrated that surgical resection alone commonly results in high local failure of 59% at 2 years[9]. To improve local control (LC) and distant brain control (DBC), adjuvant whole brain radiation therapy (WBRT) has been utilized.

With concern, for late neurocognitive toxicities from irradiating the whole brain[10], more conformal radiation treatments have been developed. Stereotactic radiation therapy (SRS) is a technique that focuses high doses of radiation therapy to the tumor while minimizing radiation therapy to the rest of the brain. Although SRS has lower rates of distant intracranial control for non-targeted subclinical disease, a prospective study has illustrated that SRS alone has similar survival rates to WBRT alone[11]. Furthermore, the addition of WBRT to SRS for patients with 1—3 brain metastases did not improve OS[9]. Retrospective analyses in the post-operative setting have also demonstrated SRS has similar LC and OS to WBRT after controlling for the number of brain metastases[12].

We at Emory have adopted this approach to treat brain metastasis, including melanoma and NSCLC, with SRS alone to delay WBRT and its related neurocognitive sequellae. Our contemporary analysis supports this regimen for brain metastasis patients: directly comparing post-operative SRS to WBRT, we found (Patel et al) both radiation treatments offer similar local control and median survival, but SRS in 80% of patients prevented the need for WBRT at 1 year[12]. In the intact brain metastases setting, we at Emory have illustrated (Prabhu et al) that 1 year local control rate with SRS was 82%[13]. The local control rate is comparable to other similar published series utilizing radiosurgery[14]. Our studies contribute to the body of evidence that SRS can help improve local intracranial control.

### 4.0.3 Radiation Necrosis

While SRS may have a radiobiological advantage and help avoid neurocognitive decline from WBRT, it is not without toxicities. Radiation necrosis is a form of radiation induced damage to white matter tissue, causing demyelination, surrounding edema, and normal tissue necrosis and death[15]. Prospective clinical trials have demonstrated grade 3 toxicity rates of 10-15% with SRS[16]. Based on these studies, the radiation therapy oncology (RTOG) recommended doses for SRS were 24 Gy for tumors ≤20 mm, 18 Gy for tumors 21-30 mm, and 15 Gy for tumors 31-40 mm[16]

Two of the largest studies have since analyzed predictive factors for the development of radiation necrosis after SRS for patients with intact brain metastasis. On multivariate analysis from both studies, the volume of disease receiving 10 and 12 Gy of radiation were predictive for developing both asymptomatic and symptomatic radiation necrosis[14,15]. To meet these criteria, while still providing adequate control, SRS has been offered over a hypofractionated (2-5 fractions) rather than a single fraction at a lower dose.

Our series and others, comparing 30Gy in 5 fractions and 27Gy over 3 fractions to single fraction SRS, identified lower risk of radiation necrosis with hypofractionation, especially for larger lesions, and those next to critical organs. These altered fractionation have become our defacto standard for larger lesions, and in those which lesions are close to critical organs. *Overall, these studies suggest that fractionated SRS is a safer way to treat brain metastases while still maintaining similar local control rates. This is important for our trial, especially since we plan to deliver SRS with pembrolizumab at the same time, thus raising some concern for potential toxicity. Thus, we have used altered SRS fractionation using SRS regimens that have been demonstrated to potentially reduce rates for radiation necrosis, even in larger lesions compared with larger, single fraction radiation doses. Furthermore, these altered radiation doses using hypofractionation may also be more immunogenic compared with the single, large doses of radiation (i.e. 21 Gy in single fraction, or 18 Gy in single fraction). Thus, biologically and from safety point of view, the altered fractionated regimens (i.e. 2-5 fractions) may be more advantageous, than single, large dose radiation fractions. However, this has never been tested concurrently with PD-1, and basis for our trial.*

### 4.1.1 The Immune System in Cancer

In 2000, Hanahan and Weinberg published their seminal review describing the 6 biological hallmarks acquired during the development from benign to malignant to metastatic tumors[17]. Eleven years later, they illustrated 2 further important processes that were since realized, including "evading the immune system"[18].

The immune system consists of two main components, innate and adaptive system. In brief, the innate system is a non-specific response to differences between innate and foreign pathogens, while the adaptive system is a more tailored response that induces memory. As part of this adaptive response, macrophages and dendritic cells present foreign antigens to the T cell's receptors. Further T cell activation is regulated by multiple factors, including both positive (co-stimulatory) and negative (co-inhibitory) surface receptors. Tumors can subvert the related immune recognition in part through increase of co-inhibitory molecule expression; two of these regulatory molecules are cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death 1 (PD-1) receptor.

### 4.1.2 Anti-PD-1 in Pre-Clinical Models

Programmed death 1 (PD-1) (or CD279) is part of the CD28 family of proteins, which includes CTLA-4 and ICOS, that regulate T cell activity[21]. PD-1 is a glycoprotein receptor that can be expressed on the surface of T cells, B cells and myeloid cells (monocytes and dendritic cells)[21]. In T cells, PD-1 expression is primarily induced by T cell receptor (TCR) engagement and ligation with PD-L1 and PD-L2, expressed on antigen presenting cells, and induces an inhibitory signal that antagonizes TCR signaling and other important pathways necessary for optimal T cell activation

Interestingly, melanoma, and to a lesser effect NSCLC, expresses abundant PD-1 ligand (PD-L1), whereas T cells of advanced cancer patients notoriously express increased levels of PD-1. The combined effect is that these cancer cells are spared from T-cell-mediated cytotoxicity, and tumor infiltrating lymphocytes are maintained in a dysfunctional state, described as T cell exhaustion. Indeed, PD-1 expression on T cells of patients has been associated with progression to metastatic disease.

Targeting the PD-1 pathway in pre-clinical models has demonstrated promising activity. Utilizing murine cancer cells, anti-PD1 antibody decreased tumor growth and decreased metastatic potential. Because B16 cells are PD-L1 expressing, the authors also used 4T1, a PD-L1 negative murine cell line and demonstrated similar efficacy of PD-1 pathway blockade. Prior studies demonstrate that PD-L1 expression varies in response to the microenvironment, including increased expression in response to cell death. Consistent with this model of variable PD-L1 expression over time, several authors have since demonstrated the efficacy of anti-PD-1 antibodies in both PD-L1 positive and negative tumors.

### 4.2.1 Efficacy of Anti-PD-1, Pembrolizumab, in Melanoma Patients

Two clinical trials have recently investigated the safety and efficacy of anti-PD-1 pembrolizumab therapy in melanoma. The first published trial by Hamid et al enrolled 135 patients who had never received ipilimumab or had completed ipilimumab greater than 6 weeks

from enrollment[19]. Patients were treated with escalating doses of pembrolizumab, from 2mg/kg q3weeks to 10mg/kg q2weeks. After 4 cycles of induction therapy, patients were continued on pembrolizumab maintenance. The overall response rate was 38% of patients. Response rate was also dose related, with 2mg/kg cohort having a 25% response compared to the 10mg/kg cohort having a 52% response. With a median follow up of 11 months, 81% of patients continued to demonstrate a response and median survival had not been reached, suggesting majority of responses are durable and correlate with survival.

The second reported by Robert et al was a phase I trial of pembrolizumab in metastatic melanoma patients. 173 patients refractory to ipilimumab were randomized in a 1:1 fashion to 2mg/kg q3weeks or 10mg/kg q3weeks[20]. Overall response rate for both dose cohorts was similar: 26%. Of the 41 responding patients, 2 had a complete response (4.9%) while 39 had a partial response (95.1%). Another 24% had stable disease, for a disease control rate of 50%. Progression free survival was 22 weeks for the 2mg/kg arm and 14 weeks for the 10mg/kg arm, with no statistical difference between cohorts. 1 year overall survival was 58% for the 2mg/kg cohort and 63% for the 10mg/kg cohort.

Taken together **(Table 3)**, these studies suggest pembrolizumab is an active agent in metastatic melanoma that is well tolerated. Based on these results, the FDA approved pembrolizumab for ipilimumab refractory patients, at a recommended dose of 2mg/kg every 3 weeks +/- 7 days.

**Table 3 - Efficacy & Safety of Anti-PD-1 Antibody, Pembrolizumab in Melanoma**

| Trial First Author | Number of Patients | Drug Dose | Overall Response Rate | Overall Survival | Grade 3-4 Toxicity |
|---|---|---|---|---|---|
| Hamid et al[19] | 135 | (i) 2mg/kg q3wks<br>(ii) 10mg/kg q3wks<br>(iii) 10mg/kg q2wks | 38% | Median Survival not reached (median follow up: 11 months) | 13% |
| Robert et al[20] | 173 | (i) 2mg/kg q3wks<br>(ii) 10mg/kg q3wks | 26% | 1 year OS: 58-63% | 12% |

### 4.2.2 Efficacy of Anti-PD-1, Pembrolizumab, in NSCLC Patients

Building upon the success of pembrolizumab in melanoma, Garon et al. investigated the safety and efficacy of pembrolizumab alone in 495 stage IV non-small cell lung cancer patients[21]. Overall response rate for entire cohort was 19.4%. Current or prior smokers had a higher response rate than never smoker: 22.5% vs. 10.3%. PD-L1 expression on tumors correlated with higher response, as the 23% of patients with a proportion staining score of 50% or higher had a response of 50%. The role of pembrolizumab in combination with SRS for

NSCLC brain metastases has not been evaluated, and is one of an additional area of investigation in our current trial.

### 4.3.1 Rationale for Pembrolizumab Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475 (pembrolizumab). The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 200 mg200 mg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 200 mg200 mg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 200 mg200 mg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 200 mg200 mg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 200 mg200 mg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks +/- 7 days will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks +/- 7 days, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

### 4.3.2 Safety and toxicity of Pembrolizumab

Pembrolizumab has been administered to a total of 308 melanoma patients, from 2 prospective clinical trials[65-66]. The first trial administered pembrolizumab at 3 different doses (2mg/kg q3weeks, 10mg/kg q3weeks, and 10mg/kg q2weeks) for 4 total cycles, followed by continued maintenance therapy until progression. Overall, 79% of patients develop any grade of toxicity. The most common toxicities were fatigue (30%), rash (21%), pruritus (21%), and diarrhea (20%). However, most of these symptoms were low grade, as only 13% developed grade 3- 4 toxicities. Furthermore, grade 3-4 adverse events were dose related: the 10mg/kg, q2week cohort was 23%, while the q3week cohorts was 4-9%. The grade 3 clinical toxicities documented included rash (2%), pruritus (1%), hypothyroidism (1%), diarrhea (1%), abdominal pain (1%), decreased appetite (1%), elevated AST (1%), and renal failure (1%). In the 2 cases of renal failure, both cases improved with discontinuation of pembrolizumab and initiation of glucocorticoid therapy

In the trial of pembrolizumab in advanced melanoma patients, the toxicity profile was similar to that reported by Hamid et al: 82% developed any grade of toxicity, while 12% developed grade 3-4 toxicities. Most common toxicities were fatigue, pruritus, and rash. Reported grade 3-4 toxicities included fatigue (3%), elevated amylase (<1%), anemia (<1%), autoimmune hepatitis (<1%), confusion (<1%), diarrhea (<1%), dyspnea (<1%), encephalopathy (<1%), hypophysitis (<1%), hypoxia (<1%), muscular weakness (<1%), musculoskeletal pain (<1%), pancreatitis (<1%), peripheral motor neuropathy (<1%), pneumonitis (<1%), rash (<1%), rash maculopapular (<1%). Overall 6 patients (7%) developed adverse events leading to discontinuation of the drug. 3 of these cases (3%) were immune mediated. No drug related grade 5 toxicities were reported.

In the phase 1 study with 495 NSCLC patients, no grade 3 or higher CNS toxicities were noted. Furthermore, the toxicity profile was similar to that identified in the two melanoma studies. Most common grade $\geq$ 3 adverse events were fatigue (0.8%), decreased appetite (1.0%), nausea (0.8%), asthenia (1.0%), dyspnea (3.8%) and pneumonitis (1.8%). 1 patient who developed pneumonitis did die; overall, these findings demonstrate pembrolizumab is well tolerated and has similar toxicity profiles among the two histologies.

### 4.4.1 Safety and Efficacy of Pembrolizumab Alone for Melanoma Brain Metastases

For both published pembrolizumab trials (Hamid et al & Robert et al), patients with melanoma brain metastases were excluded. With melanoma having a high incidence of developing brain metastases, the efficacy in this population is extremely important. To investigate this further, Kluger et al (Yale group) conducted a phase I study of pembrolizumab alone for melanoma brain metastases[22]. Only patients with asymptomatic lesions and ECOG PS 0-1 were included.

Patients were treated with 10mg/kg q2weeks for 4 total cycles, followed by maintenance therapy. All patients were asymptomatic and not requiring steroids (less than or equal to 10 mg prednisone equivalent is ok)s at the time of start of treatment. 18 patients were enrolled; however 4 (22%) were deemed not evaluable due to intralesional hemorrhage (n=1) and extracerebral progression (n=3). 4 patients (22%) developed a response, with 1 a complete response and 3 with partial responses. Another 3 patients developed stable disease. In the evaluable patients, 7 out of the 14 developed progressive disease (50%). Given the response rate (22%) is similar to the response rate seen in the extra-cranial metastases patients (Hamid et al.; Robert et al.), the authors concluded pembrolizumab does have similar intracranial efficacy.

However in comparison to the standard of care regimens such SRS alone, where 1 year LC rates in prospective studies are 67-75%[10,11], the LC rates with pembrolizumab appear significantly lower. With 11 out of the 18 patients (61%) either not completing treatment or developing progressive disease, these tolerability-efficacy rate is markedly lower for pembrolizumab for non-CNS metastases[23,24]. One possible conclusion is that delayed immunologic response characteristic of pembrolizumab may not be quick enough in the brain, where relatively smaller amounts of progression can quickly increase neurologic morbidity and mortality. Another reason may be that pembrolizumab may not penetrate the blood brain barrier to enough concentrations to make a meaningful clinical impact. Thus, the combination approach of SRS for local control of disease within the brain and pembrolizumab for the control of extra-cranial systemic disease makes the most logical sense. The safety and efficacy of these two combination delivered concurrently is not well characterized.

### 4.5.1 Combining Radiation and anti PD-1

While pembrolizumab demonstrates significant increases in median survival in advanced melanoma, response rates are modest (26-38%)[66]. Preclinical studies and case reports suggesting that combining radiation with CTLA-4 blockade can improve response rates[24,25]. Building upon these findings, numerous groups have investigated the combination of pembrolizumab and radiation therapy preclinically. Sharabi et al.[26] and Dovedi et al.[27] together demonstrate that radiation therapy increases the T cell repertoire and antigen presentation to T cells; furthermore, adding radiation to PD-1 blockade in mice models demonstrate significant improvement in systemic response and local control[28]. This combination of PD-1 blockade with radiotherapy has not been investigated in the clinical setting, and is the basis of our current protocol design.

### 4.6.1 Rationale for stereotactic radiation surgery and Anti PD-1 Therapy, pembrolizumab

Numerous preclinical findings suggest that radiation therapy augments the immune response against melanoma[25,29]. Adding pembrolizumab to radiation therapy may markedly enhance the immunologic response to tumor antigen release from necrotic tumor cells by radiotherapy[26,27]. This combination may allow for improved control at the irradiated site and un-irradiated site (abscopal effect)[27]; the net effect may be to significantly improve overall response rates in patients. With Kluger et al demonstrating that pembrolizumab alone results in low local control rates for intracranial metastases[22], there is a need for further intracranial treatment. Therefore, to build on these concepts, we propose a study to determine the safety of SRS with pembrolizumab.

Furthermore, our own preclinical work has also demonstrated that radiation can be an immunotherapy agent. Figure 2 demonstrated a phenomenon, known as the "abscopal" effect, meaning that when radiation is delivered to one tumor site on a implanted mouse, a distant site, more remote to the tumor that has not been radiated also disappears. This is believed to be immunologically mediated. Furthermore, when we comparing the 20 Gy per single fraction with the 10 Gy per single fraction, we find that the 10 Gy radiation dose per single fraction appears to be responsible for a greater abscopal effect, compared with the larger/more ablative 20 Gy per single fraction radiation dose. Thus, this is the basis for our "altered" radiation dose fractionation regimen, that we have picked in our current trial design.

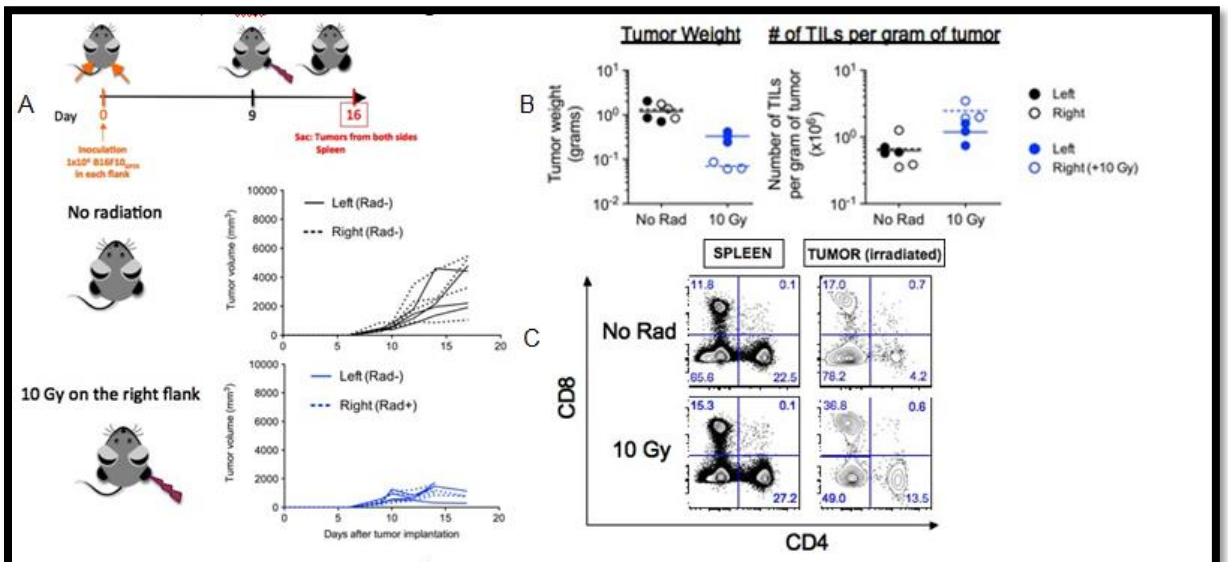



**Figure 1**. Mouse model of abscopal effect. **A**.1x10$^6$ B16F10gp33 melanoma cells were injected to both left and right flanks subcutaneously *(upper panel)*. Nine days post implantation, 10 Gy was applied to one (right) flank. The tumors were the measured every two days and then sacrificed at day 16 (lower panel); tumor growth was decreased in both the irradiated and unirradiated site. **B**. Broad phenotypes of tumors and tumor infiltrating lymphocytes (TILs) from mice with (only right side, blue symbols) or without radiation therapy, demonstrating a decreased weight of tumor on both left (closed symbol) and right (open symbol) correlates with an increased number of infiltrating lymphocytes per gram of tumors. **C**. Expansion of CD8 and CD4 T cells was found only in irradiated side of tumor (right column) but not in the spleen (left column) after radiation therapy, suggesting that radiation that targets a tumor influences immune cell phenotypes within tumor micromicroenvironments.

### 4.6.2 Rationale for sequencing for stereotactic radiation surgery and pembrolizumab

To date, no studies have reported on the efficacy of SRS and anti-PD1 checkpoint inhibitor, pembrolizumab. Three published pre-clinical studies have investigated combining radiation therapy and anti-PD1 in mouse models[26-28]. While they show a synergistic

relationship between the two therapies, these studies did not investigate the ideal sequencing of the two proposed therapies (anti-PD1 and SRS). While evidence for sequencing is therefore missing, the Memorial Sloan Kettering group retrospectively reported on the safety and efficacy of 46 patients treated with SRS and CTLA-4 checkpoint inhibitor, ipilimumab[30]. 15 patients received SRS during ipilimumab, 19 received SRS before IPI and 12 received SRS after IPI. Grade 3 or higher toxicities was 20% in the entire cohort, consistent with rates of grade 3 toxicities with ipilimumab alone[31]. Grade 3 or higher CNS adverse effects included seizure (4.6%) and CNS bleeding (10.9%). Rate of toxicities did not correlate with sequence of therapies; these findings are also consistent with our own institutional series as well as others.[32-35]

Overall survival was higher in the cohort that received SRS before or during IPI, than those treated with SRS after ipilimumab. However, an inherent selection bias may account for these findings, as patients in the SRS after IPI cohort may be selected for SRS due for salvage after ipilimumab alone. Interestingly, the authors did find that 50% of patients treated with SRS before or during IPI had an increase in size > 150%, compared to 15% with those treated with SRS after IPI. They hypothesized that this increase in size represents T cell infiltration of the tumor, thereby demonstrating potential activity. Because (1) sequence did not correlate with toxicity, (2) but did correlate with possible activity, and (3) preclinical research suggests concurrent radiation and anti-PD-1 therapy is synergistic[26-28], we will plan to utilize the approach of concurrent SRS with the checkpoint inhibitor pembrolizumab.

We suspect that the maximum T cell activation, proliferation, and entry into the blood stream occurs within 48 hours. To maximize the exposure of these cells to the increased antigen expression and MHC levels, we will plan to deliver radiation with 24 to 48 hours after pembrolizumab is delivered (and no later than 7 days after the first PD-1 inhibitor infusion).

### 4.6.3 Rationale for Primary Endpoint

For intact brain metastases treated with SRS alone, Aoyama demonstrated prospectively that 8 out of 67 patients (12%) developed an acute grade 3 CNS toxicity. RTOG 90-05 accepted a 20% acute grade 3 CNS toxicity in their trial design. Similar rates were observed in the cohort treated with SRS alone on the Kocher prospective study. For large lesions, we and others have retrospectively demonstrated a grade 2 toxicity rate of 10% for hypofractionation. For pembrolizumab alone, acute grade 3 nervous system toxicity was seen in 2 out of 18 patients (11%). Therefore, assuming toxicity is additive, we will accept a DLT toxicity rate of 25%, with a 5% room for error. Thus, our acceptable DLT is 33%. This rate is justified given that (1) each therapy alone (SRS and anti PD-1 alone) have limitations as detailed above and (2) the combination may result in significantly higher response and perhaps improved outcomes in combination.

## 5.0 ENROLLMENT CRITERIA

### 5.1.1 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be ≥ 18 years of age on the day of signing informed consent.
3. ECOG PS of 0-1 (See Appendix IV for ECOG definition); Karnofsky Performance Status ≥ 70%;
4. Patients must have histological diagnosis of melanoma or non-small cell lung cancer (biopsy will be done per standard of care, if needed to prove metastatic melanoma and/or NSCL as well as for clinically relevant mutation analysis); Additional biopsy will be per standard of care.
5. Patients can be treated either in first line or in the refractory setting; PD-L1 positivity is not required for enrollment;
6. All melanoma patients may be tested for BRAF as part of routine standard of care, but is not a requirement for the trial; All NSCLC patients may be tested for with EGFR and ALK as part of standard of care, but is not a requirement of the trial.
7. Having gotten prior PD1 therapy is allowed for, especially if they have previously progressed on it. Progression may include extra-cranial as well as intra-cranial progression. After progressing on PD1 therapy, intervening chemotherapy and/or targeted therapy (BRAFi, etc) is allowed. If they are on intervening chemotherapy and/or targeted therapy (BRAFi, etc), they have to have progression intra-cranially and/or extra-cranially and must be off intervening therapy for at least 2 weeks.
8. Patient must be asymptomatic at time of getting SRS (day 0) on trial. Prednisone ≤10mg/day for at least 7 days prior to treatment is allowed.
9. Patients with ocular, mucosal and unknown primary melanoma will also be eligible
10. Patients with 1-10 untreated brain metastases at time of initial brain metastases diagnosis (surgery to one of the brain lesions and/or biopsy of a lesion for diagnostic purposes and/or for standard of care purposes is acceptable).
11. Largest brain metastases volume measures less than 14.15$cc^3$
12. Prior radiation to the primary and/or regional radiotherapy for melanoma and/or NSCLC is acceptable.
13. Baseline labs as within standard of care (CBC, CMP, LDH, ESR, etc) are required within 14 days of enrollment
14. Have measurable disease based on RECIST 1.1.
15. Patients must have at least 14 days to recover from all prior treatment, including surgery, chemotherapy, immunotherapies, prior to enrollment on this protocol.
16. Demonstrate adequate organ function as defined in **Table 4**, all screening labs should be performed within 14 days of treatment initiation.

**Table 4** - Adequate Organ Function Laboratory Values

| System | Laboratory Value |
|---|---|
| **Hematological** | |

| | |
|---|---|
| Absolute neutrophil count (ANC) | ≥1,500 /mcL |
| Platelets | ≥100,000 / mcL |
| Hemoglobin | ≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment) |
| **Renal** | |
| Serum creatinine **OR**<br>Measured or calculated[a] creatinine clearance<br>(GFR can also be used in place of creatinine or CrCl) | ≤1.5 X upper limit of normal (ULN) **OR**<br><br>≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN |
| **Hepatic** | |
| Serum total bilirubin | ≤ 1.5 X ULN **OR** |
| | Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN |
| AST (SGOT) and ALT (SGPT) | ≤ 2.5 X ULN **OR**<br>≤ 5 X ULN for subjects with liver metastases |
| Albumin | ≥2.5 mg/dL |
| **Coagulation** | |
| International Normalized Ratio (INR) or Prothrombin Time (PT)<br><br>Activated Partial Thromboplastin Time (aPTT) | ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants<br>≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants |
| [a]Creatinine clearance should be calculated per institutional standard. | |

17. Female subject of childbearing potential should have a negative urine or serum pregnancy within 2 weeks 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.
    a. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 10.1.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
    b. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
    c. Abstinence is acceptable, if this is the usual life style and preferred contraception for the patient.

### 5.1.2 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Has a diagnosis of immunodeficiency or is receiving systemic steroids (less than or equal to 10 mg prednisone equivalent at time of start of treatment is ok) therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment
2. If they have brain metastases located in the brain stem (including midbrain, pons, or medulla);
3. Inability to undergo MRI evaluation for treatment planning and follow-up
4. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.Has a diagnosis of immunodeficiency or is receiving systemic steroids (less than or equal to 10 mg prednisone equivalent at time of start of treatment is ok) therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
5. Has a known history of active TB (Bacillus Tuberculosis)
6. Hypersensitivity to pembrolizumab or any of its recipients.
7. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.
    - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
8. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
9. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
10. Has known history of (non-infectious) pneumonitis that required steroids (less than or equal to 10 mg prednisone equivalent at time of start of treatment is ok) or current pneumonitis.
11. Has an active infection requiring systemic therapy.
12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
14. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
15. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
16. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
17. Has received a live vaccine within 30 days of planned start of study therapy.
    *Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.*

## 6.0 ADMINSTRATION OF STUDY PHARMACEUTICAL

In 2015, FDA approved Pembrolizumab (Keytruda) for the treatment of advanced melanoma and NSCLC patients; Pembrolizumab is a monoclonal antibody that targets the PD-1 receptor. Programmed death 1 (PD-1) (or CD279) is part of the CD28 family of proteins, which includes CTLA-4 and ICOS, that regulate T cell activity[21]. PD-1 is a glycoprotein receptor that can be expressed on the surface of T cells, B cells and myeloid cells (monocytes and dendritic cells)[21]. In T cells, PD-1 expression is primarily induced by T cell receptor (TCR) engagement and ligation with PD-L1 and PD-L2, expressed on antigen presenting cells, and induces an inhibitory signal that antagonizes TCR signaling and other important pathways necessary for optimal T cell activation. Clinical trials with Pembrolizumab in advanced melanoma and NSCLC patients lead to approval by the FDA. The recommended dose of Keytruda is 2mg/kg administered as IV infusion over 30 minutes every 3 weeks +/- 7 days until disease progression, or unacceptable toxicity. Alternative dosing regimens are also available.

The IV treatment to be used in this trial is outlined below in **Table** 5. Radiation treatment outline/table is listed in 10.0

**Table 5 Pembrolizumab Treatment**

| Drug | Dose | Dose Frequency | Route of Administration | Regimen/Treatment Period | Use |
|---|---|---|---|---|---|
| Pembrolizumab | 200 mg | Q3W | IV infusion | Day 1 of each 3 week cycle | Experimental |

### 6.1.1 Dose Selection

#### 6.1.1.1 Dose Selection

Patients will receive pembrolizumab 200 mg. Pembrolizumab will be delivered over a 30-minute period every 3 weeks +/- 7 days until at least 2 year, progression of disease, and/or unacceptable toxicity at the discretion of the treating physician. Infusions should be given over 30 minutes (not bolus or IV push).

The rationale for selection of the dose (200 mg) to be used in this trial is provided in Section 4.0 – Background and Rationale.

#### 6.1.1.2 Pembrolizumab Dose Calculation

Calculate Total Dose as follows: 200 mg;
Calculate Total Infusion Volume as follows:

Total dose in mg ÷ 10 mg/mL = infusion volume in mL

Calculate Rate of Infusion as follows:
Infusion volume in mL ÷ 30 minutes = rate of infusion in mL/min.

For example, a patient weighing 75 kg (165 lb.) would be administered 200 mg of pembrolizumab with an infusion volume of 20 mL (2000 mg ÷ 10 mg/mL = 20 mL) at a rate of approximately 0.66 mL/min in 30 minutes (20 mL ÷ 30 minutes).

### 6.1.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks +/- 7 days. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

### 6.1.3 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

## 6.2 Randomization Allocation

Not applicable

## 6.3 Stratification

Not applicable

### 6.4 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The sponsor-investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the sponsor-investigator and/or the subject's primary physician.

#### 6.4.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and within 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 13.2.3.2.

#### 6.4.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids (less than or equal to 10 mg of prednisone equivalent at time of start of treatment is ok). Anything more than this may be approved after consultation with the Sponsor.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

### 6.5 Administration of Pembrolizumab Beyond Progression

If the initial week 12 scan shows disease progression per RECIST 1.1, patients are allowed to continue treatment until progression is confirmed again at a subsequent 4-6 week later, to account for atypical response patterns. If the repeat imaging shows evidence of disease stabilization or objective response (relative to the previous scan that showed PD) as per RECIST I.1, pembrolizumab may be continued per treatment calendar. However, if the repeat assessment shows disease progression relative to the previous scan that showed PD, then pembrolizumab should be discontinued; The minimum criteria to continue must include absence of symptoms/signs of disease progression, no decline in performance status, and absence of rapid progression of disease at critical anatomic sites (i.e cord compression) requiring urgent alternative medical intervention.

## 7.0 DOSE MODIFICATION

### 7.0.1 Dose Modification, General

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose, or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per **Table 6** and **Table 7** below. See Section 8.0 and 9.0 as well as Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids (less than or equal to 10 mg prednisone equivalent at time of start of treatment is ok).

### 7.0.1 Dose Modification, Non CNS toxicities

**Table 6 Dose Modification Guidelines for Drug-Related Adverse Events**

| Toxicity | Hold Treatment For Grade | Timing for Restarting Treatment | Treatment Discontinuation |
|---|---|---|---|
| Diarrhea/Colitis | 2-3 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks |
| | 4 | Permanently discontinue | Permanently discontinue |
| AST, ALT, or Increased Bilirubin | 2 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose |
| | 3-4 | Permanently discontinue (see exception below)[a] | Permanently discontinue |
| Type 1 diabetes mellitus (if new onset) or Hyperglycemia | T1DM or 3-4 | Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure | Resume pembrolizumab when patients are clinically and metabolically stable |

| Toxicity | Hold Treatment For Grade | Timing for Restarting Treatment | Treatment Discontinuation |
|---|---|---|---|
| Hypophysitis | 2-4 | Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks |
| Hyperthyroidism | 3 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks |
| | 4 | Permanently discontinue | Permanently discontinue |
| Hypothyroidism | | Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted | Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted |
| Infusion Reaction | 2[b] | Toxicity resolves to Grade 0-1 | Permanently discontinue if toxicity develops despite adequate premedication |
| | 3-4 | Permanently discontinue | Permanently discontinue |
| Pneumonitis | 2 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks |
| | 3-4 | Permanently discontinue | Permanently discontinue |
| Renal Failure or Nephritis | 2 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks |
| | 3-4 | Permanently discontinue | Permanently discontinue |
| All Other Drug-Related Toxicity[c] | 3 or Severe | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks |
| | 4 | Permanently discontinue | Permanently discontinue |

**Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.**

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to Table – Infusion Treament Guidelines for further management details.

[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks +/- 7 days of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

### 7.0.2 Dose Modification, CNS toxicities

| Toxicity | Hold Treatment For Grade | Timing for Restarting Treatment | Discontinue Subject |
|---|---|---|---|
| **Central Nervous** | 2-3 | Toxicity resolves to Grade 0-1. | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to |

| Toxicity | Hold Treatment For Grade | Timing for Restarting Treatment | Discontinue Subject |
|---|---|---|---|
| **System Necrosis** | | (see exception below)[1] | 1 mg or less of dexamethasone or equivalent per day within 12 weeks. |
| | 4 | Permanently discontinue | Permanently discontinue |
| **Seizure** | 2-3 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose. |
| | 4 | Permanently discontinue | Permanently discontinue |
| **Cognitive Impairment or Cognitive Disturbance** | 2-3 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 1 mg or less of dexamethasone or equivalent per day within 12 weeks. |
| | 4 | Permanently discontinue | Permanently discontinue |
| **Stroke** | 2 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose |
| | 3-4 | Permanently discontinue | Permanently discontinue |

[1] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

## 8.0 DOSE LIMITING TOXICITIES

**Dose limiting toxicity definition**
Dose limiting toxicity is defined as symptomatic (i.e, presenting with neurological symptoms) radiation necrosis rate that exceeds 30% at 6 months as outlined in section 2; Imaging evidence post SRS (MRI and/or PET) must confirm the presence of radionecrosis along with associated clinical symptoms. The symptoms can be described as "Nervous system disorders" with a CTCAE 4.0 grade 3 or 4 or higher.

Please see APPENDIX 1 for list of all CNS Nervous system disorders and appropriate grading. Below is a table of the most common CNS Nervous System Disorders;

| Adverse Event | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|
| **Central Nervous System Necrosis** | Asymptomatic; clinical or diagnostic observations only; intervention not indicated | Moderate symptoms; corticosteroids indicated | Severe symptoms; medical intervention indicated | Life-threatening consequences; urgent intervention indicated | Death |

| | | | | | |
|---|---|---|---|---|---|
| **Seizure** (Definition: A disorder characterized by a sudden, involuntary skeletal muscular contractions of cerebral or brain stem origin.) | Brief partial seizure; no loss of consciousness | Brief generalized seizure | Multiple seizures despite medical intervention | Life-threatening; prolonged repetitive seizures repetitive seizures | Death |
| **Cognitive Impairment** | Mild inattention or decreased level of concentration | Moderate impairment in attention or decreased level of concentration; limiting instrumental ADL | Severe impairment in attention or decreased level of concentration; limiting self care ADL | | |
| **Cognitive Disturbance** | Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated | Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part time basis indicated | Severe cognitive disability; significant impairment of work/school/life performance | | |
| **Stroke** | Asymptomatic or mild neurologic deficit; radiographic findings only | Moderate neurologic deficit | Severe neurologic deficit | Life-threatening consequences; urgent intervention indicated | Death |
| **Intracranial Hemorrhage** (A disorder characterized by bleeding from the cranium.) | Asymptomatic; clinical or diagnostic observations only; intervention not indicated | Moderate symptoms; medical intervention indicated | Ventriculostomy, ICP, monitoring, intraventricular thrombolysis, or operative intervention indicated | Life-threatening consequences; urgent intervention indicated | Death |
| **Headache** (definition: A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve.) | Mild Pain | Moderate pain, limiting instrumental ADL | Severe pain, limiting self care ADL | | |

# 9.0 SUPPORTIVE CARE

## 9.1.1 Supportive Care, General

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 7.0 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

## 9.1.2 Supportive Care, Guidelines for Non-CNS toxicities

- **Pneumonitis**:
  - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
  - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis**:
  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

  - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.

- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:

  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

**Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. **Table 7** below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

**Table 7** Infusion Reaction Treatment Guidelines

| NCI CTCAE Grade | Treatment | Premedication at subsequent dosing |
|---|---|---|
| Grade 1<br>Mild reaction; infusion interruption not indicated; intervention not indicated | Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. | None |
| Grade 2<br>Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs | **Stop Infusion and monitor symptoms.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids<br>Antihistamines<br>NSAIDS<br>Acetaminophen<br>Narcotics<br>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>If symptoms resolve within one hour of stopping drug infusion, | Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with:<br><br>Diphenhydramine 50 mg po (or equivalent dose of antihistamine).<br><br>Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic). |

| NCI CTCAE Grade | Treatment | Premedication at subsequent dosing |
|---|---|---|
| | the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.<br>**Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.** | |
| <u>Grades 3 or 4</u><br>Grade 3:<br>Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequellae (e.g., renal impairment, pulmonary infiltrates)<br>Grade 4:<br>Life-threatening; pressor or ventilatory support indicated | **Stop Infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids<br>Antihistamines<br>NSAIDS<br>Acetaminophen<br>Narcotics<br>Oxygen<br>Pressors<br>Corticosteroids<br>Epinephrine<br><br>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>Hospitalization may be indicated.<br>**Subject is permanently discontinued from further trial treatment administration.** | No subsequent dosing |
| Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. | | |

### 9.1.3 Supportive Care, Guidelines for CNS toxicities

- **Central Nervous System Necrosis**:
  - For **Grade 2 events**, treat with systemic steroids, pentoxyfilline and vitamin E. Consider starting with doses less than dexamethasone 6mg PO daily (2 mg TID), if clinically acceptable and indicated.
  - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, such as hyperbaric oxygen and/or surgical intervention.
  - When symptoms improve to Grade 1 or less, steroid taper should be started immediately, continued over no less than 4 weeks.
  - It may be that a patient may need low doses of steroids long term, in that case, the goal is to achieve the lowest tolerated steroid levels to manage the radiation necrosis.
- **Seizure**:
  - For **Grade 1-2** events, treat with oral anti-seizure medications. If clinically safe and acceptable, consider starting with levetiaceram 1000mg BID, or alternative.
  - For **Grade 3-4** events, treat with oral and/or IV anti corticosteroids with consideration for surgery, if clinically feasible.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Cognitive Impairment or Cognitive Disturbance**
  - For **Grade 2 events**, treat with systemic steroids. Consider starting with doses less than 6 mg PO dexamethasone (2 mg TID), if clinically acceptable and indicated. Memantine or other Alzheimer related medication can also be considered.
  - For **Grade 3-4 events**, immediately treat with intravenous steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

## 10.0DIET/ACTIVITY/OTHER CONSIDERATIONS

### 10.1.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

### 10.1.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence[†] from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)

- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. **If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.**

### 10.1.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 13.2.2.

### 10.1.4 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

### 10.2 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the sponsor-investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons

.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed extra-cranial radiographic disease progression
- Unacceptable adverse experiences as described in section 7, 8, and 9.
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed at least 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, or whichever occurs last;
  *Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment at the discretion of their treating physician, especially if their disease is clinically stable;*
- Administrative reasons
- Confirmed radiographic disease progression per RECIST criteria.
  a. *Note*: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 6.5

The End of Treatment and Follow-up visit procedures are listed in Section 12 (Protocol Flow Chart) and Section 13. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 13.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

#### 10.2.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects

who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation.

### 10.3 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug

In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

## 11.0DELIVERY OF RADIATION THERAPY TREATMENT

Definitive SRS will be administered for up to 1-10 lesions using stereotactic radiosurgery techniques starting on day 2-3. Treatment will be timed such that the first fraction of radiation will be delivered 24-48 hours after the first infusion of pembrolizumab. SRS will consist of 1-5 treatments, depending on dose level. For multiple fraction regimens, each treatment will be delivered > 40 hours apart, and should be completed by week 2, day 14.

### 11.1.2 Radiation Simulation and Diagnostic Procedures

1. All simulation and treatment procedures represent current institutional practice and will be the same for all study participants in each dose level

**CT Simulation**: A CT simulation will be performed for radiation therapy treatment planning purposes several days to the initiation of radiation therapy. This procedure consists of a CT scan performed in the treatment position. It is not for diagnostic purposes and is not itself therapeutic, but the CT image is required for radiation planning and delivery. This procedure is standard of care prior to therapeutic radiation. The CT simulation will occur with the patient supine position in a framed and/or frameless thermoplastic head mask at discretion of treating physician.

-CT simulation scan slice thickness may not exceed 1.25 mm

2. **Pre-treatment MRI of the brain**: A high resolution MRI with and without gadolinium contrast for treatment planning will be acquired within 2 weeks before treatment delivery. This planning MRI is standard of care for patients with intracranial metastases planned for SRS.

-Treatment planning MRI slice thickness may not exceed 3 mm.

### 11.1.3 SRS Based Radiation Therapy Options Criteria

1. Treatment shall be delivered with one of two approaches:
    a. Linear accelerated (LINAC) based stereotactic radiosurgery
    b. Gamma knife based stereotactic radiosurgery

### 11.1.4 LINAC, SRS Based Radiation Therapy, Required Criteria

1. Treatment shall be delivered with megavoltage machines of a minimum energy of 4 MV photons. Selection of the appropriate photon energy should be based on optimizing the radiation dose distribution within the target volume and minimizing dose to non-target normal tissue.

2. LINAC treatment should also include isocentric conical collimators, mini-multi-leaf (5 mm or less) technology or linear accelerators mounted on robotic arms.

3. Either a framed or frameless stereotactic, relocatable immobilization system will be used for treatment simulation and delivery. These systems may include modified stereotactic frames, camera-based localization systems, etc. The immobilization/ relocalization system should be capable of reproducing the patient setup to within 3 mm.

4. Single fraction radiosurgery treatment may be delivered with intensity modulated radiation surgery (IMRS) or dynamic conformal arcs (DCA). Multiple fraction radiation treatment can be delivered by intensity modulated radiation therapy (IMRT) or volume modulated arc therapy (VMAT).

5. Patients must be positioned for each treatment using 3-dimensional imaging i.e.
    **Cone Beam CT**. Cone beam CT scans with each radiation fraction on the treatment machine will be performed daily prior to SRS with the patient in the treatment position to assure accurate repositioning of the PTVs.

6. Radiation therapy will consist of 1-5 fractions. All radiation treatment fractions should be completed by end of week 2 of treatment

7. Multiple vertex and coplanar/noncoplanar beams should be used and arranged with the goal of excluding as much normal brain tissue as possible outside of the PTV at high and intermediate dose levels.

### 11.1.5 Gamma Knife, SRS Based Radiation Therapy, Required Criteria

1. Treatment shall be delivered with megavoltage machines of a minimum energy of 4 MV photons. Selection of the appropriate photon energy should be based on optimizing the radiation dose distribution within the target volume and minimizing dose to non-target normal tissue.

2. Single fraction radiosurgery treatment may be delivered with intensity modulated radiation surgery (IMRS) or dynamic conformal arcs (DCA). Multiple fraction radiation treatment can

be delivered by intensity modulated radiation therapy (IMRT) or volume modulated arc therapy (VMAT).

3. Patients must be positioned for each treatment using 3-dimensional imaging i.e. Cone Beam CT.

Cone beam CT scans with each radiation fraction on the treatment machine will be performed daily prior to SRS with the patient in the treatment position to assure accurate repositioning of the PTVs.

4. Radiation therapy will consist of 1-5 fractions. All radiation treatment fractions should be completed

before end of week 2 of treatment.

### 11.1.6 Target Volume Determination

1. The gross tumor volume (GTV) will be defined by as the MRI defined T1 post contrast enhancing brain metastasis. Surrounding areas of edema will not be considered part of the target volume
2. The clinical target volume (CTV) will be the GTV without margin in all directions

   -for resected brain metastases, an 1mm expansion should be utilized: $CTV_{resection\text{-}cavity} = GTV_{resection\text{-}cavity} + 1mm$ expansion.

3. The planning target volume (PTV) will be the CTV + 1.5 mm margins.

### 11.1.7 Total dose determination

All three arms will initially enroll patients, followed by a 3 month toxicity assessment for dose limiting toxicity (i.e. radionecrosis); If clinically significant necrosis (as defined in section 2.0) is noted, this arm will be stopped. However, enrollment on the other arms will continue.

### 11.1.8 Dose prescription and dosimetry requirements

1. Dose will be prescribed to the isodose line that encompasses the entirety of the PTV. Treatment planning and dose acceptance will be per institutional standard of care.
   A. If intensity modulated radiosurgery (IMRS) is utilized, standard prescription isodose is to 98% (range 95-100%, acceptable)
   B. If dynamic conformal arcs (DCA) are utilized, standard prescription isodose is to 80% (range 70-90%, acceptable).
   C. If gamma knife is used, standard prescription isodose is to 50% (range 40-60% acceptable)
2. Doses are specified such that at least 95% of the PTV shall receive 100% of the prescribed dose.
3. The marginal dose and the 100% dose (isocenter dose) may be recorded for each patient.

4. For quality control, representative isodose lines (e.g. 20%, 40%, 60%, 80%, 90%) may be generated for each patient.

Quality of PTV coverage will be categorized according to selected isodose line:

A. Total – selected isodose line completely encompasses the PTV

B. Marginal – selected isodose line incompletely encompasses the PTV, but not by more than 10% of the PTV volume.

C. Subtotal - selected isodose line incompletely encompasses the PTV, but by more than 10% of the PTV volume. This will not be accepted.

5. Conformality index requirements (ratio of prescription isodose volume to the target volume *(PI/TV)*)

1. Per protocol if between 1.0 and 2.0, acceptable
2. Acceptable variation if ≥ 0.9 but < 1.0 or >2.0 but ≤ 3.5.
3. Unacceptable deviation if > 3.5.

### 11.1.9 Dose Limitation to Critical Structures

1. In addition to the above defined GTVs, CTVs and PTVs, both eyes, the lenses of both eyes, the optic nerves, the optic chiasm, cochlea, the brainstem, and the spinal must be evaluated per standard of care approaches. Dose-volume histograms will be generated and whole organ dose and maximum point dose will be recorded for each critical structure. Dose limitations to normal structures are defined in **Table 9.**

2. If the patient has received no prior cranial irradiation, the maximal point doses permissible to the structures from the current radiation therapy plan are listed below.

3. Patient cannot have received whole brain radiation or SRS prior to being enrolled on this trial. However, once on the trial, patient can have received multiple SRS and or whole brain radiation as part of the standard of care treatments for progressive disease; If the patient has received previous brain radiation therapy (while on the trial), the previous dose received to critical structures should be obtained or a representative dose distribution file should be simulated. This dose should then be converted to BED (assuming an alpha-beta ratio of 3 for late effects) and added to the BED to the critical structures from the current treatment plan. This sum BED must meet the cumulative dose constraint below¶. <u>No adjustments for time between previous radiation treatment will be made for the purpose of this protocol.</u>

**Table 9 – Normal Tissue Constraints Based on the number of radiation fractions**

Normal Tissue Constraints, 5 Radiation Fractions

| Cumulative $BED_3$ | Volume | No Previous RT* | Previous RT¶ | Endpoint ( ≥ Grade 3 AE) |
|---|---|---|---|---|
| | | Maximum Dose (Gy) | Maximum Cumulative $BED_3$ | |
| Brainstem | Max, ≤ 0.03cc | 26 | 90 | Cranial Neuropathies |

| | | | | |
|---|---|---|---|---|
| Spinal Cord | Max, ≤ 0.03cc | 22.5 | 75 | Myelitis |
| Eye (Globe), each | Max, ≤ 0.03cc | 20 | 66 | Vision Loss |
| Lens, each | Max, ≤ 0.03cc | 5 | 12 | N/A* |
| Optic Nerve, each | Max, ≤ 0.03cc | 25 | 90 | Vision Loss |
| Optic Chiasm | Max, ≤ 0.03cc | 25 | 90 | Vision Loss |
| Cochlea | Max, ≤ 0.03cc | 27.5 | 90 | Hearing Loss |

Normal Tissue Constraints, 3 Radiation Fractions

| Cumulative $BED_3$ | Volume | No Previous RT* | Previous RT¶ | Endpoint ( ≥ Grade 3 AE) |
|---|---|---|---|---|
| | | Maximum Dose (Gy) | Maximum Cumulative $BED_3$ | |
| Brainstem | Max, ≤ 0.03cc | 18 | 90 | Cranial Neuropathies |
| Spinal Cord | Max, ≤ 0.03cc | 18 | 75 | Myelitis |
| Eye (Globe), each | Max, ≤ 0.03cc | 18 | 66 | Vision Loss |
| Lens, each | Max, ≤ 0.03cc | 4 | 12 | N/A* |
| Optic Nerve, each | Max, ≤ 0.03cc | 15 | 90 | Vision Loss |
| Optic Chiasm | Max, ≤ 0.03cc | 15 | 90 | Vision Loss |
| Cochlea | Max, ≤ 0.03cc | 20 | 90 | Hearing Loss |

Normal Tissue Constraints, 1 Radiation Fraction

| Cumulative $BED_3$ | Volume | No Previous RT* | Previous RT¶ | Endpoint ( ≥ Grade 3 AE) |
|---|---|---|---|---|
| | | Maximum Dose (Gy) | Maximum Cumulative $BED_3$ | |

| | | | | |
|---|---|---|---|---|
| Brainstem | Max, ≤ 0.03cc | 10 | 90 | Cranial Neuropathies |
| Spinal Cord | Max, ≤ 0.03cc | 18 | 75 | Myelitis |
| Eye (Globe), each | Max, ≤ 0.03cc | 16 | 66 | Vision Loss |
| Lens, each | Max, ≤ 0.03cc | 2.5 | 12 | N/A* |
| Optic Nerve, each | Max, ≤ 0.03cc | 8 | 90 | Vision Loss |
| Optic Chiasm | Max, ≤ 0.03cc | 8 | 90 | Vision Loss |
| Cochlea | Max, ≤ 0.03cc | 12 | 90 | Hearing Loss |

*Lens toxicity is cataract formation, which for the purposes of this trial is not a dose limiting toxicity.

### 11.1.10 Radiation Toxicity Evaluation

Patients should undergo evaluation for development of acute and chronic radiotherapy toxicity at the time of protocol visits. This should be at done 1 month after completing SRS (between weeks 4-6 post SRS, per standard of care) and then during follow-up visits and maintenance therapy every 3 months, or as otherwise indicated. Suspected radiosurgery-related toxicity should be graded using the CTCAE 4.0 adverse events grading system. If there is a suspicion of a novel or unexpected toxicity of grade 3 or higher severity that is suspected to be related to the combination of pembrolizumab and radiosurgery, the study coordinator should be immediately notified. If possible, a determination should be made whether the toxicity is likely to be the result of immune therapy, radiosurgery or was exacerbated by the combination. The AE or SAE should be attributed as definite, probable, possible, or unlikely for each.

### 11.1.11 Progression of CNS disease

If a patient has new CNS lesions on the 6 weeks follow-up MRI, patient can undergo repeat SRS to the new lesions and/or whole brain radiation treatments (and/or CSI-if leptomeningeal disease), at the discretion of the treating physician, and per routine standard of care. However, if there is any doubt, please contact the PI. The goal is to continue to manage the patient per routine standard of care to salvage the intra-cranial disease by either repeated SRS treatments to the new lesions and/or whole brain radiation treatments (Cranio-spinal XRT can be used if significant leptomeningeal disease is suspected). The patient would still continue with anti-PD-1 treatments until progression of extra-cranial disease, undue toxicity, and/or at least 2 year, at the discretion of the treating physician. Radiation treatments should be timed with the administration of the next cycle of PD-1 treatments, or as close as possible (whenever clinically possible/applicable);

# 12.0TRIAL FLOW CHART

## 12.1 Study Flow Chart (see next page)

| | Screening Phase | Treatment Phase | | | | | | | | | Post-Treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Procedure | Pre- Treatment (within 28 days of starting) | Cycle 1, Day 1 week 1 | Cycle 1, Day 2-3 | Cycle 1, Day 4--6 | Cycle 1, Day 6-15 | Cycle 2, Day 22 | Days 24-40 (Post SRS check) | Cycle 3, Day 43 | Cycle 4, Day 64 | q3WK cycles x 2yr, or until progression** | Follow Up (q12 wks for 1 years) |
| Pre-screening for eligible patient | X | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | | | | | |
| Demographics and Medical Histor | X | | | | | | | | | | |
| Prior and Concomitant Medicatior | X | | | | | | | | | | |
| Full Physical Examination | X | | | | | X | X | X | X | X | X |
| Review of Systems | X | | | | | X | X | X | X | X | X |
| Vital Signs | X | X | | | | X | X | X | X | X | X |
| Weight | X | X | | | | X | X | X | X | X | X |
| Karnofsky Performance Status (KPS) and ECOG | X | X | | | | X | X | X | X | X | X |
| HBcAb, HepC Ab | X | | | | | | | | | | |
| Brain MRI | X | | | | | | X (SOC-4-6 wk check) | | | | X |
| Diagnostic Imaging (CTN/ C/A/P and/or PET scan) | X | | | | | | | | X (Cycle 4-5) | | X |
| Adverse effects Assessment | X | | | | | X | X | X | X | X | X |
| Labs | | | | | | | | | | | |
| CBC with differential | X | X | | | | X | | X | X | X | X |
| CMP, LDH, ESR | X | X | | | | X | | X | X | X | X |
| T3, FT4, TSH | X | X | | | | | | | | | X |
| Pregnancy Test - urine or seru | X | | | | | | | | | | |
| Urinanalysis | X | | | | | | | | | | |
| uric acid, mg, phos, Coags (PTT,a | X | | | | | | | | | | |
| Correlative Biomarkers | | | | | | | | | | | |
| Blood/Serum markers | X | X (pre-PD1) | X (Post PD1 or Pre-SRS) | x (post-SRS) | X (post SRS) | x (pre- PD-1) | | X (Pre-PD-1) | X (Pre-PD1) | X * | X at 3, 6,& 12 mo |
| Skin Biopsy site (if needed) | X | | | | | | | | | | |
| | | | | | | | | | | | |
| *Treatment* | | | | | | | | | | | |
| Pembrolizumab 200 mg IV | | X | | | | X | | X | X | x | |
| Stereotactic Radiosurgery, first fraction | | | X | | | | | | | | |
| Stereotactic Radiosurgery, fractions 2-5 (if applicable) | | | | X | x | | | | | | |
| Survival Analysis | | | | | | | | | | | |
| Grade 3 CNS | | | | | | | | | X | X (every 3 mo) | X (3,6,12 mo) |

** Pembrolizumab 200 mg IV q3wk should be given for at least 2 yr and/or until progression.
* Only collect additional samples beyond section 12.2, at the discretion of Dr. Khan

### 12.2 Blood and Srum Biomarker Correlates

We plan to monitor the immune responses of the patients enrolled in this clinical trial, by collecting peripheral blood before treatment and during treatment, as outlined above under "serum biomarkers".

When possible, blood collection will be synchronized to pembrolizumab infusion cycles (C). Blood will be collected at 14 days prior to enrollment (baseline sample), C1D1 (2nd baseline sample, pre PD-1 infusion), C1D2-3 (post PD1 or pre first fraction of SRS), C1D4-6 (Post second fraction of SRS), C1D6-15(Post SRS completion), C2D1 (Pre-PD1), C3D1 (Pre- PD1), C4D1 (Pre-PD1) and at restaging at 3 and 6 months after SRS;

A final peripheral blood collection will be obtained at 12 months follow up, which will be one year after patient completed their two year treatment plan or discontinued treatment due to disease progression.

Samples will be drawn into three 8 ml CPT tubes for PBMC and plasma isolation, and one 4.5 ml K3EDTA tube, for whole blood analysis. Only one 8 ml CPT tube of blood will be collected at C1D2-3 (Post PD1 or pre first fraction of SRS). Tubes will be labeled and logged at Emory's Winship Cancer Institute by a skilled clinical research nurse or phlebotomist. They will be maintained at room temperature until transport to Dr. Ahmed's laboratory. Samples distributed to the Ahmed laboratory will only be identifiable by an assigned donor number, study identifier and a draw date. Samples will be transported in sealed biohazard containers between sites per standard protocol. Whole blood and/or PBMC will be used fresh or will be frozen and banked for future batch analyses. Plasma will be frozen at -80C. Frozen PBMC samples will be stored in liquid nitrogen at the Emory Vaccine center. All assays will be performed as per Ahmed lab standard of practice. Briefly, frequency and absolute cell counts will be determined for the major lymphocyte populations (CD3, CD4, CD8, CD19) and monocytes (CD14) through the use of BD TruCount tubes. Detailed phenotypic analysis will be performed through whole blood staining with the following markers; CD3, CD4, CD8, Foxp3, CD45RA, CCR7, CD28, CD27, CD127, PD-1, Ki-67, Bcl-2, HLA-DR, CD38, ICOS, CD137, Tbet, eomes, Granzyme B, Perforin, CTLA-4, Tim-3, CD14, CD16, CD11c, CD123, PD-L1, CD86. HLA-A2 positive patients will be monitored for the presence and activation of MART-1 and NY-ESO-1-specific CD8 T cells. Additional phenotypic, genomic and/or proteomic analysis may be performed on banked PBMC samples. Besides flow cytometry phenotypic analysis, sample collected at early time points after irradiation, will be used for transcriptional profiling[36.] Frozen plasma will be used for monitoring cytokine expression and/or possibly other translational analysis (i.e., isolation of exosomes for proteomics and genomics analysis).

When possible, fresh tumor tissue will be collected from biopsy or surgical procedure. Depending on material availability samples will be analyzed by flow cytometry or florescence microscopy with some of the markers listed above.

# 13.0 TRIAL PROCEDURES

## 13.1 Trial Procedures

The Trial Flow Chart – Section 12.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points, if deemed clinically necessary by the investigator, and within standard of care.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

### 13.1.1 Administrative Procedures

#### 13.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

#### 13.1.1.2 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

#### 13.1.1.3 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

#### 13.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

#### 13.1.1.5 Prior and Concomitant Medications Review

##### 13.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 14 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

##### 13.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 13.2.

#### 13.1.1.6 Disease Details and Treatments

##### 13.1.1.6.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status. This includes RTOG RPA class and GPA class, as outlined in APPENDIX II and III.

##### 13.1.1.6.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

##### 13.1.1.6.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

#### 13.1.1.7 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see APPENDIX I). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab, all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs).

Please refer to section 13.2 for detailed information regarding the assessment and recording of AEs.

#### 13.1.1.8 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

#### 13.1.1.9 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

#### 13.1.1.10 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 12.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

#### 13.1.1.11 Karnofsky Performance Status Scale and ECOG Performance Scale

The investigator or qualified designee will assess ECOG and KPS status at screening. ECOG status will be assessed prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart. After the intial assessment, ECOG alone during subsequent follow-up will be the minimum that is required on the trial.

### 13.1.1.12 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5. Peripheral blood for serum biomarker analysis will also be obtained, as defined in section 12.0 at the appropriate time intervals.

**Table 5: Laboratory Tests**

| Hematology | Chemistry | Urinalysis | Other |
|---|---|---|---|
| Hematocrit | Albumin | Blood | Serum β-human chorionic gonadotropin† |
| Hemoglobin | Alkaline phosphatase | Glucose | (β-hCG)† |
| Platelet count | Alanine aminotransferase (ALT) | Protein | PT (INR) |
| WBC (total and differential) | Aspartate aminotransferase (AST) | Specific gravity | aPTT |
| Red Blood Cell Count | Lactate dehydrogenase (LDH) | Microscopic exam *(If abnormal)* | Total thriiodothyronine (T3) |
| Absolute Neutrophil Count | Carbon Dioxide ‡ | results are noted | Free thyroxine (T4) |
| Absolute Lymphocyte Count | *($CO_2$ or bicarbonate)* | Urine pregnancy test † | Thyroid stimulating hormone (TSH) |
| | Uric Acid | | PK |
| | Calcium | | |
| | Chloride | | **Blood for correlative studies** |
| | Glucose | | • **see biomarkers section 12.1**<br>• **The additional blood that is collected will be sent to Dr Rafi Ahmed's lab for this analysis** |
| | Phosphorus | | |
| | Potassium | | |
| | Sodium | | |
| | Magnesium | | |
| | Total Bilirubin | | |
| | Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)* | | |
| | Total protein | | |
| | Blood Urea Nitrogen | | |

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
‡ If considered standard of care in your region.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

#### 13.1.1.13Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.0 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete at least 24 months of treatment with pembrolizumab may stop taking the drug and discontinue the trial, at the discretion of the treating physician. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit and then proceed to the Follow-Up Period of the study.

#### 13.1.1.14Blinding/Unblinding

Not Applicable, as this is an open pilot study.

### 13.1.2 Visit Requirements

Visit requirements are outlined in Section 12.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 13.0 - Trial Procedures.

#### 13.1.2.1 Screening

#### 13.1.2.1.1 Screening Period

The screening period will be 28 days from enrollment. During this period, inclusion and exclusion criteria, and other information listed in section 12.0 and 13.0 should be conducted. A planning MRI, as detailed in the radiation section 11.0, should also be obtained during the screening period, as part of our institutional standard of care.

#### 13.1.2.2 Enrollment and Treatment Period

Enrollment period to accrue all 30 patients will be over two years, with the goal to enroll at least 18 patients, as outlined in section 2.0.

Treatment period will last from cycle 1, day 1 until disease progression and/or at least 12 months of pembrolizumab being delivered q3wks. Pembrolizumab 200 mg IV q3 weeks +/- 7 days will be given for at least 2 years as described above or until disease progression. Safety evaluations should be conducted during the first day of each cycle, as detailed in the flow sheet 12.0. All AEs that occurred leading up to these treatment visits should be recorded. Post-

Treatment Visits and all subsequent imaging and tumor assessments will be per standard of care. All required blood and imaging will be per standard of care, except for the biomarker analysis, as outlined in section 12.0.

#### 13.1.3.2.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 6.5) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

#### 13.1.2.3 Follow-up Visits

Subjects who complete treatment after 2 years or discontinue trial treatment for a reason other than disease progression should be assessed every 12 weeks (84 ± 14 days) or at physicians discretions by radiologic imaging to monitor disease. Subjects who show disease progression after the initial week 12 scan must have another assessment 4-6 weeks later by radiologic imaging to confirm evidence of disease progression. If disease progression is evident, treatment should be discontinued and subject should be assessed every 12 weeks (84 ± 14 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 6.5. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 6.5 will move from the follow-up phase to the Second Course Phase when they experience disease progression. Details are provided in Section 13.1.3.4 for Retreatment.

#### 13.1.2.4 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab with SD or better may be eligible for up to one year of additional pembrolizumab therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- **Either**
    - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1, and

- Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
- Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

**OR**

- Had SD, PR or CR and stopped pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability

**AND**

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to one additional year.

Visit requirements are outlined in Section 12.0 – Trial Flow Chart.

#### 13.1.2.4.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

## 13.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject associated with the use of a test article and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product or SRS, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product or SRS in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported to Merck and the PI by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be documented by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section

13.1.3.2 and 13.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

### 13.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose, for a 100 kg patient). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

### 13.2.2 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Merck product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

### 13.2.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck

#### 13.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of a drug product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event

- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
    - Is a new cancer (that is not a condition of the study);
    - Is associated with an overdose.

Refer to Table 6 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study, whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck Global Safety.

All subjects with serious adverse events must be followed up for outcome.

**SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220**

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

### 13.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 13.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

#### 13.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 13.2.3.- Immediate Reporting of Adverse Events to the Sponsor and to Merck, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety as a SAE within 2 working days of determination that the event is not progression of the cancer under study

Hospitalization related to convenience (e.g.transportation issues etc.) will not be considered a SAE.

### 13.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.
All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 6 Evaluating Adverse Events

Known acute side effects for SRS include: Alopecia within the portal sites, fatigue, headache, nausea, vomiting, worsening baseline neurological deficits due to increased edema or radionecrosis, seizure, skin irritation or redness; Late side effects include radiation necrosis, secondary cancer, seizure, worsening neurological deficit due to edema, death, hair loss within the portal fields.

An investigator who is a qualified physician, will evaluate all adverse events as to:

| | | |
|---|---|---|
| **V4.0 CTCAE Grading** | **Grade 1** | **Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.** |
| | **Grade 2** | **Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.** |
| | **Grade 3** | **Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.** |
| | **Grade 4** | **Life threatening consequences; urgent intervention indicated.** |
| | **Grade 5** | **Death related to AE** |
| **Seriousness** | A serious adverse event is any adverse event occurring at any dose or during any use of investigational product that: | |
| | †**Results in death**; or | |
| | †**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or | |
| | †**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or | |
| | †**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or | |
| | †**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or | |

| | | |
|---|---|---|
| | **Is a** new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or** | |
| | **Is an overdose** (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days.. | |
| | **Other important medical events** that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †). | |
| **Duration** | Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units | |
| **Action taken** | Did the adverse event cause Merck product to be discontinued? | |
| **Relationship to Merck Product** | Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information.<br><br>**The following components are to be used to assess the relationship between Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE): | |
| | **Exposure** | Is there evidence that the subject was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen? |
| | **Time Course** | Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)? |
| | **Likely Cause** | Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors |

### 13.2.5 Sponsor Responsibility for Reporting Adverse Events

Written IND safety reports will be submitted to the FDA by the IND sponsor, for serious, unexpected suspected adverse reactions within 15 calendar days of learning of its occurrence. If the event is fatal or is deemed to be life threatening, the report will be made within 7 calendar days. The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

## 14.0STATISTICAL ANALYSIS PLAN

### 14.1 Statistical Analysis Plan Summary

### 14.1.1 Study Design

The study is a pilot study to look at the safety of concurrent PD-1 inhibitor and SRS for melanoma brain metastases. An initial cohort of 6 patients will be enrolled on each radiation dose levels starting with radiation Arm A (6 Gy x 5), radiation Arm B (9 Gy x 3), and then radiation Arm C (21 Gy x 1 or 18 Gy x 1 based on tumor volume); Once 6 patients are enrolled on any given dose level, the dose limiting toxicity (DLT) interval is defined as RTOG grade 3 CNS toxicity at 3 months after first pembrolizumab dose (i.e. Day 1, cycle 1). This interval is based upon inclusion of the known median times to onset of (1) common adverse effects attributed to pembrolizumab, and of (2) unusual radiation related adverse effects beginning as early as 3 months post SRS, and (3) typical timeline used in other similar trials.

The first 18 patients (6 per dose level) will be enrolled in sequence as follows:
Arm A: patient #1-6, Arm B: patient #7-12, Arm C: patient # 13-18;

If ≤ 2/6 patients develop a DLT on a given radiation arm during, accrual on the particular dose arm will continue for another 6 patients on a given dose arm for a total of 12 patients per dose arm. RTOG 90-05 used a 20% cutoff at 3 months as the DLT endpoint. We accept 2/6 (33%) based on a biological rationale that if there is slight increase in radiation toxicity, this may be offset by increased systemic responses through immune modulation of radiation when radiation is combined with PD-1 (see section 4.0 for biological rationale);

If ≥3/6 patients develop a DLT on a given radiation dose arm, this arm will stop accrual and considered unsafe;

There will be a 3 month interim waiting period after 6 patients are enrolled on a given radiation arm and analyzed for any undue early dose limiting toxicity (DLT); The DLT toxicity definition is similar to that defined in the RTOG 90-05 (i.e, CNS grade 3 or more acute toxicity, which is considered irreversible severe neurological symptoms at 3 months requiring medications); The time point of 3 months is typical of when all post SRS acute side effects are expected to resolve. Thus, having acute side effects at 3 months would be unusual.

The second 18 patients (6 per dose level) will be enrolled in a similar sequence as follows, with arms containing 3 or more DLTs within the first 6 patients omitted from expansion:

Arm A: Closed, Arm B: patient #25-30, Arm C: patient #31-36;

### 14.1.2 Acute Toxicity, Expansion Cohorts, and Late Toxicity Assessment:

Once 6 patients are enrolled on any given dose level, there will be a waiting period of 3 months (i.e, at time of second post SRS MRI assessment after pembrolizumab dose (i.e, 3 months after Day 1, cycle 1); This time point of 3 months and the dose limiting toxicity (i.e. grade 3 RTOG CNS toxicity) is based on similar timeline used on earlier trial to determine the safest radiation dose. Late toxicity (radionecrosis noted on MRI images will also be analyzed at 6 months and at 1 year, but will not be used to stop enrollment on any given dose arm);

During this 3 month waiting period, the MRI images and the patients will be assessed for any signs or symptoms of RTOG CNS toxicity as well as early manifestations of radionecrosis. ≥Grade 3 CNS toxicity is the only DLT toxicity of principal concern, since the currently used radiation doses are based on this primary endpoint. Patient can still be accrued on other dose arms during this waiting period, while data is being analyzed for safety concerns on a given radiation arm.

Late toxicity (i.e, toxicity starting after 3 months) will also be analyzed. The principal late toxicity of interest is symptomatic radiation necrosis. This is defined as radiographic (typically on MRI) changes consistent with radiation induced necrosis, and the patient also presenting with increased neurological symptoms. Symptomatic radiation necrosis will be recorded at 6 months at at 12 months follow-up;

The radiation dose arm which meets the lowest acute and late toxicity endpoints, but also potentially provided a higher overall systemic response rate, will be considered the best radiation dose level that can be combined with pembrolizumab. Our published series of melanoma patients undergoing SRS alone had an average survival of 38.5% at 1 yr (Patel KR et al, American J. Clinic. Oncology. 2015, May 16. Epub); Our recent multi-institutional review in collaboration with Duke University suggested 1 yr overall survival of 78% for patients undergoing SRS and PD1 in combination (not published, accepted for annual presentation at American Society of Radiation Oncology Meeting, 2016). Thus, we suspect an improvement of 40% in OS compared with SRS alone. With 12 patients on the most immunogenic arm (9Gy x 3), we would be expected to have lowest acute and late toxicity as well as potentially the highest OS benefit and would likely be the arm for a future trial.

With 12 patients per group, a 2-year accrual time with an additional 1 year of follow-up (3 total years), we have 72% power to detect a difference in survival of 40% (78% vs. 38%) at 1 year.

## 14.2 Study Design for Expansion Cohort Phase

After the initial pilot phase with 6 patients per radiation dose arm, patients will then be enrolled into the expansion cohort (6 more patients) and treated assuming toxicity is acceptable during the initial enrollment period of the first 6 patients on each arm. This would bring the total

patients up to 12 per radiation dose arm: (Arm A: 6 patients total, Arm B: 12 patients, Arm C: 12 patients), for a total of 30 patients for all 3 different radiation dose arms.

The total number of patients enrolled in the entire trial will thus depend on the RTOG grade 3 CNS acute toxicity seen on each of the dose arms. If no DLT are identified, then the minimum number of patients in the expansion cohort will be 30; if each cohort has a DLT, then the maximum number of patients enrolled in the dose escalation phase is 12 (6 patients X 2 different radiation dose arms). Therefore, the range of patients to be enrolled in this study is expected to be 18-30. The expansion of arm A is stopped. Arm B and C will continue to enroll, as is currently designed.

## 14.3 Statistical Analyses

### 14.3.1 Safety

Proportion of acute and late toxicity for each arm out of 12 (or 6 if no expansion) will be reported, and 95% confidence intervals will be estimated using the Clopper-Pearson method.

### 14.3.2 Response

Both overall response and response at un-irradiated sites will be determined at week 12, 3 months after completing the first cycle of pembrolizumab and SRS (i.e C1D2-3). Responses will be determined by the RECIST and immune RECIST criteria, as described in APPENDIX II and III. Response will also be assessed at 1 year from C1D2-3. Response rates will be reported along with 95% confidence intervals will be estimated using the Clopper-Pearson method.

### 14.3.3 Overall Survival

For overall survival, death from any cause will be defined as the event. Patients will be censored at time of last follow-up. OS will be estimated using the Kaplan-Meier product-limit method.

### 14.3.4 Intracranial Outcomes

Local control (LC), anywhere intra-cranial failure (also called distant brain failure, DBR), leptomeningeal disease (LMD), radionecrosis (RN) and symptomatic (SRN) – will be estimated using cumulative incidence methodology, with death considered a competing risk. Rates for these outcomes will be censored at the time of salvage whole brain radiation and/or last follow-up.

#### 14.3.5 Biological variables

**Descriptive statistics for the frequency and absolute cell counts for the major lymphocyte populations (CD3, CD4, CD8, CD19) T cells and monocytes (CD14) along with other markers listed above will be estimated.**

## 15.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

### 15.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.
Clinical Supplies will be provided by Merck as summarized in Table 7.

Table 7 Product Descriptions

| Product Name & Potency | Dosage Form |
|---|---|
| Pembrolizumab 50 mg | Lyophilized Powder for Injection |
| Pembrolizumab 100 mg/ 4mL | Solution for Injection |

### 15.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

### 15.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

### 15.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.
Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.
Clinical supplies may not be used for any purpose other than that stated in the protocol.

### 15.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.
Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

## 16.0 DATA AND SAFETY MONITORING PLAN

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

16.1. **Data Collection:**

Data that will be captured in OnCore for the following procedures

- Inclusion/Exclusion Criteria
- Demographics and Medical History
- Vital Signs
- Weight
- Karnofsky Performance Status (KPS) & ECOG
- HBcAb, HepC Ab
- Brain MRI [RECIST]
- Diagnostic Imaging [RECIST]
- Adverse Events Assessment
- CBC with differential
- CMP, LDH, ESR
- T3, FT4, TSH
- Pregnancy Test – urine or serum b-HCG
- Urinalysis
- Uric Acid, MG, Phos, Coags (PTT, PT, INR) - [seconds]
- Serum Biomarkers
- Skin Biopsy (if needed)
- Stereotactic Radiosurgery
- Survival Analysis
- Grade 3 CNS

## 17.0 APPENDICES

## APPENDIX I

### CTCAE (Common Terminology Criteria for Adverse Events), version 4.03

The exact full criteria for toxicity assessment can be obtained at the NCI CTEP website at the following link:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

## APPENDIX II

### Tumor assessment via RECIST Criteria, Guideline Version 1.1

Eisenhauer, E.A., Therasse, P., Bogaerts, J., et al. New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (version 1.1). Europ J Cancer. 2009. 45; 228-247.

http://imaging.cancer.gov/clinicaltrials/imaging

## APPENDIX III

Tumor Assessment per Immune-Related Response Criteria

Immune-related Response Criteria (irRC) are derived from modified World Health Organization (mWHO) conventions. Assessments of lymph nodes are derived from current RECIST guidelines.

### a.) Definitions of Measurable/non-Measurable Lesions

All measurable and non-measurable lesions should be assessed at the initial Screening/enrollment, at the defined tumor assessment time points (see Time and Events Schedule), and during regular maintenance. Additional assessments may be performed, as clinically indicated for suspicion of progression. The Investigator will base response to treatment using the irRC.

#### i.) Measurable Disease

Measurable non-lymph node disease is defined as lesions that can be accurately measured in 2 perpendicular Diameters. Size criteria is defined based on the properties of the CT scan

-Spiral CT, 0.5cm thickness slice: both diameters must be at least $\geq$ 1.0cm

-For > 0.5cm thickness slices: larger diameter >2.0cm; the other > 1.0cm

Lymph nodes are measurable only if CT slice thickness is <0.5cm. Size criteria are that the lymph node be at least 15 mm in short axis.

#### ii.) Non-Measurable Lesions

Non-measurable (evaluable) lesions are all other lesions, including one-dimensional measurable disease and small lesions (not meeting the above criteria), and any of the following:

-lesions occurring in a previously irradiated, extracranial area (unless they are documented as new lesions since the completion of radiation therapy),

bone lesions,

-leptomeningeal disease,

-ascites,

-effusion (pleural or pericardial)

-cystic lesions

-abdominal masses not histological confirmed

Lymph nodes with a short axis < 10 mm are considered not pathological, and are not measurable.

**b.) Definitions of Index/non-Index Lesions**

**i.) Index Lesions**

Measurable lesions, up to a maximum of 5 lesions per organ and ten lesions in total, must be identified as index lesions to be measured at Screening. The index lesions should be representative of all involved organs. In addition, index lesions must be selected based on their size (e.g., lesions with the longest diameters), their suitability for accurate repeat assessment by imaging techniques, and how representative they are of the subject's tumor burden. At Screening, a Sum of the Product Diameters (SPD) for all index lesions will be calculated and considered the baseline SPD. The baseline sum will be used as the reference point to determine the objective tumor response of the index lesions at tumor

assessment.

**ii.) Non Index Lesions**

Measurable lesions, other than index lesions, and all sites of non-measurable disease, will be identified as non-index lesions. Non-index lesions will be evaluated at the same assessment time points as the index lesions. *After the initial assessment, changes in non-index lesions will contribute only in the assessment of complete response.*

**c.) Calculation of Sum of Product of Diameters (SPD)**

Sum of Product of Diameters is an estimate of tumor burden. The 2 greatest perpendicular diameters are used to estimate the size of each tumor lesion. The SPD is calculated as the sum of the product of the diameters for index tumor lesions. Several variations of the SPD are identified for the purpose of classification of tumor responses.

**i.) SPD at Baseline**

The sum of the product of the diameters for all index lesions identified at baseline prior to treatment on Day 1.

**ii.) SPD at tumor assessment**

For every on-study tumor assessment collected per protocol or as clinically indicated, the SPD at tumor assessment will be calculated using tumor imaging scans. All index lesions and all new measurable lesions that have emerged after baseline will contribute to the SPD at tumor assessment (irSPD).

**iii.) SPD at NADIR**

For tumors that are assessed more than 1 time after baseline, the lowest value of the SPD (SPD Baseline or SPD at tumor assessment) is used to classify subsequent tumor assessments for each subject. The SPD at tumor assessment using the irRC for progressive disease incorporates the contribution of new measurable lesions. Each net percentage change in tumor burden per assessment using irRC accounts for the size and growth kinetics of both old and new lesions as they appear. In this study the irRC as defined by the Investigator will serve as the basis of key endpoints for efficacy analyses and guide clinical care.

## APPENDIX IV

### KARNOFSKY PERFORMANCE SCALE

100 Normal; no complaints; no evidence of disease
90 Able to carry on normal activity; minor signs or symptoms of disease
80 Normal activity with effort; some sign or symptoms of disease
70 Cares for self; unable to carry on normal activity or do active work
60 Requires occasional assistance, but is able to care for most personal needs
50 Requires considerable assistance and frequent medical care
40 Disabled; requires special care and assistance
30 Severely disabled; hospitalization is indicated, although death not imminent
20 Very sick; hospitalization necessary; active support treatment is necessary
10 Moribund; fatal processes progressing rapidly
0 Dead

### ECOG Performance Status

| Grade | Description |
|---|---|
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead. |

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

## APPENDIX V

### RTOG RPA Classification System for Brain Metastasis

| | |
|---|---|
| *RPA Class I* | All of the following criteria: |
| | KPS ≥ 70% |
| | Age < 65 years |
| | Absence of extracranial metastases |
| | Controlled primary cancer |
| *RPA Class II* | KPS ≥ 70% **and** |
| | One or more of the following criteria: |
| | Age > 65 years |
| | Presence of extracranial metastases |
| | Uncontrolled primary cancer |
| *RPA Class III* | KPS < 70% |

## APPENDIX VI

### Graded Prognostic Assessment (GPA) for Brain Metastasis

| | 0 points | 0.5 points | 1 point | 2 points |
|---|---|---|---|---|
| **NSCLC** | | | | |
| Age | >60 | 50-59 | <50 | - |
| KPS | <70 | 70-80 | 90-100 | - |
| Number of Cranial Mets | > 3 | 2-3 | 1 | - |
| Extra-Cranial Mets | Present | - | Absent | - |
| **Melanoma** | | | | |
| KPS | <70 | - | 70-80 | 90-100 |
| Number of Cranial Mets | > 3 | - | 2-3 | 1 |

### Median Survival Based on GPA

**Median Overall Survival (Months)**

| **GPA score** | **NSCLC** | **Melanoma** |
|---|---|---|
| **0-1** | 3 | 3.4 |
| **1.5-2.5** | 6.5 | 4.7 |
| **3** | 11.3 | 8.8 |
| **3.5-4.0** | 14.8 | 13.2 |
| **Overall** | 7 | 6.7 |

## APPENDIX VII

### Eligibility Checklist

1. _____ Willing and able to provide consent;
2. _____ ≥ 18 yrs old on day of consent;
3. _____ Pathological proven diagnosis of one of the following:
   non-small cell lung cancer or melanoma. (biopsy per SOC, if needed)
   Ocular melanoma, mucosal melanoma, and unknown melanoma are eligible;
4. _____ Patients can be treated either in first line or in the refractory setting, as long as they can get PD-1 as standard of care; PD-L1 positivity is not required for enrollment;

5. _____ 1-10 intact brain metastasis (having had surgery to one lesion is not an exclusion criteria).

6. _____ Largest lesion ≤ 14.15$cm^3$

7. _____ Prior whole brain radiation therapy or SRS is allowed
   *Previous history of radiation to the primary tumor site is eligible;

8. _____ Having gotten prior PD1 therapy is allowed for, especially if they have previously progressed on it. Progression may include extra-cranial as well as intra-cranial progression. After progressing on PD1 therapy, intervening chemotherapy and/or targeted therapy (BRAFi, etc) is allowed. If they are on intervening chemotherapy and/or targeted therapy (BRAFi, etc), they have to have progression intra-cranially and/or extra-cranially and must be off intervening therapy for at least 2 weeks.

9. _____ Patient asymptomatic at time of SRS (day 0). Use of 10 mg prednisone equivalent at time of start of treatment is permitted as long at the dose has been less than or equal to 10mg for at least 7 days prior to treatment start.

10. _____ MRI of brain within 28 +/- 2 weeks days of enrollment showing evidence of BM

11. _____ Baseline pre-enrollment CT chest/abdomen/pelvis and/or PET/CT.
    * Baseline MRI images of chest/abdomen/pelvis can substitute
    * Baseline bone scan can also be substituted;
    (all imaging must be completed within 28 +/- 2 weeks days of enrollment)

12. _____ Photographs of any skin metastases are encouraged, but not required.

13. _____ Baseline labs (CBC, CMP, LDH, ESR, etc); collected within 14 days of enrollment

14. _____ Measurable disease based on RECIST 1.1;

15. _____ ECOG performance status 0-1 and Karnofsky Performance Status ≥ 70% on initial visit; Subsequent visits need to only document ECOG PS;

16. _____ No concurrent chemotherapy (no chemotherapy starting 14 days before start of radiation to 14 days after completion of radiation).

17. _____ Adequate organ function as defined in Table 4;

18. _____ Negative serum pregnancy test within 2 weeks of enrollment

19. _____ No active or chronic infection with TB, HIV, Hepatitis B or C

20. _____ No history of or active history of autoimmune disease.

21. _____ Can-not have a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment

22. _____ No history of active clinical diverticulitis

23. _____ No Brain metastases within the brain stem;

24. _____ All melanoma patients may be tested for BRAF as part of routine standard of care, but not required on the trial; All NSCLC patients may be tested for with EGFR and ALK as part of standard of care, but not required on the trial.

25. _____ No known history of (non-infectious) pneumonitis that required steroids (less than or equal to 10 mg prednisone equivalent at time of start is ok) or current pneumonitis.

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