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| **Protocol ID** | 2019-1091 |
| **Protocol Title** | **Phase I/II Trial of BINTRAFUSP ALFA (M7824) and Pimasertib for Treatment of Intracranial Metastases** |
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| **Protocol PI** | Hussein Tawbi, MD, PhD |
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| | |
| **Investigational Products** | **BINTRAFUSP ALFA (M7824) and Pimasertib** |
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PROTOCOL

**TITLE:** Phase I/II Trial of BINTRAFUSP ALFA (M7824) and Pimasertib for Treatment of Intracranial Metastases

**STUDY NUMBER:** MDACC: *2019-1091*

**VERSION NUMBER:** Version 5

**PROTOCOL DATE:** *26 September 2023*

**TEST PRODUCTS:** BINTRAFUSP ALFA (M7824)
Pimasertib

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TRIAL SUMMARY

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| **Title of Study** | Phase I/II Trial of Bintrafusp Alfa (M7824) and Pimasertib for Treatment of Intracranial Metastases |
| **Protocol Number** | 2019-1091 |
| **Principal Investigator** | Hussein Tawbi, MD, PhD |
| **Project Phase** | Phase 1/2 |
| **Number of Study Center(s)** | 1 |
| **Objectives** | **Phase I Primary Objective**<br>• Establish safety profile and recommended phase II dose for combining Bintrafusp Alfa (M7824) and pimasertib in patients with brain metastases.<br>**Phase II Primary Objective**<br>• Time to intracranial progression (defined as progression of existing lesions and development of new lesions by modified RECIST 1.1) and Overall survival.<br>**Secondary Objectives**<br>• Intracranial progression 4, 8, 12, 16 weeks and every 8 weeks thereafter.<br>• Intracranial objective response rate as measured by RANO-BM, iRANO, and RECIST 1.1.<br>• Time to second intracranial progression after Salvage SRS<br>• Overall survival rate at 24, 52, 68 weeks.<br>• Frequency of grade 3+ intracranial toxicities at 4, 12, 24, 36, 52, and 68 weeks..<br>• Frequency of extracranial progression and response rate at 8, 16, 24, and every 8 weeks thereafter.<br>• Frequency of neurocognitive decline at 24, 52, and 68 weeks (optional).<br>• Changes in neurocognitive function and health-related quality of life.<br>• Dose, duration and frequency of steroid use for symptomatic management.<br>**Exploratory Objectives**<br>• Identify molecular and/or immunological markers from biospecimens (tissue, blood, and CSF) that are associated with treatment response and toxicity.<br>• Identify imaging biomarkers of response and toxicity (acute radiation effect/radionecrosis and neurocognitive changes) from multiparametric MRI and/or delayed PET that predict treatment response and toxicity.<br>• Dose, duration and frequency of steroid use for symptomatic management.<br>• To evaluate the potential correlation between mutational burden and tumor response |

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| **Study Design** | • Identify correlative or surrogative relationship between systemic (blood) and imaging markers and treatment outcomes.<br><br>This study is an open-label Phase I/II trial to determine the safety and efficacy of pimasertib in combination with Bintrafusp Alfa (M7824) in patients with brain metastases. The Phase I study will accrue patients with melanoma, lung, and breast cancers to a dose escalation phase as described below. The Phase II study will include expansion cohorts, of 10 patients each with melanoma, lung, breast brain metastases, to better characterize the safety profile and efficacy of the combination and its impact on time to intracranial progression.<br><br>We have also incorporated an early imaging time point to allow the application of stereotactic radiosurgery (SRS) to intracranial lesions that are either progressing or not responding. This decision will be made in the context of multi-disciplinary care provided at the MD Anderson Brain Metastasis Clinic. |

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| | **Key Inclusion Criteria** (Please see section 5.1 for complete eligibility criteria)<br><br>1. Age ≥ 18 years old.<br>2. Life Expectancy > 12 weeks.<br>3. Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.<br>4. At least one measurable untreated brain lesion ≥ 0.5 cm and <3.0 cm in the longest axis according to modified RECIST 1.1.<br>5. Prior SRS with up to 10 lesions treated with at least a 14 day interval is allowed as long as the previous treatment volume does not overlap with the current targets. The target could be a previously irradiated lesion with clear evidence of progression.<br>6. Have a performance status of 0 or 1 on the ECOG Performance Scale.<br>7. 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.<br>8. Prior treatment with immunotherapy and targeted therapy allowed as long as it did not include a combination of MEKi + anti-PD(L)-1 antibody and is >14 days prior to start of protocol therapy. All tumor types will be eligible and included in the dose escalation phase. Dose expansions will include 10 patients each from lung, breast, and melanoma.<br>9. Patients with melanoma must have received prior PD-1 based therapy.<br>10. Patients with NSCLC must have received prior PD-1 based therapy.<br>11. Patients with TNBC and HR+ are included (any number of prior lines of therapy- including IO naïve patients).<br>12. For HR+ patients, patients are allowed to receive endocrine therapy (Arimidex, letrozole, exemestane, or fulvestrant). Concurrent CDK4/6 inhibitors will not be allowed.<br>13. Systematic radiation therapy is allowed (>14 day washout)<br>14. Prior platinum-based chemotherapy for NSCLC patients is allowed |

Exclusion Criteria

1. Patients with clinical or radiographic evidence of leptomeningeal disease.
2. Those who experienced grade 3 or 4 neurotoxicity from prior SRS.
3. Contraindications to MRI (implanted metal device or foreign bodies) or MRI contrast (insufficient renal function or allergy).
4. 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.
5. Active secondary malignancy unless the malignancy is not expected to interfere with the evaluation of safety and is approved by the PI. Examples of the latter include basal or squamous cell carcinoma of the skin, in-situ carcinoma of the cervix, and isolated elevation of prostate-specific antigen. Subjects with a completely treated prior malignancy and no evidence of disease for ≥ 2 years are eligible.
6. Has a known history of or is positive for hepatitis B (hepatitis B surface antigen [HBsAg] reactive) or known active hepatitis C virus infection (note treated and cured history of hepatitis C is allowed)(hepatitis C virus [HCV] RNA [qualitative] is detected). 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.
7. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.
8. 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.
9. 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.
10. 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.
11. Non-healing wound, ulcer.
12. Women who are breast-feeding or pregnant.
13. Subjects with a history of serious intercurrent chronic or acute illness, such as cardiac or pulmonary disease, hepatic disease, bleeding diathesis or recent major bleeding events or other illness considered by the Investigator as high risk for investigational drug treatment
14. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within the 6 months before start of study medication (except for adequately treated catheter-related venous thrombosis occurring more than 1 month before the start of study medication).
15. 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.
16. Investigational drug use within 14 days (or 5 half-lives, whichever is longer) of the first dose of bintrafusp alfa and/or pimasertib.
17. Has a history of (Grade 3 or 4) non-infectious pneumonitis that required steroids or current pneumonitis.
18. Retinal degenerative disease (hereditary retinal degeneration or age-related macular degeneration), history of retinal vein occlusion (RVO) or any eye condition that would be considered as risk factor for RVO (e.g. uncontrolled glaucoma or ocular hypertension)
20. Creatine phosphokinase level at baseline NCI CTCAE Grade ≥2 (>2.5x ULN – 5x ULN) and/or previous history of myositis or rhabdomyolysis
21. For NSCLC cohort patients whose tumor exhibit activating EGFR mutation, ALK or ROS translocation and have a standard of care molecular targeted therapy available for these mutations, will be excluded from this study. Patients who progressed or could not tolerate these standard of care molecular targeted agents are eligible for this study. Lung adenocarcinoma patients may be consented prior to the EGFR and ALK status being known, but EGFR and ALK status must be determined prior to initiating therapy
22. Administration of live, attenuated vaccine therapies for the prevention of infectious diseases within 4 weeks prior to day 1 of treatment and during therapy

## 1.0 BACKGROUND INFORMATION

### 1.1 DISEASE BACKGROUND: BRAIN METASTASES

Metastatic tumors to the brain are by far the most common intracranial malignancy, totaling about 170,000 per year and developing in about 40% of all advanced cancer patients. Patients with metastatic brain lesions far outnumber patients with primary brain tumors [1-3]. Patients with advanced malignancies have been surviving longer with improved control of extra-cerebral disease due to new targeted and immune therapies. These therapeutic approaches (e.g., anti-PD-1 antibodies and BRAF-targeted therapy in melanoma, anti-HER2 in metastatic HER2+ breast cancer, epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitors in EGFR-mutated non-small cell lung cancer (NSLSC)) [1–3] increase efficacy allowing for improved survival. Indeed the 5-year outcomes from PD-1 based therapy in melanoma indicate survivals rates of up to 40%, and in NSCLC, the 5-year OS in PD-L1 TPS 50 or above is 25%. [56] Hence, the incidence of brain metastases has been increasing. Additionally, other factors may contribute, including improved detection of small metastases by magnetic resonance imaging (MRI). Nonetheless, the incidence of BMs depends on the type of primary cancer, varying from approximately 5–50%.[4] CNS involvement occurs more commonly in lung cancer, breast cancer, melanoma, and renal cell carcinoma patients.[4] Metastatic CNS disease can have devastating neurologic effects including focal neurologic dysfunction, cognitive dysfunction, seizures, stroke-like symptoms, and death. The features that impact outcome of brain metastases include their primary histology, number, size and site of brain metastases, the status of extra-cranial disease, and the performance status of the patient. BMs are associated with a poor prognosis. Overall survival varies according to the tumor types and tumor subtypes from 3 to 25 months.[4 ]

Novel therapeutic approaches are direly needed, and consideration needs to be made for combination of effective therapies including targeted agents, immunotherapy, with radiation therapy.

### DISEASE BACKGROUND: RADIATION THERAPY FOR BRAIN METASTASES

CNS directed therapies including surgery, stereotactic radiosurgery (SRS) (gammaknife (GK), or whole brain radiation therapy (WBRT) have been the mainstay of therapy. However, the optimal treatment of multiple brain metastases is not well defined and still very inadequate. The paucity of data in the management of CNS metastases is further highlighted as patients with symptomatic brain metastases are often excluded from participation in clinical trials, thereby further limiting outcomes data in this patient population. Many

patients who have controlled systemic disease frequently develop progressive or recurrent brain metastases. For these patients, no single standard of care option for treatment exists.

Radiation is commonly utilized to treat brain metastases via WBRT or SRS. WBRT can be conducted utilizing a number of different treatment machines and is most typically performed with a conventional linear accelerated. WBRT is given through a fractionated schedule with a typical regime being 30 Gy in 10 fractions. WBRT has limited efficacy and impacts poorly on the quality of life. WBRT is associated with significant side effects and complications, with cognitive decline, including memory loss, impaired executive function and speed of processing, being the most feared one, and these late complications are usually irreversible. A recent clinical trial has demonstrated at least 65% probability of significant cognitive decline at 24 weeks associated with WBRT.[5] In addition, WBRT causes a minimum of 4-6 weeks interruption of systemic therapy, which can lead to progression of systemic disease and worse survival.[6] As a result, there has been vigorous effort in recent years to improve treatment of brain metastasis. The outcomes of 86 melanoma patients with brain metastases were widely varied: in those treated with WBRT alone, the median survival was 3 months; in those treated with SRS, the median survival was 7 months; and surgery was associated with a median survival of 11-12 months [27].

Stereotactic radiosurgery (SRS) is a type of external radiation therapy that uses multiple beams to deliver a large dose of radiation to a tumor in a single session. SRS is conducted via a number of possible modalities including Gamma Knife or a conventional linear accelerator. Treatment is either as a single fraction or hypofractionated (within 3-5 fractions). Generally speaking, SRS is utilized to treat a limited number of brain metastases while WBRT is utilized to treat more widespread disease. However, the definition of what constitutes limited versus widespread continues to evolve. SRS is highly preferred and can be utilized in 1-3 metastases according to NCCN guidelines; however in practice, SRS is frequently utilized in patients with many more brain lesions [8]. The use of immunotherapy may complement radiation therapy because the latter damages the blood brain barrier (BBB), alters the tumor microenvironment, and increases immunogenicity of tumors.

Two phase III trials in patients with 1-3 brain metastases, one conducted at MD Anderson [9] and one through a cooperative group,[10] have established SRS as the standard care in this patient population. Currently we are investigating whether the use of SRS can be expanded to patients with more brain metastases in a phase III trial randomizing patients with 4-15 brain metastases to SRS vs. WBRT (NCT01592968).

There is pre-clinical and clinical data suggesting clinical activity of systemic anti-neoplastic therapies, including immunotherapies and targeted therapies. One of the challenges of treating brain metastases is the blood-brain barrier leading to poor permeability of many drugs. The blood-brain barrier is a highly selective permeability barrier comprised of capillary endothelial cells, which are connected by tight junctions and astrocyte foot processes that limit diffusion of molecules and drugs into the CNS compartment [11, 12].

Additionally, as brain metastases tend to occur later in the disease course, these tumors may be biologically and genomically distinct from the primary site or extracranial metastatic sites and may be more resistant to cytotoxic and targeted therapies [13, 14].

### **1.2** DISEASE BACKGROUND: BRAIN METASTASES AND MELANOMA

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 [29]. 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. In 2016, there will be an estimated 76,380 new melanoma patients and 10,130 melanoma-related deaths in the USA.[29] Melanoma is one of the few tumors whose incidence is still increasing, despite being preventable with appropriate sun protection. The majority of patients present with localized disease and their prognosis is excellent if primary tumors are 1.0 mm or less in thickness. However, when there is lymph node involvement, survival rates are roughly halved due to the significant increase in the risk of distant systemic metastases including to lung, liver, and brain. Patients with metastatic disease historically face long-term survival rates of less than 10%, although this scenario is dramatically changing after the emergence of groundbreaking systemic therapies, including BRAF and MEK inhibitors for patients harboring a BRAF mutation, immunotherapeutic agents such as Cytotoxic T-Lymphocyte Antigen 4 (CTLA4) inhibitors and especially Programmed Death 1 (PD-1) inhibitors.[5-11] Long-term remissions are being increasingly observed in patients that respond to therapy, bringing new hope and excitement to the field.

Population studies demonstrate cutaneous melanoma is the third most common cause of brain metastasis development only after the lung and breast cancer, reflecting its distinctive neurotropism.[30-32] Approximately 40-50 % of stage IV melanoma patients eventually develops clinical manifestations of melanoma brain metastasis (MBM).[33] The prevalence is likely higher as autopsy series have reported 55–75 % of melanoma patients have MBM.[34, 35] Although outcomes differ for patients with MBM, overall prognosis remains poor. The overall survival reflects the effects of therapy on both intracranial and extracranial disease at the time of presentation and may not be entirely representative of intracranial disease control. Even with early diagnosis and aggressive local therapy, MBM is the cause of death in nearly 95 % of patients.[31] The bleak outcomes of MBM have not been mitigated over the past three decades, and although the last 4 years have brought tremendous promise for patients with metastatic melanoma, this has not yet translated into improved outcomes for MBM, since these patients have been systematically excluded from the vast majority of clinical trials of investigating systemic therapy.

The management of MBM has been traditionally limited to surgical or radiotherapy approaches. However, melanoma is a relatively radiation-resistant tumor; as melanoma cells were shown in early in vitro studies to have a low responsiveness to radiation, which corresponded with documented low efficacies of WBRT in clinical use.[36] Patients with MBMs who underwent WBRT treatment alone even in the early 2000's had a median survival of only 3.4 months compared with 2.1 months if they received supportive care alone.[37-40] Given this limited benefit, WBRT use is generally limited to MBM patients with no surgical options, symptomatic diffuse disease, large volume single lesions or leptomeningeal spread of disease. In contrast to the limited role of WBRT, SRS has emerged as a highly effective local therapeutic approach to MBM treatment. Since the studies performed by Patchell et al.[30, 31] in the 1990's, the overall management of brain metastases has changed significantly. The added value of WBRT to SRS is questionable; a randomized trial involving multiple tumor types showed that intracranial metastatic control following WBRT+SRS was not significantly different than after SRS alone, and OS was also equivalent.[41] Additionally, the response of brain metastases was independent of cancer type and previously designated radio-resistance.[42] Further, a small study comparing WBRT alone to WBRT+SRS was stopped early due to a 1-year local failure rate of 100% in those undergoing WBRT alone versus only an 89% failure rate in those undergoing WBRT+SRS.[43] SRS alone has therefore now become the standard treatment for the majority of patients with limited MBMs.

Systemic therapy has not been used effectively. Discovery of driver mutations in RAS-MAP-kinase signaling pathway has led to the development of agents targeting specific enzymes including BRAF and MEK. Single-agent BRAF inhibitors dabrafenib and vemurafenib have been proven safe to administer in patients with BRAF-mutated melanoma and active MBM and have activity that parallels extracranial activity with objective intracranial response rate (OIRR) of 35-42%.[45, 46] Still, progression-free and overall survivals are still lower for this population than for patients with only extracranial metastases, with few systemic alternatives for patients after progression. Furthermore, BRAF mutation is only detected in about half of melanoma patient. The combination of BRAF inhibitor dabrafenib and MEK inhibitor trametinib is being evaluated for active melanoma brain metastasis in a clinical trial (ClinicalTrials.gov Identifier: NCT02039947).

The recent approval of immunotherapeutic agents has also brought some enthusiasm for this population. Single-agent ipilimumab has been proven safe and at least as effective intracranially versus (vs) extracranially, but still with low response rates (up to 16%), and mostly in asymptomatic patients.[20] Pembrolizumab was studied in 18 patients with untreated or progressive MBM, with 4 durable responses (22%), including 2 complete responses.[21] This promising activity from immunotherapy in brain metastasis, however, is restricted by the requirement of no systemic corticosteroids to achieve maximal benefit, as was the case with ipilimumab, which can pose a problem since corticosteroids can be crucial to managing perilesional edema in the brain. In addition, immunotherapy with PD-1 antibodies itself can induce further swelling by increasing influx of inflammatory cells. In the study with pembrolizumab, 17% of treated patients experienced seizure activity, indicating a potential need for strategies to reduce or limit perilesional edema that do not curtail the immunotherapeutic effect.

Recent advances in targeted and immunotherapy of melanoma have led to intracranial responses with systemic therapy. Targeted therapy with BRAF/MEKi leads to a high rate of intracranial responses similar to extracranial disease albeit of seemingly shorter duration. Immunotherapy with combination anti-CTLA4 and anti-PD-1 antibodies has led to high response rates in patients with melanoma brain metastases that have the following characteristics: a) clinical responses as early as 6 weeks, b) complete responses in 26% and overall objective response rate in 56% of patients, c) durability in >90% of patients, d) high concordance between extracranial and intracranial disease, and e) high progression free survival rates of >60% at one year. [53, 54].

### **1.3** DISEASE BACKGROUND: BRAIN METASTASES AND BREAST CANCER

Brain metastases (BMs) are the most common central nervous system (CNS) tumors in adults. The incidence of BMs is increasing due to both improved diagnostic techniques (e.g. magnetic resonance imaging: (MRI) and increased cancer patient survival through advanced systemic treatment approaches (e.g. anti-*HER2* in metastatic *HER2* breast cancer, epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitors in EGFR-mutated non-small cell lung cancer (NSCLC) [23-25]. The incidence of BMs depends on the type of primary cancer, varying from approximately 5–50% [4]. CNS involvement occur more commonly in lung cancer, breast cancer, melanoma, and renal cell carcinoma patients[4]. BMs are associated with a poor prognosis. Overall survival varies according to the tumor types and tumor subtypes from 3 to 25 months[4]. In breast cancer, differences in survival of patients with BMs by tumor subtype (luminal, *HER2* and triple-negative metastatic breast cancer) have been observed and highlight the need for a tailored approach in this patient population[5]. Several predicting factors for BMs have been identified to date and include age, histological grade, negative status of estrogen receptor, *HER2* and number of non-CNS metastatic sites (1 *versus* >1) [26].

To date, general indications to use systemic treatments for BMs is limited to highly chemotherapy-sensitive primary tumors, BMs from primary tumors with identified molecular alterations amenable to targeted therapy crossing the BBB, asymptomatic BMs found on screening MRI with planned systemic treatment, or in cases in which other therapeutic options have been exhausted and there is a drug available [7]. This is due to the lack of efficacy of systemic treatment including in breast cancer patients with BMs. Consequently, until recently, treatment of BMs from breast cancer was focused on local therapy (surgery or radiotherapy) [27].

Indeed, adding active systemic therapy to local (radiation, surgery) therapy could be one effective way to improve the outcome of patients with BMs. The concept aims to use and to enhance both local and systemic effects of the treatment. The immune stimulatory effects of radiation therapy in combination with immunotherapy [e.g. checkpoint inhibitors, CAR (chimeric antigen receptor)-T cell [28] is an example of this innovative approach.

In breast cancer, differences in survival of patients with BMs by tumor subtype (luminal, HER2 and triple-negative metastatic breast cancer) have been observed and highlight the need for a tailored approach in this patient population.[5] Several predicting factors for BMs have been identified to date and include age, histological grade, negative status of estrogen receptor, HER2 and number of non-CNS metastatic sites (1 versus >1).[6]

### 1.4 Disease Background: Brain Metastases and Lung Cancer

Lung cancer is the leading cause of worldwide cancer mortality, and is responsible for more deaths annually in the United States than the combination of breast, colorectal, and prostate cancer, with an estimated 1.04 million new cases each year worldwide[15,16]. Non–small cell lung cancer (NSCLC) accounts for approximately 75% of all lung cancers. Of these, approximately one third will develop brain metastasis at some time during the course of their disease. Brain metastases are a common problem in patients with metastatic NSCLC. About 7%–10% of NSCLC patients present with brain metastases at the time of initial diagnosis, and as many as 20%–40% of patients develop brain metastases at some point during their illness[17-20]. Additionally, 50% of all brain metastases are from lung primary tumors[21]. Unfortunately for the vast majority of these patients, this diagnosis is associated with significant morbidity in addition to shortened survival. Present treatments for brain metastases include surgery in select patients with limited intracranial and systemic disease burden and good performance status. However, the majority of patients receive treatment for their brain metastases via whole brain radiation Therapy (WBRT) and Stereotactic Radiosurgery (SRS). These modalities are often quite effective in alleviating symptoms; however, median survival remains poor, estimated to be between 2-7 months[22]. Clearly new treatments are needed.

Radiation is commonly utilized to treat brain metastases via WBRT or SRS. Generally speaking, SRS is utilized to treat a limited number of brain metastases while WBRT is utilized to treat more widespread disease. However, the definition of what constitutes limited versus widespread continues to evolve. WBRT can be conducted utilizing a number of different treatment machines and is most typically performed with a conventional linear accelerated. WBRT is given through a fractionated schedule with a typical regime being 30 Gy in 10 fractions. On the other hand SRS is conducted via a number of possible modalities including Gamma Knife or a conventional linear accelerator. Treatment is either as a single fraction or hypofractionated (within 3-5 fractions).

## Therapeutic Agents Background: BINTRAFUSP ALFA (M7824) and Pimasertib

*Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on Bintrafusp Alfa (M7824) and Pimasertib.*

*Background on Bintrafusp Alfa (M7824)*

Bintrafusp Alfa (M7824) is a novel fusion protein comprised of the extracellular domain of the human TGFβ-RII (transforming growth factor beta –receptor II) that is covalently linked to the C-terminus of the heavy chain of the anti-PD-L1 (anti-programmed death ligand 1) antibody via a flexible (Gly4Ser) 4G linker. The anti-PD-L1 moiety of Bintrafusp Alfa (M7824) is identical to anti-PD-L1 monoclonal antibody avelumab, except for 3 amino acid substitutions in the heavy chain constant regions that result in a different human IgG1 allotype, and one amino acid substitution in the heavy chain for antibody fusion protein stability. As of June 2017, FDA has granted accelerated approval to avelumab for metastatic Merkel cell carcinoma (MCC) and locally advanced or metastatic urothelial carcinoma whose disease progressed during or following platinum-containing chemotherapy.

The TGFβRII component functions as a TGFβ neutralizing 'trap". Bintrafusp Alfa (M7824) is designed to target two negative regulatory pathways in immunosuppression: the cell-intrinsic one mediated by tumor cell-immune cell interaction, in which programmed death ligand-1 (PD-L1)/programmed

## 1.5 PIMASERTIB

Pimasertib is an orally bioavailable small-molecule inhibitor of MEK1 and MEK2 (MEK1/2) with potential antineoplastic activity. Pimasertib selectively binds to and inhibits the activity of MEK1/2, preventing the activation of MEK1/2-dependent effector proteins and transcription factors, which may result in the inhibition of growth factor-mediated cell signaling and tumor cell proliferation. MEK1/2 (MAP2K1/K2) are dual-specificity threonine/tyrosine kinases that play key roles in the activation of the RAS/RAF/MEK/ERK pathway and are often upregulated in a variety of tumor cell types.

Pimasertib (MSC1936369B) is an orally bioavailable and selective small-molecule inhibitor of MEK1 and MEK2 that prevents the activation of MEK1/2-dependent effector proteins and transcription factors [47, 48]. It has demonstrated robust antitumor activity in preclinical studies, including tumor growth reduction in murine myeloma xenografts [47] and tumor regression in a mouse model of D-MUT colorectal cancer [48] and it has also been shown to circumvent resistance to BRAF inhibition in human melanoma cells [47].

Pimasertib given as a single agent showed acceptable toxicity with a maximum tolerated dose (MTD) that depended on the treatment schedule in patients with advanced solid tumors [49]; with continuous twice daily administration, the MTD was 75 mg. When pimasertib was given in combination with FOLFIRI (5-fluorouracil/folinic acid/irinotecan), the MTD was reached at 45 mg/day in a 5 days on/2 days off schedule in patients with *KRAS*-mutated metastatic colorectal cancer [50].

## 2.0 RATIONALE FOR THE STUDY

### 2.1 RATIONALE FOR COMBINING IMMUNOTHERAPY WITH TARGETED THERAPY IN THE TREATMENT OF BRAIN METASTASES

Immunotherapies that target the interactions between antigen presenting cells (APCs), T lymphocytes, and cancer cells to potentiate an anti-tumor immune response have been developed, with many recently approved by the FDA for specific indications in many advanced malignancies. Over the past few years, immunomodulation has come to be a mainstay in the treatment algorithm in many malignancies, including melanoma and NSCLC, and a number of other cancers.
Nonclinical data show a negative association between MEK activity and active antigen presentation (MHC-1 and II expression) that appears to be coupled to simultaneous PD-L 1 expression [51-52]). These findings link the MAPK pathway activation to the tumor immune-evasion. Consistently, MEK inhibition results in an increased number of tumor-infiltrating CDS-positive T lymphocytes and PD-L 1 and MHC expression [51-52]. These effects are responsible for the enhanced anti-tumor immune response observed with the combination of MEK with PD-L 1/PD-1 inhibitors [52].

The combination of a MEKi with immunotherapy has been studied in preclinical models and confirmed the presence of additivity if not synergy. The combination of cobimetinib and atezolizumab has also shown up to 50% ORR in patients with melanoma in a Phase I study and has now moved into the Phase III setting. IMspire is a Phase III study currently examining the combination of cobimetinib+atezolizumab vs pembrolizumab in patients with BRAF-wt melanoma (NCT03273153).

While there are number of trials looking into every possible combination of targeted therapies and IO, there is no clinical trial specifically in NSCLC has been matured yet. [57]

Standard Treatment for patients with oligo-brain metastases remains stereotactic radiosurgery. In recent years, immunotherapy and MEK inhibitors have shown intracranial activity in melanoma patients with brain metastases, raising question on whether such intracranial activity from immunotherapy and target agents can have sufficient intracranial activity to hold or delay SRS with the goal to minimize SRS treatment toxicity, without compromising patients' survival or intracranial control.

Pimasertib has excellent BBB penetration and can overcome one of the major issues facing other MEKi. Finally, using a bispecific PD-L1 and TGFβ neutralizing 'trap" tackles 2 potential mechanisms of resistance to immunotherapy that are relevant for melanoma, breast, and lung cancers.

The goal of this combination is ultimately to seek synergy between MEK inhibition and the dual inhibition of PD-1/PD-L1 pathway and TGFbeta. It is also conceivable that potentiating the immune response, while augmenting tumor response, could also result in a higher rate of toxicities. At one level, immune-related toxicities could be augmented with specific attention being paid to pneumonitis and liver dysfunction. While the mechanism by which MEK inhibitors cause pneumonitis is distinct, it could still be perpetuated in the presence of an immune response. We will follow patiens closely for those events and manage promptly. Another potential overlapping toxicity is uveitis. However, MEKi have been combined safely with anti-PD-L1 previously as in the Phase III study of cobimetinib+atezolizumab +/- regorafenib in colorectal cancer [58].

### *2.2* Rationale for combining immunotherapy with stereotactic radiosurgery (SRS) in the treatment of brain metastases

There is pre-clinical and clinical data suggesting clinical activity of systemic anti-neoplastic therapies, including immunotherapies and targeted therapies. One of the challenges of treating brain metastases is the blood-brain barrier leading to poor permeability of many drugs. The blood-brain barrier is a highly selective permeability barrier comprised of capillary endothelial cells, which are connected by tight junctions and astrocyte foot processes that limit diffusion of molecules and drugs into the CNS compartment [48, 49]. Additionally, as brain metastases tend to occur later in the disease course, these tumors may be biologically and genomically distinct from the primary site or extracranial metastatic sites and may be more resistant to cytotoxic and targeted therapies [50].

Radiation, in addition to providing effective local treatment through its tumoricidal effect via generation of DNA double strand breaks, has been found in recent years to trigger an immune response, leading to improved local control and abscopal effect (tumor regression in non-irradiated sites). This is achieved through radiation induced tumor neoantigen release, MHC class I expression, and pro-inflammatory cytokine release. Additionally, radiation has been found to modulate the immune suppressive tumor microenvironment by altering cell adhesion and immunomodulatory molecules and downregulating the suppressive cytokine effects. The best radiation regimen in inducing or supporting immune response is yet to be identified. Although stereotactic radiosurgery (SRS), which delivers high dose radiation in a single fraction was thought to generate the most robust immune response, recent pre-clinical study demonstrated that fractionated stereotactic radiation therapy (FSBRT), where radiation is delivered in 3-5 fractions, had better immune modulating effect through the STING pathway and induction of IFN-I. It would be of great importance to identify the best immune-promoting radiation regimen and to gain further knowledge on how radiation can interact with other CNS-penetrant small molecules to modulate tumor microenvironment and to enhance tumor killing.

## 3.0 STUDY DESIGN

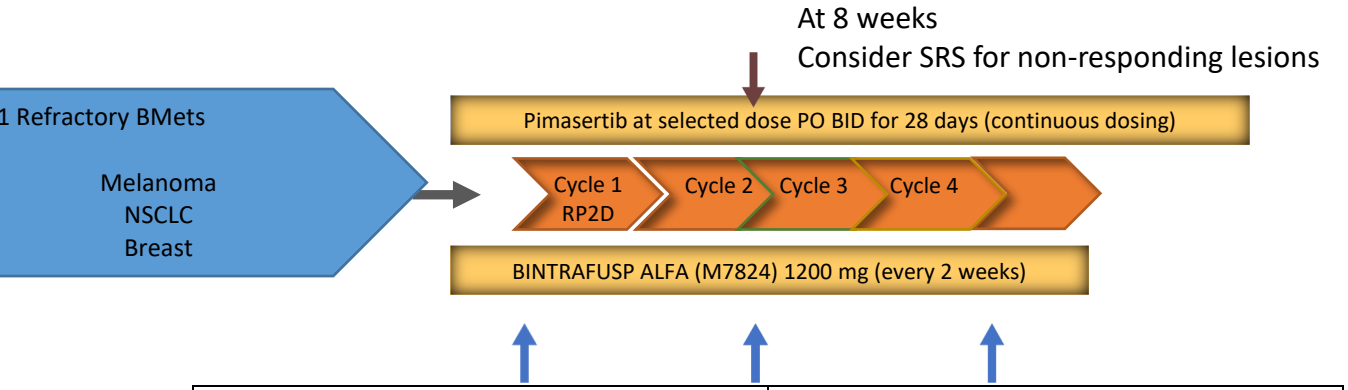
This study is an open-label Phase I/II trial to determine the safety and efficacy of pimasertib in combination with Bintrafusb Alfa (M7824) in patients with brain metastases. The Phase I study will accrue patients with melanoma, lung, and breast cancers to a dose escalation phase as described below. The Phase II study will include expansion cohorts, of 10 patients each with melanoma, lung, and breast brain metastases, to better characterize the safety profile and efficacy of the combination and its impact on time to intracranial progression.

We have also incorporated an early imaging time point to allow the application of SRS to intracranial lesions that are either progressing or not responding. This decision will be made in the context of multi-disciplinary care provided at the MD Anderson Brain Metastasis Clinic.

**Phase I:**
The phase I dose finding part of the study is to determine the recommended phase II dose (RP2D) of Bintrafusp Alfa (M7824) + pimasertib in patients with intracranial metastasis. The planned DL1 and DL2 doses are Bintrafusp Alfa (M7824) flat dose of 1200 mg every 2 weeks and pimasertib 45 mg PO BID (Dose Limit or DL1) and 60 mg PO BID (DL2), and fallback doses DL-1 are Bintrafusp Alfa (M7824) flat dose of 1200 mg every 2 weeks and Pimasertib at 30 mg PO BID. Every cycle will be 28 days. We will enroll up to 12 patients to the Phase I portion (18, should the trial de-escalate to DL-1). The standard "3+3" design will be employed to determine the RP2D. If DL1 is considered too toxic, DL-1 will be explored; if unacceptable toxicity is observed at DL-1, alternative dose schedules may be evaluated in an amendment. The recommended phase II dose (RP2D) is defined as the highest dose level with no more than 1 patient with DLT out of 6 patients that are treated. Please note that the study plans on enrolling up to 2 cohorts in Phase 1 of the trial (the 45mg and either the 30 or 60 mg, depending on the safety of Cohort 1).

**Phase II:**
The purpose of phase II part is to estimate the time to intra-cranial progression and overall survival time. In this part, we will enroll up to 24 patients into RP2D. The 6 patients treated at RP2D from phase I part of the study will be included in the Phase II part, thus resulting in a total of 30 patients at RP2D by the end of the study, with the goal of having 10 patients each of melanoma, NSCLC, and breast cancer. This phase II part is designed to collect data for future larger studies. Specifically, we would like to estimate time to intracranial progression considering death as a competing risk and overall survival time using Kaplan-Meier method, both with 95% confidence interval.

Figure 1: Study Schema




| | |
|---|---|
| DL-1 | 30 BID Pimasertib |
| DL1 | 45 BID Pimasertib |
| DL2 | 60 BID Pimasertib |

[Study Schema] – See Schedule of Assessments

## 4.0 OBJECTIVES

### 4.1 PRIMARY OBJECTIVE

#### 4.1.1 PHASE I PRIMARY OBJECTIVE

- Establish safety profile and recommended phase II dose for combining **pimasertib with bintrafusp alfa (M7824)** in patients with brain metastases.

#### 4.1.2 PHASE II PRIMARY OBJECTIVE

- Time to intracranial progression (defined as progression of existing lesions and development of new lesions by modified RECIST 1.1)
- Overall survival.

## 4.2 SECONDARY OBJECTIVES

- Intracranial progression 4, 8, 12, 16 weeks and every 8 weeks thereafter.
- Intracranial objective response rate as measured by RANO-BM, iRANO, and RECIST 1.1.
- Time to second intracranial progression after Salvage SRS
- Overall survival rateat 24, 52 and 68 weeks .
- Frequency of grade 3+ intracranial toxicities at 4, 12, 24, 36, 52, and 68 weeks.Frequency of extracranial progression and response rate at 8, 16, 24, every 8 weeks.
- Frequency of neurocognitive decline 12, 24, 36 weeks (optional).Changes in neurocognitive function and health-related quality of life.
- Dose, duration and frequency of steroid use for symptomatic management.
- Evaluation of safety and tolerability of pimasertib/bintrafusp alfa combination

## 4.3 EXPLORATORY OBJECTIVE

- Identify molecular and/or immunological markers from biospecimens (tissue, blood, and CSF) that are associated with treatment response and toxicity.
- Identify imaging biomarkers of response and toxicity (acute radiation effect/radionecrosis and neurocognitive changes) from multiparametric MRI and/or delayed PET that predict treatment response and toxicity.
- Identify correlative or surrogative relationship between systemic (blood) and imaging markers and treatment outcomes.

# 5.0 PATIENTS

## 5.1 INCLUSION CRITERIA

1. Age ≥ 18 years old.
2. Life Expectancy > 12 weeks.
3. Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.
4. At least one measurable untreated brain lesion ≥ 0.5 cm and <3.0 cm in the longest axis according to modified RECIST 1.1.
5. Prior SRS with up to 10 lesions treated with at least a 14 day interval is allowed as long as the previous treatment volume does not overlap with the current targets. The target could be a previously irradiated lesion with clear evidence of progression.
6. Have a performance status of 0 or 1 on the ECOG Performance Scale.
7. 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.
8. Prior treatment with immunotherapy and targeted therapy allowed as long as it did not include a combination of MEKi + anti-PD(L)-1 antibody and is >14 days prior to start of protocol therapy. All tumor types will be eligible and included in the dose escalation phase. Dose expansions will include 10 patients each from lung, breast, and melanoma.
9. Patients with melanoma must have received prior PD-1 based therapy.
10. Patients with NSCLC must have received prior PD-1 based therapy.
11. Patients with TNBC and HR+ are included (any number of prior lines of therapy- including IO naïve patients).
12. For HR+ patients, patients are allowed to receive endocrine therapy (anastrozole, letrozole, exemestane, or fulvestrant). Concurrent CDK4/6 inhibitors will not be allowed.
13. Systematic radiation therapy is allowed (>14 day washout)
14. Prior platinum-based chemotherapy for NSCLC patients is allowed
15. 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 | ≤1.5 × ULN OR |
| Measured or calculated [b] creatinine clearance (GFR can also be used in place of creatinine or CrCl) | ≥60 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) | ≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants |
| Activated partial thromboplastin time (aPTT) | |

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.

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 <u>not</u> a woman of childbearing potential as defined in Appendix 5.

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.
All associated toxicity from previous or concurrent cancer therapy must be
resolved (to ≤ Grade 1 or Baseline) prior to study treatment administration, unless stable status as assessed by investigator e.g. hypothyroidism, adrenal insufficiency, or other.Steroids for physiological replacement are allowed.

## 5.2 EXCLUSION CRITERIA

1. Patients with clinical or radiographic evidence of leptomeningeal disease.
2. Those who experienced grade 3 or 4 neurotoxicity from prior SRS.
3. Contraindications to MRI (implanted metal device or foreign bodies) or MRI contrast (insufficient renal function or allergy).
4. 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.
5. Active secondary malignancy unless the malignancy is not expected to interfere with the evaluation of safety and is approved by the PI. Examples of the latter include basal or squamous cell carcinoma of the skin, in-situ carcinoma of the cervix, and isolated elevation of prostate-specific antigen. Subjects with a completely treated prior malignancy and no evidence of disease for ≥ 2 years are eligible.
6. Has a known history of or is positive for hepatitis B (hepatitis B surface antigen [HBsAg] reactive) or known active hepatitis C virus infection (note treated and cured history of hepatitis C is allowed)(hepatitis C virus [HCV] RNA [qualitative] is detected). Note: Without known history, testing needs to be performed to determine eligibility. Hepatitis C antibody (Ab) testing is allowed for screening purposes.
7. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.
8. 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.

9. 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.
10. 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.
11. Non-healing wound, ulcer, or bone fracture.
12. Women who are breast-feeding or pregnant.
13. Subjects with a history of serious intercurrent chronic or acute illness, such as cardiac or pulmonary disease, hepatic disease, bleeding diathesis or recent major bleeding events or other illness considered by the Investigator as high risk for investigational drug treatment
14. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within the 6 months before start of study medication (except for adequately treated catheter-related venous thrombosis occurring more than 1 month before the start of study medication).
15. 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.
16. Investigational drug use within 14 days (or 5 half-lives, whichever is longer) of the first dose of bintrafusp alfa and/or pimasertib.
17. Has a history of (Grade 3 or 4) non-infectious pneumonitis that required steroids or current pneumonitis.
18. Retinal degenerative disease (hereditary retinal degeneration or age-related macular degeneration), history of retinal vein occlusion (RVO) or any eye condition that would be considered as risk factor for RVO (e.g. uncontrolled glaucoma or ocular hypertension)
19. Creatine phosphokinase level at baseline NCI CTCAE Grade ≥2 (>2.5x ULN – 5x ULN) and/or previous history of myositis or rhabdomyolysis
20. For NSCLC cohort patients whose tumor exhibit activating EGFR mutation, ALK or ROS translocation and have a standard of care molecular targeted therapy available for these mutations, will be excluded from this study. Patients who progressed or could not tolerate these standard of care molecular targeted agents are eligible for this study. Lung adenocarcinoma patients may be consented prior to the EGFR and ALK status being known, but EGFR and ALK status must be determined prior to initiating therapy
22. Administration of live, attenuated vaccine therapies for the prevention of infectious diseases within 4 weeks prior to day 1 of treatment and during therapy. Locally

approved COVID-19 vaccines are allowed.

# 6.0 TRIAL TREATMENT

## 6.1 BINTRAFUSP ALFA (M7824)

Bintrafusp alfa (MBINTRAFUSP ALFA (M7824) drug product is a sterile, liquid formulation formulation presented at a concentration of 600 mg/vial in United States Pharmacopeia (USP) type I glass vial closed with a rubber stopper and sealed with an aluminum plastic crimping cap.

Each vial contains 600 mg of Bintrafusp alfa (BINTRAFUSP ALFA (M7824) BINTRAFUSP ALFA (M7824) as a preservative-free histidine-buffered solution (pH=5.5) containing trehalose dihydrate, sodium chloride, L-methionine and polysorbate 20 (Tween 20). Only excipients that conform to the current USP are used for BINTRAFUSP ALFA (M7824) drug product.

Subjects will receive IV infusion of Bintrafusp alfa (BINTRAFUSP ALFA (M7824) BINTRAFUSP ALFA (M7824) over 1 hour (-10 minutes / +20 minutes) once every 2 weeks as detailed in the Schedules of Assessments. Modifications of the infusion rate due to infusion-related reactions are described in Section 6.2.3.

Bintrafusp Alfa (M7824) will be shipped in transport cool containers (2°C to 8°C) that are monitored with temperature control devices.

All IMPs will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

### 6.1.1 DOSAGE AND ADMINISTRATION

The dose for Bintrafusp Alfa (M7824) is a flat dose of 1200mg. Subjects will receive Bintrafusp Alfa (M7824) once every 2 weeks.. Subjects who have experienced a persistent, confirmed PR or CR may continue treatment through the end of 12 months, although additional treatment is possible. If the Principal Investigator believes that a subject may benefit from treatment beyond

12 months, it may be permissible after discussion with the EMD Serono. If there is no evidence of radiographic or clinical progression, then the patient may continue on study at the discretion of the principal investigator.

Participants who are discontinued due to an AE that are subsequently well managed or resolved after stopping therapy, but prior to the end of the study. Prior to reinitiation, the Principal Investigator will need to confirm that the benefit of reinitiating treatment outweighs any risk involved, such as that which led to initial treatment discontinuation. For participants with only stable disease at the time of discontinuation, the Principal Investigator should confirm that no other reasonable treatment options are available.

In addition, to be eligible for reinitiation (after dose delay), the participant must not have previously withdrawn consent for this trial and should have been followed up with regular eCRF documented evaluation scans up to reinitiation of treatment.

Prior to reinitiation of the study intervention, malignant disease must be radiologically restaged within 28 days of dosing to assess all known disease sites. Additionally, relevant safety laboratory assessments, including both full hematology and full chemistry results within 2 weeks, must be available and verified. The Principal Investigator will determine whether additional evaluation and work up are required on a case-by-case basis. A discussion with the study team is warranted to determine whether PK/biomarker testing is indicated upon restarting treatment.

The participant should reinitiate treatment at the treatment phase visit where they left off according to the Schedule of Activities. Participants who reinitiate treatment should stay on study and should be treated and monitored according the Schedule of Activities for the rest of the study.

## 6.2 PIMASERTIB

The drug substance pimasertib (recommended international non- proprietary name [INN]; also known as MSC1936369B or AS703026) is a biaryl amine derivative. Its chemical name according to International Union of Pure and Applied Chemistry (IUPAC) is N-[(2S)-2,3- dihydroxypropyl]-3-[(2-fluoro 4-iodophenyl) amino] isonicotinamide hydrochloride.

Pimasertib is formulated as 15mg and 30mg (as free base) hard gelatin size 0 capsules for oral administration. Each of the strengths of pimasertib is presented in a different color capsule (see below).

1. 15mg: Green
2. 30mg: Gray

Capsules consist of pimasertib combined with the following inactive ingredients: lactose, microcrystalline cellulose, croscarmellose sodium, poloxamer 188, and magnesium stearate.

Pimasertib drug product is manufactured according to Good Manufacturing Practices (GMP).

Pimasertib will be provided for clinical use by EMD Serono as capsules packaged in amber glass bottles with high-density polyethylene (HDPE) caps, supplied in individual cardboard boxes.

Each box and drug unit will be numbered to allow complete drug accountability.

All drugs will be supplied with Certificates of Analysis. Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable GMP Guidelines.

It is stored at room temperature (≤ 25°C/77ºF).

Please note that drug disposal will be on site according to MDACC Institutional policy.

### 6.2.1 DOSAGE AND ADMINISTRATION

Pimasertib will be administered orally at a dose of either 30 mg, 45 mg, or 60 mg twice daily (BID) continuously, based on RP2D. Starting dose level for phase 1 is 45mg orally BID.

Pimasertib can be taken in fasted state or after a light meal. The subject will be instructed to swallow the capsules without biting into breaking or opening them, or attempting to dissolve the content in water prior to taking them.

A time window of 12 ± 3 hours between the administration of the morning and evening dose of pimasertib is considered acceptable.

**Table 1: Trial Treatments and Description**

| Product | Dose | Dose Frequency | Route of Administration | Appearance | Storage Conditions (per label) |
|---|---|---|---|---|---|
| BINTRAFUSP ALFA (M7824) | 1200 mg | Every 2 Weeks | IV Infusion | | 2ºC – 8ºC |
| Pimasertib | 60mg[A] | Twice Daily | Oral | | |

A=DEPENDING ON THE PHASE OF THE STUDY THE PARTICIPANT IS PARTICIPATING IN, THEY COULD RECEIVE 30-60MG OF THE DRUG.

### 6.2.3 DOSE MODIFICATION

#### Infusion-Related Reactions

IRRs are defined as any signs or symptoms experienced by participants during the infusion of pharmacologic or biologic agents or any event occurring during or within 1 day of drug administration. IRRs are common ADRs with monoclonal antibodies timely related to drug administration and have been reported as anaphylaxis, anaphylactoid reactions, and cytokine release syndrome, among other terms used. IRRs are risks (adverse reactions) for Bintrafusp Alfa (M7824), and the precautions and management are provided in Table 6.

A. Signs and symptoms of infusion related reactions (IRRs) including hypersensitivity include but not limited to pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria, were reclassified as risks (adverse reactions).

B. Management--Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or cimetidine or another H2 receptor antagonist, as per standard practice. Serious

infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated.

**Immune-Mediated Pneumonitis**

<table>
<tr><th colspan="2">Lung Toxicities</th></tr>
<tr><td colspan="2">Pneumonitis</td></tr>
<tr><td colspan="2">Definition: Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging)<br>No symptomatic, pathologic, or radiographic features are pathognomonic for pneumonitis</td></tr>
<tr><td colspan="2">Diagnostic work-up</td></tr>
<tr><td colspan="2">Should include the following: CXR, CT, pulse oximetry<br>For G2 or higher, may include the following infectious work-up: nasal swab, sputum culture and sensitivity, blood culture and sensitivity, urine culture and sensitivity</td></tr>
<tr><td>Grading</td><td>Management</td></tr>
<tr><td>G1: Asymptomatic, confined to one lobe of the lung or < 25% of lung parenchyma, clinical or diagnostic observations only</td><td><u>Continue</u> Immune Checkpoint inhibitor (ICPi)<br><u>If clinically indicated. Monitor participants weekly or more frequently as needed with history, physical examination and pulse oximetry;</u> may also offer CXR. May offer one repeat CT scan in 3 to 4 weeks; in patients who have had baseline testing, may offer a repeat spirometry/DLCO in 3 to 4 weeks</td></tr>
</table>

| Lung Toxicities | |
|---|---|
| | **<u>If symptoms appear and/or changes in the physical exam are noted, treat as G2</u>** |
| G2: Symptomatic, involves more than one lobe of the lung or 25%-50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL | Hold ICPi until resolution to G1 or less<br>Prednisone 1 to 2 mg/kg/d and taper by 5 to 10 mg/wk. over 4 to 6 weeks Consider bronchoscopy with BAL<br>Consider empirical antibiotics<br>Monitor every 3 days with history and physical examination and pulse oximetry, consider CXR; no clinical improvement after 48 to 72 hours of prednisone, treat as G3 |
| G3: Severe symptoms, hospitalization required, involves all lung lobes or 50% of lung parenchyma, limiting self-care<br>ADL, oxygen indicated<br>G4: Life-threatening respiratory compromise, urgent intervention indicated (intubation) | Permanently discontinue ICPi<br>Empirical antibiotics; (methyl)prednisolone IV 1-2 mg/kg/d; no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide; taper corticosteroids over 4-6 weeks<br>Pulmonary and infectious disease consults if necessary<br>Bronchoscopy with BAL ± transbronchial biopsy<br>Patients should be hospitalized for further management |
| Additional considerations<br>GI and Pneumocystis prophylaxis with PPI and Bactrim may be offered to patients on prolonged corticosteroid use (> 12 weeks), according to institutional guidelines<br>Consider calcium and vitamin D supplementation with prolonged corticosteroid use<br>The role of prophylactic fluconazole with prolonged corticosteroid use (> 12 weeks) remains unclear, and physicians should proceed according to institutional guidelines<br>Bronchoscopy + biopsy; if clinical picture is consistent with pneumonitis, no need for biopsy | |

| Lung Toxicities |
|---|
| All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate. |

**Table 2: Treatment Modification for Symptoms of Infusion-related Reactions Caused by BINTRAFUSP ALFA (M7824)**

| NCI-CTCAE Grade | Treatment Modification for Bintrafusp Alfa (M7824) |
|---|---|
| Grade 1 – mild<br>• Mild reaction; infusion interruption not indicated intervention not indicated. | • Decrease the Bintrafusp Alfa (M7824) infusion rate by 50% and monitor closely for any worsening.<br>• The total infusion time for Bintrafusp Alfa (M7824) should not exceed 120 minutes |
| Grade 2 – moderate<br>• Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours. | • Stop Bintrafusp Alfa (M7824) infusion.<br>• Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening |
| Grade 3 or Grade 4 – severe or life-threatening<br>• Grade 3: Prolonged (for example, not rapidly responsive to | • Stop the Bintrafusp Alfa (M7824) infusion immediately and disconnect infusion tubing from the subject. |

| | |
|---|---|
| symptomatic medication and / or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.<br>• Grade 4: Life-threatening consequences; urgent intervention indicated. | • Subjects have to be withdrawn immediately form Bintrafusp Alfa (M7824) treatment and must not receive any further Bintrafusp Alfa (M7824) treatment |

IV = intravenous; NCI-CTCAE = National Cancer Institute – Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs

**Additional Modifications for Subjects with Grade 2 Infusion-related Reactions**

If, in the event of a Grade 2 infusion-related reaction that does not improve or worsens after implementation of the modifications indicated in **Table 2** (including reducing the infusion rate by 50%), the Principal Investigator may consider treatment with corticosteroids and the infusion of BINTRAFUSP ALFA should be stopped for that day. At the next infusion, the Principal Investigator may consider the addition of H2-blocker antihistamines (for example, famotidine or ranitidine), in addition to premedication, for select subjects. However, prophylactic steroids are NOT permitted. If the subject has a second infusion-related reaction Grade ≥ 2 on the slower infusion rate, with or without the addition of further medication to premedication, the infusion should be stopped and the investigator may consider withdrawal of this participant from the study.

**Immune-Related Adverse Events**

For reporting irAE severity/toxicity grading, refer to CTCAE v.5 toxicity grading system.

For treatment management of irAE per CTCAE v.5 criteria, refer to American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines and National Comprehensive Cancer Network irAE Management Guidelines. Refer to Appendix 6 and 7.

The recommendations for irAE management, in accordance with the joint American Society of Clinical Oncology Clinical Practice Guidelines (Brahmer, 2018) and National Comprehensive Cancer Network (NCCN Guidelines®), are listed in Appendix 6.

Treatment of irAEs is mainly dependent upon severity as defined by NCI-CTCAE v5.0. In general, management by CTCAE v5.0 grading, as per ASCO, is listed below:

- Grade 1: study treatment should be continued with close monitoring, with the exception of some neurologic, hematologic, and cardiac toxicities.
- Grade 2: study treatment may be suspended for most Grade 2 toxicities, with consideration of resuming when symptoms revert to Grade 1 or less. Corticosteroids may be administered (initial dose of 0.5 to 1 mg/kg/day of prednisone or equivalent).
- Grade 3: study treatment is generally suspended and the high-dose corticosteroids (prednisone 1 to 2 mg/kg/day or methylprednisolone 1 to 2 mg/kg/day) treatment should be initiated. Corticosteroids should be tapered over the course of at least 4 to 6 weeks. Some refractory cases may require infliximab or other immunosuppressive therapy.
- Grade 4: in general, permanent discontinuation of study treatment is recommended, with the exception of endocrinopathies that have been controlled by hormone replacement.

For organ/system specific management guidelines, review ASCO guideline tables in Appendix 7.

Since inhibition of PD-L1 stimulates the immune system, irAEs may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):

- Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring
- Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)
- Grade 3 to 4: treat with high dose corticosteroids

**Anemia**

Anemia is considered a important identified risk based on toxicological findings with Bintrafusp Alfa (M7824) in cynomolgus monkey indicating a decrease in Hgb, RBCs, and hematocrit that was fully reversible or showed a substantial trend toward recovery. Notably, there are many reasons for anemia in patients with advanced cancer, which is why a thorough investigation of new anemia cases of unspecified etiology is requested.

Risk management measures in addition to routine laboratory tests will include:

- Subjects must enter the study with Hgb values at least 9 g/dL, independent of recent (≤ 14 days) packed red blood cell transfusion and/or use of an erythropoietin-stimulating agent.
- Routine monitoring of Hgb will be performed every 2 weeks (prior to treatment).Instructions for study treatment discontinuation or modification in case of anemia will be provided, briefly described here: In case of any Hgb < 8 g/dL, the Principal Investigator should use discretion to initiate anemia work up, including Coombs, haptoglobin, indirect bilirubin and peripheral smear, and prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR); Hgb and hematocrit are to be closely monitored.
- For new anemia events assessed as treatment-related, items queried may include but are not limited to detailed relevant past medical and treatment history, bruising tendency, history of blood transfusions and/or dependency, and a request for an updated eCRF including details such as concomitant medications, all laboratory data, updated dosing information and recent tumor evaluation scans.
  If a subject experiences significant anemia, then the amount of blood to be drawn may be reduced by not taking blood at selected time points for PD-L1 target occupancy, immunomonitoring, soluble factors, and TGFβ. The decision to reduce the time points for these biomarkers will be taken by the Principal Investigator.
- **Evaluation Guidance of baseline anemia and Suspected Treatment-related Anemia AEs**

| **Baseline anemia evaluation (prior to transfusion, if feasible)** |
|---|
| Hemoglobin and CBC with differential (e.g. MCV, RDW, ANC, hematocrit, reticulocytes counts) |
| Peripheral blood smear for cell morphological assessment |
| Complete metabolic panel including liver panel-LFTs, bilirubin, LDH, renal function, and serum folate, B12 values and other chemistries |
| Coagulation factors (PT, PTT, INR) |
| Urinalysis including culture |
| Iron panel (TIBC, ferritin, Fe) |

| | |
|---|---|
| TSH/hormonal panel<br><br>Fecal-occult blood testing<br><br>haptoglobin | |
| **Further recommendation based on suspected etiology (in addition to baseline anemia testing)** | |
| Unknown etiology, suspect possible hemolysis | Coombs test, fibrinogen, d-dimer<br><br>Consider hematology consultation.<br><br>Consider blood transfusion at clinical discretion. |
| Unknown etiology, suspect possible bleeding | Consider blood transfusion at clinical discretion.<br><br>Consider surgical/interventional radiology consultation.<br><br>Consider imaging, as clinically indicated (e.g. FAST scan, CT scan, MRI, angiography).<br><br>Consider endoscopy (upper/lower) |
| Unknown etiology despite above work-up | Hematology consultation<br><br>Consider bone marrow aspiration/morphologic evaluation |

**Rash with Hyperkeratosis / Keratoacanthoma / Squamous Cell Carcinoma of the Skin**

Treatment-related skin lesions with hyperkeratosis, keratoacanthoma, cutaneous squamous cell carcinoma possibly due to TGFβ inhibition are important identified risks (adverse reactions) for Bintrafusp Alfa (M7824). They have been manageable and did not lead to permanent discontinuations in Bintrafusp Alfa (M7824) studies. Patients with known Lynch Syndrome who develop

keratoacanthomas on study are encouraged to be evaluated for Muir Torre syndrome. Monitoring will include skin assessments as defined in the Schedules of Assessments (Section 8.0), with biopsy of suspicious lesions. Management should be discussed with the Principal Investigator on a case-by-case basis. Dermatological consults should be requested as needed in the event that possible drug-related skin toxicity is suspected by the investigator.

### Impaired Wound Healing

Due to the involvement of TGFβ in repair of skin and other tissue injuries, impaired wound healing is considered an important potential risk. For any surgeries conducted post-treatment initiation, surgical wound healing will be closely monitored. Management should be discussed with the Principal Investigator on a case-by-case basis. Dermatological consults should be requested as needed.

Bleeding Adverse Events

<table>
<tr><th colspan="2">Bleeding Adverse Events</th></tr>
<tr><td colspan="2">• Bleeding adverse events are considered important identified risk for bintrafusp alfa.<br>• In general, mild and moderate mucosal bleedings resolve without discontinuation of treatment.<br>• These events may include, but are not limited to the following:<br>  ○ Epistaxis<br>  ○ Hemoptysis<br>  ○ Gingival bleeding<br>  ○ Hematuria</td></tr>
<tr><th colspan="2">Non-tumor Bleeding</th></tr>
<tr><th>Grading</th><th>Management</th></tr>
<tr><td>Grade 2</td><td>• If resolves to Grade ≤ 1 by the day before the next infusion, study intervention may be continued<br>• If not resolved to Grade ≤ 1 by the day before the next infusion, but is manageable and /or not clinically relevant, consult Medical Monitor to assess if clinically reasonable to administer the following infusion.</td></tr>
<tr><td>Grade 3</td><td>• Permanently discontinue treatment unless an alternative explanation can be identified (such as concomitant use of antithrombotic agents, traumatic events, etc.)</td></tr>
</table>

| | |
|---|---|
| | • In case of alternative explanations, hold study treatment until the event recovers to Grade ≤ 1 |
| Grade 4 | • Treatment must be permanently discontinued if no alternative explanation is identified. |
| **Tumor Bleeding** | |
| Grade ≥ 2 | • Study treatment must be held till the event recovers to Grade ≤ 1<br>• Permanently discontinue treatment if the Investigator considers the participant to be at risk for additional severe bleeding. |

Ocular toxicity

If a subject experiences Retinal Vein Occlusion the pimasertib treatment must be immediately stopped. Appropriate follow-up and treatment measures must be taken by the treating ophthalmologists.

If a subject shows a symptomatic serous retinal detachement: Withhold treatment for ≤3 weeks, if improved to grade 0/1, resume at same dose level. If not improved, resume at the lower dose level or permanently discontinue pimasertib treatment. Management should be discussed with Principal Investigator and ophthalmologist.

**Elevation of Serum Creatine Phosphokinase**

Subjects should be advised to immediately report any muscle pain, tenderness or weakness, or any macroscopic myoglobinuria (tea-colored urine). Subject-reported muscle symptoms or urine discoloration should be investigated with CPK measurements and urinalysis for myoglobinuria.

CPK measurement should be at screening and every 4 weeks; at any time for symptomatic patients. Assess with differentiation if irAE or due to Pimasertib; including DD presence/absence of further symptomatic findings: full history (including conmeds), exercises, training, muscular injury, muscular injections, CPK isoenzymes, and etc.

CPK increase G4: Withhold pimasertib treatment for ≤3 week

Any CPK elevation and myalgia: If improved to grade ≤3, resume at lower dose level, if not improved within 3 weeks, permanently discontinue pimasertib treatment.

**Dehydration**

Dehydration and renal failure secondary to GI toxicity have been reported in clinical trials with pimasertib. Therefore, subjects should be advised to maintain adequate hydration at all times. Any subject with mucositis or other GI or other conditions likely to result in dehydration must be closely monitored for signs of dehydration. Should adequate hydration not be achievable because of severe GI symptoms or mucositis, for example, subjects should return to the investigational site or seek other medical care to avoid renal impairment and renal failure.

**Dose Interruptions for Adverse Events not related to Study Drug**

In case of Grade 3 and Grade 4 AEs not study drug-related, the study treatment may be interrupted based on the Principal Investigator assessment and the subject will be medically treated for the event.

If the AE reduces to a lower tolerable grade the study treatment might be resumed in the subsequent cycle. If the AE remains the same in spite of medical treatment until the next treatment (second cycle after the AE occurred) a discussion with the Principal Investigator should occur and consideration of a possible extension of the dose interruption for up to 1 additional cycle or a permanent withdrawal from the study treatment should be considered.

If upon the resumed study treatment the subject experiences the same AE this should be re-discussed with the Principal Investigator to assess permanent withdrawal from the study treatment.

Grade 3 and 4 laboratory abnormalities that do not have clinical significance do not require dose interruption.

### 6.2.4 SRT AND DOSE INTERRUPTIONS

Patients that have to hold systemic therapy to receive SRT are allowed to resume therapy within 6 weeks of holding therapy if they meet treatment safety parameters.

### 6.2.5 RESUMPTION OF TREATMENT AFTER DOSE DELAY

Patients may resume therapy at the same doses after dose interruption as long as they continue to meet the treatment safety parameters.

### 6.2.6 CONCOMITANT AND EXCLUDED THERAPIES

Steroids are allowed to manage AEs as described in protocol. Medications or vaccinations specifically prohibited in the exclusion criteria (See section 5.2) are not allowed during the ongoing trial. The following are also prohibited and are not allowed:

- Any traditional Chinese medication used as anticancer treatment (regardless of the type of cancer) is prohibited. Traditional Chinese medication for indications other than anticancer treatment, such as supportive care, may be administered at the discretion of the Investigator.

- Herbal remedies with immunostimulating properties (e.g., mistletoe extract) or known to potentially interfere with major organ function (e.g., hypericin).

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 principal 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 principal investigator, and the subject.

### 6.2.7 ACCEPTABLE CONCOMITANT MEDICATIONS

All treatments that the Principal Investigator considers necessary for a subject's welfare may be administered at the discretion of the Principal 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.

### 6.2.8 PERMITTED THERAPIES: SRT

For patients that are deriving clinical benefit from protocol treatment, but having evidence of progression in brain lesions that are amenable to SRS, treatment with SRS is allowed and patients can remain on systemic therapy. Patients will be censored for brain metastasis response unless one measurable lesion remains unirradiated. Patients will continue to be monitored for intracranial PFS.

### 6.2.9 PERMITTED THERAPY FOR BRAIN EDEMA

Patients that develop neurologic symptoms suspected to be secondary to brain edema are allowed to receive steroids as clinically indicated.

### 6.2.10 PERMITTED THERAPY: BRAIN SURGERY

Patients that develop an indication for brain surgery will be managed as clinically indicated. They will be assessed post-operatively in the setting of the MD Anderson Brain Metastasis Clinic (or similar multi-disciplinary setting) to determine whether resuming systemic therapy on protocol is warranted. The same dose interruptions and treatment resumption criteria that apply to SRT will apply to neurosurgical interevention as well.

## 7.0 PROHIBITED CONCOMITANT MEDICATIONS

As stated for the exclusion criteria in Section 5.2, subjects must not have had chemotherapy, radiotherapy (other than palliative radiotherapy delivered in a normal organ-spearing technique), major surgery, or received another investigational agent within 14 days before the start of trial treatment.

The following treatments must not be administered during the trial:

- Immunotherapy including interferon, immunosuppressive drugs (for example, chemotherapy or systemic corticosteroids except for short term treatment of allergic reactions, endocrine replacement therapy at low dose prednisone [≤ 10 mg daily] or equivalent, or for the treatment of irAEs or other appropriate short term steroid use), or other experimental pharmaceutical products. Short term administration of systemic steroid or other immunosuppressant such as infliximab or mycophenolate (that is, for allergic reactions or the management of irAEs) is allowed. Steroids with no or minimal systemic effect (topical, inhalation) are allowed.
- Adefovir.
- Prophylactic use of corticosteroids for infusion related reactions is prohibited.
- Any live vaccine therapies for the prevention of infectious disease. Administration of inactivated vaccines is allowed (for example, inactivated influenza vaccines or approved SARS-COV-2 vaccines).
- Vaccines will be allowed and will require one week between administration and treatment.

If the administration of a non-permitted concomitant drug becomes necessary during the trial, the subject will be withdrawn from trial treatment (the Principal Investigator may be contacted to discuss whether the BINTRAFUSP ALFA must be discontinued).

Medications other than those specifically excluded in this trial (as outlined in this section) may be administered for the management of symptoms associated with the administration of Bintrafusp Alfa (M7824) as required. These might include analgesics, anti-emetics, antihistamines, diuretics, anti-anxiety medications, and medication for pain management, including narcotic agents.

Any additional concomitant therapy that becomes necessary during the trial and any change to concomitant drugs must be recorded in the corresponding section of the eCRF (Prometheus) and medical record, noting the name, dose, duration, and indication of each drug.

The following non-drug therapies must not be administered during the trial (and within 28 days before the start of trial treatment):

- Major surgery (excluding prior diagnostic biopsy).Herbal remedies with immunostimulating properties (for example, mistletoe extract) or known to potentially interfere with major organ function (for example, hypericin)
- Subjects should not abuse alcohol or other illicit drugs during the trial

Drugs known to prolong the QT interval must be used with caution if they cannot be avoided. The list of the drugs in question is given at the following web address: http://crediblemeds.org/everyone/composite-list-all-qtdrugs/?rf=All

Furthermore, caution should be exercised when starting or increasing the dose of any medication that is considered to be associated with muscle toxicity (e.g., 3-Hydroxy-3-Methylglutaryl- Coenzyme A [HMG CoA] reductase inhibitors [statins]).

Interactions

- Pimasertib is a substrate of Cytochrome P450 (CYP) Isoforms CYP3A4 and CYP2C19, and may possibly inhibit CYP2C9.

Based on this, it was concluded that concomitant administration with the following drugs should be used with caution or avoided if possible:

- Strong inhibitors of CYP3A4
- Strong inducers of CYP3A4
- Strong inhibitors of CYP2C19
- Substrates of CYP2C9 with a narrow therapeutic index

A list of drugs that should be used with caution or avoided is presented can be found here:

https://drug-interactions.medicine.iu.edu/Main-Table.aspx

**SPECIAL PRECAUTIONS**

As a routine precaution, subjects all enrolled in this trial must be observed for 2 hours in the CTRC post end of infusion, in an area with resuscitation equipment and emergency agents at least for the first two doses of treatment with Bintrafusp Alfa (M7824). If no medical problems arise during the first two treatments, then the 2 hour observation period does not need to continue starting with the third dose of treatment. At all times during Bintrafusp Alfa (M7824) treatment, immediate emergency treatment of an infusion-related reaction or a severe hypersensitivity reaction according to institutional standards must be assured. In order to treat possible anaphylactic reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation.

Infusion of Bintrafusp Alfa (M7824) will be stopped in case of Grade ≥ 2 hypersensitivity, inflammatory response, or anaphylactic reaction. The treatment recommendations for infusion-related reactions and severe hypersensitivity reactions according to the NCI are outlined in Section 6.2.3.

Principal Investigators should also monitor subjects closely for potential irAEs (described in Section 6.2.3), which may become manifest after several weeks of treatment. Such events may consist of persistent rash, diarrhea and colitis, autoimmune hepatitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions.

## 8.0 SCHEDULE OF ASSESSMENTS

**TABLE 3 SCHEDULE OF ASSESSMENTS**

| **Trial Period:** | **Screening Phase** | **Treatment Cycles [a]** | | | | | | | | | | **End of Treatment** | **Post-Treatment** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | To be repeated beyond 8 cycles | | | | | | | |
| Treatment Cycle/Title: | Screening | C1 D1 | C1 D15 | C2 D1 | C2 D15 | 3 | 4 | 5 | 6 | 7 | 8 | Discontinuation | Safety Follow-up | Follow Up Visits [b] | Survival Follow-Up[p] |
| 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 | X | X | | | |
| Trial Treatment Administration [c] | | X | X | X | X | X | X | 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 | C1 D1 | C1 D15 | C2 D1 | C2 D15 | 3 | 4 | 5 | 6 | 7 | 8 | Discontinuation | Safety Follow-up | Follow Up Visits [b] | Survival Follow-Up[p] |
| 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 |
| 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 | X | X |
| Physical Examination | X | X | X | X | X | X | X | X | X | X | X | X | | X | |
| Vital Signs, Weight, and Height[n] | X | X | X | X | X | X | X | X | X | X | X | X | | X | |
| Electrocardiogram (12-Lead ECGs) | X | | | | | | | | | | | | | | |
| ECHO/MUGA | X | | | X | | | X | | X | | X | X | | | |
| Ophthalmological Exam[l] | 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 | C1 D1 | C1 D15 | C2 D1 | C2 D15 | 3 | 4 | 5 | 6 | 7 | 8 | Discontinuation | Safety Follow-up | Follow Up Visits [b] | Survival Follow-Up[p] |
| 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 |
| ECOG Performance Status | X | X | X | X | X | X | X | X | X | X | X | X | | X | X |
| Neuro-function (NANO) | X | X | | X | | X | X | X | X | X | X | X | | | |
| Neuropsych Testing[o]/ Neurocognitive Testing | X | | | | | X | | | | | | | | | |
| **Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory** | | | | | | | | | | | | | | | |
| Pregnancy Test – Urine or Serum -HCG [d] | X | | | X | | X | X | X | X | X | X | X | | | |
| Coagulation [e] | X | | | | | | | | | | | | | | |
| CBC with Differential[k] | X | X | X | X | X | X | X | X | X | X | X | X | | X | |
| CMP[m] | X | X | X | X | X | X | X | X | X | X | X | X | | X | |
| Urinalysis | X | | | X | | X | X | X | 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 | C1 D1 | C1 D15 | C2 D1 | C2 D15 | 3 | 4 | 5 | 6 | 7 | 8 | Discontinuation | Safety Follow-up | Follow Up Visits [b] | Survival Follow-Up[p] |
| 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 |
| Lactate dehydrogenase (LDH) | X | | | X | | X | X | X | X | X | X | X | | | |
| T3, FT4 and TSH | X | X | | | | X | | X | | X | | X | | | |
| Creatinine Phosphokinase | X | X | | X | | X | X | X | X | X | X | X | | | |
| HIV, HBV, HCV Testing | X | | | | | | | | | | | | | | |
| **Efficacy Measurement** | | | | | | | | | | | | | | | |
| Tumor Imaging & Assessment of disease: MRI[f] | X | | | X | | X | X | X | | X | | X | | | |
| Tumor Imaging & Assessment of disease: CT's[f] | X | | | | | X | | X | | X | | | | | |
| **Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood** | | | | | | | | | | | | | | | |

| **Trial Period:** | **Screening Phase** | **Treatment Cycles [a]** | | | | | | | | | | **End of Treatment** | **Post-Treatment** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | To be repeated beyond 8 cycles | | | | | | | |
| Treatment Cycle/Title: | Screening | C1 D1 | C1 D15 | C2 D1 | C2 D15 | 3 | 4 | 5 | 6 | 7 | 8 | Discontinuation | Safety Follow-up | Follow Up Visits [b] | Survival Follow-Up[p] |
| 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 |
| Archival Tissue [g] | X | | | | | | | | | | | | | | |
| Serial Biopsy [h] | X | | | X | | | | X | | | | | | | |
| **Blood/Tissue Collection** | X | | | X | | X | X | X | X | X | X | | | | |
| Correlative Studies [j] | X | | | X | | | | X | | | | X | | | |
| PK and ADA | | X | | X | | X | | | X | | | X | X | | |
| CSF[i] (optional) | X | X | | | | X | | | | | | | | | |

a Cycles are 4 weeks (28 days) in duration

b Patients who discontinue trial treatment for reasons other than disease progression will move into the Follow-Up phase. Patients will be seen every 6 weeks for the first year, then every 12 weeks thereafter up to 2 years.

c M7824 1200 mg every 2 weeks. Pimasertib will be administered at 60mg twice daily. (30 to 60 mg depending on phase)

d See Page 78 if a woman of child-bearing potential becomes pregnant while on study. Negative pregnancy test within 3 days prior to initiation of dosing and continuation of birth control for 120 days after last dose of drug.

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

f MRI Scan will be performed every 4 weeks for the first 16 weeks, then every 8 weeks until progression or discontinuation of study treatment, whichever comes later. Imaging window is ± 7 days. If scans performed within 4 weeks of discontinuation, repeat scans are not required.

CT-CAP or PET-CT will be performed every 8 weeks until progression of discontinuation of study treatment, whichever comes later. Imaging window is ± 7 days. If scans performed within 4 weeks of discontinuation, repeat scans are not required.

Please note that if an MRI, CT chest/abdomen/pelvis or PET-CT is not already performed as standard of care per Schedule of Assessments in Section 8.1.4, the investigator may choose to perform either or both procedures for assessing progress of the patient.

g Obtain archival only if tissue is post PD-1 exposure for melanoma and lung cancer patients. See Section 8.7.1 for additional details.

h Patients with biopsiable extracranial disease may have tissue collected. See Section 8.8.

i Cerebrospinal Fluid may be obtained if testing for LMD. See section 8.7.3 for additional details.

j See Section 8.7.

k CBC & CMP is done every 2 weeks (+/- 7 days) prior to infusion.

l Patients will have ophthalmological evaluation at baseline and every 12 weeks. See section 8.3.
while receiving protocol therapy

m Serum chemistry includes the tests listed (glucose, BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbcionate, calcium, phosphorus, total and direct bilirubin, ALT, AST, ALP, LDH, total protein, albumin, CPK, and uric acid). CMP is done every 2 weeks prior to infusion.

n Height only taken at Screening

o There will also be a Neurocognitive exam at the 3-month mark

p A follow up call will be done at 90 days to assess patient safety.

## 8.1 PHYSICAL EXAMINATION

### 8.1.1 FULL PHYSICAL EXAM

The Principal 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 physical exams are described in Table 3.0. After the first dose of trial treatment, new clinically significant abnormal findings should be recorded as AEs.

### 8.1.2 DIRECTED PHYSICAL EXAM

The Principal 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.

### 8.1.3 VITAL SIGNS

Vital signs include temperature, pulse, respiratory rate, weight and blood pressure. The Principal 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 8.0). Height will be measured at Screening.

### 8.1.4 RESPONSE ASSESSMENT

MRI of the brain will be the primary radiological method of disease assessment using modified RECIST 1.1. Treatment decisions will be made according to modified RECIST 1.1 while other measurement criteria will be utilized as secondary endpoints including iRANO 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 4 weeks for the first 12 weeks, then every 8 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 performed within 4 weeks of discontinuation, repeat scans are not required. 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 8.0, the principal investigator may choose to perform either or both procedures for assessing the progress of the patient.

## 8.2 BIOPSY AND ARCHIVAL TUMOR TISSUE SAMPLE

### 8.2.1 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 10 unstained slides, with an associated pathology report, for correlative evaluation. Archival tissue for melanoma and lung cancer patients must be after PD1 exposure.

### 8.2.2 BIOPSY

Patients with biopsiable extracranial disease may have tissue collected pretreatment and at Cycle 2 (4 weeks after the start of treatment). An additional optional biopsy may be collected at Cycle 5, if accessible, but is not required. All biopsies are optional for enrollment, but highly encouraged for pretreatment and Cycle 2. 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.

For core-needle biopsy specimens, at least three cores should be submitted for evaluation. Cores will be distributed to FFPE and snap frozen equally.

## 8.3 OPHTHALMOLOGY

OPHTHALMOLOGIC EXAMINATION MUST BE PERFORMED AT THE BASELINE, EVERY 12 WEEKS OF TREATMENT AND AT END OF TREATMENT.

The objective of baseline ophthalmologic examination is to evaluate for evidence of retinal pathology that may be a risk factor for central serous retinopathy or RVO. Ophthalmologic examination must be performed by a qualified ophthalmologist. Riskfactors for RVO include uncontrolled serum cholesterol, hypertriglyceridemia, hyperglycemia, hypertension, and glaucoma.

Baseline and serial surveillance ophthalmologic examination will include visual acuity testing, intraocular pressure measurements by tonometry, slit lamp ophthalmoscopy, indirect ophthalmoscopy, and Spectral-domain optical coherence tomography, if not available, may be substituted with time- domain optical coherence tomography.

## 8.4 LABORATORY ASSESSMENTS

All labs will be processed locally at MDACC.

## 8.5 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.

Clinically significant abnormal findings seen on the follow-up ECGs should be recorded as adverse events.

### 8.5.1 ECHO/MUGA

An ECHO/MUGA will be done at baseline and every 2 months. Please refer to Table 3.0 for additional information. Clinically significant abnormal findings seen on the follow-up ECHOs should be recorded as adverse events.

## 8.6 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 principal 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.

Neuropsychological testing will be performed with a standardized battery routinely used to assess patients with brain metastases at MDACC, including in the previously published Chang et al. trial [55]. This evaluation will be performed by a trained psychometrist under the supervision of Dr. Wefel, a licensed, board certified clinical neuropsychologist in the Department of Neuro-Oncology. The following tests were selected because they are widely used, standardized psychometric instruments that have been shown to be sensitive to changes in neurologic disease as well as treatment effects of cancer treatment in other clinical trials. Normative data have been published for all tests that take into account age, education, sex and handedness, where appropriate. These tests were also selected to minimize practice effects associated with repeated administration. The memory test has six alternate forms and the verbal fluency test has two alternate forms. The other tests measure motor and information processing speed and are relatively resistant to the effects of practice.

The total time for neuropsychological testing, including the quality of life (QOL) and symptom measures, is about 45 minutes.

| Domain | Test | Administration Time (minutes) |
|---|---|---|
| Memory | Hopkins Verbal Learning Test-Revised (HVLT-R) | 5 |
| Attention Span | WAIS-IV Digit Span | 5 |
| Processing Speed | Trail Making Test, Part A | 3 |
| | WAIS-IV Coding | 3 |

| | | |
|---|---|---|
| Executive Function | Trail Making Test, Part B | 5 |
| Verbal fluency | Controlled Oral Word Association (COWA) | 5 |
| Motor Dexterity | Lafayette Grooved Pegboard | 5 |
| | | |
| PRO | MD Anderson Symptom Inventory – Brain Tumor | 10 |

**ECOG Evaluation**

Eastern Cooperative Oncology Group (ECOG) Evaluation will be performed at Screening and at each cycle for every patient. The principal investigator or qualified designee will assess ECOG status (see Appendix 4) at screening, additional time points for assessment of ECOG must be performed.

## 8.7 RESEARCH SAMPLE COLLECTION

Samples for 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 (EMD). 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. Upon termination of the study, any remaining blood and tissue samples will be transferred and stored in the Melanona Tissue Bank (MelCore) for future use with an IRB approved protocol.

Biospecimens will be collected accordint to the study calendar to evaluate the immunological effect of the treatment and SRS. Methods to evaluate this include but may not be limted to:

- FACS on isolated PBMCs
- Serum/plasma collection to assess circulating inflammatory cytokines
- Single stain IHC. Markers include, but are not limited to: CD3, CD4, CD8, CD20 (B cell), CD1a (DC), CD11c (myeloid lineage), Granzyme B (cytotoxic CTLs and NK cells) FOXp3 (Treg cells) and CD3/CD8/CD45RO memory CTL (as proposed in the “Immunoscore” project); IDO and PD-L1 expression.

- Inflammatory expression pattern by Nanostring may be performed on the tumor tissue to mirror evaluations of cytokines and chemokines performed in the peripheral blood

While mechanisms of resistance are relevant and central to all targeted therapy studies, the importance of this evaluation in our proposed study is in delineating the role of mechanisms of resistance assessed in extracranial metastatic melanoma tissues in predicting and describing the patterns of resistance intracranially. It is predicted that the presence or absence of resistance mechanisms extracranially may predict response and progression-free survival intracranially.

Tissue availability permitting, we propose broad investigations on tissue biopsies comparing responders and non-responders, including whole exome sequencing, RNA expression analysis, and reverse phase protein array to examine markers of MAP kinase pathway activity, parallel signaling pathways, RTK activation, and pro and anti-apoptotic factors.

Additionally, we may assess circulating free DNA from serial plasma/serum samples to determine patterns of response and early predictors of resistance. Finally, single cell analyses (including RNA sequencing) may be performed on CSF obtained.

### 8.7.1 TISSUE

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 10 unstained slides, with an associated pathology report, for local testing of tumor PD-L1 expression.

Patients with biopsiable extracranial disease may have tissue collected pretreatment and at Cycle 2 (4 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.

### 8.7.2 BLOOD

Local laboratory assessments will include the following:

- Hematology (CBC, including RBC count, hemoglobin, hematocrit, WBC count, percent and absolute differential [neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)

- Serum chemistries (glucose, BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, total and direct bilirubin, ALT, AST, ALP, LDH, total protein, albumin, CPK, and uric acid)

- Coagulation (aPTT and INR)

- Pregnancy test (for women of childbearing potential, including women who have had a tubal ligation)

- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood)

- Serum samples for auto-antibody testing (PK and ADA samples are all serum)

  PK

  PRIOR TO INFUSION AND IMMEDIATELY AFTER INFUSION (EOI)
  Cycle 1, day 1 and cycle 3 day 1
  PRIOR TO INFUSION only:
  Cycle 2 and Cycle 6 OR end of treatment (whatever comes first) and followup visit if applicable

  ADA:
  PRIOR TO INFUSION only
  Cycle 1, day 1 ( PRETREATMENT); Cycle 3, day 1 and Cycle 6 OR end of treatment (whatever comes first) and followup visit if applicable

- Blood samples for biomarker assays (up to 40 mls will be obtained to fulfill correlative biomarker plans)

**Additional Local Testing**

Perform the following tests as indicated in Study Flowchart (Table 3) and as clinically indicated.

- Thyroid function testing (TSH, total T3, and free T4)

### 8.7.3 CEREBROSPINAL FLUID (CSF)

CSF may be collected at the time of routine testing for Leptomeningeal disease (LMD). Leptomeningeal disease occurs when cancer cells migrate from your breast, lung, or some other part of your body to your cerebrospinal fluid (CSF). CSF may be obtained at Cycle 1 Day 1 and Cycle 3 Day 3. Patients will not be asked to undergo an optional lumbar puncture for the purposes of this study. At the time of diagnostic evaluation, additional CSF may be obtained for the purposes of this study.

## 8.8 TUMOR IMAGING AND ASSESSMENT OF DISEASE

All subjects will undergo CT scanning and MRI of the brain at the time points specified in the Schedule of Events. CT and MRI scans will be assessed locally per the modified RECIST 1.1, RANO-BM,and iRANO criteria. Up to 5 systemic and 5 brain lesions will be followed for efficacy per the criteria. Patients with biopsiable extracranial disease may have tissue collected.

## 8.9 THERAPY ADMINISTRATION

| Drug | Dose | Dose Frequency | Route of Administration | Treatment Period | Use |
|---|---|---|---|---|---|
| Pimasertib | 30-60 mg | BID | Oral | Continuously on 28-day cycles | Experimental |
| Bintrafusp Alfa (M7824) | 1200 mg | Every 2 Weeks | IV Infusion | Once every 2 Weeks on 28 day cycles | Experimental |

## 8.10 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 principal 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

## 8.11 SUPPORTIVE CARE GUIDELINES

Subjects should receive appropriate supportive care measures as deemed necessary by the treating principal 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 principal investigator determines the events to be related to pimasertib and bintrafusp alfa (M7824).
Note: if after the evaluation the event is determined not to be related, the principal investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 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.
  - 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.
- **Ocular reactions:**
    - Visual disturbances: for Grade 2 events, pimasertib should be discontinued until full resolution of the event and recovery of vision, assuming resolution of the event within 2 weeks to Grade 1 or less.
    - In case of visual symptoms but without vision loss, the treatment will not be discontinued.
- **Skin reactions:**
    - Early introduction of oral tetracyclines and medium to high potency topical treatment (such as 1% hydrocortisone cream with moisteriser) should be initiated in case of Grade 1 or 2 skin reaction. The dose of the investigational treatment should not be decreased.
    - If a subject experiences a severe skin reaction (Grade ≥3), pimasertib therapy must be interrupted and may be resumed at the original dose when the reaction has resolved to Grade 1 or 2. In case of second or third occurrence of severe skin reaction pimasertib therapy must again be interrupted. Treatment may only resume at a lower dose level (45 mg BID after the second occurrence and 30 mg BID after the third occurrence) if the reaction has resolved to Grade 1 or 2. In case of further recurrence another dose reduction may be proposed.

### 8.12 PATIENT DISCONTINUATION

THE PRIMARY REASON FOR STUDY TREATMENT DISCONTINUATION SHOULD BE DOCUMENTED IN THE SUBJECT'S CHART. PATIENTS WHO DISCONTINUE STUDY TREATMENT PREMATURELY WILL NOT BE REPLACED. PATIENTS WHO DISCONTINUE FROM TREATMENT WILL BE ASKED TO RETURN TO THE CLINIC NO MORE THAN 30 DAYS AFTER THE LAST TREATMENT FOR A TREATMENT DISCONTINUATION VISIT. THE

VISIT AT WHICH A RESPONSE ASSESSMENT SHOWS PROGRESSIVE DISEASE MAY BE USED AS THE TREATMENT DISCONTINUATION VISIT**8.13 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 principal 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 principal investigator that may jeopardize the patient's safety if he or she continues in the study
- Patient becomes pregnant
- Principal 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.

## 8.14 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.

## 8.15 POST STUDY DRUG 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 by phone every 12 weeks until death or the conclusion of the study.

## 8.16 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 localmethods to obtain the date and cause of death.

The site staff and PI 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 principal investigator should be reported and documented in the subject's medical records

# 9.0 STATISTICAL CONSIDERATIONS

## 9.1 PHASE I

The phase I dose finding part of the study is to determine the recommended phase II dose (RP2D) of Bintrafusp Alfa (M7824) + Pimasertib in patients with intracranial metastasis. The planned DL1 and DL2 doses are Bintrafusp Alfa (M7824) flat dose of 1200 mg every 2 weeks and Pimasertib 45 mg PO BID (DL1) and 60 mg PO BID (DL2), and fallback doses DL-1 are Bintrafusp Alfa (M7824) flat dose of 1200 mg every 2 weeks and Pimasertib at 30 mg PO BID. We will enroll up to 12 patients to the Phase I portion (up to 18 can be enrolled should the trial de-escalate to DL-1). The standard "3+3" design will be employed to determine the RP2D. If DL1 is considered too toxic, DL-1 will be explored, if unacceptable toxicity is observed at DL-1, we will consider alternative schedules in discussion with EMD Serono.

Dose limiting toxicity (DLT) is defined as below, including an intracranial and an extracranial DLT. These will be evaluated **at 4 weeks** after first administration of treatment.

Intracranial DLT (T1): Hypophysitis Grade ≥ 3; or neurologic toxicity Grade ≥3

Extracranial DLT (T2): Any Grade ≥ 3 adverse event outside CNS that is related to Bintrafusp Alfa (M7824) or Pimasertib, occurring during the DLT evaluation period
(Exceptions include: grade 3 flu-like symptoms or fever lasting less than a week, Grade 3 fatigue lasting less than a week, local reactions, headaches, nausea, and emesis leasting less than 72 hours, and grade 3 hemoglobin decrease (<8.0g/dL)).
Elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) 3 times the upper limit of normal (ULN) range and a concomitant elevation of bilirubin 2 times the ULN attributable to study drug constitutes a DLT.

The first cohort of 3 patients will be treated at Dose Level 1. New cohorts of patients will not be treated until toxicity has been fully evaluated for all current patients.

The algorithm is as follows at any dose level:

1. If 0 out 3 patients experiences DLT, the next cohort of 3 patients will be treated at the next higher dose level.
2. If 1 out of 3 patients experiences DLT, additional 3 patients will be treated at the same dose level. If no more than 1 out of 6 patients experiences DLT, the next cohort of 3 patients will be treated at the next higher dose level.

3. At any time, if greater than or equal to 2 out 3 or greater than or equal to 2 out 6 patients experience DLT, another 3 patients will be treated at the next lower dose level if no more than 3 patients have been treated at the lower dose level.

The recommended phase II dose (RP2D) is defined as the highest dose level with no more than 1 patient with DLT out of 6 patients that are treated.

### 9.2 PHASE II

The purpose of phase II part is to estimate the time to intra-cranial progression and overall survival time. In this part, we will enroll up to additional 24 patients into RP2D over the course of 12-18 months. The 6 patients treated at RP2D from phase I part of the study will be included in the Phase II part, thus resulting in a total of 30 patients at RP2D by the end of the study, with the goal of having 10 patients with each of melanoma, NSCLC, and breast cancer. This phase II part is designed to collect data for future larger studies. Specifically, we would like to estimate time to intracranial progression considering death as a competing risk and overall survival time using Kaplan-Meier method, both with 95% confidence interval.

Two dose limiting toxicities (DLT) will be monitored separately: intracranial and extracranial DLTs. If there is a high chance that probability of intracranial DLT is found to be > 15%, i.e., Pr(intra-cranial DLT Rate > 15%|Data) > 70%, or the extra-cranial DLT rate of higher than 30%, i.e., Pr(extra-cranial DLT Rate > 30%|Data) > 70%, then the regimen will be considered too toxic at current dose. Results should be discussed with EMD Serono to decide if further enrollment should be started at a lower dose level. Protocol will be amended if necessary. The window for DLT evaluation will be at 4 weeks after the start of the treatment.

Given these rules and the prior for intra-cranial DLT toxicity rate as beta(0.15, 0.85) and extra-cranial DLT toxicity rate as beta(0.3, 0.7), we claim a dose level too toxic if any of the following happens.

Number of patients with intra-cranial DLTs/total of number of patients treated >=3/10, 4/15, 5/20, 5/25, 6/30; or

Number of patients with extra-cranial DLTs/total of number of patients treated >=4/10, 6/15, 8/20, 9/25, 11/30.

The operating characteristics based on the toxicity stopping rules for 30 patients are in Table 4. The Bayesian toxicity monitoring rule are calculated by the online Shiny application Bayesian Toxicity Monitoring using posterior probability developed by Department of Biostatistics. The operating characteristics were evaluated using codes written by statistical collaborator Diane Liu.

**Table 4: Operating Characteristics (5,000 simulations)**

| True Intracranial DLT Rate | True Extracranial DLT Rate | P (Stop Early) | Average of Expected Sample Size |
|---|---|---|---|
| 0.05 | 0.1 | 0.03 | 29 |
| 0.05 | 0.2 | 0.17 | 27 |
| 0.05 | 0.3 | 0.50 | 22 |
| 0.05 | 0.4 | 0.82 | 16 |
| 0.05 | 0.5 | 0.97 | 12 |

| | | | |
|---|---|---|---|
| 0.15 | 0.1 | 0.38 | 25 |
| 0.15 | 0.2 | 0.47 | 23 |
| 0.15 | 0.3 | 0.68 | 19 |
| 0.15 | 0.4 | 0.88 | 14 |
| 0.15 | 0.5 | 0.98 | 11 |
| 0.30 | 0.1 | 0.93 | 14 |
| 0.30 | 0.2 | 0.94 | 13 |
| 0.30 | 0.3 | 0.96 | 12 |
| 0.30 | 0.4 | 0.99 | 11 |
| 0.30 | 0.5 | >0.99 | 10 |

## 9.3 RESPONSE DEFINITIONS

### 9.3.1 OVERALL SURVIVAL

Overall survival (OS) is defined as the time from treatment start date to death. Patients who are still alive at the end of the study will be censored. PFS and OS will be assessed using the Kaplan-Meier method overall and by cohort.

### 9.3.2 INTRACRANIAL PROGRESSION FREE SURVIVAL

The time to intracranial progression, determined by modified RECIST 1.1 , will be calculated from the time of study enrollment to intracranial progression (event) or the last follow-up date if the patient has not developed the intracranial progression yet (censored). The median time to intracranial progression and intracranial progression free survival rates at specific times will be estimated and reported with 95% confidence interval utilizing the method of Kaplan and Meier. This will serve as the primary analysis and will be performed overall and within each treatment group. Completing risk analysis may be considered by treating events outside of intracranial disease progression (e.g. events such as extracranial disease progression, early dropout due to toxicity, or death) as competing risks.

### 9.3.3 TOXICITY

The intracranial and extracranial toxicities and DLTs will be summarized by grade, relationship, time during the treatment, etc., for each dose in each group.

### 9.3.4 EXTRACRANIAL PROGRESSION

The time to extracranial progression, determined by RECIST 1.1 criteria, will be calculated from the time of study enrollment to extracranial progression (event) or the last follow-up date if the patient has not developed the extracranial progression yet (censored). The cumulative incidence rate may be estimated by competing risk analysis treating events outside of extracranial disease progression (e.g. events such as intracranial disease progression, early dropout due to toxicity, or death) as competing risks.

### 9.3.5 EXTRACRANIAL RESPONSE RATE

The best achieved extracranial objective response rate will be reported for each patient. The frequency of extracranial objective response will be reported overall and within each treatment group.

### 9.3.6 Duration of Response

In patients who achieve extracranial, partial response (PR)or complete response (CR) via RECIST 1.1 criteria, the time from date of first imaging identifying PR or CR until the date of first imaging identifying progressive disease is noted will be recorded. Duration will be calculated utilizing the Kaplan-Meier method with reporting of the median and range overall and within each treatment group.

### 9.3.7 Steroid Requirements

We will record and report steroid requirements for symptom management overall and within each treatment group. Patients who require at least 4 mg of dexamethasone/day for symptom management will be considered as requiring high dose steroids.

### 9.3.8 Other Endpoints

Descriptive analysis will be provided to summarize the serum, tissue and imaging markers. The relationship between the markers and response and/or toxicities may be evaluated using Kruskal-Wallis test for continuous markers and Fisher's exact test for discrete markers, when appropriate. The correlation between the serum/tissue markers and imaging parameters or between any two markers may also be assessed using Spearman correlation. Given the size of the study, these analysis are exploratory in nature.

Other statistical analysis methods may be applied when fit.

The Principal Investigator is responsible for completing toxicity/efficacy summary reports and submitting them to the IND office Medical Affairs and Safety Group for review. These should be submitted as follows:

- Phase I:

After the first 3 evaluable patients, complete 4 weeks of study treatment, and every 3 evaluable patients thereafter, IND Office approval must be obtained prior to advancing/changing dose levels.

- Phase II:

After the first 10 evaluable patients( including the six treated at RP2D from from phase I) complete 4 weeks of study treatment, and every 5 patients thereafter. Also, a toxicity report will be submitted per cohort.

A copy of the summary report should be placed in the Principal Investigator's Regulatory Binder under "sponsor correspondence".

## 10.0 Assessment of Safety

### 10.1 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 8.13. The principal investigator will make every attempt to follow all subjects with non–serious adverse events for outcome.

The principal investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

An principal investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Severity of the adverse events (AEs) -The severity of the adverse events (AEs) will be graded according to the **National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V.5.0.** Events not included in the NCI CTCAE will be scored as follows:

General grading:

- **Grade 1:** Mild: discomfort present with no disruption of daily activity, no treatment required beyond prophylaxis.

- **Grade 2:** Moderate: discomfort present with some disruption of daily activity, require treatment.
- **Grade 3:** Severe: discomfort that interrupts normal daily activity, not responding to first line treatment.
- **Grade 4:** Life Threatening: discomfort that represents immediate risk of death

For studies in which multiple agents are administered as part of a combination regimen, the principal 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 principal 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 principal investigators in accordance with all applicable global laws and regulations.

**Attribution** - the determination of whether an adverse event is related to a medical treatment or procedure.

- **Definite** - the adverse event is clearly related to the investigational agent(s).
- **Probable** - the adverse event is likely related to the investigational agent(s).
- **Possible** - the adverse event may be related to the investigational agent(s).
- **Unlikely** - The adverse event is doubtfully related to the investigational agent(s).
- **Unrelated** - The adverse event is clearly NOT related to the investigational agent(s).

**Recommended Adverse Event Recording Guidelines**

| Attribution | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|
| **Unrelated** | Phase I | Phase I | Phase I<br>Phase II | Phase I<br>Phase II<br>Phase III | Phase I<br>Phase II<br>Phase III |
| **Unlikely** | Phase I | Phase I | Phase I<br>Phase II | Phase I<br>Phase II<br>Phase III | Phase I<br>Phase II<br>Phase III |
| **Possible** | Phase I<br>Phase II | Phase I<br>Phase II<br>Phase III | Phase I<br>Phase II<br>Phase III | Phase I<br>Phase II<br>Phase III | Phase I<br>Phase II<br>Phase III |
| **Probable** | Phase I<br>Phase II | Phase I<br>Phase II<br>Phase III | Phase I<br>Phase II<br>Phase III | Phase I<br>Phase II<br>Phase III | Phase I<br>Phase II<br>Phase III |

| | | | | | |
|---|---|---|---|---|---|
| **Definitive** | Phase I<br>Phase II | Phase I<br>Phase II<br>Phase III | Phase I<br>Phase II<br>Phase III | Phase I<br>Phase II<br>Phase III | Phase I<br>Phase II<br>Phase III |

## 10.2 SERIOUS ADVERSE EVENTS

**Serious Adverse Event (SAE) Reporting**

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the principal investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices".
- All SAEs, expected or unexpected/ initial or follow up, must be reported to the IND Office **within 5 working days of knowledge of the event** regardless of the attribution.
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
    - **All life-threatening or fatal events**, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of

the event to the Safety Project Manager in the IND Office.
  - Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- The electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

**Reporting to FDA:**
- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

**It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.**

**Pregnancy and Reporting**

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). The investigator must immediately notify EMD Serono of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures within 24 hours.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form [provided upon request from EMD Serono].

Any pregnancy that occurs in a female partner of a male study participant should be reported to EMD Serono. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

**Reporting Serious Adverse Events and Adverse Events of Special Interest Serious Adverse Events**

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices".

Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

SAEs, whether related or not related to study drug as detailed below, must be reported to EMD Serono within 5 working days from the time of knowledge of the event to: Pavithra Prasad, Fax: +49 6151 72 6914; E-mail: ICSR_CT_GPS@merckgroup.comIf only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 5 working days to the EMD Serono (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

**The principal investigator** will ensure that all SAEs in the clinical database are reported to EMD Serono and any applicable health authority during the conduct of the study.

SAEs will be reported on the EMD Serono approved form for prompt reporting (full form): "Internal SAE Report Form for Prompt Reporting" Institutional Review Board.
SAEs will be submitted to both the Office of Protocol Research, Unit 1437 at The University of Texas MD Anderson Cancer Center and also sent to:

All SAEs should be faxed or e-mailed to EMD Serono to:
Fax: +49 6151 72 6914; E-mail: ICSR_CT_GPS@merckgroup.com

### 10.3 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.

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 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 product, must be reported within 2 working days.

Events of clinical interest for this trial include:
1. an overdose of product, as defined in Section 10.4, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the

upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

***Note:** These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. In addition, please note that "Events of Clinical Interest" including pregnancy, will be reported via eSAE application as "Other Important Medical Event", to the IND Office.

### 10.4 Definition and Reporting of an Overdose for This Protocol

For this study, any dose of bintrafusp alfa greater than 2 times (i.e., > 2400 mg) more than the planned dose administered within a 24-hour time period will be considered an overdose.

No specific information is available on the treatment of overdose of this drug. 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 product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

### 10.5 Reporting of Pregnancy and Lactation

Although pregnancy and infant exposure during breast feeding are not considered adverse events, it is the responsibility of principal 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 principal 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 investigational product, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the principal 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.

## 11.0 Administrative and Regulatory Details

### 11.1 Investigator Communications

All reports of overdose, pregnancy, lactation, SAEs, and ECIs must be reported within 2 working days to the MDACC IND Office via eSAE application as "Other Important Medical Events."

Additionally, any reportable event, considered by principalinvestigator, who is a qualified physician, to be related to 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.

## 11.2 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.

## 11.3 Data Management

### 11.3.1 Data Collection

The study coordinator and principal 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. Please note that CORe (Clinical Oncology Research System) will be used to register patients enrolled on the study. All source documents will be available for inspection by the FDA and the MDACC IRB.

### 11.3.2 Data Safety Monitoring Plan

Principal 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

Toxicity will be monitored as outlined in the statistical Section 9.0. All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 5. 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 events).

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.

### 11.3.3 DATA HANDLING AND RECORD KEEPING

The Principal Investigator (i.e., the study site Investigator) will maintain records in accordance with Good Clinical Practice.

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

### INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL

The principal investigator (i.e., the study site 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 principal 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.

### 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.

### 11.3.4 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.

### 11.3.5 Informed Consent

The investigator (i.e., the study site 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.

## 12.0 Study Documentation, Monitoring, and Administration

The principal 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.
- 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.

APPENDICES

**Appendix 1: immunotherapy Response Assessment for Neuro-Oncology (iRANO)**

Modified Excerpt from Original Publication

Selected sections from the immunotherapy Response Assessment for Neuro-Oncology (iRANO), are presented below.

**For the purposes of the current study, we will use a modified version of iRANO (modified iRANO) that allows intracranial tumors that are >0.5 and <1.0 cm assessed by MRI to be considered measurable disease. This will be the only modification.**

**iRANO Criteria**

The iRANO guidelines incorporate criteria previously defined by the RANO working committee to define complete response, partial response, minor response, stable disease, progressive disease, and non-evaluable disease for patients with malignant glioma,[16] low-grade glioma,[40] and brain metastases.[18] The key component of the iRANO criteria is specific additional guidance for the determination of progressive disease in patients with neuro-oncological malignancies undergoing immuno- therapy (table 1, figure 3). Specifically, the iRANO criteria advocate for the confirmation of radiographic progression in appropriate patients defined by clinical status and time from initiation of immunotherapy.

In patients who have imaging findings that meet RANO criteria for progressive disease[16–18] within 6 months of starting immunotherapy including the development of new lesions, confirmation of radiographic progression on follow-up imaging before defining the patient as non- responsive to treatment might be needed provided that the patient does not have new or substantially worse neurological deficits. Such patients might be allowed a window of 3 months before confirming disease progression with the scan that first showed initial progressive changes as the new reference scan for comparison with subsequent imaging studies. If RANO criteria for progressive disease are met on the follow-up scan 3 months later, non-responsiveness to treatment should be assumed, and the date of progressive disease should be back-dated to the initial date when it was first identified (table 1). Patients who develop substantial new or worsened neurological deficits not due to comorbid events or a change in co-administered medication at any time within the 3-month follow-up window should be designated as non-responsive to treatment and should discontinue immunotherapy. For these patients, the date of actual tumor progression should also be back-dated to the date when radiographic progressive disease was initially identified.

**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.

If radiographic findings at the 3-month follow-up meet RANO criteria for stable disease, partial response, or complete response[16–18] compared with the original scan meeting criteria for progression, and no new or worsened neurological deficits are identified, such patients should be deemed as deriving clinical benefit from therapy and allowed to continue treatment. Patients who develop worsening radiographic findings compared with the pre- treatment baseline scan more than 6 months from starting immunotherapy are expected to have a low likelihood of ultimately deriving clinical benefit and should be regarded as non-responsive to treatment with a recommendation to discontinue therapy.

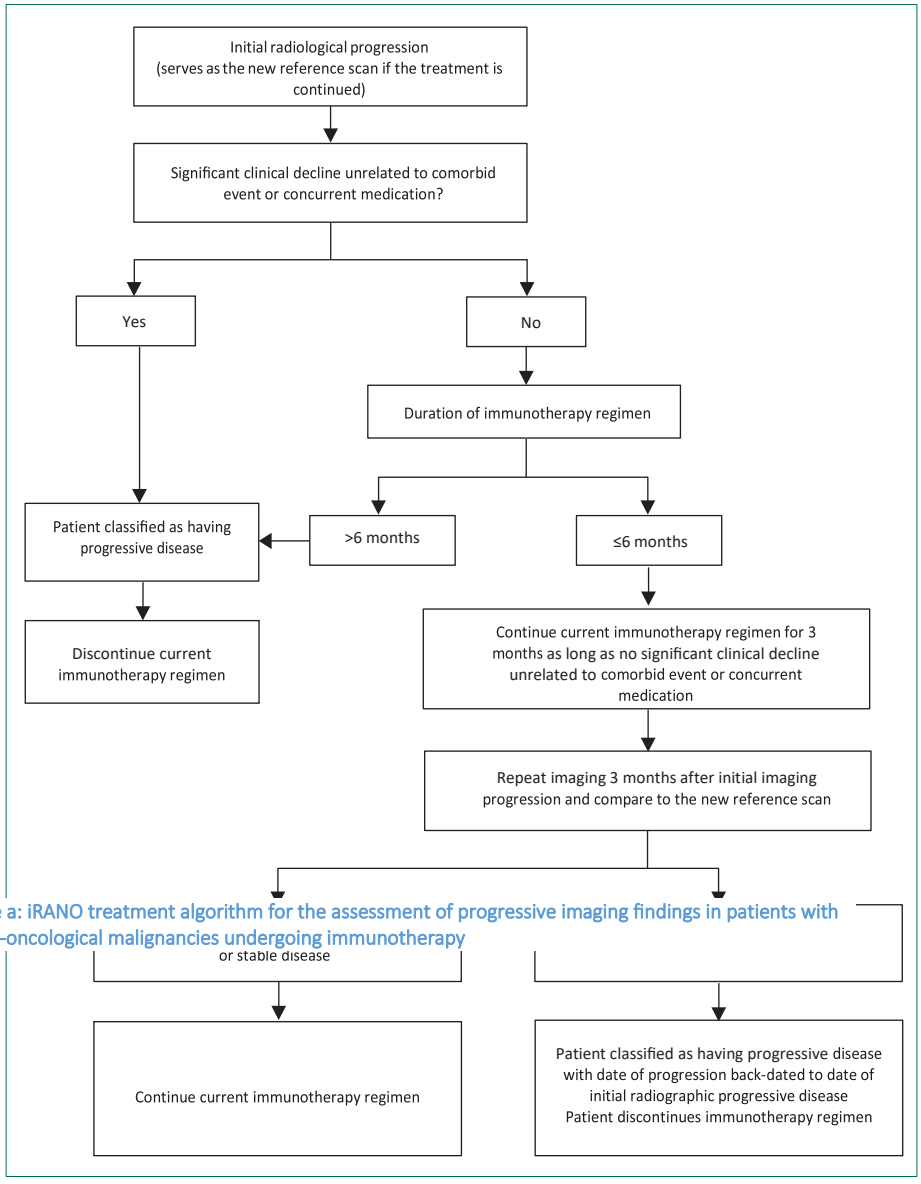



Figure a: iRANO treatment algorithm for the assessment of progressive imaging findings in patients with neuro-oncological malignancies undergoing immunotherapy

Overall, we have integrated guidance from the immune-related response criteria regarding interpretation of progressive imaging findings with existing RANO criteria to form the iRANO guidelines. A comparison of the key features associated with RANO, immune-related response criteria, and iRANO are summarized (table 2). Although application of immunotherapies for patients with neuro-oncology malignancies is in the early stages of development and much remains to be learned, the iRANO criteria provides guidelines that can be applied to provide consistent metrics in clinical trials and daily practice. Particularly, these guidelines shall raise awareness of the possibility of potentially misleading early progressive radiographic changes after initiation of immunotherapy, and provide guidance for responding to these changes to decrease the likelihood of inappropriate

premature therapy discontinuation. We expect the iRANO guidelines will be amended successively to improve their usefulness as further experience and systematic data from continuing immunotherapy trials in neuro-oncology accumulate.

**Key Considerations for RANO Criteria, Immune-Related Response Criteria, and iRANO Criteria**

| | RANO | Immune-related response criteria | iRANO (if therapy ≤6 months after start of immunotherapy | iRANO (if >6 months after start of immunotherapy) |
|---|---|---|---|---|
| **Is a repeat scan needed to confirm radiographic progressive disease for patients without significant clinical decline?** | **No** | **Yes** | **Yes** | **No** |
| **Minimum time interval for confirmation of disease progression for patients without significant clinical decline** | **NA** | **≥ 4 weeks** | **≥ 3 months** | **NA** |
| **Is further immunotherapy treatment allowed after initial radiographic progressive disease (if clinically stable) pending disease progression confirmation?** | **NA** | **YES** | **Yes** | **NA** |
| **Does a new lesion define progressive disease?** | **Yes** | **No** | **No** | **Yes** |

**iRANO=immunotherapy Response Assessment in Neuro-Oncology. N/A=not applicable.**

## Appendix 2

**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 2: Current National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 5.0)**

Please use the following link to the NCI CTCAE website:

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

**Appendix 3: 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 4: 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:

- 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 5 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 2: Highly Effective Contraceptive Methods That Have Low User Dependency**

| **Highly Effective Methods That Have Low User Dependency**<br>Failure rate of <1% per year when used consistently and correctly. |
|---|
| • Progestogen- only contraceptive implant [a, b]<br>• Intrauterine hormone-releasing system (IUS) [b]<br>• Intrauterine device (IUD) |

| |
|---|
| ● Bilateral tubal occlusion |
| ● **Vasectomized partner**<br>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**<br>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:<br>Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.<br><br>a) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation.<br>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 120 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 6 during the protocol-defined time frame.

**Table 3: Highly Effective Contraception Methods**

| |
|---|
| **Highly Effective Contraceptive Methods That Are User Dependent** [a]<br>Failure rate of <1% per year when used consistently and correctly. |
| ● Combined (estrogen- and progestogen- containing ) hormonal contraception [b, c]<br>○ Oral<br>○ Intravaginal<br>○ Transdermal<br>○ Injectable |
| ● Progestogen-only hormonal contraception [b, c]<br>○ Oral<br>○ Injectable |
| **Highly Effective Methods That Have Low User Dependency**<br>Failure rate of <1% per year when used consistently and correctly. |
| ● Progestogen- only contraceptive implant [b, c]<br>● Intrauterine hormone-releasing system (IUS) [b]<br>● Intrauterine device (IUD)<br>● Bilateral tubal occlusion |

| |
|---|
| ● **Vasectomized partner**<br>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**<br>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:<br>Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.<br><br>a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly).<br>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 120 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 .<br>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 Day 1 of every 4 week cycle 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.

Appendix 6

**NCCN GUIDELINES FOR TREATMENT OF CANCER**

https://www.nccn.org/professionals/physician_gls/default.aspx

Appendix 7

**AMERICAN SOCIETY OF CLINICAL ONCOLOGY CLICINAL PRACTICE GUIDELINES**

https://www.asco.org/practice-guidelines/quality-guidelines/guidelines

Appendix 8

Neurologic Assessment in Neuro-Oncology (NANO) Scale

Scoring assessment is based on direct observation and testing performed during clinical evaluation and is not based on historical information or reported symptoms. Please check one answer per domain. Please check "Not assessed" if testing for that domain is not done. Please check "Not evaluable" if a given domain cannot be scored accurately because of preexisting conditions, comorbid events, or concurrent medications.

Patient identifier: Date assessment performed (day/month/year):
Study time point (ie, baseline, cycle 1, day 1, etc):
Assessment performed by (please print name):

Domains Key Considerations

Gait
0 Normal
1 Abnormal but walks without assistance
2 Abnormal and requires assistance (companion, cane, walker, etc.)
3 Unable to walk Not assessed Not evaluable

Strength
0 Normal
1 Movement present but decreased against resistance
2 Movement present but none against resistance
3 No movement Not assessed Not evaluable

Ataxia (Upper Extremity)
0 Able to finger-to-nose touch without difficulty
1 Able to finger-to-nose touch but difficult
2 Unable to finger-to-nose touch Not assessed
Not evaluable

Sensation
0 Normal
1 Decreased but aware of sensory modality
2 Unaware of sensory modality Not assessed
Not evaluable

Visual Fields
0 Normal
1 Inconsistent or equivocal partial hemianopsia (≥quadrantanopsia)
2 Consistent or unequivocal partial hemianopsia (≥quadrantanopsia)
3 Complete hemianopsia Not assessed
Not evaluable

Facial Strength
0 Normal
1 Mild/moderate weakness
2 Severe facial weakness Not assessed
Not evaluable

Language
0 Normal
1 Abnormal but easily conveys meaning to examiner
2 Abnormal and difficulty conveying meaning to examiner
3 Abnormal; if verbal, unable to convey meaning
to examiner; OR nonverbal (mute/global aphasia) Not assessed
Not evaluable

Level of Consciousness
0 Normal
1 Drowsy (easily arousable)
2 Somnolent (difficult to arouse)
3 Unarousable/coma Not assessed
Not evaluable

Behavior
0 Normal
1 Mild/moderate alteration
2 Severe alteration Not assessed Not evaluable

Appendix 9

Assessment of Quality of Life (QOL)

https://www.aqol.com.au/documents/AQoL-8/AQoL-8_questionnaire.pdf

Appendix 10 Pill Diary

| | Pimasertib | | | | Comments |
|---|---|---|---|---|---|
| | AM | | PM | | |
| **Date of Dose** Day Month Year | **Time of Dose** Hr:Min 00:00-23:59 | **Dose** mg | **Time of Dose** Hr:Min 00:00-23:59 | **Dose** mg | **Patient comments for side effects related to drugs** |
| **e.g., 06 JAN 11** | **07:30** | **60** | **18:15** | **60** | **Nausea** |
| 1. | | | | | |
| 2. | | | | | |
| 3. | | | | | |
| 4. | | | | | |
| 5. | | | | | |
| 6. | | | | | |
| 7. | | | | | |
| 8. | | | | | |
| 9. | | | | | |
| 10. | | | | | |
| 11. | | | | | |
| 12. | | | | | |
| 13. | | | | | |
| 14. | | | | | |
| 15. | | | | | |
| 16. | | | | | |
| 17. | | | | | |
| 18. | | | | | |
| 19. | | | | | |
| | | | | | |
| | | | | | |

| | Pimasertib | | Comments |
|---|---|---|---|
| | AM | PM | |

| Date of Dose<br><br>Day Month Year | Time of Dose<br>Hr:Min 00:00-23:59 | Dose<br><br>mg | Time of Dose<br>Hr:Min 00:00-23:59 | Dose<br><br>mg | Patient comments for side effects related to drugs |
|---|---|---|---|---|---|
| **e.g., 06 JAN 11** | **07:30** | **60** | **18:15** | **60** | **Nausea** |
| 21. | | | | | |
| 22. | | | | | |
| 23. | | | | | |
| 24. | | | | | |
| 25. | | | | | |
| 26. | | | | | |
| 27. | | | | | |
| 28. | | | | | |
| 29. | | | | | |
| 30. | | | | | |

Patient Signature: _____ Date: _____

**The Physician's Office will complete this section:**

1. Start date: _____ End date: _____
2. Total number of pills dispensed this cycle:_____
3. Total number of pills taken this cycle: _____
4. Total number of pills returned this cycle:_____

Physician/Nurse Signature:_____

Comments:_____

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