Proprietary Information of MD Anderson

PROTOCOL

TITLE: A Phase II Study of Open Label Low Dose Ipilimumab in Combination with Pembrolizumab in Metastatic Melanoma Patients with Brain Metastases

STUDY NUMBER: MDACC: 2018-0875

Merck: 56967

VERSION NUMBER: 1.7

PROTOCOL DATE: 23 June 2023

TEST PRODUCTS: Ipilimumab

Pembrolizumab

INVESTIGATOR: **Isabella C. Glitza Oliva, MD, PhD**

Assistant Professor

Melanoma Medical Oncology

1515 Holcombe Boulevard

Houston, Texas 77030
Telephone: (713) 792-6111
Fax: (713) 745-1046
E-mail: ICGlitza@mdanderson.org

SUPPORT PROVIDED BY: Merck

CONFIDENTIAL

This is a University of Texas MD Anderson Cancer Center document that contains confidential information. It is intended solely for the recipient clinical investigator(s) and must not be disclosed to any other party. This material may be used only for evaluating or conducting clinical investigations; any other proposed use requires written consent from University of Texas MD Anderson Cancer Center.

Protocol Amendments

Protocol Version and Date	Amendment Number	Approval Date
Version 1.2 – 27 DEC 2018	1.2	
Version 1.3 –26 APR 2019	1.3	
Version 1.4 –26 APR 2019	1.4	
Version 1.5 –29 AUG 2020	1.5	
Version 1.6-12 APR 2021	1.6	
Version 1/7 – 23 JUN 2023	1/7	

Table of Contents

Proprietary Information of MD Anderson

List of Tables

Appendices

Proprietary Information of MD Anderson

1 BACKGROUND & RATIONALE

1.1 BACKGROUND

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on Ipilimumab and Pembrolizumab.

1.1.1 Disease Background

Cutaneous malignant melanoma is the most aggressive form of skin cancer, accounting for the large majority of skin cancer-related deaths. The global incidence continues to rise, with current estimates of 132,000 new diagnoses/year and 37,000 deaths [1]. Melanoma accounts for ~5% of all new cases of cancer in the United States (US). The incidence of melanoma continues to rise by almost 3% per year in the US, with 2014 estimates of 76,100 new diagnoses and 9,710 deaths. According to NCI Surveillance Epidemiology and End Results (SEER) data from 1975-2007, the five-year survival rate is 15% for late-stage disease [2]. The lifetime risk of developing invasive melanoma has been dramatically increasing, and the overall mortality from melanoma continues to rise [3], [4], [5].

Brain metastasis develops in ~50% of subjects with metastatic melanoma; in 10 - 40% of these subjects, the brain is the first site of relapse. Progressive disease in the brain is the major cause of tumor-related death in subjects with melanoma who develop metastases in this site [6]. The median survival is 4 months after diagnosis [7]. The limited activity of available agents, along with relative resistance to radiotherapy and poor central nervous system (CNS) penetration of most chemotherapeutic agents, make this one of the most daunting problems in oncology [8].

There is no optimal systemic or local therapy for melanoma metastatic to the brain. Therapy for small, single lesions or a limited number of metastases consists of surgery or stereotactic radiotherapy (SRT), with a moderate local control rate but a high incidence of new lesions that are neither prevented by nor responsive to whole brain radiation. Temozolomide, a drug with very high CNS penetration, has been studied in this setting but has a response rate of <10% in both the CNS and overall, so it contributes little benefit and has no apparent synergy with radiotherapy [6], [9], [10], [11]. Combining any of these approaches with whole brain irradiation has been of little value in the management of these subjects [12]. While antibodies are not believed to cross an intact blood-brain barrier, activated T-cells may be able to penetrate the blood brain barrier, providing a rationale for testing immunomodulatory therapies in this setting [13], [14]. Previously reported results from the Phase 2 study (CA184042) of ipilimumab monotherapy showed similar clinical benefit in the brain and systemically, with durable disease control of 24% (CNS) and 27% (extra-cranial) of these patients, providing a rationale for further study of promising immunotherapies in melanoma patients with brain metastases [15].

Similarly, ipilimumab combined with fotemustine was associated with a disease control rate (complete response [CR] + partial response [PR] + stable disease [SD]) of 50% (10/20) in patients with asymptomatic brain metastases in a Phase 2 trial (NIBIT-M1) [16]. In a Phase 1 dose escalation study (CA209004), the combination of nivolumab and ipilimumab was studied in subjects with unresectable or metastatic melanoma. An objective response rate of 53% was observed when patients were treated with the combination regimen (ipilimumab 3 mg/kg + nivolumab 1 mg/kg every 3 weeks x 4); an additional benefit of prolonged stable disease or minor response occurred in another ~20% of patients [17]. Since brain metastases in melanoma are the most frequent cause of death from this disease and the brain is a frequent site of failure even in subjects who achieve control of extra-cranial disease with systemic therapy, it is essential to discover whether the combination of ipilimumab plus pembrolizumab can provide similar promise to patients whose melanoma has metastasized to the brain.

Proprietary Information of MD Anderson

1.1.2 Pharmaceutical and Therapeutic Background

1.1.2.1 Ipilimumab

Ipilimumab (Yervoy®) is an immunoregulatory agent that blocks CTLA-4 to promote antitumor immunity. In a Phase III study of 676 subjects with unresectable or metastatic melanoma whose disease had progressed while receiving prior therapy for metastatic disease, ipilimumab administered at 3 mg/kg q3w for up to 4 doses with or without a gp100 peptide vaccine was compared with gp100 alone [40]. The median overall survival (OS) was 10.1 months and 10.0 months for the ipilimumab alone and ipilimumab plus gp100 arms respectively, while the median OS was 6.4 months for the gp100 alone arm ($p<0.001$). An overall response rate (ORR) of 10.9% was observed in ipilimumab alone arm, while the ipilimumab plus gp100 arm and gp100 alone arm had lower response rates, 5.7% and 1.5%, respectively. The median duration of response was 11.5 months in the ipilimumab plus gp100 arm, and not reached in the ipilimumab alone arm with a median follow-up period of 27.8 months. The median time to progression was 2.86 months for the ipilimumab alone arm and 2.76 months for the other two arms. In the ipilimumab alone arm, 97% of the subjects experienced an adverse event (AE) and grade 3-4 AEs occurred in 46% of the subjects. The most common AEs related to ipilimumab were immune related events, which occurred in approximately 60% of the subjects treated with ipilimumab and 32% of the subjects treated with gp100. The frequency of grade 3-4 immune-related AEs was 15%. The immune-related AEs most often affected the skin and gastrointestinal tract, including pruritus, rash, vitiligo, diarrhea, and colitis.

Based on the above Phase III trial, ipilimumab was approved by the FDA for treatment of subjects with unresectable or metastatic melanoma and by the European Commission for treatment of subjects with previously-treated advanced melanoma. The recommended regimen is 3 mg/kg administered q3w for a total of four doses.

A reduction of the risk of death (28%; $p<0.001$) was also demonstrated for ipilimumab in the first - line setting when combined with dacarbazine in comparison with dacarbazine alone, and the ORRs were 15% and 10% (Investigator assessment per RECIST 1.1) in the ipilimumab/dacarbazine arm and dacarbazine alone arm, respectively [41]. The ipilimumab/dacarbazine arm did show a statistically significant progression-free survival (PFS) improvement [hazard ratio (HR) 0.76; $p=0.006$] over the dacarbazine alone arm. Median OS in the ipilimumab/dacarbazine and dacarbazine arms was 11.2 months and 9.1 months, respectively. The one-year OS rate for the ipilimumab/dacarbazine arm was 47.3%; the rate for the dacarbazine arm was 36.3%.

In RCC, a Phase I/II trial by Yang revealed an ORR 9.8% [42], across different dose levels, in subject's treatment naïve and previously treated with interleukin-2. Given the greater response rates seen with tyrosine kinase inhibitors, ipilimumab was not further developed as monotherapy in RCC. Refer to the approved labeling for detailed background information on Ipilimumab.

1.1.2.2 Pembrolizumab

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [2]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [3], [4], [5], [6], [7]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in solid malignancies such as ovarian, colorectal and pancreatic cancer, hepatocellular carcinoma, malignant MEL and RCC. TILs can be expanded ex vivo and re- infused, inducing durable objective tumor responses in cancers such as melanoma [8], [9].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to

CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD -L1 and/or PD L2) [10], [11]. The structure of murine PD-1 has been resolved [12]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 ζ , PKC θ and ZAP70 which are involved in the CD3 T-cell signaling cascade [10], [13], [14], [15]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [16], [17]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T -cells, B-cells, regulatory T cells (T regs) and Natural Killer cells [18], [19]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [20]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including nonhematopoietic tissues as well as in various tumors [1], [16], [21], [22], [23]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs.

Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [16]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including RCC [24], pancreatic carcinoma [25], hepatocellular carcinoma [26], and ovarian carcinoma [27]. Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma [28]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab (previously known as SCH 900475 and MK-3475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

Based on the preliminary clinical data, PD-1 inhibitors such as pembrolizumab appear to be attractive candidates for pursuing the above goal. Nivolumab has an observed ORR of 28% in MEL subjects; pembrolizumab has shown a promising response rate of 25% in melanoma subjects who have received prior IPI treatment in KEYNOTE 002 [29]. Specifically, a response rate of 36% was observed with pembrolizumab in melanoma subjects who have not received prior IPI treatment in KEYNOTE 006 [30]. This response rate is much higher than the 11-15% response rate observed with IPI in IPI registration trials.

On September 4, 2014, the Food and Drug Administration (FDA) granted accelerated approval for pembrolizumab 2mg/kg q3w in advanced melanoma following disease progression with IPI and, if BRAF V600 mutation positive, a BRAF inhibitor [31]. The approval was based on a strong efficacy and safety profile demonstrated in 4 melanoma expansion parts of thePhase I trial (KEYNOTE 001) [32]; the B2 IPI-refractory population was the subject population for the approval. On December 18, 2015, the FDA granted full approval of pembrolizumab for the treatment of subjects with unresectable or metastatic MEL with pembrolizumab based on KEYNOTE 002 and 006 [33], [34].

Refer to the FDA approved labeling for additional detailed background information on Pembrolizumab.

Proprietary Information of MD Anderson

1.2 RATIONALE

The incidence of melanoma is rising, and despite efforts of early diagnosis, metastatic melanoma remains a challenge for the treating oncologist. Recently, monoclonal antibodies against different immune checkpoints have been revolutionizing the treatment of metastatic and unresectable melanoma, leading to prolonged OS in a subgroup of patients with advanced melanoma [1]. Despite the unprecedented durable response rates observed with cancer immunotherapies, the majority of patients do not benefit from the treatment (primary resistance), some responders relapse after a period of response (acquired resistance), and heterogeneous responses have been seen even between distinct tumors within the same patient [2]. Despite these advances, up to 50-60% of melanoma patients will also develop brain metastasis (MBM) during their course of treatment [3].

However, a recent study has reported a response rate of 22% for single agent pembrolizumab in MBM, with responses being durable. Importantly, two recent studies have shown that in patients with untreated MBM, the combination of ipilimumab and nivolumab yielded response rates of up to 55%. In CheckMate 204, 75 patients were treated with the ipilimumab (3mg/kg Q3 weeks x4) in combination with nivolumab (1mg/kg x4), followed by nivolumab 3mg/kg every 2 weeks until progression or unacceptable toxicity (and a maximum of 2 years). At over 9 months of follow-up, 21% of patients had reached a complete response in the brain, and the median PFS was not reached. In addition to 33% that had a partial response, 5% of patients benefitted by having stable disease. Median time to response was fast at 2.8 months (range 1-11 months). Duration of response had not been reached at time of report. Similarly as the combination trial reported by Larkin et al., 52% of patients experienced grade 3 and 4 toxicities, and 25% had to discontinue study drug. Importantly, treatment related nervous system adverse events were rare, and grade 3 and 4 toxicities only occurred in 8% of the patients [4], [5]. A second trial led by the Australian group (ABC trial) randomized patients with MBM to receive either combination therapy with ipilimumab and nivolumab, or to receive single agent nivolumab at 3mg/kg q2 weeks. Patients had a higher number of brain metastases, but in treatment naïve patients response rate for patients receiving the combination was 50% (15% CR, 35% PR), and stable disease was achieved in 10%. Of the 26 patients treated in this cohort, 46% experienced Grade 3 and 4 toxicities, leading to 27% discontinuation rate.

Recently, KEYNOTE-029 reported the outcomes of 153 melanoma patients, treated with the combination of pembrolizumab 2 mg/kg plus intravenous ipilimumab 1 mg/kg every 3 weeks for four doses, followed by intravenous pembrolizumab 2 mg/kg every 3 weeks for up to 2 years or disease progression, intolerable toxicity, withdrawal of consent, or investigator decision. Estimated 1 year PFS was 69% (95% CI 60-75), and estimated 1 year OS was 89% (95% CI 83-93). 61% of patients achieved an objective response. Grade 3 and 4 toxicities occurred in 45% of patients, which was less than the grade 3 and 4 toxicities reported for the combination of ipilimumab (3mg/kg) and nivolumab (1mg/kg in combination with ipilimumab, followed by 3mg/kg as single agent). While promising, patients with MBM were excluded.

We hypothesize that using low dose ipilimumab in combination with pembrolizumab will be beneficial to patients that had previously progressed on anti-PD1 therapy, and will have similar response as in reported trials using nivolumab and ipilimumab for PD-1 naïve patients with MBM, however, with less grade 3/4 events. In addition, we will evaluate the efficacy of this regimen in a small subset of patients that are treatment naïve to anti-PD1 agents.

Proprietary Information of MD Anderson

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

To assess clinical benefit rate (CBR), defined as CR + PR + SD > 6 months, in the brain in subjects with MBM per modified RECIST 1.1 criteria who are treatment naïve to anti-PD-1 agents in the metastatic setting (prior adjuvant anti-PD1 allowed. See inclusion and exclusion criteria).

2.2 SECONDARY OBJECTIVES

1. To assess CBR in the brain in subjects with MBM per modified RECIST 1.1 in patients who previously progressed on PD-1 inhibitors.
2. To assess OS and PFS.
3. To evaluate the brain-specific safety and tolerability of the combination regimen in subjects with or without SRT received prior to study entry, or on study.
4. To evaluate cytokine levels and changes in the T-cell population in the cerebrospinal fluid (CSF) and blood in patients treated with combination low dose ipilimumab and pembrolizumab.
5. To assess changes in relative apparent diffusion coefficient as measured by MRI as an early predictor of response.
6. To assess changes in circulating cfDNA as determinants of response and/or markers of early progression.
7. To evaluate molecular and immunological changes in extracranial lesions.

2.3 EXPLORATORY END POINT

Radiotherapy-assisted PFS defined as time from study treatment initiation to the first occurrence of disease progression or death from any cause, whichever occurs first, as determined by the investigator according to RECIST v1.1 modified by excluding ≤ 5 lesions that can be treated by SRT from the sum of largest diameters from baseline onwards.

3 STUDY DESIGN

This is a two-cohort, open-label, single site phase II study. There will be no dose escalation or expansion cohort. A total of 30 subjects will be recruited for this study; 25 in Cohort A and 5 in Cohort B.

- Cohort A: Patients who are treatment naïve to anti- PD-1 agents in the metastatic setting (prior adjuvant anti-PD1 allowed. See inclusion and exclusion criteria).
- Cohort B: Patients who previously progressed on PD-1 inhibitors.

All subjects will be treated with the same dose for both ipilimumab and pembrolizumab. The induction period consists of: intravenous pembrolizumab 200 mg plus intravenous ipilimumab 1 mg/kg every 3 weeks for up to four doses, followed by a maintenance period: intravenous pembrolizumab 200 mg every 3 weeks (as tolerated) for up to 2 years or disease progression, intolerable toxicity, withdrawal of consent, death or investigator decision.

The use of SRT (single episode) for disease progression of ≤ 5 brain lesions is permitted in this study

per protocol-defined guidelines. Any subject who receives SRT while on study will be observed for a protocol-defined period before treatment with the study drug(s) can be resumed. The length of the observation period is determined by when in the course of treatment the subject receives SRT - during induction (pembrolizumab plus ipilimumab) or during maintenance treatment (pembrolizumab q3 weeks). Any subject who meets criteria for discontinuation following SRT will proceed to follow-up. All subjects who are discontinued from treatment will continue to be followed for safety, progression, and OS after discontinuation of study medication.

Table 1: Study Drugs and Administration Details

Study Drug	Dose
Ipilimumab	1 mg/kg every 3 weeks for up to four doses
	No Additional Ipilimumab for Study Treatment
Pembrolizumab	200mg in combination with ipilimumab, every 3 weeks, up to four doses, followed by
	Administer 200mg as a single agent every 3 weeks up to 35 doses or until disease progression or unacceptable toxicity, withdrawal of consent, or investigator decision.

Subjects will undergo first CNS imaging evaluation at week 6 (± 3 days). Subsequently, subjects will be evaluated every 6 weeks (42 days ± 3 days), independently of any treatment delays, with radiographic imaging to assess response to treatment, until week 30/Cycle 10. Subjects will then undergo imaging evaluation every 12 weeks (84 ± 7 days). RECIST 1.1 will be used as the primary response rate efficacy endpoint. RECIST 1.1 will be adapted as described in Section 4. to adjust for the tumor response patterns seen with pembrolizumab treatment (e.g., tumor flare), and this adapted/modified RECIST 1.1 will be used by the sites for treatment decisions. The primary response rate efficacy endpoint will be based on independent central review using RECIST 1.1 [1]. Modified RECIST 1.1 will also be used by the local site to determine eligibility and make treatment decisions. MRI of the brain will be the primary radiological method of disease assessment using the RANO-BM criteria.

Subjects may submit an optional tumor tissue sample, if feasible, for biomarker analyses and PDL1 expression evaluation. Subjects with an inadequate archival sample may obtain a new biopsy and subjects with an inadequate newly obtained biopsy may undergo re-biopsy at the discretion of the investigator.

AEs will be monitored throughout the trial and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE) Version 4.03.

Treatment will continue as outlined in Table 1 until documented disease progression, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, completion of 24 months of treatment with pembrolizumab, or administrative reasons.

Subjects who attain an investigator-determined confirmed CR may consider stopping trial treatment after receiving up to 4 doses of ipilimumab and at least 24 weeks of pembrolizumab. In addition, if a confirmed CR per modified RECIST 1.1 is attained, at least two additional treatments of pembrolizumab must be received prior to treatment discontinuation. Subjects who stop pembrolizumab with SD or better per modified RECIST 1.1 may be eligible for retreatment with a maximum of 17 doses of pembrolizumab and 4 doses of ipilimumab if they progress after stopping pembrolizumab at the discretion of the investigator according to the criteria in section 7.1.5.2.1; this retreatment will be the second course phase. Response or progression in the second course phase will not count towards the CBR or PFS endpoints in this trial. The decision to retreat will be at the discretion of the investigator only if no cancer treatment was administered since the last dose of pembrolizumab, the subject still meets the safety parameters listed in the inclusion/exclusion criteria and the trial remains open (refer to section 7.1.5.2.1 for further details).

After the end of protocol treatment, each subject will be followed for 30 days for AE monitoring. (SAEs will be collected for 90 days after the end of treatment). Subjects who discontinue treatment for reasons other than disease progression will have survival follow-up (SFU) for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone contact for OS until death, withdrawal of consent or the end of the trial, whichever comes first

Proprietary Information of MD Anderson

4. MATERIALS AND METHODS

4.1 SUBJECTS

4.1.1 Inclusion Criteria

1. Age ≥ 18 years old.

2. Life Expectancy > 12 weeks

3. Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care.

   Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.

4. Histologically confirmed malignant melanoma with measurable metastases in the brain (≥ 0.5 cm)

5. At least one measurable intracranial target lesion, which previously was not treated with local therapy (no prior SRS to this lesion).
   - Largest diameter of ≥ 0.5cm, but ≤ 3cm as determined by contrast-enhanced MRI

6. Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (blocks are preferred) **OR** at least 4 unstained slides, with an associated pathology report, for testing of tumor PD-L1 expression:

   - Tumor tissue should be of good quality based on total and viable tumor content.

   - Patients who do not have tissue specimens may undergo a biopsy during the screening period. Acceptable samples include core-needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

   - Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable.

   - However, if repeat biopsy is not feasible, and no archival tissue available patient still may be enrolled.

7. Prior SRT and prior excision of up to 5 MBM is permitted if there has been complete recovery, with no neurologic sequelae, and measurable lesions remain. Growth or change in a lesion previously irradiated will not be considered measurable. Regrowth in cavity of previously excised lesion will not be considered measurable.

   - Any prior SRT to brain lesions or prior excision must have occurred ≥ 1 weeks before the start of dosing for this study.

8. Radiation to NON-CNS lesions. Prior radiation to NON-CNS is allowed, and does not require a washout period for treatment initiation.

9. Subjects must be free of neurologic signs and symptoms related to metastatic brain lesions and must not have required or received systemic corticosteroid therapy in the 10 days prior to beginning protocol therapy.

10. ECOG performance status ≤1.

11. Adequate organ function as described below.

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated [b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

12. Women of child-bearing potential (WOCBP) must not be breastfeeding and must have a negative pregnancy test within 3 days prior to initiation of dosing. She must agree to use an acceptable method of birth control from the time of the negative pregnancy test up to 120
days after the last dose of study drug. WOCBP must agree to adhere to the contraceptive guidance in Appendix 5. **Note:** A female participant is eligible to participate if she is not a woman of childbearing potential as defined in Appendix 5.

Proprietary Information of MD Anderson

13. Fertile men must agree to use an acceptable method of birth control as described in Appendix 5 while on study drug and up to 120 days after the last dose of study drug and also refrain from donating sperm during this period.

14. All associated toxicity from previous or concurrent cancer therapy must be resolved (to ≤ grade 1 or baseline) prior to study treatment administration. This excludes non-serious toxicities.

15. Steroids for physiological replacement are allowed.

4.1.2 Exclusion Criteria

1. History of known leptomeningeal involvement (lumbar puncture not required).

2. Previous stereotactic or highly conformal radiotherapy within 1 weeks before the start of dosing for this study. **Note:** The stereotactic radiotherapy field must not have included the brain index lesion(s).

3. Subjects previously treated with SRT > 5 lesions in the brain.

4. Brain lesion size > 3 cm.

5. Prior checkpoint inhibitor therapy (which may include molecularly-targeted agents, IFN-α, and ipilimumab):
   - Patients who received ipilimumab as adjuvant or neoadjuvant therapy must have a 6-month washout before receiving any dosing on this study.
   - Cohort A: Prior anti-PD1 in the adjuvant setting is allowed, but patients must not have progressed within six months of the last dose of adjuvant therapy.
   - Cohort B: Patients with unresectable metastatic melanoma who received either anti-PD-1 or PDL-1 in the past are eligible. Washout period a minimum 3 weeks.

6. Subjects with an active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

7. Subjects with major medical, neurologic or psychiatric condition who are judged as unable to fully comply with study therapy or assessments should not be enrolled.

8. Subject has a history of a second malignancy, unless potentially curative treatment has been completed with no evidence of malignancy for 2 years. Note: The time requirement does not apply to participants who underwent successful treatment of superficial bladder cancer, in situ cervical cancer, or other in-situ cancers' Subjects with a completely treated prior malignancy and no evidence of disease for ≥ 2 years are eligible.
   a. Skin Cancer Exclusion: Please note that basal cell carcinoma and squamous cell carcinoma is exempt from needing resection prior to treatment. (Resection can be completed after the start of treatment).

9. Has a known history of or is positive for hepatitis B (hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (hepatitis C virus [HCV] RNA [qualitative] is detected).
   a. **Note:** Without known history, testing needs to be performed to determine eligibility. Hepatitis C antibody (Ab) testing is allowed for screening purposes in countries where HCV RNA is not part of standard of care.

Proprietary Information of MD Anderson

10. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.

11. The use of corticosteroids is not allowed for 10 days prior to initiation of therapy (based upon 5 times the expected half-life of dexamethasone) except patients who are taking steroids for physiological replacement. If alternative corticosteroid therapy has been used, consultation with the PI is required to determine the washout period prior to initiating study treatment.

12. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of study initiation. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

13. Subjects with history of life-threatening toxicity related to prior ipilimumab adjuvant therapy except those that are unlikely to re-occur with standard countermeasures (e.g. hormone replacement after adrenal crisis)

14. Major surgical procedure, open biopsy (excluding skin cancer resection), or significant traumatic injury within 14 days of initiating study drug (unless the wound has healed) or anticipation of the need for major surgery during the study.

15. Non-healing wound, ulcer, or bone fracture.

16. Women who are breast-feeding or pregnant.

17. Uncontrolled intercurrent illness (i.e., active infection ≥ grade 2) or concurrent condition that, in the opinion of the Investigator, would interfere with the study endpoints or the subject's ability to participate.

18. History of clinically significant cardiac disease or congestive heart failure > New York Heart Association (NYHA) class 2. Subjects must not have unstable angina (anginal symptoms at rest) or new-onset angina within the last 3 months or myocardial infarction within the past 6 months.

19. Investigational drug use within 14 days (or 5 half-lives, whichever is longer) of the first dose of ipilimumab and pembrolizumab.

20. Has a history of non-infectious pneumonitis that required steroids or current pneumonitis.

4.2 TRIAL TREATMENTS

Treatment will consist of 3-week cycles and will continue until documented disease progression, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, completion of 35 doses of treatment with pembrolizumab, or administrative reasons.

Pembrolizumab is to be administered first when in combination with Ipilimumab.

Proprietary Information of MD Anderson

Table 2: Trial Treatments and Description

Product	Dose	Dose Frequency	Route of Administration	Appearance	Storage Conditions (per label)
Ipilimumab	1mg/kg	Every 3 Weeks for up to 4 doses	IV Infusion	Clear, colorless to pale yellow liquid. May contain particles	2ºC to 8ºC. Protect from light and freezing
Pembrolizumab	200 mg	Every 3 Weeks (up to 35 doses)	IV Infusion		

4.2.1 Dose Selection

The dose for pembrolizumab is based on the current FDA approved label; the ipilimumab dose is based on clinical research data from KEYNOTE-029 (1mg/kg every 3 weeks, for up to 4 doses). Refer to Section 1.2 for clinical trial details.

4.2.2 Dose Modification

Dose reductions or dose escalations are not permitted.

Toxicities common to ipilimumab and pembrolizumab include, but are not limited to rash, endocrinopathy, hepatotoxicity, diarrhea, and pneumonitis. Therefore, it is possible that these and/or other toxicities may be exacerbated when pembrolizumab is given in combination with ipilimumab.

Subjects who experience an unacceptable toxicity that is attributed to ipilimumab in the opinion of the Investigator, may permanently discontinue ipilimumab, but may continue with pembrolizumab, upon resolution of toxicity to Grade 0-1 or baseline, until unacceptable toxicity or progression. Subjects who discontinue pembrolizumab due to untoward toxicities may not continue on the trial receiving only ipilimumab.

For subjects who experience a recurrence of the same AE(s) at the same Grade or greater with rechallenge of study treatment(s), the Investigator should determine whether the subject should continue on the trial. However, for a subject who experiences a recurrence of the same SAE at the same Grade or greater with rechallenge, the subject must discontinue trial treatment.

Investigators should refer to the appropriate IB/label for pembrolizumab and/or ipilimumab for additional information regarding the background of each drug and the management of other AEs or potential safety-related issues. Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to trial therapy (e.g., elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on trial therapy within 3 weeks of the scheduled interruption, unless otherwise decided by with the Investigator. The reason for interruption should be documented in the subject's trial record.

Proprietary Information of MD Anderson

4.2.2.1 Pembrolizumab Dose Modifications

See the table below for Dose Modification guidelines for pembrolizumab.

Table 3: Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab monotherapy and IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
				• Participants with 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
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

[a]AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to Pembrolizumab or combination, For adverse events listed, both interventions must be held according to the criteria in the Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab table.

Holding Study Interventions:

When study interventions are administered in combination, if the AE is considered immune-related, both interventions should be held according to recommended dose modifications.

Restarting Study Interventions:

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in [Table 6].

If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.

If the toxicities do resolve and conditions are aligned with what is define then treatment may be restarted at the discretion of the investigator.[In these cases where the toxicity is attributed to Pembro or the combination, re-initiation of pembrolizumab as a monotherapy may be considered at the principal investigator's discretion.

Table 4: Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 **Mild reaction; infusion interruption not indicated; intervention not indicated**	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 **Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs**	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophe n Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the	Participant may be pre-medicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

	original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	
Grades 3 or 4 **Grade 3:** **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 sequelae (e.g., renal impairment, pulmonary infiltrates)** **Grade 4:** **Life-threatening; pressor or ventilatory support indicated**	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophe n Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. **For further information, please refer to the Common Terminology Criteria for Adverse Events v4.03 (CTCAE) at http://ctep.cancer.gov**		

4.2.3 SRT and Dose Interruptions

If a patient requires SRT for brain for a single episode of brain progression in ≤ 5 brain metastases, treatment with study drug will be interrupted as specified in Section 4.3.1.1. The protocol specified steroid treatment and taper (≤ 16 mg dexamethasone PO daily tapered in ≤ 4 weeks four week steroid) must be completed before treatment with the study drugs is resumed.

The length of dose delay/dose interruptions for patients receiving SRT is counted from the date of the last dose of study drug. Patients may resume treatment with study drug after the protocol allowed limit of 6 weeks, if approved by the Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks for any reason including on study treatment with SRT, the PI must be consulted.

4.2.4 Treatment beyond Progression

Study treatment may be continued beyond progression per RECIST v1.1 if pseudoprogression due to the effects of immunotherapy is suspected to have occurred or if disease progression is limited to ≤ 5 intracranial lesions that can be controlled with stereotactic radiotherapy (SRT). Clinically stable patients who have a favorable benefit-risk ratio may continue study treatment beyond progression per RECIST v1.1 for either reason if all of the following criteria are met:

- Clinically stable patient with evidence of clinical benefit and favorable benefit−risk ratio as determined by the investigator
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal disease progression
- No decline in Eastern Cooperative Oncology Group (ECOG) Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g. leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Documented investigator/patient discussion of treatment options alternative to continuing study treatment at the time of RECIST v1.1-defined disease progression

Study treatment will be discontinued in any patient who continues treatment beyond disease progression per RECIST v1.1 if clinical deterioration because of disease progression occurs at any time or if persistent disease growth is confirmed on follow-up disease assessments performed approximately four weeks later. Post-progression assessments may be conducted sooner if necessary e.g. due to clinical progression. The disease status of patients who continued study treatment and underwent intracranial SRT will be determined by the investigator according to RECIST v1.1 modified by excluding any treated lesions from the sum of largest diameters from baseline onwards.

Proprietary Information of MD Anderson

4.2.5 Resumption of Treatment after Dose Delay

If there is a delay in treatment due to AEs associated with study medication, when the patient resumes treatment, he/she will receive the next dose, rather than the missed dose. If the dose delay occurs during the combination treatment (induction), the patient will receive less than 4 doses of the combination treatment.

If there is a delay due to SRT or AEs not associated with study medication, when the patient resumes treatment, he/she will receive the missed dose. If the dose delay occurs during the combination treatment (induction), the patient has the opportunity to receive all four doses of the combination treatment.

4.3 CONCOMITANT AND EXCLUDED THERAPIES

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, and the subject.

4.3.1 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 eCRF including all prescription, over-the-counter (OTC) products, herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days prior to the screening visit and up to 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.

4.3.1.1 Permitted Therapies: SRT and palliative radiation to NON-CNS lesions

If a subject demonstrates clinical benefit, but disease progression in ≤ 5 brain metastases occurs, the investigator may prescribe SRT (single episode), and two scenarios are permitted as detailed below.

- If the patient is clinically stable, progression should be confirmed by follow-up imaging after 4 weeks. If progression is confirmed, the patient may undergo SRT treatment (single episode) for ≤ 5 lesions and may receive ≤ 16 mg dexamethasone PO daily tapered in ≤ 4 weeks. Treatment with the study drugs can be resumed after taper completion as long as the patient does not demonstrate criteria for discontinuation (see Section 4.2.2).

- If the patient is symptomatic as a result of the disease progression, and clinical assessment indicates a requirement for SRT without the delay imposed by the 4-week confirmatory scan, the patient may undergo SRT and may receive ≤ 16 mg dexamethasone PO daily tapered in ≤ 4 weeks. Treatment with the study drugs can be resumed after the completion of the taper as long as the patient does not demonstrate criteria for discontinuation (see Section 4.2.2).

NOTE: To continue on study after SRT, at least 1 non-irradiated target lesion must remain after SRT treatment.

Recommended Observation Period after On-Study SRT

Subjects should be evaluated for neurologic toxicity during the post-SRT treatment window as defined below:

- Subjects receiving SRT during induction (pembrolizumab combined with ipilimumab every 3 weeks for up to 4 doses) should be followed for 3 weeks following the next pembrolizumab with ipilimumab dose. The resumption of treatment with study drugs after SRT is specified in Section 4.2.3 and Section 4.2.4.

- Subjects receiving SRT during maintenance (pembrolizumab every 3 weeks) should be followed for a period of 2 weeks following the next dose. The resumption of treatment with study drugs after SRT is specified in Section 4.2.3 and Section 4.2.4.

Criteria for discontinuation can be found in Section 4.2.2.

For patients who require palliative radiation to NON-CNS lesions: this can be performed while receiving treatment with immunotherapy, and treatment does not need to be held.

4.3.1.2 Permitted Therapy for Brain Edema

Steroid treatment ≤ 16 mg dexamethasone PO daily tapered in ≤ 4 weeks is allowed only for the treatment of brain edema (single episode). If a second episode of brain edema requires steroid treatment, the overall study primary investigator must be consulted.

4.3.1.3 Permitted Therapy: Brain Surgery

If a subject has disease progression in the brain and qualifies as a medical emergency, a single surgical intervention is permitted with the approval of the PI. To remain on-study, the subject must have remaining measurable disease in the brain.

4.3.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including Second Course Phase) of this trial:

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids

  Note: Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab or ipilimumab
- 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. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and

are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from a drug-related AE of suspected immunologic etiology. Please note that inhaled or topical steroids are allowed, and systemic steroids at doses ≤ 10 mg/day prednisone or equivalent are allowed, as described in Section 5.6.
- Local surgery resulting from disease progression is prohibited. However, if indicated for palliative measure and after Sponsor approval, local surgery may be permitted beyond Week 12 tumor assessment.

Subjects who, in the assessment of 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.

4.4 STUDY ASSESSMENTS

4.4.1 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 (Section 6) and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the trial and during the follow-up period according to NCI CTCAE Version 4.03 (see [Section 12.5). Toxicities will be characterized in terms including seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with pembrolizumab or ipilimumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE). See Section 5.6.1 and the separate guidance document in the administrative binder regarding the identification, evaluation and management of AEs of a potential immunological etiology.

Please refer to Section 7.1 for detailed information regarding the assessment and recording of

AEs.

4.4.2 Informed Consent

Prior to conducting any research procedures, the study investigator or designee must obtain consent from the patient or the patient's legally authorized representative. The signed consent form must be maintained with the patient's research chart and a copy must be provided to the patient or patient's legally authorized representative. See additional guidelines on informed consent in Section 9.1.

4.4.3 Physical Examination

4.4.3.1 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. The time points for full physical exams are described in Section 5. After the first dose of trial treatment, new

Proprietary Information of MD Anderson

clinically significant abnormal findings should be recorded as AEs.

4.4.3.2 Directed Physical Exam

For cycles that do not require a full physical exam as defined in Section 5, the Investigator or qualified designee will perform a directed physical exam as clinically indicated prior to the administration of the trial treatment. New clinically significant abnormal findings should be recorded as AEs.

4.4.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 4) at screening, additional time points for assessment of ECOG must be performed as per Section 5).

4.4.5 Vital Signs

Vital signs include temperature, pulse, respiratory rate, weight and blood pressure. The Investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and during the follow-up period as specified in the Trial Flow Chart (Section 5). Height will be measured at Screening.

4.4.6 Response Assessment

MRI of the brain will be the primary radiological method of disease assessment using RECIST 1.1 and the RANO-BM criteria (See Appendix 1). Quantitative imaging changes on multiparametric MRI will be captured to determine early biomarkers of immune response. Standard of care brain MRI with intravenous gadolinium contrast and contrast enhanced CT chest/abdomen/pelvis or PET-CT, as clinically indicated, will be used to assess both intracranial and extracranial disease at Screening and every 6 weeks after the start of treatment up to cycle 9. Imaging may occur up to 72 hours prior to scheduled cycle. Screening MRI and CT assessments must occur within 28 days prior to day 1.

If an MRI, CT chest/abdomen/pelvis or PET-CT is not already performed as standard of care per Schedule of Assessments in Section 5, the investigator may choose to perform either or both procedures for assessing the progress of the patient.

4.4.7 Archival Tumor Tissue Sample

Archival tumor tissue samples obtained outside of this study for other purposes will be collected, if available, from all patients. All samples must be representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (preferred) or at least 4 unstained slides, with an associated pathology report, for local testing of tumor PD-L1 expression.

4.4.8 Biopsy

Patients with biopsiable extracranial disease may have tissue collected pretreatment and at Cycle 2 (3 weeks after the start of treatment). Optional Biopsy may be collected at Cycle 5, if accessible, but is not required. If standard of care biopsies are required, additional, optional tissue may be acquired as part of this protocol. Acceptable samples include core-needle biopsies for deep tumor tissue (minimum of three cores) or excisional, incisional, or punch biopsies for cutaneous, subcutaneous, or mucosal lesions.

Acceptable samples include core needle biopsies for deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

For core-needle biopsy specimens, at least three cores should be submitted for evaluation.

4.4.9 Laboratory Assessments

All labs will be processed locally at MDACC.

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
	Chloride	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free thyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*		Blood for correlative studies
	Uric Acid		
	Calcium		
	Creatinine		
	Glucose		
	Magnesium		
	Phosphorus		
	Potassium		
	Sodium		
	Blood Urea Nitrogen		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		

† 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.

4.4.10 Electrocardiogram

A standard 12-lead ECG will be performed using local standard procedures at Screening. Clinically significant abnormal findings should be recorded as medical history. Additional time points for standard 12-lead ECGs must be performed as per Section 5. Clinically significant abnormal findings seen on the follow-up ECGs should be recorded as adverse events.

4.4.11 Neurological Function Testing

Neurologic functioning will be evaluated using NANO. This objective and quantifiable assessment will evaluate nine major domains for subjects with brain tumors. The domains include: gait, strength, ataxia, sensation, visual field, facial strength, language, level of consciousness, behavior and overall. Each domain is rated on a scale of 0 to 3 where 0 represents normal and 3 represents the worst severity. A given domain should be scored non-evaluable if it cannot be accurately assessed due to preexisting conditions, co-morbid events and/or concurrent medications. The evaluation is based on direct observation/testing performed during routine office visits. The NANO scale will be completed by the investigator or designated study physician prior to dosing Day 1 Week 1 (baseline) and then at the time points indicated in on the schedule of events.

4.4.12 Research Sample Collection

4.4.12.1 Tumor Tissue Collection, Correlative Blood, and CSF Sampling

Correlative studies may be collected as specified in the study calendar, processed and/or stored for analysis with optional subject consent. All tissue and resulting data will be de-identified and may be shared between MD Anderson and the study supporter (Merck). All samples and data will be tracked utilizing a unique research tracking number that will not be related to any patient identifying information. The sample collections will be reported in the database and a source document will be printed for monitoring purposes. All samples will be stored at MD Anderson Melcore.

4.4.12.1.1 Tissue

Patients with biopsable extracranial disease for which tissue is collected (up to four cores) in accordance with the study schedule will be prioritized as follows:

- 25% (or one core) FFPE for histology and IHC studies
- 75% (or 3 cores) snap frozen in cryovials

Analysis of tissue, availability and quality permitting, may include the following studies:

- Immune monitoring and characterization of immune infiltrate in response to the drug combination using immunohistochemistry (IHC), characterization of PD-L1 expression, CD4, CD8 T cell infiltration.
- Molecular analyses on tissue samples and T cell infiltrates may include RNA based expression profiling (such as Nanostring via targeted panel or RNAseq) to evaluate immune gene expression signatures and the impact of the combination on treatment samples and correlating with clinical response data.

4.4.12.1.2 Blood

Blood will be collected for circulating chemokines, cell free DNA, PBMCs and T cell populations. Research blood will be drawn at each restaging imaging, and up to 40cc of blood will be drawn.

This will be collected every 6 weeks beginning with Cycle 1 (pre-treatment) until Cycle 8.

- Functionality of circulating T cells and other immune markers in peripheral blood may be assessed utilizing 34 parameter mass cytometry (CyTOF) and/or flow cytometry. Cytokine analysis may also be performed on serum obtained from the same time points.
- Analysis of blood, availability permitting, may include also include molecular evaluations, to include circulating DNA and exosomal analyses.

4.4.12.1.3 Cerebrospinal Fluid (CSF)

CSF will be obtained from up to 5 patients for optional testing at baseline prior to the start of protocol treatment and again at the time of the first restaging scans.

Cytokine and circulating T-cell population in the CSF and PK/PD of ipilimumab and pembrolizumab in the CSF will be tested. Up to 20cc of CSF will be drawn via lumbar puncture in these patients.

4.4.13 Tumor Imaging and Assessment of Disease

All subjects will undergo CT scanning and volumetric MRI of the brain at the time points specified in the Schedule of Events in Section 5. CT and MRI scans will be assessed locally per the modified RECIST 1.1 criteria. Up to 5 systemic and 5 brain lesions will be followed for efficacy per the criteria.

4.4.14 Therapy Administration

All patients will be treated with the same dose for both ipilimumab and pembrolizumab. Intravenous pembrolizumab 200 mg over 30 (±5) minutes plus intravenous ipilimumab 1 mg/kg over 90 (±15) minutes every 3 weeks for four doses, followed by intravenous pembrolizumab 200 mg every 3 weeks for up to 2 years or disease progression, intolerable toxicity, withdrawal of consent, or investigator decision.

4.4.15 Management of Patients with Disease Progression

In the absence of unacceptable toxicity, patients who meet criteria for disease progression will be permitted to continue study treatment if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values) indicating unequivocal progression of disease
- Absence of decline in ECOG Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

4.5 SUPPORTIVE CARE GUIDELINES

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 does not need to follow the treatment guidance (as outlined below). Refer to Section 8.0 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.

- **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,** administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis,** 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.

Proprietary Information of MD Anderson

- 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.

  See Table 4 for treatment guidelines for subjects who experience an infusion reaction associated with administration of Pembrolizumab.

Proprietary Information of MD Anderson

4.6 SUBJECT DISCONTINUATION

4.6.1 End of Treatment

Patients complete protocol treatment of the investigational combination after receiving 4 doses of Ipilimumab + Pembrolizumab which occurs after completion of Cycle 4.

Pembrolizumab monotherapy treatment may continue up to a total of 35 doses.

4.6.2 Withdrawal

Subjects who discontinue/withdraw from treatment prior to completion of the treatment regimen should be encouraged to continue to be followed for all remaining study visits. However, patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to the following:

- Patient withdrawal of consent at any time
- Any medical condition, determined by the investigator that may jeopardize the patient's safety if he or she continues in the study
- Patient becomes pregnant
- Investigator determines it is in the best interest of the patient
- Patient non-compliance

When a subject discontinues/withdraws from participation in the trial, 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 7.1.

Subjects who

a) attain an investigator-determined CR or

a PR and complete treatment with at least one dose of ipilimumab may discontinue treatment with IPI with the option of restarting the second course phase if they meet the criteria specified in section 7.1.5.2.1. 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 and survival follow-up.

4.6.3 End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur 24 months after the last patient is enrolled in the trial.

4.6.4 Post Study Drug Study Follow-up

In this study, clinical benefit rate is the primary endpoint of the study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required until death or the conclusion of the study.

4.6.5 Lost to Follow-up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

5 SCHEDULE OF ASSESSMENTS

Trial Period:	**Screening Phase**		**Treatment Cycles [a]**								**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Screening		1	2	3	4	To be repeated beyond 8 cycles 5	6	7	8	Discontinuation	Safety Follow-	Follow Up Visits [b]	Survival Follow-Up
Scheduling Window (Days):	-28 to 1			± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discontinuation	30 days post discontinuation ± 7	Every 6 weeks post discontinuation ± 7	Every 12 weeks ± 7
Administrative Procedures														
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
Demographics and Medical History	X													
Prior and Concomitant Medication Review	X		X	X	X	X	X	X	X	X	X			
Trial Treatment Administration [c]			X	X	X	X	X	X	X	X				
Post-study anticancer therapy status													X	X
Survival Status														X
Clinical Procedures/Assessments														
Review Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X		X	X	X	X	X	X	X	X	X		X	
Vital Signs, Weight, and Height[l]	X		X	X	X	X	X	X	X	X	X		X	
Electrocardiogram (12-Lead ECGs)	X													
ECOG Performance Status	X		X	X	X	X	X	X	X	X	X		X	
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory														
Pregnancy Test – Urine or Serum β-HCG [d]	X		X		X		X		X		X		X [k]	

Trial Period:	Screening Phase		Treatment Cycles [a]								End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening		1	2	3	4	To be repeated beyond 8 cycles 5	6	7	8	Discontinuation	Safety Follow-	Follow Up Visits [b]	Survival Follow-Up
Scheduling Window (Days):	-28 to 1			± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discontinuation	30 days post discontinuation ± 7	Every 6 weeks post discontinuation ± 7	Every 12 weeks ± 7
Coagulation [e]	X													
CBC with Differential	X		X	X	X	X	X	X	X	X	X		X	
Comprehensive Serum Chemistry Panel	X		X	X	X	X	X	X	X	X	X		X	
Urinalysis	X		X	X	X	X	X	X	X	X	X			
T3, FT4 and TSH	X		X		X		X		X		X			
Efficacy Measurement														
Tumor Imaging [f]	X				X		X		X		X			
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood														
Tissue Collection														
Archival Tissue [g]	X													
Serial Biopsy [h]	X		X	X			X							
Cerebrospinal Fluid [i]	X				X									
Blood Collection														
Correlative Studies [j]			X		X		X		X					

Trial Period:	Screening Phase	Treatment Cycles [a]								End of Treatment	Post-Treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening	1	2	3	4	5	6	7	8	Discontinuation	Safety Follow-	Follow Up Visits [b]	Survival Follow-Up
Scheduling Window (Days):	-28 to 1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discontinuation	30 days post discontinuation ± 7	Every 6 weeks post discontinuation ± 7	Every 12 weeks ± 7

[a] Cycles are 3 weeks (21 days) in duration

[b] Patients who discontinue trial treatment for reasons other than disease progression will move into Follow Up Visits where they will be seen every 6 weeks for one year and then into Survival Follow Up where they will be seen every 12 weeks for another year. Patients who successfully complete 2 years of Pembrolizumab will move directly into Survival Follow Up and be seen~ every 12 weeks for up to one year. Once a patient is in follow up or survival follow up, restaging scans done out of window will not be deviations as they will be ordered SOC.

[c] Ipilimumab 1mg/kg every 3 weeks up to 4 doses Pembrolizumab will be administered at 200mg every 3 weeks.

[d] See Section 7.4 if a woman of child-bearing potential becomes pregnant while on study.

[e] Prothrombin time/International Normalized Ratio, Activated Partial thromboplastin time.

[f] MRI scan will be performed every 6 weeks for the first year, then ~ every 12 weeks until progression or discontinuation of study treatment, whichever comes later. Imaging window is +/- 7 days. If scans were performed within 4 weeks of discontinuation, repeat scans are not required. When a patient moves into Follow-Up, they will have scans ordered as Standard of Care by their treating physician. Once a patient is in follow up or survival follow up, restaging scans done out of window will not be deviations as they will be ordered SOC.[g] See Section 4.4.7 for additional details.

[h] Patients with biopsable extracranial disease may have tissue collected. See Section 4.4.8. Screening biopsy only required if there is no archival tissue available

[i] Cerebrospinal Fluid will be obtained from up to 5 patients for optional testing. See Section 4.4.12.1.3 for additional details.

[j] See Section 4.4.12.1.2.

[k] Pregnancy testing to be completed at 120 days post treatment

[l] Height only to be collected at Screening.

.

6 STATISTICAL CONSIDERATIONS

6.1 SAMPLE SIZE JUSTIFICATION

The primary objective of the study is to assess CBR, defined as CR + PR + SD > 6 months, in the brain in subjects with MBM per modified RECIST 1.1 criteria who are treatment naïve to anti-PD-1 agents in the metastatic setting (Cohort A). A sample size of 25 subjects will achieve 84% power to detect a difference of 19% (anticipated CBR of 35% - 16% [historical control]) using a chi-squared test at a one-sided significance level of 0.10 (nQuery Advisor® 7.0). For Cohort B, assuming a CBR of 20% for patients who previously progressed on PD-1 inhibitors, the probability of observing at least one subject experiencing clinical benefit out of 5 subjects is 0.67.

Reference

Zhou, H., Lee, J. J., & Yuan, Y. (2017). BOP2: Bayesian optimal design for phase II clinical trials with simple and complex endpoints. *Statistics in Medicine*, 36(21):3302-3314.

6.2 ANALYSIS

6.2.1 Primary Endpoint

CBR will be estimated along with a corresponding exact 95% confidence interval by cohort.

6.2.2 Secondary Endpoints

OS will be defined as the time from the start of first treatment to death for any cause. Patients who are still alive at the end of the study will be censored. PFS will be defined as the time from start of first treatment to disease progression or death for any cause. Patients who are still alive at the end of the study who had not progressed will be censored. OS and PFS will be assessed using the Kaplan-Meier method.

Cytokine levels and changes in the T-cell population in the CSF and blood will be summarized using means, standard deviations, medians, minimums, and maximums. Within group changes will be evaluated using either paired t-test or Wilcoxon signed rank test, depending on the data distribution.

Differences in the change in relative apparent diffusion coefficient and circulating cfDNA by CBR (yes vs. no) will be evaluated by either two sample t-test or Wilcoxon rank-sum test, depending on the data distribution.

Lastly, safety will be assessed by adverse events and serious adverse events as well as by vital signs and laboratory assessments for all patients. Categorical measures will be summarized using frequencies and percentages while continuous variables will be summarized using means, standard deviations, medians, minimums, and maximums.

Proprietary Information of MD Anderson

7 ASSESSMENT OF SAFETY

7.1 ADVERSE EVENT ASSESSMENT AND REPORTING

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product 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 investigational products 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.

Adverse events may occur during clinical trials or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an adverse event.

From the time of initial protocol treatment through 30 days following cessation of treatment, all adverse events must be recorded. Such events will be recorded at each examination in the medical record. The reporting timeframe for adverse events meeting any serious criteria is described in Section 7.1.1. The investigator will make every attempt to follow all subjects with non–serious adverse events for outcome.

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.03. 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.

For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each adverse event causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (i.e., to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion; there is sufficient data to support full attribution of the adverse experience to the single agent.

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

Table 9: Evaluating Adverse Events

V4.03 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 Merck 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 MD Anderson IND Office 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 MD Anderson IND Office 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?	

<table>
<tr><td>Relationship to Merck Product</td><td colspan="2">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.

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):</td></tr>
<tr><td></td><td>Exposure</td><td>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?</td></tr>
<tr><td></td><td>Time Course</td><td>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)?</td></tr>
<tr><td></td><td>Likely Cause</td><td>Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors</td></tr>
<tr><td></td><td colspan="2">The following components are to be used to assess the relationship between the test drug and the AE</td></tr>
<tr><td></td><td>Dechallenge</td><td>Was Merck product discontinued or dose/exposure/frequency reduced?

• If yes, did the AE resolve or improve?
o If yes, this is a positive dechallenge.
o If no, this is a negative dechallenge.

(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Supporter's product; or (3) the trial is a single-dose drug trial); or (4) Supporter's product(s) is/are only used one time.)</td></tr>
<tr><td></td><td>Rechallenge</td><td>Was the subject re-exposed to Merck product in this study?

• If yes, did the AE recur or worsen?
o If yes, this is a positive rechallenge.
o If no, this is a negative rechallenge.

(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Supporter's product(s) is/are used only one time).

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE MD ANDERSON IND OFFICE AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.</td></tr>
</table>

	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?

The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.
No, there is not a reasonable possibility of Merck product relationship	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a subject with overdose without an associated AE.)

7.1.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's 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 another 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 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 9 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation, any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any participant must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the participant 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 participant 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 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 Merck Global Safety.

All participants 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: +1-215-661-6229

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 215-661-6229) at the time of submission to FDA.

Proprietary Information of MD Anderson

7.2 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 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

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 participant must be reported within 2 working days to Merck Global Safety if it causes the participant 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 participant 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 2 working days to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.3, 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 more 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.

7.3 DEFINITION AND REPORTING OF AN OVERDOSE FOR THIS PROTOCOL

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

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 215-661-6229)

Proprietary Information of MD Anderson

7.4 REPORTING OF PREGNANCY AND LACTATION

Although pregnancy and infant exposure during breast-feeding are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them) that occurs during the study.

Pregnancies and infant exposures during breastfeeding that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the participant 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 infant exposures during breastfeeding that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the participant 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 215-661-6229)

8 ADMINISTRATIVE AND REGULATORY DETAILS

8.1 INVESTIGATOR COMMUNICATIONS

8.1.1 Communication with Merck

All reports of overdose, pregnancy, lactation, SAEs, and ECIs must be reported within 2 working days to Merck Global Safety.

Additionally, any reportable event, considered by an investigator, who is a qualified physician, to be related to a 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 also must be reported to Merck Global Safety.

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

8.1.2 Investigator Responsibility for Reporting Events

All Adverse Events will be reported to regulatory authorities and IRB/IECs in accordance with all applicable global laws and regulations.

8.2 DATA MANAGEMENT

8.2.1 Data Collection

The study coordinator and investigators are responsible for ensuring that the eligibility checklist is completed in a legible and timely manner for every patient enrolled in the study, and that data are

recorded on the appropriate forms and in a timely manner in the electronic case report forms (eCRFs) in the Prometheus database. All source documents will be available for inspection by the FDA and the MDACC IRB.

8.2.2 Data Safety Monitoring Plan

Investigator, Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet monthly to review and discuss study data to include, but not limited to, the following:

- serious adverse events
- subject safety issues
- recruitment issues
- accrual
- protocol deviations
- unanticipated problems
- breaches of confidentiality

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 4.03. All study treatment associated adverse events that are serious, at least possibly related and unexpected will be reported to the IRB. Any modifications necessary to ensure subject safety and decisions to continue or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse e v e n t s).

All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records

8.2.3 Data Handling and Record Keeping

The Investigator (i.e., the study site principal investigator) will maintain records in a c c o r d a n c e with Good Clinical Practice.

The MDACC investigator will retain the MDACC-IND records for 5 years after study closure.

8.3 INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL

The investigator (i.e., the study site principal investigator) will obtain, from the MD Anderson Cancer Center Institutional Review Board (IRB), prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment, if applicable.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to

eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the investigator will promptly notify the MD Anderson Cancer Center IRB of the deviation.

The MD Anderson Cancer Center IRB operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice.

8.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

9 ETHICAL CONSIDERATIONS

The clinical study will be conducted in accordance with the current IRB- approved clinical protocol; ICH Guidelines on Guidelines on Good Clinical Practice; and relevant policies, requirements, and regulations of the University of Texas MD Anderson Cancer Center IRB, and applicable federal agencies.

9.1 Informed Consent

The investigator (i.e., the study site principal investigator) will make certain that an appropriate informed consent process is in place to ensure that potential research subjects, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research subjects. The investigator, or a sub-investigator(s) designated by the MD Anderson IND Office, will obtain the written, signed informed consent of each subject, or the subject's authorized representative, prior to performing any study-specific procedures on the subject. The date and time that the subject, or the subject's authorized representative, signs the informed consent form and a narrative of the issues discussed during the informed consent process will be documented in the subject's case history. The investigator or sub-investigator will retain the original copy of the signed informed consent form, and a copy will be provided to the subject, or to the subject's authorized representative.

10 STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

The investigator and the head of the medical institution (where applicable) agrees to allow the IND Office monitor direct access to all relevant documents and to allocate their time and the time to their staff to monitor to discuss findings and any issues.

- Monitoring visits will be conducted in a manner to ensure that the:
- Data are authentic, accurate, and complete.

Proprietary Information of MD Anderson

- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

11 APPENDICES

Appendix 1: Response Assessment for Neuro-Oncology (RANO)

RANO and iRANO criteria (Brain Metastases)

	Brain metastases
COMPLETE TARGET	Disappearance of all enhancing target and non-lesions for ≥4 weeks; no new lesions; no steroids; clinically stable or improved
PARTIAL RESPONSE	≥30% decrease in sum of longest diameters of target lesions for ≥4 weeks; no new lesions; stable or decreased steroid dose; clinically stable or improved
MINOR RESPONSE	NA
STABLE DISEASE	Does not qualify for complete response, partial response, or progressive disease
PROGRESSIVE DISEASE	≥20% increase in the sum of longest diameters of target lesions; or unequivocal progression of enhancing non-target lesions; or new lesions; or substantial clinical decline

The iRANO criteria integrate into the existing RANO criteria for malignant glioma, low-grade glioma, and brain metastases by providing recommendations for the interpretation of progressive imaging changes. Specifically, iRANO recommends confirmation of disease progression on follow-up imaging 3 months after initial radiographic progression if there is no new or substantially worsened neurological deficits that are not due to comorbid events or concurrent medication, and it is 6 months or less from starting immunotherapy. If follow-up imaging confirms disease progression, the date of actual progression should be back-dated to the date of initial radiographic progression. The appearance of new lesions 6 months or less from the **initia**tion of immunotherapy alone does not define progressive disease. FLAIR=fluid-attenuated inversion recovery. **iRANO=**immunotherapy Response Assessment in Neuro-Oncology. N/A=not applicable.

Appendix 2: RECIST v1.1

Response Evaluation Criteria in Solid Tumors (RECIST v1.1 Criteria)

The RECIST criteria should be used to assess response to treatment. Only patients with measurable disease should be entered in the study. Measurable extracranial disease is defined as the presence of one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥2.0 cm with conventional techniques (or as ≥1.0 cm by spiral CT). Evaluable lesions should be followed for the assessment of response. Non-measurable lesions include bone lesions, ascites, pleural/pericardial effusion, lymphangitic carcinomatosis, abdominal masses that are not confirmed by CT, and cystic lesions. Disease progression and response evaluations for intracranial and extracranial disease will be determined according to the definitions established in the Response Evaluation Criteria in Solid Tumours (RECIST v1.1). Minor modifications will be applied to the assessment of intracranial lesions:

- General: target lesions should be representative of the subject's baseline tumor burden and should be selected based on their size (i.e. lesions with the longest diameter) and their suitability for accurate repeat assessment.
- Intracranial lesions: (the modifications to RECIST v1.1. impact the number and the minimal size of the target lesions selected at baseline) up to five lesions should be selected as target lesions; all brain lesions in excess of these five target lesions have to be regarded as non-target lesions. Measurable lesions are defined as those that can be accurately measured in at least one dimension with the longest diameter ≥ 5 mm when evaluated with contrast-enhanced MRI. Contrast-enhanced MRI is the only imaging modality accepted for assessment of intracranial lesions.
- Extracranial lesions: up to two lesions per organ representative of all involved organs should be selected as target lesions; the total number of target lesions should not exceed five and all lesions in excess of these five target lesions have to be regarded as non-target lesions.

Baseline Documentation of Intracranial Target and Non-Target Lesions

- All baseline lesion assessments must be performed within 28 days of the first dose of study treatment.
- Measurable and non-measurable intracranial (i.e. brain parenchyma) lesions up to a maximum of 5 lesions should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- Cystic lesions thought to represent cystic metastases should not be selected as target lesions when other suitable target lesions are available.
- Measurable intracranial lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target

lesions. All other intracranial lesions should be identified as non-target and should also be recorded at baseline. Measurements of non-target lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Baseline Documentation of Extracranial Target and Non-Target Lesions

- All baseline lesion assessments must be performed within 28 days of the first dose of study treatment.
- Lymph nodes that have a short axis of <10mm are considered non-pathological and should not be recorded or followed.
- Pathological lymph nodes with <15mm and ≥10mm short axis are considered non measurable.
- Pathological lymph nodes with ≥15mm short axis are considered measurable and can be selected as target lesions, however lymph nodes should not be selected as target lesions when other suitable target lesions are available.
- Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved extracranial organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- Cystic lesions thought to represent cystic metastases should not be selected as target lesions when other suitable target lesions are available.
- Measurable extracranial lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered measurable.
- Bone scans, FDG-PET scans or X-rays are not considered adequate imaging techniques to measure bone lesions.
- All other lesions (or sites of disease, excluding the brain) should be identified as non-target and should also be recorded at baseline.
- Non-target lesions will be grouped by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Overall Intracranial Response - Evaluation of Intracranial Target Lesions

Definitions for assessment of response for intracranial target lesion(s) are as follows:

- Complete Response (CR): Disappearance of all target lesions.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (e.g. percent change

from baseline).

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g. percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5mm.
- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

  Note: If an intracranial target lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

- Patients, who in the opinion of the treating physician investigator have had a substantial decline in their performance status and have clinical evidence of progressive disease may be classified as having progressive disease.

Appendix 3: Current National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4.03)

Please use the following link to the NCI CTCAE website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix 4: Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about >50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Appendix 5: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Pre-menarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol as defined in Section 4.1.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 10 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Table 10: Highly Effective Contraceptive Methods That Have Low User Dependency

Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [a, b] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least [X days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 11 during the protocol-defined time frame in Section 4.1.1.

Table 11: Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal

○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least [X days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment . c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements. When applicable, this test should be repeated a maximum of 24-hours before the first dose/vaccination.

Following initiation of treatment additional pregnancy testing will be performed at 6-week intervals during the treatment period and at 120 days after the last dose of study treatment and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

Proprietary Information of MD Anderson

APPENDIX 6 NANO Scale

The NANO scale will be used in this study. Please use the following link to access the scale

https://www.ncbi.nlm.nih.gov/pubmed/28453751

Proprietary Information of MD Anderson

12 REFERENCES

[1-57]

1. Franklin, C., et al., *Immunotherapy in melanoma: Recent advances and future directions.* Eur J Surg Oncol, 2017. **43**(3): p. 604-611.
2. Sharma, P., et al., *Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy.* Cell, 2017. **168**(4): p. 707-723.
3. Cohen JV, T.H., Margolin KA, Amravadi R, Bosenberg M, Brastianos PK, Chiang VL, de Groot J, Glitza IC, Herlyn M, Holmen SL, Jilaveanu LB, Lassman A, Moschos S1, Postow MA, Thomas R, Tsiouris AJ, Wen P, White RM, Turnham T, Davies MA, Kluger HM, *Melanoma Central Nervous System Metastases: Current Approaches, Challenges, and Opportunities.* Pigment Cell & Melanoma Research, 2016.
4. Larkin, J., F.S. Hodi, and J.D. Wolchok, *Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma.* N Engl J Med, 2015. **373**(13): p. 1270-1.
5. Tawbi HA, F.P., Algazi PA, Hamid O, F. Hodi S, Moschos S, Khushalani N, Margolin KA, *Efficacy and safety of nivolumab (NIVO) plus ipilimumab (IPI) in patients with melanoma (MEL) metastatic to the brain: Results of the phase II study CheckMate 204.* J Clin Oncol 30, 2012 (suppl; abstr 8584), 2017. **35**: p. (suppl; abstr 9507).
6. *Pembrolizumab (Keytruda) for metastatic melanoma.* Med Lett Drugs Ther, 2014. **56**(1455): p. e114-5.
7. Agarwala, S.S., *Novel immunotherapies as potential therapeutic partners for traditional or targeted agents: cytotoxic T-lymphocyte antigen-4 blockade in advanced melanoma.* Melanoma Res, 2010. **20**(1): p. 1-10.
8. Agarwala, S.S., et al., *Temozolomide for the treatment of brain metastases associated with metastatic melanoma: a phase II study.* J Clin Oncol, 2004. **22**(11): p. 2101-7.
9. Al-Shibli, K.I., et al., *Prognostic effect of epithelial and stromal lymphocyte infiltration in non-small cell lung cancer.* Clin Cancer Res, 2008. **14**(16): p. 5220-7.
10. Atkins, M.B., et al., *A Cytokine Working Group phase II study of temozolomide (TMZ), thalidomide (THAL) and whole brain radiation therapy (WBRT) for patients with brain metastases from melanoma.* Journal of Clinical Oncology, 2005. **23**(16): p. 723s-723s.
11. Atkins, M.B., et al., *Temozolomide, thalidomide, and whole brain radiation therapy for patients with brain metastasis from metastatic melanoma: a phase II Cytokine Working Group study.* Cancer, 2008. **113**(8): p. 2139-45.
12. Bafaloukos, D. and H. Gogas, *The treatment of brain metastases in melanoma patients.* Cancer Treat Rev, 2004. **30**(6): p. 515-20.
13. Brown, J.A., et al., *Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production.* J Immunol, 2003. **170**(3): p. 1257-66.
14. Chew, V., et al., *Inflammatory tumour microenvironment is associated with superior survival in hepatocellular carcinoma patients.* J Hepatol, 2010. **52**(3): p. 370-9.
15. Choueiri, T.K., T.E. Hutson, and R.M. Bukowski, *Evolving role of pegylated interferons in metastatic renal cell carcinoma.* Expert Rev Anticancer Ther, 2003. **3**(6): p. 823-9.
16. Deschoolmeester, V., et al., *Tumor infiltrating lymphocytes: an intriguing player in the survival of colorectal cancer patients.* BMC Immunol, 2010. **11**: p. 19.
17. Di Giacomo, A.M., et al., *Ipilimumab and fotemustine in patients with advanced melanoma (NIBIT-M1): an open-label, single-arm phase 2 trial.* Lancet Oncol, 2012. **13**(9): p. 879-86.
18. Diez, M., et al., *Histopathologic prognostic score in colorectal adenocarcinomas.* Anticancer Res, 1998. **18**(1B): p. 689-94.
19. Disis, M.L., *Immune regulation of cancer.* J Clin Oncol, 2010. **28**(29): p. 4531-8.
20. Dong, H., et al., *Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion.* Nat Med, 2002. **8**(8): p. 793-800.
21. Eisenhauer, E.A., et al., *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Cancer, 2009. **45**(2): p. 228-47.

22. Fife, K.M., et al., *Determinants of outcome in melanoma patients with cerebral metastases.* J Clin Oncol, 2004. **22**(7): p. 1293-300.
23. Francisco, L.M., P.T. Sage, and A.H. Sharpe, *The PD-1 pathway in tolerance and autoimmunity.* Immunol Rev, 2010. **236**: p. 219-42.
24. Galon, J., et al., *Type, density, and location of immune cells within human colorectal tumors predict clinical outcome.* Science, 2006. **313**(5795): p. 1960-4.
25. Garon, E.B., et al., *Pembrolizumab for the treatment of non-small-cell lung cancer.* N Engl J Med, 2015. **372**(21): p. 2018-28.
26. Geller, A.C., et al., *Melanoma incidence and mortality among US whites, 1969-1999.* JAMA, 2002. **288**(14): p. 1719-20.
27. Goldberg, S.B., et al., *Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial.* Lancet Oncol, 2016. **17**(7): p. 976-983.
28. Greenwald, R.J., G.J. Freeman, and A.H. Sharpe, *The B7 family revisited.* Annu Rev Immunol, 2005. **23**: p. 515-48.
29. Hamid, O., et al., *Final overall survival for KEYNOTE-002: pembrolizumab (pembro) versus investigator-choice chemotherapy (chemo) for ipilimumab (ipi)-refractory melanoma.* Annals of Oncology, 2016. **27**.
30. Hillen, F., et al., *Leukocyte infiltration and tumor cell plasticity are parameters of aggressiveness in primary cutaneous melanoma.* Cancer Immunol Immunother, 2008. **57**(1): p. 97-106.
31. Hiraoka, N., *Tumor-infiltrating lymphocytes and hepatocellular carcinoma: molecular biology.* Int J Clin Oncol, 2010. **15**(6): p. 544-51.
32. Hodi, F.S. and G. Dranoff, *The biologic importance of tumor-infiltrating lymphocytes.* J Cutan Pathol, 2010. **37 Suppl 1**: p. 48-53.
33. Kloor, M., *Lymphocyte infiltration and prognosis in colorectal cancer.* Lancet Oncol, 2009. **10**(9): p. 840-1.
34. Kopf, A.W., D.S. Rigel, and R.J. Friedman, *The rising incidence and mortality rate of malignant melanoma.* J Dermatol Surg Oncol, 1982. **8**(9): p. 760-1.
35. Lee, H.E., et al., *Prognostic implications of type and density of tumour-infiltrating lymphocytes in gastric cancer.* Br J Cancer, 2008. **99**(10): p. 1704-11.
36. Leffers, N., et al., *Prognostic significance of tumor-infiltrating T-lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer.* Cancer Immunol Immunother, 2009. **58**(3): p. 449-59.
37. Liotta, F., et al., *Frequency of regulatory T cells in peripheral blood and in tumour-infiltrating lymphocytes correlates with poor prognosis in renal cell carcinoma.* BJU Int, 2011. **107**(9): p. 1500-6.
38. Margolin, K., et al., *Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial.* Lancet Oncol, 2012. **13**(5): p. 459-65.
39. Nishimura, H., T. Honjo, and N. Minato, *Facilitation of beta selection and modification of positive selection in the thymus of PD-1-deficient mice.* J Exp Med, 2000. **191**(5): p. 891-8.
40. Nobili, C., et al., *Prolonged survival of a patient affected by pancreatic adenocarcinoma with massive lymphocyte and dendritic cell infiltration after interleukin-2 immunotherapy. Report of a case.* Tumori, 2008. **94**(3): p. 426-30.
41. Oble, D.A., et al., *Focus on TILs: prognostic significance of tumor infiltrating lymphocytes in human melanoma.* Cancer Immun, 2009. **9**: p. 3.
42. Polcher, M., et al., *Foxp3(+) cell infiltration and granzyme B(+)/Foxp3(+) cell ratio are associated with outcome in neoadjuvant chemotherapy-treated ovarian carcinoma.* Cancer Immunol Immunother, 2010. **59**(6): p. 909-19.
43. Prins, R.M., et al., *NK and CD4 cells collaborate to protect against melanoma tumor formation in the brain.* Journal of Immunology, 2006. **177**(12): p. 8448-8455.

Proprietary Information of MD Anderson

44. Ribas, A., et al., *Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial.* Lancet Oncol, 2015. **16**(8): p. 908-18.
45. Rigel, D.S., J. Russak, and R. Friedman, *The evolution of melanoma diagnosis: 25 years beyond the ABCDs.* CA Cancer J Clin, 2010. **60**(5): p. 301-16.
46. Robert, C., et al., *Pembrolizumab versus Ipilimumab in Advanced Melanoma.* N Engl J Med, 2015. **372**(26): p. 2521-32.
47. Robert, C., et al., *Ipilimumab plus dacarbazine for previously untreated metastatic melanoma.* N Engl J Med, 2011. **364**(26): p. 2517-26.
48. Sasaki, A., et al., *Prognostic value of tumor-infiltrating FOXP3+ regulatory T cells in patients with hepatocellular carcinoma.* Eur J Surg Oncol, 2008. **34**(2): p. 173-9.
49. Sharpe, A.H. and G.J. Freeman, *The B7-CD28 superfamily.* Nat Rev Immunol, 2002. **2**(2): p. 116-26.
50. Shen, Z., et al., *Higher intratumoral infiltrated Foxp3+ Treg numbers and Foxp3+/CD8+ ratio are associated with adverse prognosis in resectable gastric cancer.* J Cancer Res Clin Oncol, 2010. **136**(10): p. 1585-95.
51. Suzuki, H., et al., *Intratumoral CD8(+) T/FOXP3 (+) cell ratio is a predictive marker for survival in patients with colorectal cancer.* Cancer Immunol Immunother, 2010. **59**(5): p. 653-61.
52. Talmadge, J.E., M. Donkor, and E. Scholar, *Inflammatory cell infiltration of tumors: Jekyll or Hyde.* Cancer Metastasis Rev, 2007. **26**(3-4): p. 373-400.
53. Thompson, R.H., et al., *PD-1 is expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma.* Clin Cancer Res, 2007. **13**(6): p. 1757-61.
54. Usubutun, A., et al., *Prognostic factors in renal cell carcinoma.* J Exp Clin Cancer Res, 1998. **17**(1): p. 77-81.
55. Wilson, E.H., W. Weninger, and C.A. Hunter, *Trafficking of immune cells in the central nervous system.* J Clin Invest, 2010. **120**(5): p. 1368-79.
56. Wolchok, J.D., et al., *Nivolumab plus ipilimumab in advanced melanoma.* N Engl J Med, 2013. **369**(2): p. 122-33.
57. Yang, J.C., et al., *Ipilimumab (anti-CTLA4 antibody) causes regression of metastatic renal cell cancer associated with enteritis and hypophysitis.* J Immunother, 2007. **30**(8): p. 825-30.